CONSTRUCTING CHIRAL CENTRES VIA *O→C* ARYL AND ACYL MIGRATIONS: EXPLORING REACTION POTENTIAL

By

DANA MUHAMMAD HAMAD AMEEN

A thesis submitted in partial fulfilment for the requirements for the degree of (**Doctor of Philosophy**) at the University of Central Lancashire

March/2014

STUDENT DECLARATION FORM

Concurrent registration for two or more academic awards

I declare that while registered as a candidate for the research degree, I have not been a registered candidate or enrolled student for another award of the University or other academic or professional institution

---

Material submitted for another award

I declare that no material contained in the thesis has been used in any other submission for an academic award and is solely my own work

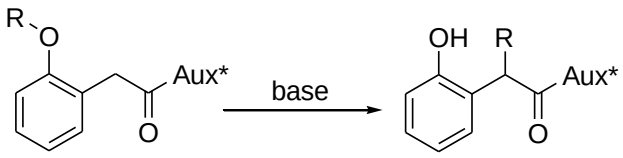
Signature of Candidate: *Dana Ameen*

Type of Award: PhD (Doctor of Philosophy) in Pharmacy (Pharmaceutical Chemistry)

School: Pharmacy and Biomedical Sciences

ABSTRACT

Detailed within this thesis are the production of diasteromerically enriched α-aryl carbonyl compounds prepared by a new and mild method based on the Truce-Smiles rearrangement; the synthesis of 1,3-dicarbonyl compounds utilising a Baker-Venkataraman rearrangement; and the synthesis of salicylic acid derivatives and amides by a novel Baker-Venkataraman-*retro*-Claisen cascade. In addition, the *in vitro* screening of the cyclooxygenase inhibitory activity of some of the diarylethers of the acetamide based substrates prepared, has been undertaken.



Aux*= known chiral auxiliaries
R= aryl (asymmetric Truce-Smiles rearrangement)
R= acyl (asymmetric Baker-Venkataraman rearrangement)

A generic scheme highlighting the transformation pursued in this thesis towards constructing new chiral centres.

The introduction summarises the significance and use of both the Truce-Smiles and Baker-Venkataraman rearrangement reactions in the synthesis of α-aryl and α-acyl carbonyl compounds, respectively. Additionally, a detailed review on some currently available chiral auxiliaries along with their applications is also mentioned. The discussion begins with the application of phase transfer catalysts, based on cinchona alkaloids, for the induction of chirality in ketone-based precursors. Further discussion continues with the synthesis of amide-based substrates from lactones and amines, and the use of C2-symmetric chiral auxiliaries to induce chirality during aryl migration. Using such an approach, a new and mild method for the production of diasteromerically enriched α-aryl carbonyl compounds has been achieved. It was found that propanamide-based substrates did not rearrange whilst acetamide-based substrates did, favouring a five-membered transition state during aryl migration. In these initial efforts, only modest diastereoselectivies (dr= max. 1.7:1) were observed.

The amide-based substrates did not undergo the Baker-Venkataraman rearrangement, but instead suffered from facile hydrolysis. Thereafter, the section focuses on the investigation of a serendipitously discovered, novel Baker-Venkataraman-*retro*-Claisen cascade and its subsequent applications in the synthesis of important amides, in which, unusually, the ketone appears to act as an alkyl donor and the carbamoyl moiety as an alkyl acceptor.

A separate chapter is given to the cyclooxygenase activity of some of the diarylethers prepared, wherein the diarylethers of certain acetamides were screened for their activities against cyclooxygenase enzymes, COX I and COX II. The preliminary results showed that the best compound was a pyrrolidyl-acetamide based precursor which showed good to modest inhibitory activity against both COX I and COX II (25-37% and 44-70%, respectively) in the *in vitro* screening assay.

The thesis concludes with the experimental section encompassing the experimental details, spectroscopic and analytical analysis of all the compounds prepared and described.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

In the name of God, who is most beneficial and merciful each individual creature on this earth is created by God to fulfil the particular role. Whatever I have achieved in life is through his help and expression of his will. His grace in me showed some outstanding teachers, colleagues, friends and family members. Whenever, I pay my tribute to those noble people I am praising his glory.

It gives me a great pleasure to thank Dr. Tim Snape, Senior Lecturer (Medicinal Chemistry), School of Pharmacy and Biomedical Sciences, University of Central Lancashire, for his interest in my work with valuable guidance and constant encouragement. His caring and humble attention for me was more than to ask for, apart from his immense knowledge of the subject.

I heartily thank to Dr. Leroy Shervington, Senior Lecturer (Medicinal Chemistry), School of Pharmacy and Biomedical Sciences, University of Central Lancashire. I record my profound sense of gratitude to him for giving me valuable suggestions and constant motivation towards the work.

I heartily thank Ministry of higher education-Hawler Medical University, Kurdistan, Iraq for financial support; the EPSRC National X-ray Crystallography Service; and the EPSRC National Mass Spectrometry Facility (NMSF), Sal, Steve, Tamar and all faculty members of the school of pharmacy and biomedical sciences for their assistance in carrying out the project.

At this opportunity, I feel fortunate to thank my dear friends Nozad, Huner, Haval, Ahmad, Viviana, Waad, Mustafa, Bahjat, Banu, Kanar, Rawand, Samridhi, Yogita, Hajira, Vinood, Sarah, Chris, Ifti, Sneha, Oshi, Tanem, Sakib, Amrit, and Mahak. I will never forget memorable moments shared with them.

Words do not suffice in extending my deep sense of gratitude to my parents, family members, my wife and my kids who are my greatest source of strength. I am blessed to have them.

ABBREVIATIONS

AcOH	Acetic acid
ADPH	10-acetyl-3,7-dihydrophenoxazepine
aq.	Aqueous
C.M	Complex mixture
Cat.	Catalyst
conc.	Concentration
COX	Cyclooxygenase
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N*,*N*′-Dicyclohexylcarbodimide
DCM	Dichloromethane
DCM	Dichloromethane
De	Diastereomeric excess
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Dr	Diastereomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodimide
Ee	Enantiomeric excess

Em	Emission
eq.	Equivalent
Et_2O	Diethyl ether
EtI	Ethyl iodide
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
Ex	Excitation
Fmoc	9-fluorenylmethoxycarbonyl
FNB	1-Fluoro-2-nitrobenzene
HIV	Human immunodeficiency virus
HOBT	Hydroxybenzotriazole
IC_{50}	Half maximal inhibitory concentration
IL	Interleukin
LDA	Lithium diisopropylamide
LiHDMS	Lithium hexamethyldisilazide
liq.	Liquid
lit.	Literature
LiTMP	Lithium tetramethylpiperidine
m.p.	Melting point
N.A	Not attempted

N.R	No reaction
NaHDMS	Sodium hexamethyldisilazide
NaO*t*-Bu	Sodium *tert*-butoxide
n-BuLi	*n*-Butyllithium
NMM	*N*-Methylmaleimide
NMP	*N*-Methyl-2-pyrrolidinone
n-PrI	*n*-Propyl iodide
NSAIDs	Non-steroidal anti-inflammatory drugs
PEG	Polyethylene glycol
PhMe	Toluene
PTC	Phase transfer catalyst
PTSA	*para*-Toluenesulfonic acid
PTT	Phenyltrimethylammonium tribromide
r.t.	Room temperature
RAMP	(*R*)-1-Amino-2-methoxymethylpyrrolidine
SAMP	(*S*)-1-Amino-2-methoxymethylpyrrolidine
sat.	Saturated
TBAI	Tetrabutylammonium iodide
t-BuLi	*tert*-Butyllithium
TEA	Triethylamine
temp.	Temperature

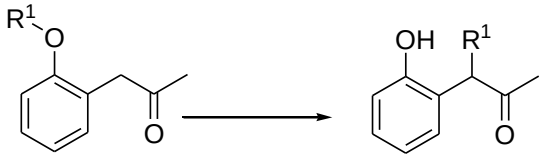
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
KO*t*-Bu	Potassium *tert*-butoxide
TMSOTf	Trimethylsilyl trifluoromethane sulfonate
UI	Ulcer index

CHAPTER 1 - INTRODUCTION

CHAPTER ONE - INTRODUCTION

1.1 Rearrangements

Rearrangement reactions are powerful tools in organic synthesis because simple, readily obtained precursors frequently produce molecules of much higher complexity.[1] To be more specific, the Truce-Smiles rearrangement and Baker-Venkataraman rearrangement are reactions which have perceived application in organic chemistry, especially for the selective formation of carbon–carbon (C–C) bonds. The Truce–Smiles rearrangement is well established as part of the synthetic chemists toolbox for the synthesis of substituted arylsulfinic acids,[2] while the Baker–Venkataraman rearrangement is often used to synthesize chromones and flavones.[3]



R^1= aryl (Truce-Smiles rearrangement)

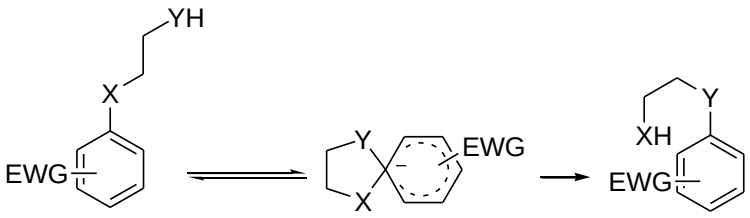
R^1= acyl (Baker-Venkataraman rearrangement)

Scheme 1. An example of the Truce-Smiles and Baker-Venkataraman rearrangements.

Both rearrangement reactions (Scheme 1) proceed via enolate formation followed by group transfer. A base abstracts the hydrogen atom alpha to the ketone, forming an enolate. Then, the enolate attacks the electrophilic carbon to form a cyclic intermediate. The cyclic intermediate is opened up to form a more stable phenolate, which is protonated during acidic workup to give the desired product.

1.1.1 The Smiles and Truce-Smiles Rearrangements

Smiles rearrangements of activated aromatic substrates are representative intramolecular S_NAr reactions.[4–8] The reaction begins by virtue of nucleophilic attack of the heteroatom on the *ipso* carbon (atom attached to the side chain connecting X and Y) (Scheme 2), which may be saturated or part of an aromatic system, but compelled to contain an atom with a lone pair of electrons (a nucleophile). X and Y represent diverse combinations of heteroatoms (O, S, and NR). In most cases the presence of a strong base is required as the displacement is by Y^- rather than by YH, but, when YH is an amino group (NH_2 or NHR), a base may or may not be necessary for reaction to start.



Scheme 2. The Smiles rearrangement.

Substituents on the ring will cause both electronic and steric effects, and the influence of these effects on the rearrangement will vary according to which ring they are placed on and also the position these groups occupy.[6]

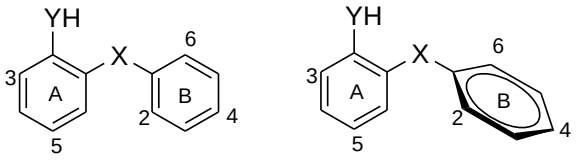
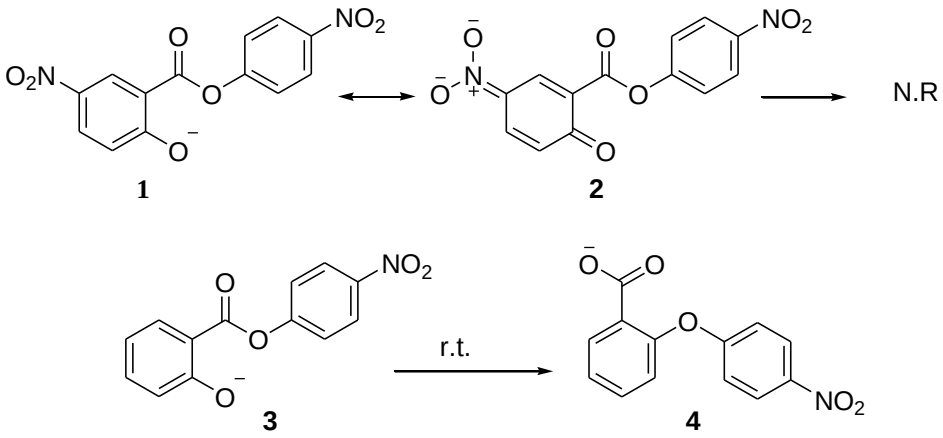


Figure 1. Positions of importance in the Smiles rearrangement.

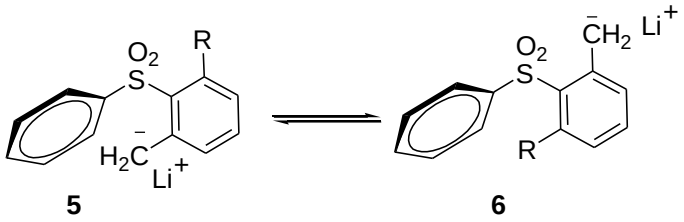
In the common depiction, Figure 1, an electron-withdrawing substituent in the 2- or 4-position of ring B will enhance the reaction whereas an electron donating group will hamper the nucleophilic attack of Y^- at the 1-position. For this reason, many rearrangements have been seen in components which have a 2- or 4-nitro substituent in ring B.[9]

Electron withdrawing groups in the 4- and 6-position of ring B will accelerate the acceptance of a negative charge by X and so assist the displacement reaction. Also, by the inductive effects of these groups, proton removal from YH may be facilitated and this will also help rearrangement. In the same vein, electron withdrawing groups in the 3- and 5-position of ring A will facilitate proton removal from YH and may also aid in electron withdrawal from the C-X bond. However, the displacement reaction will not work when EWG groups are present in the 3- or 5-position of ring A, because Y^- becomes too weakly nucleophilic to be able to attack ring B. For example, the rearrangement of compound **1** (Scheme 3) does not take place even on boiling with aqueous sodium hydroxide, while compound **3** rearranges easily to compound **4** at room temperature.[10]



Scheme 3. Illustrative example showing EWG effect on the Smiles rearrangement.

During the rearrangement the planes of the two rings are at right angles to one another, therefore, steric effects can also come to play during the Smiles rearrangement of an aromatic molecule, Figure 1, where YH is, say, OH or NH_2. This can be seen in the reaction of sulfones, where a substituent in the 6-position of ring A speeds up the rearrangement in comparison with similar sulfones having a hydrogen atom in that position. This is due to the influences on the rearrangement first by the relative orientations that the two rings may adopt, and secondly by the control which the two oxygen atoms of the sulfone group can exercise over the positions of the rings, Scheme 4.[11]

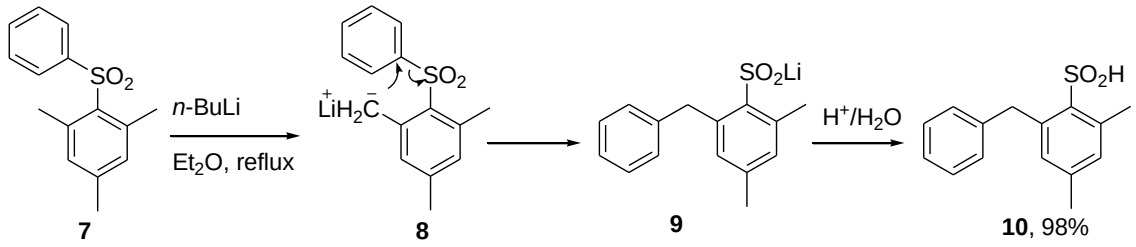


Scheme 4. The effect of conformation on the Smiles rearrangement.

In one particular modification of the Smiles rearrangement—the Truce–Smiles rearrangement—as the incoming nucleophile is a stronger carbanion the arene does not require the additional activation group. In 1958, Truce exemplified this reaction by the conversion of an aryl sulfone **7** into sulfinic acid **10** by action of the strong organolithium base *n*-butyllithium, Scheme 5.[12]

1.1.1.1 *S* to *C* Migration

Truce developed this variant within diaryl sulfone compounds (such as **7**), and proved it to be a reliable method for the synthesis of a variety of substituted aromatic sulfinic acids **10**, Scheme 5. [12]



Scheme 5. Truce's attempt towards the synthesis of a substituted aromatic sulfinic acid.

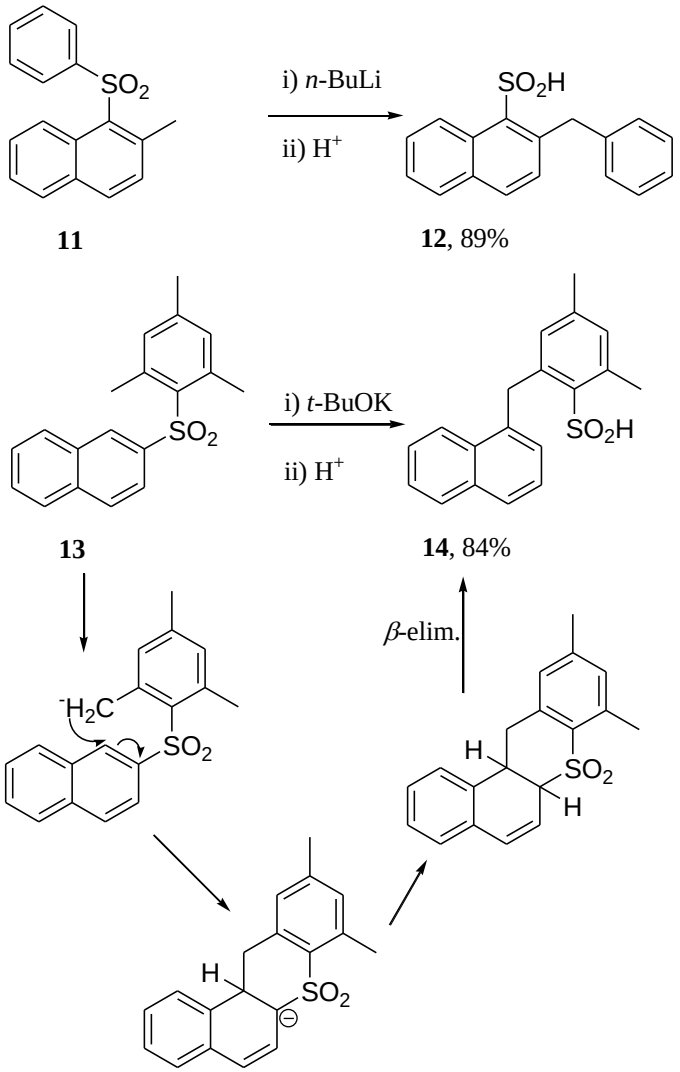
In this example the base (*n*-BuLi) deprotonates a methyl group resulting in the formation of anion **8**. This reactive nucleophile in turn attacks the *ipso*-carbon atom which is electron deficient (that bearing the sulfur atom), after which, substitution of the sulfur moiety (RSO_2^-) provides in the rearranged product **10**, after acid workup.[13]

Different circumstances, which have an effect on the orientation and reactivity in the Truce–Smiles rearrangement, have been studied. Within a variety of metalated sulfones the rate of the rearrangement has been measured and it was demonstrated to be first order with respect to the metalated sulfone when the rate of initial metalation was very high.[14] Sulfones with a 6-methyl group substituent on the ring containing the lithiated alkyl group were found to react nearly one order of magnitude more rapidly than those with no 6-position substituent. This effect can be illustrated by consideration that the metalated sulfone **5** exists in a conformational equilibrium whereby conformer **5** reacts to give the Truce–Smiles product (Scheme 4). Consequently, factors which push the equilibrium toward this favourable conformer should facilitate the rearrangement. Based on this, when R= H, conformer **6** becomes sterically more favoured and this will slow down the reaction.[9,15,16]

From the late fifties to the seventies, Truce reported the rearrangement of various *O*-methyl-diaryl sulfones into arylsulfinic acids in high yield.[12,15,17,18] It was demonstrated that only compounds with *ortho*-methyl groups rearrange, when treated with potassium *tert*-butoxide in DMSO.[18]

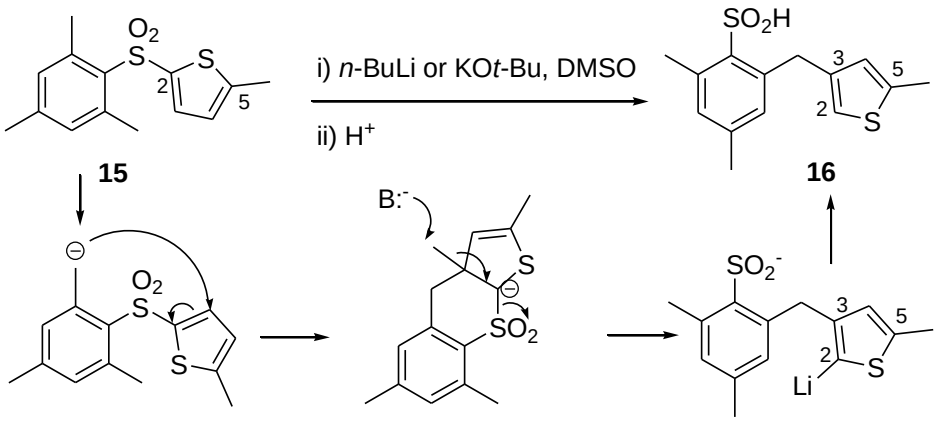
Additionally, the naphthalene nucleus has been subjected to the rearrangement, Scheme 6, whereby compound **11** and the related compound **13** were deprotonated resulting in

phenyl and naphthalene migration from sulfur to carbon to give benzyl naphthalene sulfinic acid **12** in 89% yield and product **14** in 84% yield, respectively.[13] Conversely, in the second case a different reaction takes place, the migrating group itself is naphthalene and this begins with an intramolecular nucleophilic addition across the 1,2-bond of naphthalene then followed by *β*-elimination to generate **14**, Scheme 6.[18]



Scheme 6. The naphthalene nucleus subjected to the Truce-Smiles rearrangement.

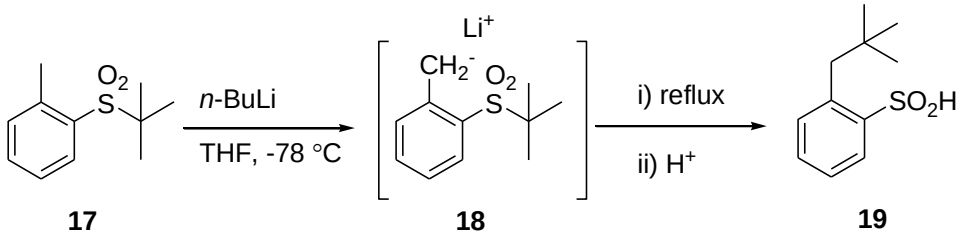
Furthermore, rearrangements within heteroaromatic systems have also been demonstrated by Truce and his co-workers. It has been shown that substituted thienyl sulfones **15** (when R= Me) undergo the Truce–Smiles rearrangement via an addition–elimination sequence to generate sulfinic acids **16**, Scheme 7. Herein, the reaction does not begin through formation of a spiro-cyclic intermediate, as usual, but proceeds via addition of the anion to the position C-3 at the thiophene ring followed by *β*-elimination from the cyclised intermediate.[17]



Scheme 7. Thienyl migration within the Truce-Smiles rearrangement.

Unlike the previously mentioned naphthyl and substituted phenyl groups, the thienyl unit migrates with a change in orientation regardless of the base/solvent system used. In 1978, Truce *et al*. showed the first example of the rearrangement (Scheme 7) proceeding with a change in aryl orientation in aprotic media. In this case, when the thiophene ring is unsubstituted two equivalents of base are needed because with one equivalent of base, the ring is deprotonated at C-5 and the resulting mono-metalated product decomposes.[17]

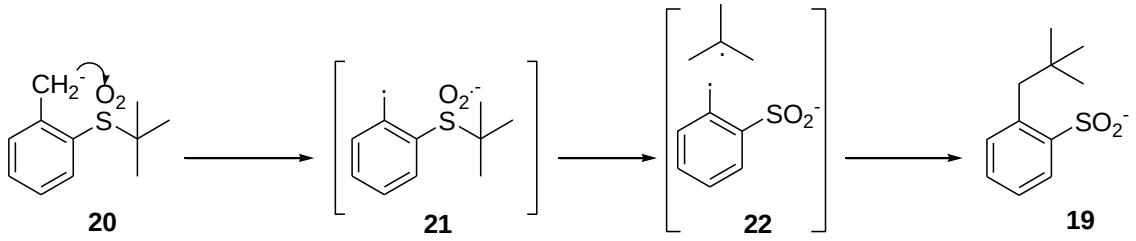
Prior to 1979, the Truce-Smiles rearrangement had only been observed in diaryl sulfone substrates, then after, when Truce investigated several reactions of metalated *o*-tolyl *tert*-butyl sulfone, it was found that refluxing the lithiated species **18** in THF for several hours led to the formation of *o*-neopentylbenzenesulfinic acid **19** in 75–80% yield, Scheme 8. This case was reported as the first example in which an alkyl group migrates rather than aryl group.[19]



Scheme 8. Formation of *o*-neopentylbenzenesulfinic acid **19**.

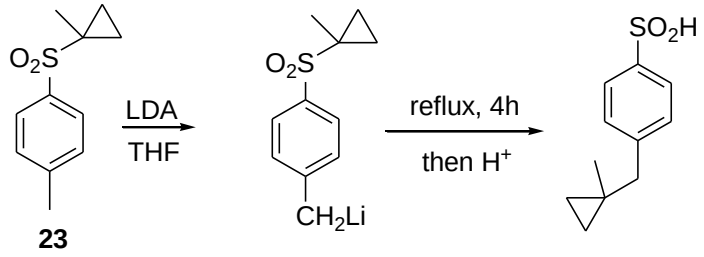
Truce *et al*. rationalised this novel rearrangement in terms of an electron-transfer radical-anion pathway, Scheme 9, contrary to the mechanism described in Scheme 5. They believed that the transfer of an electron from the benzylic carbanion **20**, accelerated by the close proximity of the -SO- group, forms a stable benzylic radical and the sulfonyl radical anion **21**. After which homolytic cleavage of the sulfur *tert*-

butyl bond would generate the sulfinate anion and *tert*-butyl radical **22**. Finally the desired product **23** will come from immediate radical combination, within the solvent cage.[17]



Scheme 9. Plausible radical-based mechanism for the formation of **19**.

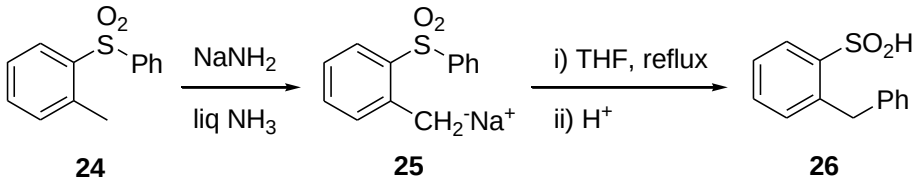
After eight years, the same group showed that lithiation of appropriate methylaryl alkyl sulfones is followed by migration of the alkyl group from sulfur to the benzylic carbon. Product studies, relative reactivities and cross-over experiments are consistent with a radical–radical anion chain process for this rearrangement, consistent with that viewed in Scheme 9. They have also demonstrated that, with the use of amide bases, *p*-methyl groups (such as **23** in Scheme 10) can undergo metalation then rearrangement in the same vein to **20**.[20]



Scheme 10. Migration of a quaternary centre in the Truce-Smiles rearrangement.

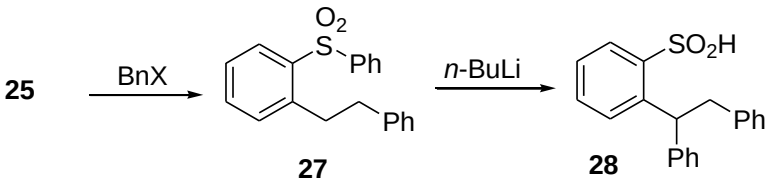
1.1.1.1.1 *S* to *C* Migration under alternative reaction conditions

Crowther and Hauser (1968) found that using sodium amide as base the deprotonation products of phenyl *o*-tolyl sulfones underwent the Truce–Smiles rearrangement when the solvent (ammonia) was replaced by tetrahydrofuran and the resulting mixture was refluxed. This alternate reaction condition gave a good yield for benzylbenzenesulfinic acid **26** (~70%), Scheme 11.[21]



Scheme 11. Alternative conditions for the Truce-Smiles rearrangement.

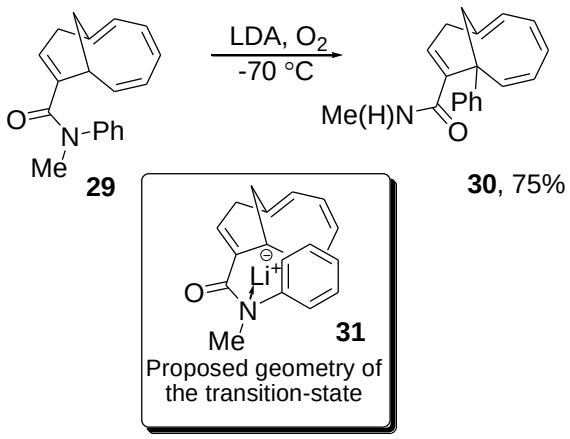
Additionally, the sodium salt **25** could be trapped by various intermolecular electrophiles, therefore, the yields would be better than those obtained using Truce's developed conditions. They found that these condensation products (e.g. **27**) could also undergo the Truce–Smiles rearrangement, Scheme 12.[21]



Scheme 12. "A double Truce-Smiles": Phenyl migration in a Truce-Smiles product.

1.1.1.2 *N* to *C* migration

The synthesis of 1,5-methano[10]annulene addressed by Itô *et al*. during their studies towards crystallographic analysis and they discovered a distinctive Truce–Smiles rearrangement of *N*-methylanilide intermediate **29** after subjecting it to LDA, Scheme 13. On exposure to an oxidative process (LDA, THF, O_2, -70 °C) the rearranged product **30** was formed in 75% yield rather than the desired oxidation product.[22]

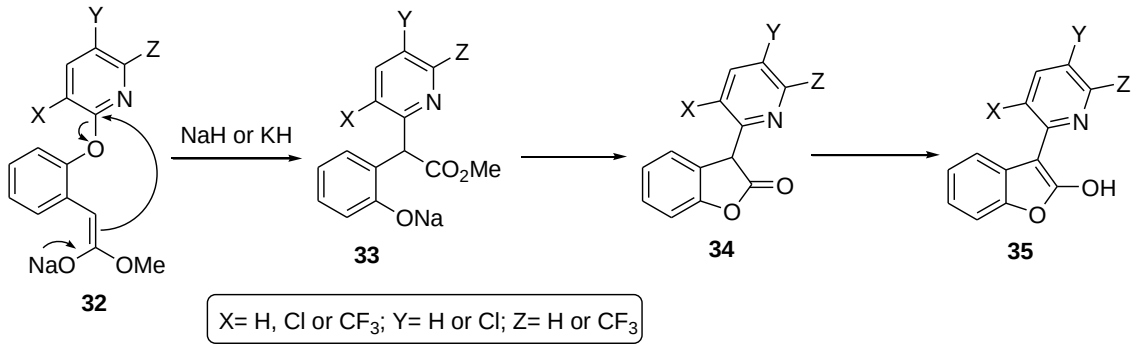


Scheme 13. *N* to *C* aryl migration in an *N*-methylanilide.

It was believed that this rearrangement was the outcome of a Truce–Smiles rearrangement which happens through the intramolecular nucleophilic attack of a bulky carbanion on the *ipso* position of the anilide **31**, followed by extrusion of the amide nitrogen to give the product in good yield.[22]

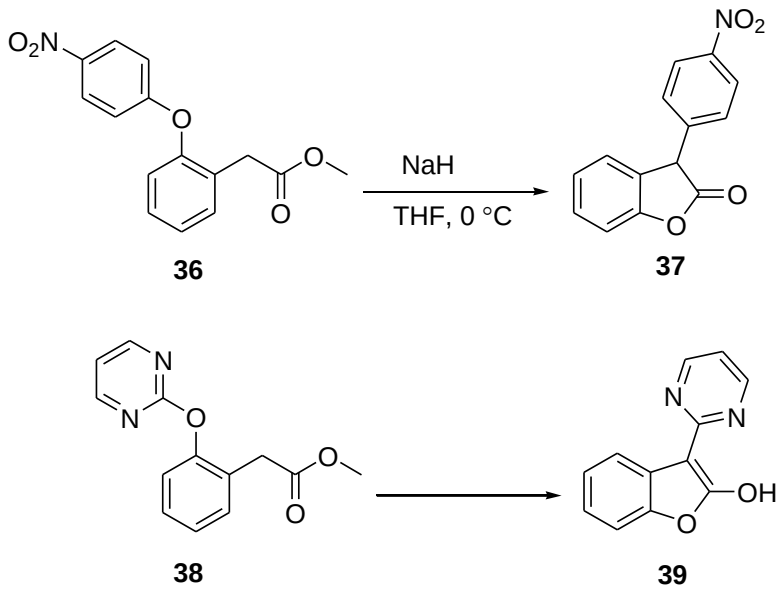
1.1.1.3 *O* to *C* migration

The Truce-Smiles rearrangement has also been observed with O to C migration, when it was unexpectedly observed by Erickson and McKennon (2000), during their work on the synthesis of some anti-fungal compounds. When they attempted to apply a straight-forward protocol for the formylation of an ester enolate followed by *O*-methylation, Scheme 14, formylated products were not produced when compounds such as **32** were exposed to the literature conditions. Rather, products were produced in which the pyridine ring was attacked by the enolate.[23] They justified the results as a Truce–Smiles rearrangement product and initially they stated it as an undesired transformation, but, also as a new method to make 3-pyridyl-2-benzofuranones **34**. When a number of esters (for example **32**) were exposed to either NaH or KH at temperatures above 0 °C, the rearrangement was induced by producing an intermediate phenoxide (ArO^-M^+, **33**) which immediately cyclised to the lactone (benzofuranone) **34**. In certain cases, the benzofuranone tautomerised resulting in the isomeric products **35** if X=H, Scheme 14.[23]



Scheme 14. A method to make 3-pyridyl-2-benzofuranones.

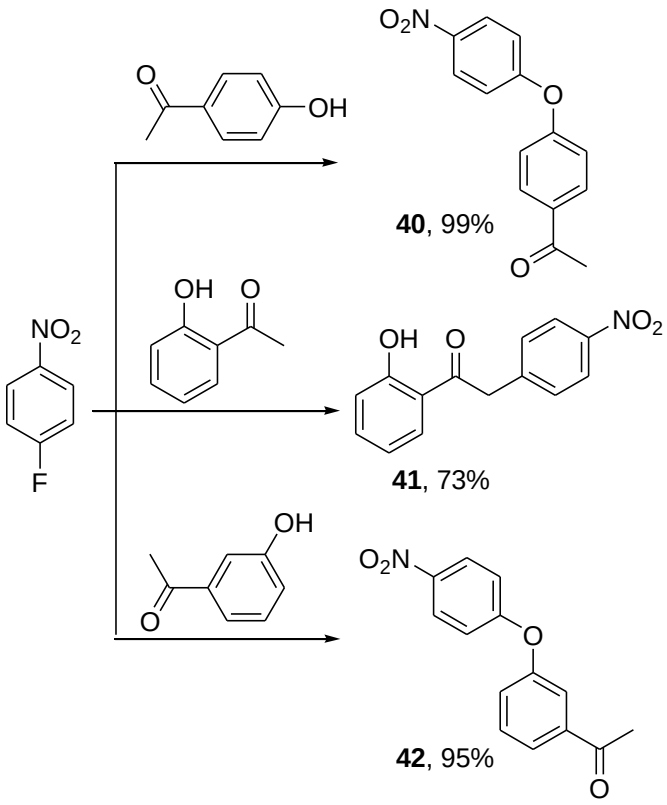
To achieve a generic rearrangement method, other activated aromatic systems were studied by the authors, for example treating **36** with NaH in THF at 0 °C offers the lactone **37**, Scheme 15. Moreover, the transformation of **38** smoothly gave hydroxybenzofuran **39** too.[23]



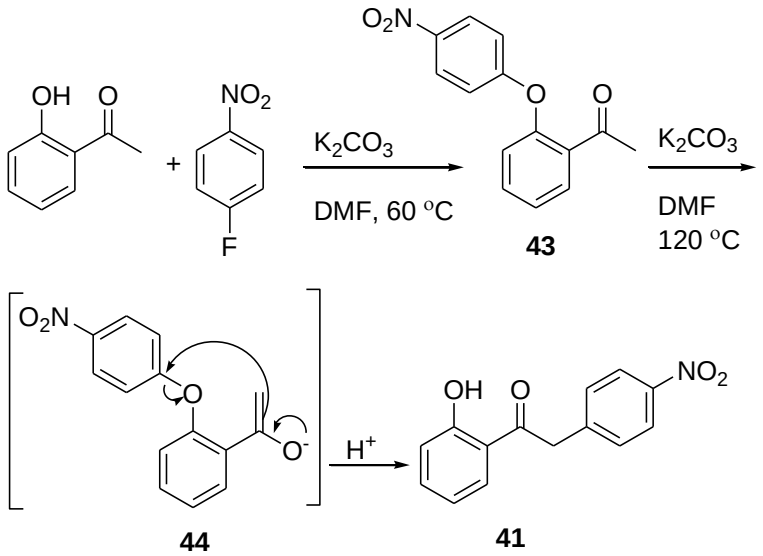
Scheme 15. Ester substrates undergoing the Truce-Smiles rearrangement.

Later, when Mitchell and Barvian (2004) attempted the synthesis of a series of diphenyl ethers by the S_NAr reaction of activated aryl fluorides with phenols, they noticed an aberration with 2'-hydroxyacetophenone, Scheme 16. They analysed the unexpected products obtained from the reaction of 2'-hydroxyacetophenone and both 2- and 4-fluoronitrobenzene, then they documented that this deviation is due to the involvement of Truce–Smiles rearrangement in their preparations.[24] The story came after they treated three isomers of hydroxyacetophenone (2'-, 3'- and 4'-hydroxyacetophenone) separately with 4-fluoronitrobenzene (K_2CO_3, DMF, 120 °C) and found that 2'-hydroxyacetophenone did not give required diphenyl ethers analogous to **40** and **42** but instead gave product **41** (Scheme 16). The unexpected product from the reaction showed a phenolic signal in the ^1H NMR and was deprived of the signal correlating to the methyl group of the methyl ketone; alternatively, a two proton singlet at 4.64 ppm was seen, which justified that the product was indeed isomeric compound **41** (C-arylated rather than O-arylated), Schemes 16 and 17.

The authors considered that the C-arylated product **41** was not formed directly because no C-arylated product was identified in the case of the isomeric acetophenones. Moreover, a similar reaction with 2'-methoxyacetophenone gave only unreacted starting materials. Consequently, there was no doubt that the product came from a Truce–Smiles rearrangement. Thus, this unexpected transformation provided a method for carbon–carbon bond formation under mild conditions.



Scheme 16. Synthesis of α-aryl ketones.



Scheme 17. Conversion of diarylether **43** to the *C*-arylated product.

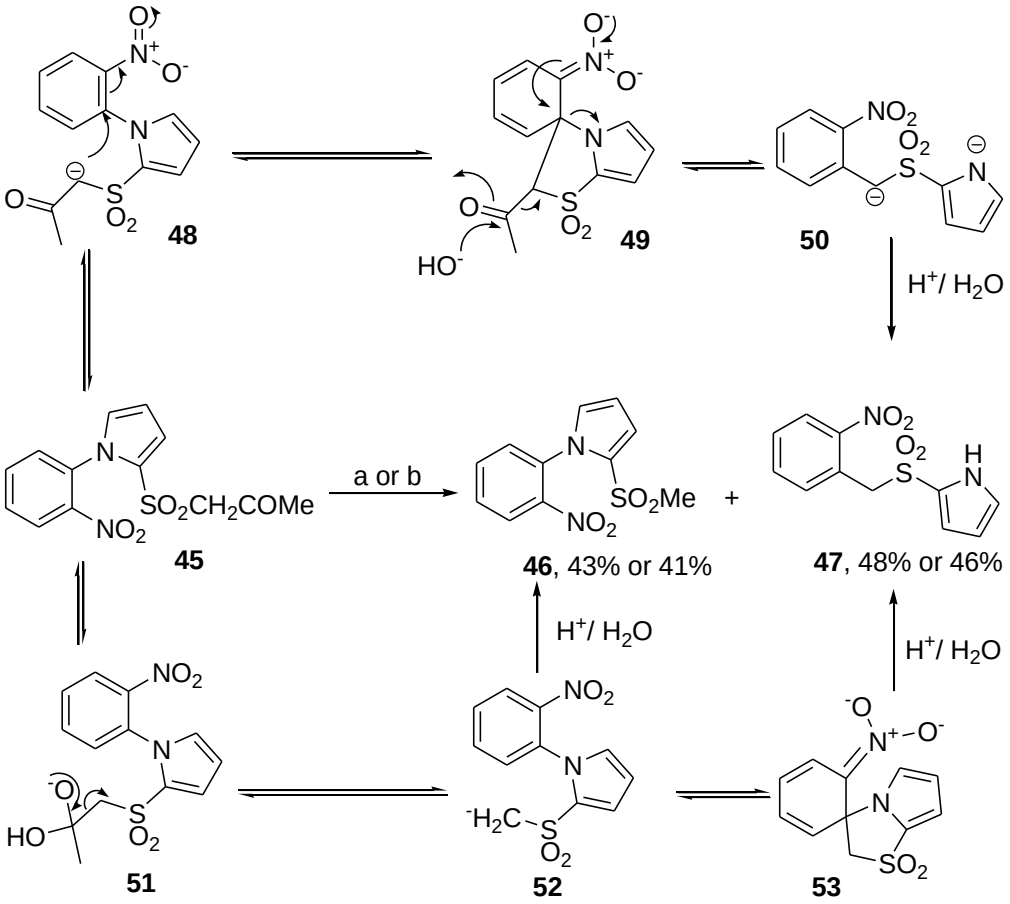
In fact, Mitchell and Barvian observed that the intermediate (diarylether **43**) in the Truce–Smiles rearrangement could be isolated (in 21% yield) after lowering the reaction temperature to 60 °C, Scheme 17.[24] More evidence for the rearrangement was obtained by subjecting the diarylether **43** to the previously used reaction conditions (K_2CO_3, DMF, 120 °C) and quantitative conversion to the C-arylated product **41** was

demonstrated. A few remarkable traits of the reaction have been analysed by the authors: (a) the exact conditions essential for the rearrangement to take place are substrate dependent, (b) this first example of a homologous enolate Truce–Smiles rearrangement involves a six-membered transition state, and (c) the same conditions are responsible for producing the diarylether intermediate **43** and forcing it to undergo the rearrangement to give the C-arylated product **41**. Thus, this is a novel one-pot two-step reaction.[24]

1.1.1.4 *C* to *S* migration: (an unusual Truce–Smiles type rearrangement)

An unusual Truce–Smiles type rearrangement was discovered by Varvounis and co-workers in 2004,[25] while attempting the synthesis of the pyrrolo[1,2-a][3.1.6]benzothiadiazocine ring system, Scheme 18. As an illustration, compound **45**, when treated with hot aqueous ethanolic sodium hydroxide, gave a mixture of two unexpected compounds **46** and **47** in 43% and 48% yield, respectively. A conjectural mechanism was postulated for the synthesis of **47** where the hydroxide anion can act as a base and as well as nucleophile, Scheme 18; the carbanion **48** can intramolecularly attack the benzene ring to give the Meisenheimer type intermediate **49** that would suffer from ring-opening pre- or post- addition of the hydroxide anion to the acetyl group to offer the pyrrolyl dianion **50**, after losing an acetate anion.

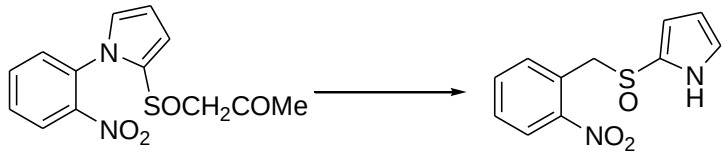
In a second proposed mechanism, after addition of hydroxide to the acetyl group of **45**, the intermediate **51** would form and in turn would lose the acetate anion giving the products **52** and **53**. Because compound **47** has been formed, therefore, it is regarded as an uncommon case of a Truce–Smiles rearrangement. Generally, it is convincing that wherever an electron deficient arene takes part in the rearrangement the reaction would occur via an intermediate anionic spiro adduct in a similar fashion to that represented by **49**.[26]



Reaction conditions: (a) Zn, NaOH, H_2O, EtOH, reflux; (b) NaOH, H_2O, EtOH, reflux.

Scheme 18. Plausible mechanism for the unusual Truce–Smiles type rearrangement.

Similarly, the comparable sulfoxide **54** was tested under similar conditions (NaOH, H_2O, EtOH, reflux) and it was shown to give the product **55** in 72% yield, presumably as a result of a Truce–Smiles type rearrangement, Scheme 19. The sulfoxide analogue of carbanion **50** was formed, because the sulfoxide analogue is less stabilised in comparison to sulfone intermediate **50**, Scheme 18.[25]



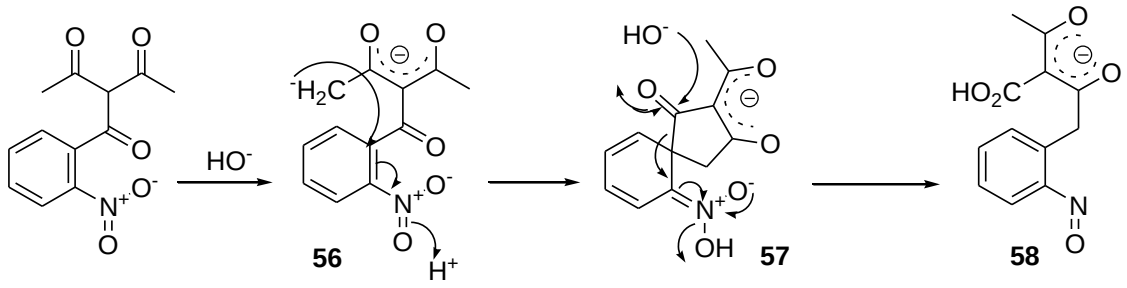
54 **55**, 72%

Reaction conditions: Zn, NaOH, H_2O, EtOH, reflux; or NaOH, H_2O, EtOH, reflux.

Scheme 19. Sulfoxide containing substrates undergoiog an unusual Truce–Smiles type rearrangement.

1.1.1.5 Fragmented Truce–Smiles rearrangement

This variant of the Truce–Smiles rearrangement was first demonstrated by Tennant and co-workers (1975) to make 2-acyl-3-hydroxyquinolines from 2-(2'-nitrobenzoyl) derivatives of certain 1,3-diketones by base-catalysed cyclisation; products that were previously unreachable, Scheme 20.[27] The postulated mechanism for this transformation (**56** to **58**) would involve the intramolecular nucleophilic attack of the enolate at the *ipso* carbon generating spirocyclic intermediate **57**. In contrast to the usual species in the Truce–Smiles rearrangement (see **56**, CO replaces SO_2), **58** cannot achieve stabilisation by ejection of the sulfonyl leaving group. As a consequence, the carbonyl group could be attacked by hydroxide to undergo ring scission and subsequent reduction of the nitro group to nitroso, Scheme 20.[27]



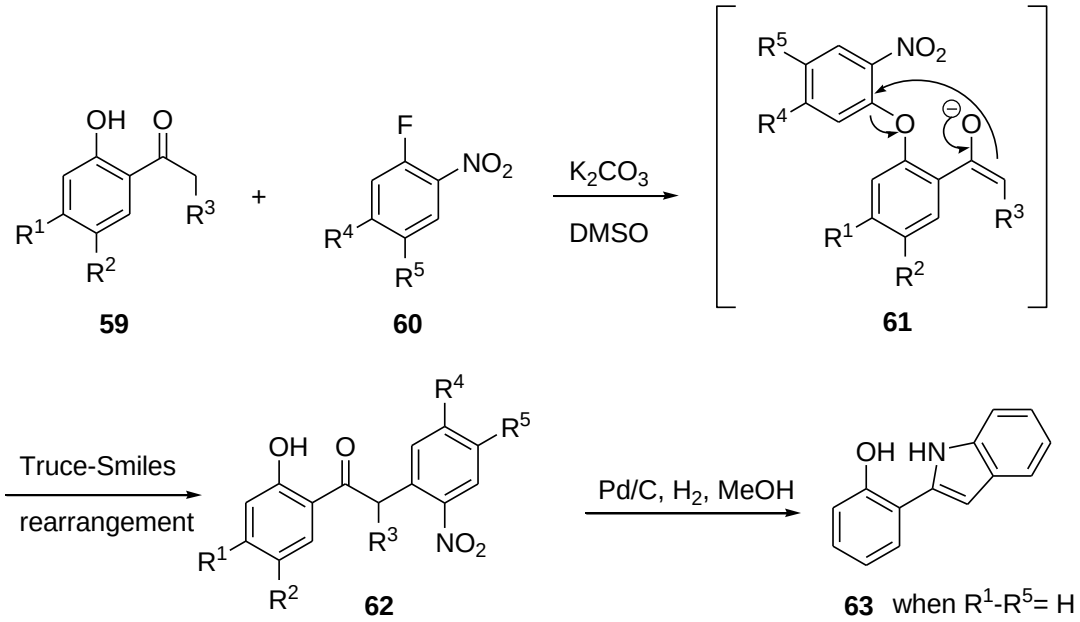
Scheme 20. Fragmented Truce–Smiles rearrangement.

1.1.1.6 The importance of the Truce-Smiles rearrangement

The synthetic utility of the Truce–Smiles rearrangement was first recognised by Mitchell and Barvian in their summary where they projected that the rearrangement provides a method for carbon–carbon bond formation under mild conditions, and may also prove useful if the acetyl, or a substituted acetyl was coupled after diphenyl ether formation, or if alternative diaryl ether formations were used. For example, they suggested reversing the sense of the coupling such that an *ortho*-fluoroacetophenone was the electrophilic partner. Additionally, they considered that it would be interesting to contemplate whether this reaction could be used successfully for ring-expansion or contraction in cases where the two aryl rings were linked.[24]

α-Arylated carbonyl compounds are commonly occurring motifs in biologically interesting molecules[28] and important classes of medication such as typical antipsychotics[29] and opioids,[30] however, the synthesis of such compounds is synthetically challenging and are therefore of high interest to the pharmaceutical

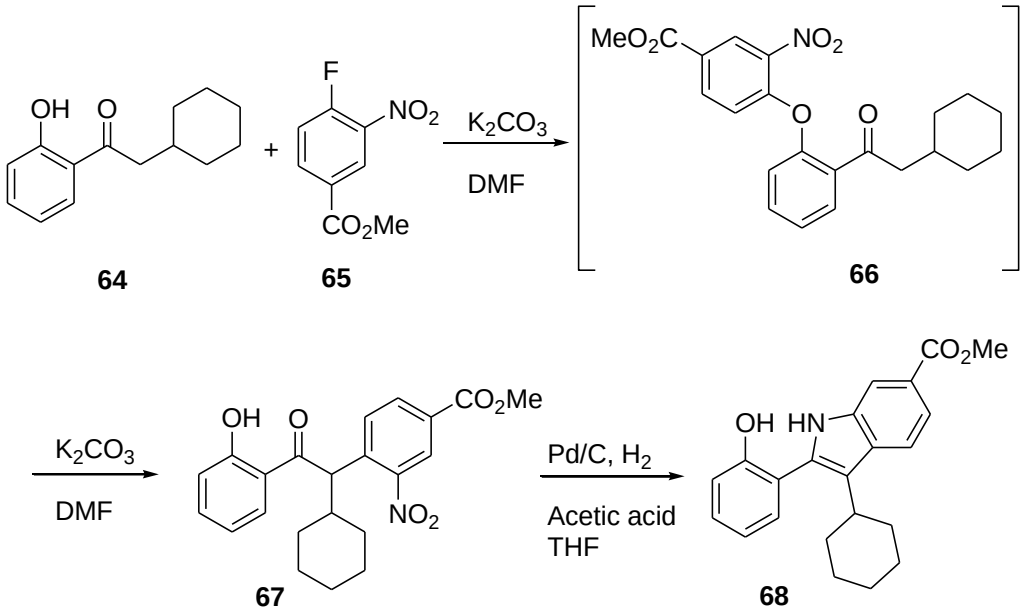
industry. Therefore, in 2008 Snape extended the scope of the Truce–Smiles rearrangement (*O* to *C* aryl migration) and established the conditions to allow synthetically useful substituted α-arylated aryl ketones (7 entries have been examined, **62**) to be prepared under very mild conditions (K_2CO_3, DMSO, room temperature). Furthermore, the synthetic utility of these compounds has been demonstrated with the facile conversion of the Truce–Smiles rearrangement product **62** into substituted indole 2-(1*H*-indol-2-yl)phenol **63** in good yield (72%), Scheme 21.[31]



Scheme 21. The synthetic utility of the Truce–Smiles rearrangement to offer substituted indoles.

As the indole motif is prevalent in a large number of target molecules, there is an extensive demand for finding efficient large-scale synthetic routes towards these compounds.[32] To find a practical, scalable, and high-yielding synthesis of target indole **68**, the approach outlined in Scheme 21[31] has been optimised by the researches of Merck, Sharp and Dohme toward a novel synthesis of a 2-substituted indole using a Truce−Smiles rearrangement as a key step (Scheme 22).[33].

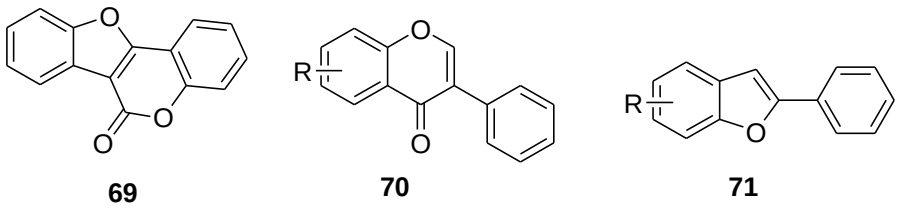
The synthetic scheme for this approach is shown in Scheme 22. An S_NAr reaction to **66** and its rearrangement to **67** proved to be both selective and high yielding under the published DMF/ potassium carbonate conditions. Investigations therefore focused on the synthesis of the phenolic ketone fragment **67** and its final hydrogenation/ring closure to afford >50 kg of the target indole **68**.[33]



Scheme 22. Multi-kilo synthesis of a 2-substituted indole using Snape's Truce−Smiles rearrangement as a key step.

A wide range of substituted α-arylated ketones were synthesized in moderate to excellent yields via a Truce-Smiles rearrangement. The main scaffold has various applications in medical and biochemical fields. This process also provides a facile and direct method for the C–C bond formation.

Like indole motifs, α-arylated ketones are important components of many natural products, synthetic intermediates, and precursors of natural analogues such as coumestan **69**,[34] isoflavones **70**, [35] and the intermediates to phenylbenzofurans **71**, Figure 2.[36] Therefore, many synthetic approaches have been reported to construct these scaffolds; however, most of the procedures use metal catalysts or Grignard reagents, which are not eco-friendly or are sensitive to air and moisture. As such, the Truce-Smiles rearrangement has been investigated for the synthesis of these scaffolds.[31]

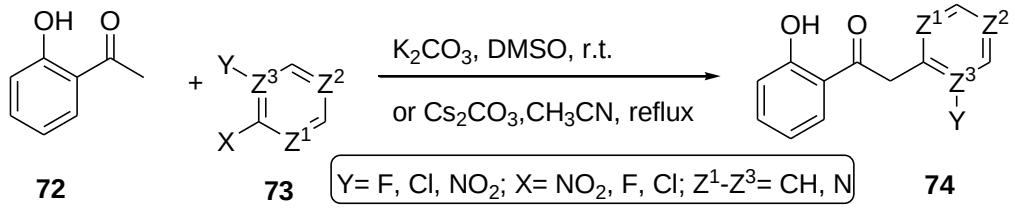


69 **70** **71**

Figure 2. Natural products: coumestan **69**, isoflavones **70**, and phenylbenzofurans **71**.

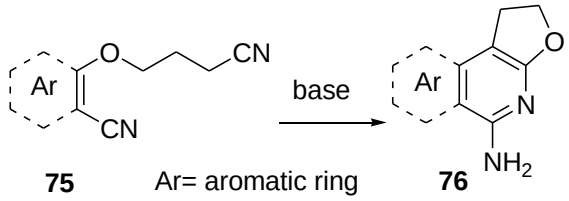
Recently, through expanding the Truce-Smiles rearrangement conditions, an efficient metal free C–C bond formation reaction under mild condition has been reported by Yanli *et al*.. They generated an efficient method for the synthesis of a variety of

functionalized and substituted α-arylated ketones (**74**) using readily available 2-hydroxyacetophenone (**72**) and substituted benzenes or pyridines (**73**), Scheme 23.[37]



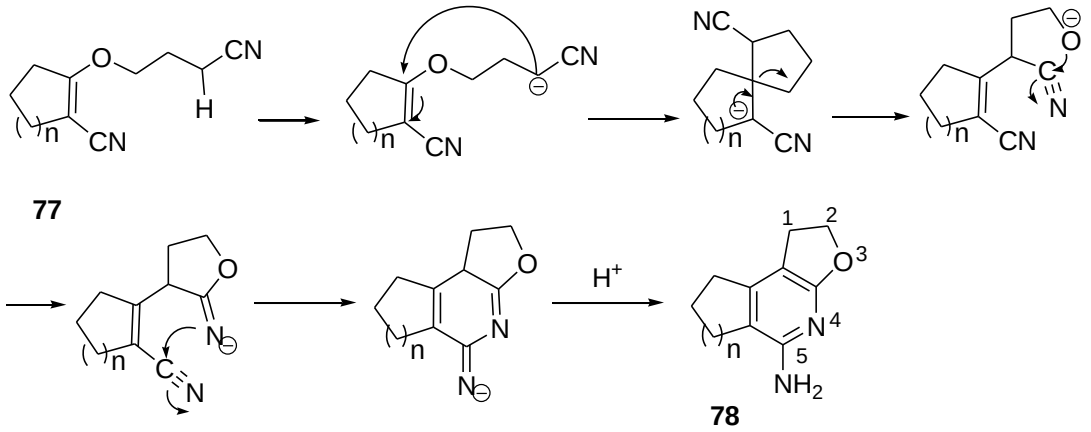
Scheme 23. The synthesis of heterocyclic α-arylated ketones.

In 1996 Okuda *et al*. began a research programme on the synthesis of polycyclic *N*-heterocyclic compounds (for example: 5-aminocycloalkeno[1,2-d]furo[2,3-b]pyridines **76**, Scheme 24) for medicinal applications and this started by developing a general one step preparation of aromatic ring-fused furo[2,3-b]pyridines **76** from aryl-1-carbonitriles having a 3-cyanopropoxy group adjacent to the cyano (carbonitrile) group **75**.[38–41] A Truce–Smiles rearrangement was the key step (**75**→**76**) by the action of potassium *tert*-butoxide and followed by an intramolecular cyclisation, Scheme 24.[42]



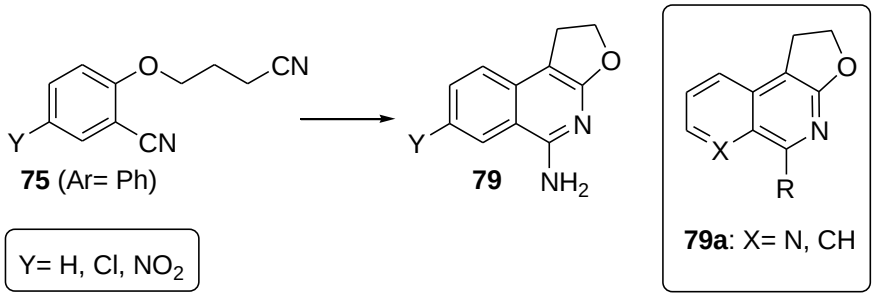
Scheme 24. The synthesis of polycyclic *N*-heterocyclic compounds.

They further explored the reaction sequence of 2-(3-cyanopropoxy)cycloalkene-1-carbonitriles **77**, and found that it followed the same mechanism to that seen previously for the synthesis of **76**; the general mechanism is shown in Scheme 25.[42]



Scheme 25. Proposed mechanism for the synthesis of compound **78**.

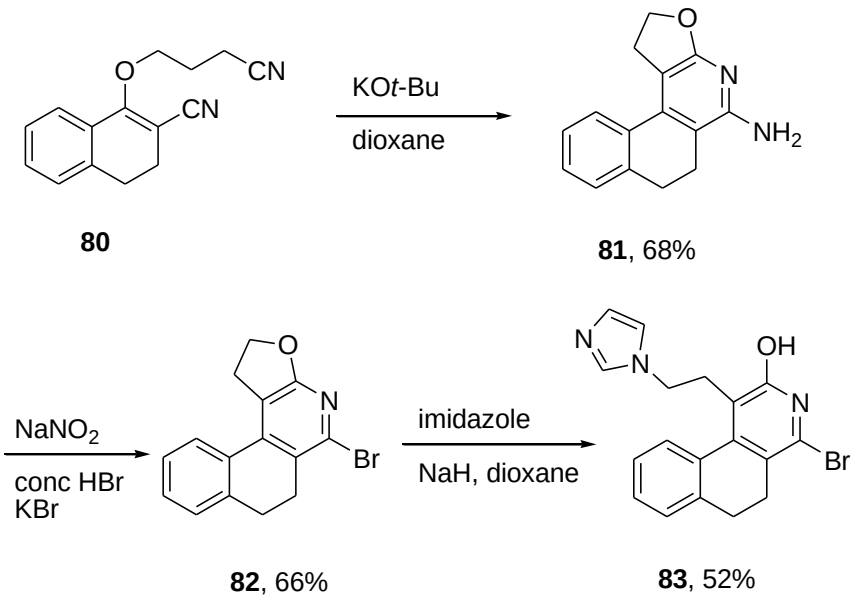
Again, Okuda *et al*. have expanded the method to include the synthesis of 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline derivatives (eg. **79**) based on the Truce–Smiles rearrangement, Scheme 26.[43]



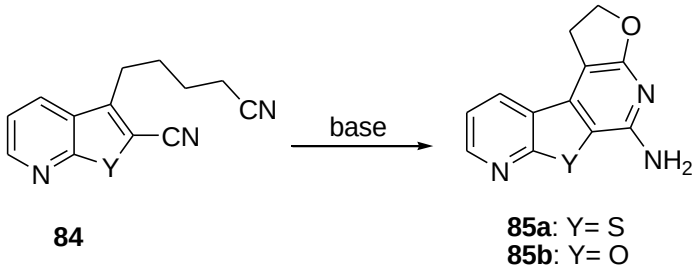
Scheme 26. The synthesis of 5-amino-1,2-dihydrofuro[2,3-*c*]isoquinoline derivatives.

In the same vein, the same authors developed a method for the synthesis of benzo-fused 5-aminocycloalkeno[1,2-*d*]furo[2,3-*b*]pyridines **81**, in which the 5-amino group was transformed to the bromo derivative **82**, which was allowed to react with cyclic amines (such as imidazole) to give amino-substituted derivatives (eg. **83**) which has showed bronchodilator activity, Scheme 27.[44]

Similarly, using the same protocol, further polycyclic *N*-heterocyclic compounds have been prepared by this group for example: 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-***b***]pyridines **85b**,[45] 5-substituted 1,2-dihydrofuro[3,2-*f*][1,7]naphthyridines **79a** (X= N) which revealed bronchodilator effects[46] 5-amino-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridines **85a**,[47] and 5-substituted 1,2-dihydrofuro[2,3-c]isoquinolines **79a** (X= CH) [48] both as inducers of lipoprotein lipase mRNA expression, Scheme 28.

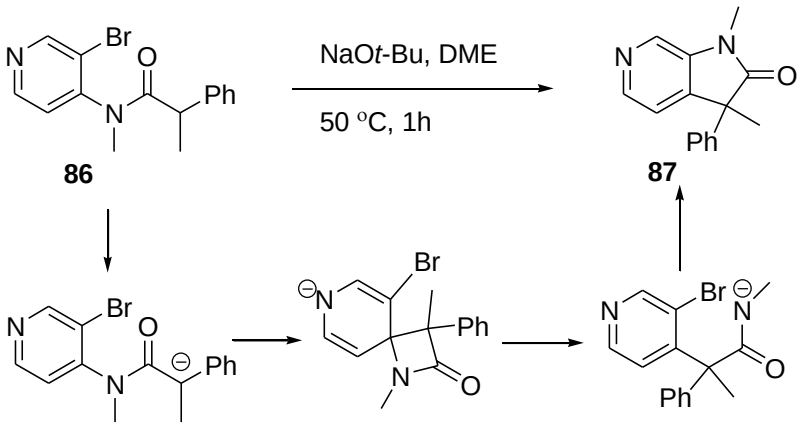


Scheme 27. The synthesis of the bronchodilator agent **83**.



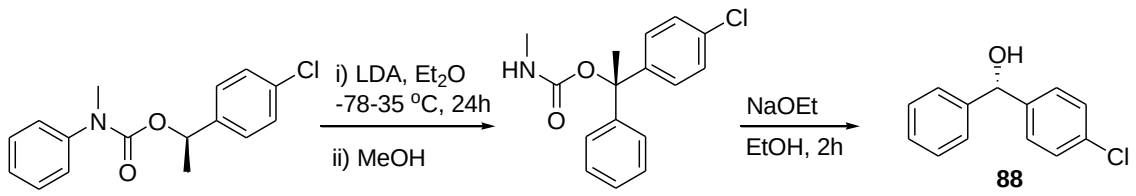
Scheme 28. The synthesis of polycyclic *N*-heterocyclic compounds as inducers of lipoprotein lipase mRNA expression and as bronchodilator agents.

Further exploitation of the Truce-Smiles rearrangement has seen the synthesis of 3,3-disubstituted aza-oxindoles being addressed; the aza-oxindole structural motif is prevalent in compounds exhibiting interesting biological properties such as oral anti-inflammatory activity, and potent neurotrophic kinase receptor type-1 (TrkA) and Janus kinase (JAK-3) inhibition.[49–51] Kündig *et al*. found a novel, efficient, inexpensive strategy for the synthesis of 3,3-disubstituted aza-oxindoles **87** (13 different derivatives and up to 99% yield) via a NaO*t*-Bu-mediated Truce–Smiles rearrangement–cyclisation pathway, Scheme 29.



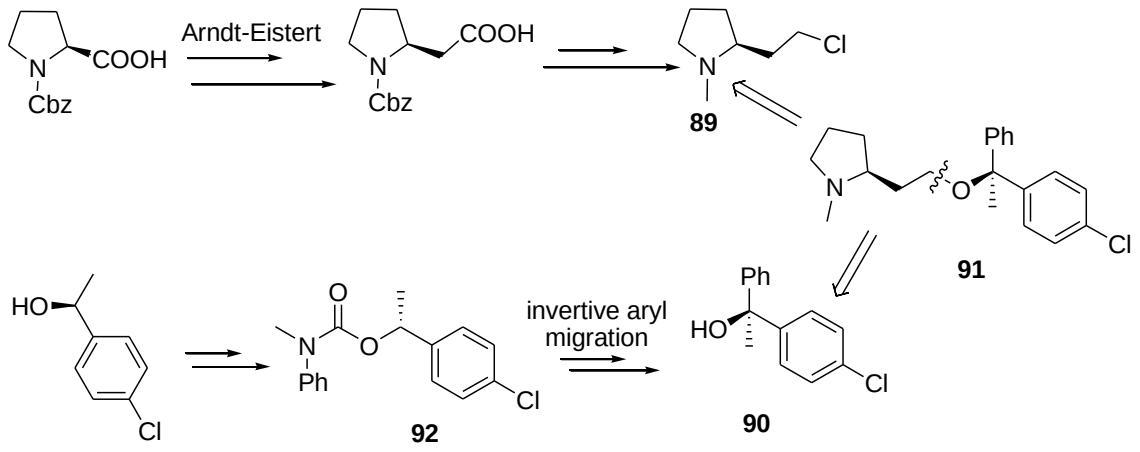
Scheme 29. The synthesis of 3,3-disubstituted aza-oxindoles.

Alongside, the Truce-Smiles rearrangement was also utilised to make diarylmethanol motifs. The diarylmethanol framework is considered to be a privileged structure in important intermediates and precursors for the synthesis of pharmacologically and biologically active compounds such as: antihistaminic pheniramines, methyl phenidates, clemastine and pipradrols, 1,4-dihydropyridine derivatives (with potent and long-lasting hypotensive effect) and cizolirtine (a novel non-opioid analgesic).[52–59] At the same time, chiral diarylmethanols are important motifs in drug discovery, and developing novel routes to such compounds will help with their continued exploitation in medicinal chemistry.[60] Therefore, the Truce-Smiles rearrangement has been utilised as a method to obtain enantiopure diarylmethanols where aryl migration from N to C in lithiated carbamates afforded a secondary or a tertiary alcohol (example **88**), Scheme 30.[61]



Scheme 30. The synthesis of chiral diarylmethanols (invertive aryl migration).

Although the yield of the chiral tertiary alcohol (up to 50%) and the ee (up to 77%) was not as good as expected in 2010, Clayden *et al*. applied the same methodology to the first enantioselective synthesis of the antihistamine agent (−)-(*S*,*S*)-clemastine **91**. To achieve this target, an ether was formed between a proline-derived chloroethylpyrrolidine **89** and an enantiomerically enriched tertiary alcohol **90**. The tertiary alcohol **90** was formed from the corresponding carbamate **92** by invertive aryl migration on lithiation (i.e. Truce-Smiles rearrangement) , Scheme 31. [62]



Scheme 31. Retrosynthesis of clemastine **91**.

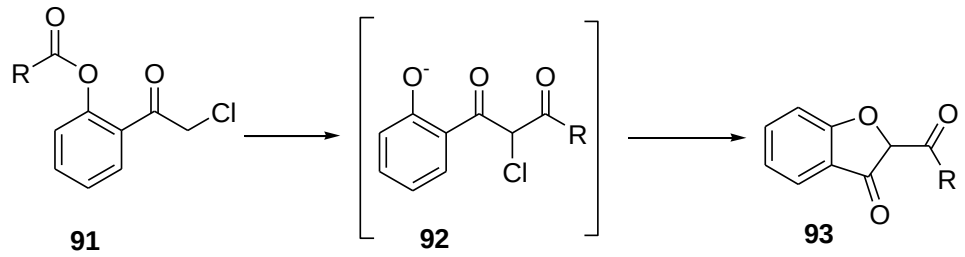
In conclusion, the Truce-Smiles rearrangement has been shown to be a powerful reaction to generate new C-C bonds under mild conditions, and has been useful for the synthesis of α-arylated ketones, indoles, polycyclic *N*-heteroaromatic compounds, 3,3-disubstituted aza-oxindoles, and diarylmethanols. However, to date, no examples have been reported which attempt to develop an enantioselective Truce-Smiles rearrangement and thus make compounds containing new chiral centres in an asymmetric manner.

1.1.2 The Baker-Venkataraman rearrangement

The Baker-Venkataraman rearrangement is an extremely reliable reaction in organic synthesis allowing the rapid construction of ß-diketones in high yield. ß-Diketones are important synthetic intermediates, and they are widely used for synthesis of chromones, flavones, isoflavones, and coumarins. As mentioned, the Baker-Venkataraman rearrangement is regarded as an analogue of the Truce-Smiles rearrangement in terms of mechanism of the reaction, however, the difference is the migrating group; acyl group and aryl group for the Baker-Venkataraman and Truce-Smiles rearrangements respectively.

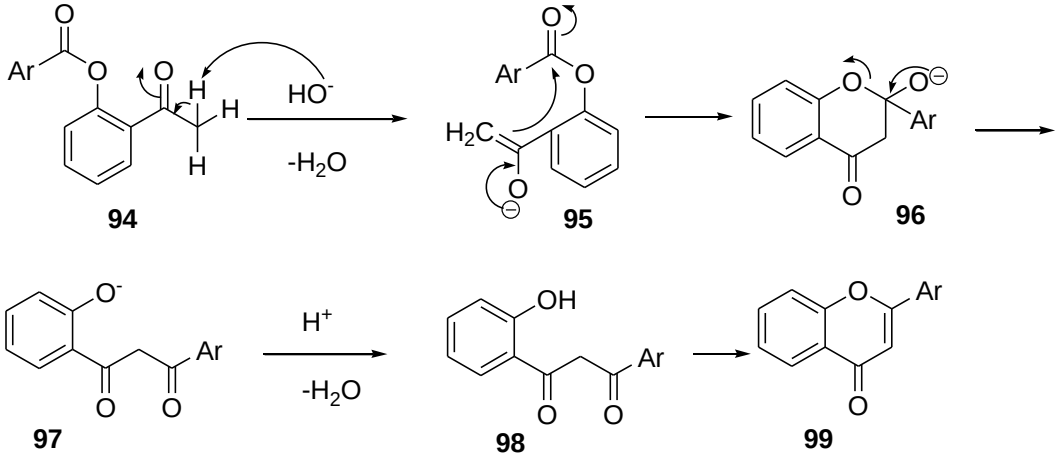
1.1.2.1 Historical perspective and the mechanism

In 1910, it was observed by Auwers that esters of 2-chloro-2'-hydroxyacetophenone **91**, reacted with potassium carbonate to form 2-substituted coumaran-3-ones **93** and it was suggested that the reaction probably proceeded through a 1,3-diketone **92**, Scheme 32.[63]



Scheme 32. The first example of the Baker-Venakataraman rearrangement by Auwers.

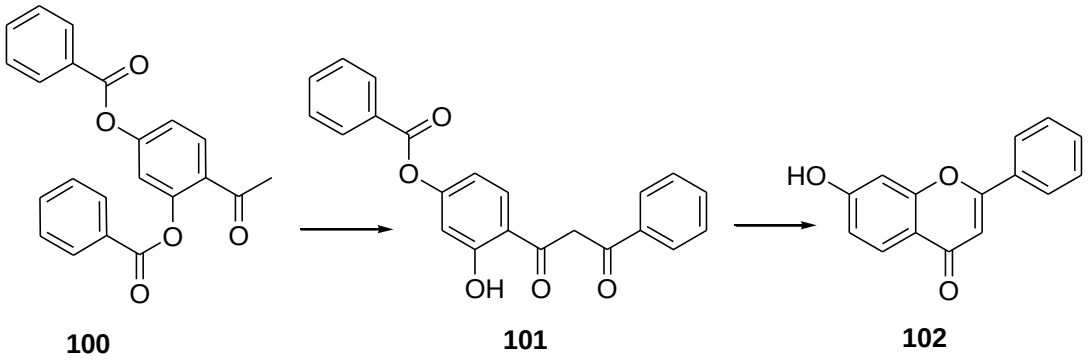
Later in 1933, Harbhajan Mahal and Krishnasami Venkataraman[64] and independently, Wilson Baker,[65] reported the isolation of 1,3-diketone **98** after the rearrangement of *o*-aroyloxyacetophenone **94**, Scheme 33. Since then, the reaction, now known as the Baker-Venkataraman rearrangement, has been shown to be of prime importance in flavone synthesis.[66]



Scheme 33. The mechanism of the Baker-Venkataraman rearrangement.

This rearrangement reaction proceeds via enolate formation (**95**) followed by acyl transfer, Scheme 33. A base abstracts the hydrogen atom alpha to the aromatic ketone **94**, forming an enolate (**95**). The enolate **95** attacks the ester carbonyl to form a cyclic alkoxide **96**. The cyclic intermediate **96** is opened up to form a more stable phenolate **97**, which is protonated during acidic work-up to give the desired product **98**. Additionally the 1,3-diketone **98** can cyclise to flavones **99**, Scheme 33.

Baker attempted the preparation of the benzyl ether of 4-*O*-benzoylresacetophenone **100** (4-*O*-benzoylresacetophenone was heated in benzene with benzyl chloride (1 mol.) and anhydrous potassium carbonate), however, the product obtained was 2,4-dibenzoylresacetephenone (20% yield) **101**. Cold concentrated sulfuric acid converted **101** smoothly into 7-hydroxy-flavone **102**, Scheme 34.[65]



Scheme 34. Baker's attempt at the synthesis of 7-hydroxy-flavone **102**.

Later was found that 4-*O*-benzoylresacetophenone **100**, when heated with benzene or toluene and potassium carbonate, underwent intramolecular rearrangement, giving 2,4-dibenzoylresacetophenone **101**, Scheme 34.

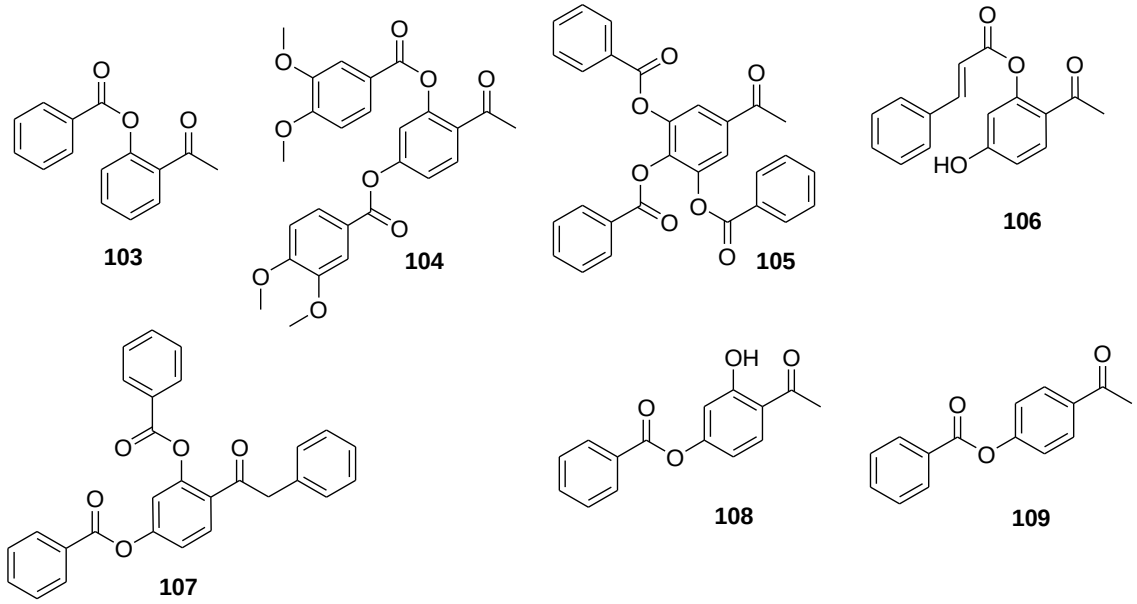
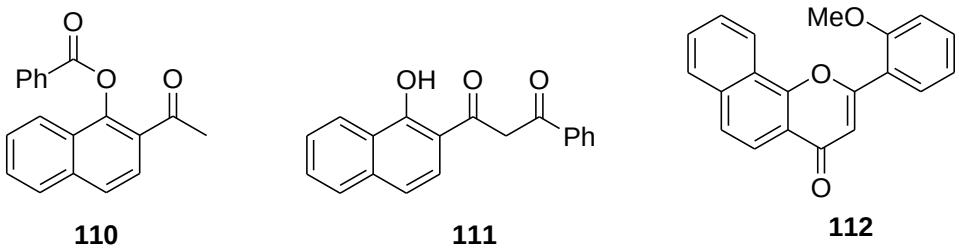


Figure 3. Early examples studied in the Baker-Venkataraman rearrangement.

The same author tried to declare the generality of this new rearrangement by evidencing a variety of examples (*O*-benzoyloxyacetophenone (**103**), resacetophenone diveratrate (**104**), gallacetophenone tribenzoate (**105**), cinnamoylresacetophenone (**106**) and 2,4-dibenzyloxyphenyl benzyl ketone (**107**), Figure 3). Thus, it was proved that the migration involves solely the *ortho*- and *meta*-aryloxy group, since it occurs neither in 4-*O*-benzoylresacetophenone (**108**) nor in 4-*O*-benzoyloxyacetophenone (**109**), Figure 3.[65]

In the same year (1933), continued attempts made by Venkataraman *et al*. to effect the dehydration of 2-acetyl-1-naphthyl benzoate **110** to 1,4-*α*-naphthapyrones, found that

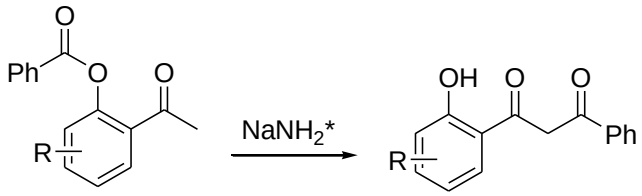
the action of sodamide on an ethereal solution of 2-acetyl-1-naphthyl benzoate **110** at room temperature, followed by decomposition of the precipitate with acid, gave the diketone **111**, Figure 4.[67] The diketone **111** and its 3,4,5-trimethoxy-derivative were convertible into the corresponding α-naphthaflavones (**112**, in the case of the *O*-methoxy-analogue) in the usual manner by means of sulfuric acid, Figure 4.[67]



110 **111** **112**

Figure 4. Preparation of α-naphthaflavones by Venkataraman *et al*.

Furthermore, the rearrangement of *O*-aroyloxyacetophenones **113** to *O*-hydroxydibenzoylmethane **114** by basic reagents such as sodium amide, was reported in the review on the chemistry of the alkali amides (part II and III).[68,69] The rearrangement has been studied and extended by a number of workers[70,71,71–76] and the rearrangement of *O*-aroyloxyacetophenones **113** to *O*-hydroxydibenzoylmethanes **114** in the presence of basic reagents is typical, Scheme 35.[73]



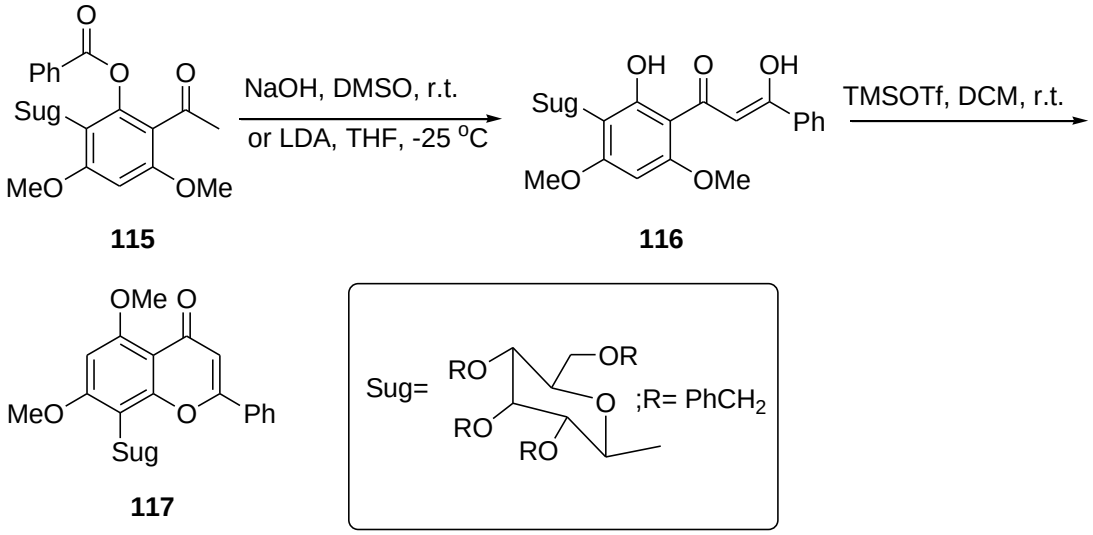
113 **114**

R= Alk, OH, OAlk
*also EtONa, Na, K_2CO_3, NaOH

Scheme 35. The rearrangement of *O*-aroyloxyacetophenones **113** to *O*-hydroxydibenzoylmethane **114** under basic conditions.

During this period of time, the mechanism of these rearrangements has been studied.[77] These transformations, by which *β*-diketones are formed, have been regarded as intramolecular Claisen acylations. While in ordinary Claisen acylations the ketone and ester functions are not present in the same molecule, both of these functions are present in the ortho position to one another in compounds undergoing the Baker-Venkataraman transformation.[77]

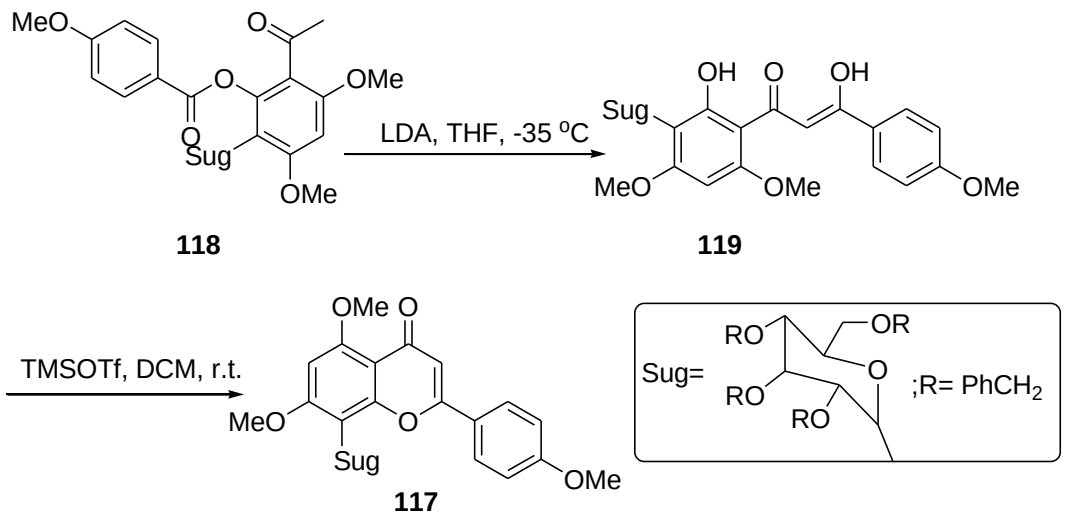
Until the 1950s, there were scant reports of the Baker–Venkataraman rearrangement used in synthesis. To this end, the approach mentioned in Scheme 36 sees the *O*-benzoyl ester of *C*-glycoside **115** undergoing rearrangement into the 1,3-dicarbonyl compound **116** formed as a keto–enol mixture in 48% yield.[78]



115 **116** **117**

Scheme 36. *O*-Benzoyl ester of *C*-glycoside **115** undergoing rearrangement.

In another approach, the *para*-anisoyl ester of *C*-glycoside **118**, was treated with lithium diisopropylamide (LDA) to give the enol dibenzoylmethane **119**, Scheme 37.[78]

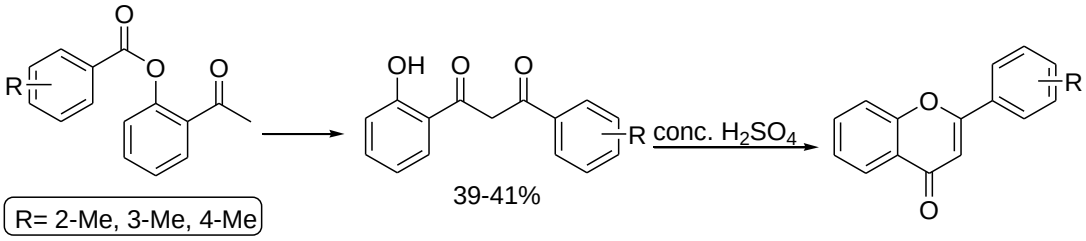


118 **119** **117**

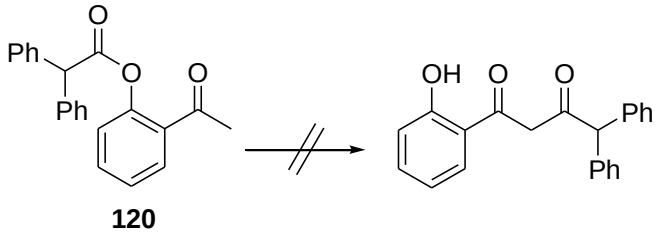
Scheme 37. Lithiated *para*-anisoyl ester of *C*-glycoside **118** undergoing the rearrangement.

For a few decades (1933 to 1950) the conditions of the Baker–Venkataraman rearrangement were investigated, Scheme 38.[79] It was found that sodium ethoxide in benzene was the best reagent for this reaction. It was also shown that this rearrangement failed in the case of the ester **120** due to the deprotonation of the acidic proton (the

enolate will abort the migration) as well as the steric clash with the newly incorporated diphenyl rings, Scheme 39.

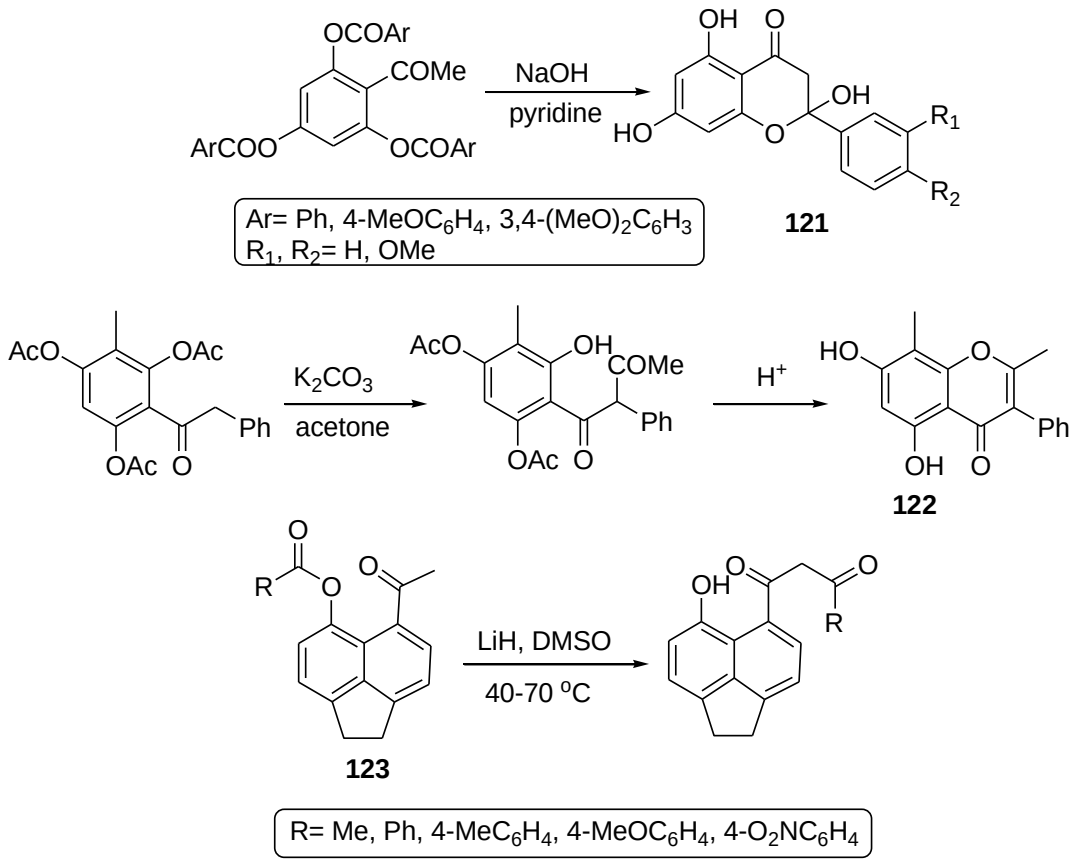


Scheme 38. The Baker–Venkataraman rearrangement using sodium ethoxide in benzene.



Scheme 39. Ester **120** does not undergo the rearrangement.

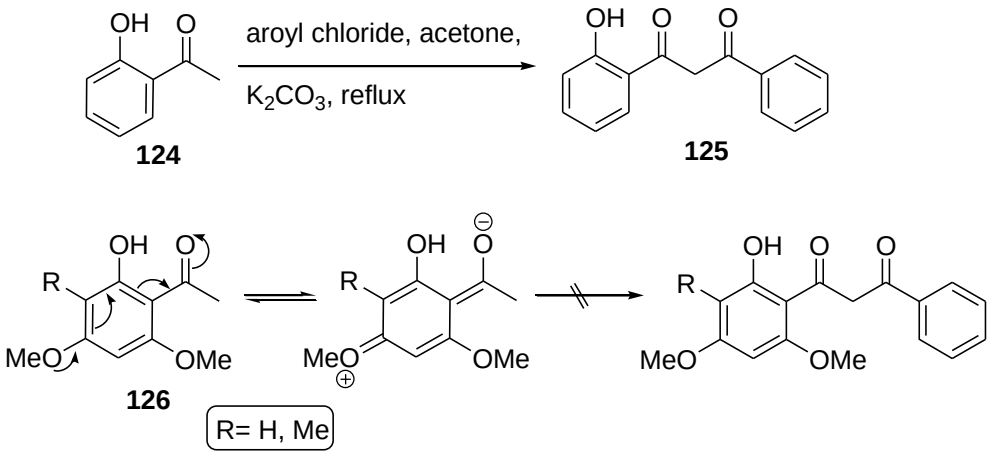
The Baker–Venkataraman rearrangement has also been used as a key step in syntheses of trihydroxyflavanones **121**[80] as well as isoflavones **122**[81], Scheme 40. An interesting example of the Baker–Venkataraman rearrangement was reported for *peri*acyloxyketones **123**[82], Scheme 40.



Scheme 40. The Baker–Venkataraman rearrangement as a key step in the synthesis of trihydroxyflavanones **121**, isoflavones **122** and *peri*acyloxyketones **123**.

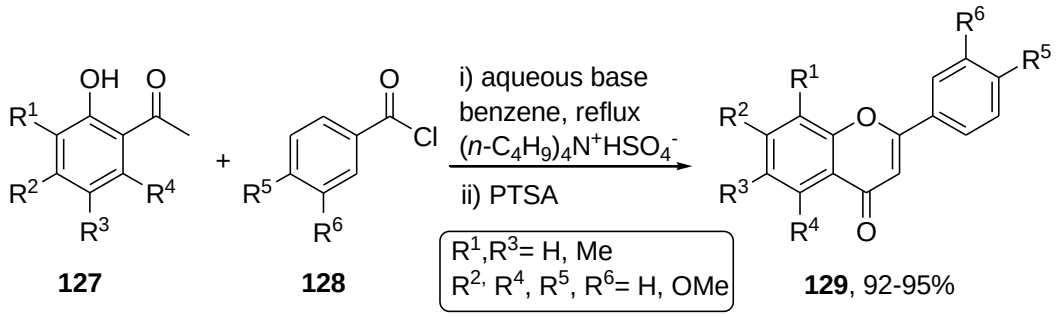
1.1.2.2 Modified Baker-Venkataraman rearrangement

The first modified Baker-Venkataraman rearrangement (offering directly the rearranged product: 1,3-diketones) was declared by Seshadri *et al*. (1957) in which *o*-hydroxyacetophenones **124** and aroyl chlorides were refluxed in acetone containing anhydrous potassium carbonate, to give directly the *o*-hydroxydibenzoylmethanes **125**, required for cyclisation to flavones, Scheme 41.[83] However, this simplified procedure was reported to have its limitations. Thus, 2-hydroxy-4,6-dimethoxy- and 2-hydroxy-3'-methyl-4,6-dimethyoxyacetophones **126** failed to undergo conversion into the corresponding dibenzoylmethanes, Scheme 41.[84] The lack of activity of these acetophenones was attributed to the resonance effect of the methoxy groups.[31]



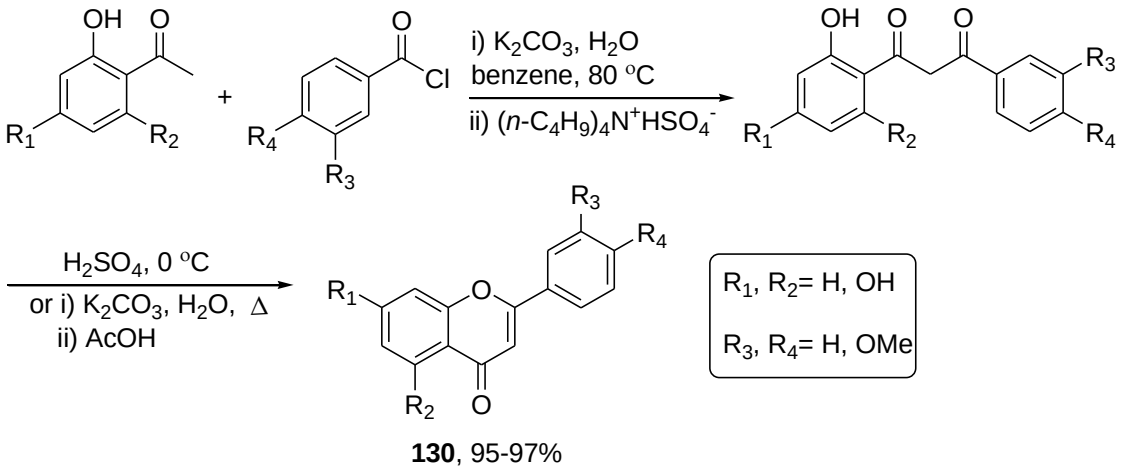
Scheme 41. The first example of a modified Baker-Venkataraman rearrangement.

Later, in 1982 Makrandi *et al*. presented an extremely facile procedure for the synthesis of flavones depicted by **129**. The *o*-hydroxyacetophenone **127**, containing methoxy or methyl groups at various positions (Scheme 42), was treated with an aroyl chloride **128** and aqueous potassium carbonate or potassium hydroxide solution in benzene under phase transfer-catalysed conditions, using *n*-tetrabutylammonium hydrogen sulphate, resulting in the formation of the corresponding *o*-hydroxydibenzoylmethanes, Scheme 42.[84] The benzene solution, on treatment with *p*-toluenesulphonic acid afforded the flavones **129** in excellent yields. The method was of general applicability; even 2-hydroxy-4,6-dimethoxy- and 2-hydroxy-3-methyl-4,6-dimethyoxyacetophones (**126**) were found to undergo smooth conversion under their conditions.[84]



Scheme 42. The synthesis of flavones by a modified Baker-Venkataraman rearrangement.

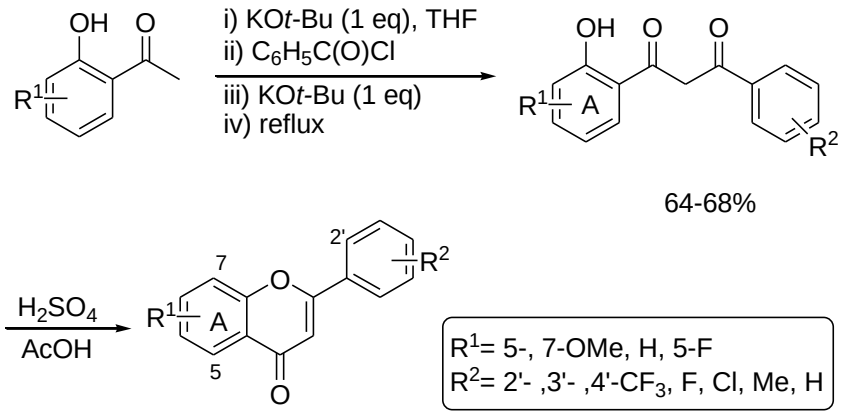
In the same vein, the same authors were able to synthesise a variety of hydroxyflavones **130** (Scheme 43) using their modified phase transfer-catalysed Baker-Venkataraman transformations.[85]



130, 95-97%

Scheme 43. The synthesis of hydroxyflavones.

While attempting to a find the most convenient route for the synthesis of **131** (when R^1= 5-OMe), Scheme 44, Jeffery *et al*. found that the conventional Baker-Venkataraman approach[65,67] was not suitable for synthesizing large amounts of **131**, since low yields and product isolation complications were encountered in the benzoylation and Claisen condensation steps, respectively, Scheme 44.[86] In addition, newer methods for directly converting hydroxyacetophenones into the required diketones, such as potassium carbonate,[87] organolithium reagents,[88,89] or phase-transfer catalysis[84] proved to be ineffective or impractical for large-scale use. Therefore, a convenient large-scale preparation of 5-methoxyflavone has been developed using a KO*t*-Bu-mediated diketone synthesis (modified Baker-Venkataraman rearrangement) as the key step.[86]



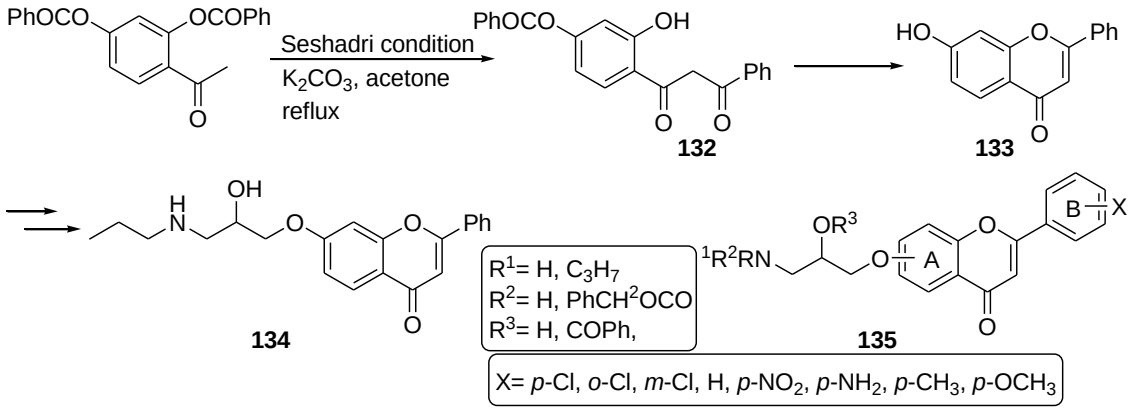
131, 70-75%

Scheme 44. Preparation of 5-methoxyflavones.

The method has been successfully applied to the convenient synthesis of a number of flavone analogues (monosubstituted flavones substituted in either aromatic ring, as well as flavones substituted in both rings). It has also been combined with a phenolic

alkylation step, thereby providing a short and efficient means of transforming dihydroxyacetophenones into A-ring alkoxyflavones. Moreover, the same method was adapted for the synthesis of certain A-ring alkoxyflavones from dihydroxyacetophenones, Scheme 45.[86]

However, the products' overall isolated yields are slightly lower than that of the conventional Baker-Venkataraman sequence, but the method is simple practically, scalable and takes far less time to operate.[86]

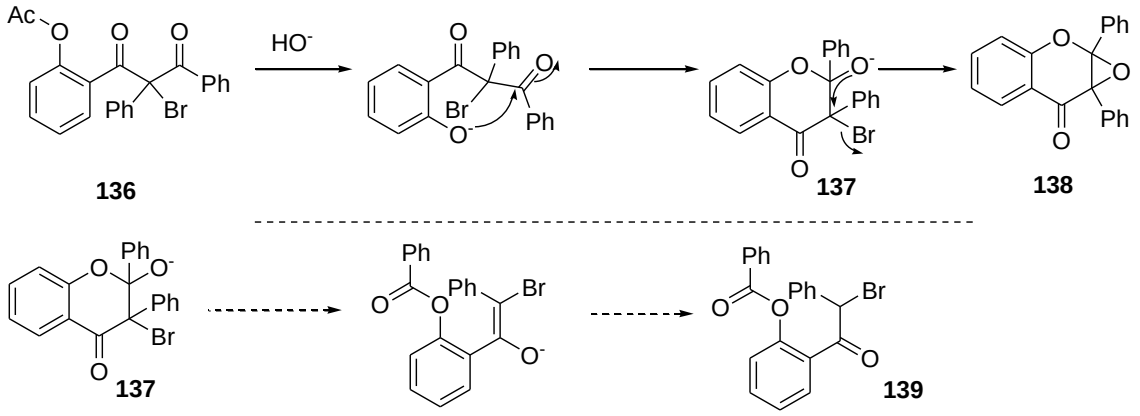


Scheme 45. Synthesis of hydroxyflavone **133**, an intermediate for flavodilol **134**.

In the approach for the synthesis of a novel class of antihypertensive agents with catecholamine depleting properties (flavodilol **134** and its analogues **135**, Scheme 45), Wu *et al*. demonstrated that the modified Seshadri protocol[83] (potassium carbonate in refluxing acetone) would offer directly the diketone **132** then cyclisation to 7-hydroxyflavone **133** in a good yield, Scheme 45.[87]

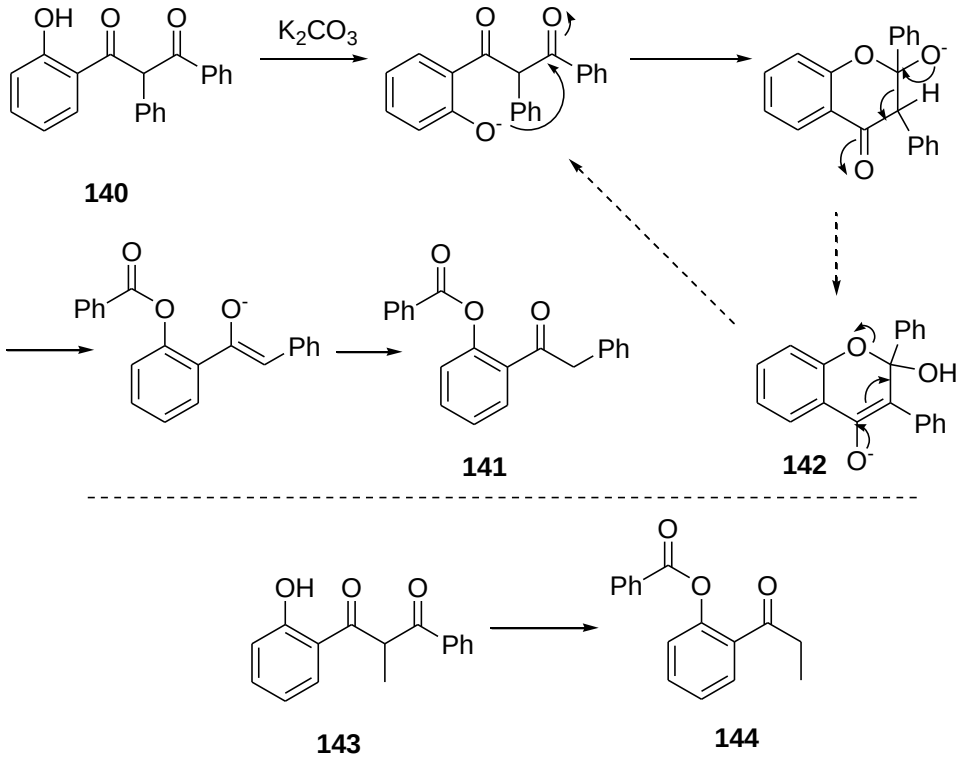
1.1.2.3 *Retro*-Baker-Venkataraman rearrangement

In 1979, Donnelly and Maloney reported that when 2-bromo-1,3-diketone **136** reacted with a base it forms 2,3-diphenylchromone epoxide **138**.[90] They rationalised this transposition to occur through the intermediate, 2-hydroxyflavanone conjugate base **137**, and also considered that without a nucleophile (eg. bromide ion) fragmentation might occur to offer an o-aroyloxyacetopheneone **139**, Scheme 46.[90]



Scheme 46. The first example of a *retro*-Baker-Venkataraman rearrangement.

The unbrominated analogue **140** of the 1,3-diketone **136** has also been well documented that on reaction with potassium carbonate at 0 °C in chloroform, afforded the deoxybenzoin ester **141**, via a *retro*-Baker-Venkataraman rearrangement, Scheme 47.[91]

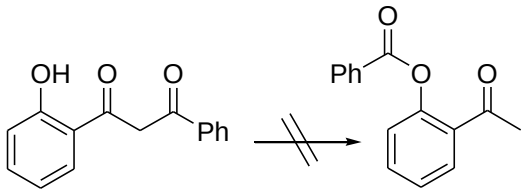


Scheme 47. The unbrominated analogue **140** undergoing the *retro*-Baker-Venkataraman rearrangement.

When the 2-phenyl substituent of the 1,3-diketone **140** is exchanged for a methyl group (ie. **143**) a *retro*-Baker-Venkataraman rearrangement also occurs, though very slowly. Refluxing under the same reaction conditions for several days gave 2'-benzoyloxypropiophenone **144** in 54% yield. Treating the 1,3-diketone **140** with

potassium hydroxide at room temperature afforded the decomposed products: 2'-hydroxypropiophenone and propiophenone.[91]

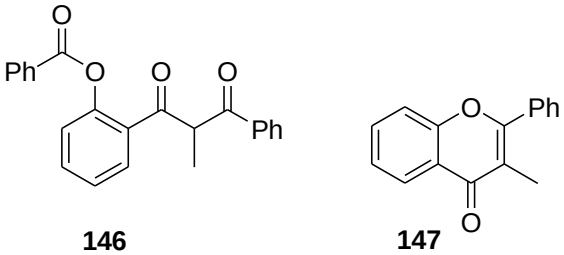
Moreover, different conditions failed to force the diketone **145** to undergo the reverse rearrangement, Scheme 48. Therefore, the rate of *retro*-Baker-Venkataraman rearrangement depends on the 2-substituent of the 1,3-diketone. A rapid decrease in rate has been seen in the order of Ph> Me> H.[91]



145

Scheme 48. Diketone **145** does not undergo the reverse rearrangement.

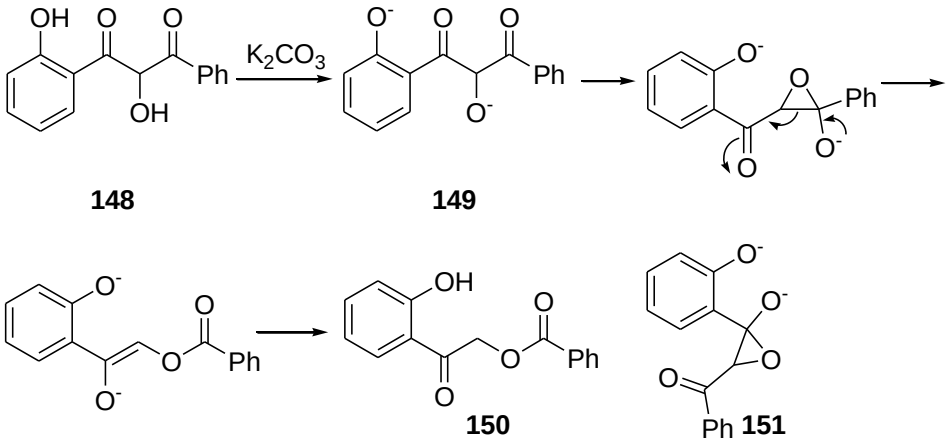
As mentioned, efforts by Dunne *et al*. were unsuccessful in demonstrating the Baker-Venkataraman rearrangement of the ester **144** to the 2-methyl-1,3-diketone **143**, Scheme 47.[92] Though, the same ester **144** treated with potassium hydroxide in pyridine at -8 °C gave the diketone **143** in 53% yield as well as 1-(2-benzyloxyphenyl)-2-methyl-3-phenyl-1,3-propanedione **146** and 2'-hydroxypropiophenone, Figure 4. The *trans*-esterification of the initially formed hydroxy-1,3-diketone **143** with 2'-benzyloxypropiophenone is the possible explanation for the formation of the benzyloxy-1,3-diketone **146** and 2'-hydroxypropiophenone, Figure 5. At 0 °C the same Baker-Venkataraman rearrangement product has been formed in a yield of 41%. Despite increasing the reaction temperature to 50 °C, the yield was lowered to 18%, and only when the reaction was carried out for few minutes were the 2'-hydroxypropiophenone and propiophenone elucidated. However, 3-methylflavone **147** was formed after cyclisation of the diketone **143** by acetic acid, Figure 5.[91]



146 **147**

Figure 5. Structure of benzyloxy-1,3-diketone **146**, and 3-methylflavone **147**.

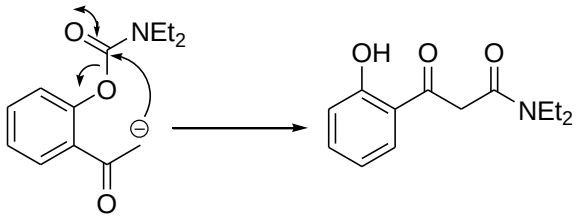
Occupying the 2-position of a 1-(-hydroxyphenyl)-1,3-propanedione with a hydroxyl group gave rise to *retro*-Baker-Venkataraman failure, Scheme 49. Instead, an alternative ester forming transformation was demonstrated.[93] Reaction of 2-hydroxyl-1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione **148** with potassium carbonate offered 2-benzyloxy-2'-hydroxyacetophenone **150**. The proximal carbonyl group in the dianion **149** was deactivated by the phenoxide, thus, aborting the formation of alternative intermediate **151**, Scheme 49.[91]



Scheme 49. Occupying the 2-position of **148** with a hydroxyl group causes the *retro*-Baker-Venkataraman to fail.

1.1.2.4 A carbamoyl variant of the Baker-Venkataraman rearrangement

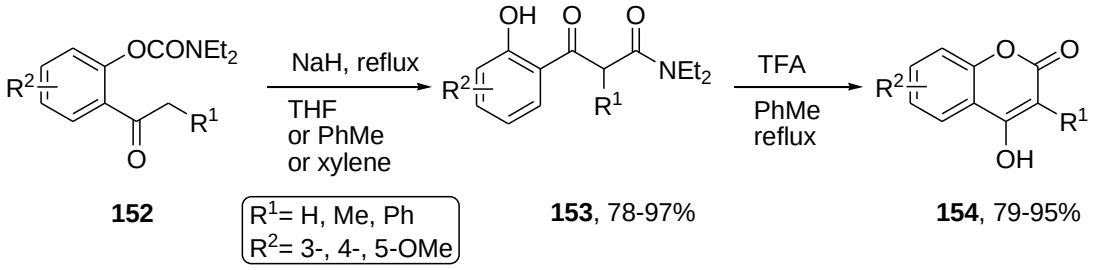
The first major variant (the carbamoyl version) of the Baker-Venkataraman rearrangement (Scheme 50) was reported by Victor Snieckus,[94] in which the requisite *ortho*-acyl arylcarbamates **152** were rapidly and efficiently converted into substituted 4-hydroxycoumarins **154** in 79-95% yields: a large and highly diverse class of natural products exhibiting a broad spectrum of bioactivity.[95–97]



Scheme 50. A carbamoyl variant of the Baker-Venkataraman rearrangement.

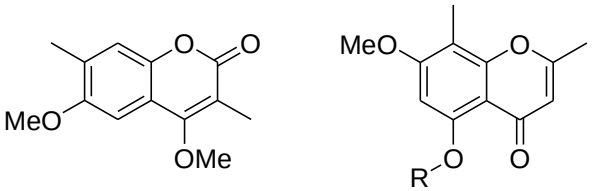
Furthermore, the authors demonstrated the application of the carbamoyl Baker-Venkataraman strategy to the construction of a putative coumarin natural product and provide its structural revision.[94]

In their prototype study of the Baker-Venkataraman rearrangement on **152** (R^2= H), Scheme 51, exploration of conditions gave varying results: (LDA/THF/0 °C (complex mixture); LDA/PhMe/r.t. (54% yield); BrMgN(*i*-Pr)$_2$/PhMe/r.t.-70 °C (62% yield); K_2CO_3/l8-crown-6/PhMe/reflux (no reaction) led to NaH in several solvents (2.5 equiv NaH, THF or PhMe or Xylene 0.2 M, reflux/~2h) as the optimal conditions affording the 2-hydroxyarylacetamide **153** (R^2= H) in high yield, whose conversion into **154** (R^2= H) was effected smoothly with trifluoroacetic acid (3 equiv) in refluxing toluene (0.25 M), Scheme 51.[94]



Scheme 51. Snieckus's protocol for the synthesis of coumarins exemplified by **154**.

Due to the absence of side products in the carbamoyl migration reaction, even at relatively high (0.2 M) concentrations, suggests; as demonstrated in the ester Baker-Venkataraman equivalent,[98] an intramolecular mechanism is taking place. For this reason, this route is regarded as a convenient, efficient method which offers 4-hydroxycoumarins **154**, and with particular preparative advantages that 3-substituted (alkyl and aryl) coumarins are obtained directly, Scheme 51.[94]



155

156a: R= H
156b: R= Me

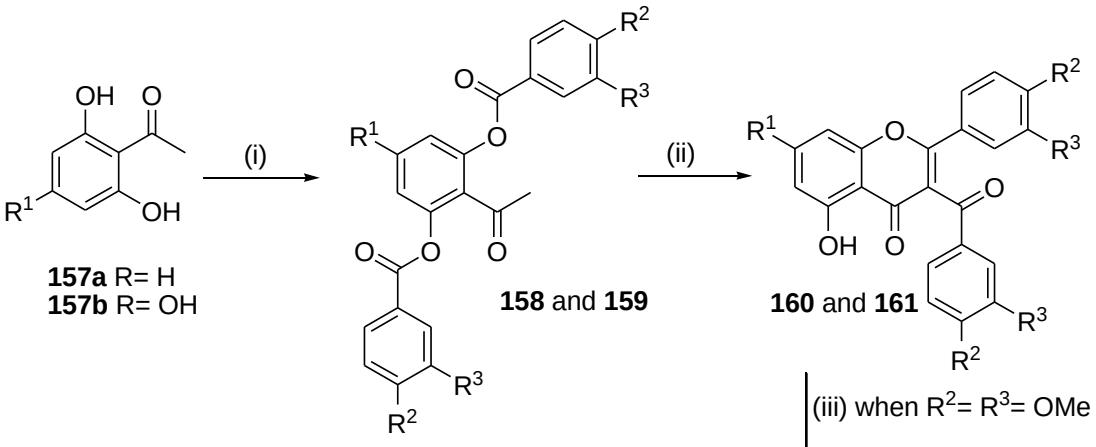
Figure 6. Sturcture of 4,6-dimethoxy-3,7-dimethylcoumarin (**155**), isoeugenetin (**156a**), and its methyl ether **156b.**

Using the same strategy, the authors demonstrated the total synthesis of 4,6-dimethoxy-3,7-dimethylcoumarin (**155**), the putative natural product isolated from *Colchicum*

decaisnei, and isoeugenetin methyl ether (**156b**), a synthetic derivative of the isoeugenetin (**156a**), isolated from *Eugenia carvophyllata*, Figure 6.[99]

1.1.2.5 A microwave assisted Baker-Venkataraman rearrangement

As part of their continuing work on the synthesis and antioxidant evaluation of polyhydroxy-2-styrylchromones,[100] Silva *et al*. have considered the synthesis of polyhydroxy-3-aroylflavones **162**, which are new chromone-type compounds with essential features of good antioxidant and anti-inflammatory agents, Scheme 52.[101]



157a R= H
157b R= OH

158 and **159**

160 and **161**

162 R^1= H, OH

158a R^1= R^2= R^3= H
158b R^1= R^3= H; R^2= NO_2
158c R^1= H; R^2= R^3= OBn
159a R^1= $OC(O)C_6H_3R^2R^3$; R^2= R^3= H
159b R^1= $OC(O)C_6H_3R^2R^3$; R^3= H; R^2= NO_2
159c R^1= $OC(O)C_6H_3R^2R^3$; R^2=R^3= OBn
160a R^1= R^2= R^3= H
160b R^1= R^3= H; R^2= NO_2
160c R^1= H; R^2= R^3= OBn
161a R^1= OH; R^2= R^3= H
161b R^1= OH; R^3= H; R^2= NO_2
161c R^1= OH; R^2= R^3= OBn

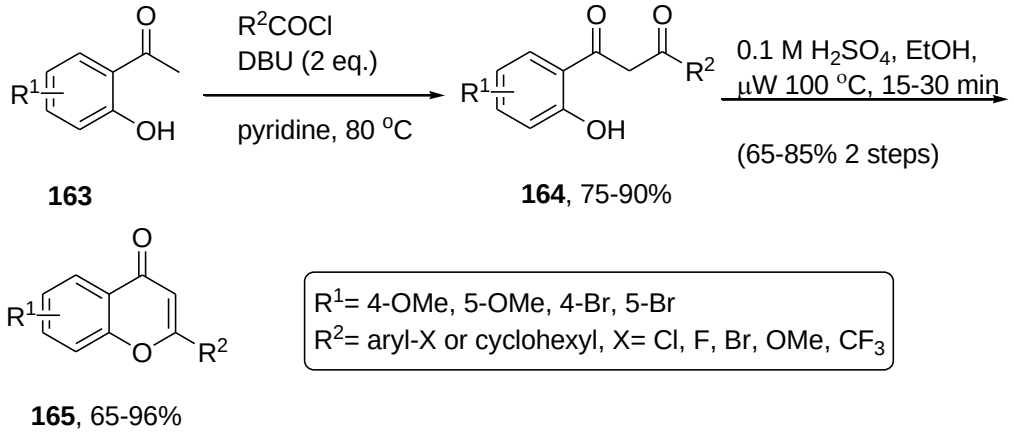
Reaction conditions: (i) DCC, 4-pyrrolidinopyridine, $HO_2CC_6H_3R^2R^3$, CH_2Cl_2, r.t.; (ii) classical heating conditions: K_2CO_3, anhydrous pyridine, 120 °C, under nitrogen, 2 h; microwave conditions: K_2CO_3, anhydrous pyridine, 400 W, 10 min; (iii) BBr_3, anhydrous CH_2Cl_2, r.t..

Scheme 52. The synthesis of polyhydroxy-2-styrylchromones.

A new and successful methodology has been established, in which microwave irradiation selectively induces the Baker–Venkataraman rearrangement of 2',6'-diaroyloxyacetophenones to give the corresponding 3-aroyl-5-hydroxyflavones **160** and **161**, in very short reaction times (10 min) and in good yields (68–72%). Under classical thermal conditions these reactions afforded 5-hydroxyflavones **160** and **161** as by-products, Scheme 52.[101]

The scope of the reaction and its utility as a new synthetic methodology to obtain 3-aroyl-5-hydroxyflavones **160** and **161** via the Baker–Venkataraman rearrangement of 2',6'-diaroyloxyacetophenones, was determined and extended to include other derivatives, for example; the use of 2',6'-diaroyloxyacetophenones with strong electron-withdrawing substituents in the aromatic ring of the aroyl groups. The Baker–Venkataraman rearrangement of 2',6'-diaroyloxyacetophenones **158** and **159** under their preferred microwave experimental conditions allowed for the synthesis of 3-aroyl-5-hydroxyflavones **160** and **161** in good yields (68–72%), Scheme 52.[101]

In addition, a practical and economical method has been developed by Brown *et al*. for the synthesis of eleven flavonoid derivatives **165** from 2-hydroxyacetophenones **163** using a modified Baker–Venkataraman rearrangement, followed by microwave-assisted condensation of the diones **164** to close the heterocyclic ring (simply using EtOH containing a small amount of concentrated H_2SO_4 (100:1 by volume), Scheme 53.[102]

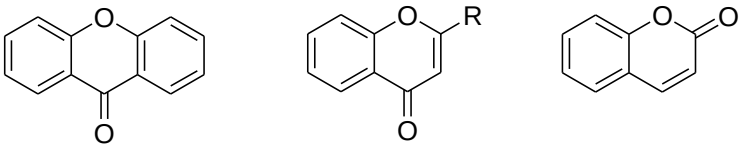


Scheme 53. The synthesis of flavonoid derivatives.

All of the synthetic flavonoids **165** displayed antifungal activity against *Aspergillus niger* and *Fusarium oxysporium*, and two of the analogues **165** (when R^2= cyclohexyl) exhibited significant activity against methicillin-resistant *Staphylococcus aureus*.[102]

1.1.2.6 Applications of the Baker-Venkataraman rearrangement

The use of the Baker-Venkataraman rearrangement in the context of total synthesis has become increasingly more important, particularly as 1,3-diketone starting materials are becoming more widely utilised. As such, this rearrangement is regarded as one of the most common methods for synthesising xanthones **166**, chromones **167**, flavones **168**, and coumarins **169**, Figure 7.

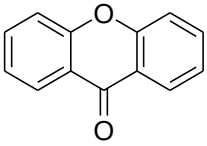


166 **167** R= H **168** R= Ph **169**

Figure 7. General structures of xanthones **166**, chromones **167**, flavones **168**, and coumarins **169**.

1.1.2.6.1 Synthesis of xanthones

Xanthones (9*H*-xanthen-9-one **166**, Figure 8) are a class of oxygenated heterocyclic compounds widely occurring as secondary metabolites in some higher plant families, such as Gentianaceae, Guttiferae, fungi and lichens.[103] These natural derivatives are found with numerous substitutions at different positions of their skeleton: methoxy, hydroxyl and glycosyl groups being the most frequently occurring ones.[104,105]



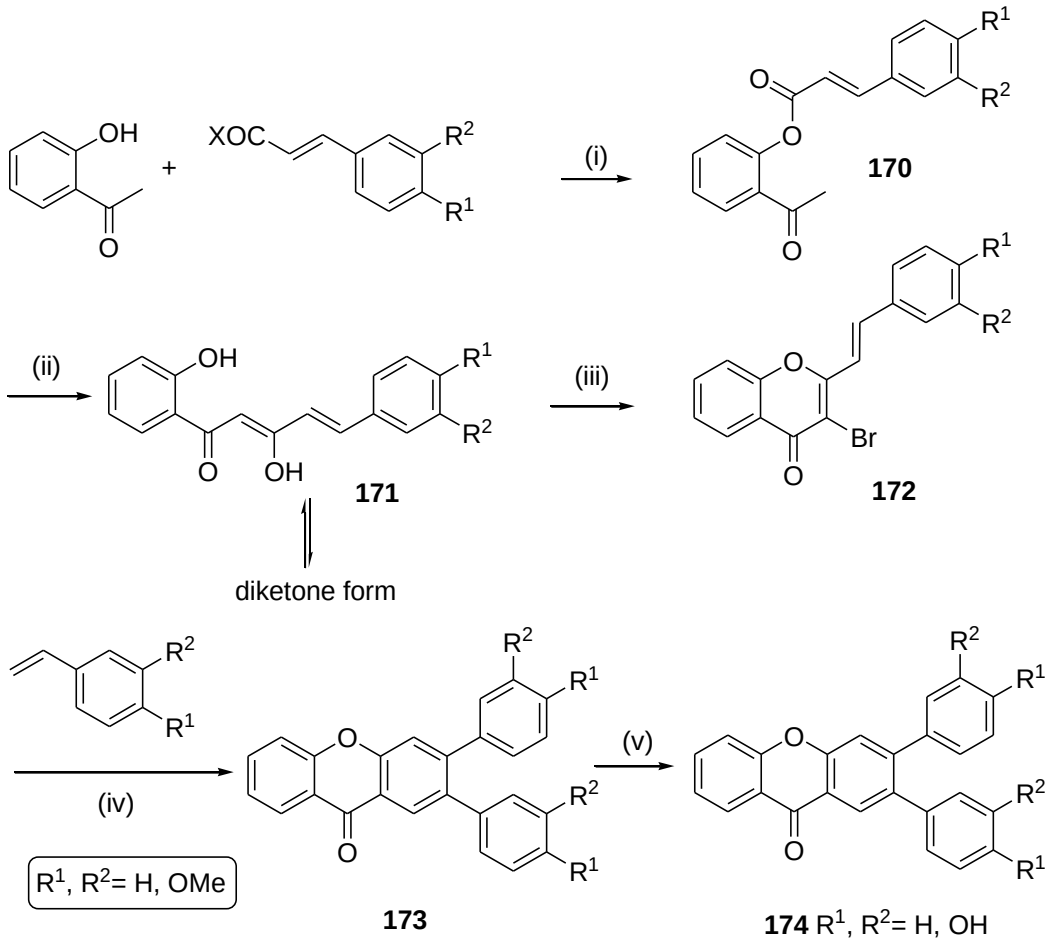
166

Figure 8. General structure of xanthones **166**.

The pharmacological properties of both natural and synthetic xanthone derivatives have been extensively reported in the literature;[106] they include antiallergic,[107] antifungal,[108] anti-inflammatory,[109] antimalarial[110] and antitumour activities[111] and this reveals the growing interest in this type of compounds. Furthermore, xanthones have been widely applied as antioxidant agents.[112]

Additionally, there are already two formulations on the market containing oxygenated and prenylated xanthones, as antioxidants.[113] The aromatic character and the presence of hydroxyl groups and/ or catechol moieties at certain positions of the xanthone core are crucial requirements for a strong antioxidant activity.[109]

Silva *et al*. found an efficient and general route toward the synthesis of hydroxylated 2,3-diarylxanthones **174**, in which the key intermediate of this synthesis (3-bromo-2-styryl-chromone **172**), is obtained by a Baker–Venkataraman rearrangement of the appropriate 2'-cinnamoyloxyacetophenone **170**, Scheme 54.[3]



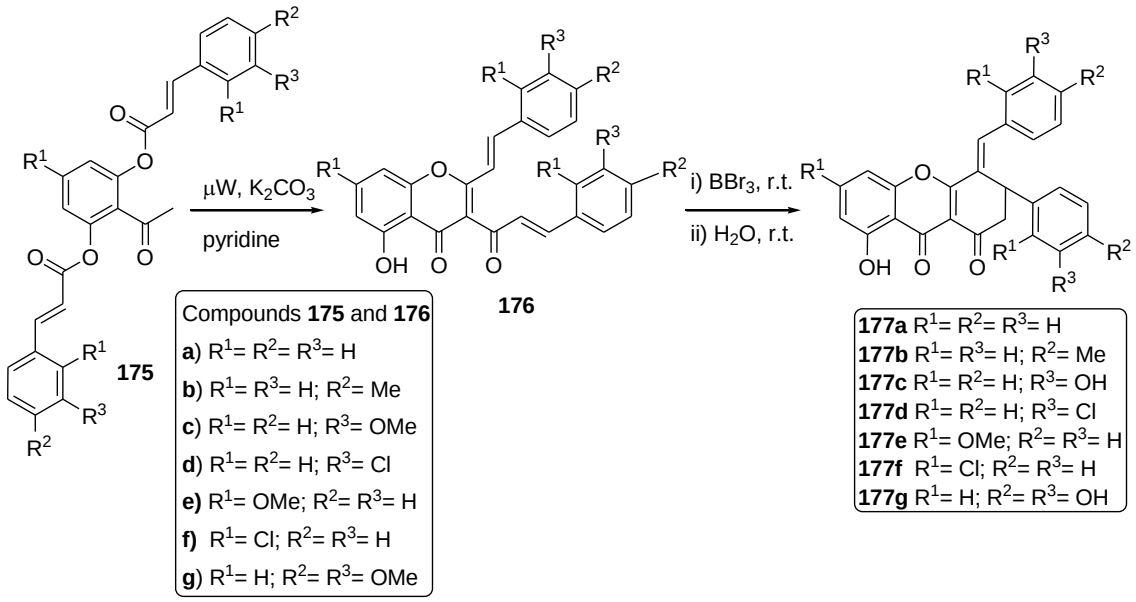
Reaction conditions: i) (a) X = Cl, anhydrous pyridine, r.t., 2 h; (b) X = OH, $POCl_3$, anhydrous pyridine, 60 °C, 2 h; ii) DMSO, KOH, r.t., 2 h; iii) PTT, THF, r.t., 12 h; iv) NMP, Et_3N, PPh_3, $Pd(PPh_3)_4$; v) anhydrous CH_2Cl_2, BBr_3, –78 °C to r.t.

Scheme 54. The synthesis of hydroxylated 2,3-diarylxanthones **174**.

The key step consisted of the cinnamoyl group transposition from the 2'- position to the 2-position of the acetophenone moiety **170→171**. It was performed by treatment of **170** with potassium hydroxide in DMSO to afford 5-aryl-3-hydroxy-1- (2-hydroxyphenyl)-

2,4-pentadiene-1-ones **171**, in good yields (73–95%) and cyclisation to the desired 3-bromo-2-styrylchromones **172** (53–67%). After two more steps the hydroxylated 2,3-diarylxanthones **174** were obtained in good yields (70– 94%), Scheme 54.[3]

The growing interest in the synthesis of biologically active compounds, especially polyhydroxy-2-styrylchromones, built up a simple and successful programme by Pinto *et al*. towards the synthesis of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **176**, Scheme 55.[114]

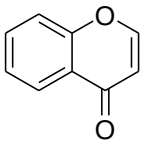


Scheme 55. The synthesis of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **176**.

In their programme, to use the less expensive reagents and shorter reaction times, they applied two-step approach (double esterification of the appropriate 2'-hydroxyacetophenone with cinnamoyl chloride derivatives followed by the Baker–Venkataraman rearrangement of the formed diester (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylates)) **175**.[115] Additionally, a great improvement in yield was achieved by using microwave irradiation (at constant power of 400 W for 17 min), Scheme 55.[101] Another beneficial effect of using microwave irradiation was the shortening of the reaction time from 1 hour to 17 minutes. This methodology was successfully employed for the rearrangement of (*E*,*E*)-2-acetyl-1,3-phenylene *bis*(3-phenylacrylate) (**175**) leading to (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromone (**176**) in good yield (86%, Scheme 55).[114]

1.1.2.6.2 Synthesis of chromones

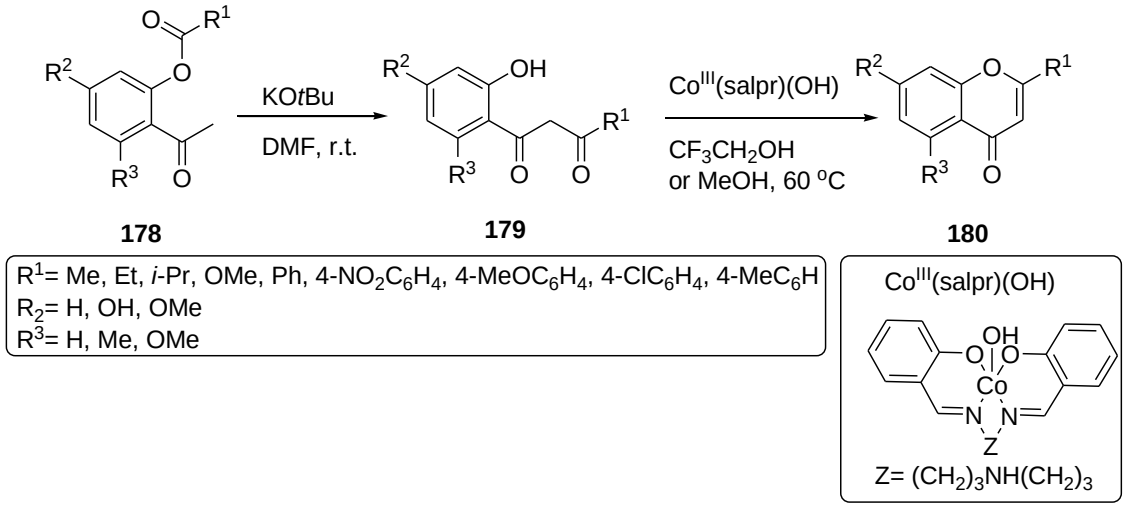
Chromones (4*H*-1-benzopyran-4-one, **167**) are one of the most abundant classes of naturally occurring oxygen-heterocycles, Figure 9.[116] Chromone motifs are found in a wide variety of naturally occurring and synthetic products. The significance of these compounds is due not only to the important biological functions they play in nature, but also because certain derivatives have shown considerable pharmacological, biocidal, antioxidant,[116] anticancer,[117–119] anti-inflammatory activities,[120] and for the treatment of some cardiovascular disorders.[121] Some of the more successful candidates are also marketed as drugs (such as cromolyn).[122]



167

Figure 9. General structure of chromone.

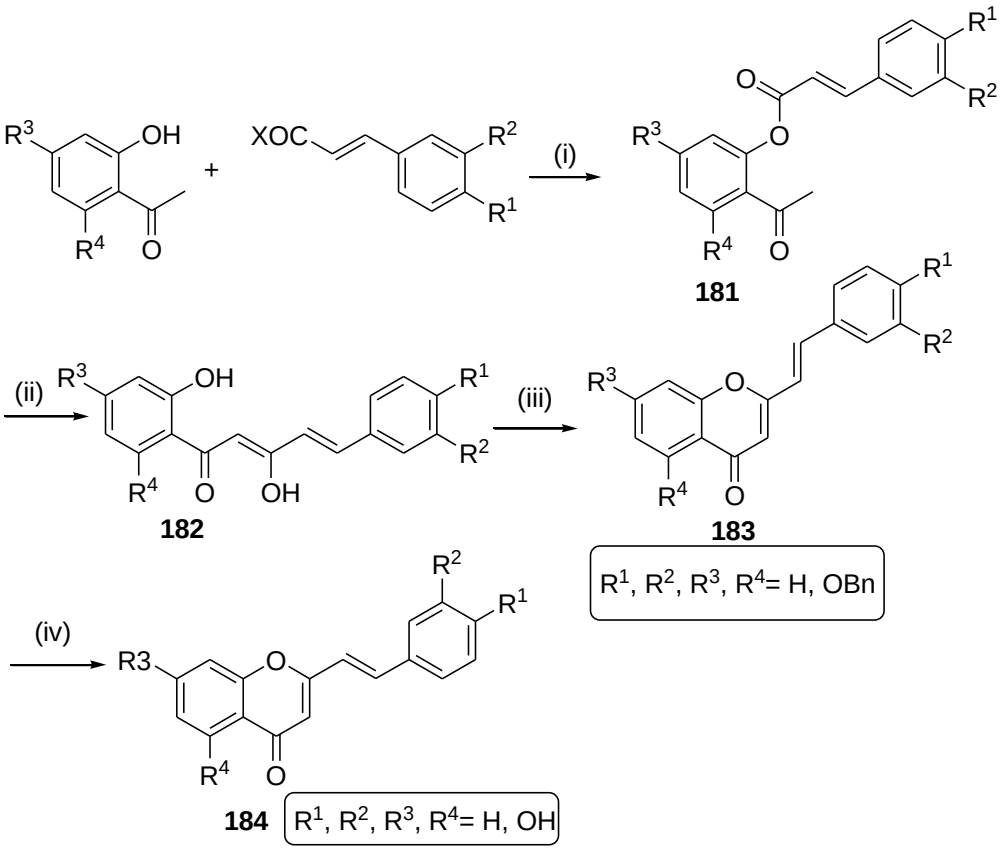
Nishinaga *et al*. attempted the synthesis of ten different chromone derivatives through a Baker-Venkataraman rearrangement.[123] In their approach, the starting compounds **179** (54-89%) were prepared conveniently by the potassium *tert*-butoxide induced Baker-Venkataraman rearrangement of *O*-acyloxyacetophenones (**178**) in dimethylformamide (DMF) at room temperature. The 1-(*O*-hydroxyaryl)-1,3-diketones (**179**) were then cyclised in methanol or trifluoroethanol containing Co^{III}(salpr)(OH)[124] at 60 °C to offer the chromones **180** in 70-100% yield, Scheme 56.[123]



Scheme 56. The synthesis of chromones such as **180**.

Other classes of chromones, which are less widely-occurring in nature, have also exhibited important biological activities. For example, within the newly-discovered group of 2-styrylchromones, only two natural derivatives have been found, but they have shown potent *in vitro* cytotoxicity against human leukaemia cells.[125,126] Prior to the isolation of these natural 2-styrylchromones, studies had already been carried out on numerous synthetic derivatives,[127] which also showed promising antitumour and anti-allergic activities.[128] More recently, it has been demonstrated that certain synthetic derivatives are inhibitors of the replication of the human anti-rhinovirus,[129] while the authors have found that 3'-allyl-5,7,4'-trimethoxy-2-styrylchromone inhibits oxidative phosphorylation,[130] and that some hydroxy-2-styrylchromones act as potent xanthine oxidase inhibitors.[100]

Silva *et al*. prepared several hydroxy-2-styrylchromones **184** by the Baker−Venkataraman method, Scheme 57. In which, transformation of compounds **181** into 5-aryl-3-hydroxy-1-(2-hydroxyaryl)-2,4-pentadien-1-ones **182** was carried out by their treatment with an excess of potassium hydroxide in DMSO, Scheme 57. Compounds **182** were subjected to cyclodehydration to offer the corresponding benzyloxy-2-styrylchromones **183**. Subsequent debenzylation of the benzyloxy-2-styrylchromones **183** was achieved by their treatment with a solution of hydrogen bromide in acetic acid at reflux, to give the corresponding hydroxy-2-styrylchromones **184** in moderate yields, Scheme 57.



Reaction conditions: i) X=Cl, dry pyridine or X=OH, $POCl_3$ in dry pyridine; ii) KOH, DMSO; iii) *p*-Toluenesulfonic acid or I_2, iv) DMSO; HBr/AcOH.

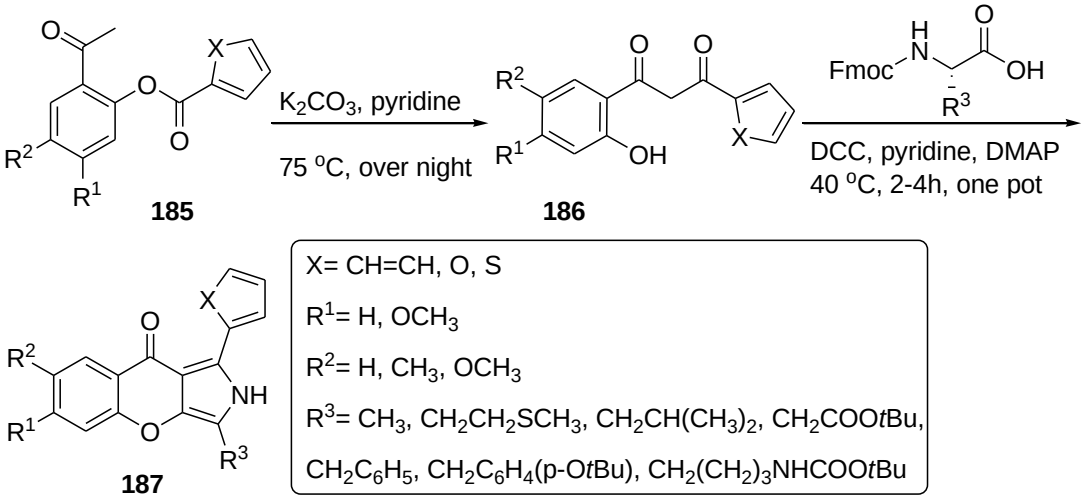
Scheme 57. Preparation of hydroxy-2-styrylchromones **184**.

Moreover, the Baker–Venkataraman rearrangement,[131] in combination with oxidative or acidic catalytic cyclisation,[132,133] has been revealed as an efficient method for chromone formation, Scheme 58.[134]

For example, in their search for potent anticancer molecules, Bu *et al*. found an efficient one-pot synthesis of multi-functionalized chromeno[2,3-c]pyrrol-9(2H)-ones.[134] Acylation of *o*-hydroxylated diaryl 1,3-diketones followed by a Baker–Venkataraman rearrangement would accomplish the achievement of increasing substrate diversity. For example, the synthesis of 1,3-diaryl-1,3-diketones from **186** (after esterification (86-90%) and Baker–Venkataraman rearrangement) was achieved. In this method, *o*-acylated phenol esters **185** underwent Baker–Venkataraman rearrangement (K_2CO_3 (1 eq.) in pyridine at 75 °C) to afford **186** in 70–83% yields, Scheme 58.[134]

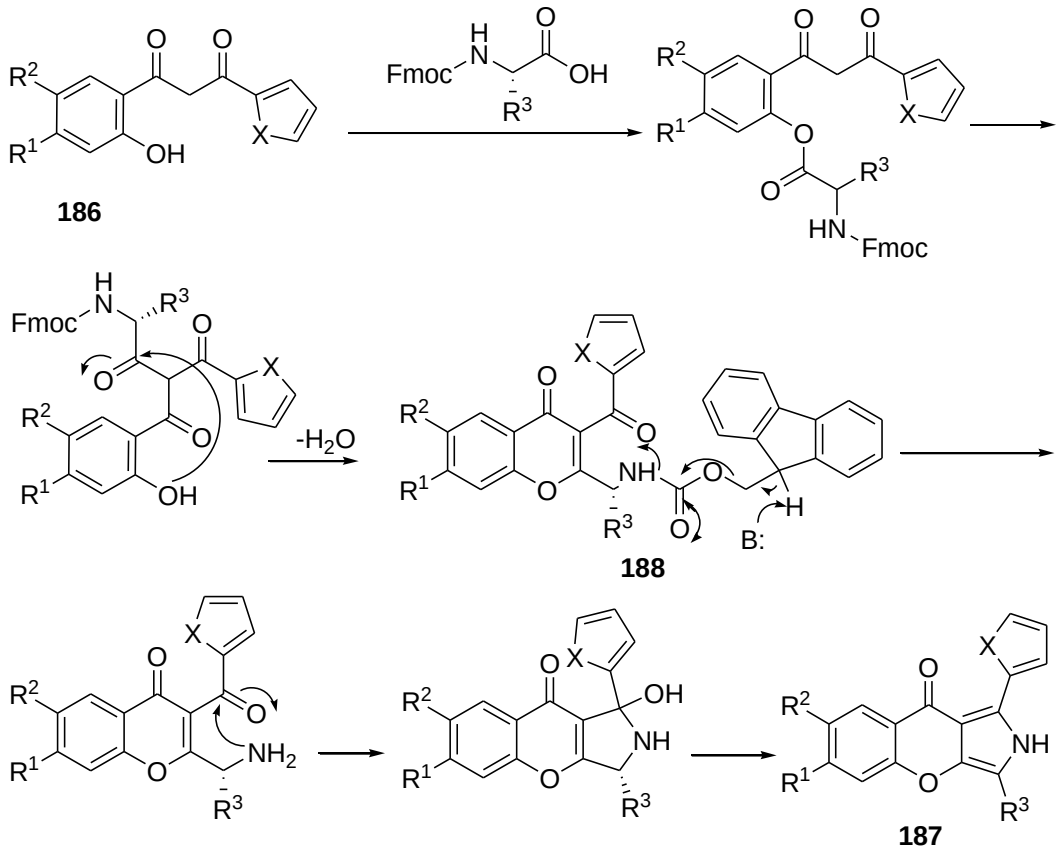
The *β*-diketone intermediates **186** were then esterified with various protected amino acids (lysine, aspartic acid, alanine, leucine, phenylalanine, tyrosine, and methionine), using 4-(dimethylamino)-pyridine (DMAP) as a catalyst in pyridine at 25 °C, to offer

the final product, 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **187** in 44–89% yields, Scheme 58.[134]



Scheme 58. The synthesis of 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **187**.

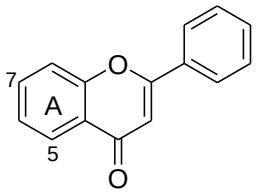
The proposed mechanism for the formation of the 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **187** involves two steps. Firstly, DMAP-catalysed Baker–Venkataraman rearrangement occurs immediately after the esterification of **186**, giving the chromone intermediate **188**, Scheme 59. Secondly, the 9-fluorenylmethyloxycarbonyl (Fmoc) group can be removed by DMAP under the same conditions.[135] Subsequently, the liberated amino group of **188** undergoes intramolecular carbonyl addition and is followed by elimination to afford the final products **187**, Scheme 59.[134]



Scheme 59. The proposed mechanism for the formation of the 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **187**.

1.1.2.6.3 Synthesis of flavones

The flavone nucleus (2-phenylchromones (**168**), Figure 10) seems to be an important scaffold to prepare pharmaceutical agents, since both natural and synthetic derivatives are responsible for a great variety of biological and pharmacological activities, including antitumour, anti-inflammatory, antiviral, and antioxidant properties.[136] The presence of hydroxyl groups in the flavone skeleton is very important for their capacity to act as antioxidants,[137] as exemplified by quercetin (3,3',4',5,7-pentahydroxyflavone), a well-known antioxidant agent and a very important compound with numerous biological activities, such as an inhibitory effect on tumour growth.[138] Another important structural feature of flavones is the presence of a 3-aroyl group; in fact it has been reported that flavones bearing this substituent possess antibacterial, antifungal, and antimalarial activities.[139–141] More recently, it was also reported that some 3-aroylflavones present antitubulin activity.[142]



168

Figure 10. General structure of flavone **168**.

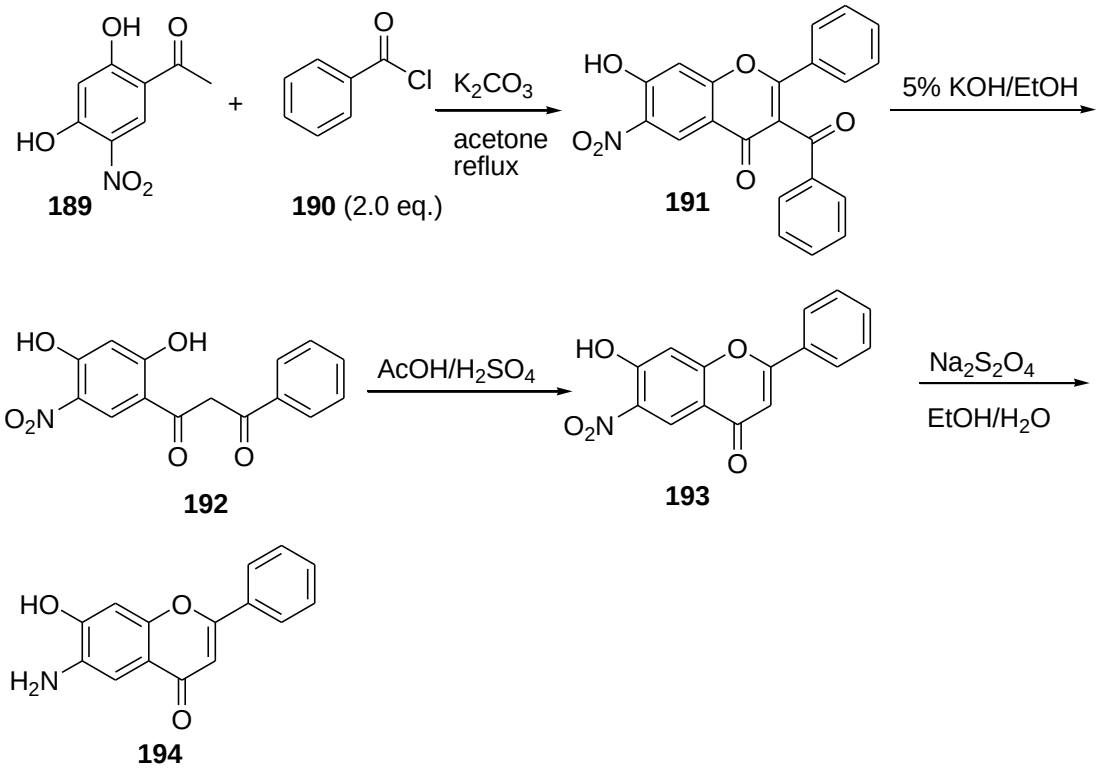
The initial application of the, now called, Baker-Venkataraman rearrangement was by Venkataraman himself, when he attempted the synthesis of α-naphthaflavone **112** from 2-acetyl-1-naphthyl benzoate, Figure 4 (*vide supra*).[67]

Thereafter, a variety of flavones have been synthesised via the Baker-Venkataraman rearrangement, for example, a modified Baker-Venkataraman transformation was the key step in the preparation of fourteen flavone derivatives **129**, Scheme 42 (*vide supra*).[84] Furthermore, aroyl-5-hydroxyflavones (nine analogues **160** and **161**) have been synthesised under microwave assisted Baker-Venkataraman transposition, Scheme 52 (*vide supra*).[101]

Additionally, it has been observed that the presence of hydroxyl groups at position -5 or 7 is frequently required for higher biological activities.[143,144] On the other hand, aminoflavones have been studied as tyrosine kinase inhibitors[145] and as antimitotic agents.[146] In light of these results, interest in the synthesis of flavones bearing both hydroxyl and amino groups on the A-ring grew, Figure 10.

The synthesis of flavone **193** by a modified Baker-Venkataraman method has been reported recently.[147] In this process, the 1,3-diketone intermediate **192** was prepared in one step by the reaction of **189** and benzoyl chloride (**190**), but this route required the use of relatively expensive lithium hexamethyldisilazide (LiHMDS) and low temperature (-78 °C). Furthermore, compound **192** was neither isolated nor fully characterized. However, the method needs improving to avoid both the lengthy synthesis of the corresponding chalcone precursor and inconvenient low temperature preparation of the 1,3-diketone intermediate **192**.[147] Therefore, to avoid both the lengthy synthesis of the corresponding chalcone precursor and inconvenient low temperature preparation of the 1,3-diketone intermediate **192** the commonly used Baker-Venkataraman rearrangement conditions was reinvestigated by Shufen *et al.*[148] In their efforts, the synthesis of **191** was achieved from 2′,4′-dihydroxy-5′-nitroacetophenone (**189**) using 2.0 equivalents of benzoyl chloride in refluxing dry acetone in the presence

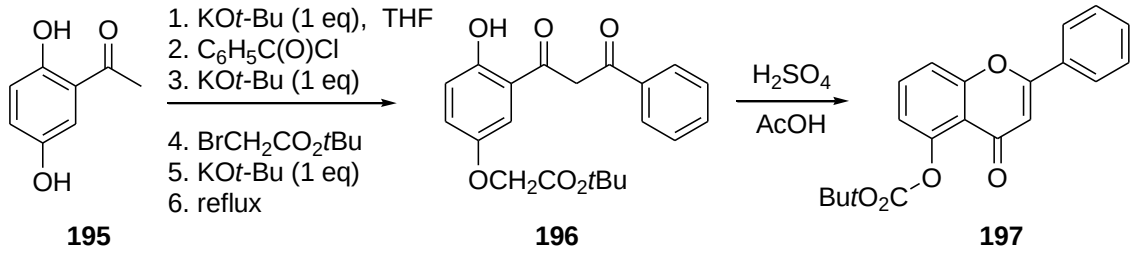
of anhydrous potassium carbonate, Scheme 60. Yields of the separated compounds 3-benzoyl-7-hydroxy-6-nitroflavone (**191**) and 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**192**) were 43%, and 13% respectively.[148]



Scheme 60. The synthesis of flavone **194** by a modified Baker-Venkataraman method.

These results showed that the hydroxyl group adjacent to the nitro group in **189** cannot be acylated under the selected reaction conditions. This was attributed to the strong intramolecular hydrogen bonding between the nitro and hydroxyl groups, i.e., resonance deactivation, which hinder the acylation of the latter.

In a similar manner, Ares *et al*. found a convenient large-scale preparation of 5-*O*-pivaloylflavone **197** using KO*t*-Bu (2.2 equivalent) mediated diketone **196** synthesis as the key step, Scheme 61. The method has been successfully applied for the convenient synthesis of a number of flavone analogues. They combined a phenolic alkylation step with the rearrangement to provide a short and efficient means of transforming dihydroxyacetophenones **195** into A-ring alkoxyflavones **197**, Scheme 61.[86]

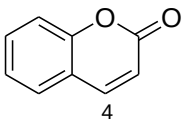


195 **196** **197**

Scheme 61. Preparation of 5-*O*-pivaloylflavone **197**.

1.1.2.6.4 Synthesis of coumarins

Coumarin (2*H*-1-benzopyran-2-one (**169**), Figure 11) is a plant-derived natural product which possesses a variety of pharmacological activities, such as anti-inflammatory,[149] antifungal,[150] antimicrobial[151] and anti-HIV activities.[152] Furthermore, examples of isolated naturally occurring coumarins (dicoumarol, warfarin, and umbelliferone) are well known for their anticoagulant properties.[153] Victor Snieckus documented a general method for the synthesis of substituted 4-hydroxycoumarins (**154)** (10 derivatives in 79-95% overall yields) using his carbamoyl version of the Baker-Venkataraman rearrangement, (see Scheme 51 *vide supra*).[94] In addition, the same authors declared that the strategy was also applicable for the synthesis of 4,6-dimethoxy-3,7-dimethylcoumarins **155** and **156**, (see Figure 6 *vide supra)*.[94]



169

Figure 11. General structure of coumarin **169**.

1.1.2.6.5 Synthesis of anthrapyran antibiotics

Indomycinones[154] belong to the anthrapyran antibiotic family and occur mainly as their C-glycosides (eg. pluramycines, hedamycines, riboflavines, altromycines and indomycines), Figure 12.[155,156] Due to their selective binding to DNA and their specific alkylation of guanine,[157,158] they have found renewed interest in structural biology.[159] Additionally, a number of aglycones with the anthra[*b*]pyran nucleus have also been found in nature. For example, *β*-indomycinone (**198**)[160] and *δ*-indomycinone (**199**)[160] have a C-6 side chain at C-2 while *γ*-indomycinone (**200**),[154] kidamycinone (**201**),[161] the

antihepatitic antibiotic AH-1763 IIa (**202**), and the neuroprotective espicufolin (**203**) have a C-4 side chain, Figure 11.[162] Recently, several researchers have attempted the syntheses of premithramycinone (**204**),[163] espicufolin (**203**),[164,165] altromycinone (**205**) and kidamycinone (**201**),[166] and AH-1763 IIa[162] (**202**) and this remarkable interest is attributed to their great biological properties, Figure 12.

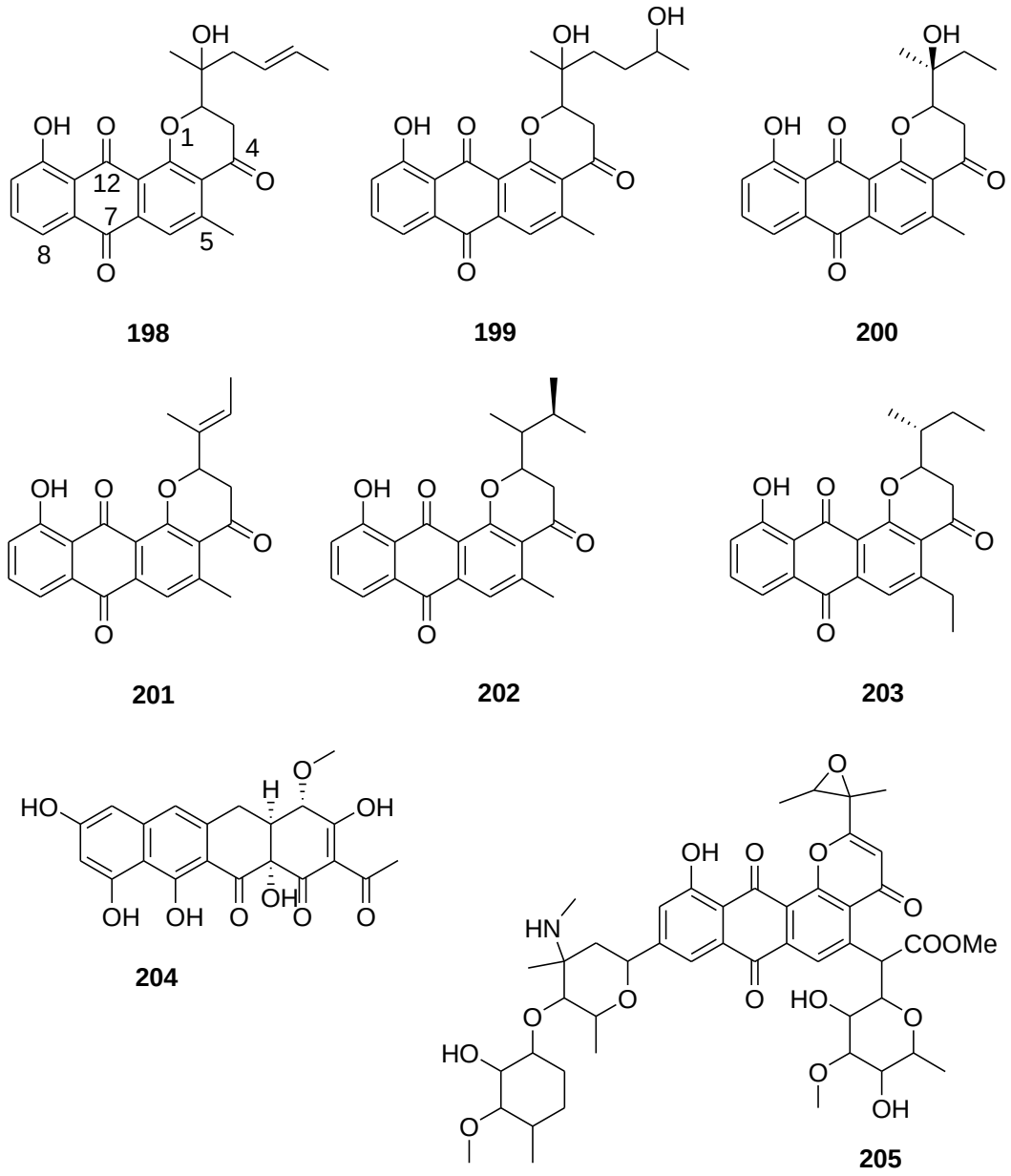
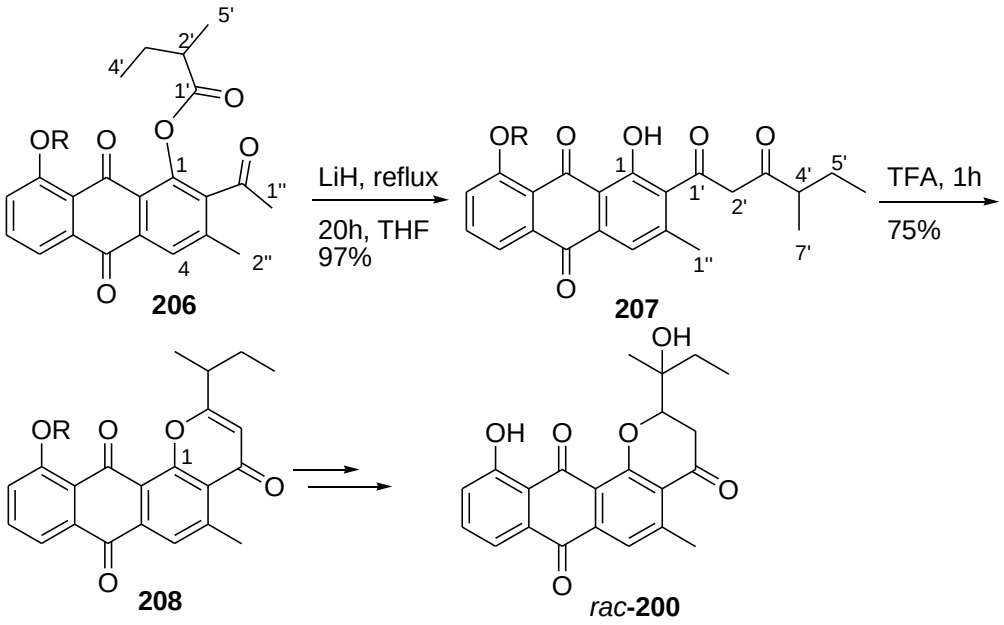


Figure 12. Examples of anthrapyran antibiotics synthesised using the Baker-Venakataraman rearrangement

In an approach made by Krohn *et al*. for the synthesis of rac-*γ*-indomycinones, the Baker–Venkataraman rearrangement was employed for the chain elongation to avoid the reduction and/ or oxidation steps connected with the organometallic reactions on the anthraquinone skeleton.[163,167] The key Baker–Venkataraman rearrangement was induced

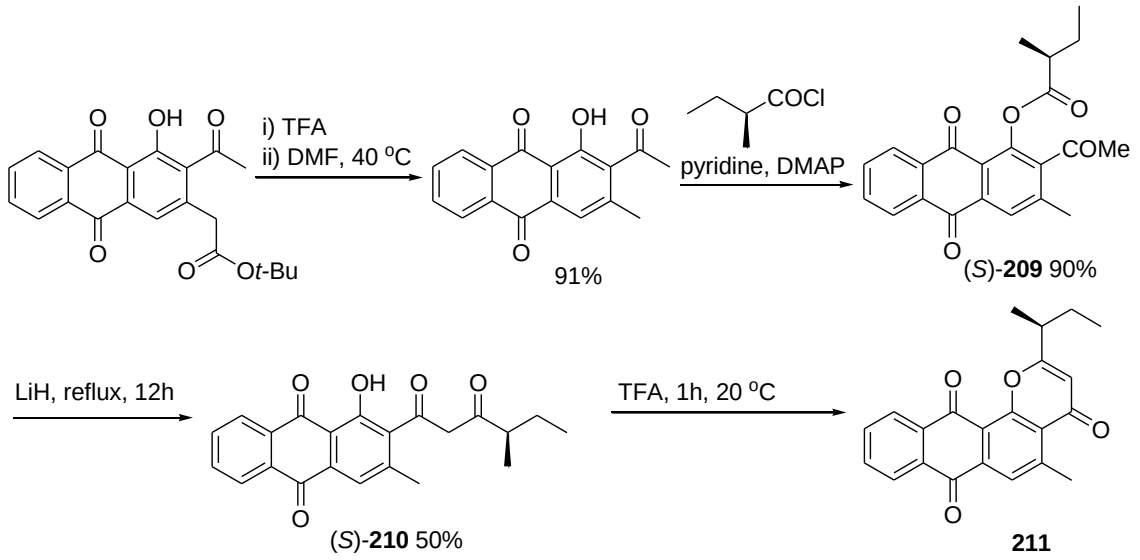
by refluxing the ester **206** in THF with lithium hydride to offer the *β*-diketo-anthraquinone **207** in 97% yield, Scheme 62.[162] The acid-catalysed cyclisation to anthrapyranone **208**, then underwent a few further steps to offer *rac*-**200**. A similar protocol has been used to prepare the corresponding 11-methyl ether of *γ*-indomycinone **200** as well, Scheme 62.[162]



Scheme 62. The synthesis of rac-*γ*-indomycinones.

The Baker–Venkataraman reaction has become employed widely in the synthesis of a large group of anthrapyran antibiotics.[161,163,168] Similarly, the synthesis of aromatic polyketide derived natural products and the biomimetic-type synthesis of anthracylines[169] and angucyclines[170] includes the construction of *β*-diketo side chains on an aromatic or quinoide nucleus.[171] As such, to produce such *β*-diketo products Krohn *et al*. attempted an enantioselective acyl transfer reaction with α-oxygenated esters under Baker–Venkataraman conditions, Scheme 63.[167]

In this effort, the base-catalysed acyl transfer (Baker–Venkataraman reaction) of chiral 2-acetyl-1-hydroxyanthraquinone esters (**209**) or (**215**) proceeds with virtually no racemisation to *β*-diketo-anthraquinone (*S*)-**210** and (*S*)-**216**, Scheme 63 and 64. The next cyclisation step offered the enantiomerically enriched (>97% ee) anthra[1,2-b]pyran **211** which is a close derivative of neuroprotective espicufolin (**203**).



Scheme 63. Synthesis of enantioenriched anthra[1,2-b]pyran **211**.

Furthermore, the Baker–Venkataraman reaction was applied to transform enantiomerically pure *O*-allyl-lactic ester **215** to ketides **216**, Scheme 64, as well as, its cyclisation to anthrapyrans **217**. The model reaction opened the way to synthesise enantiomerically pure 10-hydroxy-anthrapyranones of the indomycinones, rubiflavinones **212**, pluramycines **213**, or hedamycines **214**, Figure 13.[156]

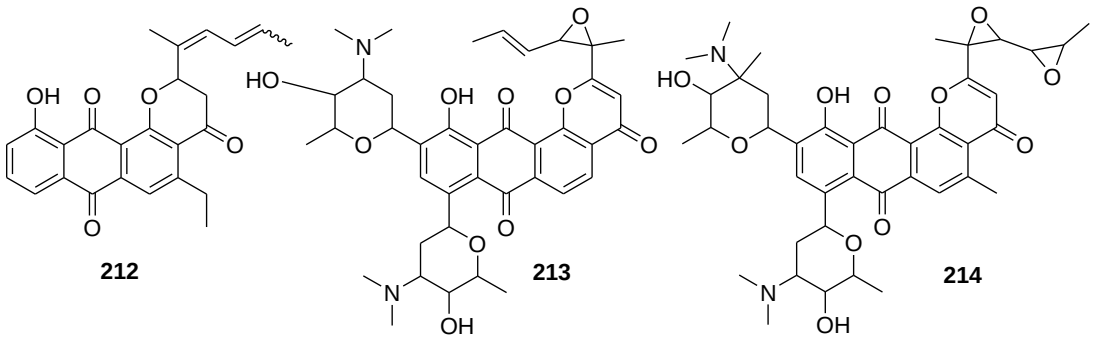
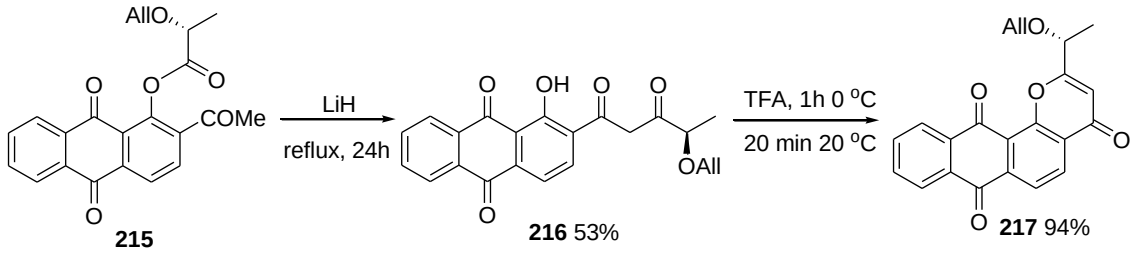


Figure 13. Examples of indomycinones containing a 10-hydroxy-anthrapyranone nucleus.

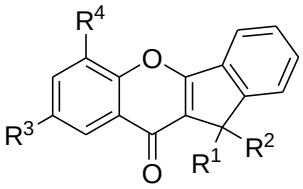


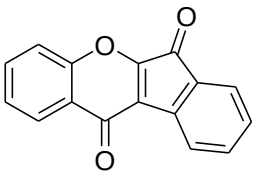
Scheme 64. Preparation of 2-allyloxy-substituted anthrapyranone **217**.

The Baker–Venkataraman rearrangement of ester **215** afforded 53% of *β*-diketoalkyl-anthraquinone **216**. In the end, cyclisation of the *β*-diketoalkyl phenol **216** to 2-allyloxy-substituted anthrapyranon **217** (94% yield) was excellent, since no cleavage and no isomerisation of the allyl protecting group occurred.[167]

1.1.2.6.6 Synthesis of benzopyran derivatives

Benz[*b*]indeno[2,1-*e*]pyran-10,11-diones **218,** Figure 14, are known to enhance the biosynthesis of erythropoietin, a hematopoietic growth factor which stimulates differentiation and supports the survival of cells of the erythroid lineage.[172] The methanol extract of the dried leaves and stems of *Wrightia tomentosa* revealed weak activity against human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT). Thasana and Somsak showed that this effect was due to wrightiadione **219** Figure 14,[173] which is a rare and unusual oxygen heterocycle isolated from the bark of this medicinal plant of Thailand.[174] This finding, and the reported interesting biological activity of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones **218**, motivated the authors to undertake a study of the synthesis of these compounds.[175]



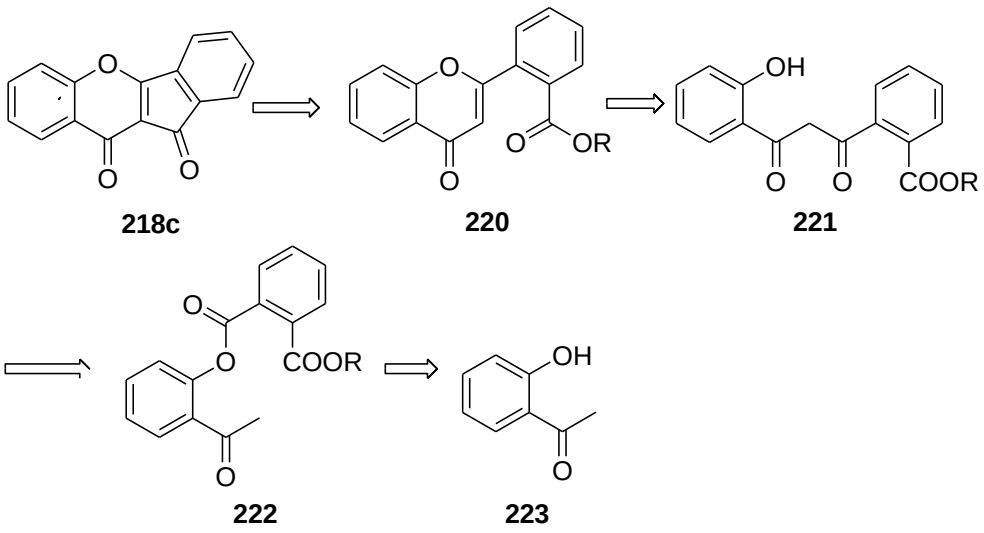


219

218a $R^{1,}$ R^2= O, R^3= R^4= Me
218b R^1= OH, R^2= H, R^3= R^4= Me
218c $R^{1,}$ R^2 = O, R^3= R^4= H

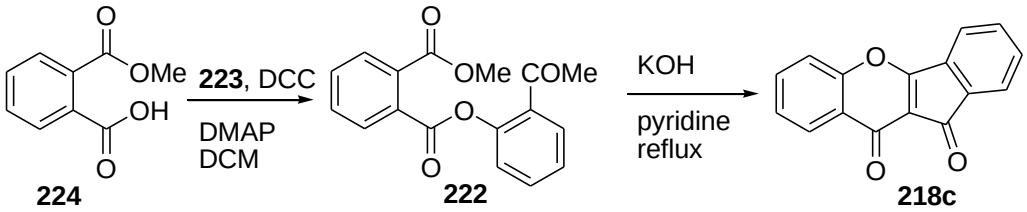
Figure 14. General structure of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones **218** and wrightiadione **219**.

Therefore, to develop an operationally simple, highly efficient reaction for the synthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones **218**, the same authors envisaged that benz[*b*]indeno[2,1-*e*]pyran-10,11- dione **218c** (isowrightiadione) could be obtained via the synthetic route shown in the retrosynthetic analysis in Scheme 65. It was expected that flavone **220** could be obtained by application of the Baker–Venkataraman rearrangement.[86,131,176–179] Further cyclisation directly could then lead to the required compound, Scheme 65.[175]



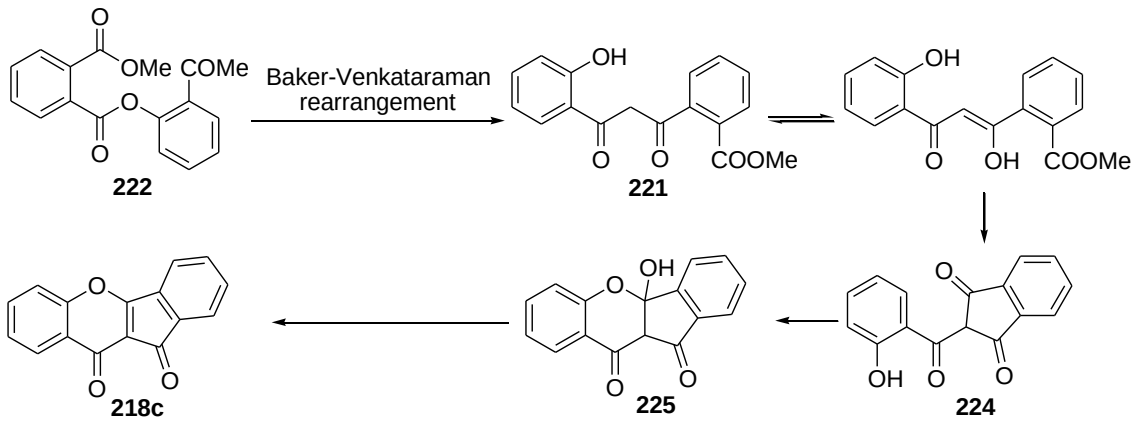
Scheme 65. Retrosynthesis of isowrightiadione (**218c**).

To investigate this route, acylation of **223** with *mono*-methylphthalate **224** using a Steglich esterification gave *o*-benzoylacetophenone **222** in 68% yield (Scheme 66). The intramolecular acylation of **222** was carried out with potassium hydroxide in pyridine, under reflux for 30 minutes to give the desired 1,3 diketone **221**, Scheme 66. The mixture was then poured into 2M hydrochloric acid solution which led to the precipitation of a yellow solid in 72% yield.[175]



Scheme 66. Synthesis of isowrightiadione (**218c**).

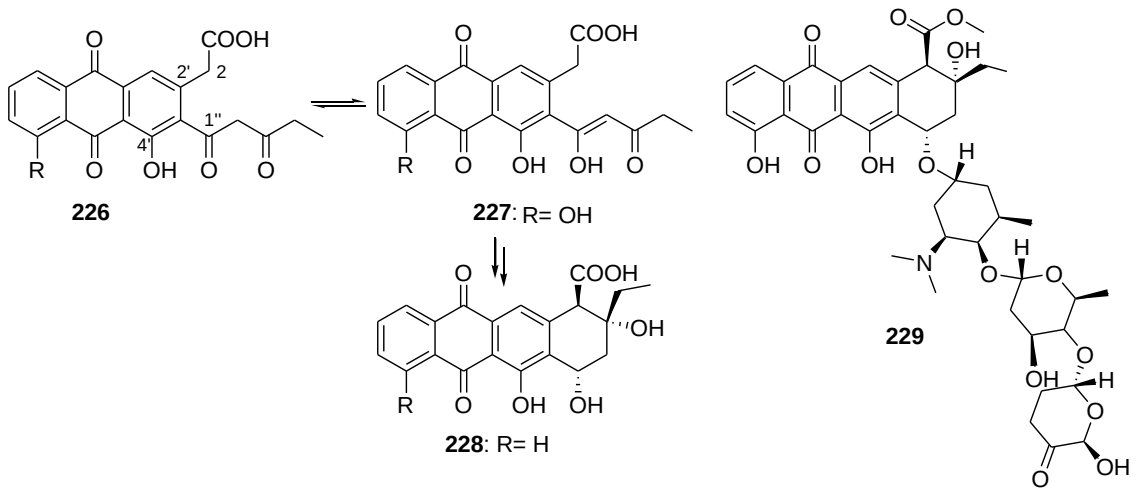
The elucidated structure of the recrystallized product was not the expected flavanone **220** (R= Me) but instead the final target compound **218c**. The rationalized mechanism for the formation of **218c** could involve formation of the 1,3-diketone intermediate **221** through the Baker–Venkataraman rearrangement, Scheme 67. After which, the diketone **221** will intramolecularly cyclise to afford the 1,3-indanedione **225**. Subsequently, the formed hemiketal **225** can dehydrate to give the ultimate product **218c** as shown in Scheme 67.[175]



Scheme 67. The rationalised mechanism for the formation of **218c**.

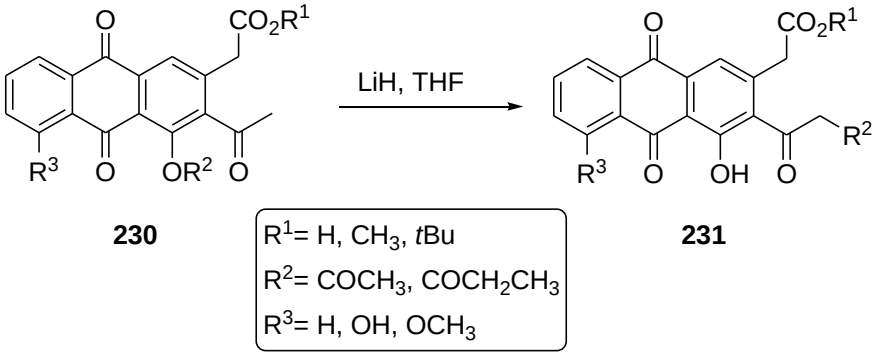
1.1.2.6.7 Synthesis of aklanonic acid

Aklanonic acid (**226**, which exists in equilibrium with the enol form **227** (when R= OH), Scheme 68) and its derivatives such as 4-deoxyaklavinone **228** (R= H) are starting materials of great interest for the microbial conversion of synthetically inaccessible derivatives of the antitumor agent aclacinomycin A (**229**).[180]



Scheme 68. Starting materials for the synthesis of aclacinomycin A (**229**).

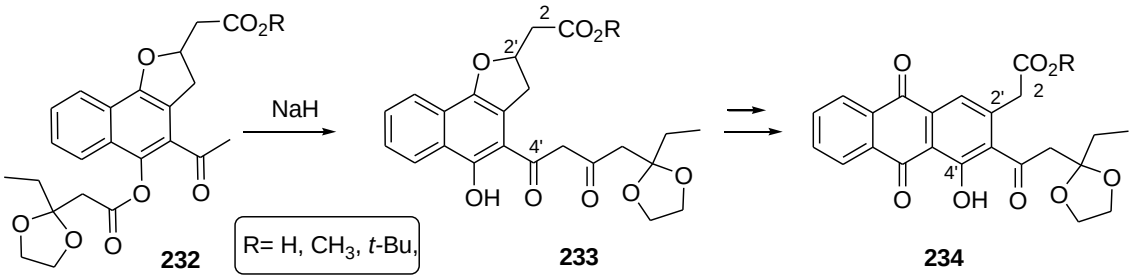
In this scene, the Baker-Venkataraman rearrangement (lithium hydride in THF) has been utilised as a flexible method for the introduction of ketide side chains on anthraquinones **230** to afford the aklanonic acid derivatives (e.g. **231)** in a very pure state and in high yield, Scheme 69.[169]



230 **231**

Scheme 69. Preparation of aklanonic acid derivatives **231**.

Similarly, the attachment of different oligoketide side chains to the naphthoquinone nucleus have been carried out by Krohn and Schafer.[181] In this case, after a number of trials they proved that the Baker-Venkataraman rearrangement of ester **232** was the best protocol for the side chain elongation with a variety of ketides, Scheme 70. Sodium hydride in THF was found to give the best results in the transformation of **232** to the rearranged product **233** (66%). The corresponding naphthoquinone precursors **233** underwent base-catalysed cascade reactions to yield the 4-deoxyaklanonic acids **234**, Scheme 70.



232 **233** **234**

Scheme 70. Attachment of oligoketide side-chains to the naphthoquinone nucleus.

In conclusion, like its analogue, the Truce-Smiles rearrangement, the Baker-Venkataraman rearrangement is regarded as a valuable reaction to construct new C-C bonds under mild conditions, as has been demonstrated with the synthesis of chromones, flavones, isoflavones, and coumarins, amongst other motifs. However, as with the Truce-Smiles rearrangement, to date, no enantioenriched chiral centres have been synthesised by virtue of this practical rearrangement.

CHAPTER 2 - RESULTS AND DISCUSSION

CHAPTER TWO - RESULTS AN DISCUSSION

2.1 Hypothesis and aims of the work

Taking together all the applications and limitations of the asymmetric α-arylation and α-acylation of carbonyl compounds, it was envisaged that it would be possible to produce an asymmetric α-arylation and α-acylation of carbonyl compounds via the Truce-Smiles and Baker-Venkataraman rearrangements; which to date have not been reported.

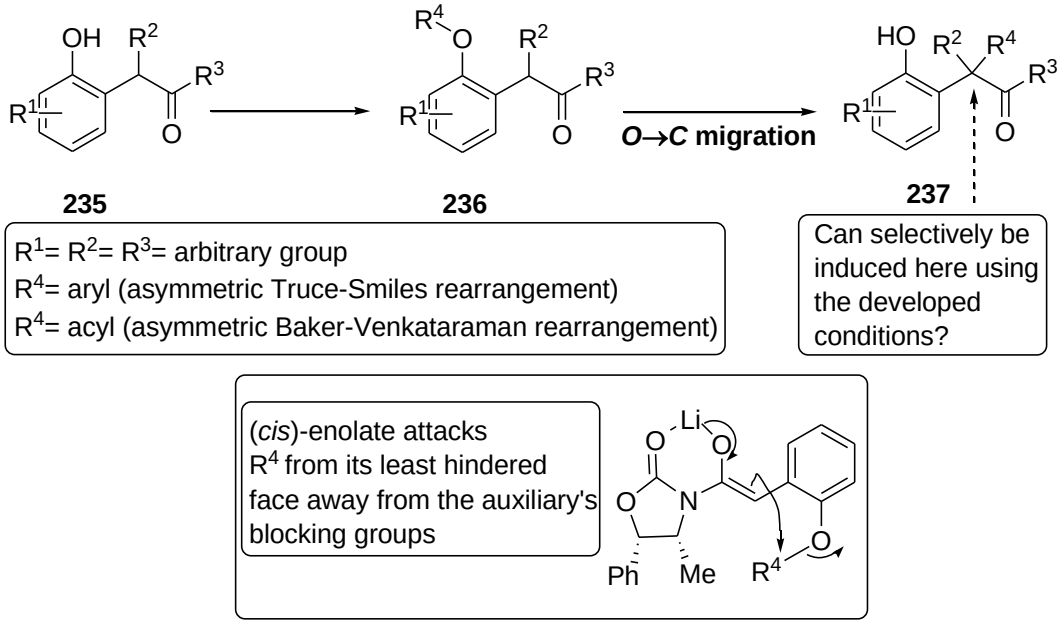
2.1.1 Working hypothesis

It is possible to synthesise asymmetric, sterically hindered tertiary or quaternary centres, through the Truce-Smiles and Baker-Venkataraman rearrangements.

2.1.2 Aims of the work

The study was intended to lead to the development of a novel method for the synthesis of asymmetric α-arylated and α-acylated carbonyl compounds through the Truce-Smiles and Baker-Venkataraman rearrangements respectively, with the following aims:

1. To design and develop a novel method for the asymmetric synthesis of sterically hindered tertiary or quaternary centres via the Truce-Smiles and Baker-Venkataraman rearrangements, Scheme 71.
2. To expand the potential of the developed methodology towards the synthesis of pharmaceutically relevant intermediates and drugs.



Scheme 71. Expected asymmetry induction (shown when R^3= chiral auxiliary).

2.2 Asymmetric α-arylation of carbonyl compounds via the Truce-Smiles rearrangement

α-Arylated carbonyl compounds are commonly occurring motifs in biologically interesting molecules[28] and important classes of medication such as cannabinoid CB1-receptor ligands **238**, phosphodiesterase inhibitor **239**, disopyramide[29] **240** and opioids (for example: diphenoxylate **241**),[30] (see Figure 15), however, the synthesis of such compounds is synthetically challenging and new methods are therefore of high interest to the pharmaceutical industry.[182]

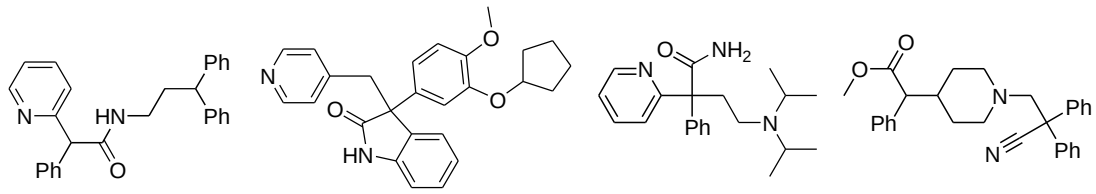
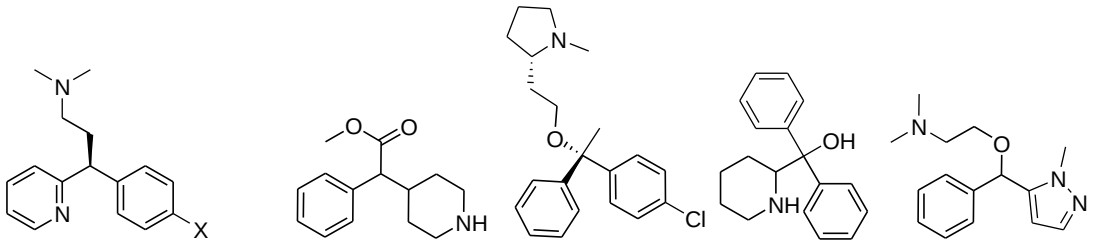


Figure 15. α-Arylated carbonyl compounds.

Equally, the diarylmethanol and diarylmethane framework are considered to be privileged structures in important intermediates and precursors for the synthesis of pharmacologically and biologically active compounds, such as: antihistaminic pheniramines **243a-c**, methyl phenidates (**244**), clemastine (**245**) and pipradrols **246**,

1,4-dihydropyridine derivatives (with potent and long-lasting hypotensive effect), and cizolirtine (a novel non-opioid analgesic **247**), Figure 16.[52–59]



243a X= H; pheniramine
243b X= Br; brompheniramine
243c X= Cl; chlorpheniramine

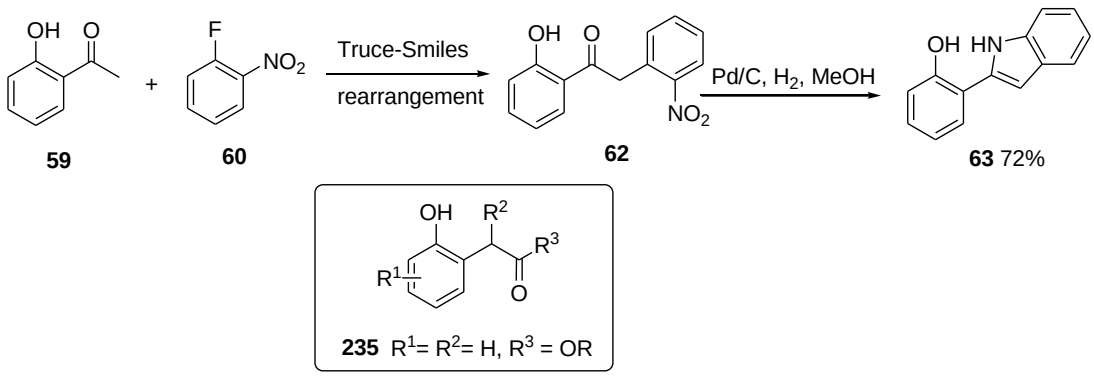
methylphenidate **244** clemastine **245** pipradol **246** cizolirtine **247**

Figure 16. Pharmacologically active compounds prepared from diarylmethanol and diarylmethane frameworks.

Therefore, developing novel routes to such compounds will help with their continued exploitation in medicinal chemistry. These requirements inspired us to study the development of asymmetric metal-free α-arylations of carbonyl compounds as an alternative synthetic approach that operates under mild conditions, especially since wide-ranging achiral substrates have recently been successful in this rearrangement under relatively mild conditions,[42,43,183,184] but also because such a mild, scalable method, amenable to asymmetric induction, has yet to be developed. The question therefore was, could the Truce–Smiles rearrangement be developed to meet these needs?

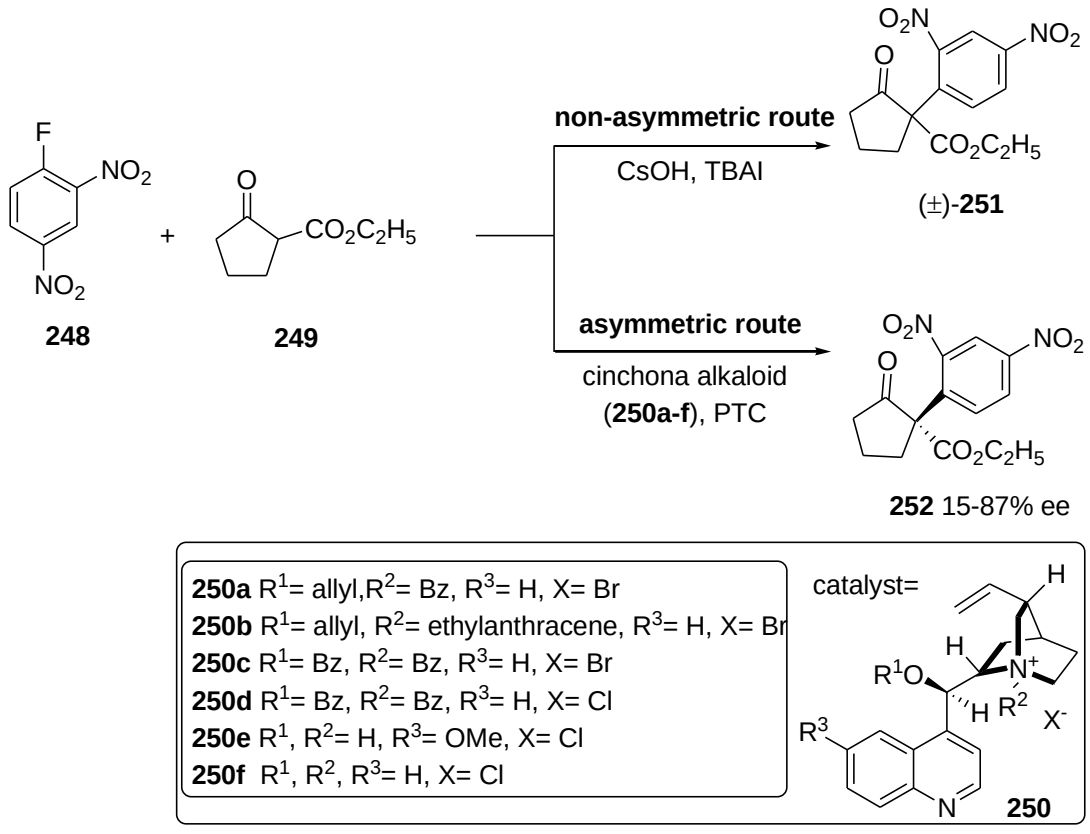
2.2.1 The use of phase transfer catalysts

Recently, our group expanded the Truce-Smiles rearrangement by applying it to functionalised substrates in order to make them more synthetically useful building blocks (for example, as demonstrated with the synthesis of indole **63**, Scheme 72), and it was shown that homologous ketones **235**[23] could also react resulting in chiral, racemic, α-arylated products.[31]



Scheme 72. Expanding the Truce-Smiles rearrangement to synthesise indole **63**.

To further expand the utility of this method towards asymmetric α-arylated carbonyl compounds, the development of new asymmetric conditions were required to enable the synthesis of products not currently covered under the conditions known to date. For example, increasing substrate functional group tolerance; preventing any product racemisation, therefore allowing access to products with high enantioselectivities; as well as controlling regioselectivity in substrates with more than one enolisable position.



Scheme 73. Non-asymmetric α-arylation method developed into asymmetric variant.[182]

The best way to overcome such drawbacks is to exploit established non-asymmetric methods and develop them into asymmetric variants (Scheme 73) by the judicious

choice of chiral auxiliary reagents, by which, a quick and efficient method for generating chiral products could potentially be achieved.

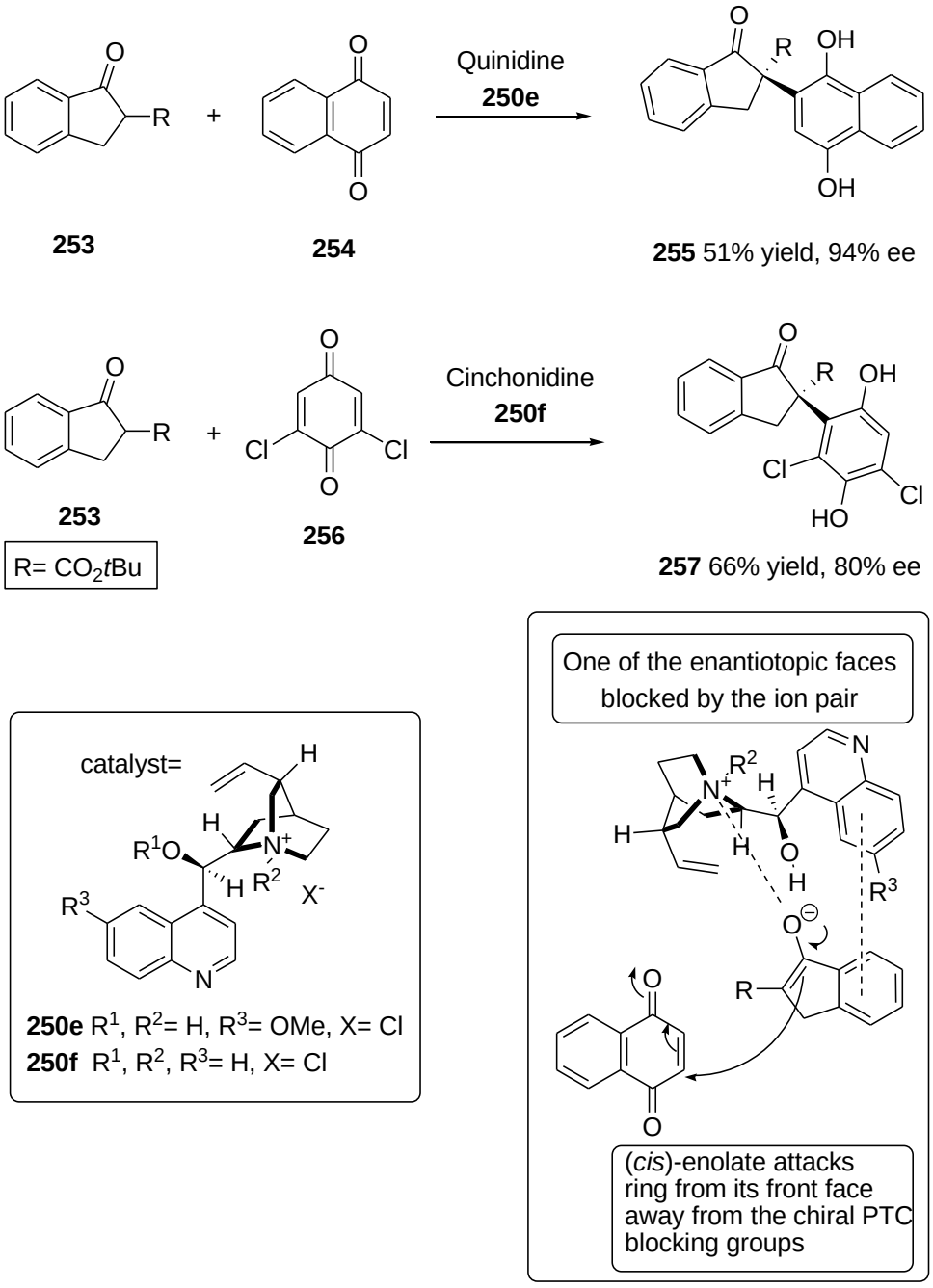
Jørgensen developed non-asymmetric methods for α-arylation of 1,3-dicarbonyl compounds into asymmetric variants, and he demonstrated that chiral induction could also be achieved using chiral phase-transfer catalysts based on the cinchona alkaloids (such as **250a-f**), when he worked on an asymmetric nucleophilic aromatic substitution reactions (S_NAr) (Scheme 73, Table 1).[182,185]

Table 1. Screening catalysts and conditions for the organocatalytic (15 mol %) S_NAr addition of 2-carboethoxy-cyclopetanone (**249**) to 2,4-dinitro-1-fluorobenznene (**248**).

Entry	Catalyst (temp, °C)	Yield (%)	ee (%)
1	TBAI (r.t.)	90	-
2	**250a** (r.t.)	80	15
3	**250b** (r.t.)	80	10
4	**250c** (r.t.)	70	-7
5	**250d** (r.t.)	90	rac
6	**250d** (-20)	90	rac
7	**250e** (r.t.)	82	46
8	**250e** (0)	85	60
9	**250e** (-20)	89	80
10	**250e** (-40)	89	87

Further relevant examples of interest by Jørgensen (Scheme 73 and 74) reveals various nucleophilic aromatic substitution reactions to produce enantioenriched products (e.g. **252**, **255**, and **257**).[182,185] In their work, 1,3-dicarbonyl compounds react with 2,4-dinitro-1-fluorobenznene (**248**) or 1,4-quinones (**254**, **256**) to undergo enantioselective α-arylation using organocatalysts (cinchona alkaloids (**250a-f**)). The high

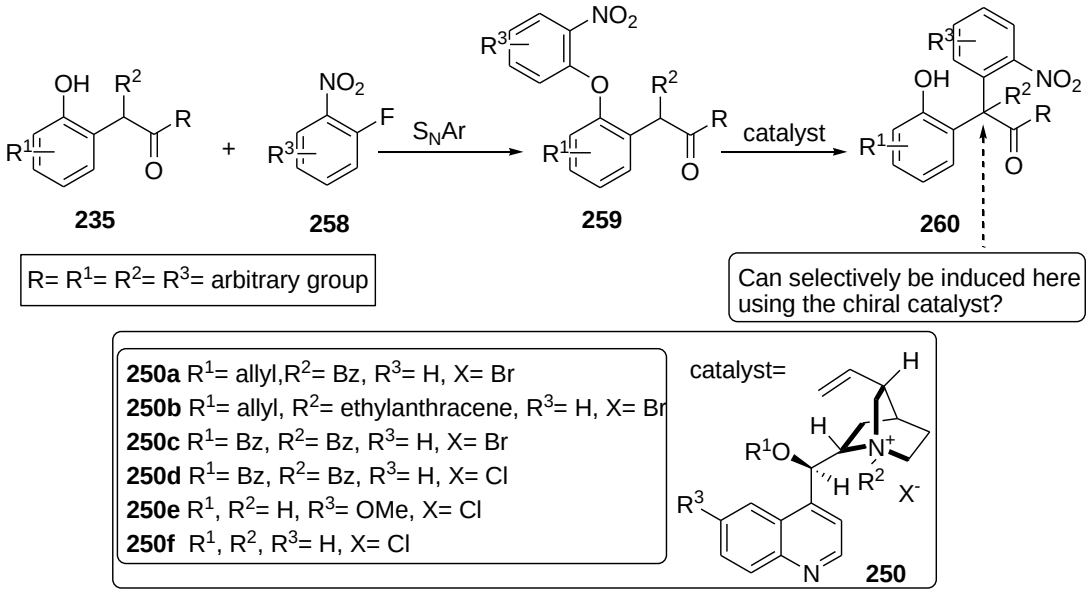
enantioselectivities observed in the PTC-mediated reactions normally arise from electrostatic interactions in the ion pair between the quaternary ammonium salt and the nucleophile, which then react in a stereocontrolled manner with the electrophile.



Scheme 74. Jørgensen's work (enantioselective α-arylation of 1,3-dicarbonyl compounds).[182,185]

However, although the enantiomeric excesses obtained were excellent (**252**→ 15-87%, **255**→ 94% and **257**→ 80% ee), there is still room for improvement if the method is to become generic, since this method was solely restricted to the α-arylation of 1,3-dicarbonyl compounds (e.g. **249**), Scheme 73.[182,185]

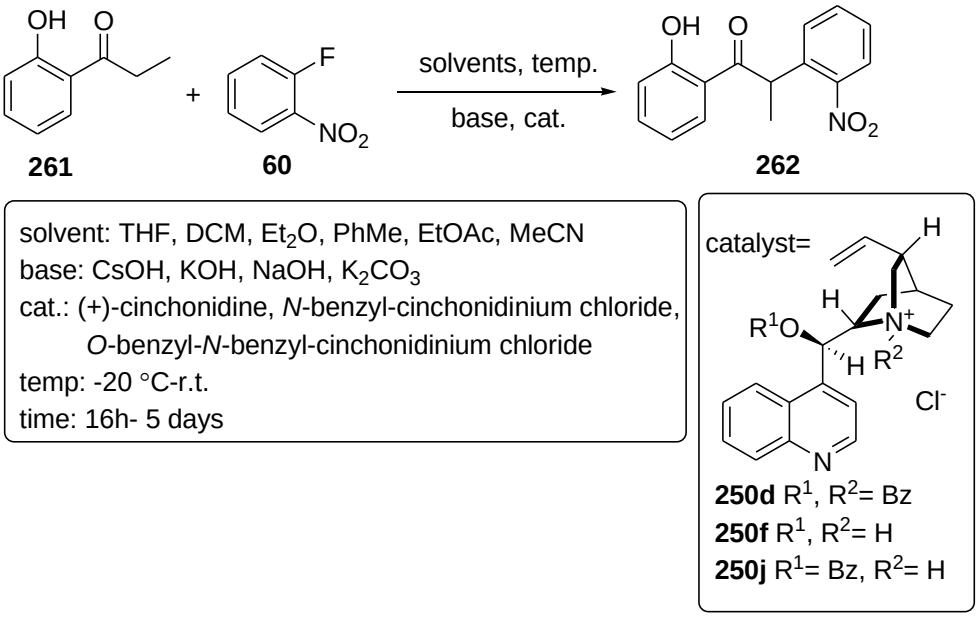
Since the Truce-Smiles rearrangement is an intramolecular variation of the S_NAr reaction,[2] it was expected that such phase-transfer catalysts (e.g. **250**) could force asymmetry in this rearrangement in a similar fashion to Jørgensen's work (Scheme 75).



Scheme 75. Postulated asymmetric induction using a chiral phase-transfer catalyst based on the cinchona alkaloids.[186,187]

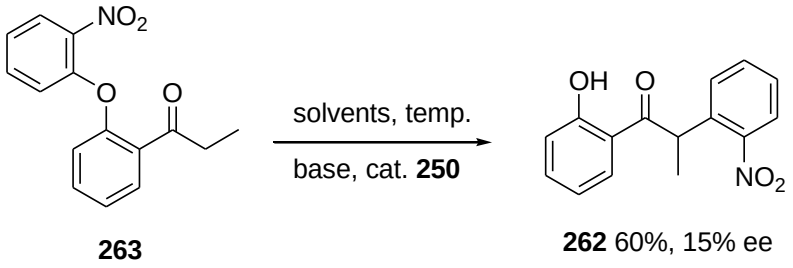
This work originates from the need to develop new methods for the asymmetric α-arylation of carbonyl compounds, and this is expected to be achieved by extending previous work on the Truce-Smiles rearrangement (Scheme 75).[2]

Unfortunately, previous efforts by our group to develop an asymmetric Truce-Smiles rearrangement based on Jørgensen's work met with failure.[188] Despite screening a number of phase transfer catalyst based on the cinchona alkaloids (varying the loading amount of the catalyst), different solvents, bases, varying temperature (from -20 °C- r.t.) and varying the reaction time from 16 hours to 5 days, the maximum enantiomeric excess obtained for the aryl transfer was 1.2% which is arguably within experimental error, Scheme 76.



Scheme 76. Previous efforts to develop an asymmetric Truce-Smiles rearrangement based on Jørgensen's work.

In addition, in order to see if better level of enantioselectivities could be achieved via an intramolecular variant, the rearrangement of diarylether **263**, under the same conditions as above, was attempted. However, in this case, even with 50% loading of the catalyst **250d** in DCM (0.1 M) using KOH (5 eq.) at -20 °C for 2 days, only 15% ee was obtained, Scheme 77.

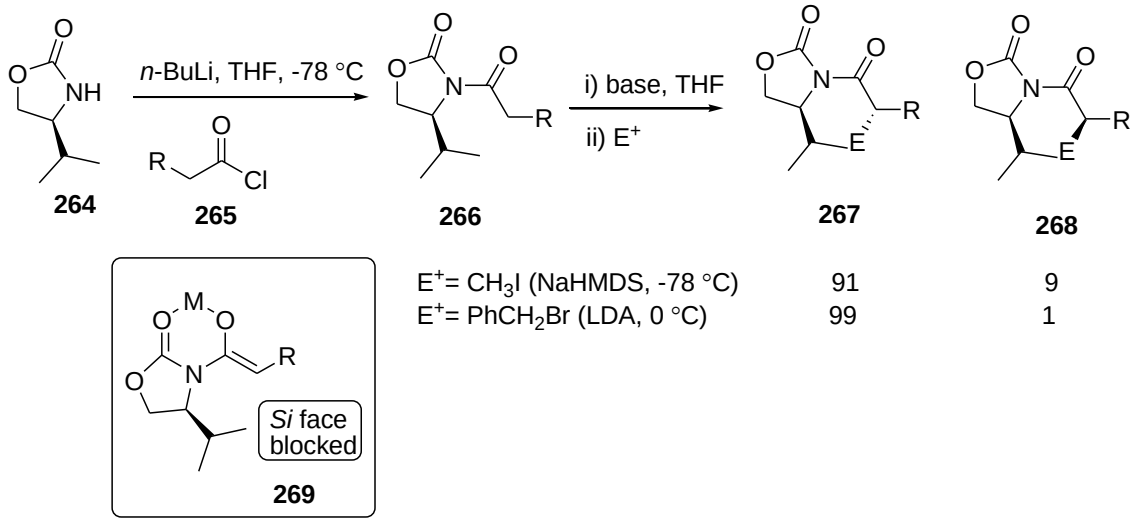


Scheme 77. The enantioselective rearrangement of diarylether **263** using a phase transfer catalyst based on the cinchona alkaloids. For conditions see Scheme 76.

Based on these low levels of enantioselectivity, this route was temporarily abandoned, since it was anticipated that better levels of selectivity may be achieved with chiral auxiliaries as an approach to develop an asymmetric variant of the Truce-Smiles rearrangement. By performing the reaction under already existing established conditions, but with addition of a chiral auxiliary, the hope of inducing asymmetry in Truce-Smiles rearrangement could be achieved; such methods will be described in more details below.

2.2.2 The use of chiral auxiliaries[189]

In 1981 chiral oxazolidin-2-one auxiliaries were introduced, popularised by David Evans in 1982, and have been used widely in organic synthesis since to influence the outcome of numerous asymmetric reactions like the aldol reaction,[190] alkylation reactions[191] and Diels-Alder reactions[192,193] and the conditions for their synthesis and use are widespread.[189] The oxazolidinones are substituted at the 4 and 5 positions to render them chiral. Through steric hindrance and chelation the substituents influence the direction of incoming groups, Scheme 78, causing a preference for facial selectivity to occur.

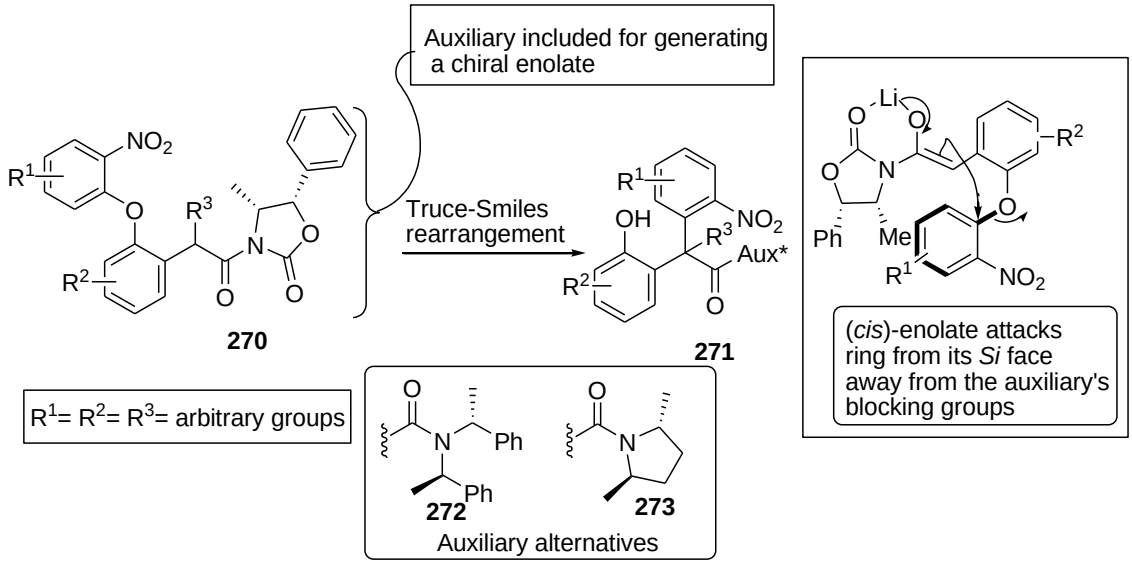


Scheme 78. Chiral oxazolidin-2-one auxiliaries in asymmetric alkylation reactions.

As shown in Scheme 78, the *N*-acyl oxazolidinones (**266**) are able to form enolates (**269**), most commonly with LDA or NaHMDS. Using such strong bases, the enolates are formed entirely in the *Z*-form. The metal counterion is chelated to the oxazolidinone oxygen atom (**269**), making one face of the enolate (the *Re* face), point away from the isopropyl group of the oxazolidinone **264**, and therefore much more available to the electrophile than the *Si* face. The selectivity obtained ranges from good (small electrophiles, such as CH_3I and EtBr) to excellent (for more bulky electrophiles).[191] The auxiliary can be subsequently removed e.g. through hydrolysis.

Even though there is only a single rotatable bond linking oxazolidinones to the substrate, other factors such as chelation or dipole-moment minimization often enhance the production of the preferred conformations in which the oxazolidinone's substituent(s) efficiently shields one of the molecule's diastereotopic faces. As a

consequence of that, certain rotamers possess greater energetic preferences which lead to better stereoselectivities being achieved in different cases (Scheme 78).[189]



Scheme 79. Proposed use of chiral auxiliaries to introduce chirality into the Truce-Smiles rearrangement (left) and a proposed transition-state (right).

The ready availability of these auxiliaries (Figure 17), high diastereoselectivity obtained for their transformations and facile introduction and cleavage of the auxiliary make them popular.[189] The Truce-Smiles precursor, with the incorporated chiral auxiliary (**270**), should therefore give rise to the required stereoselective rearrangement, and give up enantiopure products, presumably via a chelated 5-membered chiral transition-state (Scheme 79). Therefore, by judicious choice of substituted starting materials which incorporate the chiral auxiliary it was hoped it would be possible to prepare asymmetric quaternary centres as shown in Scheme 79.

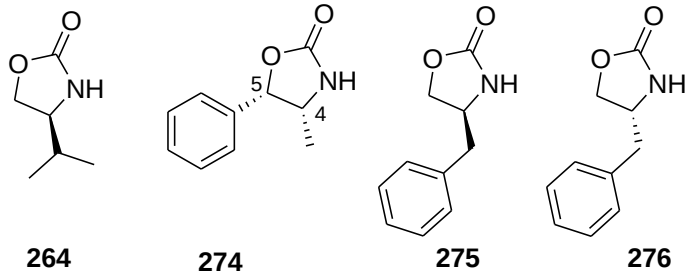


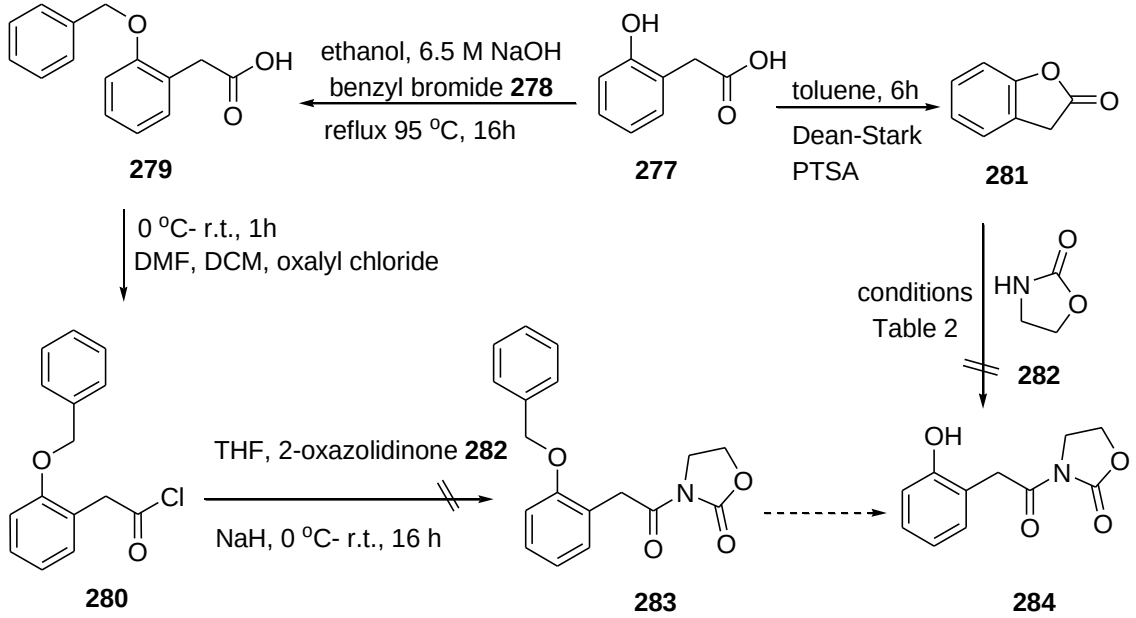
Figure 17: Some of the commercially available oxazolidinone chiral auxiliaries.

2.2.2.1 The Truce-Smiles rearrangement on oxazolidinone-based substrates

Based on the known success of oxazolidinone chiral auxiliaries (Figure 17) in imparting asymmetry in the reactions in which they take part, initial attempts were focused on preparing achiral oxazolidinone-based substrates and to test them (for example, those compounds containing an 2-oxazolidinone **284**, Scheme 80) and see whether they would undergo a Truce-Smiles rearrangement or not, before moving on and explore the chiral enantiopure analogues. Unfortunately, despite attempting both reported[194] and unreported conditions (Table 2) to make the 2-oxazolidinone-based substrates **284** from the reaction between 2-coumaranone (**281**) and 2-oxazolidinone (**282**), no success in preparing them was achieved.

Table 2. Conditions attempted for the synthesis of 2-oxazolidinone based substrates **284** from 2-coumaranone (**281**) in THF.

Auxiliary	Base	Temp	Duration
2-oxazolidinone (1.55 eq.)	NaH (1.5 eq.)	r.t.	5 h
2-oxazolidinone (1.55 eq.)	NaH (1.5 eq.)	60 °C	3 h
2-oxazolidinone (2.0 eq.)	*n*-BuLi (2.1 eq.)	r.t.	16 h



Scheme 80. Failed attempts to make the 2-oxazolidinone based substrate **284**.

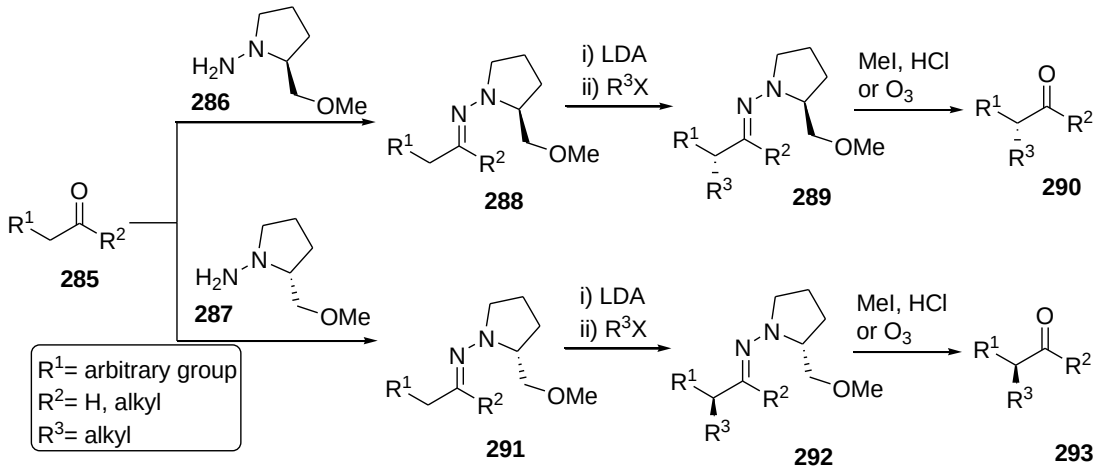
A probable reason for the lack of success here could be due to the fact that either 2-coumaranone (**281**) is not reactive enough as an electrophile, or the deprotonated 2-oxazolidinone is not nucleophilic enough; a proposal which is partly supported by the complete lack of literature detailing a reaction between 2-oxazolidinone (**282**) and lactones in general. Similarly, further support is gleaned from the fact that most reactions of 2-oxazolidinone (**282**) as a nucleophile react with acyl chloride counterparts (e.g. **280**) not cyclic esters.[24,195,196] As such, attempts to make the acid chloride from our precursor (2-hydroxyphenyl acetic acid (**277**)), which is more reactive than the lactone (2-coumaranone (**281**)), were performed, Scheme 80. For such a route it was necessary to protect the phenolic hydroxyl group to prevent it from cyclising onto the soon to be formed acid chloride and forming 2-coumaranone (**281**) on treatment with base, therefore the phenolic hydroxyl group was protected as its benzyl ether using benzyl bromide (**278**)[197] in the hope that it could be deprotected (to the required substrate **284**) at a later date ready to perform the Truce-Smiles rearrangement, Scheme 80.

Despite, a number of reported protocols for such a transformation, the reaction failed to produce the protected 2-oxazolidione-based Truce-Smiles substrate **283** in our hands.[24,195,196]

2.2.2.2 RAMP or SAMP as chiral auxiliaries

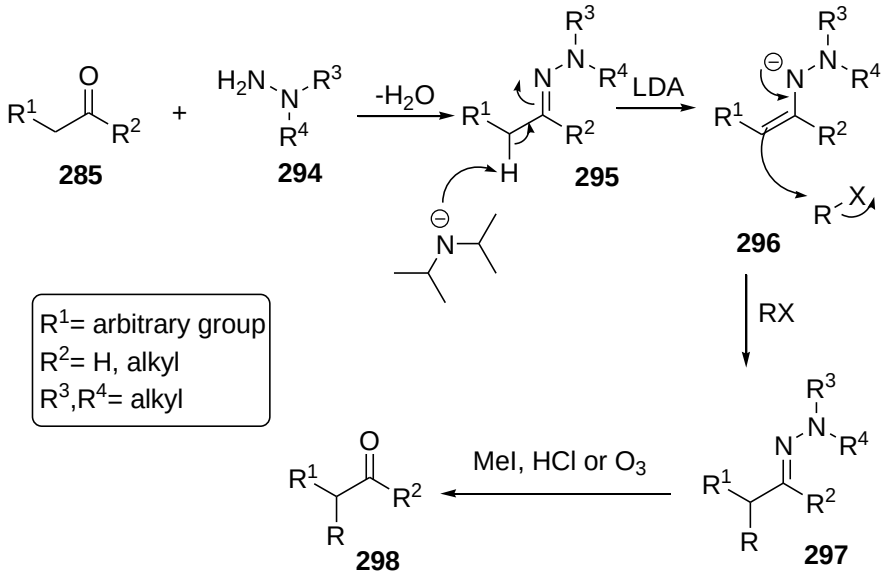
The Enders SAMP/RAMP hydrazone alkylation reaction is one of the most common methods for the asymmetric alkylation of aldehydes and ketones, in which an asymmetric carbon-carbon bond formation reaction is facilitated by pyrrolidine chiral auxiliaries. This method was pioneered by E. J. Corey[198] and D. Enders in 1976, and was further developed by D. Enders and his group.[189]

The method is usually a three-step sequence; the first step is to form a hydrazone between (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP **286**) or (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP **287**) (both are commercially available) and a ketone or aldehyde, Scheme 81. Afterwards, the hydrazone (**288** or **291**) is deprotonated by lithium diisopropylamide (LDA) to form an aza-enolate, which reacts with alkyl halides or other suitable electrophiles to give alkylated hydrazone species with the simultaneous generation of a new chiral centre. Finally, the alkylated ketone or aldehyde can be regenerated by ozonolysis or hydrolysis, Scheme 81.[199]



Scheme 81. The asymmetric alkylation of aldehydes and ketones.

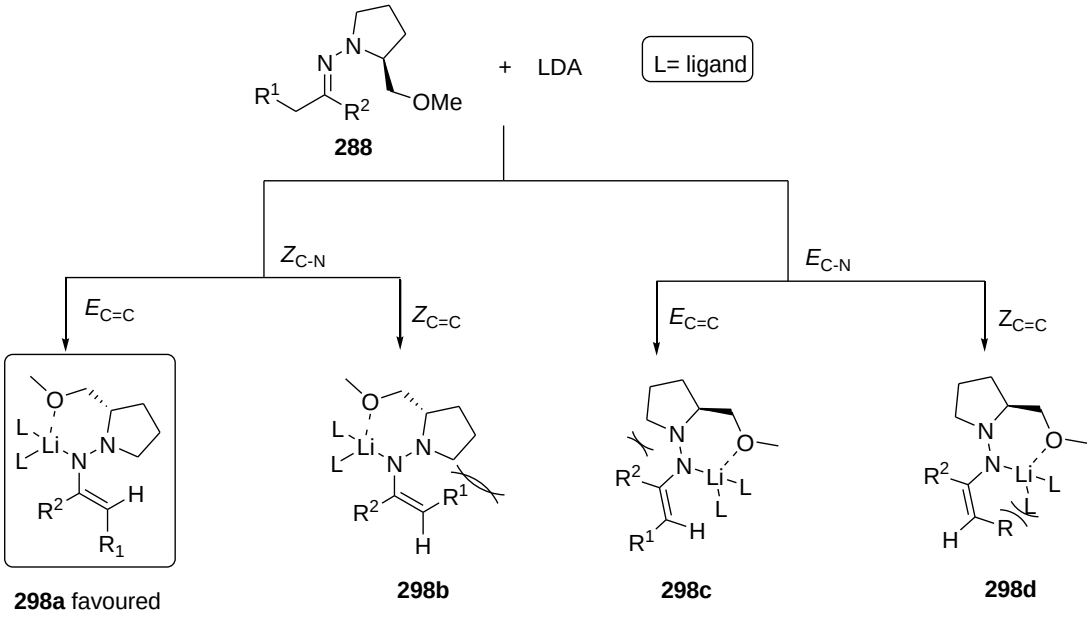
The first Enders SAMP/RAMP hydrazone alkylation began with the synthesis of the hydrazone from a *N*,*N*-dialkylhydrazine and a ketone or aldehyde, Scheme 82.[200] The hydrazone was deprotonated on the α-carbon by a strong base, such as LDA, leading to the formation of a resonance stabilized anion - an aza-enolate.



Scheme 82. The first Enders SAMP/RAMP hydrazone alkylation.

After deprotonation, the aza-enolate chelates with the lithium cation chelating both the nitrogen and oxygen, Scheme 83. There are two possible options for lithium chelation. One is that lithium is antiperiplanar to the C=C bond, leading to the conformation of $Z_{C\text{-}N}$; the other one is that lithium and the C=C bond are on the same side of the C-N bond, leading to the $E_{C\text{-}N}$ conformer. There are also two available orientations for the chelating nitrogen and R^2 group, being either $E_{C=C}$ or $Z_{C=C}$. Accordingly, the possible four different aza-enolate geometries corresponding to rotation around the C=C and C–N

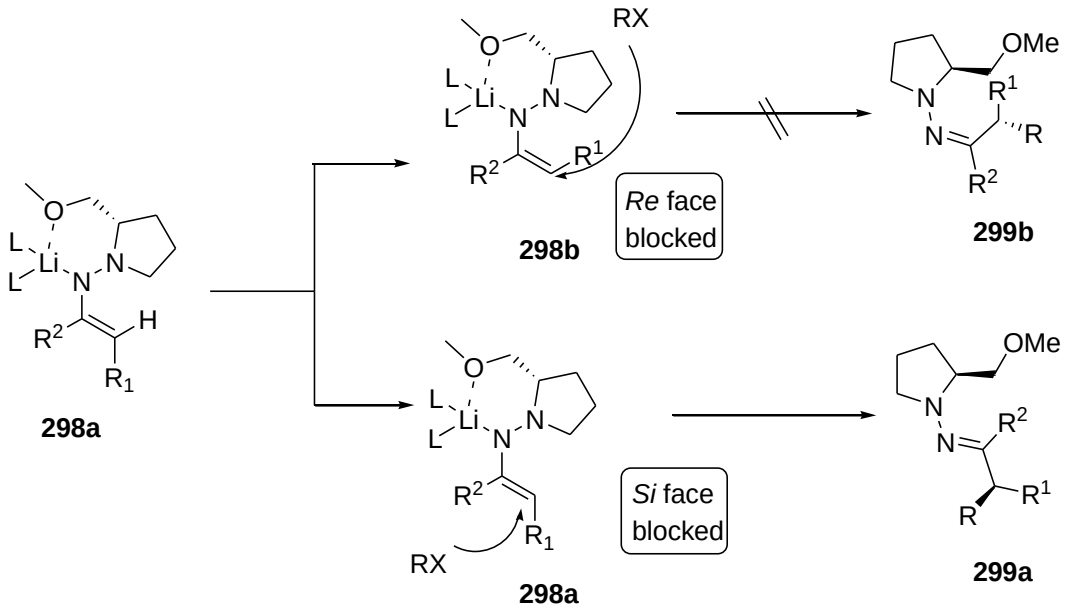
bonds are **298a**, **298b**, **298c** and **298d** for the Enders' SAMP/RAMP hydrazone alkylation reaction, Scheme 83.



Scheme 83. The possible conformations of the aza-enolate chelates.

In both cyclic and acyclic systems, trapping experiments,[201] x-ray analysis[202] and spectroscopic investigations and calculations[203,204] have showed that one specific stereoisomer of the aza-enolate is favoured over the other three possible candidates. Therefore, although four isomers are possible for the aza-enolate, only one (**298a** or $E_{CC}Z_{CN}$), with the stereochemistry of its C=C double bonds being *E* and that of its C-N bond being *Z* stereochemistry, is dominant ($E_{C=C}$ Z_{C-N}) for both cyclic and acyclic ketones.[202]

The favoured aza-enolate **298a** is the dominant intermediate for the subsequent alkylation reaction. There are two possible faces for accessing any electrophile to react with, Scheme 84. The steric interaction between the pyrrolidine ring and the electrophilic reagent hinders the attack of the electrophile from the top face. On the contrary, when the electrophile attacks from the bottom face, such unfavourable interaction does not exist. Therefore, the electrophilic attack proceeds from the sterically more accessible face (**298a**).[205]



Scheme 84. Diastereoselective alkylation of a SAMP hydrazone.

Furthermore, chelation of the lithium cation with the methoxy group is one of the most important features of the transition state for Enders' hydrazone alkylation reaction. It is necessary to have this chelation effect to achieve high stereoselectivity. The development and modification of Enders' hydrazone alkylation reaction mainly focus on the addition of more steric hindrance on the pyrrolidine rings of both SAMP and RAMP, while preserving the methoxy group for lithium chelation. The most famous four variants of SAMP and RAMP are SADP (**300**), SAEP (**301**), SAPP (**302**) and RAMBO (**303**), Figure 18.[206,207]

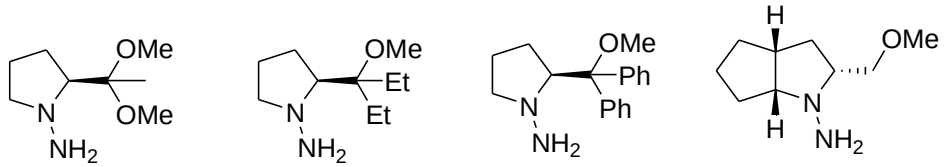
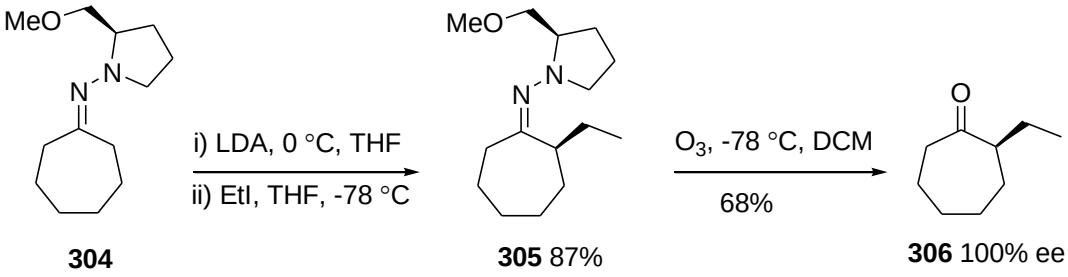


Figure 18. Some variants of RAMP and SAMP.

Hydrazones are usually very stable towards hydrolysis or other solvolysis conditions, suggesting that they require rather vigorous reaction conditions to be removed from the products. So far, three methods for cleaving the hydrazones have been reported.[208] Oxidative cleavage is the most frequently used method due to the high yields obtained, but most oxidants may also react with olefins and other

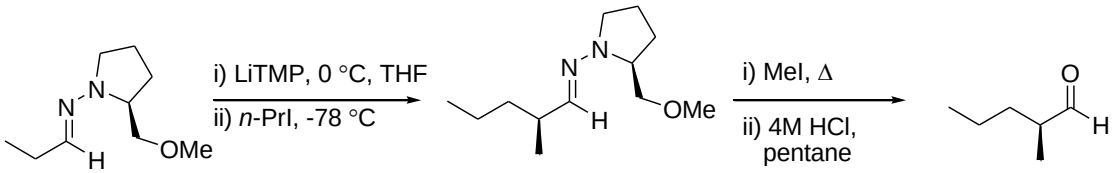
oxidisable functional groups present. The oxidants most used are ozone (e.g. Scheme 85, **305**→ **306**), sodium periodate, mCPBA, and peracetic acid.



304 **305** 87% **306** 100% ee

Scheme 85. Ozonolysis of hydrazone **305**.

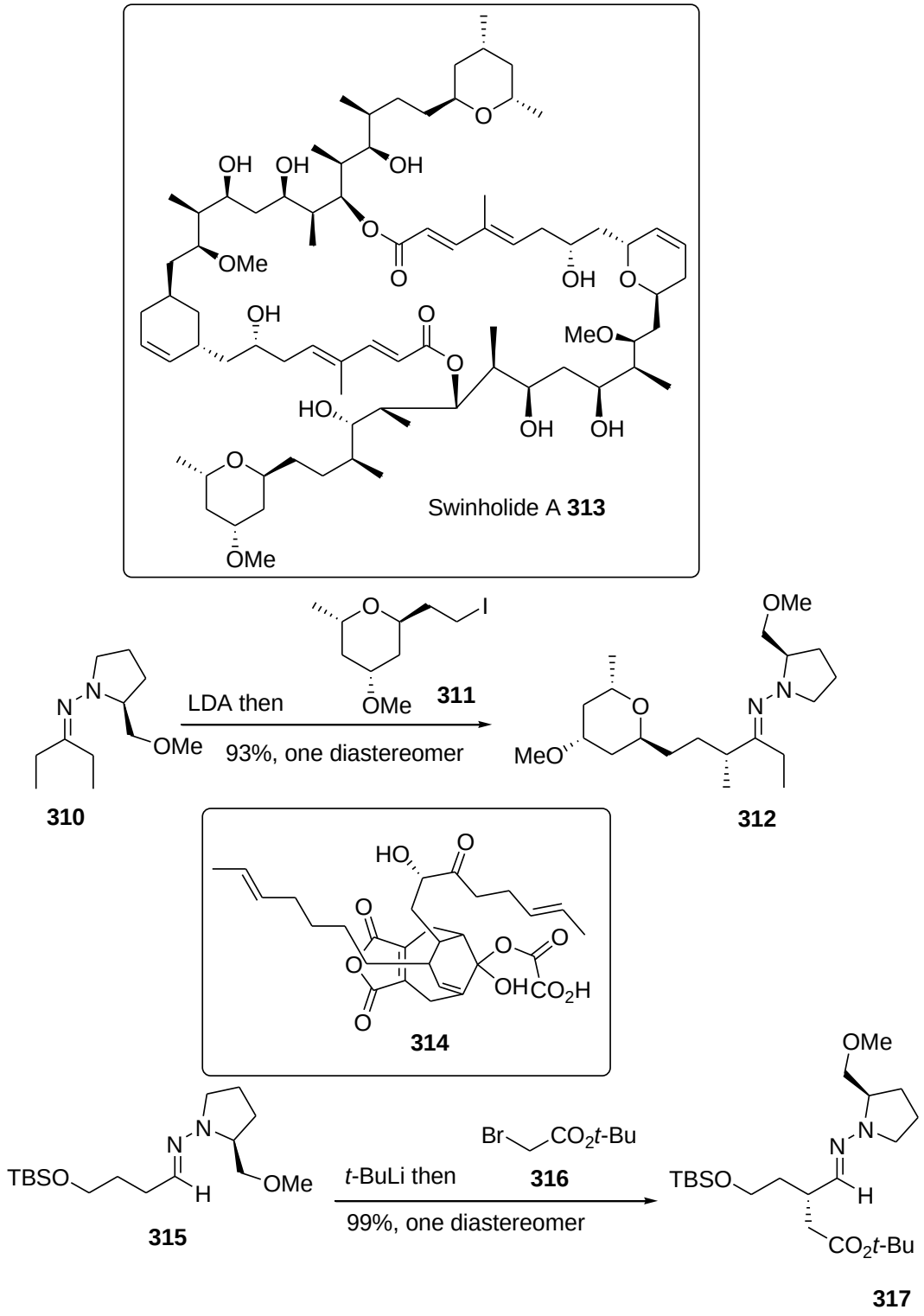
Although hydrolytic cleavage is the mildest method, the low yields obtained for relatively complicated substrates is a major problem. The reagents that are frequently used are methyl iodide with aqueous hydrogen chloride (Scheme 86, **308**→ **309**),[209] cupric salts, and other Lewis acids.[210]



307 **308** 97:3 dr, 94% de **309** 80%, 94% ee

Scheme 86. Hydrolysis of hydrazone **308**.

Interestingly, Nicolaou attempted successfully the total syntheses of swinholide A (**313**) (an antifungal and cytotoxic marine isolate)[211] and CP-225,917 (**314**) (a potent inhibitor of squalene synthase and farnesyl transferase)[212] by utilising this alkylation methodology on both ketone- and aldehyde-derived RAMP hydrazones, as illustrated in Scheme 87.



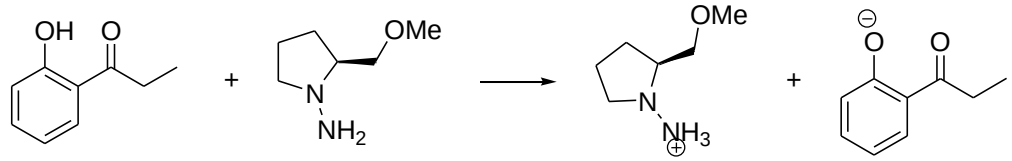
Scheme 87. RAMP-hydrazone alkylations in natural product synthesis.

Furthermore, the mild conditions used in the construction and removal of the hydrazones have made them an attractive protocol in the synthesis of synthetic intermediates for medicinally interesting natural products and other related organic compounds, such as the natural products (-)-C_{10}-desmethyl arteannuin B, a structural analogue of the antimalarial, artemisinin,[213] the polypropionate metabolite (-)-

denticulatin A and B isolated from *Siphonaria denticulata*,[214] the potent inhibitor of sterol synthesis, zaragozic acid A,[215] and the effective anticancer drugs epothilones A and B.[216]

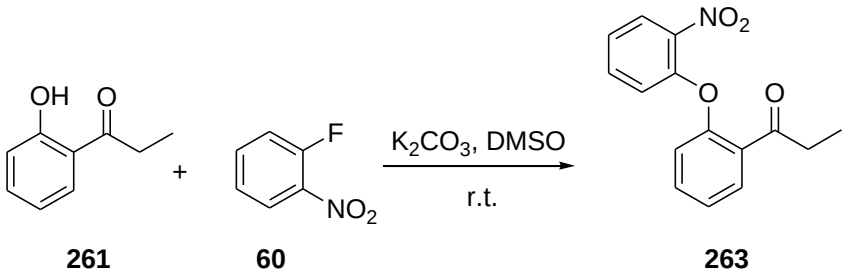
Such precedent inspired the use of RAMP or SAMP to induce chirality into our Truce-Smiles rearrangement substrates. In order to apply such Enders' auxiliaries to the rearrangement, it was decided to obtain ketone-based substrates, and react them (for example 2-hydroxypropiophenone (**261**)) with RAMP (**286**) or SAMP (**287**).

Unfortunately, despite the wide range of literature precedent no reaction occurred between **261** and **286**, presumably because of salt formation occurring between the NH_2 of RAMP (**286**) and the phenolic OH from **261**, Scheme 88.



Scheme 88. Salt formation occurring between RAMP (**286**) and 2-hydroxyacetophenone (**261**).

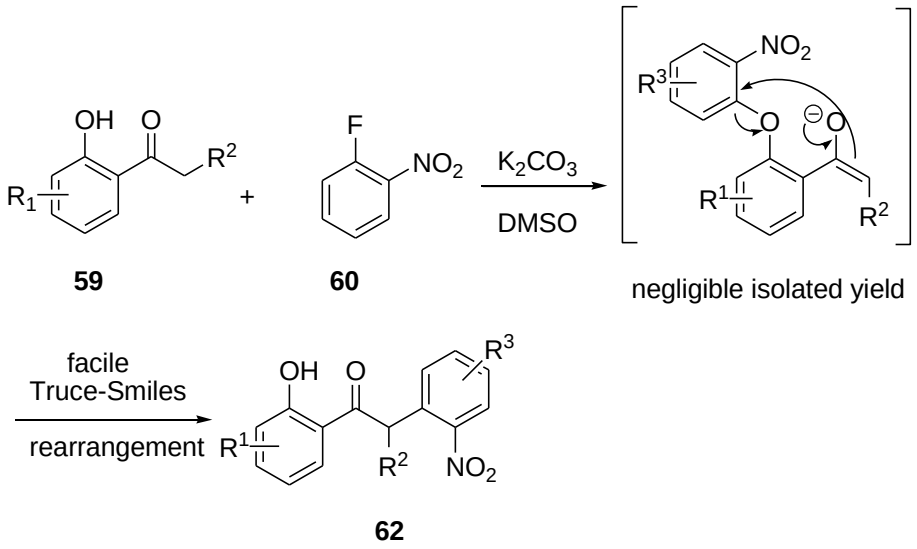
Based on this undesired reaction, it was proposed to mask the phenolic hydroxyl group using the migrating aryl group (for example (1-fluoro-2-nitrobenzene (**60**)) rather than to resort to a protection/deprotection strategy. It is shown that extremely mild conditions can be used to prepare the similar substrates directly from commercially available material, in which the reactions are performed using equimolar amounts of both the ketone **261** and 1-fluoro-2-nitrobenzene (**60**) along with potassium carbonate (2.5 equiv) in dimethyl sulfoxide at room temperature, Scheme 89.[31]



Scheme 89. Masking the phenolic hydroxyl group using the migrating aryl group.

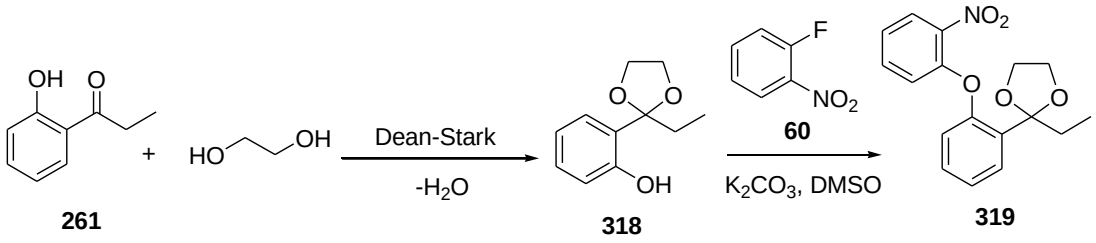
However, as demonstrated by Snape, while revisiting the Truce-Smiles rearrangement, it was observed that on such exact substrates the isolated yield of the arylated ketone

intermediate was negligible because of the faster Truce-Smiles rearrangement, Scheme 90.[31]



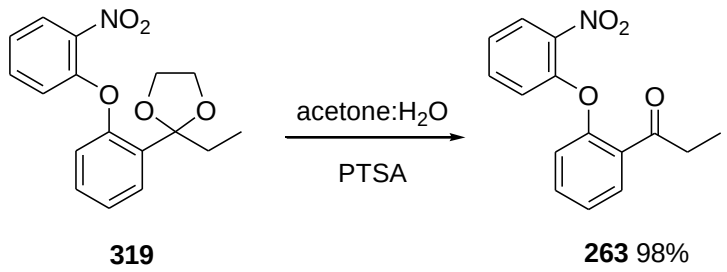
Scheme 90. Facile rearrangement of **59** to the *C*-arylated product **62**.

Therefore, in order to try and isolate the *O*-arylated product **263**, it was better to protect the ketone functional group first. This can be achieved by the reaction of ketone **261** with ethylene glycol, under Dean-Stark conditions, to prepare an acetal **318**, Scheme 91.



Scheme 91. Protection of the ketone functional group by formation of an acetal.

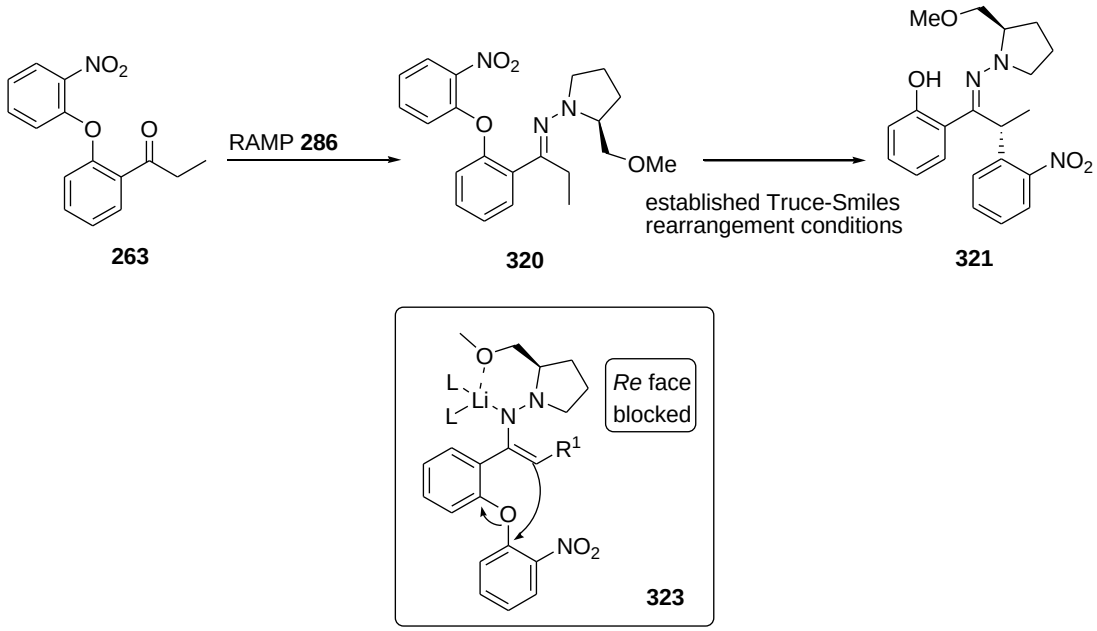
Following this scheme, acetal **318** was successfully prepared, and reacted with **60** to offer the *O*-arylated acetal **319** in 85% yield, Scheme 91. Following a successful synthesis of **319**, the next step was the hydrolysis of the acetal in a mixture of acetone:water, containing *para*-toluenesulfonic acid (PTSA) as catalyst, to regenerate the required carbonyl **263** in quantitative yield, Scheme 92.



319 **263** 98%

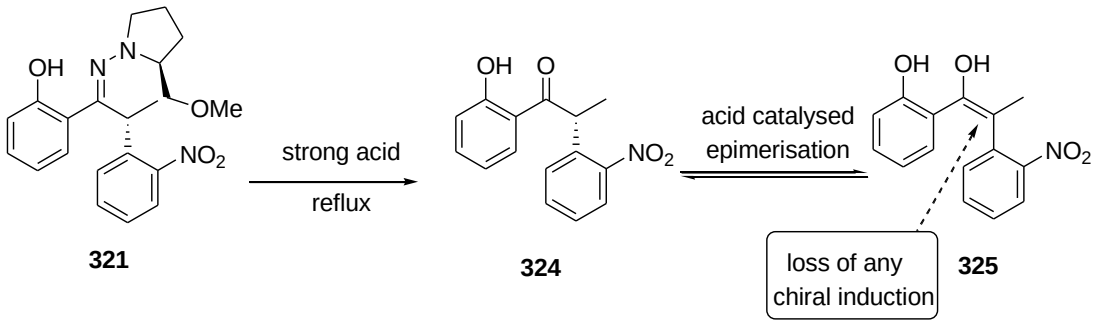
Scheme 92. Hydrolysis of acetal **319**.

Having now prepared the required substrate (**263**), the synthesis of hydrazone **320** could be attempted between **263** and both RAMP (**286**) and SAMP (**287**), after which the prepared hydrazone **320** could undergo the attempted Truce-Smiles rearrangement under the established reaction conditions, in the hope of generating the diastereomerically enriched product **321**, Scheme 93.



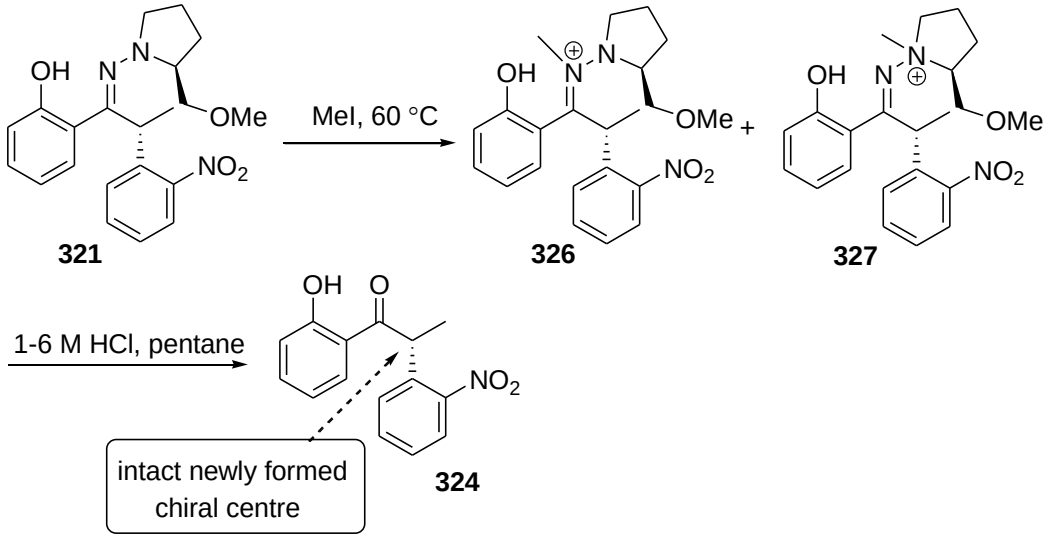
Scheme 93. Proposed rationale for generating diastereomerically enriched products.

The final step would then be the hydrolysis of the diastereomeric product **321** to give the enantiopure product **324** (Scheme 94). Hydrazones are a particular type of imine and therefore can be hydrolysed in strong acid at reflux. Unfortunately, in this case, such vigorous conditions may cause racemisation at the carefully crafted chiral centre due to acid catalysed keto-enol tautomerism (epimerisation, see compound **325**) which would lead to a loss of chiral induction (Scheme 94). As such other means would be needed which are applicable to hydrolyse the hydrazone under mild conditions, e.g. quaternisation followed by hydrolysis (Scheme 95) or by applying an oxidation/ozonolysis protocol, Scheme 96.

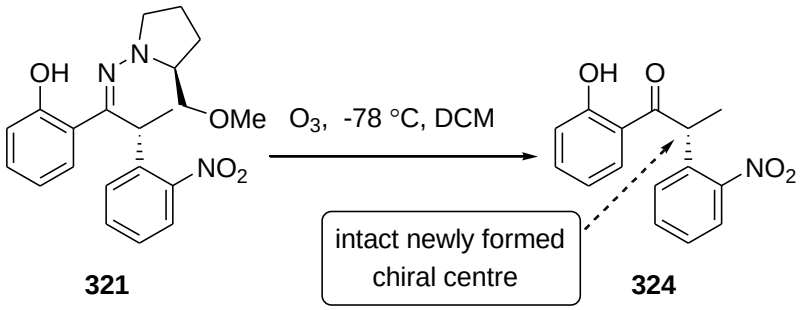


Scheme 94. Racemisation under vigorous reaction conditions.

In order to perform such quaternisation and hydrolysis, the hydrazine **321** would be subjected to methyl iodide in order to alkylate one of the nitrogens of the auxilary. These ionic species (**326**, **327**) are more readily hydrolysed under less aggressive acidic conditions and this hopefully without the concomitant racemisation, to offer the final enantiopure product **324**, Scheme 95.



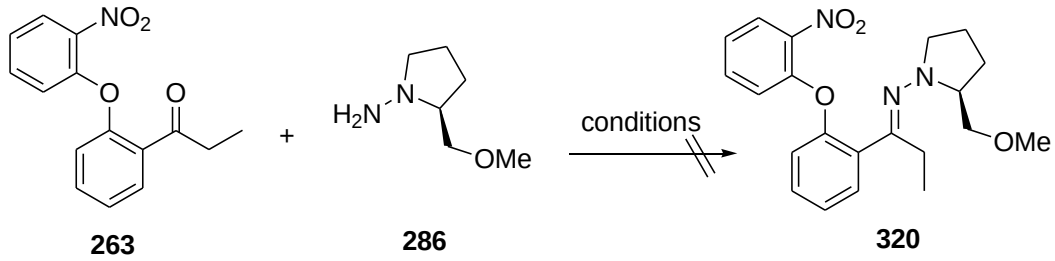
Scheme 95. Quaternisation and hydrolysis of hydrazones.



Scheme 96. Ozonolysis of **321** for hydrazone removal.

Additionally, oxidation/ozonolysis may also be applicable by cleaving the double bond of the hydrazone **321** with ozone to generate the asymmetric product **324**, Scheme 96.

Unfortunately, when attempting the strategy outlined in Scheme 93, the prepared diaryl ketone-based substrates **263** did not react with RAMP (**286**) under all conditions attempted, Scheme 97.



263 **286** **320**

Reaction conditions: diaryl ketone **263** (1 eq.), RAMP (**286**) (1 eq.), toluene (0.1 M), Dean-Stark; or diaryl ketone **263** (1 eq.), RAMP (**286**) (1.1 eq.), toluene-4Å molecular sieves (0.1 M), Dean-Stark.

Scheme 97. Attempts to make hydrazone **320**.

Nevertheless, despite this disappointment, and the fact that more success was being observed in a parallel strategy (Figure 19, page 77), the RAMP/SAMP strategy was temporarily abandoned in the hope of developing the rearrangement with amide substrates.

2.2.2.3 The Truce-Smiles rearrangement on amide based-substrates

Initial attempts focused on preparing achiral derivatives because the chiral version is costly and it was necessary to establish the reaction conditions rapidly, yet affordably. Therefore, it was decided to prepare and test a range of amide based-substrates **328** (Figure 19, Box 1) to acertain their suitability in the Truce-Smiles rearrangement, and which were prepared because, to our knowledge, these kind of substrates have not been studied as precursors in the Truce-Smiles rearrangement before. Moreover, such amide substrates can be rendered chiral by the judicious choice of additional substituents (for a detailed explanation on the C2-symmetric auxiliaries attempted see section 2.2.2.4), Figure 19 Box 2.

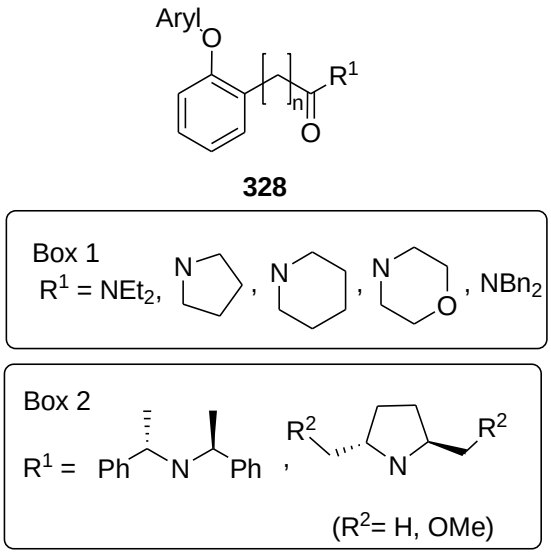
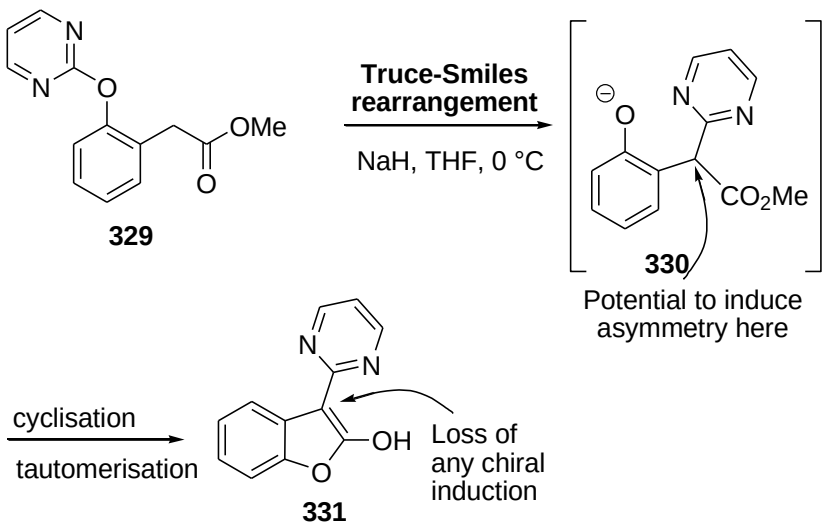


Figure 19. Attempted Truce-Smiles rearrangement substrates (achiral, Box 1); Box 2 shows three commercially available chiral amines with which to potentially make the reaction asymmetric.

Work by Erickson and McKennon had demonstrated that the analogous ester substrates had been seen to undergo a Truce-Smiles rearrangement, during their work on the synthesis of some anti-fungal compounds,[217] and that under typical rearrangement conditions (NaH, THF, T≥0 °C) such esters undergo the rearrangement through an intramolecular nucleophilic attack of the ester enolate onto the electrophilic proximal diarylether to generate an α–aryl compound, Scheme 98. However, unfortunately, such Truce-Smiles products spontaneously cyclise and tautomerise to form substituted benzofuran derivatives, which in doing so, racemises any chiral induction that may have been incorporated through other means (see enol form of **331**, Scheme 98).

Unfortunately, since ester substrates (i.e. **329**, Scheme 98) readily tautomerise they cannot induce chirality so easily. Moreover, due to facile *C-O* bond rotation, C2-symmetric auxiliaries cannot be used to develop a simple asymmetric variant.

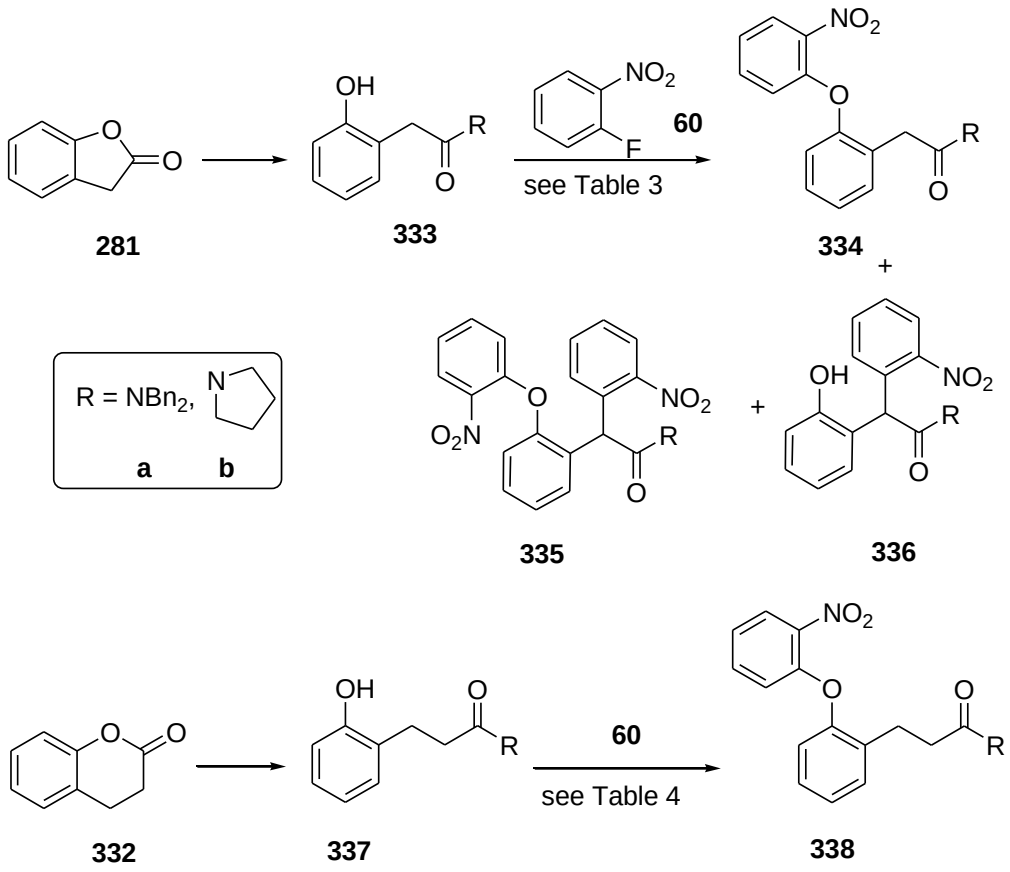


Scheme 98. Loss of any induced chirality in **331**.

However, C2-symmetrical chiral auxiliaries can render amide enolates (Figure 19, Box 2) enantiopure, compounds which maintain their selectivity due to the associated restricted *C-N* bond rotation.[218–220] Moreover, since amide substrates are less vulnerable to cyclisation, the loss of any induced stereochemistry through tautomerisation should be minimal.

The amide substrates (acetamide **333a** and propanamide **337a**, Scheme 99) were prepared from the ring opening of 2-coumaranone (**281**) or dihydrocoumarin (**332**) by nucleophilic attack of the amine (dibenzylamine or pyrrolidine) to prepare the corresponding amides; the products which theoretically could also be rendered enantiomerically pure with chiral amines (Figure 19, Box 2), ready for an asymmetric Truce-Smiles rearrangement to be attempted, if suitable conditions for an achiral rearrangement could be identified.

At room temperature in dimethyl sulfoxide for 18.5 hours the diarylethers (**334a** and **338a**) were obtained, compounds that did not rearrange further, despite similar conditions being well established for such a rearrangement.[2,31] It was proposed that the bulkiness of the dibenzylamine moieties was preventing any rearrangement taking place through a steric clash with the newly incorporated phenyl ring (see compound **334a**, Figure 20).



Reaction conditions: lactone **281** or **332** (1 eq.), amine (1 eq.), toluene (0.1M), reflux, 4-6 h; See Table 3 and 4 for the second step.

Scheme 99. Preparation of amide substrates and their subsequent rearrangement.

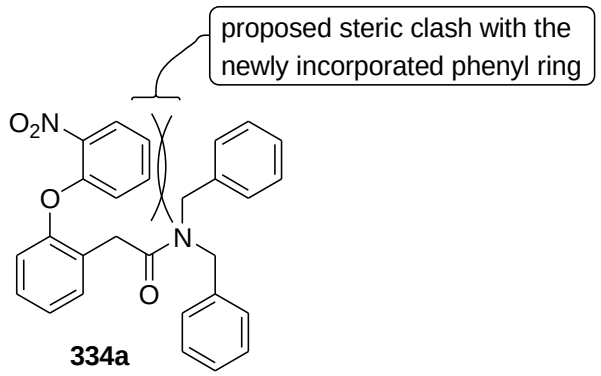


Figure 20. Proposed clash between the phenyl rings in the diarylether of an acetamide based substrate preventing Truce-Smiles rearrangement.

As such, a less bulky amide moiety, such as pyrrolidine, was sought to test if this was the case. However, after preparation of the pyrrolidyl-amides based substrates (**333b** and **337b**) by the same method (Scheme 99), again there was no rearrangement observed under the same reaction conditions for either substrates.

Despite this, partial success in the reaction was achieved when it was found that leaving the reaction for longer and at higher temperatures resulted in rearranged diarylethers (**335**) and rearranged product (**336**) along with the corresponding diarylethers (**334**), Scheme 99 (see Table 3 for the results and conditions attempted).

Table 3. Yield and conditions for making diarylethers (**334**), rearranged diarylethers (**335**), and rearranged product (**336**) of acetamide-based substrates in DMSO with K_2CO_3.

Entry	FNB (**60**) eq.[a]	Temp. (°C)	Time (h)	(**334a**) %[b]	(**335a**) %	(**336a**) %
1	0.5	r.t.[c]	19	57	0	0
2	0.5	60	8	12	27	8
3	1	r.t.	19	37	5	6
4	1	60	2	complex mixture		
5	1	r.t.-60	5	58	14	17
6	1	r.t.-60	7	27	72	0
7	1	r.t.	68	58	40	0
8	2	r.t.	21	98	0	0
9	2	60	20	complex mixture		
				(**334b**) %	(**335b**) %	(**336b**) %
10	1	r.t.	5	90	0	0
11	1	60	5	43	19	20

[a] FNB= 1-fluoro-2-nitrobenzene (**60**), [b] isolated yields based on the stoichiometry of FNB, [c] r.t.= room temperature.

As shown in Table 3, it was found that increasing the temperature from room temperature to 60 °C (compare entries 3 with 5 or 6) allowed the rearranged product to be formed, however when increasing the number of equivalents of 1-fluoro-2-nitrobenzene (**60**) to two equivalents, rather than the reaction going to completion, as expected, it stopped at the diarylether stage (entry 8). Therefore, it was proposed, rather impractically, that reducing the equivalents of **60** to 0.5 eq. may increase the ratio of rearranged products, through some unknown effects. Unfortunately, in the event at room temperature (entries 1, 3 and 8), this hypothesis was found not to be true.

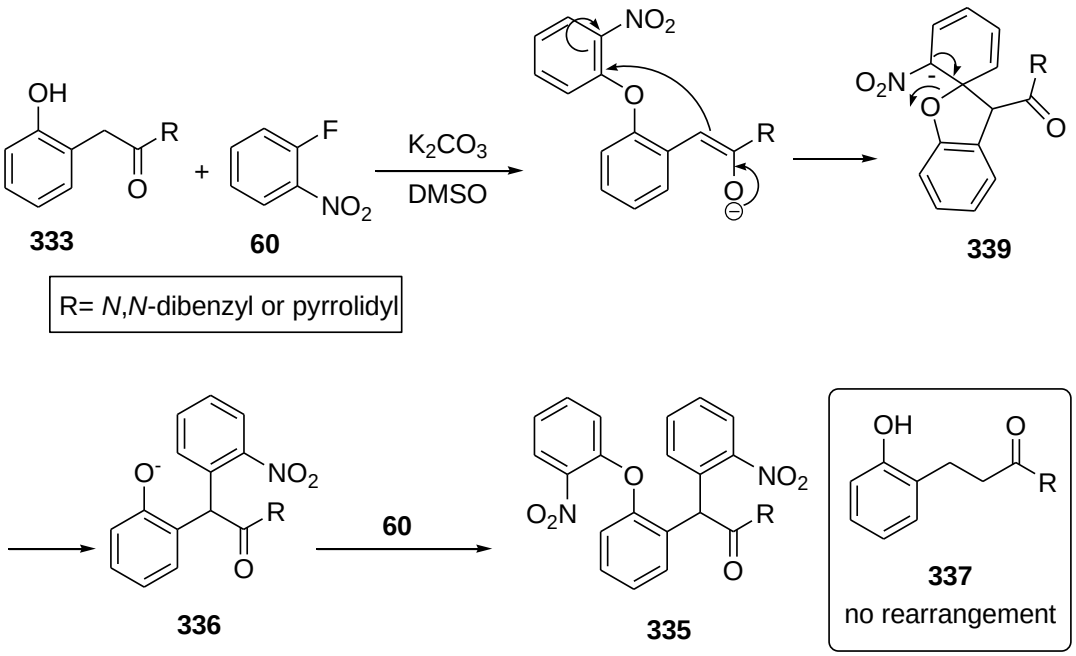
Moving on to study the homologous substrates **337**, The extended chain between the aryl ring and amide moiety in the propanamide-based diarylethers are longer by one extra methylene unit, a feature which was incorporated to prevent the proposed steric clash with the newly incorporated phenyl ring (as shown previously in Figure 20). In these substrates a 6-membered transition state should be adopted which appears be more common for the rearrangement.

In that regard, there is evidence for both a 6-membered transition state for this type of rearrangement[23,24,196] as well as for 5-membered transition states,[22,25,27,196,221] both of which proceed via a spirocyclic-intermediate, whereby the spirocyclic Meisenheimer complex **339** (Scheme 100) is stabilised by the presence of the electron withdrawing nitro group at the *ortho* position.[222,223] However, despite such precedent, only the acetamide-based substrates **333** gave any rearranged products, albeit in modest to good yields, whereas, despite testing a range of known conditions for similar rearrangements, the propanamide-based substrates **337** don't rearrange and stop at the diarylether stage in quantitative yields (see Table 4 for results).[23,24,196]

Table 4. Yield and conditions for making diarylethers of propanamide-based substrates (**337**) using K_2CO_3 in DMSO.

FNB (**60**) eq.[a]	Temp. (°C)	Time (h)[b]	**338a** %[c]
1	r.t.[d]	6	90
1	60	2	98
1	60	3	100
			338b %
1	r.t.	5	92

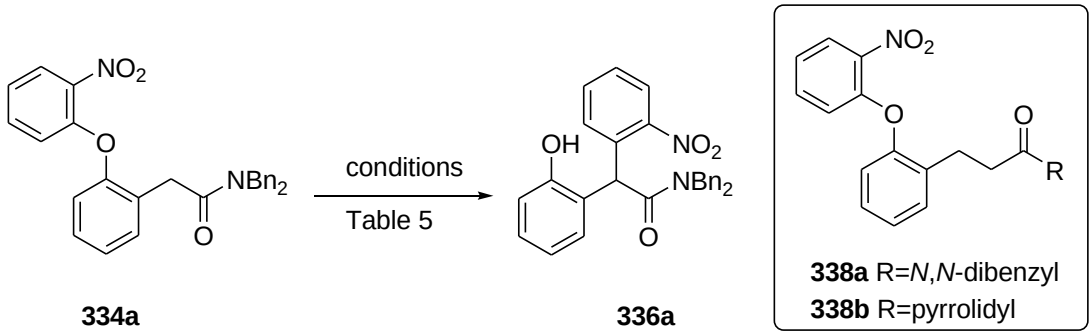
[a] FNB= 1-fluoro-2-nitrobenzene (**60**); [b] when these reactions were left for 3 days only **338** was observed; [c] isolated yields; [d] r.t.= room temperature.



Scheme 100. Five-membered transition state for the Truce-Smiles rearrangement of acetamide-based substrates **333**.

In order to find the best conditions for the Truce-Smiles rearrangement to occur, and before the chiral derivatives could be tested, a range of alternative conditions were studied using different solvents, bases, and temperatures, as shown in Table 5. Here it was deemed prudent to study the intramolecular rearrangement process alone (**334a** to **336a**, Scheme 101) rather than the two step process, since that would simplify the analysis of the crude reaction products as well as allowing efforts to concentrate on the complicated rearrangement step as opposed to the simple and established intramolecular S_NAr step.

In this regard, diarylether **334a** was prepared and isolated from its corresponding amide and fluoro-2-nitrobenzene (**60**) and its rearrangement studied under a variety of conditions, Table 5. With regards to the diarylether of the analogous propanamide substrates (i.e. **338**), trying to force the reaction conditions to rearrange the pure, isolated diarylethers (**338b** and **338a**), met with failure, despite varying the solvent (DMSO, DMF, THF and DCM), base (K_2CO_3, CsOH, NaH, NaOMe) and temperature (r.t.→100 °C) for a reaction time of 6 hours; in all cases and conditions tested, this diarylether did not rearrange and only ever gave the unreacted starting materials.



334a **336a**

Scheme 10. The attempted rearrangement of diarylether of acetamide-based substrate **334a**.

Table 5. The conditions tested for the attempted rearrangement of diarylether of acetamide-based substrate **334a**.

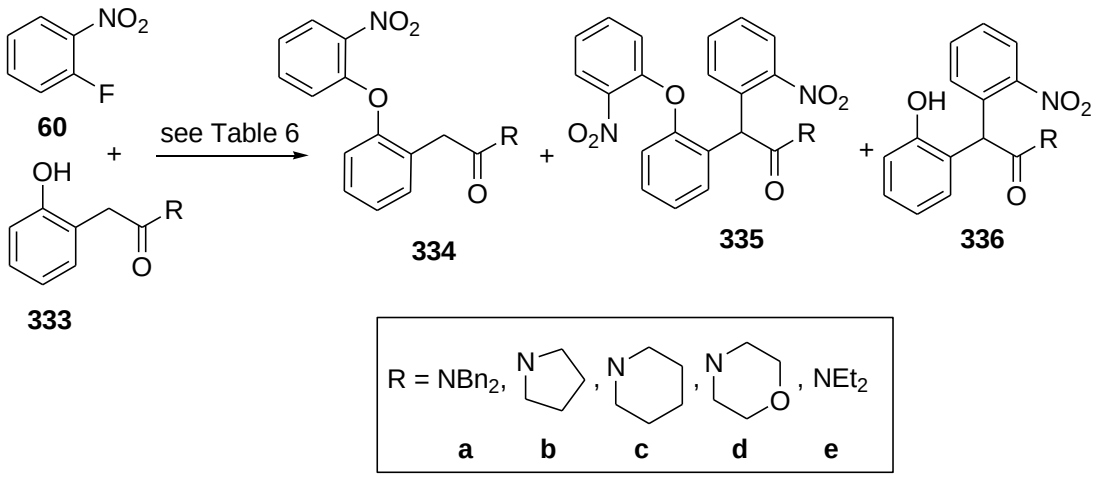
Solvent	Base (1.5 eq.)	Room temp	60 °C	100 °C
DMSO	K_2CO_3	N.R[a]	C.M[c]	C.M
	NaH	trace[b]	C.M	C.M
	NaOMe	N.R	trace	C.M
	CsOH	N.R	trace	C.M
DCM	K_2CO_3	N.R	N.R	N.R
	K_2CO_3 (+TBAI)	N.R	N.A[d]	N.A
	NaOMe	N.R	N.R	N.R
	CsOH	trace	N.R	N.R
	CsOH (+TBAI)	~19 %	N.A	N.A
THF	K_2CO_3	N.R	N.R	N.R
	NaH	N.R	N.R	N.R
	NaOMe	N.R	N.R	N.R
	CsOH	N.R	N.R	N.R
DMF	K_2CO_3	N.R	N.R	N.R
	NaH	N.R	N.R	N.R
	NaOMe	trace	N.R	N.R

[a] N.R= no reaction; [b] by NMR; [c] C.M= complex mixture; [d] N.A= not attempted.

As can be seen from Table 5, all reactions in DCM, THF and DMF failed to give any rearranged products, except when CsOH/DCM or DMF/NaOMe were used, and in those cases, only trace amounts of product were observed by crude NMR. However, when explored further, the reaction in DCM with cesium hydroxide monohydrate as base, was

partially optimised and shown capable of supporting the rearrangement of diarylether **334a**, but only in the presence of a phase transfer catalyst (TBAI), which presumably transfers the inorganic base into the organic reaction media. Conversely, complex mixtures are often observed in DMSO with this intramolecular rearrangement, especially at elevated temperatures; nevertheless, product was observed with NaH, NaOMe and CsOH as base. This is contradictory to the intermolecular case (Scheme 72) where clean rearrangement occurs in DMSO.

Having attempted to optimise the rearrangement and observing only a poor relationship between the conditions used, and the success of the rearrangement, it was decided to push forward with the previously established conditions (DMSO, K_2CO_3) and pursue the reaction further. Moreover, during this optimisation stage, it was found (Table 3) that the ratio of products obtained was dependent on the amide used. Therefore, attention was turned to acetamide-based substrates (**333**, Scheme 103), and a small study was embarked upon to see what effects on the rearrangement ratios were seen with amides prepared from a range of different amines, Scheme 102 and Table 6. For the synthesis of amides **333a-e**, see the chemistry outlined in Scheme 99.



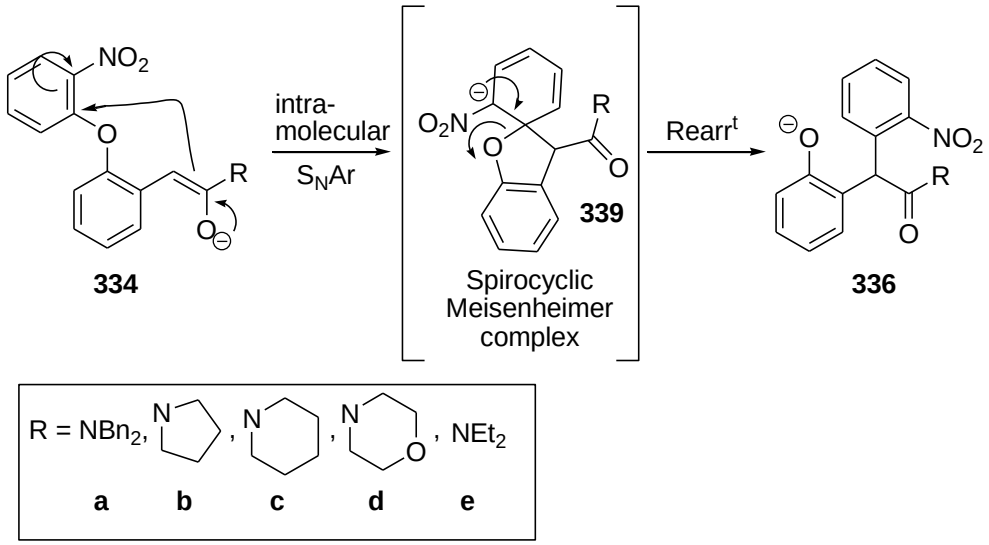
Scheme 102. Truce-Smiles rearrangement with acetamide substrates (**333a-e**[218]). See Table 6 for the reaction conditions.

Table 6. Reaction of acetamide substrates (**333**) with **60**.[a]

Entry	Rearrangement precursor	Product	Yield (%)[b]
1	**333a**	**334a**	40
		335a	23
		336a	37
2	**333b**	**334b**	61
		335b	0
		336b	33
3	**333c**	**334c**	54
		335c	24
		336c	21
4	**333d**	**334d**	45
		335d	6
		336d	45
5	**333e**	**334e**	68
		335e	21
		336e	10

[a] *Reaction conditions*: **60** (1.05 eq.), **333** (1.0 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1M), 60 °C, 24 h. [b] Isolated yields based on the stoichiometry of FNB (**60**).

As can be seen from Table 6, the diarylether (**334**) is the major isolated product in all cases. Since the α-protons of the amide are also benzylic they should be acidic enough to be readily abstracted to form the desired amide enolate with K_2CO_3, prior to its intramolecular attack onto the proximal diarylether, formed *in situ*. In the event, the rearrangement appears to occur via a five-membered cyclic intermediate **339**, Scheme 103, and the desired rearranged diarylether (**335**) and rearranged only (**336**) products are also produced in modest yields.



Scheme 103. Proposed mechanism for the successful rearrangement via a five-membered transition state and intermediate.

Despite consuming all starting material (**333**) in these reactions, a mixture of the three possible products was usually formed (Table 6) with only 1.05 eq. of **60**. As must be the case here, diarylether **334** rearranges intramolecularly to **336** faster than **60** reacts intermolecularly with **333**. As such, **336** and **333** exist together during the reaction; reaction of **333** ultimately giving **334** and/or **336**, and reaction of **336** giving **335**. It was also demonstrated that isolated diarylethers (i.e. **334**), can rearrange cleanly to **336** under the standard rearrangement conditions (K_2CO_3, DMSO) in good yield (50% isolated yield, 100% based on recovered starting material). Additionally, attempts at reaction optimisation show that when the reaction is performed for 24 hours, the rearrangement (**334** to **336**) proceeds in other solvents (DCM, DMF, PhMe and THF), and with alternative bases (CsOH, NaH, NaOMe) as well, although such reactions were only studied by crude NMR, unlike the reaction/rearrangement of **333** to **334**/**335**/**336** which only works in polar aprotic solvents such as DMSO and DMF; the x-ray crystal structure of **336a** can be seen in Figure 21.

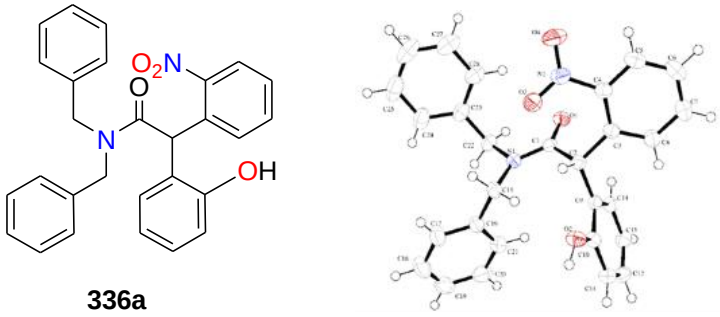


Figure 21. X-ray crystal structure of **336a** (see appendix).[224]

In order to facilitate the future development of this reaction as an asymmetric variant, attempts were made to force the reaction by increasing the molar equivalents of 1-fluoro-2-nitrobenzene (**60**), increasing the reaction temperature and changing base, Table 7, in the expectation that the complete formation of the rearranged products (**335** or **336**) would occur.

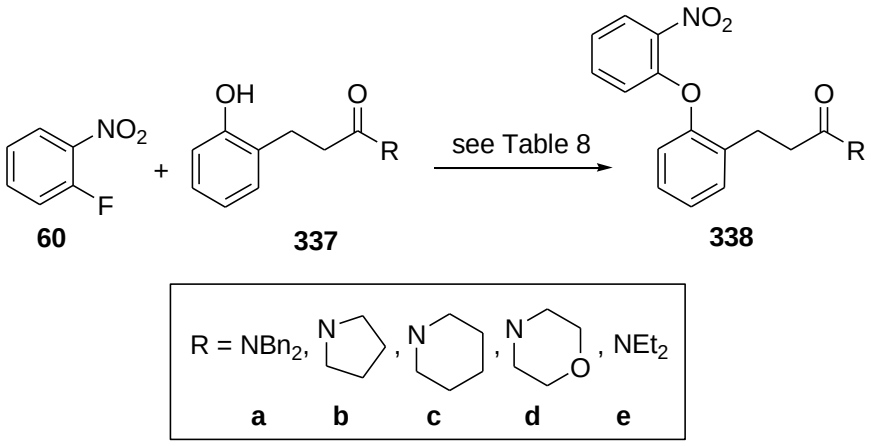
Table 7. Optimisation of the reaction between **333b** and **60**.[a]

Entry	**60** (eq.)	Base (eq.)	Temp. (°C)	Product ratio[b]		
				334b	**335b**	**336b**
1	2.0	K_2CO_3 (2.5)	25	80	20	0
2	2.0	K_2CO_3 (2.5)	60	58	42	0
3	2.0	K_2CO_3 (2.5)	100	49	51	0
4	2.0	NaH (2.5)	60	40	55	5
5	5.0	K_2CO_3 (2.5)	25	97	3	0
6	5.0	K_2CO_3 (2.5)	60	70	30	0
7	5.0	K_2CO_3 (2.5)	100	62	38	0
8	5.0	NaH (2.5)	60	71	29	0
9	10.0	K_2CO_3 (2.5)	25	100	0	0
10	10.0	K_2CO_3 (2.5)	60	100	0	0
11	10.0	K_2CO_3 (2.5)	100	100	0	0
12	10.0	NaH (2.5)	60	54	46	0

[a] *Reaction conditions*: All reactions were carried out with **333b** (1.0 eq.), in DMSO (0.1 M) for 24 h. [b] Ratios based on ^{1}H NMR integration of diagnostic signals relating to the newly generated C*H* of the rearranged products (**335b** and **336b**) and the CH_2 of the diarylether (**334b**).

Surprisingly, upon increasing the number of molar equivalents of **60** from 2.0→5.0→10.0 eq. the amount of diarylether (**334b**) also increased (Table 7), at all temperatures studied (25, 60, 100 °C), rather than an increase in the ratio of the rearranged products (**335b** and **336b**), as was expected. The proposed rationale for the reaction halting at the diarylether (**334b**) stage may be due to the increase in the equivalents of the electrophile stabilising the electron-rich enolate of the diarylether (**334b**) formed during the first stage of the reaction rendering it unable to react further.

The assumption that the presence of excess **60** may be affecting the stability of the enolate resulted in a stronger base and alternative counter ion being examined; Table 7 outlines the results of replacing K_2CO_3 with NaH. As can be seen, increasing the number of equivalents of **60** with NaH as base, at 60 °C, results in an irreversible deprotonation, which leads to an increase in the amount of rearranged diarylether (**335b**) formed compared to **334b**, which peaks in the case with 10 eq., where an increase in the total rearranged products increased from zero (with K_2CO_3) to 46% (with NaH). Possibly, the smaller counterion (Na^+) and irreversible deprotonation enables the formation of a tighter ion-pair thus favouring the rearrangement, whereas the more dissociated ion-pair with K^+ is stabilised by the excess electrophile.



Scheme 104. Attempted Truce-Smiles rearrangement with propanamide-based substrates (**337a-e**[218]); see Table 8 for the reaction conditions.

Despite observing a variety of products from these amides in the acetamide case, when the equivalent propanamide substrates were prepared and tested, Scheme 104 and Table 8, again, only the diarylether products were observed under all conditions attempted (see below). Such results confirm that, at least on these substrates and under these conditions, the Truce-Smiles rearrangement doesn't occur via a six-membered transition state.

Table 8. Reaction products of propanamide-based substrates **337** with **60**.[a]

Entry	Rearrangement precursor	Product	Yield (%) [b]
1	**337a**	**338a**	92
2	**337b**	**338b**	92
3	**337c**	**338c**	87
4	**337d**	**338d**	90
5	**337e**	**338e**	90

[a] *Reaction conditions*: **337** (1.0 eq.), **60** (1.05 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1M), 60 °C, 24 h. [b] Isolated yields.

As can be seen from Table 8, with precursors based on propanamide (**337**) structures no Truce-Smiles rearrangement occurred; instead only the diarylether products (**338a-e**) were isolated in near quantitative yields. In efforts to force the propanamide based substrates to undergo the rearrangement, the reaction temperature was increased to 100 °C, but no rearrangement was observed at all, neither with the pyrrolidyl (**337b**) nor the dibenzyl (**337a**) derivatives; only the diarylethers (**338b** and **338a**) were isolated, again in quantitative yields. Similarly, even when the reaction was left for 3 days at room temperature resulted in the same products being formed.

Based on these collective findings, it is proposed that the rearrangement fails on the propanamide substrates due to the relatively high pKa of the α-protons of the amide (**337**), either when formed *in situ* or from isolated material. This is partially confirmed in the acetamide cases above where the same protons are also benzylic as well as alpha to the amide carbonyl, and the rearrangement works in those cases.

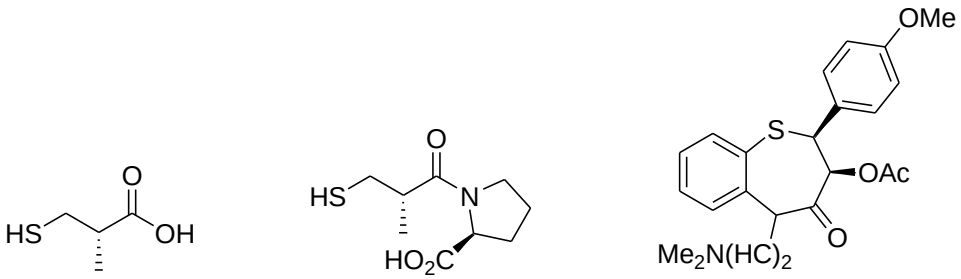
2.2.2.4 Synthetic efforts to prepare chiral derivatives of the Truce-Smiles rearrangement precursors

2.2.2.4.1 Amide-based chiral derivatives

Chiral auxiliaries with C2-symmetry are well established at providing high levels of asymmetric control in numerous organic reactions, such as: reductions,[225–227] Diels–Alder reactions,[226,228] halolactonisations,[229,230]epoxidation reactions[231] and alkylation reactions of enolates.[229,232]Additionally, chiral amides have been extensively used as their lithium amides[233–239] within organic synthesis as effective reagents for a wide range of chemical transformations including enantioselective addition reactions,[240,241]

reductions,[242,243] alkylations,[244] deprotonations,[245–247] desymmetrisations[248,249] and kinetic resolutions.[250,251]

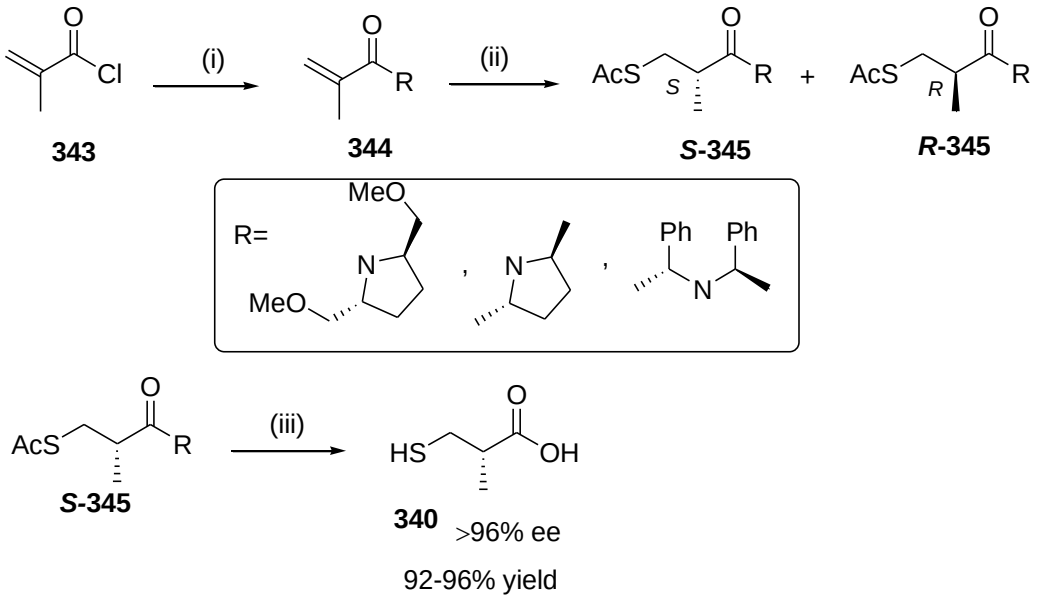
One particular example of interest is the work carried out by Kim *et al*. who attempted the synthesis of enantiopure β-mercaptocarboxylic acid (**340**) via the asymmetric conjugate addition of thioacetic acid to methacrylamide with chiral amine auxiliaries, Scheme 105.[252] The enantiopure β-mercaptocarboxylic acid derivatives are key intermediates in the synthesis of some pharmaceutically important compounds, such as the antihypertensive drug captopril[253] (**341**) and diltiazem (**342**),[254] Figure 22.



340 **341** **342**

Figure 22. Structure of enantiopure β-mercaptocarboxylic acid (**340**), captopril (**341**) and diltiazem (**342**).

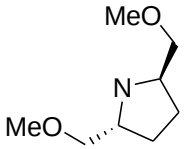
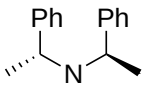
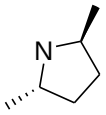
Kim *et al*. showed that the use of chiral auxiliaries with C2-symmetry resulted in excellent stereoselectivities (>99% de) and good yields (80-90%) in the conjugate addition of thioacetic acid to the chiral methacrylamides, Scheme 105 (see Table 9 for conditions, yields, diastereomeric excess and the configuration of the major product).[252]



Reaction conditions: i) chiral amines, DCM, TEA, 0 °C-r.t.; ii) AcSH, toluene, r.t.; iii) BBr_3, DCM, 0.5 h and then aq. 1 M HCl, 70 °C, 4 h.

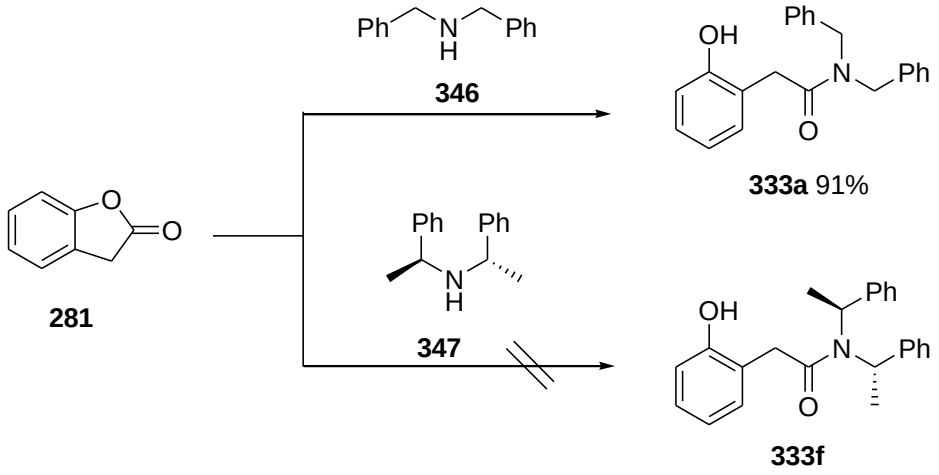
Scheme 105. The conjugate addition of thioacetic acid to the chiral methacrylamides

Table 9. Conditions, yield, percent de and major enantiomers of **345**.

Entry	R	Temp. (°C)/ time	Yield (%)	de (%)	*R*/*S* (major) **345**
1		r.t./ 7 days	88	>99	S
2		r.t./ 14 h	40	60	R
3		r.t./ 20 h	82	>99	S

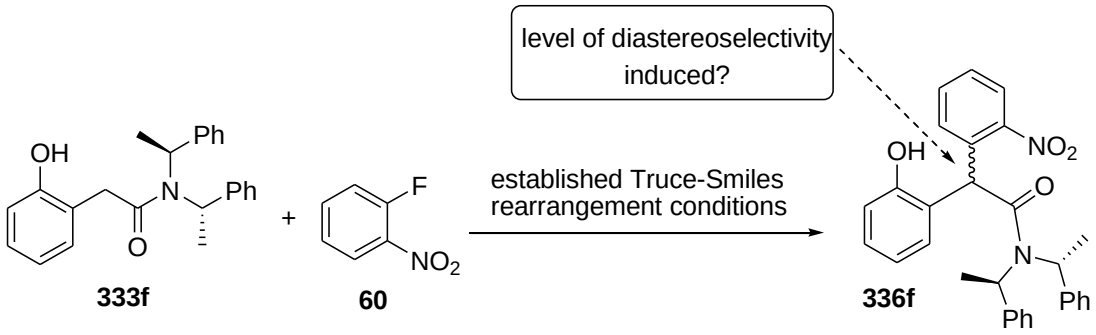
Based on this work and having established promising conditions for the achiral version of the amide-based substrates for the Truce-Smiles rearrangement (Scheme 103), preparation of the chiral substrate (for example **333f**, Scheme 106) began starting with the reaction between 2-coumaranone (**281**) and (−)-*bis*[(*S*)-1-phenylethyl]amine (**347**) (see Table 10 for conditions studied). Unfortunately, under all conditions attempted (Table 10), none of the desired product (**333f**) was observed. Despite the exact same reaction being reported in the literature.[218] This failure was attributed to the mild basicity and nucleophilicity of the chiral amine as well as the presence of α-substituents

(two methyl groups), which presumably increases the steric repulsion in the formation of an amide when it attacks the carbonyl carbon of 2-coumaranone (**281**), Scheme 106.[255]



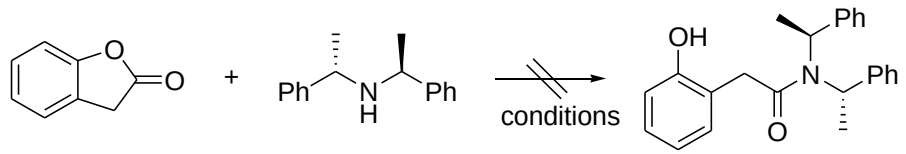
Scheme 106. The achiral and chiral versions of the amide-based substrates for the proposed Truce-Smiles rearrangement.

Once prepared, the chiral acetamide-based substrate **333f** would be subjected to the already established Truce-Smiles rearrangement conditions to ascertain the level of any diastereoselectivity induced, Scheme 107.



Scheme 107. The proposed enantioselective Truce-Smiles rearrangement.

Despite numerous attempts it was not possible to prepare the chiral acetamide based substrate **333f** by applying the procedure shown in Scheme 106. A strong base (*n*-butyl lithium) and established literature methods (see Table 10 for conditions attempted)[256] were tested in order to make the chiral acetamide based substrate **333f** from the ring opening of 2-coumaranone (**281**) with (-)-*bis*[(*S*)-1-phenylethyl]amine (**347**) (Scheme 108), but unfortunately, the product could not be prepared.



281 **347** **333f**

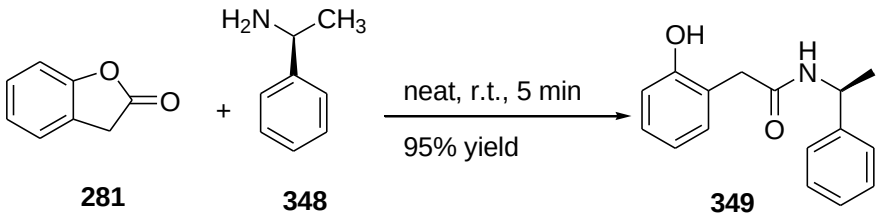
Reaction conditions: 2-Coumaranone (**281**) (1.0 eq.), (-)-*bis*[(*S*)-1-phenylethyl]amine (**347**) (1.5 eq.). For different conditions attempted see Table 10.

Scheme 108. Failed attempts to prepare the chiral acetamide based substrate **333f**.

Table 10 Conditions attempted for making a chiral version of the Truce-Smiles rearrangement precursor **333f**.

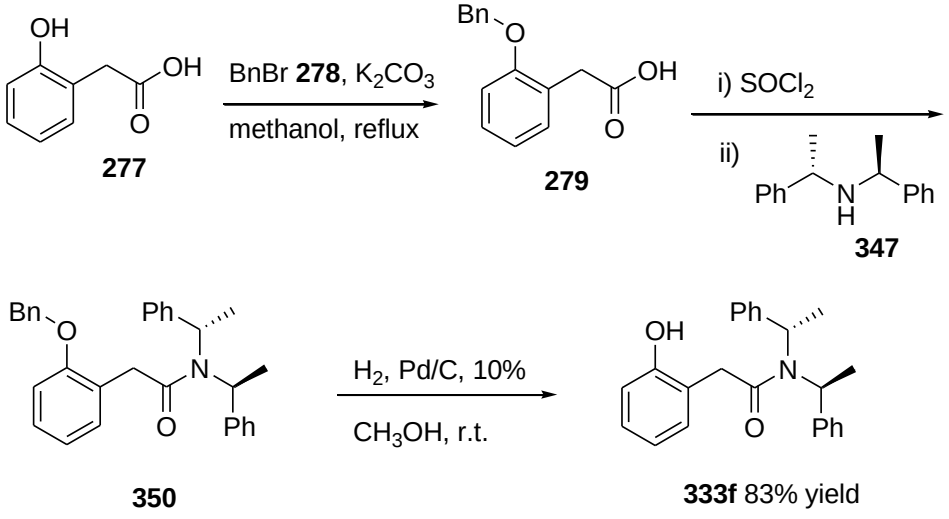
Solvent	Base	Temp.	Duration
toluene	-	Reflux	19 h
THF	*n*-BuLi (1.5 eq.)	r.t.	6 h
toluene	-	Reflux	24 h
THF	*n*-BuLi (1.5 eq.)	r.t.	46 h
toluene	-	Microwave: 150 °C, 300 W then 180 °C, 300 W	30 minutes then 15 minutes
ethanol	-	Microwave: 150 °C, 150 W then 170 °C, 150 W	30 minutes then 30 minutes

Furthermore, this unsuccessful result also can be partially supported by the corrigendum of Juaristi *et al*. when they attempted the synthesis of β-amino acids by the enantioselective alkylation and protonation of prochiral enolates.[257] They declared that the preparation of 2-(2-hydroxyphenyl)-*N*,*N*-bis-(1*S*-a-phenylethyl)acetamide (**333f**), by refluxing 2-coumaranone (**281**) and (*S*,*S*)-bis-α-phenylethylamine (**347**) in toluene (Scheme 108) would not occur, and also that the reaction did not proceed even in the presence of strong Lewis acids such as diethylaluminium chloride, in a sealed ampoule, or under microwave irradiation. Moreover, Juaristi *et al*. demonstrated that the less bulky chiral amine **348** does react readily with 2-coumaranone (**281**) even under mild conditions to afford the chiral amide **349**, Scheme 109.[256] However, the chiral compound **349** was not prepared and used here since it is not C2-symmetric.



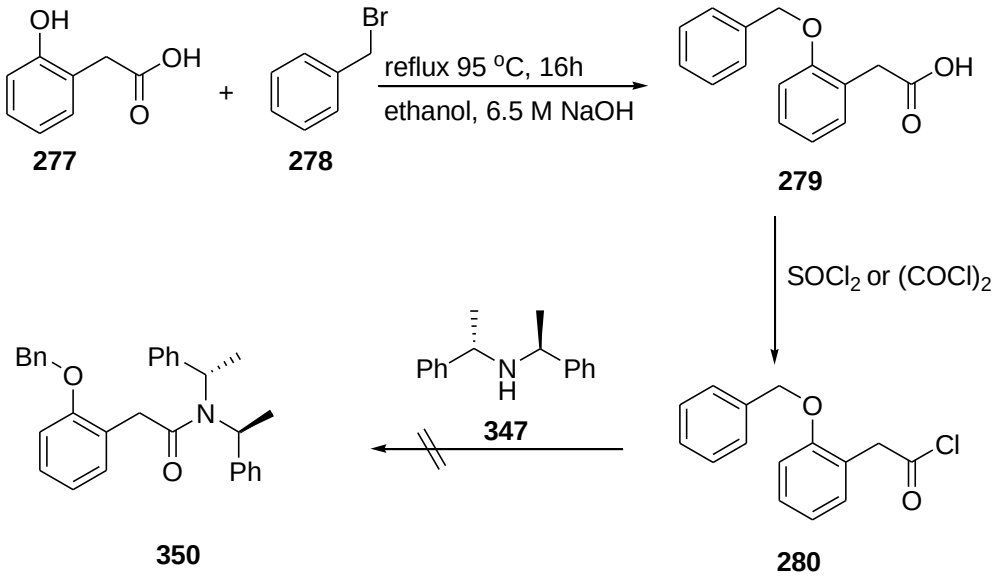
Scheme 109. The less bulky chiral amine **348** does react readily with **281**.

After the failure to secure a synthesis of **333f** by the reaction of **347** with lactone **281** (Scheme 108), attention turned to the precedent set by Muniz *et al*. who developed a successful route to the chiral acetamide-based substrate **333f**, using (2-hydroxyphenyl)-acetic acid (**277**) as starting material (Scheme 110). In their work, they protected the phenolic hydroxyl group of (2-hydroxyphenyl)-acetic acid (**277**) with a benzyl group, then converted the protected acid **279** to its acid chloride by reaction with thionyl chloride. The freshly prepared acid chloride intermediate was then reacted with (*S*,*S*)-bis-phenylethylamine (**347**) to offer the protected enantiopure chiral amide **350** in 45% yield. Finally the protected amide (**350**) underwent hydrogenolysis to afford the desired enantiopure chiral substrate **333f**, Scheme 110.



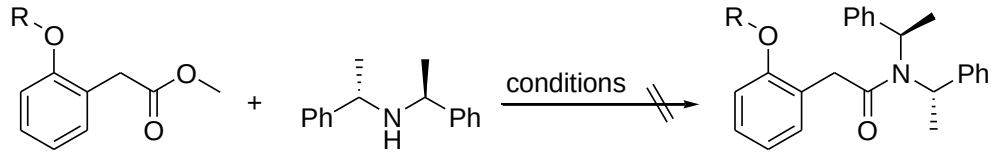
Scheme 110. Alternate approaches to the chiral acetamide-based substrate **333f**.

When applying the above same protocol to our case, the protected acid **279** was successfully prepared in 85% yield. Unfortunately, the reaction between the prepared acid chloride *in situ* with the chiral amine (**347**) did not offer the required protected chiral substrate **350**, Scheme 111.



Scheme 111. The attempted preparation of **350** using an alternative approach.

In order to check whether the failure of the reaction was due to the substrate (the acid chloride formation step) or the chiral amine, the methyl ester of 2-hydroxyphenyl acetic acid (**277**) was used after masking the phenolic OH (with benzoyl **351a** or benzyl **351b**, Scheme 112). In the hope of offering the chiral amide which can be hydrolysed (in case of **350b**) or hydrogenated (in case of **350a**) to give the desired chiral amide substrate. Again, because the chiral amine **347** was poorly nucleophilic it could not attack the carbonyl of the ester substrate, therefore, no reaction occurred, Scheme 112.



351a R= benzyl
351b R= benzoyl

347

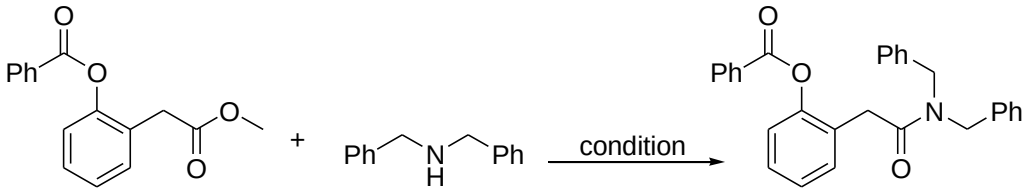
350a R= benzyl
350b R= benzoyl

Scheme 112. The attempted synthesis of the masked chiral amide **350**.

Reaction conditions: microwave: **351a-b** (1 eq.) and **347** (1 eq.), 150 °C, 300 W for 30 minutes in toluene or 200 °C, 300 W for 2 h in ethanol; or 200 °C, 300 W for 30 minutes in chlorobenzene; or **351a-b** (1 eq.) and **347** (1 eq.) refluxed in toluene for 24 h; or refluxed in ethanol for 24 h.

Surprisingly, under the same reaction conditions, substrate **351b** reacted with an achiral amine (dibenzylamine, **346**) and gave the achiral amide analogue **352b** in 98% yield, Scheme 113. This result supports the fact that the chiral amine (**347**) is too bulky (due

the presence of the two methyl groups) than the achiral amine (dibenzylamine, **346**) and thus cannot attack the carbonyl carbon of **351b** and make the corresponding chiral amide substrate **350b**.

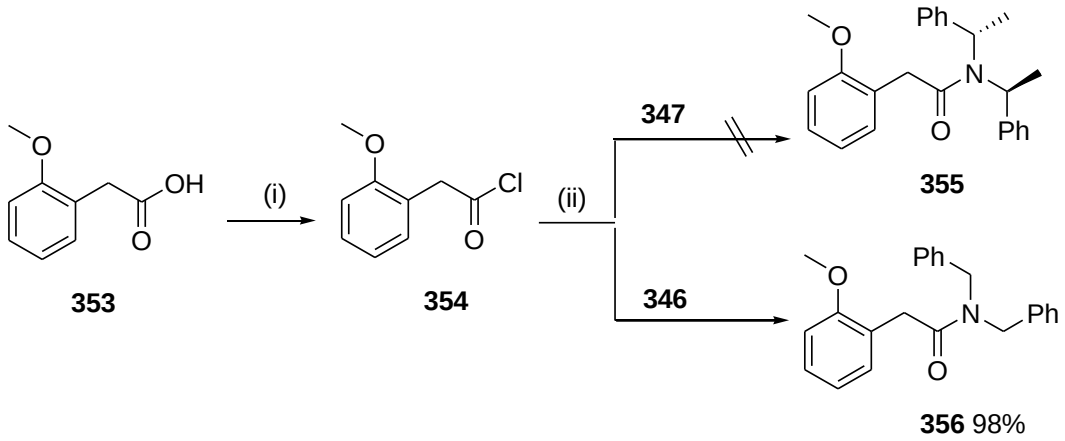


351b **346** **352b** 98%

Reaction condition: **351b** (1 eq.) and **346** (1 eq.) refluxed in toluene for 24 hours.

Scheme 113. Preparation of the achiral amide **352b**.

Furthermore, the acid chloride of the derivative 2-methoxyphenyl acetic acid (**353**) was also subjected to the reaction with chiral amine **347** in a hope of preparing the *O*-methylated chiral substrate **355**, Scheme 114. If prepared successfully it could be potentially demethylated with borontribromide.



353 **354** **356** 98%

Reaction conditions: i) $(COCl)_2$, DCM, DMF, 1-3 h; ii) TEA, DMAP, DCM, r.t.→ 40 °C, 24 h; or **354** (1 eq.), **347** (1 eq.), toluene, reflux, 24 h.

Scheme 114. The attempted preparation of the *O*-methylated chiral substrate **355**.

Unfortunately, this procedure only gave a negligible yield of the corresponding chiral amide **355**, Scheme 114. In order to determine why the reaction failed, i.e., whether the acid chloride intermediate **354** had been formed or not, during a subsequent reaction a small sample was taken from the reaction mixture and reacted with the less bulky achiral amine **346**. This reaction did give the corresponding achiral amide **356** in 98% yield, confirming the formation of the acid chloride **354** *in situ*, Scheme 114, and that

failure of the reaction was more likely due the undesired steric bulk of **347**, as seen before.

2.2.2.4.2 Ketone-based chiral derivatives

Having experienced problems in preparing enantiomerically pure amide-based Truce-Smiles rearrangement analogues, it was proposed that a possible reason might be the position of the carbonyl group on the alkyl section of the amide-based Truce-Smiles rearrangement precursors, i.e., the problems might be due to the amide-based substrates. As such, a shift back towards the attempted synthesis of 2-hydroxyacetophenone- or 2-hydroxypropiophenone-based substrates (**357**) for the rearrangement was made (Figure 24, Box 1), but this time with C2-symmetrical chiral amine auxiliaries, Figure 24, Box 2.

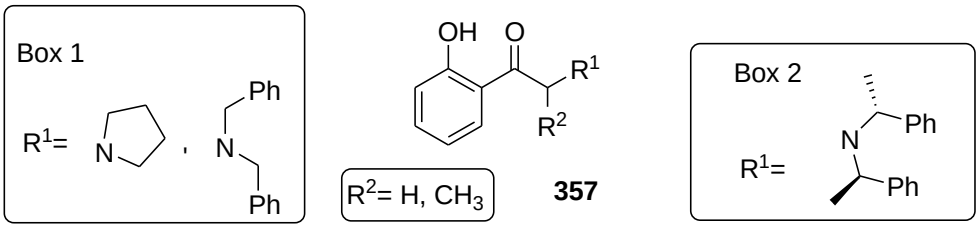
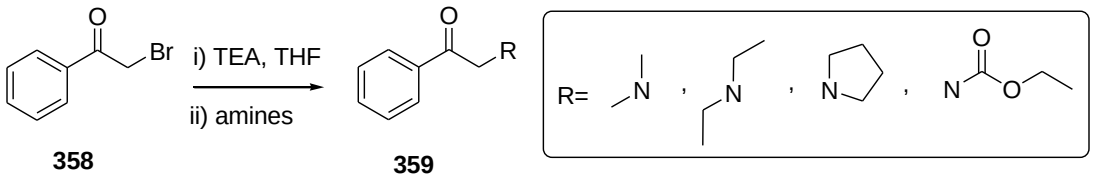


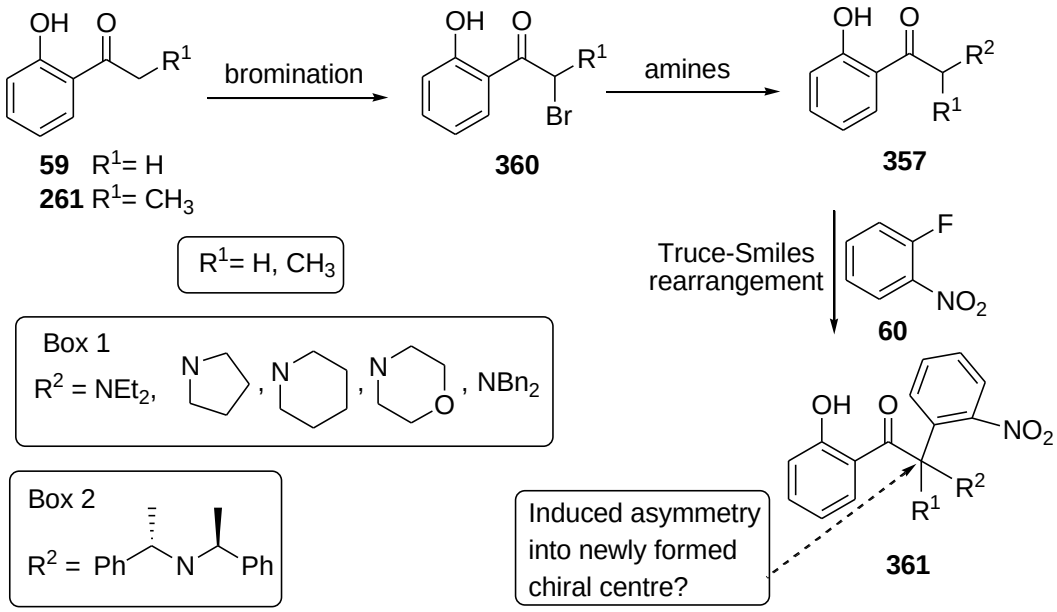
Figure 24. 2-Hydroxyacetophenone- and 2-hydroxypropiophenone-based Truce-Smiles rearrangement substrates **357** with their chiral version (Box 2).

This plan began by applying the literature precedent shown in Scheme 115,[258] with the attempted bromination of 2-hydroxyacetophenone (**59**) and 2-hydroxypropiophenone (**261**),[259] which would give the mono-brominated ketones **360**. These brominated compounds **360** could then be reacted with amines (see Scheme 116 Box 1 and Box 2 for achiral and chiral amines, respectively) to offer the required ketone-based Truce-Smiles rearrangement precursors **357**.[258] Any subsequent successful Truce-Smiles rearrangement products would then give compound **361**, Scheme 116.



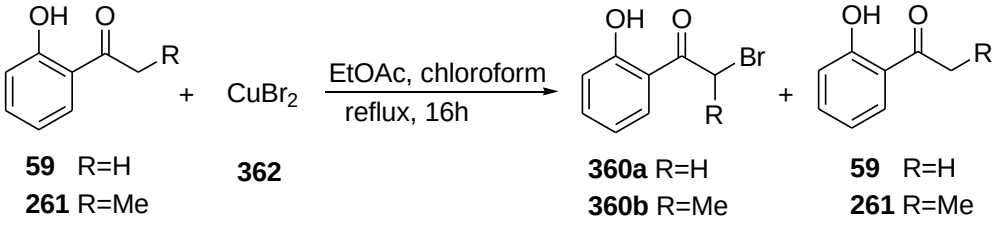
358 **359**

Scheme 115. Literature precedent for the preparation of α-amino ketone based substrates **359**.



Scheme 116. The proposed ketone based substrates to undergo the rearrangement.

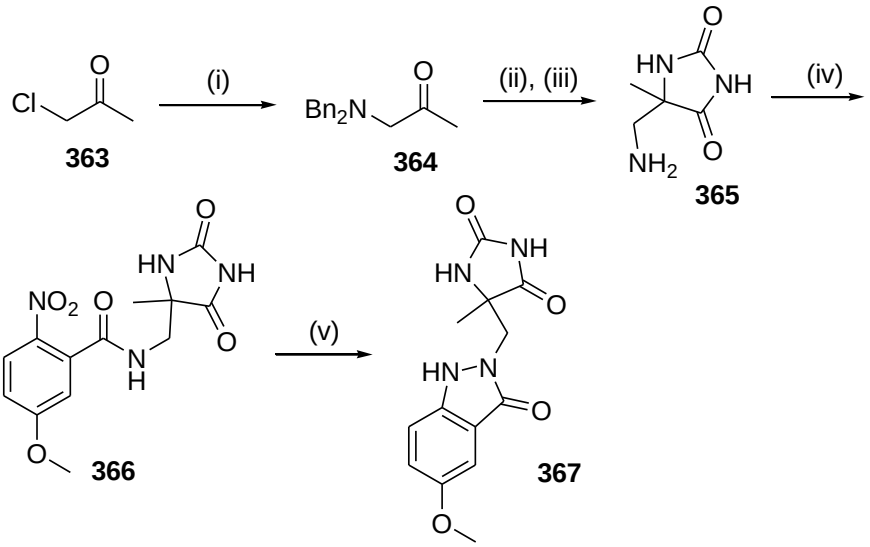
Unfortunately, the bromination reaction[259] (Scheme 117) only gave 66% yield (by NMR) of the mono-brominated product **360a**, but due to its similar R_f value to the corresponding precursor (2-hydroxyacetophenone (**59**)) its isolation was not possible. We were unable to separate it by derivatisation with either 1-fluoro-2-nitrobenzene (**60**) or acetyl chloride. Furthermore, in an attempt to achieve its isolation, the mixture was reacted with (-)-*bis*[(*S*)-1-phenylethyl]amine (**347**) and pyrrolidine in separate experiments but they did not give rise to any products either. Similarly, bromination of 2-hydroxypropiophenone (**261**) to prepare **360b** was also unsuccessful.



Scheme 117. Bromination of 2-hydroxyacetophenone (**59**) and 2-hydroxypropiophenone (**261**)

Precedent for such a reaction was also taken from Yu *et al*. who attempted the synthesis of the hydantoin based tumour necrosis factor-α (TNF-α) converting enzyme inhibitors (TACE). As shown in Scheme 118, the chlorinated propanone **363** reacted with dibenzylamine to give **364**, which was further converted to a hydantoin via the Bucherer–Bergs reaction.[260] Reductive debenzylation yielded the desired amine **365**.

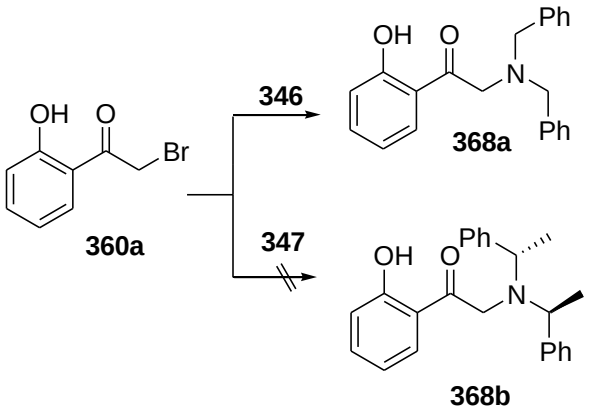
Hydantoin **365** was coupled with 5-methoxy-2-nitrobenzoic acid to afford amide **366** which was converted to **367** in the presence of zinc and NaOH in low to moderate yield.[261]



Reaction conditions: i) Bn_2NH, Et_3N, THF, r.t., 3 days, 89%; ii) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 70 °C 8 h, 86%; iii) H_2, 50 psi, $Pd(OH)_2$/C, EtOH/MeOH (5:1), r.t., 48 h, 95%; iv) 5-methoxy-2-nitrobenzoic acid, EDCI, HOBT, NMM, DMF, r.t., 16 h, 85%; v) Zn, NaOH, MeOH/H_2O (1:1), 75 °C, 20 h.

Scheme 118. The synthesis of hydantoin based tumour necrosis factor-α (TNF-α) converting enzyme inhibitors (TACE).

Supported by such precedent, and in light of the failure met in Scheme 117, pure bromo-2-hydroxyacetophenone (**360a**) was purchased from Sigma Aldrich and reacted with dibenzylamine (**346**) in dichloromethane in the presence of triethylamine to give 2-(dibenzylamino)-1-(2-hydroxyphenyl)ethanone (**368a**)) in 52% yield which was characterised by ^{1}H NMR and ^{13}C.[260] However, in a similar manner to that already observed with other substrates, reaction with chiral (-)-*bis*[(*S*)-1-phenylethyl]amine (**347**) using the same reaction conditions failed to give the corresponding chiral product **368b**, Scheme 119.



Scheme 119. The attempted preparation of the chiral ketone-based susbtrates.

Based on these failed results, and on the assumption that the anomaly was due the bulky chiral amine not the substrate, attempts at the reaction were made with other related C2-symmetrical chiral amines (**369** and **370**) which are also comercially available, Figure 23.

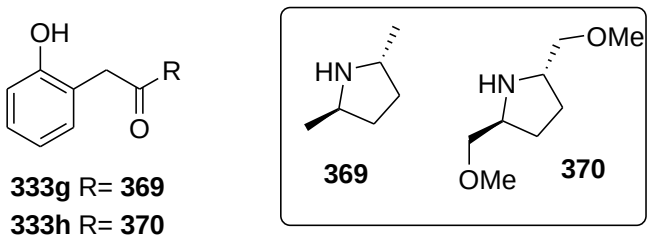
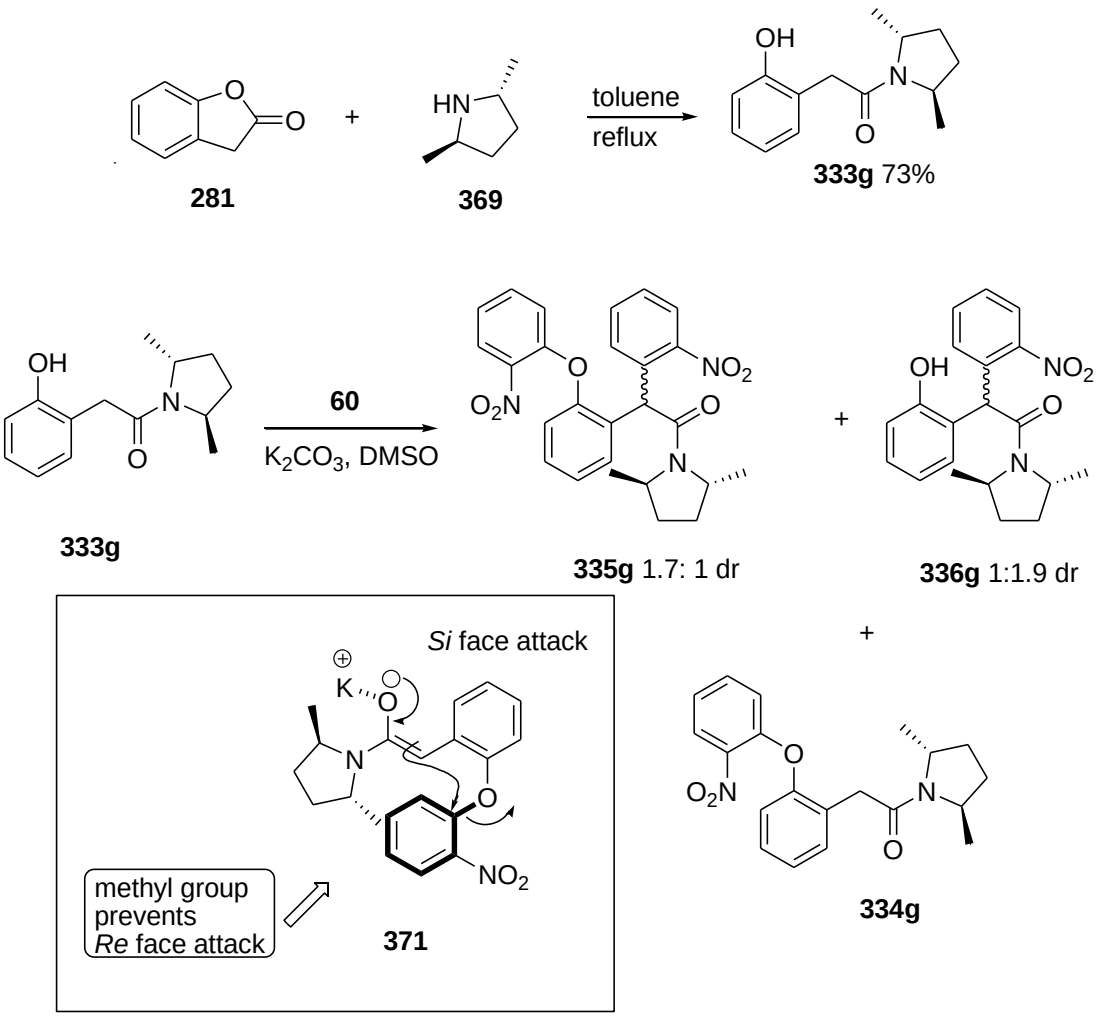


Figure 23. Other commercially available C2-symmetrical chiral amines

In the event, the trial began with (2*R*,5*R*)-(-)-2,5-*bis*(methyl)pyrrolidine (**369**). Like its achiral derivative (pyrrolidine), it was hoped that (2*R*,5*R*)-(-)-2,5-*bis*(methyl)pyrrolidine (**369**) would reacted with 2-coumaranone (**281**) at reflux in toluene,[218] to offer the desired product **333g** (Scheme 120). Fortunately, this time, the chiral substrate **333g** was prepared and isolated in good yield (73%), presumably because the small methyl groups cause less steric hindrance than the two phenyl groups of **347** and therefore, they do not prevent the nucleophilic substitution with **281** occurring. After which, **333g** was subjected to the typical rearrangement reaction conditions (**60** (1.05 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1M), r.t., 24 h), a reaction which resulted in a diastereomeric mixture of rearranged products **335** (1.7:1 dr, 5%), **336** (1:1.9 dr, 36%), along with the diarylether **334** (54%), Scheme 115.

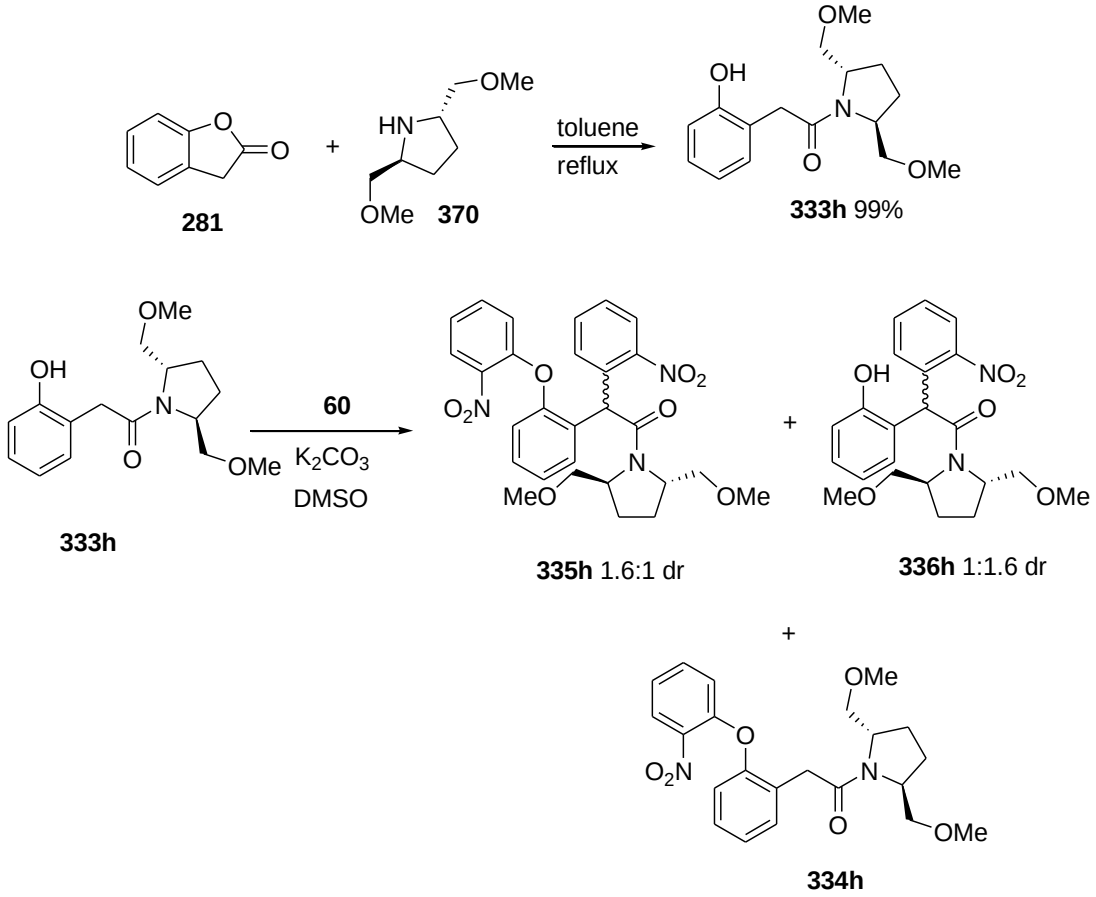


Scheme 120. Reaction between enantiomerically pure amide **333g**, and **60**, showing the diastereomeric rearranged products produced. Compound **371** outlines a suggested mechanism through which the partial diastereoselectivity was achieved.

Despite the successful rearrangement, the overall yields of rearranged products when using (2*R*,5*R*)-(-)-2,5-*bis*(methyl)pyrrolidine (**369**) was only 41% (**335** (5%) and **336** (36%)), therefore, the reaction was repeated with (2*S*,5*S*)-(+)-2,5-*bis*(methoxymethyl)pyrrolidine (**370**) in the hope of giving improved yields the of rearranged products, Scheme 121.

Accordingly, the same reaction as that depicted in Scheme 121 was repeated and an enantiomerically pure substrate (**333h**) was prepared from the reaction of (2*S*,5*S*)-(+)-2,5-*bis*(methoxymethyl)pyrrolidine (**370**) with 2-coumaranone (**281**) at reflux in toluene;[257] the product **333h** was isolated in excellent yield (99%). Again, presumably the success of the reaction means that the amine (**370**) must not be too bulky as to prevent reaction with lactone **281**. In the event, subjecting **333h** to the typical rearrangement reaction conditions (**60** (1.05 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1M), r.t.,

24 h) resulted in a slightly improved yield of diastereomeric mixtures of rearranged products (**335h** (1.6:1 dr, 10%) and **336h** (1:1.6 dr, 45%)), Scheme 121.



Scheme 121. Reaction between enantiomerically pure amide 333h, and 60, showing the diastereomeric rearranged products produced.

Through observation of all related ^{1}H NMR of the rearanged products, it appears as though there is a diagnostic ^{1}H NMR signal for the C*H* proton for amides **336a-e** and **335a-e**, where, in all cases with compound **335**, the newly formed C*H* resonates furthest downfield at values greater than 6.0ppm (presumably the result of an additional electron-deficient ring in these structures), whilst four out of the five amides incorporating the structure of compound **336**, resonate at upfield values of less than 6.0ppm, such that their average values can be summarised as 6.29±0.15 (for **335a-e**, where the error is ± standard deviation) and 5.77±0.42 (for **336a-e** – see Experimental Section). As such, this diagnostic feature enabled us to both determine the identity of rearranged products (**335h** and/or **336h**) formed in the asymmetric reaction from the crude ^{1}H NMRs, and determine the diastereomeric ratios obtained for each (i.e. (*S*,*S*,*S*)-**335h**:(*R*,*S*,*S*)-**335h** and (*S*,*S*,*S*)-**336h**:(*R*,*S*,*S*)-**336h**.[262] Figure 24 outlines the diagnostic

section of the ^{1}H NMR of the crude reaction mixture from the scheme shown in Scheme 121.

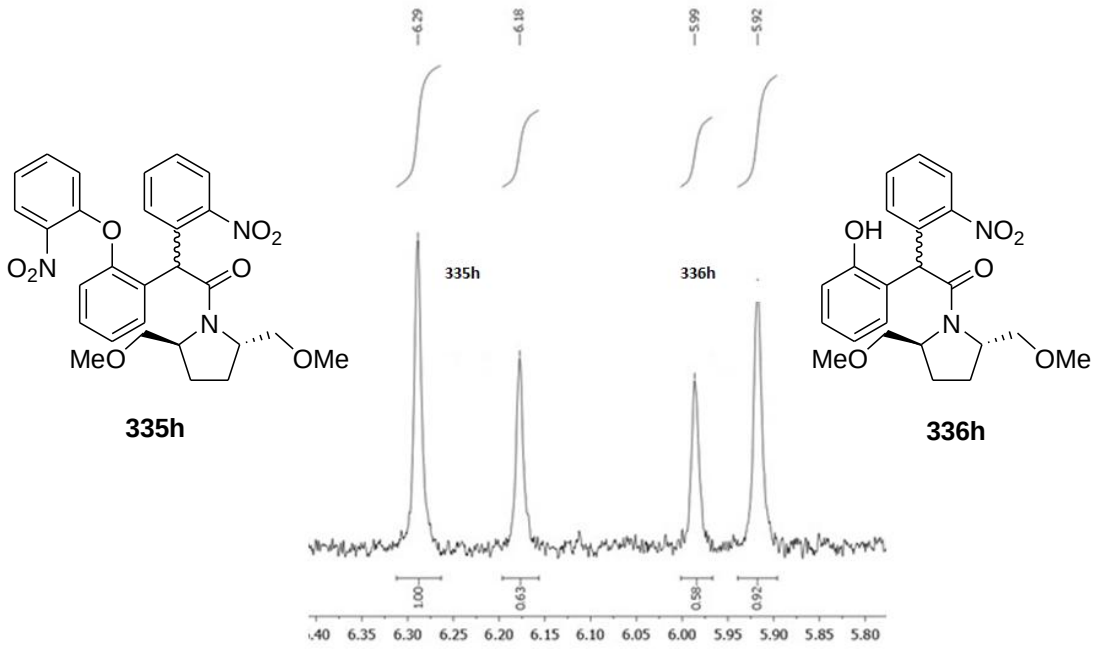


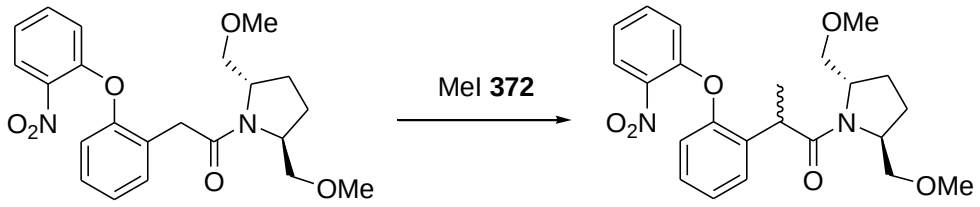
Figure 24. Diagnostic section of the ^{1}H NMR of the diastereomers of **335h** (6.29 and 6.18ppm) and **336h** (5.99 and 5.92ppm) as determined from the C*H* signal of the α-proton to the amide.

Using these diagnostic signals it can be calculated that the presence of the enantiopure auxiliary resulted in rearranged products with a dr= 1.6:1 (**335h**) and dr= 1:1.6 (**336h**). Furthermore, when the rearrangement was carried out on the chiral analogue of **333f** possessing the chiral auxiliary—*trans*-dimethylpyrrolidine (**333g**)—the ratios were dr= 1.7:1 and dr= 1:1.9 respectively for the analogous products. Moreover, it is also possible that the dr induced during the reaction is actually higher than that observed in the crude ^{1}H NMR since the rearranged products are prone to racemisation due to the increased acidity of the C*H* proton on migration of the aromatic ring (pKa of phenol ~18.0 (DMSO) and pKa of 1,1-diphenylcarbonyls ≥18.75 (DMSO).[263] Therefore, in an effort to ascertain whether the dr observed was kinetic or thermodynamic, a rearrangement of pure isolated **334h** was performed in which aliquots were taken and quenched every hour, and their NMR analysis performed. The results indicated an initial dr of 1:1 (after 1 h) which changed to 1.35:1 (after 4 hours), and then surprisingly swapped over to 1:1.54 after 5 hours, a ratio that did not change further over the course of the reaction (7 hours). Although these diastereomeric ratios are relatively low, they are un-optimised,

and thus suggest potential may exist in this mild method for generating enantio-enriched chiral centres with chiral auxiliaries via an aryl-migration rearrangement reaction.

Moreover, attempts to optimise the dr were attempted by subjecting **334h** to a range of rearrangement conditions [solvent (DMSO, DMF, THF, PhMe, $CHCl_3$ and DCM), base (K_2CO_3, CsOH, NaH, NaOMe)], but under all conditions tested, the same (thermodynamic) ratio of ~1:1.6 was obtained. These results prompted us to propose that the rearrangement is not as simple as first presumed, but that the known role of the starting (and presumably product) phenols (i.e. **333h** and **336h**) to act as enantiopure Brønsted acids (as has been shown in the asymmetric protonation of amide enolates),[256] may be playing a part; an effect that needs further investigation.

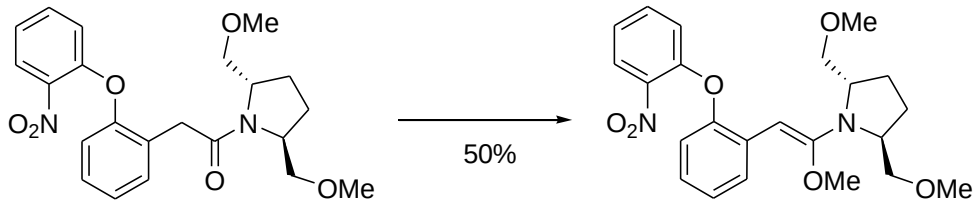
This proposed limitation of *in situ* epimerisation could potentially be mitigated through the preparation of quaternary centres, therefore, to this end, diarylether **334h** was subjected to α-methylation with methyl iodide (**372**) prior to its attempted rearrangement, upon which, if successful, a non-epimerisable quaternary carbon centre would be formed, Scheme 122.



334h **373**

Scheme 122. The attempted preparation of a *C*-methylated product.

Unfortunately, α-methylation did not result in a *C*-methylated product, but instead gave the methyl enol ether **374** (50% yield), Scheme 123.

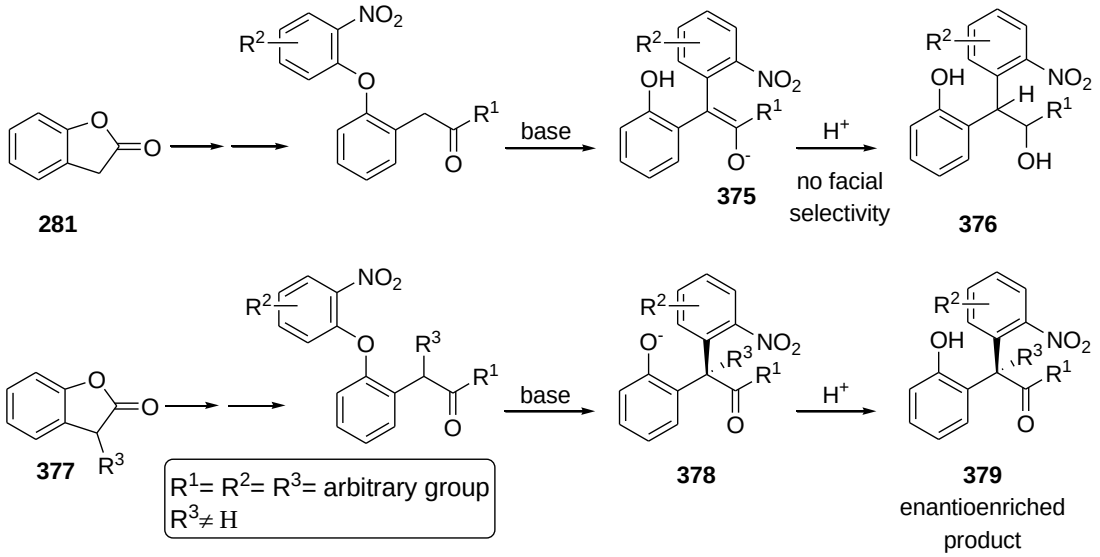


334h **374**

Reaction conditions: diarylether **334h** (1 eq.), NaH (1 eq.), MeI (1 eq.), THF (0.1 M), r.t., 24 h.

Scheme 123. Attempted α-methylation of diarylether **334h**.

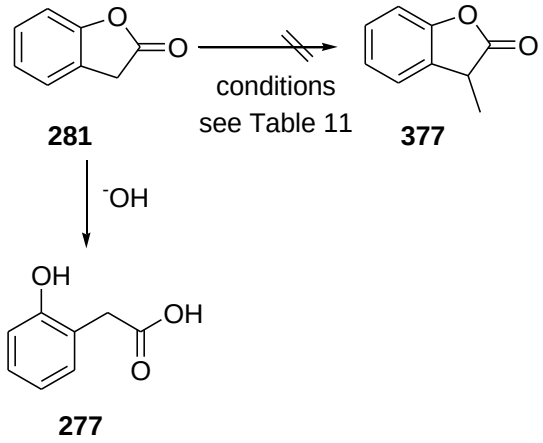
To prevent waste of the costly chiral diarylether **334h**, it was proposed to alkylate the starting material (2-coumaranone (**281**)) with an alkylating agent at the start, to make 3-methyl-2-coumaranone (**377** R= CH_3) in order to prevent the rearranged products (**379**) from racemisation (Scheme 124). As shown in Scheme 124, if the substrate is not alkylated at the α-position it would undergo Truce-Smiles rearrangement to give a compound which in turn may enolise (**375**). After work up, the enolate intermediate would be protonate non-selectively giving racemised products (see compound **376**). However, when the Truce-Smiles rearrangement precursor is alkylated at the α-position to the carbonyl carbon (such as compound **377**) it should undergo such a rearrangement, with no enolisation (see compound **378**) as there is no α-proton to the carbonyl carbon to be abstracted by the base, and therefore there will be no loss in any asymmetry which is generated during the aryl transformation step, Scheme 124.



Scheme 124. Proposed mechanism for racemisation in the Truce-Smiles product (top) and α-alkylated precursors which may give enantioenriched products (bottom).

To test the hypothesis shown in Scheme 124, α-alkylation of 2-coumaranone (**281**) with methyl iodide was attempted as a method to make 3-methyl-2-coumaranone (**377**, Scheme 125). Unfortunately, none of the reported conditions attempted provided the desired methylated product **377**, Table 11. The pK_a for the α-hydrogen in cyclic esters (i.e., lactones such as **281**) is about ~23-25 however using stronger bases such as LDA (pK_a ~35) should easily be able to abstract the α-proton to give the enolate intermediate to attack methyl iodide. Despite this, there are no known reported methods for the α-methylation of **281**, and in all cases attempted here the reaction provided 2-

hydroxyphenyl acetic acid (**277**), which suggested base catalysed hydrolysis was taking place despite efforts being made to remove water in these reactions.[264]



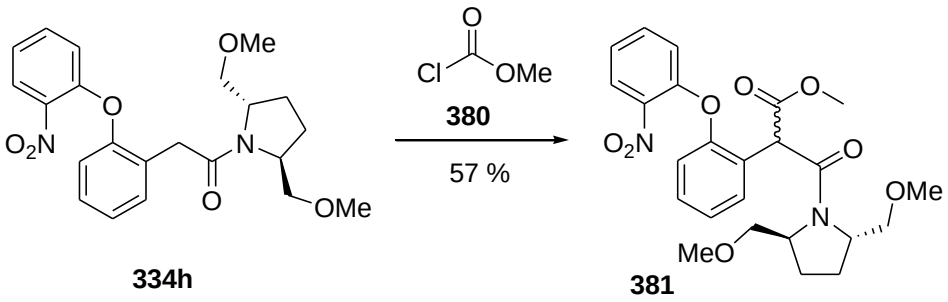
Scheme 125. The attempted α-methylation of 2-coumaranone (**281**). For conditions attempted see Table 11.

Table 11. Conditions attempted to make 3-methyl-2-coumaranone (**377**) using methyl iodide (1 eq.) and 2-coumaranone (1 eq.).

Condition	Solvent	Base	Time	Temp
1	THF	NaH (1 eq.)	16 h	r.t.
2	THF	TEA (1 eq.)	16 h	r.t.
3	DMF	K_2CO_3 (1 eq.)	16 h	r.t.
4	THF	LDA (1.2 eq.)	16 h	-5 °C

Due to the negative results of α-alkylation, both prior to and after arylation, attention was turned to a more reactive species in the hope of α-acylating diarylether **334h** with methylchloroformate (**380**) prior to its attempted rearrangement. In this case, with such a Truce-Smiles substrate as **381** (Scheme 126), a non-epimerisable quaternary carbon centre would be formed.

With methylchloroformate (**380**) as electrophile, the diarylether **334h** was successfuly α-acylated and a pleasing diastereomeric ratio of 11:1 (83% de) was achieved in the 1,3-dicarbonyl product **381** in 57% yield, indicating that the chiral auxiliary is capable of inducing diastereoselectivity in these substrates, although no efforts was made to ascertain the absolute structure of the newly incorporated chiral centre.



Reaction conditions: diarylether **334h** (1 eq.), NaH (1.5 eq.), methylchloroformate **380** (1.05 eq.), THF (0.1 M), r.t., 24 h.

Scheme 126. The α-acylation of diarylether **334h** with methylchloroformate (**380**).

Despite Jørgensen's work, who has revealed a successful nucleophilic aromatic substitution reaction to produce eneantiopure products from 1,3-dicarbonyl compounds (see section 2.2.1),[182,185] attempts to produce a quaternatry carbon centre via aryl migration of this 1,3-dicarbonyl compound **381**, using the standard rearrangement conditions, resulted in failure; possibly due to competing ester hydrolysis consuming base, or the newly introduced group imparting increased steric hindrance that cannot be overcome under the standard conditions of rearrangement. Nevertheless, that a major diastereomer of the 1,3-dicarbonyl had indeed been produced was confirmed when, subject to the rearrangement conditions, it was shown to epimerise to 54% de by crude NMR.

In summary, the preliminary efforts to produce an asymmetric Truce-Smiles rearrangement—a new and potentially mild method to produce enantiomerically enriched α-aryl carbonyl compounds—met with modest success as demonstrated in the application of the rearrangement to novel amide substrates. It has also been demonstrated that amide precursors that proceed through a five-membered spirocyclic transition state rearrange, whereas those proceeding through a six-membered transition state don't, but stop at the diarylether stage. In the initial efforts, only modest diastereoselectivies (dr= max. 1.7:1) are observed.

2.3 Towards an asymmetric α-acylation of carbonyl compounds via the Baker-Venkataraman rearrangement

1,3-Dicarbonyl compounds (the products from the Baker-Venkataraman rearrangement) are very useful synthetic platforms owing to the presence of contiguous reaction sites

with an alternative electrophilic and nucleophilic character, which can be modulated by the nature of the substituents, Figure 25. Recent studies revealed that 1,3-dicarbonyl compounds can undergo different mono, domino and multi-component reactions to offer a variety of achiral and chiral products,[265] such as the naturally occurring anti-Alzheimer product huperzine A,[266] the polyprenylated phloroglucinol natural product clusianone,[267] the potassium channel opener ZD0947,[268] 1,4-dihydropyridines (an important class of bioactive molecules and also interesting biomimetic reducing agents),[269] the *Ipecacuanha* alkaloid emetine and *Alagium* alkaloid tubolisine,[270] SNAP-7941, a potent melanin concentrating hormone receptor antagonist,[271] and the alkaloid (–)-lupinine,[272] Figure 25.

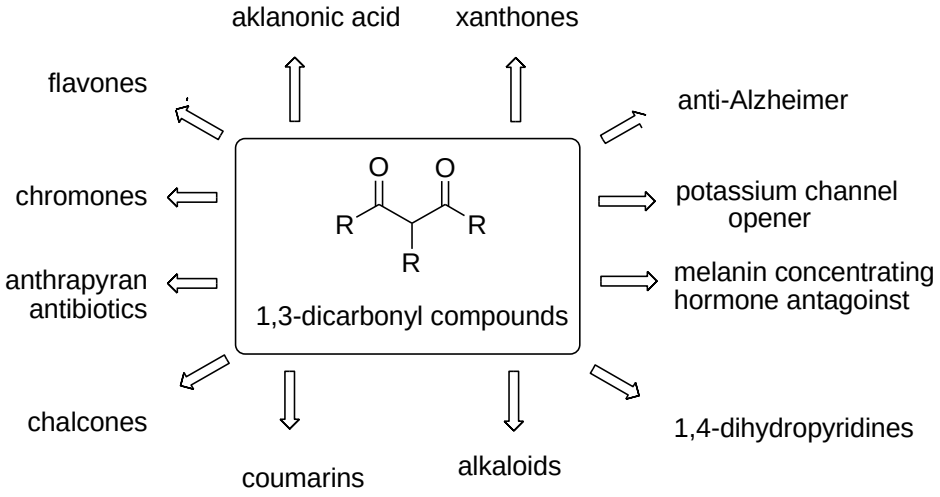
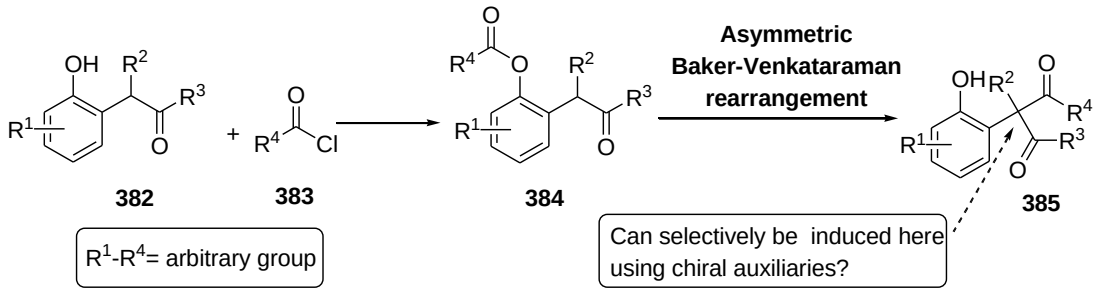


Figure 25. 1,3-Dicarbonyl compounds: a powerful synthetic platform.

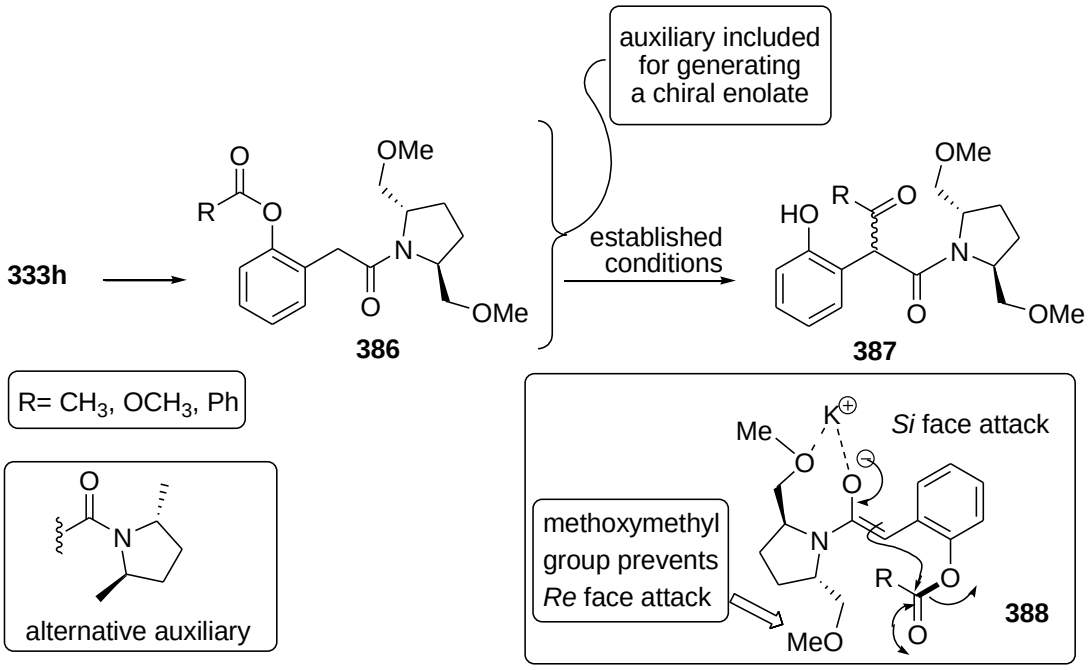
As mentioned previously (Section 1.2), the Baker-Venkataraman rearrangement can be regarded as an *O→C* acyl migration with a mechanism similar to its Truce-Smiles aryl rearrangement analogue. Based on this, it was considered that in a similar manner chiral auxiliaries could be used to induce chirality during acyl group migration, Scheme 127.



Scheme 127. Expected asymmetry induction (R^3= chiral auxiliary).

2.3.1 The Baker-Venkataraman rearrangement on amide based-substrates

In order to assess the strategy depicted in Scheme 127 and attempts to make a chiral version of the Baker-Venkataraman rearrangement, it was decided to utilise the already prepared Truce-Smiles rearrangement precursors, because it had been proven that such acetamide-based substrates (**333a-e**) are susceptible to the related Truce-Smiles rearrangement. Accordingly the plan was to acylate these precursors with variety of acetylating groups, Scheme 128.

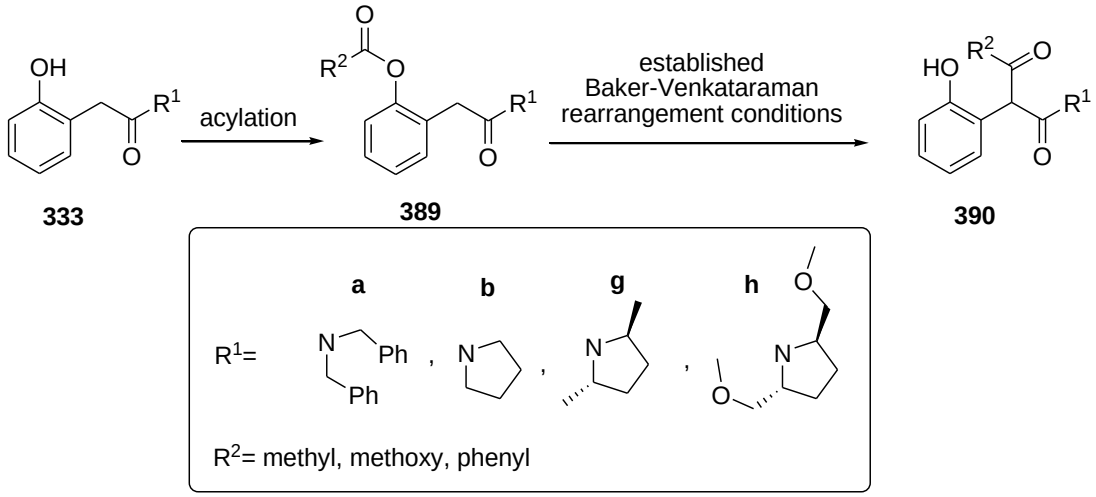


Scheme 128. Attempted rearrangement of an enantiomerically pure amide, such as **386**. Compound **388** outlines a plausible mechanism through which the asymmetry could be induced.

Once the reaction conditions had been established for an achiral version of the Baker-Venkataraman rearrangement, the chiral version would be attempted. To do that the already chiral Truce-Smiles rearrangement precursors would be utilised to induce the asymmetry during the acyl transformation (Scheme 128) since it was observed that they can induce (albeit weak) asymmetry in the case of the Truce-Smiles rearrangement and that excellent diastereoselectivities are seen when an acyl group is involved, Scheme 126.

The process began with acetamide-based rearrangement precursors (**333**) because successful rearrangements had been observed with both the chiral and achiral versions previously (with both a bulky R^1 group (**333a**) and a small R^1 group (**333b**)). The plan

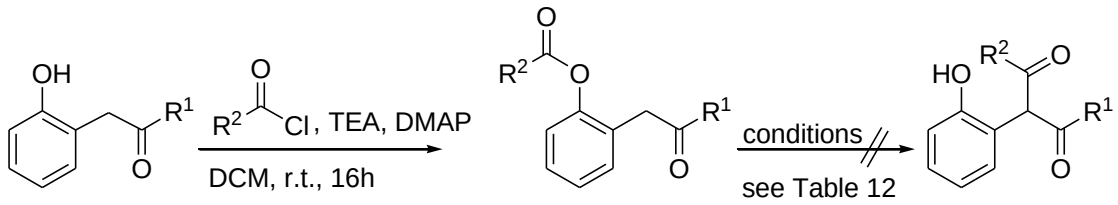
was to acylate these acetamides with different acyl groups and then to perform the Baker-Venkataraman rearrangement using established conditions found in the literature for such a rearrangement, Scheme 129, and determine types of product produced.



Scheme 129. The proposed acylation and subsequent rearrangement on amide-based substrates.

The acetamide-based rearrangement precursors **333a,b** acylated cleanly with a variety of acetylating groups to offer the acetylated Baker-Venkataraman rearrangement precursors **389a-f** in excellent yield (93-100%), Scheme 130 and Table 12. Consequently, the acetylated acetamides were subjected to a variety of reaction conditions to give the corresponding Baker-Venkataraman rearranged 1,3-dicarbonyl products (**390a-f**).

However, during the reactions, despite the strenuous use of anhydrous solvents, molecular sieves and following procedures found in the literature,[3,82,86,123,273] none of the acetylated Baker-Venkataraman rearrangement precursors **389a-f** (see Table 12) gave the rearranged product **290a-f** presumably because, these acetamide derived precursors suffered from facile hydrolysis (see Table 12 for percent of hydrolysis), Scheme 130.



333a R^1= *N*,*N*-dibenzyl amino
333b R^1= pyrrolidyl

389a-f **390a-f**

	R^1	R^2
a	*N*,*N*-dibenzyl amino	methyl
b	*N*,*N*-dibenzyl amino	phenyl
c	*N*,*N*-dibenzyl amino	methoxy
d	pyrrolidyl	methyl
b	pyrrolidyl	phenyl
f	pyrrolidyl	methoxy

Reaction conditions: NaH (2.5 eq.), anhydrous THF (0.1M), reflux, 1-2 h; or NaH (3 eq.), DMSO (0.1M), r.t., 2-3 h; NaH (2.5 eq.), toluene-4Å molecular sieves (0.1M), 100 °C, 1-2 h; KO*t*Bu (2.2 eq.), anhydrous THF-4Å molecular sieves (0.1M), reflux, 1 h; KO*t*Bu (2 eq.), DMF (0.1M), r.t., 1-2 h; NaH (2.5 eq.), anhydrous THF-4Å molecular sieves (0.2M), reflux, 1-2 h.

Scheme 130. Attempted acylation and concomitant rearrangement of acetamide-based precursors.

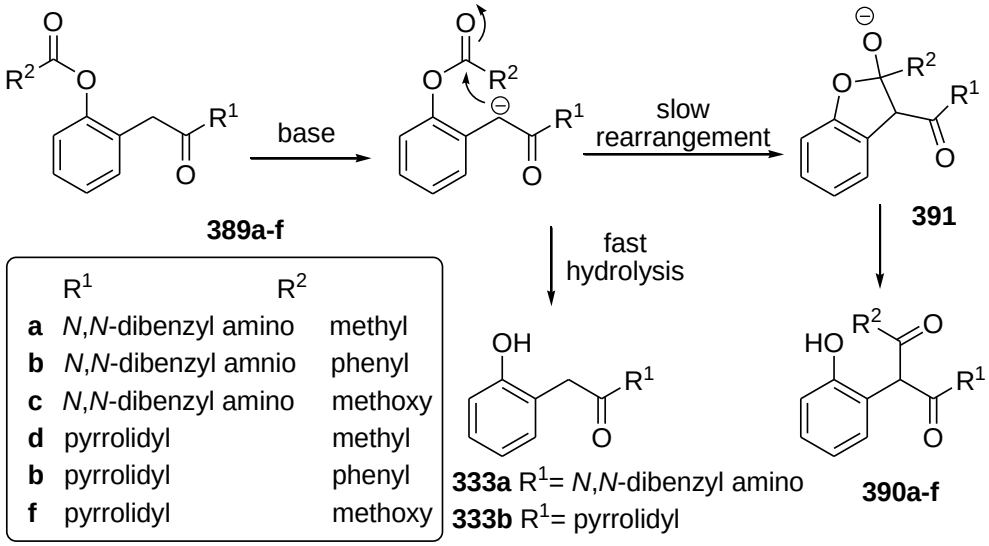
Table 12 Acetamide-based precursors **389a-f** used in the Baker-Venkataraman rearrangement

Entry	R^1	R^2	Acylated products (%)[a]	Hydrolysed products (%)
a	*N*,*N*-dibenzyl amino	methyl	96	100
b	*N*,*N*-dibenzyl amino	phenyl	100	100
c	*N*,*N*-dibenzyl amino	methoxy	99	100
d	pyrrolidyl	methyl	100	100
e	pyrrolidyl	phenyl	93	100
f	pyrrolidyl	methoxy	100	100

[a] Isolated yields.

As can be seen from Table 12, the acylated acetamide-based substrates **389a-f** fully hydrolysed under the rearrangement conditions used. These results can partially be supported by the fact that the acylated acetamide-based substrates **389a-f** presumably

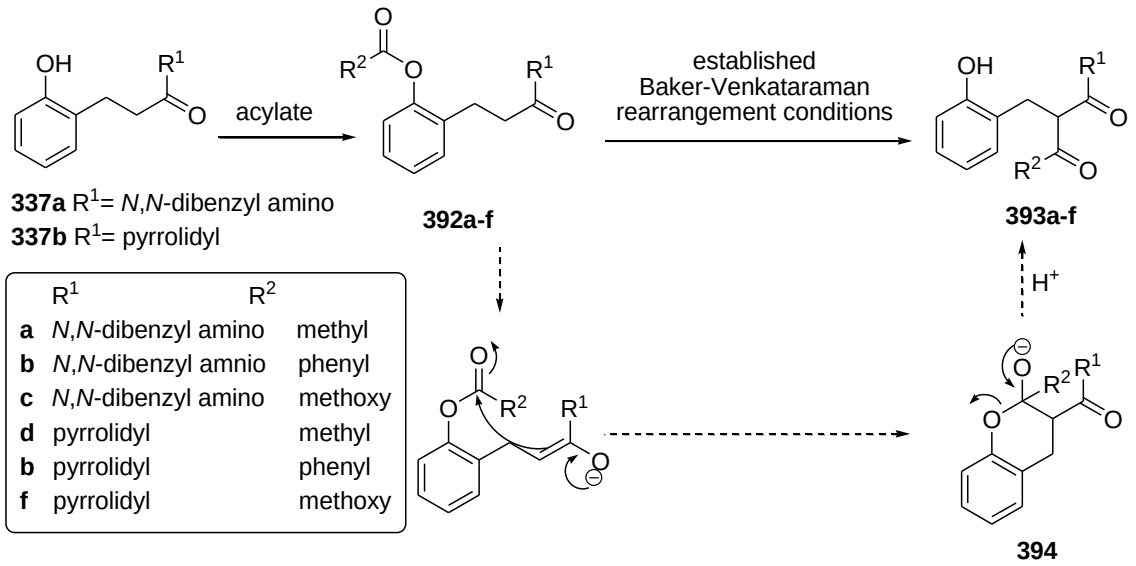
rearrange via a five-membered cyclic intermediate **391** (Scheme 131), which can undergo a presumably slower Baker-Venkataraman rearrangement, or a faster hydrolysis to give the rearranged product **390a-f** or the hydrolysed product **333a,b**, respectively, Scheme 131.



	R^1	R^2
a	*N*,*N*-dibenzyl amino	methyl
b	*N*,*N*-dibenzyl amnio	phenyl
c	*N*,*N*-dibenzyl amino	methoxy
d	pyrrolidyl	methyl
b	pyrrolidyl	phenyl
f	pyrrolidyl	methoxy

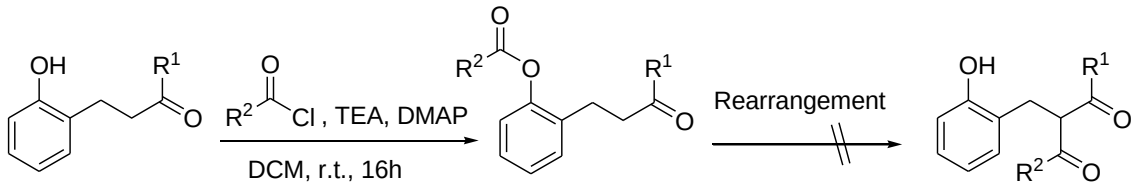
Scheme 131. A plausible mechanism behind the hydrolysis of the acylated acetamide-based substrates **389a-f**.

It was proposed that the Baker-Venkataraman rearrangement failed here because the acylated acetamide based substrates **389a-f** were not able to form a six-membered cyclic intermediate **394** as is the case in almost all Baker-Venkataraman rearrangements reported.[64,67] On this basis, the acylated propanamide-based rearrangement precursors **392a-f** were employed in hope that they would undergo the rearrangement via a six-membered cyclic intermediate **394**, Scheme 132.



Scheme 132. The proposed acylation and subsequent rearrangement of propanamide-based substrates.

Although, the propanamide-based substrates **337a,b** acetylated successfully (89-100% yield, as shown in Table 13), despite attempting different documented conditions the acylated propanamide-based substrates **392a-f** failed to undergo the Baker-Venkataraman rearrangement. Instead, like their acylated acetamide-based analogues **389a-f**, they underwent facile hydrolysis, Scheme 132 and Table 13.[3,14,86,273]



337a R^1= *N*,*N*-dibenzyl amino
337b R^1= pyrrolidyl

392a-f

	R^1	R^2
a	*N*,*N*-dibenzyl amino	methyl
b	*N*,*N*-dibenzyl amnio	phenyl
c	*N*,*N*-dibenzyl amino	methoxy
d	pyrrolidyl	methyl
b	pyrrolidyl	phenyl
f	pyrrolidyl	methoxy

393a-f

Reaction conditions: NaH (2.5 eq.), anhydrous THF (0.1M), reflux, 1-2 h; or NaH (3 eq.), DMSO (0.1M), r.t., 2-3 h; NaH (2.5 eq.), toluene-4Å molecular sieves (0.1M), 100 °C, 1-2 h; KO*t*Bu (2.2 eq.), anhydrous THF-4Å molecular sieves (0.1M), reflux, 1 h; KO*t*Bu (2 eq.), DMF (0.1M), r.t., 1-2 h; NaH (2.5 eq.), anhydrous THF-4Å molecular sieves (0.2M), reflux, 1-2 h.

Scheme 132. The attempted acylation and concomitant rearrangement of propanamide-based precursors.

Table 13. Propanamide-based rearrangement precursors **337a,b** prepared for the attempted Baker-Venkataraman rearrangement

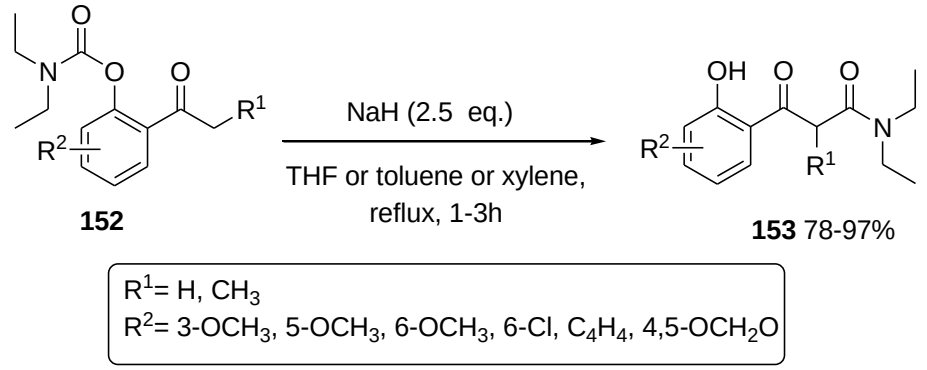
Entry	R^1	R^2	Acylated products (%)[a]	Hydrolysed products (%)
a	*N*,*N*-dibenzyl amino	methyl	91	100
b	*N*,*N*-dibenzyl amino	phenyl	100	100
c	*N*,*N*-dibenzyl amino	methoxy	93	100
d	pyrrolidyl	methyl	100	100
e	pyrrolidyl	phenyl	94	100
f	pyrrolidyl	methoxy	89	100

[a] Isolated yields.

In order to determine whether the Baker-Venkataraman rearrangement reaction failure was due to the amide-based substrates or the acyl group, a literature example using a carbamoyl group was prepared and tested.

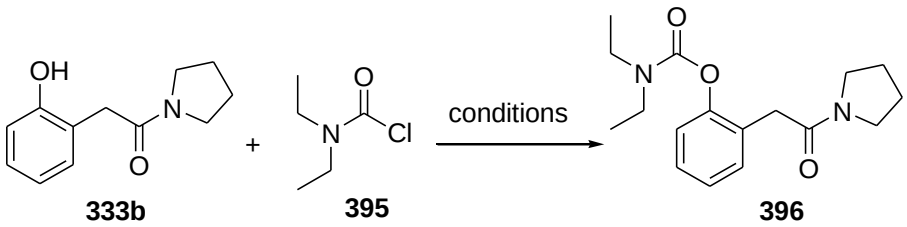
When Snieckus *et al*. attempted the synthesis of substituted 4-hydroxycoumarins (Scheme 134), they found that *N*,*N*-diethyl-carbamoyl Baker-Venkataraman

rearrangement precursors **152** underwent such a rearrangement to afford the 1,3-dicarbonyl products **153** in modest to excellent yields (78-97%), Scheme 134.[94]



Scheme 134. *N*,*N*-Diethyl-carbamoyl precursors **152** rearranged to 1,3-dicarbonyl products **153**.

Accordingly, the pyrrolidine-based substrate (**333b**) (Scheme 135) was acylated successfully using *N*,*N*-diethyl carbamoyl chloride (**395**) to give the carbamoyl-based Baker-Venkataraman rearrangement precursors **396** in good yield (57%), Scheme 135.

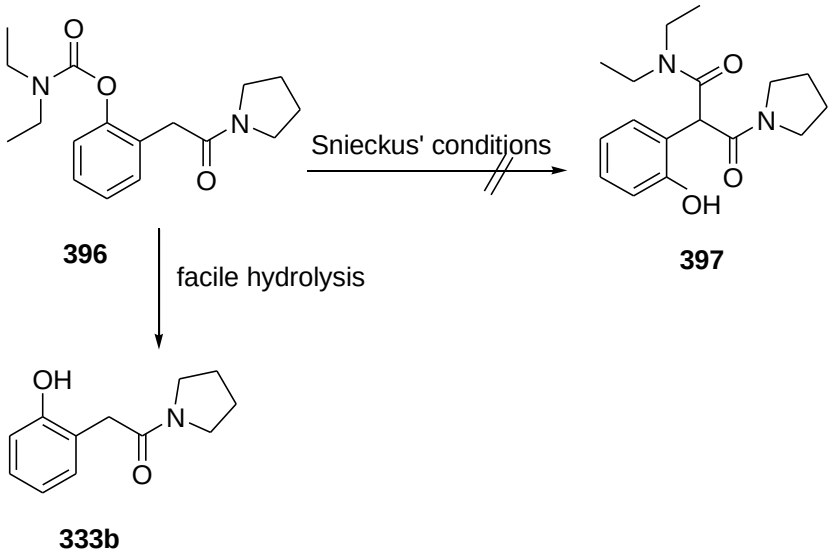


Reaction condition: pyrrolidine-based substrate (**333b**) (1 eq.), *N*,*N*-diethyl carbamoyl chloride (**395**) (1.1 eq.), TEA (1.5 eq.), DMAP (0.1 eq.), DCM (0.1 M), r.t., 16 h.

Scheme 135. Carbamoylation of pyrrolidine-based substrate (**333b**).

Despite the precedent set by Snieckus *et al*. showing that carbamoyl groups readily undergo the Baker-Venkataraman rearrangement using sodium hydride (2.5 equivalent) (Scheme 134), the reaction again failed in our case. The diagnostic signal in the crude ^{1}H NMR would be a singlet for one proton around 4.00 ppm as an indication for the rearranged product, however instead we found a singlet for two protons at 3.70 ppm with a singlet for a phenolic OH at 10.37 ppm, which both indicate the hydrolysed product (**333b**). Additionally, more documented Baker-Venkataraman rearrangement conditions were also tried but in all cases they resulted in 100% hydrolysed product.[68,69] These results would support that the problem with the Baker-Venkataraman

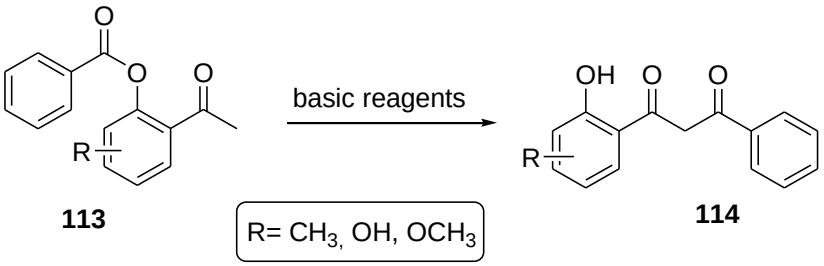
rearrangement reaction can be attributed to the amide-based substrate, as presumably they suffer from faster hydrolysis compared to the rate of rearrangement, Scheme 136.



Scheme 136. Attempted rearrangement of the carbamoylated pyrrolidine-based substrate (**333b**).

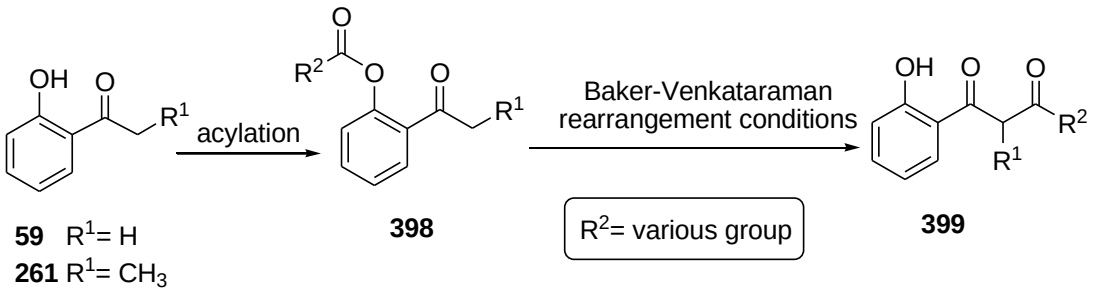
2.3.2 The Baker-Venaktaraman rearrangement on ketone-based substrates

The rearrangement of *o*-aroyloxyacetophenones **113** to *o*-hydroxydibenzoylmethanes **114** by basic reagents (such as sodium amide, sodium ethoxide, potassium carbonate, sodium hydroxide) have been reported numerous times in the literature, Scheme 137. [68-76]



Scheme 137. The rearrangement of *o*-aroyloxyacetophenones **113** to *o*-hydroxydibenzoylmethanes **114**.

With such a huge precedent, therefore, instead of using the amide-based (acetamide and propanamide-based) precursors, ketone-based substrates were prepared, and subjected to different literature based Baker-Venkataraman rearrangement conditions in the hope of forcing the Baker-Venkataraman rearrangement, Scheme 138.[68,69]



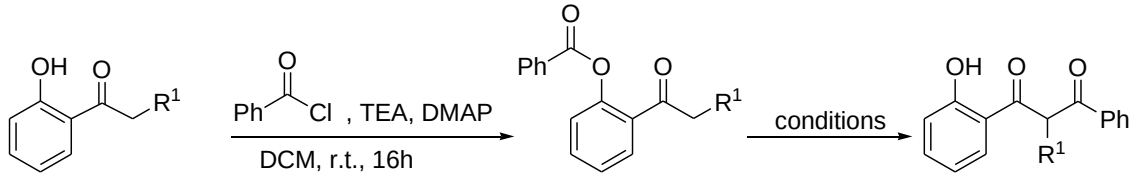
59 R^1= H
261 R^1= CH_3

398

399

Scheme 138. The proposed ketone-based substrates studied in the rearrangement.

Although the ketone-based Baker-Venkataraman rearrangement substrates could be acylated successfully with benzoyl chloride, when subjected to the rearrangement (see Scheme 139) no rearranged products were detected in any of the conditions attempted except NaH/DMSO (when R^1=H). Interestingly, under these NaH/DMSO conditions, the acylated ketone-based substrate **398a** (R^1=H, Scheme 139) did undergo the Baker-Venkataraman rearrangement when refluxed for one hour to give the rearranged product **400a** (R^1= H) in excellent yield (96%), Scheme 139. However, repeating the same procedure with compound **398b** failed to give the Baker-Venkataraman rearranged product (see Table 14 for results).



59 R^1= H
261 R^1= Me

398a R^1= H
398b R^1= Me

400a R^1=H

Reaction conditions: NaH (2.5 eq.), toluene-4Å molecular sieves (0.1M), 100 °C, 2 h; or KO*t*Bu (2.2 eq.), anhydrous THF-4Å molecular sieves (0.1M), reflux, 1 h; or KO*t*Bu (2.2 eq.), DMF (0.1M); or NaH (3 eq.), DMSO (0.1M), reflux, 1 h.

Scheme 139. The attempted rearrangement of ketone-based substrates.

Table 14. Ketone-based substrates (**59** and **261**) for the attempted Baker-Venkataraman rearrangement using NaH (3 eq.), DMSO (0.1M), reflux, 1 h.

Entry	R^1	Acylated products **398** %[a]	Rearranged products **400** %	Hydrolysed products %
a	H	100	96	4
b	Me	61	0[b]	100

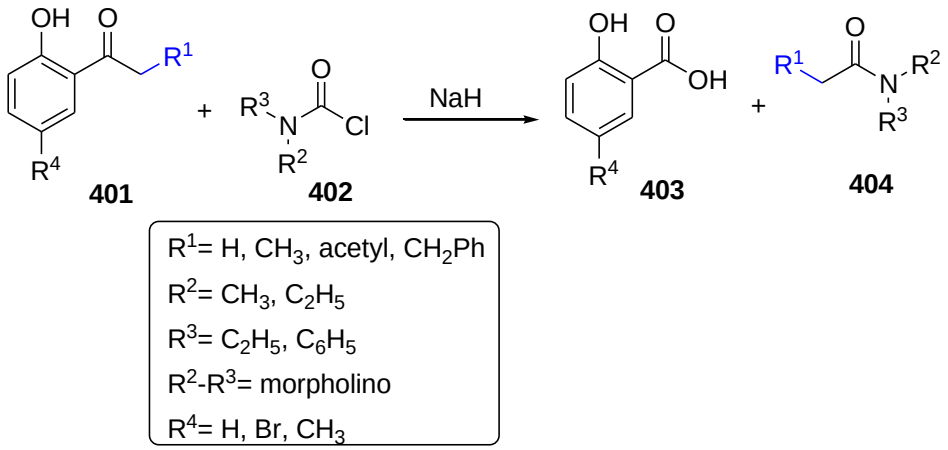
[a] Isolated yields; [b] In all cases the remaining yield is made up of the corresponding hydrolysed products (**59** and **261**).

Having experienced little success in preparing and rearranging chiral racemic Baker-Venkataraman substrates (**400**, R^1=Me), attention was turned to the conditions of Snieckus, wherein his group demonstrated some success in the development of a carbamoyl variant of the rearrangement. As such, a couple of Sniekus's compounds were prepared in order to repeat his results and gain confidence in being able to successfully perform the Baker-Venkataraman rearrangement. Once this success had been achieved efforts would turn back to the rearrangement in the presence of chiral auxiliaries.

In the event, while optimising the conditions for this carbamoyl version of the Baker-Venkataraman rearrangement, it was noticed that the substrates underwent a dual process which includes a Baker-Venkataraman rearrangement-*retro*-Claisen cascade under the reaction conditions in which water was not strenuously removed. A phenomenon that was not observed under strictly anhydrous conditions (wherein the desired rearrangement occurred).

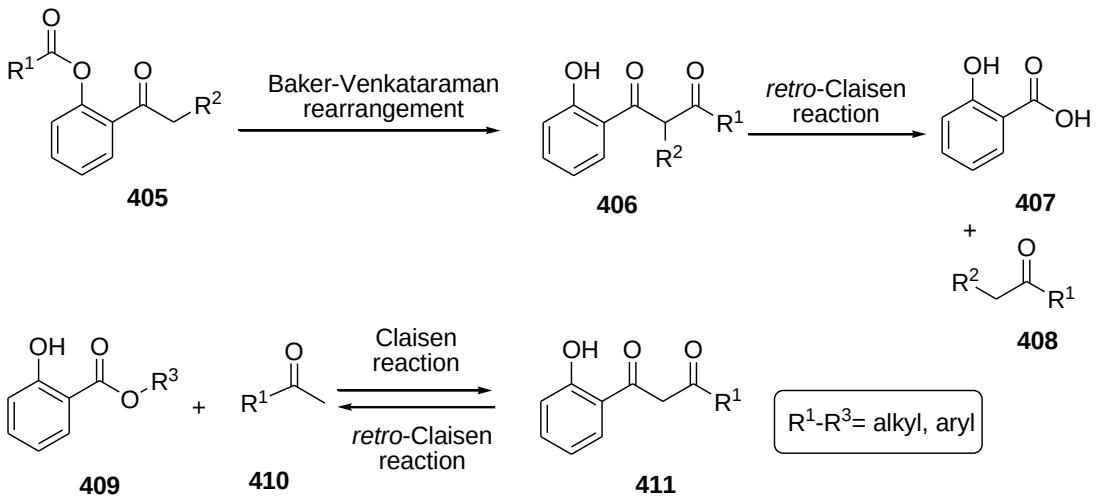
2.3.3 The Baker-Venkataraman-*retro*-Claisen cascade

Having observed this interesting cascade process taking place, along with the fact that up to now, difficulty had been experienced in preparing compounds such as **401** with chiral R^1 groups, it was decided to focus a little effort onto this process to see if it was A] general to this class of compounds, and B] synthetically useful. Scheme 140 shows the summary of the newly discovered cascade reaction whereby the starting material (**401**) appears to act as an "R^1" donor and the carbamoyl chloride (**402**) acts as an "R^1" acceptor to generate the new amide products **404**.



Scheme 140. The Baker-Venkataraman-*retro*-Claisen cascade.

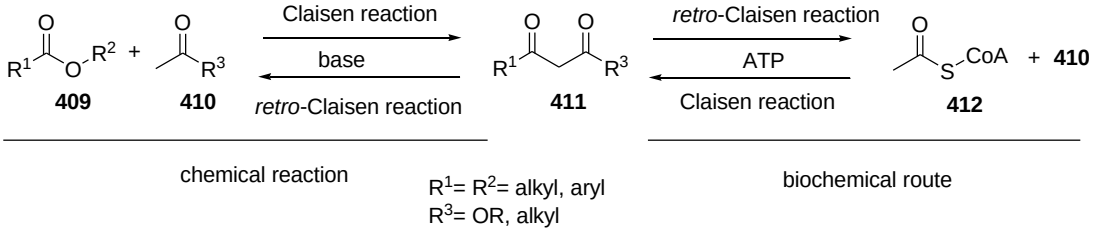
The Baker-Venkataraman rearrangement, by which 1,3-diketones (**406**) are formed, has been regarded as an intramolecular Claisen acylation, Scheme 141. However, in the classical Claisen acylation reaction the ketone (**410**) and ester functions (**409**) are not present in the same molecule, however, both of these functions are present *ortho* to one another in compounds **405** undergoing the Baker-Venkataraman transformation, Scheme 141.[77] This rearrangement is not to be confused with the Dieckmann rearrangement which is considered to be an intramolecular Claisen in which cyclised (not rearranged) products are obtained.



Scheme 141. The difference between the Baker-Venkataraman-*retro*-Claisen cascade and *retro*-Claisen reaction.

2.3.3.1 The Claisen and *retro*-Claisen reactions

The Claisen condensation is a powerful reaction for carbon-carbon bond formation and was discovered by Rainer Ludwig Claisen in 1881.[274] From his publications from 1881 to 1896, it was shown that this reaction can occur with two different substrates sets; either two different carboxylic esters (**409**) with **410** (R^3= OR) or esters **409** with ketones **410** (R^3= alkyl), reacting in basic media to offer β-keto esters or β-diketone (1,3-dicarbonyl compounds) **411**, Scheme 142.[275,276]



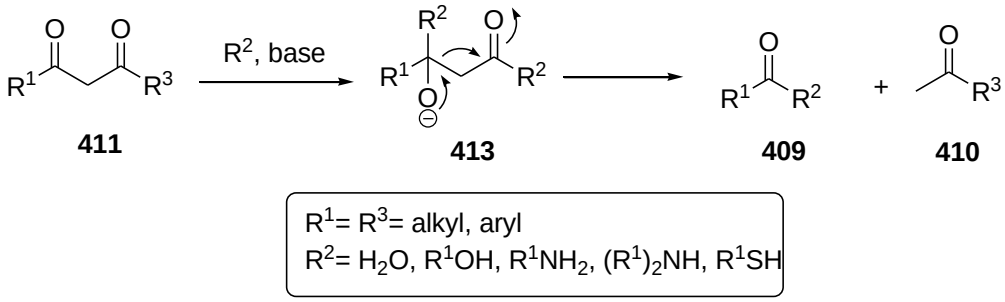
Scheme 142. The Claisen and *retro*-Claisen reactions.

For the Claisen rearrangement to be successful, at least one of the starting materials must be enolisable (have an α-proton next to the carbonyl group and be able to undergo deprotonation to form the enolate anion). Initially, the reaction begins through enolate formation, followed by a nucleophilic attack of it on the ester, this is followed by elimination of the leaving group (alkoxide), and an aqueous acidic work up will offer the final product. If the conditions are not carefully selected, the Claisen condensation is accompanied by side-reactions such as *O*-acylation, self-condensation, decarboxylation, and the retrograde process known as the *retro*-Claisen reaction.[277]

From a biochemical point of view, both the Claisen condensation and *retro*-Claisen reaction are widely observed in the biochemistry of 1,3-dicarbonyl compounds (**411**). The required thioesters (**412**) are biosynthesised through a biocatalysed condensation, and both the Claisen condensation and *retro*-Claisen reaction have powerful parts in the biosynthesis of fatty acids and polyketides and in the degradation of fatty acids and in β-oxidation, respectively, Scheme 142. These reactions are catalysed by an enzyme and the enzymatic Claisen condensation and *retro*-Claisen reaction have been extensively studied and reviewed.[278–281]

The *retro*-Claisen reaction is regarded as a preferable choice in the breakdown of carbon-carbon bonds, attributed to early demonstrations of the *retro*-process under concentrated or basic reaction conditions.[282] Furthermore, the *retro*-Claisen reaction has been extended beyond simple hydrolysis to a variety of substrates, and a wide range of

reactants, catalysts and reaction conditions have been used. In addition, different nucleophiles (*O, N, S* functionalities) have been documented to participate in the *retro*-Claisen cleavage of the parent 1,3-dicarbonyl compounds **411**, through intermediate **413** that undergoes carbon-carbon bond scission to regenerate **409** and **410** from, Scheme 143.[283]



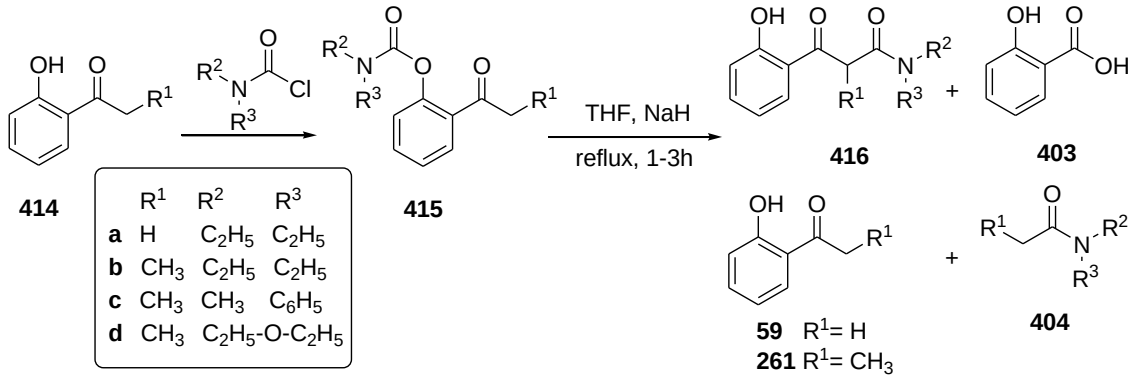
Scheme 143. The *retro*-Claisen cleavage of the 1,3-dicarbonyl compounds **411**.

Connor and Adkins discovered that 1,3-dicarbonyl compounds (**411**, R^1= R^3= alkyl) are more prone to basic hydrolysis and alcoholysis resulting in carbon-carbon bond cleavage, than keto esters (**411**, R^1=alkyl; R^3= OR), Scheme 143.[284] Changing the concentration of the base in the alcoholic media has only superficial influence on the rate of the *retro*-reaction. Profoundly, α-substitutions between the carbonyls has a crucial effect on the cleavage scenario. For example, α,α-disubstituted 1,3-dicarbonyl compounds are cleaved more easily than the α-mono-substituted compounds, since in the presence of base, α-mono-substituted compounds enolise and any subsequent reaction stops, whereas α,α-disubstituted cannot enolise at all and can therefore undergo the *retro*-reaction.[285,286] It was also found that water, sodium alkoxides and aluminium alkoxides can effectively induce *retro*-Claisen pathways.[284]

2.3.3.1.1 The Baker-Venkataraman-*retro*-Claisen cascade on ketone-based substrates

While attempting to expand the achiral version of the Baker-Venkataraman rearrangement a new series of carbamoyl-based substrates **415** were attempted. Unexpectedly, it was demonstrated that the carbamoyl-based substrate (R^2= R^3= C_2H_5) when heated at reflux with sodium hydride (2.5 eq.) in THF for 1-3 hours, afforded a mixture of the desired rearranged products **416**, unwanted hydrolysed products (**59** or **261**) as well as unexpected by-products, salicylic acid (**403**) and amide **404**, Scheme

144. However, as mentioned previously, Snieckus *et al*. demonstrated that using 2.5 equivalents of sodium hydride in THF, toluene or xylene forced the carbamoylated Baker-Venkataraman rearrangement precursors **152** (Scheme 134, *vide supra*) to undergo such a rearrangement when heated at reflux for 1-3 hours to offer the 1,3-dicarbonyl products **153** in good to excellent yields (78-97%). Therefore, based on these conflicting results, attempts were made to study and exploit them to see if the unexpected reaction was more general.



Scheme 144. The Baker-Venkataraman-*retro*-Claisen cascade on ketone-based substrates.

Upon examining this reaction in more detail, it was observed (Table 15) that refluxing the carbamoyl-based Baker-Venkataraman rearrangement substrate **415c** (R^1= R^2= Me; R^3= Ph) with sodium hydride (2.5 equivalents) in THF (0.2 M) for an extended period of 24 hours, again offered a mixture of hydrolysed product (**261**, 17%), salicylic acid (**403**, 42%) and the amide (**404**, 41%), but on this occasion, no rearranged product **416c** was observed. As can be seen in Table 15, when a longer reaction time is employed (i.e. 24 h rather than 1-3 h) the Baker-Venkataraman rearranged product (**416c**) must form *in situ* and subsequently undergo the second reaction, i.e. the intramolecular *retro*-Claisen rearrangement, to give increased yields of salicylic acid (**403**) and amide **404c**.

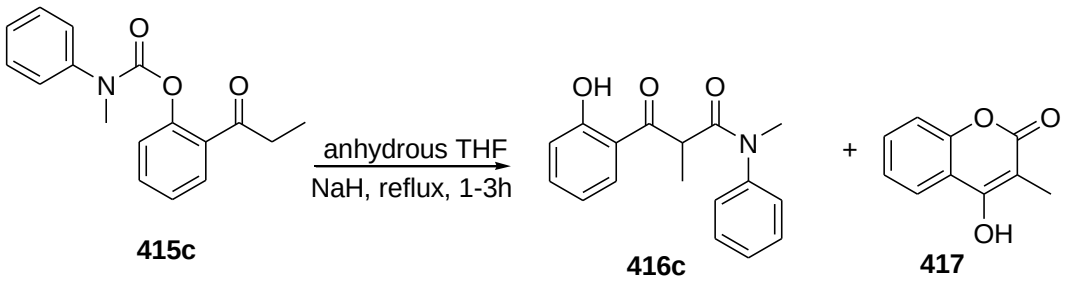
Table 15. A Table to show the product yields in three separate reactions: i) carbamoylation; ii) Baker-Venkataraman rearrangement (anhydrous); and iii) Baker-Venkataraman-*retro*-Claisen cascade.

Substrates	Carbamoylation reaction	Baker-Venkataraman reaction	Baker-Venkataraman-*retro*-Claisen cascade reaction	
414	**415** %[a]	**416**%	**404**%	**403**%
a	27	74	0[c]	45
b	32	N.A[b]	0[c]	50
c	76	92	41	42
d	94	N.A	0[c]	27

[a] Isolated yields; [b] N.A= not attempted; [c] In these cases the 0% yield may be the result of having lost the amide product through evaporation of the reaction mixture, not necessarily that was not formed during the reaction.

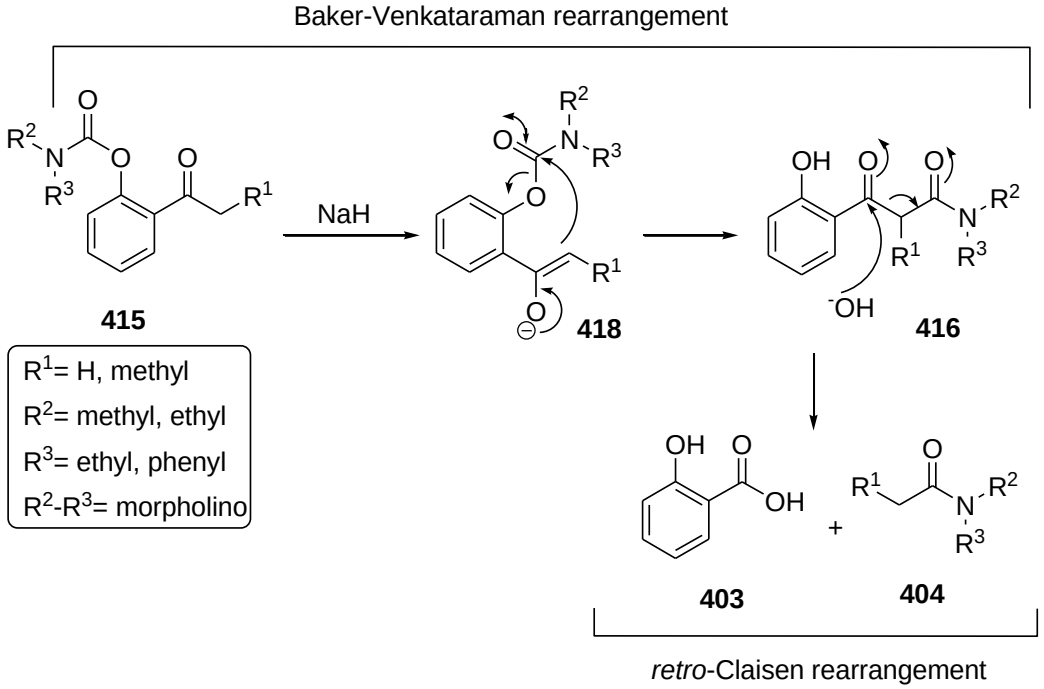
As can be seen from Table 15 carbamates **415a,b,d** did not yield any isolated amide (**404**) products, whilst carbamate **415c** gave amide **404c** in 41% yield. However, this does not mean that amides **404a,b,d** did not form during the reaction, simply that they might be volatile, due to their low molecular weight, and thus would be evaporated *in vacuo* after workup. Nevertheless, that the amide must have formed during the reaction is evidenced by the formation of salicylic acid (**403**, 27-50%) - see the proposed mechanism in Scheme 146.

However, as expected, when the same carbamoyl-based Baker-Venkataraman rearrangement substrates **415** were heated at reflux for the shorter time of 1-3 hours, in anhydrous THF containing sodium hydride and 4Å molecular sieves, only the rearranged products **416** were obtained, as well as the cyclised product **417**, Scheme 145. For example, when compound **415c** (R^1= R^2= CH_3; R^3= C_6H_5) was exposed to the these conditions it gave 48% of rearranged product **416c** and 44% cyclised product **417**, Scheme 145.



Scheme 145. The Baker-Venkataraman rearrangement of carbamoyl-based substrates **415c** in anhydrous THF.

Based on these results, it was postulated that a Baker-Venkataraman-*retro*-Claisen cascade had occurred to give this mixture of products (see Scheme 146 for a plausible mechanism). Here, a proton would be abstracted by sodium hydride to form enolate **418** and in turn this enolate would attack the carbonyl of the acyl group to form a six-membered cyclic intermediate which would collapse to generate the Baker-Venkataraman rearranged product **416**. Nucleophilic addition of trace water could attack the rearranged product and consequently a *retro*-Claisen carbon-carbon bond cleavage would occur to give salicylic acid **403** and amide derivatives **404**.

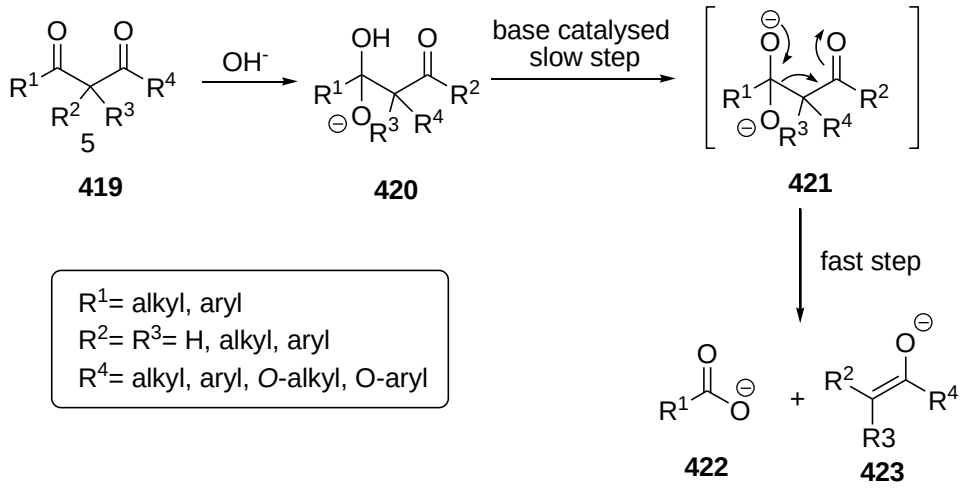


Scheme 146. The postulated mechanism for the Baker-Venkataraman-*retro*-Claisen cascade.

Evidence for this proposed mechanism was obtained when the reaction was performed with an *N*-Me, *N*-Ph-carbamate (i.e. **415**), in a THF:MeOH solution and the

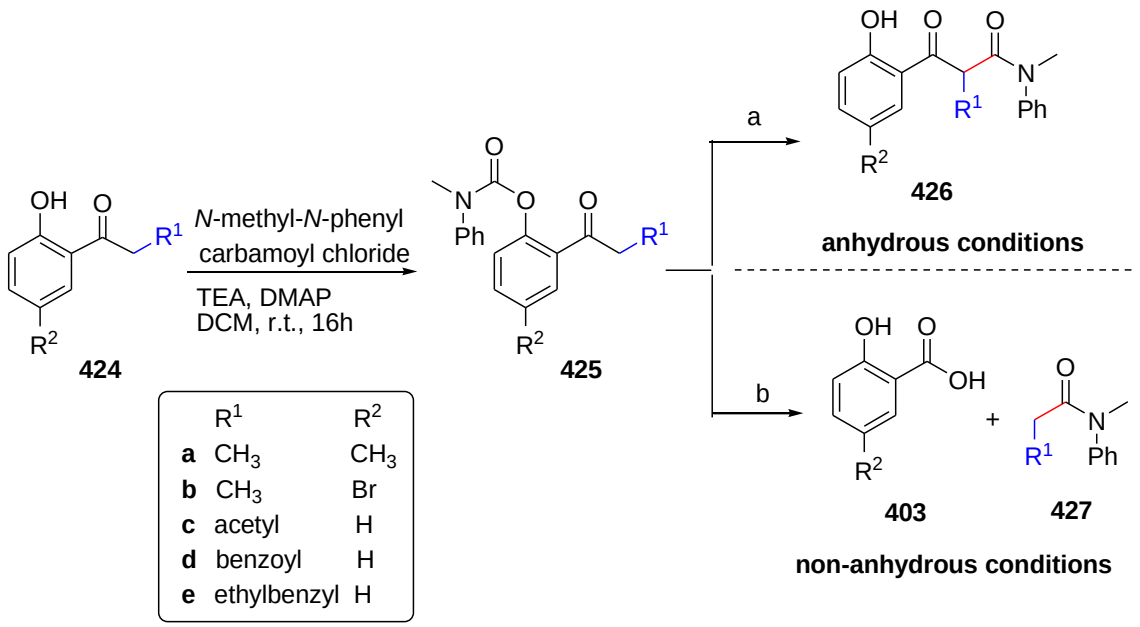
corresponding methyl salicylate was obtained, and its presence confirmed, by NMR and mass spec., rather than the usual salicylic acid which is obtained when water is present.

The reaction kinetic profiles of 1,3-dicarbonyl substrates in aqueous alkali media have been reported by Pearson and Mayerle.[287] In their kinetic studies, they proposed that the reaction begins through an intermediate **420**. A general base-catalysed limiting step produces a double ionic intermediate **421**, followed by fast carbon-carbon bond cleavage offering the cleavage products **422** and **423**, Scheme 147.[287]



Scheme 147. The reaction kinetic profiles of 1,3-dicarbonyl substrates **419** in aqueous alkali media.

However, in order to demonstrate the generality of this proposed Baker-Venkataraman-*retro*-Claisen cascade, five more 2'-hydroxypropiophenone derivatives **424** were acylated successfully with *N*-methyl-*N*-phenyl carbamoyl chloride to give the corresponding carbamoyl-based Baker-Venkataraman rearrangement substrates **425**. Repeatedly, it was found that four of the carbamoyl-based substrates attempted **425a-e** (except **425c**) underwent the Baker-Venkataraman-*retro*-Claisen cascade to give the corresponding salicylic acid derivatives **403** and the amides **427**, when refluxed with sodium hydride in THF for 24 hours, Scheme 148. For different R groups see Table 16.



Reaction conditions: a) sodium hydride (2.5 eq.), reflux, 1-3 h, anhydrous THF-4Å molecular sieves (0.2 M); b) sodium hydride (2.5 eq.), reflux, 24 h, THF.

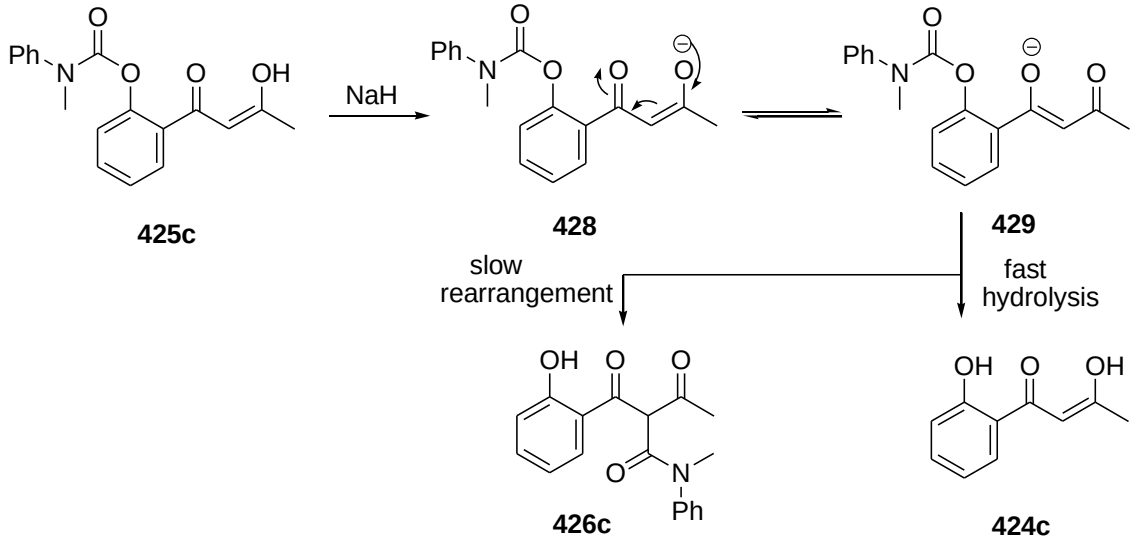
Scheme 148. Attempts to demonstrate the generality of this proposed Baker-Venkataraman-*retro*-Claisen cascade.

Table 16. A Table to show the product yields in three separate reactions: i) carbamoylation; ii) Baker-Venkataraman rearrangement (anhydrous); and iii) Baker-Venkataraman-*retro*-Claisen cascade.

Substrates	Carbamoylation reaction	Baker-Venkataraman reaction	Baker-Venkataraman-*retro*-Claisen cascade reaction	
424	**425** %[a]	**426**%	**427**%	**403**%
a	63	22	85	25
b	96	N.A[b]	60	43
c	50	N.A	100% hydrolysis[c]	
d	91	0	8[d]	0
e	99	58	42	42

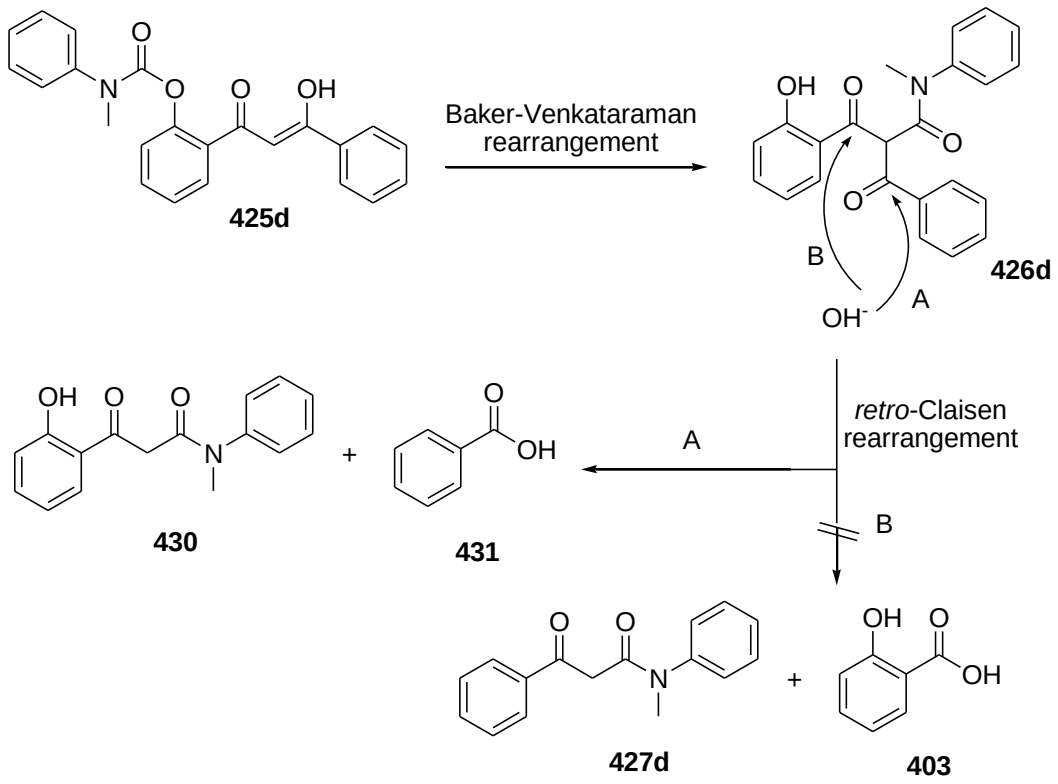
[a] Isolated yields; [b] N.A= not attempted; [c] In all cases the remaining yields is made of the corresponding hydrolysed products (**424**). [d] In the case of substrate **425d**, a different rearranged product **430** was formed instead of the expected amide **427d** (for a detailed explanation see Scheme 150).

As can be seen from Table 16, only substrate **425c** (R^1= acetyl, R^2= H) failed to undergo the Baker-Venkataraman-*retro*-Claisen cascade. Instead the hydrolysed product **424c** was detected as the sole product. This result can be rationalised by the fact that the 1,3-dicarbonyl system in **425c** could enolise, tautomerise and stabilise the enolate intermediate **428**, therefore, although it might undergo a slow rearrangement it would no doubt suffer from a faster hydrolysis step, Scheme 149.



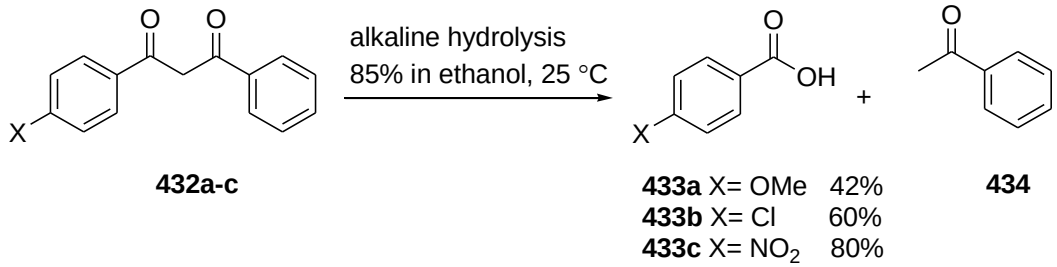
Scheme 149. The rationalised mechanism behind the hydroylsis of **425c**.

In the case of substrate **425d**, a different rearranged product (**430**) was formed instead of the expected amide **427d**. The rationale behind the formation of compound **430** from substrate **425d** (R^1= benzoyl, R^2= H) was that there was a choice of electrophile for the hydrolysis step to choose from. For example, this substrate underwent the Baker-Venkataraman rearrangement step to give the rearranged intermediate **426d** (Scheme150), then in the *retro*-Claisen rearrangement step, the nucleophilic water has two options where to attack (see pathways A and B, Scheme 150) based on the near-symmetrical compound **426d**. Based upon product structure the water must have attacked the benzoyl carbon (pathway A) during the *retro*-Claisen step to give product **430** and benzoic acid (**431**), which was simply washed away during the aqueous workup. This result was observed only in anhydrous conditions giving 33% yield of **430**, and in normal THF only 8% of **430** was detected due to faster competing hydrolysis of **425d** to give **424d** in 92% yield, Scheme 150.



Scheme 150. The proposed mechanism for the formation of compound **430**.

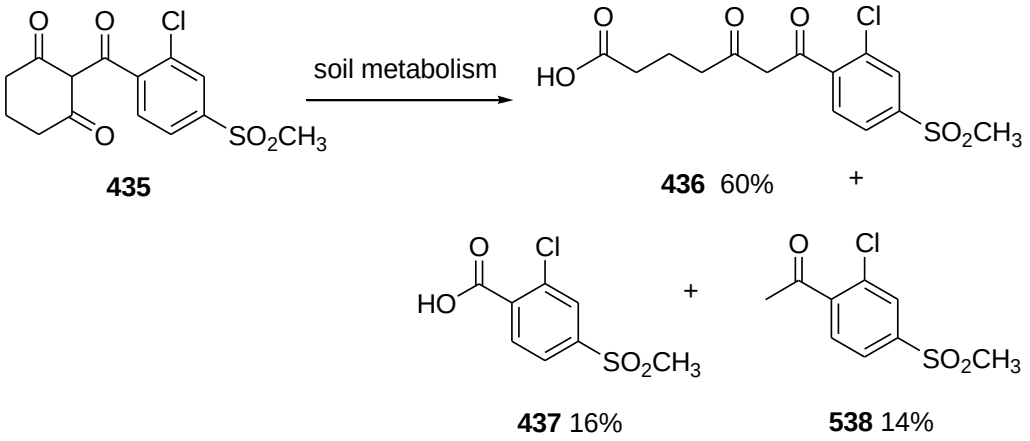
The above rationalisation is also supported by the work of Hauser *et al*. when they documented alcoholysis experiments on the asymmetric aryl substituted diketones (*p*-methoxy (**432a**), *p*-chloro (**432b**), *p*-nitro dibenzoylmethanes (**432c**)), Scheme 151.[288] They demonstrated that there are two possible ester cleavage products, independent of the α-substitution, but the ester of the stronger acid was identified and isolated in higher yields (42%, 60% and 80% for *p*-methoxy, *p*-chloro, *p*-nitro dibenzoylmethanes, respectively). They noticed that the cleavage on the aroyl side of 1,3-diketone towards benzoate **433a-c** was chemoselective, and was attributed to the charge delocalisation capability and stability of the anion intermediates.



Scheme 151. Alcoholysis of the asymmetric aryl substituted diketones **432a-c**.

Furthermore, unexpectedly Rouchaud *et al*. observed similar chemoselectivity, when they studied sulcotrione (herbicide agent **435**) soil metabolism in summer corn crops,

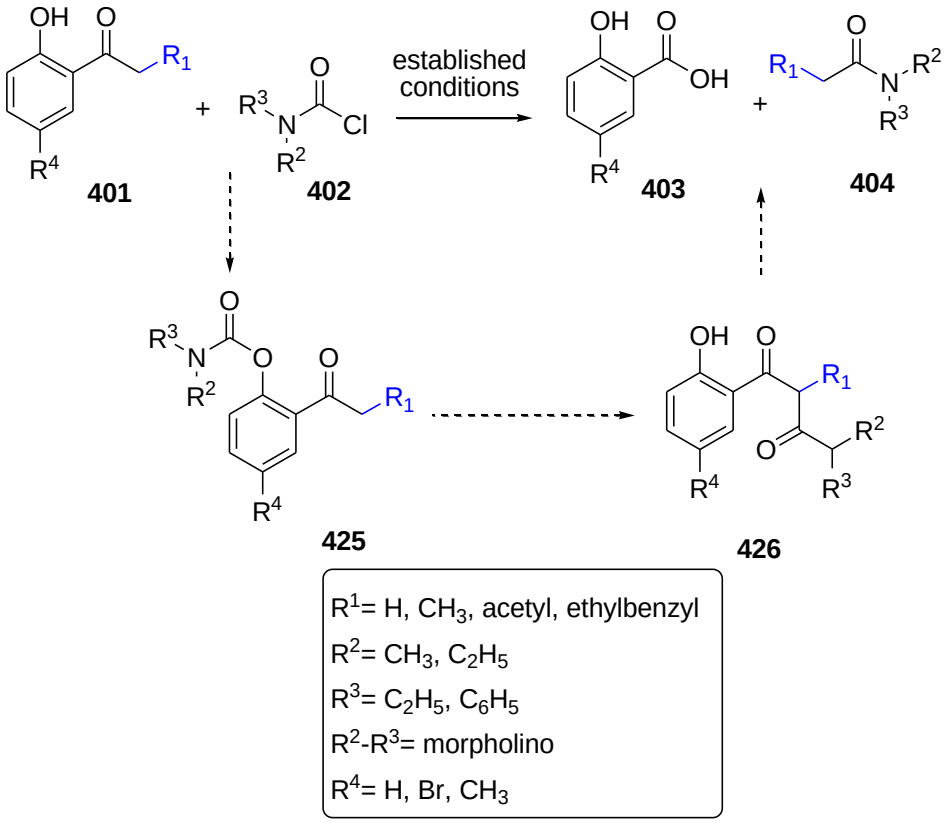
Scheme 152.[289] They found that in the soil of summer corn crops, sulcotrione (**435**) was transformed into the herbicide metabolite **436**, and thereafter successively into ketone **437** and acid **438**.



Scheme 152. Sulcotrione's (**435**) soil metabolism in summer corn crops.

Having followed up and investigated this novel Baker-Venkataraman rearrangement-*retro*-Claisen cascade, further work is required if it is to become an established synthetic protocol in the chemists' repertoire of reactions. Moreover, such development may also suggest that opportunities occur to apply the reaction to molecules of biological interest and natural products. Similarly, as a result of following up this interesting reaction, it was necessary to abandon the asymmetric Baker-Venkataraman rearrangement (Scheme 129 (*vide supra*)) - a reaction which also appears worthy of further investigation for similar reasons.

In summary, the acylated amide-based substrates (**389a-f** and **392a-f**) did not rearrange, instead they suffered from facile hydrolysis, while the carbamoylated ketone-based substrates (**415a-d** and **425a-e**) did, however, the latter substrates underwent Baker-Venkataraman rearrangement-*retro*-Claisen cascade under established conditions. In this cascade, the starting material **401** acted as the alkyl donor and the carbamoyl (**402**) as alkyl acceptor, Scheme 153.



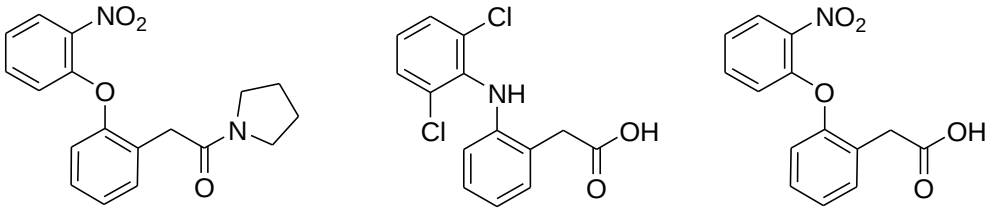
Scheme 153. General scheme for the Baker-Venkataraman rearrangement-*retro*-Claisen cascade.

CHAPTER 3 - CYCLOOXYGENASE ACTIVITY

CHAPTER THREE - CYCLOOXYGENASE ACTIVITY

3.1 Cyclooxygenase (COX) activity of diarylethers 334b, 440, diclofenac sodium (445) and its methyl ester, 452

The synthesis of diarylether derivatives has been studied in recent times and numerous reviews observed that they possess anticancer, antimicrobial, and anti-inflammatory activities.[290–293] Moreover, the diarylethers of the amide-based Truce-Smiles rearrangement precursors (e.g. **334b**) prepared herein have close structural similarity to non-steroidal anti-inflammatory drugs (NSAIDs), especially diclofenac (**439**) which is the most commonly prescribed of the NSAIDs, Figure 28, and these were also studied for their COX-inhibition activity.



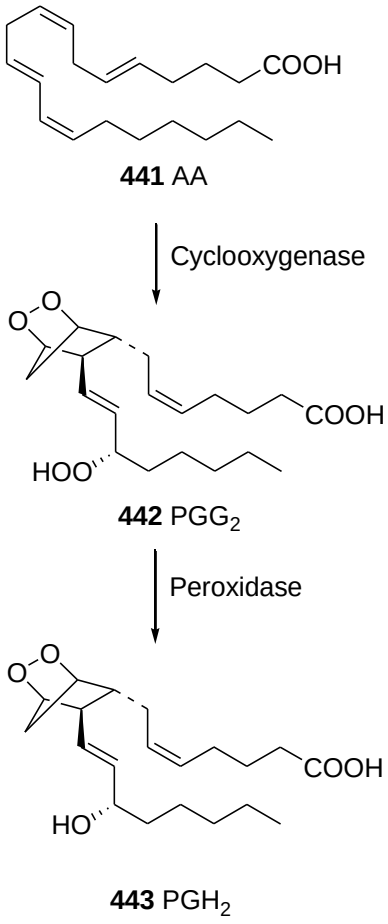
334b **439** **440**

Figure 28. Structure of diarylethers **334b**, **440** and diclofenac sodium (**445**).

3.1.1 COX and prostaglandin production

Cyclooxygenase (COX, also known as prostaglandin H synthase or PGHS) is a bifunctional enzyme exhibiting both COX and peroxidase activities. The COX component is the rate-limiting enzyme responsible for the conversion of arachidonic acid (AA **441**) to a hydroperoxy endoperoxide (PGG_2 **442**), Scheme 154. While the peroxidase component reduces the endoperoxide to the corresponding alcohol (PGH_2 **443**), the precursor of prostaglandins, thromboxanes and prostacyclines.[294,295] It is now well established that there are two distinct isoforms of COX, COX I and COX II, which contain distinct peroxidase and active COX sites.[296] The most expressed COX isoform is COX I which is detected constitutively in almost all tissues such as kidney, spleen and the gastrointestinal mucosa and is involved in normal cellular homeostatsis,[297] while the COX II isoform expression is low, or not detected during normal and non-pathological conditions in most mammalian tissues. Although COX

I is constitutively expressed in almost all tissues, both COX I and COX II are of pharmacological importance in pathological states.[296]



441 AA

442 PGG_2

443 PGH_2

Scheme 154. The biosynthesis of prostaglandins.

A variety of stimuli, such as phorbol esters, lipopolysacharides and cytokines, growth factors, tumour promoters and environmental stresses leads to the induced expression of the COX II isoform, leading to the production of prostaglandins, mediating inflammation and pain.[298] COX II is largely expressed by resident activated macrophages with predominantly proinflammatory effects, therefore, COX II is regarded as a possible target for treating metabolic disorders associated with overweight and obesity.[299] Inducible COX II is responsible for the biosynthesis of prostaglandins under acute inflammatory conditions.[300,301] Therefore, COX II is believed to be the target enzyme for the anti-inflammatory activity of non-steroidal anti-inflammatory drugs (NSAIDs).[300] Arachidonic acid (AA **441**) enzymatically converts to the hydroperoxy endoperoxide prostaglandin G_2 (PGG_2 **442**) by the action of the COX isoforms. Afterwards, PGG_2 is converted to prostaglandin H_2 (PGH_2 **443**), a precursor of the series-2 prostanoids, through peroxidase activity after diffusion to

the peroxidase site (Figure 29).[296] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are also metabolised by COX isoforms, and compete for the same set of enzymes. Arachidonic acid is converted mainly into pro-inflammatory mediators, which act as potent mediators producing cytokines.[302] On the other hand the produced mediators such as PGE_3 and LTB_5 are known to have anti-inflammatory properties.[303] PGH_2 is converted to PGE_2 (the most studied of the prostaglandins) by prostaglandin E synthase (PGES). PGE_2 has been shown to have one of the highest concentrations in adipose tissue compared to other prostaglandins, however, because of the large number of prostaglandins and their complex regulation, through multiple receptors, it is hard to point out a specific function of each prostaglandin.[304] Prostaglandins have several physiological functions in the body and are found in most tissues and organs.[305] In addition, during acute inflammation, prostaglandins are synthesised by local cells; while in chronic inflammation, prostaglandins will be formed by monocytes and macrophages.

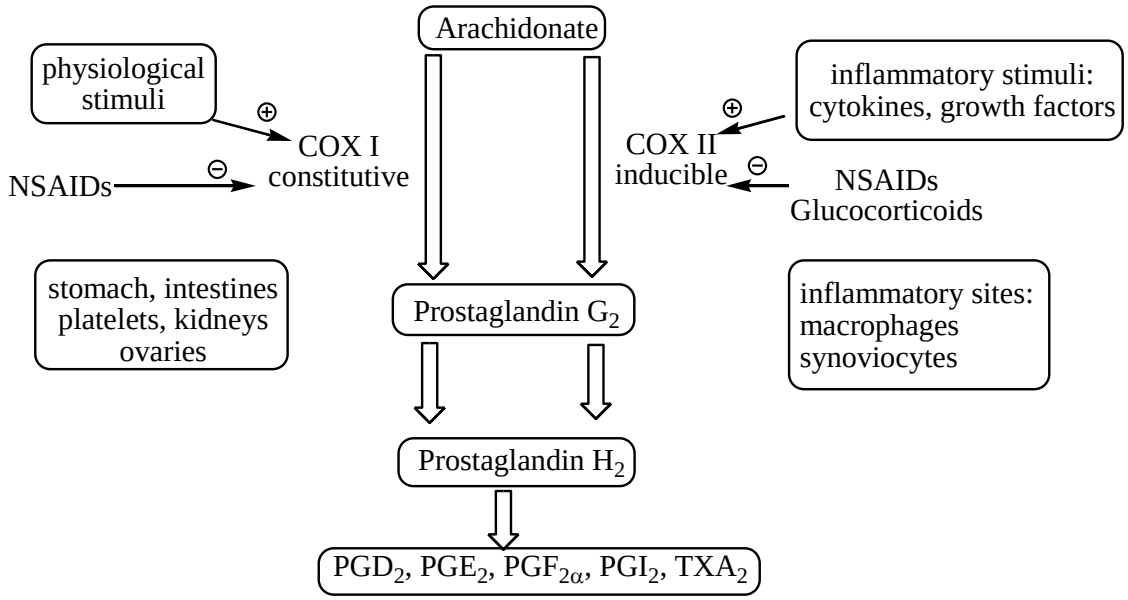


Figure 29. Prostaglandin production depends on COX I and COX II activity. Overview of the pathways of prostanoids derived from PGH_2.[306] NSAIDs affect both the constitutive and inducible form of COX activity. COX I and COX II activity play different roles in physiological processes. (+) means induction and (-) means inhibition of activities.

3.1.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (generally abbreviated: NSAIDs) are a class of medications possessing anti-inflammatory, analgesic and anti-pyretic activities, by virtue of their abilities to inhibit the COX isoforms.[307] NSAIDs impact upon COX I and COX II, (Figure 29), and inhibit production of both prostacyclin and thromboxane (TXA_2), and differ from selective COX II inhibitors which affect only prostacyclin production but not TXA_2. NSAIDs are among the most prescribed drugs worldwide for the treatment of acute and chronic pain, with 70 million prescriptions annually, and over 30 billion over-the-counter tablets sold.[308] NSAIDs reduce prostaglandin syntheses by inhibiting the rate-limiting COX enzyme, and the accessibility of the enzyme is shown to be directly related to the quantity of prostaglandin production (Figure 29).[309]

Furthermore, it has recently been revealed that there is an inflammatory component in the pathogenesis of Alzheimer disease.[310,311] In fact, immunochemistry completed on post mortem Alzheimer disease brains revealed that numerous inflammatory components are associated with neuritic plaques[312] and epidemiological studies have shown that therapy with anti-inflammatory drugs reduces the risk of developing Alzheimer disease.[313–317] Few researchers have attempted to understand the mechanisms by which NSAIDs can protect the nervous system from the ravages caused by Alzheimer disease, but importantly, many observations have shown data which indicate that an anti-inflammatory therapy reduces the risk of developing Alzheimer disease in subjects without a genetic predisposition.[318,319]

3.1.3 Diclofenac analogues

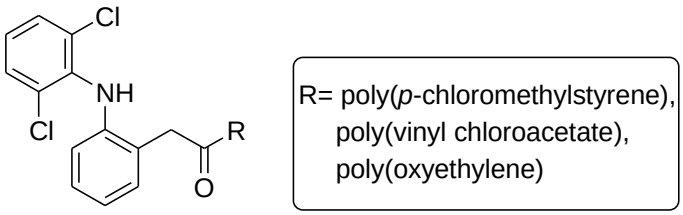
Diclofenac belongs to the non-steroidal anti-inflammatory class of drugs (NSAIDs) which play an important role in the treatment of osteoarthritis, rheumatoid arthritis,[320] spondylitis[321] and ocular inflammation.[322,323] Diclofenac is a widely used drug which acts through inhibition of the cyclooxygenase enzyme isoforms (COX I and COX II), leading to the peripheral inhibition of prostaglandin synthesis. Due to the fact that prostaglandins cause sensitisation of the pain receptors, the inhibition of their synthesis is responsible for its analgesic effects.[324] Nevertheless there are numerous side effects associated with the long-term use of diclofenac.

The common side effects associated with NSAID therapy may vary from gastrointestinal irritation to internal bleeding, and a few cases even turn out to be fatal.[325–327] The gastrointestinal irritation in the NSAID therapy is due to the interaction of the drug with COX I, while the clinical efficacy is attributed to the COX II inhibition. Additionally, the therapeutic utility in the treatment of inflammation by a few selective COX II inhibitors like celecoxib, rofecoxib, valdecoxib and etoricoxib have already been established.[328,329] These studies suggest that a single amino acid replacement, an isoleucine residue at position 523 in COX I by valine in COX II, is responsible for the selectivity of many COX II inhibitors.[330]

Unfortunately, the analysis of clinical trial data revealed that vascular events associated with the use of COX II inhibitors, such as non-fatal myocardial infarction (MI), non-fatal stroke, and death might be from a vascular event such as MI or stroke.[331,332] Therefore, Merck started to voluntarily withdraw its COX II inhibitors rofecoxib from the market in September 2004.[331] Moreover, traditional NSAIDs were also found to have cardiovascular risks, leading to similar boxed warnings.[331] The cause of the cardiovascular problems became, and remains, a subject of intense research.[333] Results in 2012 confirmed that the adverse cardiovascular effects are most likely due to inhibition of COX II in blood vessels leading to a decrease in the production of prostacyclin in blood vessels. Prostacyclin usually prevents platelet aggregation and vasoconstriction, so its inhibition can lead to excess clot formation and higher blood pressure.[333]

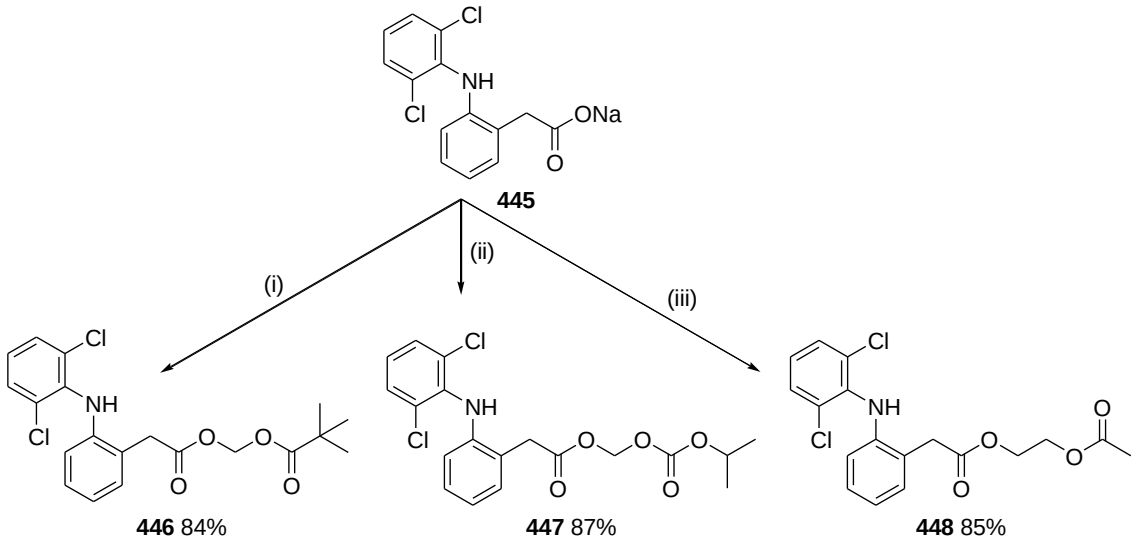
Therefore, a prodrug formation approach has been considered through the masking of the carboxylate moiety of these drugs in order to minimise gastrointestinal related side effects and also to improve their delivery characteristics.[334,335] Taking advantage of the presence of enzymes in living systems capable of hydrolysing esters, bioreversible esters have received considerable attention among the many possible prodrug approaches. In drug discovery, as well as drug development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical, or pharmacokinetic properties of pharmacologically potent compounds, thereby increasing developability and usefulness of a potential drug.[336,337] By utilising the prodrug approach, one strategy that could be useful is to temporarily mask the carboxylic acid function of the NSAIDs so that the prodrug hydrolyses *in vivo* to release the active parent NSAID.[338–340]

In order to counter the side effects of sodium diclofenac many papers report on the controlled release of diclofenac,[341,342] and the use of the polymeric prodrugs (such as **444**). In the latter case, diclofenac was attached to poly(*p*-chloromethylstyrene), polyvinyl chloroacetate or polyoxyethylene by esterification methods, Figure 30.[343] The results obtained from their synthesis and *in vitro* hydrolysis gives an insight into *in vivo* behaviour. However, the development of such systems into a drug product will require a truly multidisciplinary approach.



444

Figure 30. Enzyme-cleavable prodrug of diclofenac.



Reaction conditions: i) $ICH_2OCOC(CH_3)_3$, Na_2CO_3, DMA, -15 °C, 1h; ii) $ICH_2OCOOCH(CH_3)_2$, Na_2CO_3, DMA, -10 °C, 0.75 h; iii) $BrCH_2CH_2OCOCH_3$, Na_2CO_3, DMA, 55 °C, 5.5 h.

Scheme 155. Synthesis of some diclofenac ester prodrugs.

Bandgar *et al*. attempted the synthesis of new diclofenac ester prodrugs with the aim of obtaining enzymatically labile drugs with less ulceration than the parent drug diclofenac sodium **445**. In their approach, treatment of diclofenac sodium **445** with iodomethyl pivolate, iodomethylisopropyl carbonate, and 2-acetoxyethyl bromide in the presence of sodium carbonate in dimethylacetamide (DMA), offered diclofenac ester prodrugs **446**,

447, and **448** in a straightforward manner in good yields (84%, 87%, 85%, respectively), as illustrated in Scheme 155.

Interestingly, ulcer index (UI) studies showed that the diclofenac ester prodrugs **446**, **447**, and **448** possess substantially less ulcerogenicity (UI= 6, 8 and 40, respectively) than the parent diclofenac sodium (UI= 63). These diclofenac ester prodrugs underwent facile enzymatic transformation to regenerate the parent drug diclofenac in both rat liver microsome and rat plasma. Additionally *in vitro* and *in vivo* studies, revealed that prodrug **446** could potentially emerge as a potent and an alternative drug to diclofenac sodium (**445**) for the prevention of gastrointestinal disorders.

3.1.4 *In vitro* COX assays

Non-steroidal anti-inflammatory agents can inhibit COX I and/ or COX II action in one of several ways: 1) by inhibition of enzymatic activity, or 2) by inhibition of COX II mRNA and protein levels in cells. COX inhibitors of natural origin are reported to interfere on several levels, as reviewed by Perera *et al*.[344] A variety of assays have been described to evaluate the *in vitro* inhibition of COX. Experimental conditions, which differ between assays, include among others the following: the enzyme source (human or animal), the cell system used (intact normal cells, cell lines, or transfected cells), the method of enzyme purification (purified enzymes, microsomal, or whole cells assays), and the COX II inducing agent (e.g., lipopolysaccharide (LPS), tumour necrosis factor (TNFα), or interleukin-1 (IL-1)).[345]

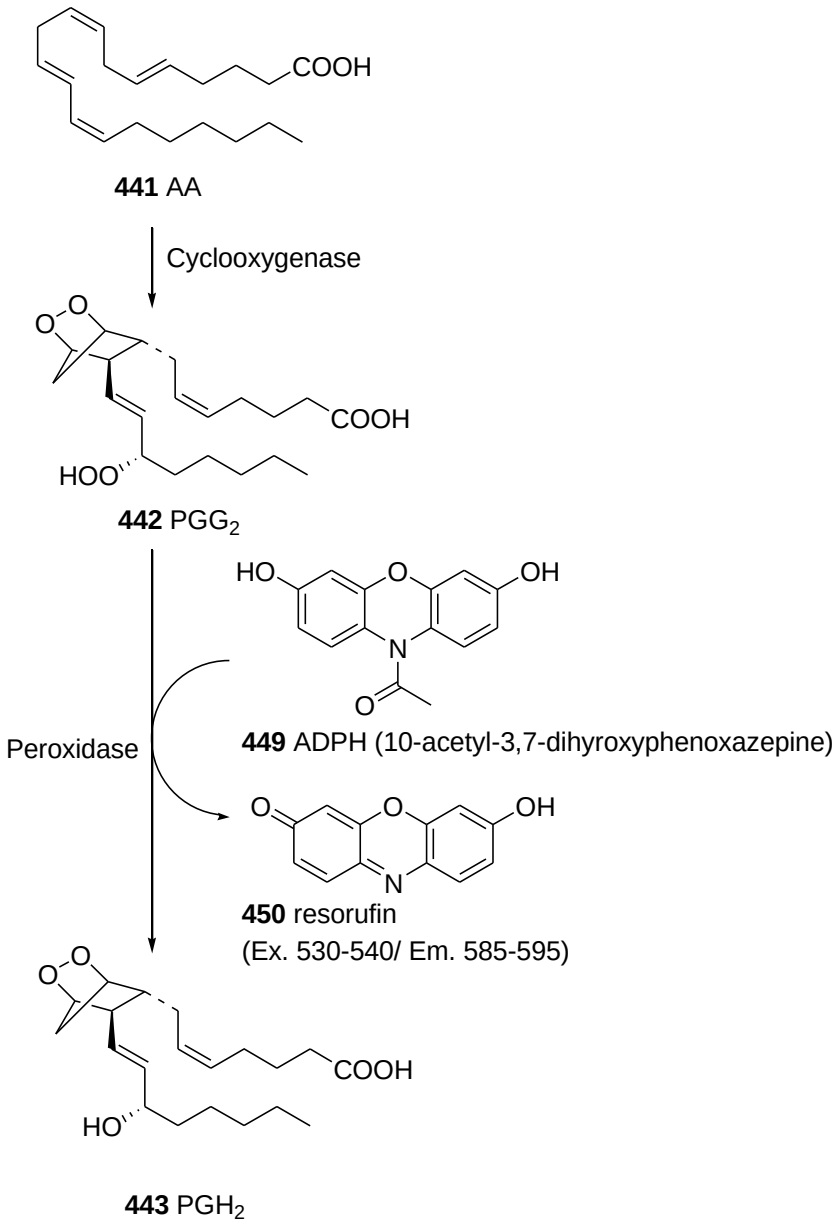
In addition to the above mentioned parameters, the source and concentration of arachidonic acid, incubation time with drug, protein concentration, and the method for detection of activity (i.e., prostaglandins or thromboxanes produced) vary in enzymatic activity assays. Consequently, all of these experimental conditions have contributed to significant variation in IC_{50} values and COX II selectivity ratios reported in the literature.[346] Commonly used detection methods to analyse the amount of produced prostaglandins and thromboxanes are: enzyme immunoassay (EIA), radio immunoassay (RIA), or a radiotracer method.[347,348] The latter method, which mostly uses radio-labelled substrates to measure the amount of radio-labelled prostaglandins produced after the COX catalysis, is quantified with scintillation counting or HPLC.[349,350] The scintillation proximity assay (SPA), a development of traditional scintillation counting, is widely used in high throughput screenings (HTS), since the method can be adapted to

robotics.[351] To detect enzymatic activity, another approach is to use a polarographic oxygen electrode to measure the amount of oxygen consumed during conversion of arachidonic acid to PGG_2.[352]

Furthermore, COX enzyme assays can be selected by various criteria, although they must be feasible and reproducible, and be appropriate for the investigation. The assay that most resembles *in vivo* situations is the human whole-blood assay that uses intact human cells.[345] Assays with purified enzymes are appropriate for studying drug-interactions with the active sites of an enzyme. Human cell lines or human recombinant enzymes in microsomal assays are more convenient for high-throughput investigations of structure-activity relationships.[345] The latter assays are also more suited for investigations of clinical relevance. For initial investigations of COX I and COX II inhibition of plant extracts and fractions containing a complex biomass, an assay using purified enzyme is preferable. Furthermore, a bioassay used for plant extracts needs to be suitable to a complex biomass with compounds that are coloured, sticky, and hydrophobic.[353] In addition, the assay must be reproducible, feasible, and reasonably inexpensive.

3.1.5 The principle of *in vitro* COX activity assay

The COX activity assay carried out here was Cayman's COX fluorescent inhibitor screening assay[354] which uses a convenient fluorescence-based method for screening both bovine COX I and human recombinant COX II for isozyme-specific inhibitors. The COX component converts arachidonic acid (**441**) to a hydroperoxy endoperoxide (**442** PGG_2), and the peroxidase component reduces the endoperoxide to the corresponding alcohol (**443** PGH_2), the precursor of prostaglandins, thromboxanes and prostacyclines, Scheme 156.[294,295] The assay utilises the peroxidase component of COXs. The reaction between PGC_2 (**442**) and 10-acetyl-3,7-dihydroxyphenoxazine (**449** ADPH) produces the highly fluorescent compound resorufin (**450**). Resorufin fluorescence can be easily analysed with an excitation wavelength of 530-540 nm and an emission wavelength of 585-595 nm, Scheme 156.



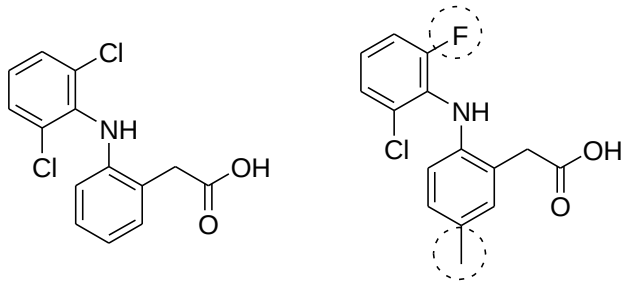
Scheme 156. The principle of Cayman's COX fluorescent inhibitor screening assay.

3.2 Synthesis of diclofenac analogues

3.2.1 Previous work

A search for non-steroidal anti-inflammatory drugs that had reduced toxicities and a longer duration of action was commenced by number of researchers.[355,356] Unexpectedly, it was noticed that some NSAIDs (e.g. indomethacin, ibufenac) and a series of experimental compounds investigated by Smith, Kline and French resembled plant growth regulators, such as indole-3-acetic acid,[357] phenylacetic acid[358] and naphthalene-1-acetic acid.[359]

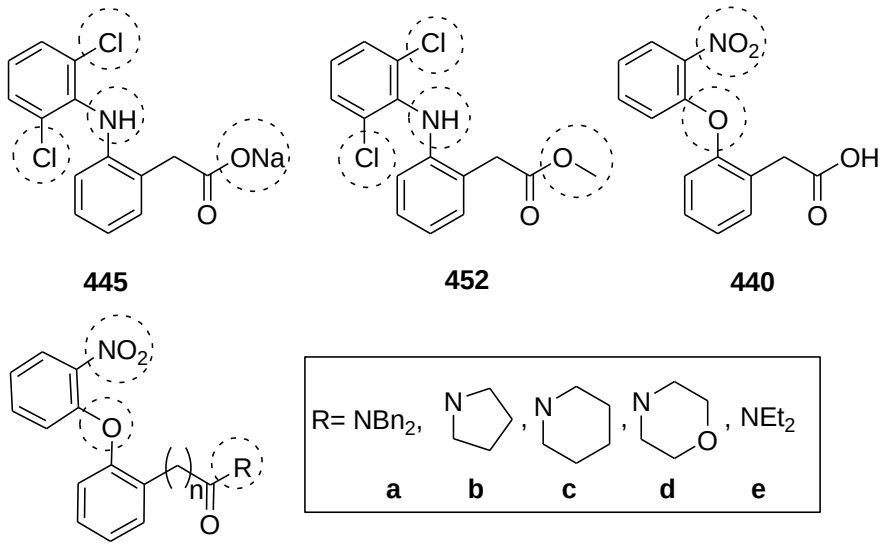
Modifying well known NSAIDs into selective COX II inhibitors represents an interesting strategy, and diclofenac and many other NSAIDs have been successfully elaborated into selective COX II inhibitors. For example, Novartis have described the conversion of diclofenac (**439**) into lumiracoxib (**451**), a compound which exhibits 500-fold selectivity for COX II over COX I (Figure 31).[360]



Diclofenac (**439**) Lumiracoxib (**451**)

Figure 31. Modification of diclofenac (**439**) to lumriacoxib (**451**).

Additionally, recent studies and reviews have shown that diarylether derivatives possess anticancer, antimicrobial, and anti-inflammatory activities.[290–293] In addition, the amide-based Truce-Smiles rearrangement precursors **334a-e** and **338a-e** are structurally analogous to diclofenac **439** the most widely used NSAID, Figure 32 (the dashed circles indicate the differences between diclofenac sodium (**445**) and its analogous compounds prepared herein **452**, **440, 334a-e** and **338a-e**).



445 **452** **440**

334a-e; n= 1
338a-e; n= 2

Figure 32. The differences between diclofenac sodium (**445**) and its analogous compounds prepared herein.

Furthermore, Sivaraj *et al*., in their attempt to discover new, safer and potent agents for the treatment of inflammatory diseases, designed some heterocyclic analogues of diclofenac (such as **453**, **454**) by replacing the carboxylic acid of diclofenac with less acidic heterocycles, Figure 33.[293]

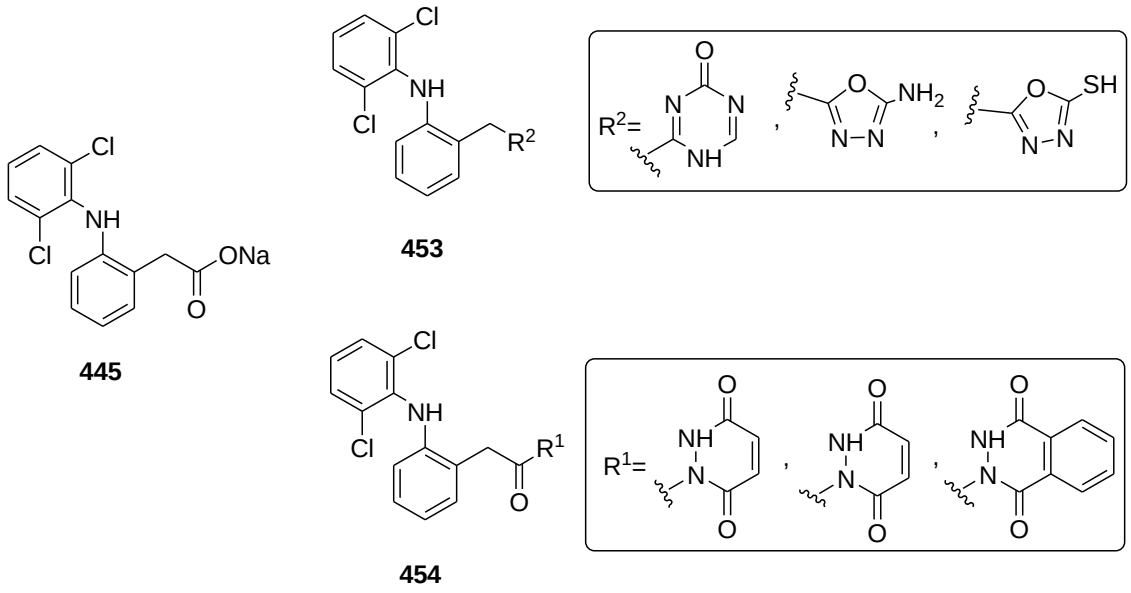


Figure 33. Some heterocyclic analogues of diclofenac.

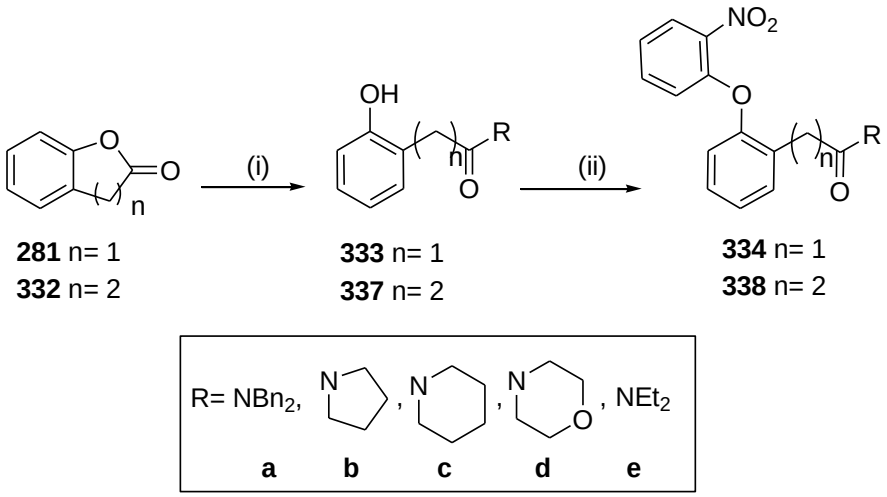
Sivaraj *et al*. screened their prepared heterocyclic analogues for analgesic, anti-inflammatory and ulcerogenic potential. Most compounds exhibited significant analgesic and anti-inflammatory activity and are devoid of the deadlier gastrointestinal toxicities, however the heterocyclic analogues denoted by **453** exhibited the most prominent and consistent anti-inflammatory activity.[293]

3.2.2 This work

Based on Sivaraj and others work, it was proposed that the diarylethers of amide-based Truce-Smiles rearrangement precursors **334a-e** and **338a-e** (section 2.2.2.3) might have useful anti-inflammatory, analgesic, and antipyretic properties like diclofenac, due to their close structural similarity.

In order to test this hypothesis, the compounds **334a-e** and **338a-e**, previously prepared and discussed in Chapter 2, by refluxing the lactones (**281** or **332**, Scheme 157) with the amines in toluene to afford the corresponding amides (**333a-e** and **337a-e**) in excellent

yields, were studied. The amides were subsequently reacted with 1-fluoro-2-nitrobenzene (**60**) in DMSO at room temperature (to minimise Truce-Smiles rearrangement for substrates based on **333**) to offer the desired diarylethers **334a-e** and **338a-e** in moderate to good yields (see Table 17 and Scheme 157).



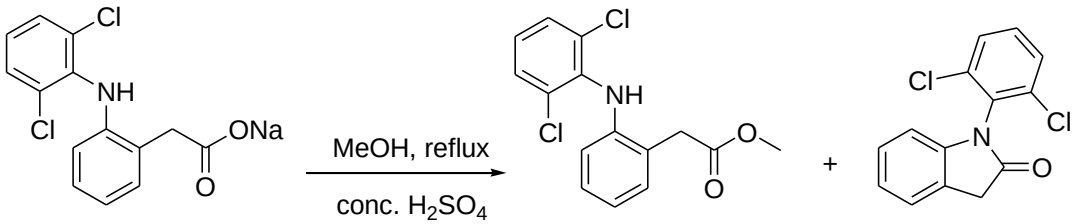
Reaction conditions: i) amine (1.5 eq.), lactone **281** or **332** (1 eq.), toluene (0.1 M), reflux, 6 h; ii) amide **333a-e** and **336a-e** (1 eq.), 1-fluoro-2-nitrobenzene (**60**) (1.05 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1 M), r.t., 24 h.

Scheme 157. Synthesis of diarylethers **334a-e** and **338a-e**.

Table 17. Isolated yields of the amides **333a-e** and **337a-e** and their corresponding diarylethers **334a-e** and **338a-e.**

Entry	n	Amides **333** (%)	Diarylethers **334** (%)
a	1	95	64
b	1	89	93
c	1	98	83
d	1	81	40
e	1	96	74
		Amides **337** (%)	Diarylethers **338** (%)
a	2	98	100
b	2	100	100
c	2	78	87
d	2	82	90
e	2	100	90

Along with the amide-based Truce-Smiles precursors above, diclofenac methyl ester **452**, has also prepared from refluxing diclofenac sodium (**445**) in methanol containing a few drops of conc. H_2SO_4. The desired methyl ester of diclofenac (**452**) was prepared in 88% yield, along with a lactam product **453** in 12% yield, presumably formed from attack of the nitrogen onto the methyl ester carbonyl, Scheme 158.

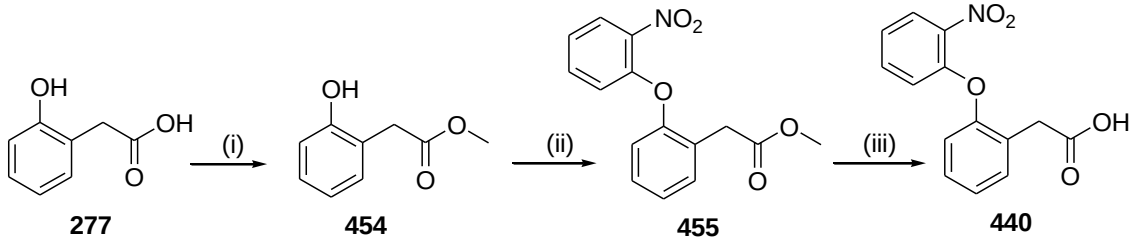


445 **452** 88% **453** 12%

Reaction conditions: diclofenac sodium (**445**) (1 eq.), conc. H_2SO_4 (few drops), methanol (0.1 M), reflux, 3 h.

Scheme 158. Synthesis of diclofenac methyl ester.

Furthermore, a closely related analogue to diclofenac, 2-(2-(2-nitrophenoxy)phenyl)acetic acid (**440**) was also prepared through three successive steps, Scheme 159. The first step was the preparation of 2-hydroxyphenyl acetate methyl ester (**454**) (100%) from refluxing 2-hydroxyphenyl acetic acid (**277**) in acidic methanol. This esterification procedure was required to protect the acid **277**, since exploratory work in the early stages of this thesis had shown that the Truce-Smiles rearrangement does not work on acid substrates. Secondly, the methyl ester **454** was reacted with 1-fluoro-2-nitrobenzene (**60**) in the presence of K_2CO_3 in DMSO at room temperature to give the desired methyl ester of 2-(2-(2-nitrophenoxy)phenyl)acetic acid (**455**) in 30% yield. Finally, 2-(2-(2-nitrophenoxy)phenyl)acetate methyl ester (**455**) was hydrolysed in aqueous basic THF to afford the final product (**440**) in 100% yield.



277 **454** **455** **440**

Reaction conditions: i) 2-hydroxyphenylacetic acid (**277**) (1 eq.), conc. H_2SO_4 (few drops), methanol (0.1 M), reflux, 16 h; ii) 2-hydroxyphenylacetate methyl ester (**454**) (1 eq.), 1-fluoro-2-nitrobenzene (**60**) (1.05 eq.), K_2CO_3 (1 eq.), DMSO (0.1 M), r.t., 16 h; iii) methyl 2-(2-(2-nitrophenoxy)phenyl)acetate (**455**) (1 eq.), basic THF solution (THF: 1M NaOH; 50:50; 0.1 M), r.t., 16 h.

Scheme 159. Synthesis of 2-(2-(2-nitrophenoxy)phenyl)acetic acid (**440**).

3.2.3. *In vitro* COX assay

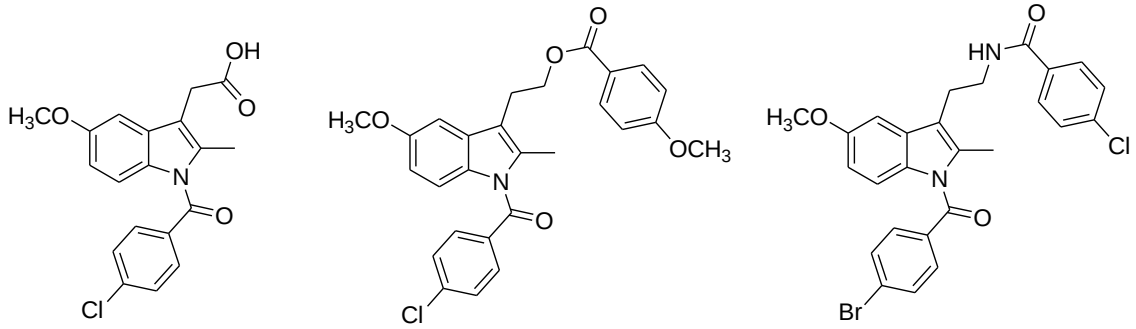
Upon closer inspection of the literature, it appears as though the distance between the acidic centre and the flat aryl surface is critical for the analgesic and anti-inflammatory activities observed by the diarylethers which have to-date been studied, and that increasing this distance to two or three carbons generally diminishes activity.[361–363]. As such, the propanamide-based Truce-Smiles rearrangement precursors (**338a-e**) were not tested because of their increased distance between the amide carbonyl and the flat aryl surface. Therefore, instead, only the acetamide-based Truce-Smiles rearrangement substrates were screened, since the distance between the amide carbonyl and the flat surface is the same as the distance in diclofenac itself.

The diarylether of pyrrolidyl-acetamide (**334b**) was selected as a prototype within its group in the hope that its chiral analogue may be more active as a pure enantiomer. Moreover, to enable a comparison with diclofenac sodium (**445**) to be made its methyl ester **452** as well as 2-(2-(2-nitrophenoxy)phenyl)acetic acid (**440**) were screened for their activity against COX. The reason behind testing the methyl ester of diclofenac (**452**) was to compare it directly with the diarylether of pyrrolidyl acetamide (**334b**) and also to see how the decrease in acidity affects the interaction with its target receptor.

The COX inhibitory activity assay was carried out by applying the *in vitro* Cayman's COX fluorescent inhibitor screening protocol in which the inhibitors were tested against both bovine COX I and human recombinant COX II, Table 18. [354]

Table 18. *In vitro* COX assay results.

COX I % inhibition				
Conc. nM	diclofenac sodium **445**	diclofenac methyl ester **452**	diarylether acid **440**	diarylether pyrrolidyl acetamide **334b**
20	62	10	26	25
200	76	35	33	37
2000	92	58	45	37
COX II % inhibition				
Conc. nM	diclofenac sodium **445**	diclofenac methyl ester **452**	diarylether acid **440**	diarylether pyrrolidyl acetamide **334b**
20	68	22	28	44
200	88	33	28	53
2000	98	54	29	70



Indomethacin **456** ester analogue **457** amide analogue **458**

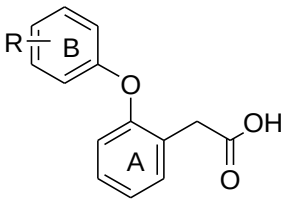
Figure 34. Indomethacin and its ester and amide analogues.

As can be seen from Table 18, only the diarylether of pyrrolidyl amide **334b** showed any appreciable activity (70% inhibition at 2000 nM) against COX II. This greater COX II selectivity is attributed to introducing larger substituents (COOH replace by pyrrolidyl amide) to fit into the active site volume of COX II.[364] Marnett *et al*. demonstrated similar results when they attempted to shift the enzyme selectivity of indomethacin (**456**) from COX I to COX II while maintaining potency at the same level and reducing the unwanted side-effects at the same time.[365] In their studies they converted the non-selective NSAID **456** to esters **457** and amides **458** in order to obtain selective COX II inhibitors, Figure 34.

The acidic centre of diclofenac is crucial for activity as it interacts with the cationic site of the receptor, therefore, the more acidic the better the inhibition. Based on this, the reason behind the reduced activity of diarylether pyrrolidyl acetamide **334b** against

COX I (25-37% inhibition) might be attributed to the fact that the amides are not acidic whereas their carboxylic acid analogues are.[361–363]

Research by Atkinson *et al.* tested 117 derivatives of substituted (2-phenoxyphenyl)acetic acids **459** (known as fenclofenac when R=2,4-Cl_2) for their anti-inflammatory activity, and demonstrated that those derivatives in which the ring B is substituted by mono- or di-nitro groups show the least activity, Figure 35.[366,367] Consistent with Atkinson *et al*. the diarylether acetic acid **440** prepared herein showed around 33% and 28% inhibitory activity against COX I and COX II, respectively (Table 18). In their work, Atkinson attributed the reduced activity to a reduced interaction (through hydrophobic or charge transfer interactions) with the receptor in comparison to those derivatives **459** substituted by mono- or di-chloro group, Figure 35.[366,367]



459

		COX II % inhibition at 50 nM
R=	2,3-Cl_2	51
	2,4-Cl_2	36
	2,4-$(NO_2)_2$	0
	2,4-$(NH_2)_2$	0
	4-Cl, 2-NO_2	4
	4-Cl, 2-NH_2	4
	2-Cl, 4-NO_2	19

Figure 35. Atkinson's derivatives of substituted (2-phenoxyphenyl)acetic acids **459** with their COX II percent of inhibiton.

In summary, it was observed that the diarylether of pyrrolidyl acetamide **334b** possesses an appreciable activity against COX II which can be attributed to incorporating larger substituents to enable a better fit into the active site volume of COX II. However, the diarylether acetic acid **440** showed around 35% and 28% inhibitory activity against COX I and COX II respectively, due to a reduced interaction with the receptor, the result of being mono-nitro-substituted, a similar result of which was seen by Atkinson.[366,367]

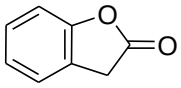
CHAPTER 4 - EXPERIMENTAL

CHAPTER FOUR - EXPERIMENTAL

4.1 General information

Commercially available reagents were used as received without purification. Analytical thin layer chromatography (TLC) was performed with plastic-backed TLC plates coated with silica G/UV_{254}, in a variety of solvents. The plates were visualised by UV light (254 nm), *p*-anisaldehyde solution or $KMnO_4$ solution. Flash column chromatography was conducted with Davisil silica 60Å (40-63 μm) under bellows pressure. Low resolution mass spectra were recorded on a Thermo FinniganLCQ Advantage MAX using electron spray ionisation (ESI) and high resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service, UK. ^{1}H and ^{13}C NMR spectra were recorded on a BrukerAvanceDPX 300 (300MHz) or a Bruker 400 (400MHz) spectrometer. All chemical shifts (δ) are quoted in parts per million (ppm) relative to a calibration reference of the residual protic solvent; C*H*Cl_3 (δ_H 7.26, s) or DMSO-*d6* (δ_H 2.50, pent.) was used as the internal standard in ^{1}H NMR spectra, and ^{13}C NMR shifts were referenced using *C*DCl_3 (δ_C 77.16, t) or DMSO-*d6* (δ_C 39.5, m) with broad band decoupling and the *J* values are measured in Hertz. Petroleum ether refers to the fraction which boils between 40-60 °C. Melting points were measured on a Stuart® SMP10 melting point apparatus and are uncorrected. $[\alpha]_D$ was measured on JASCO P-2000 polarimeter and IR spectra were recorded on a NICOLET iS10.

4.2 Procedure for the synthesis of 2-coumaranone

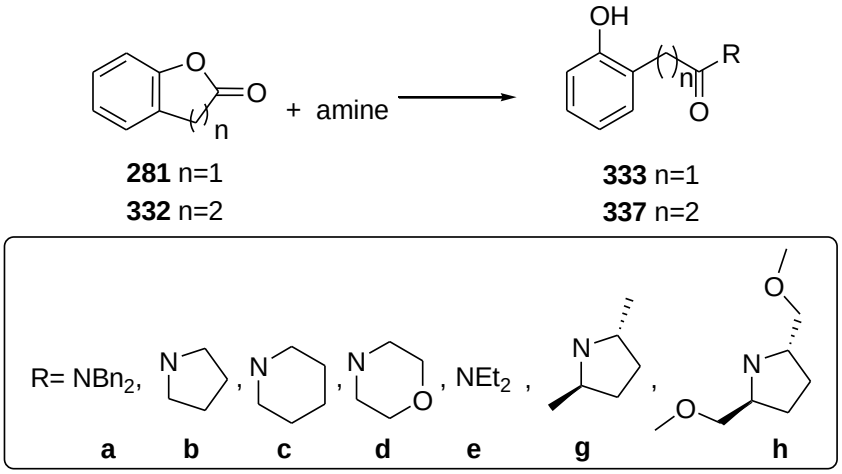


281

To a solution of 2-hydroxyphenyl acetic acid (5g, 32.9 mmol) in toluene (70mL) was added *p*-toluenesulfonic acid (0.62g, 3.28 mmol). The resulting solution was stirred at 110 °C under Dean-Stark conditions for 6 hours, after which it was allowed to cool, washed with sat. aq. $NaHCO_3$ (3×30mL), brine (30mL) and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled water (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford 2-coumaranone (4.23 g, 96%) as yellow crystals; R_f (30% EtOAc in petroleum ether): 0.76; m.p.= 51-53 °C (EtOAc/petroleum) [(lit. m.p. 49-51 °C)[368] (toluene)]; IR (neat, cm^{-1}): ν_{max} 1794

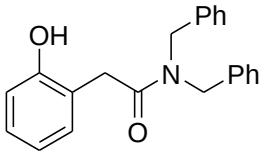
(C=O stretching), 1051 (C-O stretching; ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.77 (s, 2H, CH_2), 7.12-7.21 (m, 2H, Ar), 7.29-7.36 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 33.13 (CH_2), 110.91, 123.16, 124.22, 124.76 (CH), 129.01, 154.81, 174.24 (C). MS (APCI *m*/*z*): 135 $[M+H)^+$, (100%)].

4.3 General procedure for the synthesis of amides 333 and 337



To a solution of 2-coumaranone (**281**) or dihydrocoumarin (**332**) (1 eq.) in toluene (0.1 M) was added the amine (1.5 eq.). The resulting solution was stirred at 110 ^oC for 4-6 hours, after which it was allowed to cool, acidified (1 M HCl to pH ca. 1-2), and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the pure amide directly or after flash column chromatography.

N,*N*-Dibenzyl-2-(2-hydroxyphenyl)acetamide, 333a

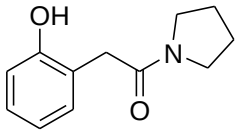


333a

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as yellow crystals (91%). R_f (20% EtOAc in petroleum ether): 0.66; m.p.= 139-141 ^oC (toluene); IR (neat, cm^{-1}): ν_{max} 1613 (C=O stretching), 3064 (O-H

stretching), 1477 (C-O stretching), ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.81 (s, 2H, CH_2), 4.63 (s, 2H, NCH_2), 4.64 (s, 2H, NCH_2), 6.68-6.76 (m, 2H, Ar), 7.02 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.14-7.21 (m, 5H, Ar), 7.26-7.41 (m, 6H, Ar), 10.07 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 37.18, 49.33, 51.26, (CH_2), 118.33, 120.14 (CH), 120.99 (C), 126.52, 127.91, 128.15, 128.42, 128.90, 129.23, 129.28, 130.70 (CH), 135.70, 136.28, 157.06, 174.45 (C); MS (APCI *m*/*z*): 332 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 332.1645, $C_{22}H_{21}NO_2+H^+$ requires 332.1651.

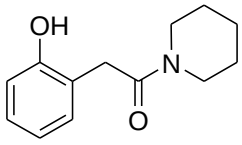
2-(2-Hydroxyphenyl)-1-(pyrrolidin-1-yl)ethanone, 333b



333b

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as colourless crystals (89%). R_f (20% EtOAc in toluene): 0.42; m.p.= 120-122 °C (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1610 (C=O stretching), 2959 (OH stretching), 1094 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.89 (pent, 2H, *J*= 6.0Hz, CH_2CH_2), 2.01 (pent, 2H, *J*= 6.0Hz, CH_2CH_2), 3.48 (t, 2H, *J*= 6.0Hz, CH_2), 3.68 (t, 2H, *J*= 6.0Hz, NCH_2), 3.70 (s, 2H, NCH_2), 6.81 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 6.99 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.03 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.19 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 10.37 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.53, 26.12, 39.03, 46.34, 47.77 (CH_2), 118.44, 119.99, 121.06, 129.17 (CH), 130.56, 157.35, 171.60 (C); MS (APCI *m*/*z*): 206 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 206.1176, $C_{12}H_{15}NO_2+H^+$ requires 206.1176.

2-(2-Hydroxyphenyl)-1-(piperidin-1-yl)ethanone, 333c

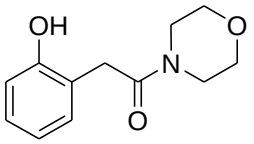


333c

Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as a yellow crystals (98%). R_f (30% EtOAc in petroleum ether): 0.48; m.p.=

107-109 °C (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1616 (C=O stretching), 3166 (OH stretching), 1039 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.52-1.63 (m, 6H, CH_2CH_2), 3.55 (t, 2H, *J*= 6.0Hz, NCH_2), 3.61 (t, 2H, *J*= 6.0Hz, NCH_2), 3.73 (s, 2H, CH_2), 6.81 (t, 1H, *J*= 7.5Hz, Ar), 6.95 (d, 1H, *J*= 9.0Hz, Ar), 7.03 (d, 1H, *J*= 9.0Hz, Ar), 7.16 (t, 1H, *J*= 7.5Hz, Ar), 9.87 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.25, 25.36, 26.52, 36.41, 43.45, 48.16, (CH_2), 117.99, 120.03 (CH), 121.11 (C), 128.91, 130.18 (CH), 157.03, 171.17 (C); MS (APCI *m*/*z*): 220 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 220.1331, $C_{13}H_{17}NO_2+H^+$ requires 220.1332.

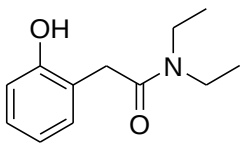
2-(2-Hydroxyphenyl)-1-morpholinoethanone, 333d



333d

Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow crystalline solid (81%). R_f (30% EtOAc in petroleum ether): 0.34; m.p.= 123-125 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): ν_{max} 1615 (C=O stretching), 2931 (OH stretching), 1092 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.65-3.68 (m, 8H, CH_2CH_2), 3.74 (s, 2H, CH_2), 6.83 (td, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 6.99 (t, 2H, *J*= 6.0Hz, Ar), 7.19 (td, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 9.56 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 36.31, 42.59, 47.29, 66.51, 66.65 (CH_2), 118.32, 120.36 (CH), 120.62 (C), 129.9, 130.17 (CH), 165.95, 171.71 (C); MS (APCI *m*/*z*): 222 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 222.1125, $C_{12}H_{15}NO_3+H^+$ requires 222.1125.

***N*,*N*-Diethyl-2-(2-hydroxyphenyl)acetamide, 333e**

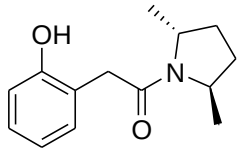


333e

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as an off-white solid (96%). R_f (30% EtOAc in petroleum ether): 0.54; m.p.=

88-90 °C (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1618 (C=O stretching), 3173 (OH stretching), 1090 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.13 (t, 3H, *J*= 7.5Hz, CH_3), 1.29 (t, 3H, *J*= 6.0Hz, CH_3), 3.39 (q, 2H, *J*= 6.0Hz, CH_2CH_3), 3.50 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 3.71 (s, 2H, CH_2), 6.82 (td, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 6.97-7.04 (m, 2H, Ar), 7.19 (td, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 10.47 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.05, 14.94 (CH_3), 37.06, 41.47, 43.67 (CH_2), 118.41, 119.97 (CH), 121.31 (C), 129.15, 130.54 (CH), 157.43, 172.83 (C); MS (APCI *m*/*z*): 208 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 208.1332, $C_{12}H_{17}NO_2+H^+$ requires 208.1332.

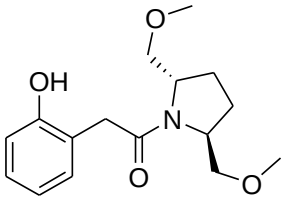
1-[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]-2-(2-hydroxyphenyl)ethanone 333g



333g

Flash column chromatography (SiO_2; 5% EtOAc in toluene) afforded the title compound as a colourless solid (73%). R_f (20% EtOAc in toluene): 0.56; m.p. =142-144 °C (EtOAc in toluene). $[\alpha]_D$= −69.8 (ethanol, c = 0.2 g/100ml). IR (neat, cm^{-1}): ν_{max} 1560 (C=O stretching), 2965 (OH stretching), 1035 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.15 (d, 3H, *J*= 6.0Hz, CH_3), 1.31 (d, 3H, *J*= 6.0Hz, CH_3), 1.57-1.61 (m, 1H, CH), 1.66-1.71 (m, 1H, CH), 2.07-2.29 (m, 2H, CH_2), 3.67 (d, 1H, $H_{A/B}$, *J*= 15.0Hz, CH_AH$_B$Ar), 3.73 (d, 1H, $H_{B/A}$, *J*= 15.0Hz, CH_BH$_A$Ar), 4.21-4.28 (m, 2H, CH_2), 6.80 (t, 1H, *J*= 7.5Hz, Ar), 6.97-7.03 (m, 2H, Ar), 7.17 (t, 1H, *J*= 7.5Hz, Ar), 11.01 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 19.02, 22.56 (CH_3), 29.20, 30.84, 39.32 (CH_2), 53.99, 55.04 (CH), 118.54, 119.77 (CH), 121.62 (C), 129.14, 130.73 (CH), 157.55, 172.18 (C); MS (APCI *m*/*z*): 234 $[M+H)^+$, (100%)].

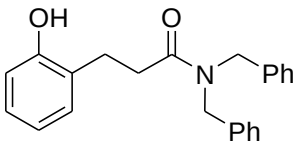
1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-hydroxyphenyl)ethanone, 333h



333h

Flash column chromatography (SiO_2; 60% EtOAc in petroleum ether) to afford the title compound as yellow sticky oil (99%). R_f (30% EtOAc in petroleum ether): 0.42. $[\alpha]_D$= −53.43 (ethanol, c = 0.46 g/100ml). IR (neat, cm^{-1}): ν_{max} 1618 (C=O stretching), 2929 (OH stretching), 1040 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.88-2.01 (m, 3H, CH_2CH_2), 2.12-2.21 (m, 1H, CH_2CH_2), 2.25-3.54 (m, 10H includes 2×(s, 3H) @ 3.24 and 3.37, CH_2OCH_3), 3.73 (d, 1H, $H_{A/B}$, *J*= 14.0Hz, C*H*$_A$H$_B$Ar), 3.82 (d, 1H, $H_{B/A}$, *J*= 14.0Hz, C*H*$_B$H$_A$Ar), 4.20-4.27 (m, 2H), 6.81 (t, 1H, *J*= 6.0Hz, Ar), 6.97 (d, 1H, *J*= 8.0Hz, Ar), 7.03 (d, 1H, *J*= 7.0Hz, Ar), 7.18 (t, 1H, *J*= 7.5Hz, Ar), 10.59 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.81, 27.54, 39.53 (CH_2), 57.69, (CH), 59.15 (CH_3), 59.41 (CH), 71.29, 74.79 (CH_2), 118.49, 119.95 (CH), 121.62 (C), 129.18, 130.08 (CH), 157.23, 173.46 (C); MS (APCI *m*/*z*): 294 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 294.1702, $C_{16}H_{23}NO_4+H^+$ requires 294.1700.

***N*,*N*-Dibenzyl-3-(2-hydroxyphenyl)propanamide, 337a**

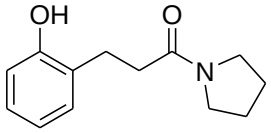


337a

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as a colourless solid (92%). R_f (10% EtOAc in toluene): 0.63; m.p.= 148-150 ^oC (EtOAc/toluene); IR (neat, cm^{-1}): ν_{max} 1613 (C=O stretching), 3181 (O-H stretching), 1142 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.82 (t, 2H, *J*= 6.0Hz, CH_2CH_2), 3.01 (t, 2H, *J*= 6.0Hz, CH_2C=O), 4.41 (s, 2H, NCH_2), 4.58 (s, 2H, NCH_2), 6.82 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 6.96-7.01 (m, 4H, Ar), 7.13-7.20 (m, 3H, Ar), 7.27-7.30 (m, 6H, Ar), 9.31 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.00, 35.11, 48.98, 49.97

(CH_2), 118.19, 120.40, 126.37, 127.78, 127.90 (CH), 128.10 (C), 128.15, 128.50, 128.82, 129.17, 130.75 (CH), 135.48, 136.63, 155.37, 174.99 (C); MS (APCI *m*/*z*): 346 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 346.1807, $C_{23}H_{23}NO_2+H^+$ requires 346.1802.

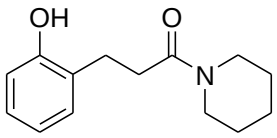
Pyrrolidyl-2-(2-hydroxyphenyl)propanamide, 337b



337b

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as colourless crystals (100%). R_f (50% EtOAc in petroleum ether): 0.51; m.p.= 151-153 ^oC (EtOAc/toluene); IR (neat, cm^{-1}): v_{max} 1622 (C=O stretching), 1039 (C-N stretching), 3283 (OH stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.78-1.98 (m, 4H, CH_2CH_2), 2.66 (t, 2H, *J*= 6.0Hz, CH_2CH_2Ar), 2.94 (t, 2H, *J*= 6.0Hz, $CH_2C=O$), 3.33 (t, 2H, *J*= 7.5Hz, NCH_2), 3.45 (t, 2H, *J*= 6.0Hz, NCH_2), 6.82 (t, 1H, *J*= 6.0Hz, Ar), 6.92 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.04-7.12 (m, 2H, Ar), 9.90 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.40, 24.44, 26.05, 36.74, 46.31, 46.66 (CH_2), 118.32, 120.12, 128.09, 128.62 (CH), 130.73, 155.70, 172.42 (C); MS (APCI *m*/*z*): 220 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 220.1332, $C_{13}H_{17}NO_2+H^+$ requires 220.1332.

3-(2-Hydroxyphenyl)-1-(1-piperidyl)propan-1-one, 337c

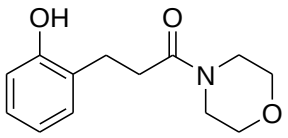


337c

Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as colourless crystals (78%). R_f (30% EtOAc in petroleum ether): 0.46; m.p.= 130-132 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): v_{max} 1619 (C=O stretching), 3278 (OH stretching), 1013 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.55-1.62 (m, 6H, CH_2CH_2), 2.71 (t, 2H, *J*= 4.5Hz, CH_2CH_2Ar), 2.94 (t, 2H, *J*= 4.5Hz, $CH_2C=O$), 3.34 (t, 2H, *J*= 4.5Hz, NCH_2), 3.55 (t, 2H, *J*= 4.5Hz, NCH_2), 6.82 (t, 1H, *J*= 6.0Hz, Ar), 6.91 (d, 1H, *J*= 9.0Hz, Ar), 7.5 (d, 1H, *J*= 9.0Hz, Ar), 7.11 (t, 1H, *J*= 7.5Hz, Ar), 9.87 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.39, 24.82, 25.51, 26.21, 35.25, 43.39, 46.45,

(CH_2), 118.14, 120.12, 128.06 (CH), 128.55 (C), 130.77 (CH), 155.69, 172.00 (C); MS (APCI *m/z*): 234 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 234.1489, $C_{14}H_{19}NO_2+H^+$ requires 234.1489.

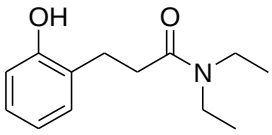
3-(2-Hydroxyphenyl)-1-morpholino-propan-1-one, 337d



337d

Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as a colourless solid (82%). R_f (30% EtOAc in petroleum ether): 0.29; m.p.= 129-131 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): ν_{max} 1618 (C=O stretching), 2974 (OH stretching), 1035 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.71 (t, 2H, *J*= 6.0Hz, CH_2CH_2Ar), 2.96 (t, 2H, *J*= 6.0Hz, $CH_2C=O$), 3.42 (t, 2H, *J*= 6.0Hz, NCH_2), 3.62 (m, 6H, NCH_2OCH_2), 6.84 (t, 1H, *J*= 5.5Hz, Ar), 6.92 (d, 1H, *J*= 9.0Hz, Ar), 7.05 (d, 1H, *J*= 9.0Hz, Ar), 7.13 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 9.43 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.59, 35.11, 42.48, 45.73, 66.34, 66.76 (CH_2), 118.11, 120.34, 128.14 (CH), 128.21 (C), 130.76 (CH), 155.45, 172.64 (C); MS (APCI *m/z*): 236 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 236.1283, $C_{13}H_{17}NO_3+H^+$ requires 236.1283.

***N,N*-Diethyl-3-(2-hydroxyphenyl) propionamide, 337e[26]**



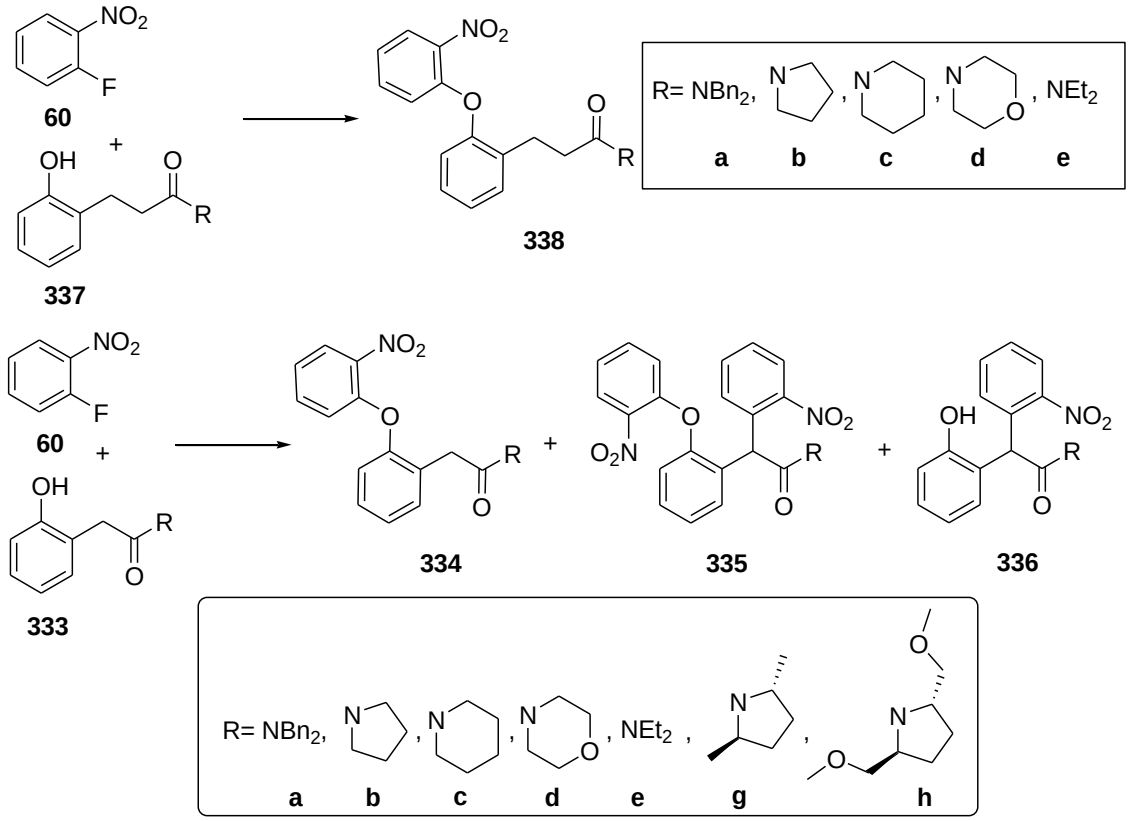
337e

The solvent was evaporated *in vacuo* to afford the title compound as a pale yellow solid (100%). R_f (30% EtOAc in petroleum ether): 0.41; m.p.= 128-130 °C (EtOAc/petroleum ether), IR (neat, cm^{-1}): ν_{max} 1613 (C=O stretching), 3175 (OH stretching), 1071 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.08 (t, 3H, *J*= 4.5Hz, CH_3), 1.11 (t, 3H, *J*= 4.5Hz, CH_3), 2.71 (t, 2H, *J*= 6.0Hz, $CH_2C=O$), 2.94 (t, 2H, *J*= 6.0Hz, CH_2Ar), 3.26 (q,

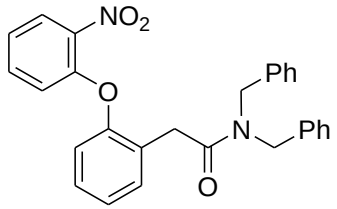
2H, *J*= 9.0Hz, NCH_2), 3.36 (q, 2H, *J*= 9.0Hz, NCH_2), 6.81 (td, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 6.91 (dd, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 7.04 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.11 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 9.76 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.02, 13.88 (CH_3), 24.90, 35.04, 40.95, 42.09 (CH_2), 118.13, 120.08, 128.05, 128.48 (CH), 130.70, 155.69, 173.13 (C); MS (APCI *m*/*z*): 222 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 222.1485, $C_{13}H_{19}NO_2+H^+$ requires 222.1489.[369]

4.4 General procedure for the Truce-Smiles rearrangement reactions

To a solution of the amide (**333a-h**, **337a-e**) (1 eq.) in dimethylsulfoxide (0.1 M) was added potassium carbonate (2.5 eq.) and the resulting solution was stirred at room temperature for 30 minutes. 1-Fluoro-2-nitrobenzene (1.05 eq) was added and the reaction stirred for 24 hours at 60 °C. After which, the mixture was acidified with hydrochloric acid solution (1 M, 30mL). The product was extracted with ethyl acetate (2×30mL) and the combined organic layers were washed with distilled water (2×20mL), brine (10mL), dried ($MgSO_4$), filtered and the solvent evaporated in *vacuo* to afford the crude residue which was purified by flash column chromatography.



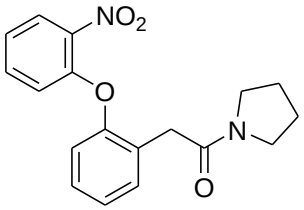
2-(2-(2-Nitrophenoxy)phenyl)-*N*,*N*-dibenzylacetamide, 334a



334a

Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as a yellow oil (40%). R_f (30% EtOAc in petroleum ether): 0.49; IR (neat, cm^{-1}): ν_{max} 1644 (C=O stretching), 1079 (C-O stretching), 1523, 1349 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.90 (s, 2H, $CH_2C{=}O$), 4.55 (s, 2H, NCH_2), 4.59 (s, 2H, NCH_2), 6.88 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.07 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.12-7.15 (m, 3H, Ar), 7.18-7.36 (m, 10H, Ar), 7.45 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.50 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.97 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 34.80, 48.65, 50.38 (CH_2), 118.83, 120.41, 123.04, 125.08, 125.67, 126.53, 127.41, 127.64, 128.34, 128.61, 128.76, 128.98, 131.99, 134.46 (CH), 136.43, 137.29, 141.00, 150.76, 153.65, 171.19 (C); MS (APCI *m*/*z*): 453 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 453.1810, $C_{28}H_{24}N_2O_4+H^+$ requires 453.1809.

2-(2-(2-Nitrophenoxy)phenyl)-1-(pyrrolidin-1-yl)ethanone, 334b

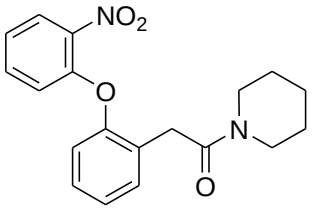


334b

Flash column chromatography (SiO_2; 100% petroleum ether) afforded the title compound as yellow oil (90%). R_f (30% EtOAc in petroleum ether): 0.39; IR (neat, cm^{-1}): ν_{max} 1636 (C=O stretching), 1247 (C-N stretching), 1098 (C-O stretching), 1522, 1345 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.69-1.92 (m, 4H, CH_2CH_2), 3.31 (t, 2H, *J*= 6.0Hz, NCH_2), 3.43 (t, 2H, *J*= 7.5Hz, NCH_2), 3.67 (s, 2H, CH_2Ar), 6.90 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 6.95 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.13-7.26 (m, 3H, Ar), 7.41 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.45 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar),

7.92 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.43, 26.15, 35.89, 45.93, 46.89 (CH_2), 119.49, 119.56, 122.68, 125.41, 125.51 (CH), 127.84 (C), 128.60, 132.01, 134.35 (CH), 140.64, 150.92, 153.09, 168.74 (C); MS (APCI *m*/*z*): 327 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 327.1343, $C_{18}H_{18}N_2O_4+H^+$ requires 327.1339.

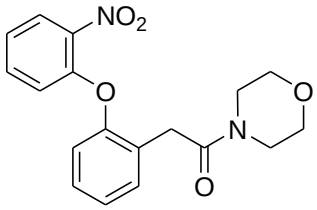
2-[2-(2-Nitrophenoxy)phenyl]-1-(1-piperidyl)ethanone, 334c



334c

Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compoundas a lemon-yellow solid (54%). R_f (50% EtOAc in toluene): 0.55; m.p.= 74-76 °C (EtOAc in toluene). IR (neat, cm^{-1}): ν_{max} 1642 (C=O stretching), 1068 (C-O stretching), 1584, 1350 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.48-1.57 (m, 4H, CH_2CH_2), 1.65-1.7 (m, 2H, CH_2CH_2), 3.52 (t, 2H, *J*= 6.0Hz, NCH_2), 3.61 (t, 2H, *J*= 6.0Hz, NCH_2), 3.86 (s, 2H, CH_2Ar), 7.03 (t, 2H, *J*= 9.0Hz, Ar), 7.29 (d, 1H, *J*= 6.0Hz, Ar), 7.34-7.41 (m, 2H, Ar), 7.53-7.62 (m, 2H, Ar), 8.04 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.37, 25.45, 26.16, 34.24, 42.88, 46.99 (CH_2), 119.28, 119.35, 122.72, 125.23, 125.52, 128.40, 131.31, 134.25 (CH), 127.70, 140.55, 150.65, 152.55, 168.54 (C); MS (APCI *m*/*z*): 341 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 341.1498, $C_{19}H_{20}N_2O_4+H^+$ requires 341.1496.

2-(2-(2-Nitrophenoxy)phenyl)-1-morpholinoethanone, 334d

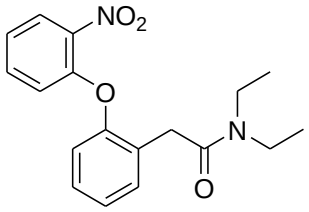


334d

Flash column chromatography (SiO_2; 40% EtOAc in toluene) afforded the title compound as a lemon-yellow oil (45%). R_f (50% EtOAc in toluene): 0.37; IR (neat,

cm^{-1}): ν_{max} 1642 (C=O stretching), 1068 (C-O stretching), 1584, 1350 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.47-352 (m, 8H, NCH_2OCH_2), 3.71 (s, 2H, CH_2Ar), 6.89 (m, 2H, Ar), 7.12-7.18 (m, 2H, Ar), 7.23 (t, 1H, *J*= 7.5Hz, Ar), 7.38-7.47 (m, 2H, Ar), 7.89 (d, 1H, *J*= 9.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 34.09, 42.25, 46.37, 66.64, 66.79 (CH_2), 119.27, 119.53, 123.05, 125.44, 125.74 (CH), 127.09 (C), 128.79, 131.46, 134.41 (CH), 140.75, 150.55, 152.62, 169.20, (C); MS (APCI *m*/*z*): 343 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 343.1288, $C_{18}H_{18}N_2O_5+H^+$ requires 343.1288.

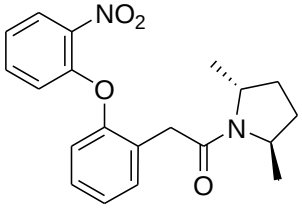
_N_,_N_-Diethyl-2-[2-(2-nitrophenoxy)phenyl]acetamide, 334e



334e

Flash column chromatography (SiO_2; 100% EtOAc in toluene) afforded the title compound as a yellow oil (74%). R_f (50% EtOAc in toluene): 0.73; IR (neat,cm^{-1}): ν_{max} 1638 (C=O stretching), 1098 (C-O stretching), 1526, 1368 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.97 (t, 3H, *J*= 7.5Hz, CH_3), 1.09 (t, 3H, *J*= 7.5Hz, CH_3), 3.52 (m, 4H, CH_2CH_3), 3.71 (s, 2H, CH_2Ar), 6.90-6.98 (m, 2H, Ar), 7.15-7.29 (m, 3H, Ar), 7.39-7.48 (m, 2H, Ar), 7.90 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 12.74, 14.02 (CH_3), 34.25, 40.31, 42.33 (CH_2), 119.12, 119.34, 123.60, 125.11, 125.39 (CH), 127.90 (C), 128.33, 131.49, 134.21 (CH), 140.44, 150.60, 152.73, 169.37 (C); MS (APCI *m*/*z*): 329 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 329.1495, $C_{18}H_{20}N_2O_4+H^+$ requires 329.1496.

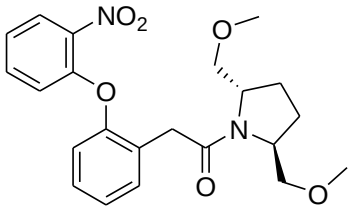
2-(2-(2-Nitrophenoxy)phenyl)-1-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)ethanone 334g



334g

Flash column chromatography (SiO_2; 3% EtOAc in toluene) afforded the title compound as a yellow solid (54%). R_f (30% EtOAc in toluene): 0.40. m.p.= 110-112 ºC (EtOAc/toluene); $[\alpha]_D$= −22.53 (ethanol, c = 0. 3 g/100ml). IR (neat, cm^{-1}): ν_{max} 1635 (C=O stretching), 1163 (C-O stretching), 1521, 1356 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): 0.86 (d, 3H, *J*= 6.3Hz, CH_3), 1.17 (d, 3H, *J*= 6.3Hz, CH_3), 1.42 (q, 1H, *J*= 4.5Hz, CH), 1.53 (q, 1H, *J*= 4.5Hz, CH), 2.01-2.08 (m, 2H, NCH_2), 3.48 (d, 1H, $H_{A/B}$, *J*= 15.6Hz, CH_AH$_B$Ar), 3.92 (d, 1H, $H_{B/A}$, *J*= 15.6Hz, CH_BH$_A$Ar), 4.07-4.15 (m, 2H, NCH_2), 6.91 (d, 1H, *J*= 8.0Hz, Ar), 6.97 (d, 1H, *J*= 8.0Hz, Ar), 7.11 (td, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.18-7.22 (m, 2H, Ar), 7.23-7.43 (m, 2H, Ar), 7.90 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 18.87, 21.73, (CH_3), 29.20, 30.89, 36.14 (CH_2), 53.36, 54.06, 119.40, 122.53, 125.34, 125.51 (CH), 128.47, 128.58, 132.28, 134.38 (CH), 140.65, 145.76, 151.07, 152.96, 168.72 (C); MS (APCI *m*/*z*): 355 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 355.1652, $C_{22}H_{22}N_2O_4$+H^+ requires 355.1652.

1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-(2-nitrophenoxy)phenyl)ethanone, 334h

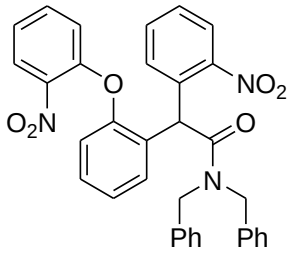


334h

Flash column chromatography (SiO_2; 40% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow sticky oil (45%). R_f (60% EtOAc in petroleum ether): 0.50. $[\alpha]_D$= −51.02 (ethanol, c = 0.2 g/100ml). IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 1107 (C-O stretching), 1583, 1350 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.83-1.98 (m, 4H, CH_2CH_2), 2.97 (t, 1H, *J*= 6.0Hz, NCH), 3.18 (s, 3H, OCH_3), 3.20-3.41 (m, 6H, includes (s, 3H) @ 3.29, OCH_3, NCH, OCH_2), 3.64 (d, 1H, $H_{A/B}$, *J*= 15.0Hz, CH_AH$_B$Ar), 3.94 (d, 1H, $H_{B/A}$, *J*= 15.0Hz, CH_BH$_A$Ar), 4.08-4.14 (m, 2H, OCH_2), 6.89 (d, 1H, *J*= 8.0Hz, Ar), 7.02 (d, 1H, *J*= 8.0Hz, Ar), 7.15-7.26 (m, 3H, Ar), 7.37 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.46 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.90 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.34, 27.09, 36.54 (CH_2), 57.07, 57.93 (CH_3), 58.79, 59.09 (CH), 70.88, 74.20 (CH_2), 119.109, 119.67,

122.71, 125.21, 125.49 (CH), 128.18 (C), 128.52, 132.21, 134.26 (CH), 140.84, 150.82, 153.21, 169.80 (C); MS (APCI *m*/*z*): 415 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 415.1861, $C_{22}H_{26}N_2O_6+H^+$ requires 415.1864.

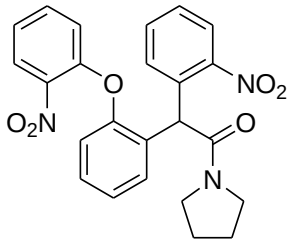
2-(2-(2-Nitrophenoxy)phenyl)-*N*,*N*-dibenzyl-2-(2-nitrophenyl)acetamide, 335a



335a

Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as orange crystals (54%). R_f (30% EtOAc in petroleum ether): 0.44; m.p.= 170-172 ^oC (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1647 (C=O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 4.39 (d, 1H, $H_{A/B}$, *J*= 15.0Hz, NCH_AH_B), 4.52 (d, 1H, $H_{C/D}$, *J*= 15.0Hz, NCH_CH_D), 4.64 (d, 1H, $H_{D/C}$, *J*= 15.0Hz, NCH_DH_C), 4.88 (d, 1H, $H_{B/A}$, *J*= 15.0Hz, NCH_BH_AAr), 6.45 (dd, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 6.15 (s, 1H, CHAr), 6.75 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 6.94-6.98 (m, 2H, Ar), 7.11 (td, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 7.16-7.38 (m, 13H, Ar), 7.50 (d, 2H, *J*= 6.0Hz, Ar), 7.88 (dt, 2H, *J*= 3.0Hz, *J*= 9.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 44.27 (CH), 48.44 50.68 (CH_2), 118.59, 120.21 123.65, 124.84, 124.93, 125.95, 127.45, 127.48, 127.96, 128.59, 128.65, 128.74, 129.63, 130.95, 132.33, 132.95, 134.10 (CH), 135.73, 136.91, 140.96, 148.89, 149.29, 153.25, 171.08 (C); MS (APCI *m*/*z*): 574 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 574.1963, $C_{34}H_{27}N_3O_6+H^+$ requires 574.1973.

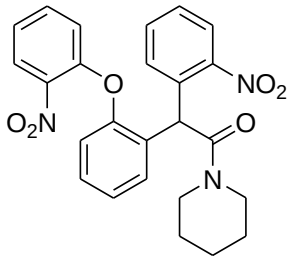
2-[2-(2-Nitrophenoxy)phenyl]-2-(2-nitrophenyl)-1-pyrrolidin-1-yl-ethanone, 335b



335b

Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a yellow solid (19%). R_f (30% EtOAc in toluene): 0.46; m.p.= 160-162 °C (EtOAc/toluene); IR (neat, cm^{-1}): ν_{max} 1638 (C=O stretching), 1187 (C-O stretching), 1234 (C-N stretching),1518, 1341 (N-O stretching); (^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.77-1.95 (m, 4H, CH_2CH_2), 3.18-3.25 (m, 1H, NCH_2), 3.35-3.44 (m, 1H, NCH_2), 3.49-3.55 (m, 1H, NCH_2), 3.58-3.66 (m, 1H, NCH_2), 6.08 (s, 1H, CHAr), 6.55 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 6.80 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.06 (td, 1H *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.14-7.29 (m, 5H, Ar), 7.39-7.46 (m, 2H, Ar), 7.77 (d, 1H, *J*= 8.0Hz, Ar) 7.84 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.45, 26.81 (CH_2), 45.88 (CH), 46.31, 46.46 (CH_2), 118.63, 119.80, 123.47, 124.63, 125.21, 125.95, 127.81, 129.07, 129.43, 130.53, 132.23, 132.91 (CH), 133.91, 134.10, 140.74, 148.99, 149.46, 153.27, 168.53 (C); MS (APCI *m*/*z*): 448 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 448.1495, $C_{24}H_{21}N_3O_6+H^+$ requires 448.1503.

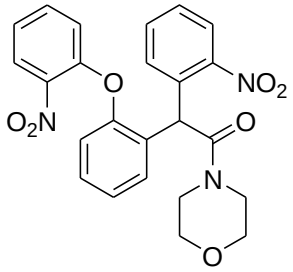
2-[2-(2-Nitrophenoxy)phenyl]-2-(2-nitrophenyl)-1-(1-piperidyl)ethanone, 335c



335c

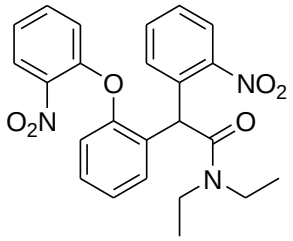
Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a lemon-yellow oil (24%). R_f (50% EtOAc in toluene): 0.63; IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 1094 (C-O stretching), 1521, 1346 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.48-1.60 (m, 6H, CH_2CH_2) 3.29-3.36 (m, 1H, NCH_2), 3.51-3.57 (m, 2H, NCH_2), 3.68-3.74 (m, 1H, NCH_2), 6.32 (s, 1H, CHAr), 6.60 (d, 1H, *J*= 9.0Hz, Ar), 6.88 (d, 1H, *J*= 9.0Hz, Ar), 7.09-7.37 (m, 6H, Ar), 7.47 (t, 2H, *J*= 6.0Hz, Ar), 7.85 (d, 1H, *J*= 9.0Hz, Ar), 7.90 (d, 1H, *J*= 6.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.55, 25.67, 25.86, 43.42, 47.03 (CH_2), 44.32, 118.68, 119.89, 123.57, 124.65, 125.08, 125.95, 127.67 (CH), 128.84 (C), 129.51, 130.86, 132.11, 132.80, 134.08 (CH), 134.55, 140.69, 148.70, 149.26, 152.82, 168.49 (C); MS (APCI *m*/*z*): 462 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 462.1654, $C_{25}H_{23}N_3O_6+H^+$ requires 462.1660.

2-(2-(2-Nitrophenoxy)phenyl)-1-morpholino-2-(2-nitrophenyl)ethanone, 12d



Flash column chromatography (SiO_2; 30% EtOAc in toluene) afforded the title compound as a sticky orange oil (6%). R_f (50% EtOAc in toluene): 0.48; IR (neat, cm^{-1}): ν_{max} 1645 (C=O stretching), 1111 (C-O stretching), 1522, 1347 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.35-3.45 (m, 2H, OCH_2), 3.62-3.79 (m, 6H, OCH_2NCH_2), 6.31 (s, 1H. CHAr), 6.61 (d, 1H, *J*= 8.0Hz, Ar), 6.85 (d, 1H, *J*= 8.0Hz, Ar), 7.11-7.18 (m, 2H, Ar), 7.23-7.37 (m, 4H, Ar), 7.45-7.50 (m, 2H, Ar), 7.90 (t, 2H, *J*= 9.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 42.82 (CH_2), 44.44 (CH), 46.47, 66.59, 66.95 (CH_2), 118.38, 120.41, 123.97, 124.93, 125.18, 126.18, 127.98, 129.85, 130.89, 132.02, 133.06, 134.16 (CH), 134.40, 140.88, 148.93, 149.93, 153.08, 169.43 (C); MS (APCI *m*/*z*): 464 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 464.1455, $C_{24}H_{21}N_3O_7+H^+$ requires 464.1452.

[2-[2-(Diethylamino)-1-[2-(2-nitrophenoxy)phenyl]-2-oxo-ethyl]phenyl]azinic acid, 335e

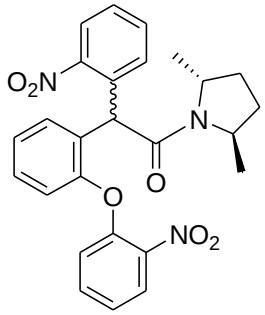


335e

Flash column chromatography (SiO_2; 15% EtOAc in toluene) afforded the title compound as a lemon-yellow solid (21%). R_f (50% EtOAc in toluene): 0.82; m.p.= 124-126 °C (EtOAc/toluene); IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 1091 (C-O stretching), 1520, 1346 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.12 (t, 3H, *J*= 7.5Hz, CH_3), 1.17 (t, 3H, *J*= 7.5Hz, CH_3), 3.24-3.57 (m, 4H, NCH_2), 6.27 (s, 1H, CHAr), 6.63 (d, 1H, *J*= 9.0Hz, Ar), 6.87 (d, 1H, *J*= 9Hz, Ar), 7.16 (t, 1H, *J*= 7.5Hz, Ar),

7.24-7.37 (m, 5H, Ar), 7.44-7.52 (m, 2H, Ar), 7.86 (d, 1H, *J*= 9.0Hz, Ar), 7.95 (d, 1H, *J*= 9.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 12.69, 13.66 (CH_3), 40.73, 42.45 (CH_2), 44.44, 118.49, 120.08, 123.65, 124.63, 125.08, 126.04, 127.74, 129.33, 129.51, 130.59, 132.30, 132.74 (CH), 134.16, 134.40, 140.88, 148.93, 149.93, 153.08, 169.43 (C); MS (APCI *m*/*z*): 450 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 450.1660, $C_{24}H_{23}N_3O_6+H^+$ requires 450.1654.

2-(2-(2-nitrophenoxy)phenyl)-1-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)-2-(2-nitrophenyl)ethanone, 335g



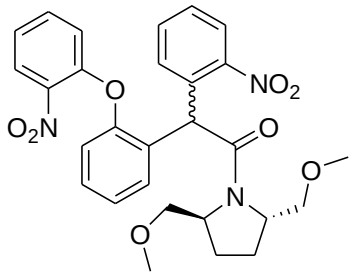
335g

Flash column chromatography (SiO_2; 2% EtOAc in toluene) afforded the title compound (as a mixture of two diastereomers) as a yellow solid (5%). R_f (30% EtOAc in toluene): 0.58; m.p.= 90-92 ºC (EtOAc/toluene); $[\alpha]_D$= −36.25 (ethanol, c = 0.14 g/100ml). IR (neat, cm^{-1}): ν_{max} 1634 (C=O stretching), 1160 (C-O stretching), 1521, 1348 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.75-0.81 (m, 1H, $CHCH_3$), 0.92 (d, 3H, *J*= 6.6Hz), 1.20 (d, 3H, *J*= 6.6Hz, CH_3), 1.27-1.29 (m, 6H, includes (d, 3H) @ 1.28, CH_3), 1.185-1.55 (m, 4H, CH_2CH_2), 1.90-1.99 (m, 2H, CH_2), 2.08-2.12 (m, 2H, CH_2), 3.88 (m, 1H,), 6.13 (s, 1H, CHAr), 6.22 (s, 1H, CHAr), 6.54 (d, 1H, *J*= 8.4Hz, Ar), 6.73 (d, 1H, *J*= 8.4Hz, Ar), 6.82 (d, 2H, *J*= 8.4Hz, Ar), 7.18 (d, 1H, *J*= 8.4Hz, Ar), 7.21-7.25 (m, 3H, Ar), 7.27-7.34 (m, 7H, Ar), 7.37-7.40 (m, 2H, Ar), 7.47 (d, 1H, *J*= 8.0Hz, Ar), 7.72 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.90 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.94 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 18.83, 21.96 (CH_3), 29.72, 31.74 (CH_2), 46.22, 54.32, 54.63, 117.89, 119.72, 120.55, 123.82, 124.71, 124.99, 126.04 (CH), 127.77 (C), 129.37, 129.59, 130.11 (CH), 130.81 (C), 132.24 (CH), 132.68, 134.07 (C), 134.31 (CH), 149.50, 153.66, 168.46 (C); MS (APCI *m*/*z*): 476 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 476.1811, $C_{26}H_{25}N_3O_6+H^+$ requires 476.1816.

Diagnostic signals corresponding to the major diastereomer are: δ_H 1.27-1.29 (m, 6H, includes (d, 3H) @ 1.28, CH_3), 6.22 (s, 1H, CHAr), 6.73 (d, 1H, *J*= 8.4Hz, AR), 7.72 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.90 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.94 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar).

Diagnostic signals corresponding to the minor diastereomer are: δ_H 6.13 (s, 1H, CHAr), 6.54 (d, 1H, *J*= 8.4Hz, Ar), 7.47 (d, 1H, *J*= 8.0Hz, Ar), 7.72 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.90 (d, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar).

1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-(2-nitrophenoxy)phenyl)-2-(2-nitrophenyl)ethanone, 335h



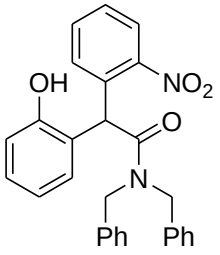
335h

Flash column chromatography (SiO_2; 35% EtOAc in petroleum ether) afforded the title compound (as a mixture of two diastereomers) as a lemon-yellow sticky oil (10%). R_f (60% EtOAc in petroleum ether): 0.65; $[\alpha]_D$= −62.85 (ethanol, c = 0. 24 g/100ml). IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 1109 (C-O stretching), 1524, 1348 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.75-0.79 (m, 1 H, CH_2), 1.73-1.92 (m, 8H, CH_2CH_2), 2.83 (s, 3H, CH_3O), 2.95-3.09 (m, 5H, includes (s, 3H) @ 3.09, CH_3O, CH_2CH), 3.18 (s, 3H, CH_3O), 3.21-3.27 (m, 6H, includes (s, 3H) @ 3.23, CH_3O, CH_2CH_3), 3.36 (dd, 1H, *J*= 9.0Hz, CHN), 3.52 (td, 3H, *J*= 6.0Hz, *J*= 9.0Hz, CH_2O, CHN), 3.71-3.73 (m, 1H, CHN), 4.08-4.15 (m, 1H, CHN), 4.16-4.20 (m, 2H, CH_2O), 6.07 (s, 1H, CHAr), 6.18 (s, 1H CHAr), 6.48 (d, 1H, *J*= 8.0Hz, Ar), 6.69 (t, 1H, *J*= 9.0Hz, Ar), 6.75 (t, 3H, *J*= 9.0Hz, Ar), 7.00-7.40 (m, 15H, Ar), 7.65 (d, 1H, *J*= 9.0Hz, Ar), 7.81 (dd, 3H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.49, 25.58, 27.48, 27.73 (CH_2), 45.61, 46.20, 57.82, 57.89 (CH_3), 58.59, 58.75, 58.81, 58.90 (CH), 70.60, 70.71, 73.76,73.79 (CH_2), 117.97, 118.88, 119.76, 120.72, 123.32, 123.82, 124.51, 124.68, 124.75, 125.04, 125.81, 127.78, 128.01, 129.10, 129.25(CH), 129.42 (C),130.20, 130.40 (CH), 130.66 (C), 132.15,132.57, 132.80, 132.89 (CH), 133.74,

133.94 (C), 134.09, 134.27(CH), 140.85, 141.39, 149.05, 149.36, 149.62, 152.98, 153.75, 168.92, 169.50 (C); MS (APCI *m/z*): 536 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 536.2015, $C_{28}H_{29}N_3O_8+H^+$ requires 536.2027.

Diagnostic signals corresponding to the major diastereomer are: δ_H 2.95-3.09 (m, 5H, includes (s, 3H) @ 3.09, CH_3O, CH_2CH), 3.21-3.27 (m, 6H, includes (s, 3H) @ 3.23, CH_3O, CH_2CH_3), 3.36 (dd, 1H, *J*= 9.0Hz, CHN), 3.71-3.73 (m, 1H, CHN), 4.16-4.20 (m, 2H, CH_2O), 6.18 (s, 1H CHAr), 6.69 (t, 1H, *J*= 9.0Hz, Ar), 6.75 (t, 3H, *J*= 9.0Hz, Ar), 7.81 (dd, 3H, *J*= 1.0Hz, *J*= 8.0Hz, Ar).
Diagnostic signals corresponding to the minor diastereomer are: δ_H 2.83 (s, 3H, CH_3O), 3.18 (s, 3H, CH_3O), 4.08-4.15 (m, 1H, CHN), 6.07 (s, 1H, CHAr), 6.48 (d, 1H, *J*= 8.0Hz, Ar), 7.65 (d, 1H, *J*= 9.0Hz, Ar).

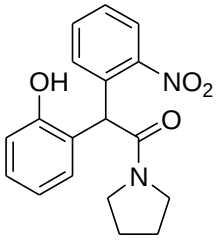
_N,N_-Dibenzyl-2-(2-hydroxyphenyl)-2-(2-nitrophenyl)acetamide, 336a



336a

Flash column chromatography (SiO_2; 25% EtOAc in petroleum ether) afforded the title compound as a colourless solid (37%). R_f (30% EtOAc in petroleum ether): 0.60; m.p.= 195-197 ºC (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1618 (C=O stretching), 1599, 1344 (N-O stretching), 3267 (H-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 4.21 (d, 1H, $H_{A/B}$, *J*= 15.0Hz, NC$H_A$$H_B$), 4.53 (d, 1H, $H_{C/D}$, *J*= 15.0Hz, NC$H_C$$H_D$), 4.73 (d, 1H, $H_{D/C}$, *J*= 15.0Hz, NC$H_D$$H_C$), 4.88 (d, 1H, $H_{B/A}$, *J*= 15.0Hz, NC$H_B$$H_A$), 6.15 (s, 1H, CHAr), 6.82 (t, 1H, *J*= 7.5Hz), 6.94 (m, 3H), 7.01 (d, 1H, *J*= 6.0Hz), 7.14 (m, 2H), 7.24-7.31 (m, 8H), 7.44 (t, 1H, *J*= 7.5Hz), 7.53 (t, 1H, *J*= 7.5Hz), 7.79 (s, 1H, OH), 8.01 (d, 1H, *J*= 6.0Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 48.35 (CH_2), 49.36 (CH), 50.90 (CH_2), 118.21, 121.00 (CH), 121.51, 125.20, 127.63, 127.69, 127.88, 128.35, 128.68, 128.86, 130.19, 131.48 (CH), 131.82 (C), 133.00 (CH), 133.31, 135.17, 136.30, 148.97, 155.85, 172.98 (C); MS (APCI *m/z*): 451 $[M-H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 453.1805, $C_{28}H_{24}N_2O_4+H^+$ requires 453.1809.

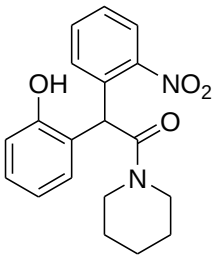
2-(2-Hydroxyphenyl)-2-(2-nitrophenyl)-1-pyrrolidin-1-yl-ethanone, 336b



336b

Flash column chromatography (SiO_2; 16% EtOAc in toluene) afforded the title compound as a colourless solid (33%). R_f (30% EtOAc in toluene): 0.67; m.p.= 189-191 ºC (EtOAc in toluene); IR (neat, cm^{-1}): ν_{max} 1615 (C=O stretching), 1584, 1345 (N-O stretching), 2951 (H-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.81-1.97 (m, 3H, CH_2CH_2), 2.03-2.10 (m,1H, CH_2CH_2), 3.38-3.62 (m, 3H, NCH_2), 3.87-3.94 (m, 1H, NCH_2), 5.64 (s, 1H, CHAr), 6.92-6.99 (m, 2H, Ar), 7.15 (t, 2H, *J*= 7.5Hz, Ar), 7.28 (t, 1H, *J*= 7.5Hz, Ar), 7.40-7.50 (m, 2H, Ar), 7.99 (d, 1H, *J*= 7.5Hz, Ar), 8.74 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.44, 26.14, 46.68 (CH), 52.87, 52.90 (CH_2), 119.04 (CH), 120.27 (C), 120.67, 125.22, 128.40, 130.36, 131.21, 132.20 (CH), 132.39 (C), 133.44 (CH), 148.88, 157.25, 170.60 (C); MS (APCI *m*/*z*): 327 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 327.1343, $C_{18}H_{18}N_2O_4+H^+$ requires 327.1339.

2-(2-Hydroxyphenyl)-2-(2-nitrophenyl)-1-(1-piperidyl)ethanone, 336c

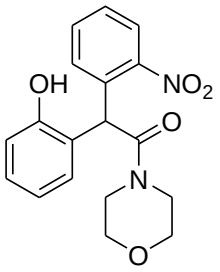


336c

Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a colourless solid (21%). R_f (50% EtOAc in toluene): 0.81; m.p.= 177-179 ºC (EtOAc/toluene); IR (neat, cm^{-1}): ν_{max} 1618 (C=O stretching), 1596, 1352 (N-O stretching), 3177 (H-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.44-1.75 (m, 6H, CH_2CH_2), 3.44-3.51 (m, 1H, NCH_2), 3.56-3.65 (m, 3H, NCH_2), 5.96 (s, 1H, CHAr), 6.88-6.92 (m, 2H, Ar), 7.11 (d, 1H, *J*= 7.5Hz, Ar), 7.17 (d, 1H, *J*= 7.5Hz, Ar), 7.25 (t,

1H, *J*= 7.5Hz, Ar), 7.39 (t, 1H, *J*= 7.5Hz, Ar), 7.46 (t, 1H, *J*= 7.5Hz, Ar), 8.00 (d, 1H, *J*= 7.5Hz, Ar), 8.46 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75MHz): δ_C 24.45, 25.64, 25.73, 43.86, 47.51 (CH_2), 49.45, 118.16, 120.70 (CH), 121.39 (C), 125.06, 128.08, 129.99, 131.46, 131.51, 133.30, (CH), 133.62, 148.82, 156.24, 170.32 (C); MS (APCI *m*/*z*): 341 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 341.1499, $C_{19}H_{20}N_2O_4+H^+$ requires 341.1496

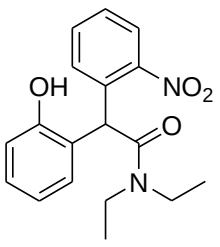
2-(2-Hydroxyphenyl)-1-morpholino-2-(2-nitrophenyl)ethanone, 336d



335d

Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a yellow solid (45%). R_f (50% EtOAc in toluene): 0.22; m.p.= 157-159 ºC (EtOAc/toluene); IR (neat, cm^{-1}): ν_{max} 1619 (C=O stretching), 1112 (C-O stretching), 1515, 1343 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.08-3.18 (m, 2H, OCH_2), 3.35-3.57 (m, 6H, OCH_2NCH_2), 5.99 (s, 1H, CHAr), 6.88-6.92 (m, 3H, Ar), 7.04 (d, 1H, *J*= 6.0Hz, Ar), 7.19 (t, 1H, *J*= 7.5Hz, Ar), 7.46 (t, 1H, *J*= 7.5Hz, Ar), 7.56 (t, 1H, *J*= 7.5Hz, Ar), 7.99 (d, 1H, *J* = 9.0Hz, Ar), 9.86 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 75MHz): δ_C 41.95, 45.55, 65.30, 65.88 (CH_2), 43.39, 115.42, 119.41 (CH), 122.50 (C), 124.08, 127.63, 128.83, 128.98, 131.06, 132.83, (CH), 134.50, 148.73, 154.15, 168.78 (C); MS (APCI *m*/*z*): 343 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 343.1288, $C_{18}H_{18}N_2O_5+H^+$ requires 343.1289.

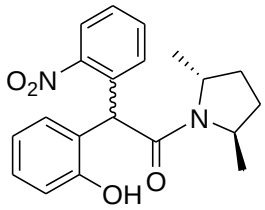
[2-[2-(Diethylamino)-1-(2-hydroxyphenyl)-2-oxo-ethyl]phenyl]azinic acid, 336e



336e

Flash column chromatography (SiO_2; 15% EtOAc in toluene) afforded the title compound as a yellow solid (10%). R_f (50% EtOAc in toluene): 0.62; m.p.= 161-163 °C (EtOAc/toluene). IR (neat, cm^{-1}): ν_{max} 1616 (C=O stretching), 1590, 1376 (N-O stretching); ^1H NMR (DMSO-d_6, 300MHz): δ_H 0.09-0.17 (m, 6H, CH_3), 2.22-2.47 (m, 4H, NCH_2), 5.09 (s, 1H, CHAr), 5.99-6.08 (m, 3H, Ar), 6.15 (d, 1H, *J*= 6.0Hz, Ar), 6.33 (t, 1H, *J*= 7.5Hz, Ar), 6.61 (t, 1H, *J*= 7.5Hz, Ar), 6.71 (t, 1H, *J*= 7.5Hz, Ar), 7.09 (d, 1H, *J*= 9.0Hz, Ar), 8.96 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75MHz): 12.30, 13.08 (CH_3), 39.38, 41.09 (CH_2), 43.40, 115.22, 119.28 (CH), 123.42, 123.81 (C), 127.43, 128.49, 128.74, 131.18, 132.47, 134.57 (CH), 149.00, 154.29, 169.04 (C); MS (APCI *m*/*z*): 329 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 329.1497, $C_{18}H_{20}N_2O_4+H^+$ requires 329.1496.

2-(2-Hydroxyphenyl)-1-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)-2-(2-nitrophenyl)ethanone, 336g



336g

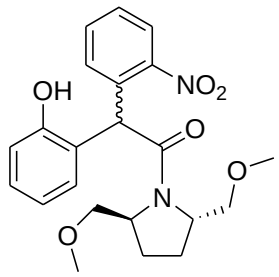
Flash column chromatography (SiO_2; 2% EtOAc in toluene) afforded the title compound (as a mixture of two diastereomers) (36%) as yellow solid. R_f (30% EtOAc in toluene): 0.67; m.p.= 101-103 ºC (EtOAc/toluene); $[\alpha]_D$= −30.35 (ethanol, c = 0.29 g/100ml). IR (neat, cm^{-1}): ν_{max} 1615 (C=O stretching), 1113 (C-O stretching), 1554, 1367 (N-O stretching), 3390 (O-H stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 0.82-0.89 (m, 2H, CH_2), 1.09 (d, 3H, *J*= 6.3Hz, CH_3), 1.15 (d, 3H, *J*= 6.6Hz, CH_3), 1.21 (d, 3H, *J*= 6.6Hz, CH_3), 1.41 (d, 3H, *J*= 6.6Hz, CH_3), 1.48-1.67 (m, 4H, CH_2), 1.98-2.08 (m, 3H, CH_2, CH), 2.10-2.29 (m, 1H, CHN), 4.11-4.18 (m, 1H, CHN), 4.20-2.34 (m, 1H, CHN), 4.44-4.51 (m, 1H, CHN), 5.70 (s, 1H, CHAr), 5.83 (s, 1H, CHAr), 6.83-6.94 (m, 3H, Ar), 7.11 (d, 1H, *J*= 7.5Hz, Ar), 7.15-7.23 (m, 4H, Ar), 7.29 (d, 1H, *J*= 7.5Hz, Ar), 7.32 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.36-7.44 (m, 3H, Ar), 7.46-7.50 (m, 1H, Ar), 7.79 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.88 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 8.43 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 18.30, 18.63, 21.22, 21.93 (CH_3), 29.08, 29.26, 31.04, 31.30 (CH_2), 51.39, 54.04, 54.67, 54.97, 55.4 118.67, 119.24, 120.32, 120.43 (CH), 121.88, 122.23 (C), 124.95, 124.98, 128.18 (CH), 128.32 (C),

130.12, 130.21, 130.87, 130.91, 131.74, 132.32, 132.37, 132.45, 133.79 (CH), 133.03, 149.24, 149.64, 156.37, 157.18, 170.46, 170.99 (C); MS (APCI *m/z*): 355 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 355.1652, $C_{20}H_{22}N_2O_4+H^+$ requires 355.1652.

Diagnostic signals corresponding to the major diastereomer are: δ_H 1.09 (d, 3H, *J*= 6.3Hz, CH_3), 1.41 (d, 3H, *J*= 6.6Hz, CH_3), 5.70 (s, 1H, CHAr), 7.88 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar).

Diagnostic signals corresponding to the minor diastereomer are: δ_H 1.15 (d, 3H, *J*= 6.6Hz, CH_3), 1.21 (d, 3H, *J*= 6.6Hz, CH_3), 5.83 (s, 1H, CHAr), 7.79 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar).

1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-hydroxyphenyl)-2-(2-nitrophenyl)ethanone, 336h



336h

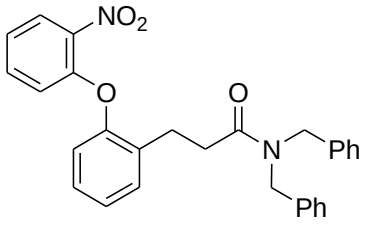
Flash column chromatography (SiO_2; 35% EtOAc in petroleum ether) afforded the title compound (as a mixture of two diastereomers) as a yellow solid (45%). R_f (60% EtOAc in petroleum ether): 0.73. m.p.= 126-128 ºC (EtOAc in petroleum ether); $[\alpha]_D$= −75.76 (ethanol, c = 0.5 g/100ml). IR (neat, cm^{-1}): ν_{max} 1620 (C=O stretching), 1113 (C-O stretching), 1524, 1356 (N-O stretching), 3243 (O-H stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 0.62-0.66 (m, 1H, CH_2CH_2), 1.58-1.63 (m, 4H, CH_2CH_2), 1.69-1.76 (m, 2H, CH_2CH_2), 1.92-1.98 (m, 1H, CH_2CH_2), 2.78 (s, 3H, CH_3O), 2.93 (d, 1H, *J*= 3.0Hz, CHN), 2.99 (s, 3H, CH_3O), 3.02 (s, 3H, CH_3O), 3.08 (s, 3H, CH_3O), 3.13 (d, 1H, *J*= 9.0Hz, CHN), 3.22 (t, 1H, *J*= 9.0Hz, CHN), 3.39 (td, 2H, *J*= 2.0Hz, *J*= 9.0Hz, CH_2O), 3.51-3.59 (m, 2H, CH_2O), 3.99-4.06 (m, 2H, CH_2O), 5.73 (s, 1H, CHAr), 5.81 (s, 1H, CHAr), 6.43 (d, 2H, *J*= 7.5Hz, Ar), 6.60-6.63 (m, 2H, Ar), 6.85 (d, 1H, *J*= 7.5Hz, Ar), 6.88 (m, 3H, Ar), 6.95-7.12 (m, 6H, Ar), 7.60 (d, 1H, *J*= 7.5Hz, Ar), 7.66 (d, 1H, *J*= 7.5Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.23, 27.04, 27.30 (CH_2), 46.90, 47.33, 57.21, 57.68 (CH_3), 58.06, 58.26, 58.47, 58.57 (CH), 70.26, 70.40, 73.11 (CH_2), 116.01,

116.19, 119.77, 119.95 (CH), 122.86, 122.95 (C), 124.29, 124.32, 127.43, 127.68, 129.14, 129.24, 129.42, 129.82, 131.68, 131.84, 132.66, 132.75 (CH), 133.85, 133.94, 148.86, 149.12, 154.75, 154.85, 171.02, 171.25 (C); MS (APCI *m*/*z*): 415 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 415.1861, $C_{22}H_{26}N_2O_6+H^+$ requires 415.1864.

Diagnostic signals corresponding to the major diastereomer are: δ_H 2.93 (d, 1H, *J*= 3.0Hz, CHN), 3.02 (s, 3H, CH_3O), 3.08 (s, 3H, CH_3O), 5.81 (s, 1H, CHAr), 7.66 (d, 1H, *J*= 7.5Hz, Ar).

Diagnostic signals corresponding to the minor diastereomer are: δ_H 2.78 (s, 3H, CH_3O), 2.99 (s, 3H, CH_3O), 5.73 (s, 1H, CHAr), 7.60 (d, 1H, *J*= 7.5Hz, Ar).

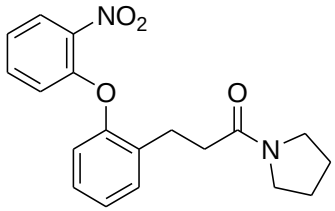
3-(2-(2-Nitrophenoxy)phenyl)-*N*,*N*-dibenzylpropanamide, 338a



338a

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as a yellow oil (100%). R_f (10% EtOAc in toluene): 0.46; IR (neat, cm^{-1}): ν_{max} 1644 (C=O stretching), 1101 (C-O stretching), 1524, 1347 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.82 (t, 2H, *J*= 7.5Hz, $CH_2C=O$), 3.06 (t, 2H, *J*= 7.5Hz, CH_2Ar), 4.42 (s, 2H, NCH_2), 4.57 (s, 2H, NCH_2), 6.78 (dd, 1H, *J*= 1.0Hz, *J*= 9.0Hz, Ar), 6.82 (dd, 1H, *J*= 1.0Hz, *J*= 9.0Hz, Ar), 7.05 (d, 2H, *J*= 9.0Hz, Ar), 7.11-7.15 (m, 4H, Ar), 7.20 (dd, 1H, *J*= 1.5Hz, *J*= 9.0Hz, Ar), 7.23-7.31 (m, 6H, Ar), 7.34-7.39 (m, 2H, Ar), 7.91 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 26.95, 33.43, 48.23, 49.90 (CH_2), 119.05, 119.33, 122.74, 125.37, 125.04, 126.51, 127.42, 127.54, 128.19, 128.27, 128.68, 128.94, 131.83, 132.93 (CH), 134.41, 136.52, 137.38, 140.63, 150.98, 153.31, 172.92 (C); MS (APCI *m*/*z*): 467 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 467.1973, $C_{29}H_{26}N_2O_4+H^+$ requires 467.1965.

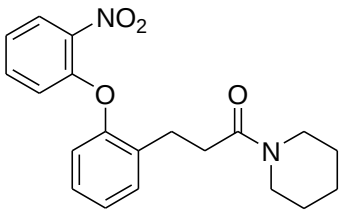
3-(2-(2-Nitrophenoxy)phenyl)-1-(pyrrolidin-1-yl)propan-1-one, 338b



338b

Flash column chromatography (SiO_2; 100% petroleum ether) afforded the title compound as a yellow oil (92%). R_f (30% EtOAc in petroleum ether): 0.32; IR (neat, cm^{-1}): ν_{max}1604 (C=O stretching), 1039 (C-N stretching), 1100 (C-O stretching), 1523, 1344 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.80 (tt, 2H, *J*= 6.0Hz, CH_2CH_2), 1.88 (tt, 2H, *J*= 6.0Hz, CH_2CH_2), 2.65 (t, 2H, *J*= 9.0Hz, CH_2C=O), 2.95 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.34 (t, 2H, *J*= 7.5Hz, NCH_2), 3.42 (t, 2H, *J*= 6.0Hz, NCH_2), 6.90 (dd, 1H, *J*= 3.0Hz, *J*= 6.0Hz, Ar), 6.90 (dd, 1H, *J*= 3.0Hz, *J*= 6.0Hz, Ar), 7.15 (td, 2H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.12-7.20 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.38 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.46 (td, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.97 (dd, 1H, *J*= *J*= 1.5Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.52, 26.20, 26.49, 35.02, 45.74, 46.56 (CH_2), 118.81, 119.52, 122.65, 125.49, 126.06, 128.14, 131.81, 133.40 (CH), 134.48, 140.58, 151.16, 153.13, 170.84 (C); MS (APCI *m*/*z*): 341 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 341.1503, $C_{19}H_{20}N_2O_4+H^+$ requires 341.1496.

2-[2-(2-Nitrophenoxy)phenyl]-1-(1-piperidyl)propanone, 338c

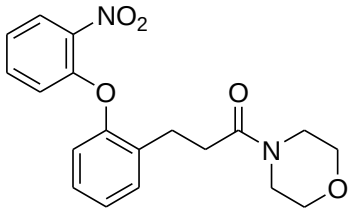


338c

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as a yellow oil (87%). R_f (30% EtOAc in petroleum ether): 0.36; IR (neat, cm^{-1}): ν_{max} 1631 (C=O stretching), 1098 (C-O stretching), 1583, 1348 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.55-1.67 (m, 6H, CH_2CH_2), 2.77 (t, 2H, *J*= 7.5Hz, CH_2C=O), 3.01 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.42 (t, 2H, *J*= 6.0Hz, NCH_2), 3.60 (t, 2H, *J*=

6.0Hz, NCH_2), 6.79 (d, 2H, *J*= 6.0Hz, Ar), 7.22-7.34 (m, 3H, Ar), 7.45 (d, 1H, *J*= 6.0Hz, Ar), 7.55 (t, 1H, *J*= 7.5Hz, Ar), 8.04 (d, 1H, *J*= 6.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.39, 25.44, 26.18, 26.76, 33.32, 42.52, 46.42 (CH_2), 118.63, 119.17, 122.53, 125.22, 125.77, 127.94, 131.42 (CH), 132.93 (C), 134.29 (CH), 140.32, 150.75, 152.89, 170.24 (C); MS (APCI *m*/*z*): 355 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 355.1646, $C_{20}H_{22}N_2O_4+H^+$ requires 355.1652.

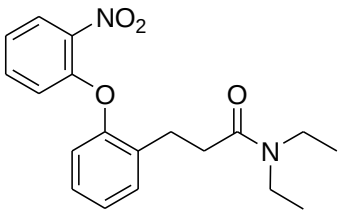
2-[2-(2-Nitrophenoxy)phenyl]-1-(1-morpholino)propanone, 338d



338d

Flash column chromatography (SiO_2; 50% petroleum ether) afforded the title compound as a yellow oil (90%). R_f (30% EtOAc in petroleum ether): 0.36; IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 1023 (C-O stretching), 1582, 1349 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.72 (t, 2H, *J*= 7.5Hz, CH_2C=O), 2.94 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.42 (t, 2H, *J*= 7.5Hz, NCH_2), 3.53 (t, 2H, *J*= 7.5Hz, NCH_2), 3.61 (t, 4H, *J*= 7.5Hz, OCH_2), 6.89 (dd, 2H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.15-7.28 (m, 3H, Ar), 7.36 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.47 (t, 1H, *J*= 8.0Hz, Ar), 7.97 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 26.72, 32.75, 41.73, 45.73, 66.36, 66.58 (CH_2), 118.69, 118.96, 122.66, 125.15, 125.75, 128.06, 131.50 (CH), 132.37 (C), 134.31 (CH), 140.35, 150.45, 152.90, 170.71, (C); MS (APCI *m*/*z*): 357 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 357.1444, $C_{19}H_{20}N_2O_5+H^+$ requires 357.1445.

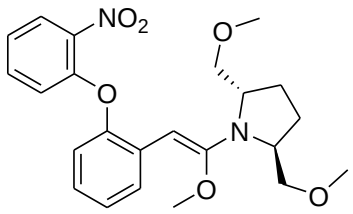
***N*,*N*-Diethyl-2-[2-(2-nitrophenoxy)phenyl]propanamide, 338e**



338e

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as a yellow oil (90 %). R_f (30% EtOAc in petroleum ether): 0.37; IR (neat, cm^{-1}): ν_{max} 1631 (C=O stretching), 1098 (C-O stretching), 1524, 1349 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 0.95-1.01 (m, 6H, CH_3), 2.59 (t, 2H, *J*= 7.5Hz, $CH_2C=O$), 2.87 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.15 (q, 2H, *J*= 7.5Hz, NCH_2), 3.24 (q, 2H, *J*= 7.5Hz, NCH_2), 6.79 (t, 2H, *J*= 7.5Hz, Ar), 7.02-7.15 (m, 3H, Ar), 7.27 (d, 1H, *J*= 6.0Hz, Ar), 7.38 (t, 1H, *J*= 7.5Hz, Ar), 7.85 (d, 1H, *J*= 9.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 12.92, 14.01 (CH_3), 26.69, 33.14, 39.96, 41.75 (CH_2), 118.72, 119.05, 122.54, 125.13, 125.74, 127.89, 131.46 (CH), 132.93 (C), 134.29 (CH), 140.33, 150.74, 152.95, 171.08 (C); MS (APCI *m*/*z*): 343 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 343.1646, $C_{19}H_{22}NO_2+H^+$ requires 343.1652.

4.5 Procedure for the synthesis of (2*S*,5*S*)-1-((*Z*)-2-(2-(2-nitrophenoxy)phenyl)-1-methoxyvinyl)-2,5-bis(methoxymethyl)pyrrolidine, 373

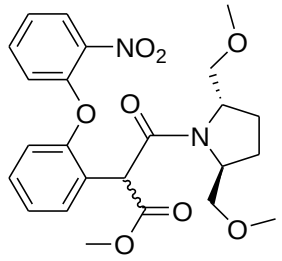


373

1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-(2-nitrophenoxy)phenyl)ethanone, **334h** (0.06g, 0.144 mmol) and sodium hydride (5mg, 0.144 mmol) was dissolved in tetrahydrofuran (2mL, 0.1 M) and stirred at room temperature for 15 minutes. Methyl iodide (**372**) (0.02g, 0.144 mmol) was added and the reaction mixture was left stirring for 24 hours. The solvent was evaporated, the residue washed with hydrochloric acid solution (3×30mL, 1 M) and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue which was purified by flash column chromatography. Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as lemon-yellow crystalline solid (50%). R_f (30% EtOAc in petroleum ether): 0.66; m.p.= 179-181 °C (DCM). $[\alpha]_D$= −18.74 (ethanol, c = 0.18 g/100ml). IR (neat, cm^{-1}): ν_{max} 1104 (C-O stretching), 1520, 1361 (N-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 0.84-0.94 (m, 1H, CH_2CH), 1.88-2.19 (m, 4H, CH_2CH_2), 2.95-3.09 (m,

4H, includes (s, 3H) @ 2.99, CH_3O, CH_2CH), 3.27-3.34 (m, 4H, includes (s, 3H) @ 3.30, CH_3O, CH_2O), 3.65-3.74 (m, 4H, includes (s, 3H) @ 3.68, CH_3O, CH_2O), 4.21-4.32 (m, 2H, CH_2O), 6.03 (s, 1H, CHAr), 6.48 (d, 1H, J= 9.0Hz, Ar), 6.75 (t, 1H, J= 9.0Hz, Ar), 7.00-7.40 (m, 4H, Ar),7.65 (d, 1H, J= 9.0Hz, Ar), 7.81 (dd, 1H, J= 9.0Hz, J= 9.0Hz, Ar); ^{13}C NMR (CDCl3, 75MHz): δ_C 25.27, 27.49 (CH_2), 44.82, 55.49, 57.99, (CH_3), 58.65, 58.88, (CH), 70.61, 73.34, (CH_2), 110.64, 120.93, 124.21 (CH), 127.30 (C), 127.67, 129.05, 129.39, 132.50, 132.78 (CH), 134.63, 149.43, 156.46, 169.74 (C); MS (APCI m/z): 429 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 429.2013, $C_{23}H_{28}N_2O_6+H^+$ requires 429.2020.

4.6 Procedure for the synthesis of methyl 3-[(2*S*,5*S*)-2,5-*bis*(methoxymethyl)pyrrolidin-1-yl]-2-[2-(2-nitrophenoxy)phenyl]-3-oxo-propanoate, 381



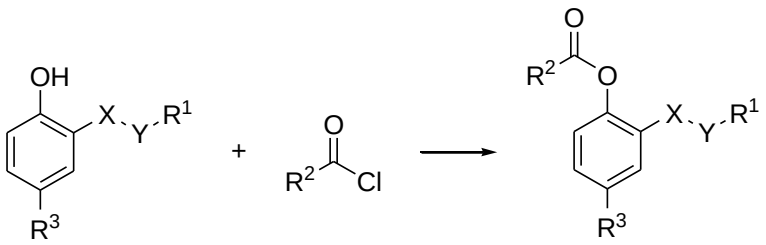
381

1-((2*S*,5*S*)-2,5-*Bis*(methoxymethyl)pyrrolidin-1-yl)-2-(2-(2-nitrophenoxy)phenyl)ethanone, **334h** (0.062g, 1.149 mmol) and sodium hydride (8mg, 0.223 mmol) was dissolved in tetrahydrofuran (2mL, 0.1 M) and stirred at room temperature for 15 minutes. Methyl chloroformate (**380**) (0.012g, 0.157 mmol) was added and the reaction mixture was left stirring for 16 hours. The solvent was evaporated, the residue washed with hydrochloric acid solution (3×30mL, 1 M) and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue which was purified by flash column chromatography. Flash column chromatography (SiO_2; 36% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow solid (as a mixture of two diastereomers) (57%). R_f (60% EtOAc in petroleum ether): 0.63. m.p.= 191-193 °C (EtOAc/petroleum ether). $[\alpha]_D$= −40.75 (ethanol, c = 0.16 g/100ml). IR (neat, cm^{-1}): ν_{max} 1766 (C=O

stretching, ester), 1646 (C=O stretching), 1113 (C-O stretching), 1521, 1340 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.87-2.08 (m, 3H, CH_2CH_2), 2.13-2.25 (m, 1H, CH_2CH_2), 2.94-3.00 (m, 5H, includes (s, 3H) @ 2.94, CH_3O, CH_2O), 3.25-3.32 (m, 4H, includes (s, 3H) @ 3.28, CH_3O, CH_2O), 3.61-3.76 (m, 4H, includes (s, 3H) @ 3.65, CH_3O, CH_2O), 4.22-4.28 (m, 1H, CHN), 4.31-4.35 (m, 1H, CHN), 5.97 (s, 1H, CHAr), 7.17 (d, 1H, *J*= 7.83Hz, Ar), 7.24 (d, 1H, *J*= 9.0Hz, Ar), 7.30 (d, 1H, *J*= 9.0Hz, Ar), 7.37 (t, 2H, *J*= 9.0Hz, Ar), 7.48 (d, 1H, *J*= 9.0Hz, Ar), 7.53 (d, 1H, *J*= 9.0Hz, Ar), 7.90 (d, 1H, *J*= 9.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 25.47, 27.76 (CH_2), 45.58, 55.55, 58.21 (CH_3), 58.30, 58.63, 58.88 (CH), 70.58, 73.80, (CH_2), 122.71, 124.23, 126.57, 128.06, 129.11, 130.05 (CH), 131.12 (C), 133.18, 133.26 (CH), 133.96, 148.73, 153.30, 168.55 (C); MS (APCI *m*/*z*): 471 $[M-H)^+$, (40%)], 457 $[M-CH_3)^+$, (100%)]. HRMS FAB $[M+H]^+$ 473.1914, $C_{24}H_{28}N_2O_8+H^+$ requires 473.1918.

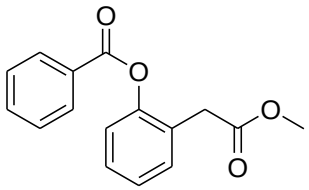
4.7 General procedure for the synthesis of the acetylated Baker-Venkataraman rearrangement precursors

To a solution of the phenol derivative (1 eq.) in dichloromethane (0.1 M) was added the acid chloride (1.5 eq.). The resulting solution was stirred at 0 ^{o}C for 10 min, after which triethylamine (1.5 eq.) and 4-dimethylaminopyridine (0.1 eq.) were added and the reaction mixture allowed to warm up to room temperature and left stirring for 16 hours. The mixture was washed with 1 M HCl (3×30mL), and extracted with dichloromethane (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the pure acylated phenols directly or after flash column chromatography.



	X	Y	R^1	R^2	R^3
315a	CH_2	C=O	OCH_3	benzoyl	H
389a	CH_2	C=O	NBn_2	methyl	H
389b	CH_2	C=O	NBn_2	benzoyl	H
389c	CH_2	C=O	NBn_2	methoxy	H
389d	CH_2	C=O	pyrrolidyl	methyl	H
389e	CH_2	C=O	pyrrolidyl	benzoyl	H
389f	CH_2	C=O	pyrrolidyl	methoxy	H
392a	CH_2CH_2	C=O	NBn_2	methyl	H
392b	CH_2CH_2	C=O	NBn_2	benzoyl	H
392c	CH_2CH_2	C=O	NBn_2	methoxy	H
392d	CH_2CH_2	C=O	pyrrolidyl	methyl	H
392e	CH_2CH_2	C=O	pyrrolidyl	benzoyl	H
392f	CH_2CH_2	C=O	pyrrolidyl	methoxy	H
396	CH_2	C=O	pyrrolidyl	NEt_2	H
398a	C=O	CH_2	H	benzoyl	H
398b	C=O	CH_2	CH_3	benzoyl	H
415a	C=O	CH_2	H	NEt_2	H
415b	C=O	CH_2	CH_3	NEt_2	H
415c	C=O	CH_2	CH_3	$N(CH_3)Ph$	H
415d	C=O	CH_2	CH_3	morpholino	H
425a	C=O	CH_2	CH_3	$N(CH_3)Ph$	CH_3
425b	C=O	CH_2	CH_3	$N(CH_3)Ph$	Br
425c	C=O	CH_2	acetyl	$N(CH_3)Ph$	H
425d	C=O	CH_2	benzoyl	$N(CH_3)Ph$	H
425e	C=O	CH_2	$CH_2C_6H_5$	$N(CH_3)Ph$	H

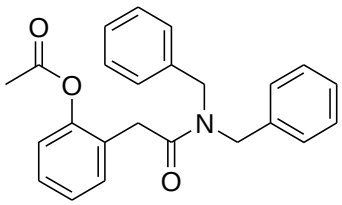
2-((Methoxycarbonyl)methyl)phenyl benzoate, 351a



351a

After aqueous work-up the solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow oil (100%). R_f (30% EtOAc in petroleum ether): 0.68. IR (neat, cm^{-1}): ν_{max} 1733 (C=O stretching), 1060 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ 3.58 (s, 3H, CH_3), 3.64 (s, 2H, CH_2), 7.25 (t, 2H, *J*= 6.0Hz, Ar), 7.34-7.38 (m, 2H, Ar), 7.51 (t, 2H, *J*= 7.5Hz, Ar), 7.64 (t, 1H, *J*= 7.5Hz, Ar), 8.20 (d, 2H, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 36.40 (CH_2), 52.17 (CH_3), 122.79, 126.33, 128.73, 129.30, 130.26,131.46, 133.82 (CH), 126.75, 130.67, 149.37, 164.76, 171.24 (C); MS (APCI *m*/*z*): 271 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 271.0963, $C_{16}H_{14}O_4+H^+$ requires 271.0963.

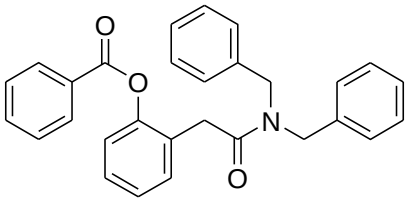
[2-[2-(Dibenzylamino)-2-oxo-ethyl]phenyl] acetate, **389a**



389a

The solvent was evaporated *in vacuo* to afford the title compound as an off-white solid (96%). R_f (30% EtOAc in petroleum ether): 0.63; m.p.= 89-91°C (DCM). IR (neat, cm^{-1}): ν_{max} 1653 (C=O stretching), 1196 (C-O stretching, ester) 1746 (C=O stretching, ester); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.08 (s, 3H, CH_3), 3,65 (s, 2H, CH_2Ar), 4.49 (s, 2H, NCH_2), 4.61 (s, 2H, NCH_2), 7.05 (dd, 1H, *J*= 1.0Hz, *J*= 9.0Hz, Ar), 7.10 (d, 2H, *J*= 9.0Hz, Ar), 7.17-7.22 (m, 3H, Ar), 7.23 (d, 1H, *J*= 9.0Hz, Ar), 7.27-7.36 (m, 7H, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 20.52 (CH_3), 35.39, 48.34, 49.80 (CH_2), 122.35, 126.00, 126.87, 127.16, 127.25, 127.39 (CH), 127.98 (C), 128.13, 128.36, 128.73, 130.41 (CH), 136.10, 137.03, 148.65, 168.83, 170.44 (C); MS (APCI *m*/*z*): 374 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 374.1751, $C_{24}H_{23}NO_3+H^+$ requires 374.1751.

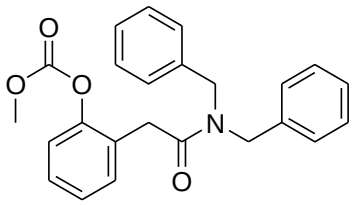
2-((Dibenzylcarbamoyl)methyl)phenyl benzoate, **389b**



389b

The solvent was evaporated *in vacuo* to afford the title compound as an off-white solid (100%). R_f (30% EtOAc in petroleum ether): 0.62; m.p.= 140-142 °C (DCM). IR (neat, cm^{-1}): ν_{max} 1642 (C=O stretching), 1179 (C-O stretching, ester) 1730 (C=O stretching, ester); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.74 (s, 2H, CH_2Ar), 4,38 (s, 2H, NCH_2), 4.60 (s, 2H, NCH_2), 7.02 (dd, 2H, *J*= 3.0Hz, *J*= 6.0Hz, Ar), 7.17-7.20 (m, 6H, Ar), 7.21-7.30 (m, 4H, Ar), 7.34 (dd, 1H, *J*= 3.0Hz, *J*= 6.0Hz, Ar), 7.40-7.45 (m, 3H, Ar), 7.63 (dt, 1H, *J*= 3.0Hz, *J*= 9.0Hz, Ar), 8.05 (dd, 2H, *J*= 3.0Hz, *J*= 7.5Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 35.46, 48.51, 50.10 (CH_2), 122.70, 126.35, 126.48, 127.56, 127.61 (CH), 127.67 (C), 128.48, 128.57, 128.69, 128.73, 128.96 (CH), 129.20 (C), 130.31, 130.78, 133.79 (CH), 136.20, 137.36, 149.13, 164.92, 170.81 (C); MS (APCI *m*/*z*): 436 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 436.1901, $C_{29}H_{25}NO_3+H^+$ requires 436.1907.

2-((Dibenzylcarbamoyl)methyl)phenyl methyl carbonate, **389c**

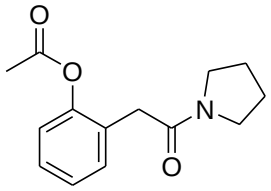


389c

The solvent was evaporated *in vacuo* to afford the title compound as a pink oil (99%). R_f (30% EtOAc in petroleum ether): 0.50; IR (neat, cm^{-1}): ν_{max} 1651 (C=O stretching), 1177 (C-O stretching, carbonate) 1761 (C=O stretching, carbonate); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.74 (s, 2H, CH_2Ar), 3,79 (s, 3H, CH_3), 4.45 (s, 2H, NCH_2), 4.62 (s, 2H, NCH_2), 7.15 (dd, 2H, *J*= 1.5Hz *J*= 7.5Hz, Ar), 7.19 (t, 1H, *J*= 1.0Hz, Ar), 7.21 (dd, 4H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.23 (d, 2H, *J*= 7.5Hz, Ar), 7.26 (d, 2H, *J*= 7.5Hz, Ar), 7.32-7.34 (m, 2H, Ar), 7.35 (d, 1H, *J*= 7.5Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 35.29, 48.51, 50.14 (CH_2), 55.57 (CH_3), 119.74, 122.02, 126.52, 127.34, 127.56 (CH), 127.70 (C), 128.46 128.57, 128.70, 129.05, 130.86 (CH), 136.40, 137.37, 149.34, 153.96,

170.68 (C); MS (APCI *m/z*): 390 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 390.1701, $C_{24}H_{23}NO_4+H^+$ requires 390.1700.

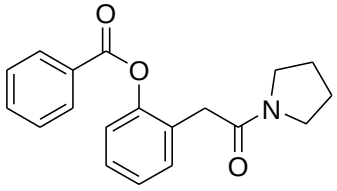
[2-(2-Oxo-2-pyrrolidin-1-yl-ethyl)phenyl] acetate, 389d



389d

The solvent was evaporated *in vacuo* to afford the title compound as yellow oil (100%). R_f (30% EtOAc in petroleum ether): 0.33; IR (neat, cm^{-1}): ν_{max} 1632 (C=O stretching), 1169 (C-O stretching, ester) 1759 (C=O stretching, ester); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.80-1.89 (m, 4H, CH_2CH_2), 2.32 (s, 3H, CH_3), 3.31 (t, 2H, *J*= 6.0Hz, NCH_2), 3.48 (t, 2H, *J*= 6.0Hz, NCH_2), 3.57 (s, 2H, CH_2Ar), 7.06 (d, 1H *J*= 7.5Hz, Ar), 7.19 (t, 1H, *J*= 7.5Hz, Ar), 7.25-7.32 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 21.10, (CH_3), 24.43, 26.33, 37.51, 46.17, 46.99 (CH_2), 122.65, 126.42 (CH), 127.51(C), 128.21, 130.73 (CH), 149.16, 168.67, 169.46 (C); MS (APCI *m/z*): 248 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 248.1284, $C_{14}H_{17}NO_3+H^+$ requires 248.1281.

[2-(2-Oxo-2-pyrrolidin-1-yl-ethyl)phenyl] benzoate, 389e

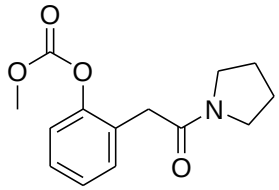


389e

The solvent was evaporated *in vacuo* to afford the title compound as pink oil (93%). R_f (30% EtOAc in petroleum ether): 0.20; IR (neat, cm^{-1}): ν_{max} 1636 (C=O stretching), 1196 (C-O stretching, ester), 1731 (C=O stretching, ester); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.71-1.81 (m, 4H, CH_2CH_2), 3.28 (t, 2H, *J*= 7.5Hz, NCH_2), 3.43 (t, 2H, *J*= 7.5Hz, NCH_2), 3.61 (s, 2H, CH_2Ar), 7.21 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.25 (dd, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.35 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.38 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.52 (td, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.66 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 8.21 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.41,

26.81, 36.93, 46.08, 46.97 (CH_2), 122.57, 126.51, 127.95, 128.29, 128.78, 129.34, 130.32 (CH), 130.83, 133.91, 149.27, 164.90, 168.77 (C); MS (APCI *m/z*): 310 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 310.1437, $C_{19}H_{19}NO_3+H^+$ requires 310.1438.

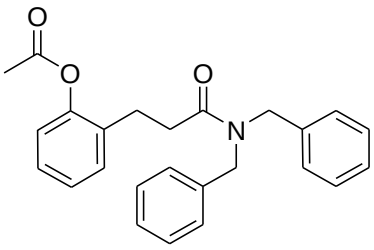
Methyl 2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl carbonate, 389f



389f

The solvent was evaporated *in vacuo* to afford the title compound as an orange oil (96%). R_f (30% EtOAc in petroleum ether): 0.41; IR (neat, cm^{-1}): ν_{max} 1634 (C=O stretching), 1169 (C-O stretching, carbonate), 1759 (C=O stretching, carbonate); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.79-1.97 (m, 4H, CH_2CH_2), 3.39 (t, 2H, *J*= 7.5Hz, NCH_2), 3.48 (t, 2H, *J*= 7.5Hz, NCH_2), 3.62 (s, 2H, CH_2Ar), 3.90 (s, 3H, CH_3), 7.18 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.21 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.28 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.35 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.51, 26.32, 36.43, 46.12, 46.99 (CH_2), 55.59 (CH_3), 121.96, 126.61 (CH), 127.38 (C), 128.26, 130.79 (CH), 149.34, 154.03, 168.57 (C); MS (APCI *m/z*): 264 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 264.1224, $C_{14}H_{17}NO_4+H^+$ requires 264.1228

[2-[3-(Dibenzylamino)-3-oxo-propyl]phenyl] acetate, 392a

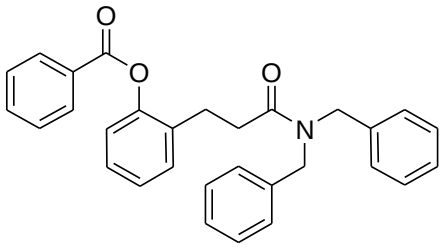


392a

The solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow sticky oil (91%). R_f (50% EtOAc in petroleum ether): 0.34; IR (neat, cm^{-1}): ν_{max} 1643 (C=O stretching), 1169 (C-O stretching, ester) 1759 (C=O stretching, ester); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.24 (s, 3H, CH_3), 2.67 (t, 2H, *J*= 7.5Hz, $CH_2C=O$), 2.98 (t, 2H, *J*= 7.5Hz, CH_2Ar), 4.38 (s, 2H, NCH_2), 4.61 (s, 2H, NCH_2), 6.99 (dd, 1H, *J*= 1.0Hz, *J*=

8.0Hz, Ar), 7.10 (d, 2H, *J*= 8.0Hz, Ar), 7.12 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.16-7.21 (m, 3H, Ar), 7.22-7.24 (m, 2H, Ar), 7.25-7.29 (m, 4H, Ar), 7.35 (d, 1H, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 20.99 (CH_3), 26.99, 33.53, 48.43, 49.92 (CH_2), 122.50, 126.35, 126.39, 127.52, 127.58, 127.71, 128.36, 128.69, 129.05, 130.58 (CH), 133.00, 136.45, 137.29, 149.03, 169.69, 172.75 (C); MS (APCI *m*/*z*): 388 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 388.1908, $C_{25}H_{25}NO_3+H^+$ requires 388.1907.

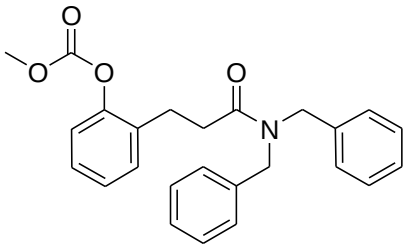
[2-[3-(Dibenzylamino)-3-oxo-propyl]phenyl] benzoate, 392b



392b

The solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow sticky oil (100%). R_f (30% EtOAc in petroleum ether): 0.62; IR (neat, cm^{-1}): v_{max} 1644 (C=O stretching), 1170 (C-O stretching, ester) 1731 (C=O stretching, ester); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.72 (t, 2H, *J*= 7.5Hz, CH_2C=O), 3.05 (t, 2H, *J*= 7.5Hz, CH_2Ar), 4.32 (s, 2H, NCH_2), 4.55 (s, 2H, NCH_2), 7.03 (t, 2H, *J*= 7.5Hz, Ar), 7.12 (td, 3H, *J*= 1.0Hz, *J*= 7.5Hz, Ar), 7.19 (td, 2H, *J*= 1.0Hz, *J*= 7.5Hz, Ar), 7.25-7.29 (m, 4H, Ar), 7.32 (dd, 3H, *J*= 1.0Hz, *J*= 7.5Hz, Ar), 7.47 (td, 2H, *J*= 1.0Hz, *J*= 7.5Hz, Ar), 7.64 (td, 1H, *J*= 1.0Hz, *J*= 7.5Hz, Ar), 8.11 (dd, 2H, *J*= 1.0Hz, *J*= 7.5Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 26.45, 33.68, 48.29, 49.90 (CH_2), 122.61 (CH), 123.44 (C), 126.45, 127.46, 127.66, 127.73, 128.29, 128.67, 128.79, 129.00 (CH), 129.31 (C), 130.26, 130.88, 133.22, 133.81 (CH), 136.38, 137.29, 149.30, 165.29, 172.72 (C); MS (APCI *m*/*z*): 450 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 450.2058, $C_{30}H_{27}N_1O_3+H^+$ requires 450.2064.

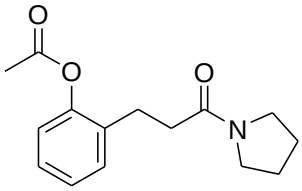
[2-[3-(Dibenzylamino)-3-oxo-propyl]phenyl] methyl carbonate, 392c



392c

The solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow solid (93%). R_f (30% EtOAc in petroleum ether): 0.58; m.p.= 65-67 °C (DCM). IR (neat, cm^{-1}): v_{max} 1643 (C=O stretching), 1169 (C-O stretching, carbonate) 1759 (C=O stretching, carbonate); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.71 (t, 2H, *J*= 7.5Hz, CH_2C=O), 3.04 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.82 (s, 2H, NCH_2), 4.39 (s, 2H, NCH_2), 4.59 (s, 3H, CH_3), 7.10 (d, 3H, *J*= 8.0Hz, Ar), 7.15-7.19 (m, 3H, Ar), 7.21 (d, 1H, *J*= 8.0Hz, Ar), 7.24-7.26 (m, 2H, Ar), 7.29-7.31 (m, 4H, Ar), 7.34-7.36 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 50.52 (CH_3), 26.27, 35.65, 48.23, 49.88 (CH_2), 121.98, 126.53, 126.61, 127.51, 127.69, 127.74, 128.41, 128.70, 129.04, 130.78 (CH), 132.95, 136.49, 137.38, 149.45, 154.36, 172.62 (C); MS (APCI *m*/*z*): 404 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 404.1855, $C_{25}H_{25}NO_4+H^+$ requires 404.1856.

2-(3-Oxo-3-(pyrrolidin-1-yl)propyl)phenyl acetate, **392d**

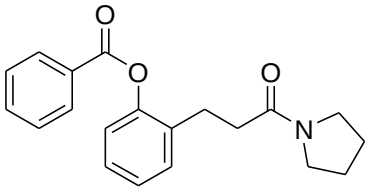


392d

The solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow oil (100%). R_f (30% EtOAc in petroleum ether): 0.66; IR (neat, cm^{-1}): v_{max} 1624 (C=O stretching), 1169 (C-O stretching, ester), 1756 (C=O stretching, ester); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.77-1.91 (m, 4H, CH_2CH_2), 2,33 (s, 3H, CH_3), 2.49 (t, 2H, *J*= 7.5Hz, CH_2C=O), 2.90 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.26 (t, 2H, *J*= 6.0Hz, NCH_2), 3.45 (t, 2H, *J*= 7.5Hz, NCH_2), 7.01 (d, 1H, *J*= 6.0Hz, Ar), 7.16-7.20 (m, 2H, Ar), 7.22-7.30 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 21.02 (CH_3), 24.37, 25.50, 26.02, 35.15, 45.70, 46.56 (CH_2), 122.38, 126.23, 126.40, 130.43 (CH), 133.28, 148.90, 169.78, 170.59 (C);

MS (APCI *m/z*): 262 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 262.1437, $C_{15}H_{19}NO_3+H^+$ requires 262.1438.

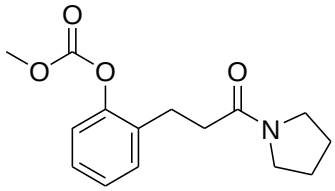
[2-(3-Oxo-3-pyrrolidin-1-yl-propyl)phenyl] benzoate, 392e



392e

The solvent was evaporated *in vacuo* to afford the title compound as a lemon-yellow waxy oil (94%). R_f (50% EtOAc in petroleum ether): 0.37; IR (neat, cm^{-1}): ν_{max} 1643 (C=O stretching), 1169 (C-O stretching, ester) 1759 (C=O stretching, ester); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.75-1.80 (m, 4H, CH_2CH_2), 2.54-2.60 (m, 2H, $CH_2C=O$), 3.00 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.20 (br. s, 2H, *J*= 7.5Hz, NCH_2), 3.40 (br. s, 2H, *J*= 7.5Hz, NCH_2), 7.15 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.23 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.35 (d, 1H, *J*= 8.0Hz, Ar), 7.52 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.55-7.60 (m, 2H, Ar), 7.63-7.66 (m, 1H, Ar), 8.21 (dd, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.33, 25.80, 25.94, 35.31, 45.80, 46.69 (CH_2), 122.48, 126.30, 127.52, 128.23 (CH), 129.26 (C), 130.17, 130.65 (CH), 133.34 (C), 133.76 (CH), 149.10, 165.29, 170.79 (C); MS (APCI *m/z*): 324 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 324.1592, $C_{20}H_{21}NO_3+H^+$ requires 324.1594.

Methyl [2-(3-oxo-3-pyrrolidin-1-yl-propyl)phenyl] carbonate, **392f**

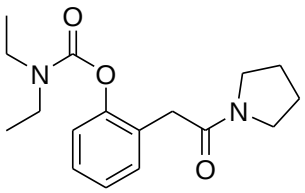


392f

The solvent was evaporated *in vacuo* to afford the title compound as a colourless oil (89%). R_f (30% EtOAc in petroleum ether): 0.67; IR (neat, cm^{-1}): ν_{max} 1632 (C=O stretching), 1178 (C-O stretching, carbonate) 1759 (C=O stretching, carbonate); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.77-1.93 (m, 4H, CH_2CH_2), 2,52 (t, 2H, *J*= 7.5Hz, $CH_2C=O$), 2.95 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.29 (t, 2H, *J*= 7.5Hz, NCH_2), 3.45 (t, 2H, *J*=

7.5Hz, NCH_2), 3.90 (s, 3H, CH_3), 7.11 (dd, 1H, *J*= 1.5Hz, *J*= 8.0 Hz), 7.21-7.25 (m, 2H), 7.30 (dd, 1H, *J*= 1.5Hz *J*= 8.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.48, 25.64, 26.41, 35.25, 45.75, 46.59 (CH_2), 55.63 (CH_3), 121.91, 126.57, 127.62, 130.79 (CH), 133.29, 149.39, 154.40, 170.58 (C); MS (APCI *m*/*z*): 278 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 278.1389, $C_{15}H_{19}NO_4+H^+$ requires 278.1387.

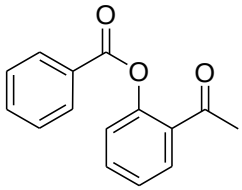
2-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)phenyl diethylcarbamate, 396



396

Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as a colourless oil (57%). R_f (30% EtOAc in petroleum ether): 0.52; IR (neat, cm^{-1}): ν_{max} 1610 (C=O stretching), 1192 (C-O stretching, carbamate), 1715 (C=O stretching, carbamate); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.17-1.25 (m, 2H, CH_2CH_2), 1.39 (t, 2H, *J*= 7.5Hz, CH_2CH_2), 1.85-1.91 (m, 3H, CH_3), 1.97-2.03 (m, 3H, CH_3), 2.95 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 3.33-3.40 (m, 2H, CH_2CH_3), 3.46 (t, 2H, *J*= 7.5Hz, NCH_2), 3.55-3.66 (m, 2H, NCH_2), 3.68 (s, 2H, CH_2Ar), 6.80 (t, 1H, *J*= 7.5Hz, Ar), 6.96-7.03 (m, 2H, Ar), 7.17 (t, 1H, *J*= 7.5Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 24.50, (CH_3), 26.10, 38.95, 46.32, 47.73 (CH_2), 118.34, 119.95 (CH), 121.06 (C), 129.11, 130.55 (CH), 157.25, 171.55 (C); MS (APCI *m*/*z*): 305 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 305.1860, $C_{17}H_{24}N_2O_3+H^+$ requires 305.1860.

2-Acetylphenyl benzoate, 398a

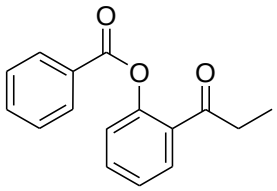


398a

The solvent was evaporated *in vacuo* to afford the title compound as colourless crystals (100%). R_f (10% EtOAc in petroleum ether): 0.44; m.p.= 88-89 °C (dichloromethane)

[(lit. m.p. 87-88 °C)[370] (ethanol)]; IR (neat, cm^{-1}): *v* 1634 (C=O stretching), 1176 (C-O stretching, ester), 1759 (C=O stretching, ester); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.27 (s, 3H, CH_3), 6.96 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.10 (t, 1H, *J*= 7.5Hz, Ar), 7.44-7.60 (m, 4H, Ar), 7.59 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.95 (dd, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 29.95, (CH_3), 124.05, 126.32, 128.84, (CH), 129.33 (C), 130.43 (CH), 131.36 (C), 133.57, 133.97 (CH), 149.48, 165.30, 197.72 (C); MS (APCI m/z): 258 $[M+NH_4)^+$, (100%)].

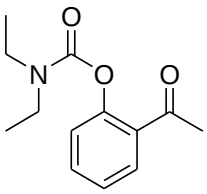
2-Propionylphenyl benzoate, 398b



398b

Flash column chromatography (SiO_2; 5% EtOAc in petroleum ether) afforded the title compound as colourless solid (61%). R_f (10% EtOAc in petroleum ether): 0.43; m.p.= 58-60 °C (EtOAc/petroleum ether) [(lit. m.p.= 58-59 °C)[371] (petroleum ether)]; IR (neat, cm^{-1}): *v* 1684 (C=O stretching), 1194 (C-O stretching, ester), 1726 (C=O stretching, ester); ^1H NMR ($CDCl_3$, 300MHz): δ 1.16 (t, 3H, *J*= 7.5Hz, CH_3), 2.96 (q, 2H, *J*= 7.5Hz, CH_2), 7.29 (d, 1H, *J*= 7.5Hz, Ar), 7.40 (t, 1H, *J*= 7.5Hz, Ar), 7.49-7.60 (m, 1H, Ar), 7.64-7.72 (m, 1H, Ar), 7.86 (dd, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 8.15 (dd, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 8.24 (dd, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 8.33 (CH_3), 35.08 (CH_2), 123.97, 126.42, 128.60 (CH), 128.80 (C), 129.86, 130.31 (CH), 130.42 (C), 133.09, 133.94 (CH), 149.13, 165.30, 172.47 (C); MS (APCI m/z): 272 $[M+NH_4)^+$, (100%)].

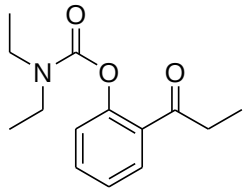
2-Acetylphenyl diethylcarbamate, 415a



415a

Flash column chromatography (SiO_2; 17% EtOAc in petroleum ether) afforded the title compound as a colourless oil (27%). R_f (30% EtOAc in petroleum ether): 0.55; IR (neat, cm^{-1}): ν_{max} 1686 (C=O stretching), 1150 (C-O stretching, carbamate), 1713 (C=O stretching, carbamate); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.21 (t, 3H, *J*= 7.5Hz, CH_3CH_2), 1.29 (t, 3H, *J*= 7.5Hz, CH_3CH_2), 2.55 (s, 3H, CH_3), 3.38 (q, 4H, *J*= 6.0Hz, CH_2CH_3), 3.49 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 7.12 (d, 1H, *J*= 9.0Hz, Ar), 7.25 (t, 1H, *J*= 7.5Hz, Ar), 7.9 (td, 1H, *J*= 7.5Hz, Ar), 7.74 (dd, 1H, *J*= 9.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.48, 14.30, 29.72 (CH_3), 42.08, 42.44 (CH_2), 123.93, 125.42, 129.78 (CH), 132.06 (C), 133.13 (CH), 149.95, 153.85, 198.43 (C); MS (APCI *m*/*z*): 236 $[M+H)^+$, (100%)].[372]

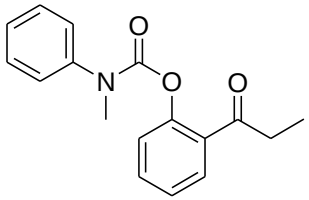
2-Propionylphenyl diethylcarbamate, **415b**



415b

Flash column chromatography (SiO_2; 8% EtOAc in petroleum ether) afforded the title compound as a colourless oil (32%). R_f (10% EtOAc in petroleum ether): 0.52; IR (neat, cm^{-1}): ν_{max} 1603 (C=O stretching), 1152 (C-O stretching, carbamate), 1714 (C=O stretching, carbamate); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.17-134 (m, 6H, CH_3CH_2N), 1.31 (t, 3H, *J*= 7.5Hz, CH_3CH_2C=O), 2.94 (q, 2H, *J*= 7.5Hz, CH_2CH_3C=O), 3.40 (q, 4H, *J*= 6.0Hz, CH_2CH_3N), 3.51 (q, 2H, *J*= 6.0Hz, CH_2CH_3N), 7.15 (d, 1H, *J*= 9.0Hz, Ar), 7.30 (t, 1H, *J*= 4.5Hz, Ar), 7.50 (t, 1H, *J*= 7.5Hz, Ar), 7.71 (d, 1H, *J*= 6.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 8.32, 13.49, 14.32 (CH_3), 34.99, 42.14, 42.47 (CH_2), 123.75, 125.33, 129.08, 132.47 (CH), 132.54, 149.50, 153.86, 201.85 (C); MS (APCI *m*/*z*): 250 $[M+H)^+$, (100%)].[372]

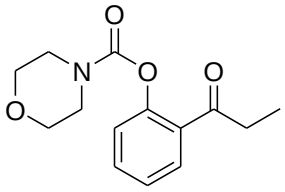
2-Propionylphenyl methylphenylcarbamate, 415c



415c

Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as a colourless oil (76%). R_f (20% EtOAc in petroleum ether): 0.48; IR (neat, cm^{-1}): ν_{max} 1689 (C=O stretching), 1134 (C-O stretching, carbamate), 1721 (C=O stretching, carbamate); ^1H NMR ($CDCl_3$, 300MHz): δ_H 0.96 (t, 3H, *J*= 6.0Hz, CH_3CH_2), 2.63 (br. s, 2H, CH_2CH_3), 3.26 (s, 3H, CH_3N), 6.99 (d, 1H, *J*= 8.0Hz, Ar), 7.08 (t, 3H, *J*= 7.5Hz, Ar), 7.11-7.33 (m, 4H, Ar), 7.53 (d, 1H, *J*= 8.0Hz, Ar). ^{13}C NMR (DMSO-*d6*, 400MHz at 60 °C): δ_C 7.47 (CH_3), 34.04 (CH_2), 37.68 (CH_3), 122.89, 125.40, 125.73, 128.37, 128.68, 128.75 (CH), 131.56 (C), 132.23 (CH), 142.45, 148.36, 152.32, 201.57 (C); MS (APCI *m*/*z*): 284 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 284.1281, $C_{17}H_{17}NO_3+H^+$ requires 284.1281.

2-Propionylphenyl morpholine-4-carboxylate, **415d**

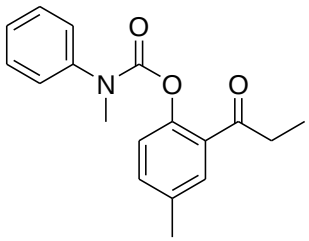


415d

Flash column chromatography (SiO_2; 40% EtOAc in petroleum ether) afforded the title compound as colourless solid (94%). R_f (30% EtOAc in petroleum ether): 0.44; m.p.= 102-104 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): ν_{max} 1686 (C=O stretching), 1718 (C=O stretching, carbamate), 1053 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 1.17 (t, 3H, *J*= 7.5Hz, CH_3CH_2), 2.88 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 3.55 (br. s, 2H, OCH_2), 3.66-3.78 (m, 6H, OCH_2NCH_2), 7.13 (d, 1H, *J*= 7.5Hz, Ar), 7.25 (t, 1H, *J*= 7.5Hz, Ar), 7.47 (td, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.79 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 8.18, (CH_3), 34.44, 44.23, 45.06, 66.52 (CH_2), 123.76, 125.51, 129.26, 131.45 (CH), 132.69, 149.22, 153.26, 200.99 (C); MS (APCI

m/*z*): 264 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 264.1230, $C_{14}H_{17}NO_4+H^+$ requires 264.1230.

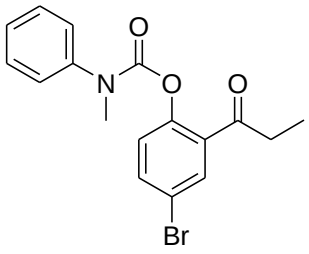
4-Methyl-2-propionylphenyl methylphenylcarbamate, 425a



425a

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as a colourless solid (63%). R_f (30% EtOAc/petroleum ether): 0.57; m.p.= 67-69 °C (methanol). IR (neat, cm^{-1}): ν_{max} 1679 (C=O stretching), 1135 (C-O stretching, ester), 1711 (C=O stretching, ester); ^{1}H NMR (CDCl3, 300MHz): δ 1.11 (br. t, 3H, *J*= 6.0Hz, CH_3CH_2), 2.35 (s, 3H, CH_3Ar), 2.77 (br. s, 2H, CH_2CH_3), 3.41 (br. s, 3H, CH_3N), 7.02 (d, 1H, *J*= 7.5Hz, Ar), 7.26 (br. t, 2H, *J*= 3.0Hz, Ar), 7.36-7.42 (m, 4H, Ar), 7.48 (br. s, 1H, Ar). ^{13}C NMR (DMSO-*d6*, 400MHz at 60 °C): δ_H 7.48, 19.92 (CH_3), 33.99 (CH_2), 37.53 (CH_3), 122.62, 125.38, 125.71, 128.33, 128.94 (CH), 131.22 (C), 132.66 (CH), 134.52, 142.50, 146.22, 152.47, 200.79 (C); MS (APCI *m*/*z*): 298 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 298.1433, $C_{18}H_{19}NO_3+H^+$ requires 298.1438.

4-Bromo-2-propionylphenyl methylphenylcarbamate, 425b

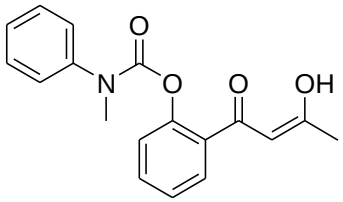


425b

The solvent was evaporated *in vacuo* to afford the title compound as a colourless solid (96%). R_f (30% EtOAc in petroleum ether): 0.87. Mp= 77-79 °C (dichloromethane). IR (neat, cm^{-1}): ν_{max} 1694 (C=O stretching), 1138 (C-O stretching, carbamate), 1720 (C=O stretching, carbamate); ^{1}H NMR (DMSO *d6*, 300MHz): δ_H 0.98 (br. s, 3H, *J*= 6.3Hz, CH_3CH_2), 2.82 (br. s, 2H, CH_2CH_3), 3.39 (br. s, 3H, CH_3N), 7.21 (d, 1H, *J*= 7.89Hz,

Ar), 7.28 (t, 1H, *J*= 6.3Hz, Ar), 7.39-7.44 (m, 4H, Ar), 7.74 (d, 1H, *J*= 7.89Hz, Ar), 7.93 (br. s, 1H, Ar). ^{13}C NMR (DMSO-*d6*, 400MHz at 60 °C): δ_C 7.26 (CH_3), 7.65 (CH_2), 34.16 (CH_3), 117.31 (C), 125.19, 125.41, 125.75, 128.41, 128.79 (CH), 130.92 (C), 133.53 (CH), 142.23, 147.48, 151.93, 199.65 (C); MS (APCI m/z): 362 (^{79}Br), 364 (^{81}Br) $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 362.0383, $C_{17}H_{16}BrNO_3+H^+$ requires 362.0386.

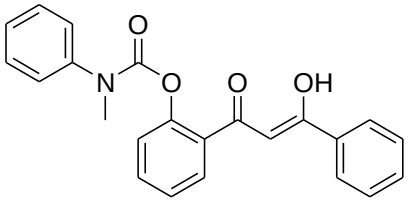
[2-[(*Z*)-3-Hydroxybut-2-enoyl]phenyl] *N*-methyl-*N*-phenyl-carbamate, 425c



425c

Flash column chromatography (SiO_2; 17% EtOAc in petroleum ether) afforded the title compound as a colourless solid (50%). R_f (30% EtOAc in petroleum ether): 0.58; m.p.= 75-77 °C (EtOAc/Petrol). IR (neat, cm^{-1}): ν_{max} 1722 (C=O stretching, ester), 1129 (C-O stretching) ; ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.97 (s, 3H, CH_3), 3.29 (s, 3H, CH_3N), 5.71 (s, 1H, CH), 7.04 (d, 1H, *J*= 7.5Hz, Ar), 7.13 (m, 3H, Ar), 7.24-7.35 (m, 4H, Ar), 7.55 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 15.85 (s, 1H, OH). ^{13}C NMR (CDCl3, 75MHz): δ_C 25.69, 38.47 (CH_3), 100.52, 123.80, 125.74, 129.16, 129.42, 132.29 (CH), 149.28, 193.14 (C); MS (APCI *m*/*z*): 310 $[M-H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 312.1232, $C_{18}H_{17}NO_4+H^+$ requires 312.1230.

2-((*Z*)-3-Hydroxy-3-phenylacryloyl)phenyl methylphenylcarbamate, 425d

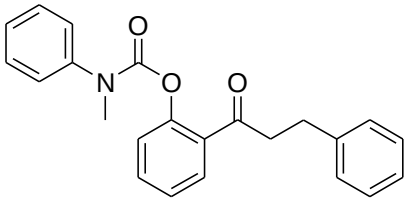


425d

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as a colourless solid (91%). R_f (20% EtOAc in petroleum ether): 0.52; m.p.= 70-72 °C (DCM). IR (neat, cm^{-1}): ν_{max} 1128 (C-O stretching, carbamate), 1721 (C=O

stretching, carbamate); ^{1}H NMR (CDCl3, 300MHz): δ_H 3.38 (s, 3H, CH_3N), 6.55 (s, 1H, CH), 7.19-7.24 (m, 2H, Ar), 7.29-7.35 (m, 5H, Ar), 7.44-7.49 (m, 3H, Ar), 7.53-7.58 (m, 1H, Ar), 7.75 (d, 1H, *J*= 7.5Hz, Ar), 7.81 (d, 2H, *J*= 7.5Hz, Ar). ^{13}C NMR (DMSO-*d6*, 400MHz at 60 °C): δ_C 37.61 (CH_3), 96.73, 123.35, 123.73, 125.11, 125.49, 125.83, 126.28, 126.70, 128.42, 128.75 (CH), 129.08 (C), 132.54 (CH), 134.05, 142.33, 148.76, 152.27, 183.87, 185.36 (C); MS (APCI *m*/*z*): 374 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 374.1381, $C_{23}H_{19}NO_4+H^+$ requires 374.1387.

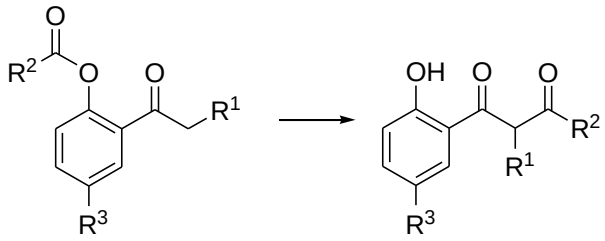
2-(3-Phenylpropanoyl)phenyl methylphenylcarbamate, 425e



425e

Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as a colourless oil (99%). R_f (20% EtOAc/petroleum ether): 0.57; m.p. = 56-58 °C (dichloromethane). IR (neat, cm^{-1}): ν_{max} 1686 (C=O stretching), 1131 (C-O stretching, carbamate), 1721 (C=O stretching, carbamate); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.99 (br. s, 2H, CH_2C=O), 3.01 (br. s, 2H, CH_2Ar), 3.38 (s, 3H, CH_3N), 7.14-7.36 (m, 12H, Ar), 7.48 (t, 1H, *J*= 7.5Hz, Ar), 7.72 (d, 1H, *J*= 7.5Hz, Ar). ^{13}C NMR (DMSO-*d6*, 400MHz at 60 °C): δ_C 29.10 (CH_2), 37.70 (CH_3), 42.36 (CH_2), 123.06, 123.48, 125.32, 125.70, 127.63, 128.07, 128.34, 128.73, 128.88 (CH), 131.36 (C), 132.49 (CH), 140.66, 142.36, 148.56, 152.33, 199.07 (C); MS (APCI *m*/*z*): 360 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 360.1590, $C_{23}H_{21}NO_3+H^+$ requires 360.1594.

4.8 General procedure for the Baker-Venkataraman rearrangement reactions

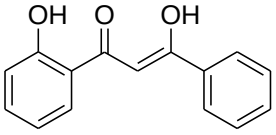


398a, 415a,c, 425a,e **399a, 416a,c, 426a,e, 430**

	R^1	R^2	R^3
399a	H	C_6H_5	H
416a	H	NEt_2	H
416c	CH_3	$N(CH_3)C_6H_5$	H
426a	CH_3	$N(CH_3)C_6H_5$	CH_3
426e	$CH_2C_6H_5$	$N(CH_3)C_6H_5$	H
430	H	$N(CH_3)C_6H_5$	H

To a solution of the *O*-acylated phenols (1 eq.) in anhydrous tetrahydrofuran (0.2 M) was added sodium hydride (2.5 eq.) and the resulting solution was heated at reflux for 1-2 hours. After which, the mixture was cooled down and acidified with hydrochloric acid solution (1 M, 30mL). The product was extracted with ethyl acetate (2×30mL) and the combined organic layers were washed with distilled water (2×20mL), brine (10mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue which was purified by flash column chromatography.

(*Z*)-3-Hydroxy-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-on, 399a

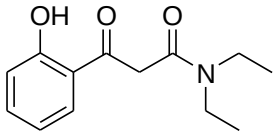


399a

Flash column chromatography (SiO_2; 4% EtOAc in petroleum ether) afforded the title compound as white solid (96%). R_f (10% EtOAc in petroleum ether): 0.56; m.p.= 130-132 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): ν_{max} 1601 (C=O stretching), 1087 (C-O stretching), 3045 (OH stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 6.85 (s, 1H, CH), 6.93 (t, 1H, *J*= 7.5Hz, Ar), 7.01 (d, 1H, *J*= 9.0Hz, Ar), 7.44-7.60 (m, 4H, Ar), 7.79 (d,

1H, *J*= 9.0Hz, Ar), 7.94 (d, 2H, *J*= 9.0Hz, Ar), 12.11 (s, 1H, ArOH), 15.55 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 92.41, 118.95, 119.09 (CH), 119.23 (C), 126.95, 128.65, 128.93, 132.57, 135.99 (CH), 133.72, 162.60, 177.61, 195.81 (C); MS (APCI *m*/*z*): 241 $[M+H)^+$, (100%)].[373]

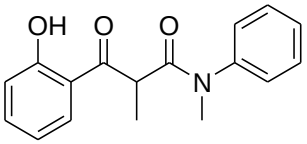
_N_,_N_-Diethyl-3-(2-hydroxyphenyl)-3-oxopropanamide, 416a



416a

Flash column chromatography (SiO_2; 45% EtOAc in petroleum ether) afforded the title compound as an orange solid (74%). R_f (30% EtOAc in petroleum ether): 0.43; m.p.= 86-88 °C (EtOAc/petroleum ether) [(lit. m.p.= 85 °C)[99] (EtOAc/hexane)]; IR (neat, cm^{-1}): ν_{max} 1624 (C=O stretching), 2967 (OH stretching), 1096 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.17-1.26 (m, 6H, CH_3), 3.32-3.44 (m, 4H, CH_2CH_3), 4.07 (s, 2H, CH_2C=O), 6.88-6.96 (m, 2H, Ar), 7.47 (t, 1H, *J*= 8.0Hz, Ar), 7.79 (d, 1H, *J*= 7.5Hz, Ar), 11.96 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 12.98, 14.35 (CH_3), 40.48, 42.91, 45.50 (CH_2), 118.59, 119.39, 119.44 (C), 130.98, 137.02 (CH), 162.71, 165.64, 200.30 (C); MS (APCI *m*/*z*): 236 $[M+H)^+$, (100%)].

3-(2-Hydroxyphenyl)-_N_,2-dimethyl-3-oxo-_N_-phenylpropanamide, 416c

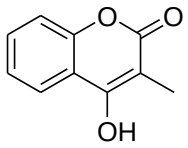


416c

Flash column chromatography (SiO_2; 6% acetone in toluene) afforded the title compound as a lemon-yellow solid (48%). R_f (20% acetone in toluene): 0.50; m.p.= 89-91 °C (acetone/toluene). IR (neat, cm^{-1}): ν_{max} 1659 (C=O stretching, amide), 1611 (C=O stretching, ketone), 3060 (OH stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.44 (d, 3H, *J*= 6.0Hz, CH_3CH), 3.31 (s, 3H, CH_3N), 4.32 (q, 3H, *J*= 6.0Hz, CH), 6.68 (t, 1H, *J*= 7.5Hz, Ar), 6.89 (d, 1H, *J*= 9.0Hz, Ar), 7.12-7.18 (m, 5H, Ar), 7.23-7.29 (m, 1H, Ar), 7.37 (t, 1H, *J*= 7.5Hz, Ar), 11.96 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 15.60,

37.94 (CH_3), 46.64, 117.96, 118.68 (CH), 128.09 (C), 128.35, 128.46, 129.17, 130.07, 136.55 (CH), 142.79, 162.91, 169.76, 203.86 (C); MS (APCI *m*/*z*): 284 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 284.1282, $C_{17}H_{17}NO_3+H^+$ requires 284.1281.

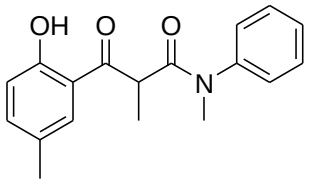
4-Hydroxy-3-methyl-2H-chromen-2-one, 417



417

Flash column chromatography (SiO_2; 30% acetone in toluene) afforded the title compound as white solid (44%). R_f (20% acetone in toluene): 0.45; m.p.= 230-232 °C (acetone/toluene) [(lit. m.p.= 227-228 °C)[374] (ethanol)]; IR (neat, cm^{-1}): ν_{max} 1662 (C=O stretching), 1083 (C-O stretching), 3151 (OH stretching); ^{1}H NMR (DMSO- *d6*, 300MHz): δ_H 1.99 (s, 3H, CH_3), 7.31-7.36 (m, 2H, Ar), 7.58 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 7.89 (d, 1H, *J*= 8.0Hz, Ar), 11.30 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 9.78 (CH_3), 100.23 (C), 116.06 (CH), 116.26 (C), 122.97, 123.84, 131.46, (CH), 151.64, 159.75, 163.16 (C); MS (APCI *m*/*z*): 175 $[M-H)^+$, (100%)].

3-(2-Hydroxy-5-methylphenyl)-N,2-dimethyl-3-oxo-N-phenylpropanamide, 426a

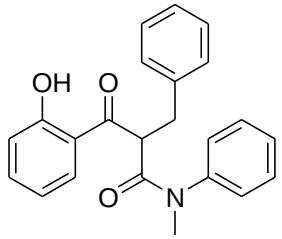


426a

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow solid (22%). R_f (30% EtOAc in petroleum ether): 0.53; m.p.= 91-93 °C (EtOAc/petroleum ether). IR (neat, cm^{-1}): ν_{max} 1657 (C=O stretching, amide), 1613 (C=O stretching, ketone), 2923 (O-H stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.44 (d, 3H, *J*= 7.0Hz, CH_3CH), 2.17 (s, 3H, CH_3Ar), 3.31 (s, 3H, CH_3N), 4.33 (q, 1H, *J*= 7.0Hz, CH), 6.80 (d, 2H, *J*= 8.0Hz, Ar), 7.14-7.20 (m, 4H, Ar), 7.21-7.31 (m, 2H, Ar), 11.81 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 15.64, 20.51, 37.99 (CH_3), 46.19 (CH), 117.69 (C), 118.40 (CH), 127.69 (C), 128.31, 128.44, 128.77 (CH),

130.19 (C), 137.68 (CH), 160.87, 169.87 (C); MS (APCI m/z): 298 [M+H)+, (100%)]. HRMS FAB $[M+H]^+$ 298.1438, $C_{18}H_{19}NO_3+H^+$ requires 298.1438.

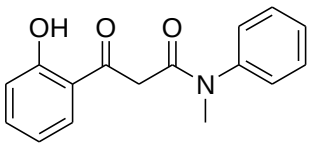
2-Benzyl-3-(2-hydroxyphenyl)-*N*-methyl-3-oxo-*N*-phenyl-propanamide, 426e



426e

Flash column chromatography (SiO_2; 6% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow crystalline solid (58%). R_f (30% EtOAc in petroleum ether): 0.68. m.p.= 117-119 °C (EtOAc in petroleum ether). IR (neat, cm^{-1}): ν_{max} 1656 (C=O stretching, amide), 1634 (C=O stretching, ketone), 3169 (O-H stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.10 (dd, 1H, *J*= 6.15Hz, *J*= 13.77Hz, CH_2Ar), 3.27 (s, 3H, CH_3N), 3.47 (dd, 1H, *J*= 7.72Hz, J= 13.77Hz, CH_2Ar), 4.6 (dd, 1H, *J*= 6.35Hz, *J*= 7.5Hz, CH), 6.7 (td, 2H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 6.82-6.87 (m, 4H, Ar), 6.89-6.93 (m, 2H, Ar), 7.09-7.24 (m, 5H, Ar), 7.34 (td, 1H, *J*= 1.0Hz, *J*= 8.0Hz, Ar), 12.03 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 36.52 (CH_2), 38.09 (CH_3), 53.57, 118.48 (CH), 118.60 (C), 126.80, 128.08, 128.51, 128.65, 129.04, 129.37, 130.09, 136.59 (CH), 138.81, 142.79, 162.99, 167.88, 201.96 (C); MS (APCI m/z): 360 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 360.1592, $C_{23}H_{21}NO_3+H^+$ requires 360.1594.

3-(2-Hydroxyphenyl)-*N*-methyl-3-oxo-*N*-phenylpropanamide, 430

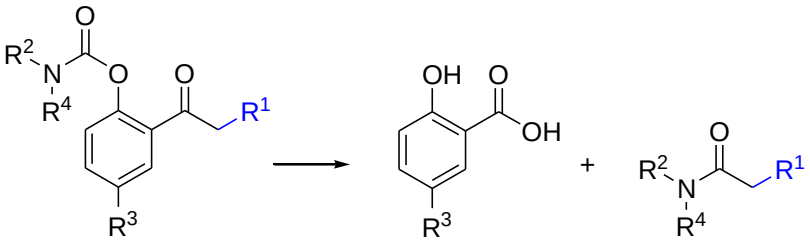


430

Flash column chromatography (SiO_2; 12% EtOAc in toluene) afforded the title compound as a colourless sticky oil (33%). R_f (30% EtOAc in toluene): 0.53. IR (neat, cm^{-1}): ν_{max} 1632 (C=O stretching), 1118 (C-O stretching), 2932 (O-H stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.34 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 6.81 (t, 1H, *J*= 8.0Hz,

Ar), 6.92 (d, 1H, *J*= 8.0Hz, Ar), 7.24 (d, 2H, *J*= 8.0Hz, Ar), 7.24 (d, 1H, *J*= 8.0Hz, Ar), 7.37-7.45 (m, 4H, Ar), 11.88 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 37.59 (CH_3), 45.32 (CH_2), 118.54, 119.119, 127.23, 128.54, 130.12, 130.25, 136.81 (CH), 143.43, 162.50, 166.55, 200.17 (C); MS (APCI m/z): 270 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 270.1125, $C_{16}H_{15}NO_3+H^+$ requires 270.1125.

4.9 General procedure for the Baker-Venkataraman-*retro*-Claisen cascade reactions



415a,c
425a,d,e

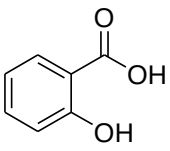
403

404d, **427**

	R^3		R^1	R^2	R^4
403	H	**404d**	H	CH_3	C_6H_5
403a	CH_3	**427e**	$CH_2C_6H_5$	CH_3	C_6H_5
403b	Br				

To a solution of the acylated phenols **415a,c** or **425a,d,e** (1 eq.) in tetrahydrofuran (0.2 M) was added sodium hydride (2.5 eq.) and the resulting solution was heated at reflux for 24 hours. After which, the mixture was allowed to cool, and acidified with hydrochloric acid solution (1 M, 30mL). The product was extracted with ethyl acetate (2×30mL) and the combined organic layers were washed with distilled water (2×20mL), brine (10mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue which was purified by flash column chromatography.

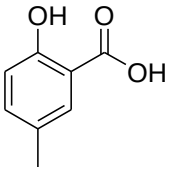
2-Hydroxybenzoic acid, salicylic acid, 403



403

Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as a colourless crystals (50%). R_f (30% EtOAc in petroleum ether): 0.65; m.p.= 157-159 °C (EtOAc/Petrol) [(lit. m.p.= 158-161 °C)[375] (EtOAc)]. IR (neat, cm^{-1}): ν_{max} 1689 (C=O stretching), 1134 (C-O stretching), 3151 (OH stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 6.94 (t, 1H, *J*= 7.5Hz, Ar), 7.00 (d, 1H, *J*= 7.5Hz, Ar), 7.53 (td, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 7.92 (dd, 1H, *J*= 1.5Hz, *J*= 7.5Hz, Ar), 10.36 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 111.36, 117.99, 119.76, 131.10 (CH), 137.19, 162.31, 174.86 (C); MS (APCI *m/z*): 137 $[M-H)^+$, (100%)].

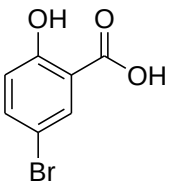
2-Hydroxy-5-methylbenzoic acid, 403a



403a

Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow solid (25%). R_f (10% EtOAc in petroleum ether): 0.54. m.p.= 150-152 °C (EtOAc/petroleum) [(lit. m.p.= 148-150 °C)[376] (ethanol/water)]; IR (neat, cm^{-1}): ν_{max} 1655 (C=O stretching), 1198 (C-O stretching), 2922 (OH stretching); ^1H NMR ($CDCl_3$, 300MHz): δ_H 2.31 (s, 3H, CH_3), 6.91 (d, 1H, *J*= 8.0Hz, Ar), 7.34 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.71 (d, 1H, *J*= 8.0Hz, Ar), 10.21 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 20.50 (CH_3), 110.94 (C), 117.73 (CH), 128.97 (C), 130.63, 138.20 (CH), 160.26, 174.90 (C); MS (APCI m/z): 151 [M-H)+, (100%)].

5-Bromo-2-hydroxybenzoic acid, 403b

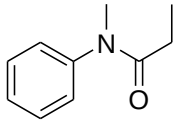


403a

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow crystalline solid (43%). R_f (30% EtOAc in petroleum

ether): 0.58; m.p.= 63-65 °C (EtOAc/petroleum) [(lit. m.p.= 60-62 °C)[377] (solvent not quoted)]; IR (neat, cm^{-1}): ν_{max} 1739 (C=O stretching), 3023 (OH stretching), 1124 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 6.91 (d, 1H, *J*= 8.0Hz, Ar), 7.59 (dd, 1H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 8.02 (s, 1H, Ar), 10.34 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 111.27 (C), 119.93, 133.18, 139.67 (CH), 161.26 (C); MS (APCI *m*/*z*): 215 (^{79}Br), 217 (^{81}Br) [M^+, (100%)].

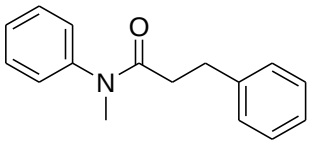
_N_-Methyl-_N_-phenylpropanamide, 404d



404d

Flash column chromatography (SiO_2; 14% EtOAc in petroleum ether) afforded the title compound as a yellow oil (50%). R_f (20% EtOAc in petroleum ether): 0.39; IR (neat, cm^{-1}): ν_{max} 1640 (C=O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.04 (t, 3H, *J*= 7.5Hz, CH_3CH_2), 2.07 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 3.25 (s, 3H, CH_3N), 7.17 (d, 2H, *J*= 7.5Hz, Ar), 7.35 (t, 1H, *J*= 7.5Hz, Ar), 7.40 (t, 2H, *J*= 7.5Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 9.87, 37.51 (CH_3), 27.64 (CH_2), 127.38, 127.85, 129.86 (CH), 144.25, 174.33 (C); MS (APCI *m*/*z*): 164 $[M+H)^+$, (100%)].[378]

_N_-Methyl-_N_,3-diphenylpropanamide, 427e



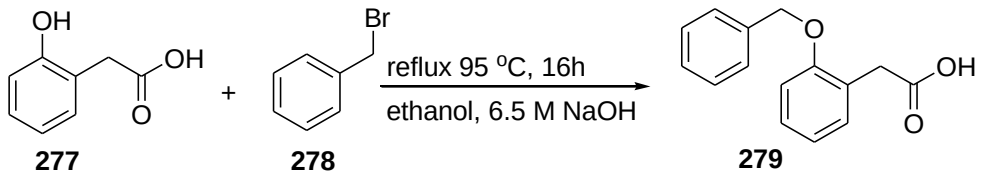
427e

Flash column chromatography (SiO_2; 14% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow oil (42%). R_f (20% EtOAc in petroleum ether): 0.47. IR (neat, cm^{-1}): ν_{max} 1650 (C=O stretching), 1119 (C-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.41 (t, 2H, *J*= 7.5Hz, CH_2C=O), 2.94 (t, 2H, *J*= 7.5Hz, CH_2Ar), 3.28 (s, 3H, CH_3N), 7.03-7.10 (m, 4H, Ar), 7.17-7.28 (m, 3H, Ar), 7.31-7.42 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 31.83, 36.04 (CH_2), 37.45 (CH_3), 126.07, 127.31, 127.86,

128.39, 128.47, 129.79 (CH), 141.23, 143.92, 172.42 (C); MS (APCI m/z): 240 $[M+H)^+$, (100%)].[378]

4.10 Miscellaneous procedures

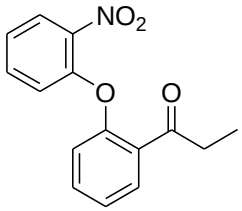
4.10.1 Procedure for the synthesis of 2-benzyloxyphenyl acetic acid, 279



277 **278** **279**

2-Hydroxyphenyl acetic acid (**277**) (0.25g, 16.44 mmol) was solubilised in a mixture of sodium hydroxide solution (6.5 M, 10mL) and ethanol (20mL) and heated at reflux for 30 minutes. Benzyl bromide (**278**) (6mL, 49.34 mmol) was added and the resulting mixture was heated at reflux for 16 hours. The solvent was concentrated and the mixture acidified with hydrochloric acid solution (1 M, pH ca 1-2). The crude extract was washed with ethyl acetate (3×30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue. Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as colourless crystals (3.4g, 85%). R_f (60% EOAc in Petrol): 0.88. m.p.= 91-93 °C (EtOAc/petroleum ether) [(lit. m.p.= 94 °C)[379] (benzene)]; IR (neat, cm^{-1}): *v* 1706 (C=O stretching), 2920 (OH stretching), 1294 (C-O stretching), 1079 (ether C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ 3.72 (s, 2H, $CH_2C=O$), 5.08 (s, 2H, CH_2O), 6.95 (t, 2H, *J*= 9.0Hz, Ar), 7.23 (dd, 1H, *J*= 9.0Hz, Ar), 7.28-7.41 (m, 6H, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 36.16, 70.14 (CH_2), 111.95, 121.05, 122.82, 127.19, 127.98, 128.68, 129.01 (CH), 131.95, 136.95, 156.64, 177.33: MS (APCI *m/z*): 241 $[M-H)^+$, (100%)].

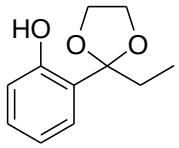
4.10.2 Procedure for the synthesis of 1-(2-(2 nitrophenoxy)phenyl)propan-1-one, 263



263

2-(2-(2-Nitrophenoxy)phenyl)-2-ethyl-1,3-dioxolane (**319**) (315 mg, 1.0 mmol) and *para*-toluenesulfonic acid (190 mg, 1.0 mmol) were dissolved in acetone:water (8mL: 2mL) and the reaction heated at 75 °C for 2.5 h. The reaction was allowed to cool and the acetone removed *in vacuo*. EtOAc (10mL) was added and the mixture washed with sat. aq. $NaHCO_3$ (2×10mL). The combined aqueous layers were extracted with EtOAc (10 mL) and the combined organic layers washed with brine (10mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as a pure pale yellow oil (98%). R_f (20% ethyl acetate in petroleum ether, eluted twice); 0.62; IR (neat, cm^{-1}): ν_{max} 1682 (C=O), 1240 (Ar-O-Ar); ^1H NMR (300 MHz; $CDCl_3$): δ_H 1.15 (t, 3H, *J*= 7.0Hz, CH_3), 3.03 (q, 2H, *J*= 7.0Hz, CH_2), 6.89 (d, 1H, *J*= 8.8Hz, Ar), 6.99 (d, 1H, *J*= 8.8Hz, Ar), 7.28-7.24 (m, 2H, Ar), 7.45 (t, 1H, *J*= 8.0Hz, Ar), 7.54 (t, 1H, *J*= 8.0Hz, Ar), 7.82 (d, 1H, *J*=7.5Hz, Ar), 8.01 (d, 1H, *J*= 8.0Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 8.1 (CH_3), 36.5 (CH_2), 119.0, 120.5, 123.8, 124.7, 125.9, 130.5 (CH), 130.8 (C), 133.3, 134.5 (CH), 141.2 149.7, 154.1, 201.7 (C); MS (APCI *m*/*z*): 272 $[M+H)^+$, (100%)]; HRMS FAB $[M+H]^+$ 272.0911, $C_{15}H_{13}NO_4$ ($M+H^+$) requires 272.0923.[31]

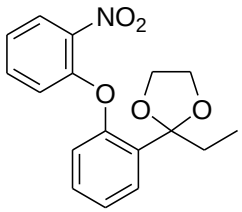
4.10.3 Procedure for the synthesis of 2-(2-ethyl-1,3-dioxolan-2-yl)phenol, 318



318

2'-Hydroxypropiophenone (**261**) (10g, 66.6 mmol), *para*-toluenesulfonic acid monohydrate (1.27g, 6.66 mmol) and ethylene glycol (4.39mL, 79.9 mmol) were suspended in toluene (250mL) and heated to reflux under Dean-Stark conditions for 18 h, upon cooling the reaction was washed with brine (2×100mL) and the brine layer extracted with EtOAc (100mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product flash chromatographed (SiO_2; 2% EtOAc in petroleum ether) to give the title compound as a partially purified colourless oil before being taken onto the next step. Diagnostic signals in the ^1H NMR (300 MHz; $CDCl_3$): δ_H 1.00 (t, 3H, *J*= 7.5Hz, CH_3), 2.02 (q, 2H, *J*= 7.5Hz, CH_2CH_3), 3.95 (t, 2H, *J*= 7.5Hz, CH_2O), 4.15 (t, 2H, *J*= 7.5Hz, CH_2O), 6.88-6.84 (m, 2H, Ar), 7.20 (td, 1H, *J* = 1.5Hz, 7.5 Hz, Ar), 7.25 (dd, 1H, *J* = 1.5Hz, 8.0Hz, Ar), 8.29 (s, 1H, OH).[31]

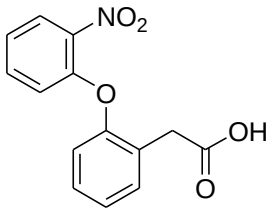
4.10.4 Procedure for the synthesis of 2-(2-(2-nitrophenoxy)phenyl)-2-ethyl-1,3-dioxolane, 319



319

2-(2-Ethyl-1,3-dioxolan-2-yl)phenol (**318**) (1.58g, 8.1 mmol) and 1-fluoro-2-nitrobenzene (**60**) (0.86mL, 8.1 mmol) were dissolved in dimethyl sulfoxide (80mL). Potassium carbonate (2.8g, 20.3 mmol) was added and the reaction stirred at room temperature for 17 h. Upon consumption of the starting material (TLC) water (75mL) and EtOAc (75mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2×50mL). The combined organic layers were washed with water (2×50mL) and brine (50mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to give the title compound as a pale yellow solid (85%). R_f (10% EtOAc in petroleum ether: 0.24; m.p.= 72-74 °C (EtOAc/petroleum ether); IR (neat, cm^{-1}): ν_{max} 1246 (Ar-O-Ar); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 0.86 (t, 3H, *J*= 7.5Hz, CH_3), 2.16 (q, 2H, *J*= 7.6Hz, CH_2CH_3), 3.76-3.68 (m, 2H, CH_2O), 3.96-3.88 (m, 2H, CH_2O), 6.78 (d, 1H, *J*= 8.0Hz, Ar), 6.96 (d, 1H, *J*= 8.0Hz, Ar), 7.10 (t, 1H, *J*= 7.5 Hz, Ar), 7.20 (t, 1H, *J*= 7.5 Hz, Ar), 7.33 (t, 1H, *J*= 7.5Hz, Ar), 7.42 (t, 1H, *J*= 8.0 Hz, Ar), 7.61 (d, 1H, *J*= 8.0 Hz, Ar), 7.97 (d, 1H, *J*= 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 7.84 (CH_3), 31.4 (CH_2), 64.7, 110.2 (C), 118.6, 121.6, 121.8, 124.8, 125.7, 128.6, 129.6, 133.7, (CH), 134.1 140.4, 152.1, 152.3, (C); MS (APCI *m*/*z*): 316 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 316.1173, $C_{17}H_{17}NO_5+H^+$ requires 316.1185.[31]

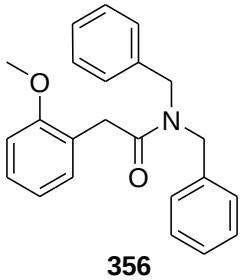
4.10.5 Procedure for the synthesis of 2-(2-(2-nitrophenoxy)phenyl)acetic acid, 440



440

2-(2-(2-Nitrophenoxy)phenyl)acetate methyl ester (**455**) (0.1g, 0.34 mmol) was stirred in 5mL of a basic THF solution 50% (1 M NaOH: THF) for 16 hours at room temperature. The solvent was evaporated, the residue acidified with conc. HCl (1mL) and extracted with dichloromethane (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the title compound as a yellow solid (0.095g, 100%). m.p.= 158-160 °C (DCM) [(lit. m.p.= 156-157 °C)[380] (solvent not quoted)]; IR (neat, cm^{-1}): ν_{max} 1704 (C=O stretching), 1525 (C-O stretching), 1582, 1340 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.76 (s, 2H, CH_2), 6.88 (d, 1H, *J*= 9.0Hz, Ar), 7.00 (d, 1H, *J*= 6.0Hz, Ar), 7.14-7.21 (m, 2H, Ar), 7.27 (d, 1H, *J*= 6.0Hz, Ar), 7.33 (t, 1H, *J*= 7.5Hz, Ar), 7.47 (td, 1H, *J*= 7.5Hz, Ar), 7.93 (dd, 1H, *J*= 9.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 35.44 (CH_2), 118.70, 120.38, 123.41, 124.96, 125.46, 129.32, 132.07, 134.36 (CH), 125.86, 134.38, 150.39, 154.09, 171.20 (C); MS (APCI *m*/*z*): 272 $[M-H)^+$, (100%)].

4.10.6 Procedure for the synthesis of *N*,*N*-dibenzyl-2-(2-methoxyphenyl)acetamide, 356

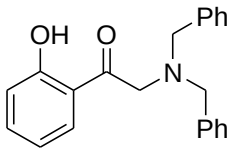


356

To a solution of 2-methoxyphenyl acetic acid (**353**) (0.5g, 3.0 mmol) in dichloromethane (20mL, containing two drops of *N*,*N*-dimethylformamide) was added

oxalyl chloride (588µL, 4.51 mmol). The resulted solution was stirred at room temperature for 1 hour, after which the solvent was evaporated to give a crude residue. The residue and dibenzylamine (1156µL, 6.0 mmol) were dissolved in toluene (30mL, 0.1 M) and the resulting solution stirred at room temperature for 4 hours and at 40°C for 20 hours. The solution was allowed to cool, washed with 1 M HCl (3×30mL), and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled brine (30mL) and water (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to yield the title compound as a lemon-yellow solid (1.01g, 98%). R_f (30% EtOAc in petroleum ether): 0.71. m.p.= 65-67°C (EtOAc). IR (neat, cm^{-1}): *v* 1645 (C=O stretching), 1079 (C-O stretching); ^1H NMR ($CDCl_3$, 300MHz): δ 3.73 (s, 3H, CH_3), 3.76 (s, 2H, $CH_2C=O$), 4.48 (s, 2H, CH_2N), 4.58 (s, 2H, CH_2N), 6.81 (d, 1H, *J*= 6.0Hz, Ar), 6.91 (t, 1H, *J*= 7.5Hz, Ar), 7.14 (d, 2H, *J*= 9.0Hz, Ar), 7.31-741 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 34.89, 48.17, 50.20 (CH_2), 55.36 (CH_3), 110.37, 120.81, 126.71, 127.42, 127.59, 128.33, 128.50, 128.61, 128.91, 130.66 (CH), 124.05, 136.85, 137.64, 156.90, 172.20 (C); MS (ESI^+, APCI *m/z*): 346 (100%). HRMS FAB $[M+H]^+$ 346.1799, $C_{23}H_{23}NO_2+H^+$ requires 346.1802.

4.10.7 Procedure for the synthesis of 2-(dibenzylamino)-1-(2-hydroxyphenyl)ethanone, 357a

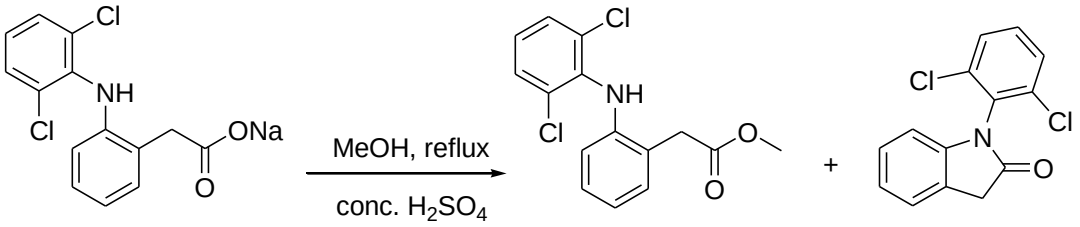


357a

To a solution of dibenzylamine (**246**) (448µL, 0.23 mmol) in dichloromethane (5mL, 0.1 M) was added triethylamine (65µL, 0.46 mmol) and the resulting solution was stirred at room temperature for 30 minutes. Bromo-2-hydroxyacetophenone (0.05g, 0.23 mmol) was added and the reaction stirred for 2 hours at room temperature. After which, the mixture was washed with hydrochloric acid solution (1 M, 2×10mL). The product was extracted with dichloromethane (2×10mL) and the combined organic layers were washed with distilled water (2×10mL), brine (10mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the title compound as a yellow solid (0.04g, 52%). R_f (20% EtOAc in petroleum ether): 0.60. ^1H NMR ($CDCl_3$, 300MHz): δ_H 3.86 (s, 2H, $CH_2C=O$), 4.63 (s, 4H, CH_2N), 7.07-7.15 (m, 4H, Ar), 7.32-7.39 (m, 4H, Ar), 7.51 (dd,

2H, *J*= 1.5Hz, *J*= 8.0Hz, Ar), 7.63 (td, 2H, *J*= 1.2Hz, *J*= 7.2Hz, Ar), 7.26-7.41 (d, 2H, *J*= 7.5Hz, Ar), 10.23 (s, 1H, OH).

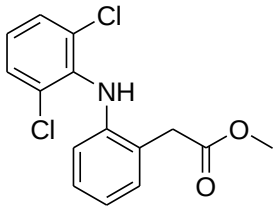
4.10.8 Procedure for the synthesis of methyl 2-(2-(2,6-dichlorophenylamino)phenyl)acetate (452), and 1-(2,6-Dichlorophenyl)indolin-2-one (453)



445 **452** **453**

Diclofenac sodium (**445**) was heated at reflux in methanol (plus two drops of conc. H_2SO_4) for 2 hours. The solvent was evaporated, the residue washed with saturated sodium bicarbonate solution (3×30mL) and extracted with ethyl acetate (2×30mL). The combined organic layers were washed with distilled water (2×30mL) and brine (30mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the crude residue which was purified by flash column chromatography.

Methyl 2-(2-(2,6-dichlorophenylamino)phenyl)acetate, 452

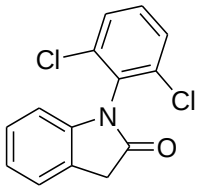


452

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as white crystalline solid (0.42g, 88 %). R_f (30% EtOAc in petroleum ether): 0.85. m.p.= 90-92 °C (ethyl acetate/petroleum ether) [(lit. m.p.= 87 °C)[291] (methanol)]; IR (neat, cm^{-1}): *v* 1715 (C=O stretching), 1576 (C-O stretching), 3303 (O-H stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.75 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 6.93-7.01 (m, 3H, Ar), 7.13 (t, 1H, *J*= 7.5Hz, Ar), 7.23 (d, 1H, *J*= 6.0Hz, Ar), 7.34 (d, 2H, *J*= 9.0Hz, Ar).

^{13}C NMR ($CDCl_3$, 75MHz): δc 38.65 (CH_2), 52.60 (CH_3), 118.21, 122.06, 124.06, 128.13, 129.01, 131.02 (CH), 124.18, 129.62, 137.85, 142.77, 172.78 (C); MS (APCI *m*/*z*): 310 $[M+H)^+$, (100%)].

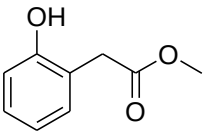
1-(2,6-Dichlorophenyl)indolin-2-one, 453



453

Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as an orange crystalline solid (0.05g, 12%). R_f (30% EtOAc in petroleum ether): 0.63. m.p.= 118-120 °C (ethyl acetate/petroleum ether) [(lit. m.p.= 124-125 °C)[323] (methanol)]; IR (neat, cm^{-1}): *v* 1611 (C=O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.78 (s, 2H, CH_2), 6.40 (d, 1H, *J*= 6.0Hz, Ar), 7.09 (t, 1H, *J*= 7.5Hz, Ar), 7.20 (t, 1H, *J*= 7.5Hz, Ar), 7.33-7.40 (m, 2H, Ar) 7.51 (d, 2H, *J*= 9.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 35.85 (CH_2), 109.25, 123.18, 124.92, 128.03, 129.15, 130.59 (CH), 124.39, 130.51, 135.59, 143.38, 173.77 (C); MS (APCI *m*/*z*): 278 $[M+H)^+$, (100%)].

4.10.9 Procedure for the synthesis of methyl 2-(2-hydroxyphenyl)acetate, 454

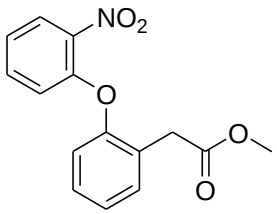


454

2-Hydroxyphenylacetic acid (**277**) (5.0g, 32.9 mmol) was heated at reflux in 50mL of methanol (plus ~1mL of conc. H_2SO_4) for 16 hours. The solvent was evaporated, the residue washed with saturated sodium bicarbonate solution (3×25mL) and extracted with ethyl acetate (2×25mL). The combined organic layers were washed with distilled water (2×25mL) and brine (2×25mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to afford the title compound as a white solid (5.46g, 100%), R_f (30% EtOAc in petroleum ether): 0.68. m.p.= 61-63°C (ethyl acetate) [(lit. m.p.= 61-62 °C)[381] (ethyl acetate)]. IR (neat, cm^{-1}): *v* 1717 (C=O stretching), 1098 (C-O stretching),

3420 (O-H stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.69 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 6.88 (t, 1H, *J*= 8.0Hz, Ar), 6.94 (d, 1H, *J*= 8.0Hz, Ar), 7.10 (d, 1H, *J*= 8.0Hz, Ar), 7.20 (d, 1H, *J*= 8.0Hz, Ar), 7.39 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75MHz): δ 37.82 (CH_2), 52.94 (CH_3), 117.76, 120.65, 129.37, 131.13 (CH), 121.05, 155.23, 174.49 (C); MS (APCI *m*/*z*): 167 $[M+H)^+$, (100%)].

4.10.10 Procedure for the synthesis of methyl 2-(2-(2-nitrophenoxy)phenyl)acetate, 455



455

To a solution of the methyl2-(2-hydroxyphenyl)acetate (**454**) (0.2g, 1.20 mmol) in dimethyl sulfoxide (12mL, 0.1 M) was added potassium carbonate (0.16g, 1,20 mmol) and the resulting solution was stirred at room temperature for 30 minutes. 1-Fluoro-2-nitrobenzene (134µL, 1.23 mmol) was added and the reaction stirred for 24 hours at room temperature. After which, the mixture was acidified with hydrochloric acid solution (1 M, 30mL). The product was extracted with ethyl acetate (2×30mL) and the combined organic layers were washed with distilled water (2×20mL), brine (10mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Flash column chromatography (SiO_2; 20% EtOAc in toluene) afforded the title compound as an orange oil (0.1g, 30%). R_f (10% EOAc in toluene): 0.62. IR (neat, cm^{-1}): *v* 1735 (C=O stretching), 1604 (C-O stretching), 1583, 1346 (N-O stretching); ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.60 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 6.90 (d, 1H, *J*= 8.0Hz, Ar), 6.98 (d, 1H, *J*= 8.0Hz, Ar), 7.17 (t, 2H, *J*= 8.0Hz, Ar), 7.29 (dd, 1H, *J*= 1.2Hz, *J*= 8.0Hz, Ar), 7.35 (d, 1H, *J*= 8.0Hz, Ar), 7.48 (td, 1H, *J*= 1.2Hz, *J*= 8.0Hz, Ar), 7.94 (dd, 1H, *J*= 1.2Hz, *J*= 8.0Hz, Ar). ^{13}C NMR ($CDCl_3$, 75MHz): δ 35.70 (CH_3), 52.12 (CH_2), 119.08, 119.84, 123.10, 125.08, 126.29, 129.07, 132.06, 134.24 (CH), 125.81, 141.02, 150.60, 153.76, 171.52 (C); MS (APCI *m*/*z*): 288 $[M+H)^+$, (100%)]. HRMS FAB $[M+H]^+$ 288.0868, $C_{15}H_{13}NO_5+H^+$ requires 288.0866.

4.11 General procedure for the COX inhibitor screening assay

1. 100% initial activity wells: added 150 µl of assay buffer, 10 µl of heme, 10 µl of ADHP (10-acetyl-3,7-dihyroxyphenoxazepine), 10 µl of enzyme (either COX I or COX II), and 10 µl of DMSO.
2. Background wells: added 160 µl of assay buffer, 10 µl of heme, 10 µl of ADPH, and 10 µl of DMSO.
3. Inhibitor wells: added 150 µl of assay buffer, 10 µl of heme, 10 µl of ADPH, 10 µl of enzyme (either COX I or COX II), and 10 µl of inhibitors*.
4. The reactions were initiated by quickly adding 10 µl of arachidonic acid solution to all the wells being used.
5. The wells were incubated for two minutes at room temperature.
6. The plate was read using an excitation wavelength between 530-540 nm and an emission wavelength between 585-595 nm.
7. The average fluorescence of each sample was determined.
8. The fluorescence of the background wells was subtracted from the fluorescence of the 100% initial activity and the inhibitor wells.
9. The percent inhibition was determined for each sample by subtracting each inhibitor sample value from the 100% initial activity sample value, the result divide by the 100% initial activity value and then multiplied by 100 to give the percent inhibition.

*Inhibitor (diclofenac sodium **445**, diclofenac methyl ester **452**, diarylether pyrrolidyl-acetamide **334b** and diaryl acetic acid **440**) solutions were prepared in concentration of 20, 200 and 2000 nm using DMSO as a solvent.

CHAPTER 5 - CONCLUSIONS

CHAPTER FIVE - CONCLUSIONS AND FUTURE WORK

5.1 Conclusion

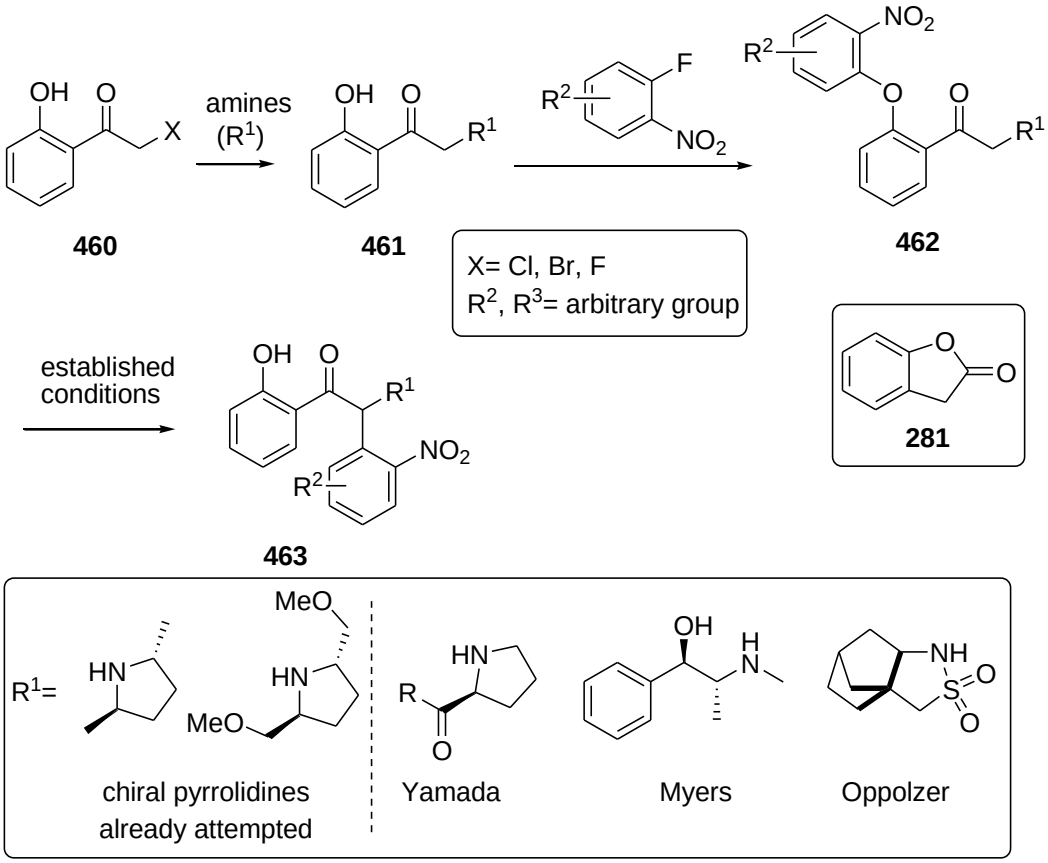
In a preliminary effort to produce the first example of an asymmetric Truce-Smiles rearrangement—a new and potentially mild method to produce enantiomerically enriched α-aryl carbonyl compounds—modest success in the application of the rearrangement to novel amide substrates has been demonstrated. It has also been demonstrated, for the first time, that amide precursors that proceed through a five-membered spirocyclic transition state rearrange, whereas those proceeding through a six-membered transition state don't, but stop at the diarylether stage. In the case of the enantiopure rearrangement substrates bearing a chiral auxilliary, it has been shown that initial efforts only gave modest diastereoselectivies (dr= max. 1.7:1), but it was also demonstrated that potential exists in this rearrangement to develop it further, as was evidenced by the high d.e. observed in the synthesis of the 1,3-dicarbonyl compound **381**.

Similarly, to further try and investigate the scope of the mechanistically-related Baker-Venkataraman rearrangement reaction, the same amide substrates, including both acetamides, and propanamides were employed with a range of acylating agents, but because of facile, competing hydrolysis, no rearranged products were obtained with ester or carbonate substrates. Nevertheless, a series of carbamoyl ketone based substrates were also studied, in the hope of applying an established literature method to the synthesis of 1,3-dicarbonyl compounds. During this study, a novel Baker-Venkataraman-*retro*-Claisen cascade was developed, in which the Baker-Venkataraman rearrangement precursors acted as an alkyl donor and the carbamoyl chloride partner as an alkyl acceptor, to afford salicylic acid derivatives and (novel) amides. The results obtained proved the utility of the hypothesised Baker-Venkataraman-*retro*-Claisen cascade in the synthesis of amides.

This work also included the partial eradication of cyclooxygenase activity using the diarylether of one of the acetamide-based precursors (**334b**), which showed good to modest activity against both COX I and COX II.

5.2 Future work

Whilst attempts have been made to optimise the method developed, with respect to α-alkylation of the substrates prior to, and after, the Truce-Smiles rearrangement step, limited success was achieved. If further optimisation, was to take place better diastereoselectivities may be achieved through the use of α-alkylated 2-coumaranone prior to the rearrangement step. In order to find better substrates which give enriched α-arylated compounds, ketone based substrates could be further explored with C2-symmetrical chiral pyrrolidine-based auxiliaries. In addition, alternative chiral auxiliaries can also be included into ketone-based (starting from **460**) or amide-based substrates (starting from **281**) and attempt to force a better diaseteroselectivity, Scheme 160.

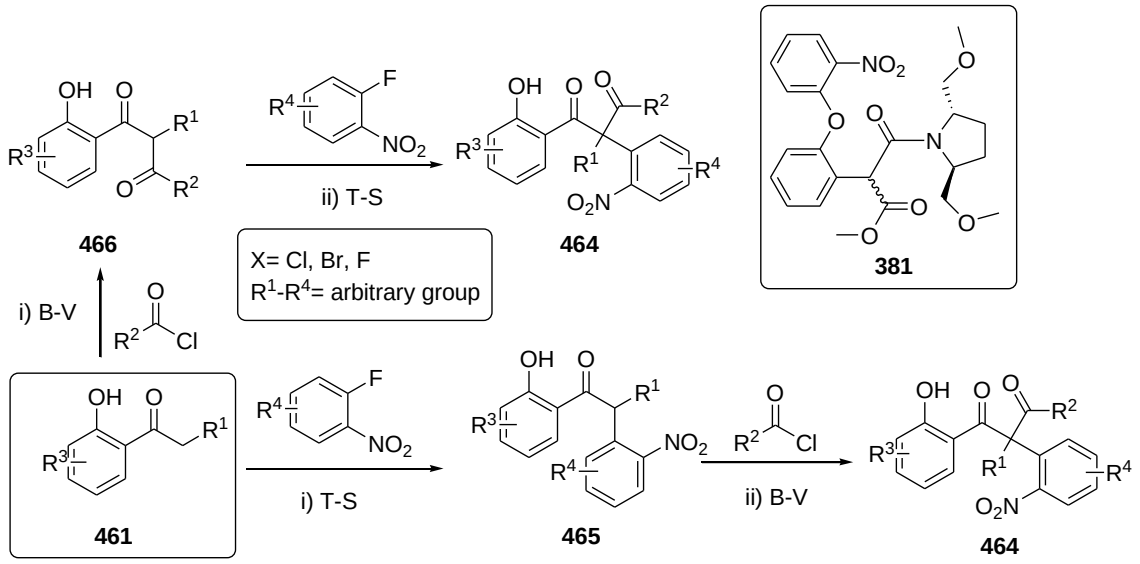


Scheme 160. Proposed future work on the enantioselective Truce-Smiles rearrangement.

In respect to the Baker-Venkataraman-*retro*-Claisen cascade it is also possibly worth incorporating suitable chiral auxiliaries to attempt to prepare an asymmetric variant, in order to explore the enantioselectivities obtained through both the acyl migration and

the *retro*-Claisen steps, in the hope of offering enantiopure 1,3-dicarbonyl compounds and novel chiral amides, respectively.

Since better selectivity was observed with 1,3-dicarbonyl compounds (e.g. **381**, 83% de), a domino rearrangement reaction could be set up by performing the Baker-Venkataraman rearrangement first, followed by the Truce-Smiles rearrangement or *vice versa*, to afford enantioenriched products e.g. **464**, Scheme 161.



Scheme 161. The proposed domino rearrangement reaction. For different R groups see Scheme 160; T-S= Truce-Smiles rearrangement; B-V= Baker-Venkataraman rearrangement.

REFERENCES

REFERENCES

1. Harwood, L. M. *Polar rearrangements*. (Oxford University Press, 1992).
2. Snape, T. J. A truce on the Smiles rearrangement: revisiting an old reaction-the Truce-Smiles rearrangement. *Chem. Soc. Rev.* **37**, 2452–2458 (2008).
3. Santos, C., Silva, A. & Cavaleiro, J. A Novel and Efficient Route for the Synthesis of Hydroxylated 2,3-Diarylxanthones. *Synlett* **2007**, 3113–3116 (2007).
4. Evans, W. J. & Smiles, S. A rearrangement of o-acetamido-sulphones and -sulphides. *J. Chem. Soc. Resumed* 181–188 (1935). doi:10.1039/JR9350000181
5. Truce, W. E., Kreider, E. M. & Brand, W. W. in *Org. React.* (John Wiley & Sons, Inc.) (John Wiley & Sons, Inc., 2011). at <http://organicreactions.org/index.php/Smiles_and_Related_Rearrangements_of_Aromatic_Systems>
6. Shine, H. J. *Aromatic rearrangements*. (Elsevier, New York, 1967).
7. Bernasconi, C. F., De Rossi, R. H. & Gehriger, C. L. Intermediates in nucleophilic aromatic substitution. X. Synthesis of N-methyl-.beta.-aminoethyl nitroaryl ethers via an unusual Smiles rearrangement. *J. Org. Chem.* **38**, 2838–2842 (1973).
8. Sekiguchi, S. & Shiojima, T. Aromatic Nulceophilic Substitution. I. Preparation of Spiro Meisenheimer Complexes of Arenes. *Bull. Chem. Soc. Jpn.* **46**, 693–694 (1973).
9. Bunnett, J. F. & Okamoto, T. Steric Acceleration through Regulation of Rotational Conformation: The Smiles Rearrangement1,2. *J. Am. Chem. Soc.* **78**, 5363–5367 (1956).
10. Tozer, B. T. & Smiles, S. A rearrangement of aryl salicylates. *J. Chem. Soc. Resumed* 1897–1900 (1938). doi:10.1039/JR9380001897
11. McClement, C. S. & Smiles, S. The rearrangement of ortho-hydroxy-sulphones. Part VI. *J. Chem. Soc. Resumed* 1016–1021 (1937). doi:10.1039/JR9370001016
12. Truce, W. E., Ray, W. J., Norman, O. L. & Eickemeyer, D. B. Rearrangements of Aryl Sulfones. I. The Metalation and Rearrangement of Mesityl Phenyl Sulfone1. *J. Am. Chem. Soc.* **80**, 3625–3629 (1958).
13. Truce, W. E. & Hampton, D. C. Butyllithium-Induced Rearrangement of Methylnaphthyl Phenyl Sulfones1,2. *J. Org. Chem.* **28**, 2276–2279 (1963).
14. Drozd, V. & Trifonov.di. Mechanism of Smiles Rearrangement of Ortho Methyldiaryl-Sulfones - Rearrangement of Ethylphenylmesitylsulfones. *Zhurnal Organicheskoi Khimii* **7**, 2388–& (1971).
15. Truce, W. E. & Ray, W. J. Rearrangements of Aryl Sulfones. II. The Synthesis and Rearrangement of Several o-Methyldiaryl Sulfones to o-Benzylbenzenesulfinic Acids1. *J. Am. Chem. Soc.* **81**, 481–484 (1959).
16. Okamoto, T. & Bunnett, J. F. The Synthesis and Smiles Rearrangement of 2-Hydroxy-5-methyl-2'-nitrodiphenyl Sulfone and Several of its Methyl and Halogen Derivatives1,2. *J. Am. Chem. Soc.* **78**, 5357–5362 (1956).
17. Truce, W. E., VanGemert, B. & Brand, W. W. Base-induced rearrangements of mesityl thienyl sulfones. *J. Org. Chem.* **43**, 101–105 (1978).
18. Truce, W. E., Robbins, C. R. & Kreider, E. M. Rearrangement of Mesityl Naphthyl Sulfones via a Novel Nucleophilic Addition-β Elimination Sequence1. *J. Am. Chem. Soc.* **88**, 4027–4033 (1966).

19. SNYDER, D. & TRUCE, W. EXAMPLE OF ALKYL GROUP TRANSFER IN A TRUCE-SMILES REARRANGEMENT. *J. Am. Chem. Soc.* **101**, 5432–5433 (1979).

20. Madaj, E. J., Snyder, D. M. & Truce, W. E. Rearrangement of benzylically lithiated methylaryl alkyl sulfones. *J. Am. Chem. Soc.* **108**, 3466–3469 (1986).

21. Crowther, G. P. & Hauser, C. R. Condensations at methyl groups of phenyl o- and p-tolyl sulfones with electrophilic compounds by sodium amide. Truce-Smiles rearrangement. *J. Org. Chem.* **33**, 2228–2233 (1968).

22. Fukazawa, Y., Kato, N. & Ito, S. Phenyl Migration in Bicyclo[5.3.1]undeca-1,3,5,8-Tetraene-8-Carboxy-N-Methylanilide - a Unique Truce-Smiles Type Rearrangement of an Anilide. *Tetrahedron Lett.* **23**, 437–438 (1982).

23. Randal Erickson, W. & McKennon, M. J. Unexpected Truce–Smiles type rearrangement of 2-(2′-pyridyloxy) phenylacetic esters: synthesis of 3-pyridyl-2-benzofuranones. *Tetrahedron Lett.* **41**, 4541–4544 (2000).

24. Mitchell, L. H. & Barvian, N. C. A homologous enolate Truce–Smiles rearrangement. *Tetrahedron Lett.* **45**, 5669–5671 (2004).

25. Kimbaris, A., Cobb, J., Tsakonas, G. & Varvounis, G. Novel pyrrolo[1,2-a][3.1.6]benzothiadiazocine ring synthesis. Unusual Truce-Smiles type rearrangement of 1-{[1-(2-nitrophenyl)-1H-pyrrol-2-yl]sulfonyl(or sulfinyl)}acetone. *Tetrahedron* **60**, 8807–8815 (2004).

26. Kimbaris, A., Cobb, J., Tsakonas, G. & Varvounis, G. Novel pyrrolo[1,2-a][3.1.6]benzothiadiazocine ring synthesis. Unusual Truce–Smiles type rearrangement of 1-{[1-(2-nitrophenyl)-1H-pyrrol-2-yl]sulfonyl(or sulfinyl)}acetone. *Tetrahedron* **60**, 8807–8815 (2004).

27. Bayne, D., Nicol, A. & Tennant, G. Synthesis of 2-Acyl-3-Hydroxyquinolines Embodying a Novel Variant of Smiles Rearrangement. *J. Chem. Soc.-Chem. Commun.* 782–783 (1975).

28. Millard, A. A. & Rathke, M. W. A nickel catalyst for the arylation and vinylation of lithium ester enolates. *J. Am. Chem. Soc.* **99**, 4833–4835 (1977).

29. Chen, Y. *et al.* Design, Synthesis, and Pharmacological Evaluation of Haloperidol Derivatives as Novel Potent Calcium Channel Blockers with Vasodilator Activity. *PLoS ONE* **6**, e27673 (2011).

30. Chen, Z. *et al.* Design and synthesis of 4-phenyl piperidine compounds targeting the mu receptor. *Bioorg. Med. Chem. Lett.* **14**, 5275–5279 (2004).

31. Snape, T. α-Arylation of Aryl Ketones: Expanding the Scope of the Truce-Smiles Rearrangement. *Synlett* **2008**, 2689–2691 (2008).

32. Taber, D. F. & Tirunahari, P. K. Indole synthesis: a review and proposed classification. *Tetrahedron* **67,** 7195–7210 (2011).

33. Alorati, A. D., Gibb, A. D., Mullens, P. R. & Stewart, G. W. An Efficient Process for the Large-Scale Synthesis of a 2,3,6-Trisubstituted Indole. *Org. Process Res. Dev.* **16**, 1947–1952 (2012).

34. Tang, L. *et al.* Synthesis of Coumestan Derivatives via FeCl3-Mediated Oxidative Ring Closure of 4-Hydroxy Coumarins. *J. Org. Chem.* **76**, 2744–2752 (2011).

35. Chittimalla, S. K., Chang, T.-C., Liu, T.-C., Hsieh, H.-P. & Liao, C.-C. Reactions of 2-hydroxybenzophenones with Corey-Chaykovsky reagent. *Tetrahedron* **64**, 2586–2595 (2008).

36. Xiang, H. *et al.* Synthesis and biological evaluation of isoflavone fatty acid esters with potential weight loss and hypolipidemic activities. *Bioorg. Med. Chem.* **18**, 3036–3042 (2010).

37. Liu, Y., Zhang, X., Ma, Y. & Ma, C. An efficient C–C bond formation reaction for the synthesis of α-arylated ketones under mild conditions. *Tetrahedron Lett.* **54**, 402–405 (2013).

38. Hirota, T., Matsushita, T., Sasaki, K. & Kashino, S. Polycyclic N-Heterocyclic Compounds. 49 New Synthetic Method of Furo[3,2-f][1,7]naphthyridine Skeleton. *HETEROCYCLES* **41**, 2565 (1995).

39. Sasaki, K., Rouf, A. S. S. & Hirota, T. Polycyclic N-heterocyclic compounds. 48. syntheses of furo[2,3-h]-[1,6]naphthyridine and imidazo(or pyrimido)[2,1-f]-[1,6]naphthyridines with rearrangement. *J. Heterocycl. Chem.* **33**, 49–52 (1996).

40. Hirota, T. *et al.* Polycyclic N-Heterocyclic Compounds. 57 Syntheses of Fused Furo(or Thieno)[2,3-b]pyridine Derivatives via Smiles Rearrangement and Cyclization. *HETEROCYCLES* **55**, 741 (2001).

41. Okuda, K., Deguchi, H., Hirota, T. & Sasaki, K. Polycyclic *N*-Heterocyclic Compounds. Part 65: Ring Cleavage Reactions of Fused Furo[2,3-*c*]isoquinolines and Related Compounds with Various Nucleophiles. *Chem. Pharm. Bull. (Tokyo)* **58**, 755–757 (2010).

42. Okuda, K., Watanabe, N., Hirota, T. & Sasaki, K. Polycyclic N-heterocyclic compounds. Part 61: A novel Truce-Smiles type rearrangement reaction of 4-(2-cyanovinyloxy)butanenitriles to give cycloalkeno[1,2-d]furo[2,3-b]pyridines. *Tetrahedron Lett.* **51**, 903–906 (2010).

43. Okuda, K., Yoshida, M., Hirota, T. & Sasaki, K. Polycyclic N-heterocyclic compounds. Part 63: Improved synthesis of 5-amino-1,2-dihydrofuro[2,3-c]isoquinolines via truce-smiles rearrangement and subsequent formation to furo[2,3-c]isoquinoline. *Chem. Pharm. Bull. (Tokyo)* **58**, 363–368 (2010).

44. Okuda, K., Deguchi, H., Kashino, S., Hirota, T. & Sasaki, K. Polycyclic N-Heterocyclic Compounds. Part 64: Synthesis of 5-Amino-1,2,6,7-tetrahydrobenzo[f]furo[2,3-c]isoquinolines and Related Compounds. Evaluation of Their Bronchodilator Activity and Effects on Lipoprotein Lipase mRNA Expression. *Chem. Pharm. Bull. (Tokyo)* **58**, 685–689 (2010).

45. Okuda, K., Takano, J., Hirota, T. & Sasaki, K. Polycyclic N-heterocyclic compounds, part 69: Synthesis of 5-amino-1,2-dihydro[1]benzofuro[3,2-d]furo[2,3-b]pyridines and their transformations to related compounds. *J. Heterocycl. Chem.* doi:10.1002/jhet.772

46. Okuda, K., Matsushita, T., Hirota, T. & Sasaki, K. Polycyclic N-Heterocyclic Compounds, Part 71: Synthesis and Bronchodilator Evaluation of 5-Substituted 1,2-Dihydrofuro[3,2-f][1,7]naphthyridines and Related Compounds. *J. Heterocycl. Chem.* **49**, 742–747 (2012).

47. Okuda, K., Takechi, H., Hirota, T. & Sasaki, K. POLYCYCLIC N-HETEROCYCLIC COMPOUNDS. PART 70: SYNTHESIS OF 5-AMINO-1,2-DIHYDROFURO[2,3-b]PYRIDO[3',2':4,5]-THIENO[3,2-d]PYRIDINES AND RELATED COMPOUNDS. EVALUATION OF EFFECTS ON LIPOPROTEIN LIPASE mRNA EXPRESSION. *Heterocycles* **83**, 1315–1328 (2011).

48. Okuda, K., Yoshida, M., Hirota, T. & Sasaki, K. Polycyclic N-Heterocyclic Compounds 73: Synthesis and Evaluation of 5-Substituted 1,2-Dihydrofuro[2,3-c]isoquinolines as Inducers of Lipoprotein Lipase mRNA Expression. *J. Heterocycl. Chem.* **50**, E9–E11 (2013).

49. Ting, P. C. *et al.* Substituted 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-ones as potential antiinflammatory agents. *J. Med. Chem.* **33**, 2697–2706 (1990).

50. Adams, C. *et al.* Mapping the kinase domain of janus kinase 3. *Bioorg. Med. Chem. Lett.* **13**, 3105–3110 (2003).

51. Wood, E. R. *et al.* Discovery and in vitro evaluation of potent TrkA kinase inhibitors: oxindole and aza-oxindoles. *Bioorg. Med. Chem. Lett.* **14**, 953–957 (2004).

52. Shafi'ee, A. & Hite, G. Absolute configurations of the pheniramines, methyl phenidates, and pipradrols. *J Med Chem* **12**, 266–270 (1969).

53. Ebnöther, A. & Weber, H. P. Synthesis and absolute configuration of clemastine and its isomers (author's transl). *Helv. Chim. Acta* **59**, 2462–2468 (1976).

54. Meguro, K., Aizawa, M., Sohda, T., Kawamatsu, Y. & Nagaoka, A. New 1,4-dihydropyridine derivatives with potent and long-lasting hypotensive effect. *Chem. Pharm. Bull. (Tokyo)* **33**, 3787–3797 (1985).

55. Toda, F., Tanaka, K. & Kōshiro, K. A new preparative method for optically active diarylcarbinols. *Tetrahedron Asymmetry* **2**, 873–874 (1991).

56. Casy, A. F., Drake, A. F., Ganellin, C. R., Mercer, A. D. & Upton, C. Stereochemical studies of chiral H-1 antagonists of histamine: the resolution, chiral analysis, and biological evaluation of four antipodal pairs. *Chirality* **4**, 356–366 (1992).

57. Stanchev, S., Rakovska, R., Berova, N. & Snatzke, G. Synthesis, absolute configuration and circular dichroism of some diarylmethane derivatives. *Tetrahedron Asymmetry* **6**, 183–198 (1995).

58. Botta, M., Summa, V., Corelli, F., Di Pietro, G. & Lombardi, P. Synthesis of aryl 2-benzofuranyl and aryl 2-indolyl carbinols of high enantiomeric purity via palladium-catalyzed heteroannulation of chiral arylpropargylic alcohols. *Tetrahedron Asymmetry* **7**, 1263–1266 (1996).

59. Torrens, A., Castrillo, J. A., Claparols, A. & Redondo, J. Enantioselective Synthesis of (R)- and (S)-Cizolirtine; Application of Oxazaborolidine-Catalyzed Asymmetric Borane Reduction to Azolyl Phenyl Ketones. *Synlett* **1999**, 765–767 (1999).

60. Ameen, D. & Snape, T. J. Chiral 1,1-diaryl compounds as important pharmacophores. *MedChemComm* **4**, 893–907 (2013).

61. Clayden, J. *et al.* N to C Aryl Migration in Lithiated Carbamates: α-Arylation of Benzylic Alcohols. *J Am Chem Soc* **131**, 3410–3411 (2009).

62. Fournier, A. M., Brown, R. A., Farnaby, W., Miyatake-Ondozabal, H. & Clayden, J. Synthesis of (−)-(S,S)-clemastine by Invertive N → C Aryl Migration in a Lithiated Carbamate. *Org Lett* **12**, 2222–2225 (2010).

63. Auwers, K. C- and O-acyl derivatives of coumaranones or 2-hydroxycoumarones. *Chem Ber* **43**, 2192–202 (1910).

64. Mahal, H. S. & Venkataraman, K. Synthesis of flavones at room temperature. *Curr. Sci.* **2**, 214–15 (1933).

65. Baker, W. Molecular rearrangement of some o-acyloxyacetophenones and the mechanism of the production of 3-acylchromones. *J. Chem. Soc.* 1381–9 (1933). doi:10.1039/jr9330001381

66. Wheeler, T. S. FLAVONE. *Org Synth* **32**, 72–6 (1952).

67. Mahal, H. S. & Venkataraman, K. Synthetical experiments in the chromone group. Part XIV. The action of sodamide on 1-acyloxy-2-acetonaphthones. *J Chem Soc* 1767–1769 (1933). doi:10.1039/JR9340001767

68. Levine, R. & Fernelius, W. C. The Chemistry of the Alkali Amides. *Chem. Rev.* **54**, 449–573 (1954).

69. Bergstrom, F. W. & Fernelius, W. C. The Chemistry of the Alkali Amides. II. *Chem. Rev.* **20**, 413–487 (1937).

70. Nity Anand, K.Venkataraman & D. M. Patel. Azoic dyes. Part IX. The behaviour of w-Benzoyl-2-acetyl-1-naphthol towards diazonium salts. *Indian Acad Sci* 545 (1948).

71. Baker, W. 204. The synthesis of 5 : 6-dihydroxyflavone and the structure of primetin. *J. Chem. Soc. Resumed* 956–961 (1939). doi:10.1039/JR9390000956

72. Doyle, B. G., Gogan, F., Gowan, J. E., Keane, J. & Wheeler, T. S. The mechanism of the transformation of o-aroyloxyacetoarones into o-hydroxydiaroylmethanes, and the synthesis of flavones. *Sci Proc R Dublin Soc* **24**, 291–305 (1948).

73. Gulati, K. C. & Venkataraman, K. 58. Synthetical experiments in the chromone group. Part XVIII. Demethylation with aluminium chloride. *J. Chem. Soc. Resumed* 267–269 (1936). doi:10.1039/JR9360000267

74. Horri. *J Pharm Soc Jpn.* **81**, (1940).

75. Nakazawa K. *Chem. Abs.* **34**, (1940).

76. Appel, H., Baker, W., Hagenbach, H. & Robinson, R. 148. Experiments on the synthesis of brazilin and hæmatoxylin. Part V. *J. Chem. Soc. Resumed* 738–744 (1937). doi:10.1039/JR9370000738

77. Dahlbom, R., Smith, B. & Sillén, L. G. Antihistamine Agents. IV. Piperidino- and Morpholinoalkyl Derivatives of Phenothiazine. *Acta Chem. Scand.* **3**, 247–255 (1949).

78. Mahling, J.-A., Jung, K.-H. & Schmidt, R. R. Glycosyl imidates, 69. Synthesis of flavone C-glycosides vitexin, isovitexin, and isoembigenin. *Liebigs Ann.* **1995**, 461–466 (1995).

79. Cramer, F. & Elschnig, G. H. Über Einschluß-verbindungen, IX. Mitteil.: Die blauen Jodverbindungen der Flavone. *Chem. Ber.* **89**, 1–12 (1956).

80. Hauteville, M., Chadenson, M. & Chopin, M. J. *Acad Sci Paris* **278**, 471 (1974).

81. Rahman, W. & Nasim, K. T. Studies on the C-Methyl-γ-benzopyrone System. Orientation in the Isoflavone Series. II1. *J. Org. Chem.* **27**, 4215–4220 (1962).

82. Mezheritskii, V. V., Pikus, A. L. & Tregub, N. G. *Zhurnal Organicheskoi Khimii* **27**, 2198 (1991).

83. Gupta, V. N. & Seshadri, T. R. *J Sci Ind. Res India B* **16**, 116 (1957).

84. Jain, P. K., Makrandi, J. K. & Grover, S. K. A Facile Baker-Venkataraman Synthesis of Flavones using Phase Transfer Catalysis. *Synthesis* **1982**, 221–222 (1982).

85. Saxena, S., Makrandi, J. & Grover, S. Synthesis of 5- and/or 7-Hydroxyflavones using A Modified Phase Transfer-Catalysed Baker-Venkataraman Transformation. *Synthesis* **1985**, 697–697 (2002).

86. Ares, J. J., Outt, P. E., Kakodkar, S. V., Buss, R. C. & Geiger, J. C. A convenient large-scale synthesis of 5-methoxyflavone and its application to analog preparation. *J Org Chem* **58**, 7903–7905 (1993).

87. Wu, E. S. C. *et al.* Flavones. 2. Synthesis and structure-activity relationship of flavodilol and its analogs. A novel class of antihypertensive agents with catecholamine depleting properties. *J. Med. Chem.* **32**, 183–192 (1989).

88. Banerji, A. & Goomer, N. C. A New Synthesis of Flavones. *Synthesis* **1980**, 874–875 (1980).

89. Cushman, M. & Nagarathnam, D. A method for the facile synthesis of ring-A hydroxylated flavones. *Tetrahedron Lett.* **31**, 6497–6500 (1990).

90. Donnelly, J. A. & Maloney, D. E. α-Halogenoketones—XIII: Chromone epoxides; their synthesis and acid-catalysed rearrangement. *Tetrahedron* **35**, 2875–2881 (1979).

91. Claffey, P. J., Donnelly, J. A. & Maloney, D. E. 1,3-Diketones. The Retro Baker-Venkataraman Rearrangement. *Proc. R. Ir. Acad. [B]* **89B**, 119–123 (1989).

92. Dunne, A. T. M. *et al.* 255. Thermal cyclization of o-aroyloxyacetoarones. A new synthesis of flavones. *J. Chem. Soc. Resumed* 1252–1259 (1950). doi:10.1039/JR9500001252

93. Karrer, P., Kebrle, J. & Thakkar, R. M. Oxidationof acetoacetic ester, ethyl benzoylacetate and dibenzylmethane by peracid. *Helv. Chim. Acta* **33**, 1711–1724 (1950).

94. Kalinin, A. V., da Silva, A. J. M., Lopes, C. C., Lopes, R. S. C. & Snieckus, V. Directed ortho metalation - cross coupling links. Carbamoyl rendition of the baker-venkataraman rearrangement. Regiospecific route to substituted 4-hydroxycoumarins. *Tetrahedron Lett.* **39**, 4995–4998 (1998).

95. Gorelik, E. Augmentation of the Antimetastatic Effect of Anticoagulant Drugs by Immunostimulation in Mice. *Cancer Res.* **47**, 809–815 (1987).

96. Wang, S. *et al.* Discovery of Novel, Non-Peptide HIV-1 Protease Inhibitors by Pharmacophore Searching. *J. Med. Chem.* **39**, 2047–2054 (1996).

97. Pauli, R. M. *Handbook of Experimental Pharmacology*. **Anticoagulants**, (1997).

98. Hauser, C. R., Swamer, Frederic W. & Adams, Joe T. Acylation of Ketones to Form β-Diketones or β-Keto Aldehydes. *Org React* **8**, 90 (1954).

99. Kalinin, A. V. & Snieckus, V. 4,6-Dimethoxy-3,7-dimethylcoumarin from Colchicum decaisnei. Total synthesis by carbamoyl Baker-venkataraman rearrangement and structural revision to isoeugenetin methyl ether. *Tetrahedron Lett.* **39**, 4999–5002 (1998).

100. Fernandes, E. *et al.* 2-Styrylchromones As Novel Inhibitors of Xanthine Oxidase. A Structure-activity Study. *J. Enzyme Inhib. Med. Chem.* **17**, 45–48 (2002).

101. Pinto, D., Silva, A. & Cavaleiro, J. Baker-Venkataraman Rearrangement Under Microwave Irradiation: A New Strategy for the Synthesis of 3-Aroyl-5-hydroxyflavones. *Synlett* **2007**, 1897–1900 (2007).

102. Abdel Ghani, S. B. *et al.* Microwave-assisted synthesis and antimicrobial activities of flavonoid derivatives. *Bioorg. Med. Chem. Lett.* **18**, 518–522 (2008).

103. Gales, L. & Damas, A. M. Xanthones--a structural perspective. *Curr. Med. Chem.* **12**, 2499–2515 (2005).

104. Vieira, L. M. M. & Kijjoa, A. Naturally-Occurring Xanthones: Recent Developments. *Curr. Med. Chem.* **12**, 2413–2446 (2005).

105. Roberts, J. C. Naturally Occurring Xanthones. *Chem. Rev.* **61**, 591–605 (1961).

106. Pinto, M., Sousa, M. & Nascimento, M. Xanthone Derivatives: New Insights in Biological Activities. *Curr. Med. Chem.* **12**, 2517–2538 (2005).

107. Pfister, J. R., Ferraresi, R. W., Harrison, I. T., Rooks, W. H. & Fried, J. H. Synthesis and antiallergic activity of some mono- and disubstituted xanthone-2-carboxylic acids. *J. Med. Chem.* **21**, 669–672 (1978).

108. Habsah, M. *et al.* Screening of Zingiberaceae extracts for antimicrobial and antioxidant activities. *J. Ethnopharmacol.* **72**, 403–410 (2000).

109. Park, K. H. *et al.* Anti-atherosclerotic and anti-inflammatory activities of catecholic xanthones and flavonoids isolated from Cudrania tricuspidata. *Bioorg. Med. Chem. Lett.* **16**, 5580–5583 (2006).

110. Riscoe, M., Kelly, J. X. & Winter, R. Xanthones as antimalarial agents: discovery, mode of action, and optimization. *Curr. Med. Chem.* **12**, 2539–2549 (2005).

111. Zhang, H.-Z. *et al.* Discovery, characterization and SAR of gambogic acid as a potent apoptosis inducer by a HTS assay. *Bioorg. Med. Chem.* **12**, 309–317 (2004).

112. Merza, J. *et al.* Prenylated xanthones and tocotrienols from Garcinia virgata. *Phytochemistry* **65**, 2915–2920 (2004).

113. Núñez Sellés, A. J. *et al.* Isolation and Quantitative Analysis of Phenolic Antioxidants, Free Sugars, and Polyols from Mango (Mangifera indica L.) Stem Bark Aqueous Decoction Used in Cuba as a Nutritional Supplement. *J. Agric. Food Chem.* **50**, 762–766 (2002).

114. Pinto, D., Seca, A., Leal, S., Silva, A. & Cavaleiro, J. A Novel Short-Step Synthesis of New Xanthenedione Derivatives from the Cyclization of 3-Cinnamoyl-2-styrylchromones. *Synlett* **2011**, 2005–2008 (2011).

115. Pinto, D. C. G. A., Silva, A. M. S. & Cavaleiro, J. A. S. A convenient synthesis of new (E)-5-hydroxy-2-styrylchromones by modifications of the Baker–Venkataraman method. *New J. Chem.* **24**, 85–92 (2000).

116. Ellis, G. P. *Chromenes, chromanones, and chromones*. (Wiley, 1977).

117. Recanatini, M. *et al.* A New Class of Nonsteroidal Aromatase Inhibitors: Design and Synthesis of Chromone and Xanthone Derivatives and Inhibition of the P450 Enzymes Aromatase and 17α-Hydroxylase/C17,20-Lyase. *J. Med. Chem.* **44**, 672–680 (2001).

118. Gobbi, S. *et al.* Synthesis and Antitumor Activity of New Derivatives of Xanthen-9-one-4-acetic Acid. *J. Med. Chem.* **45**, 4931–4939 (2002).

119. Palmer, B. D. *et al.* Synthesis and Biological Activity of Azido Analogues of 5,6-Dimethylxanthenone-4-acetic Acid for Use in Photoaffinity Labeling. *J. Med. Chem.* **50**, 3757–3764 (2007).

120. Carvalho, J. C. T. *et al.* Anti-inflammatory activity of flavone and some of its derivates from Virola michelli Heckel. *J. Ethnopharmacol.* **64**, 173–177 (1999).

121. Matin, A. *et al.* 7-Hydroxy-benzopyran-4-one Derivatives: A Novel Pharmacophore of Peroxisome Proliferator-Activated Receptor α and -γ (PPARα and γ) Dual Agonists. *J. Med. Chem.* **52**, 6835–6850 (2009).

122. Manthey, J. A., Grohmann, K. & Guthrie, N. Biological properties of citrus flavonoids pertaining to cancer and inflammation. *Curr. Med. Chem.* **8**, 135–153 (2001).

123. Nishinaga, A., Ando, H., Maruyama, K. & Mashino, T. A New Metal Complex Promoted System for Highly Selective Synthesis of Chromen-4-ones (Chromones). *Synthesis* **1992**, 839–841 (1992).

124. Nishinaga, A., Kondo, T. & Matsuura, T. Oxygenation of Cobalt(ii) Schiff Base Complexes in Alcohols. *Chem. Lett.* **14**, 905–908 (1985).

125. Gerwick, W. H. *et al.* Hormothamnione, a novel cytotoxic styrylchromone from the marine cyanophyte hormothamnion enteromorphoides grunow. *Tetrahedron Lett.* **27**, 1979–1982 (1986).

126. Gerwick, W. H. 6-Desmethoxyhormothamnione, a New Cytotoxic Styrylchromone from the Marine Cryptophyte Chrysophaeum taylori. *J. Nat. Prod.* **52**, 252–256 (1989).

127. Price, W. A., Silva, A. M. S. & Cavaleiro, J. A. S. 2-Styrylchromones: Biological Action, Synthesis, and Reactivity. *Heterocycles* 2601–2612 (1993).

128. Brion, J. D., Le Baut, G., Zammattio, F., Pierre, A. & Atassi, G. *Chem Abstr* 106092k (1992).

129. Desideri, N., Conti, C., Mastromarino, P. & Mastropaolo, F. Synthesis and anti-rhinovirus activity of 2-styrylchromones. *Antivir. Chem. Chemother.* **11**, 373–381 (2000).

130. Hatakeyama, M., Zou, E. & Matsumura, F. Comparison of the characteristic of estrogenic action patterns of β-HCH and heregulin β1 in MCF-7 human breast cancer cells. *J. Biochem. Mol. Toxicol.* **16**, 209–219 (2002).

131. Fougerousse, A., Gonzalez, E. & Brouillard, R. A convenient method for synthesizing 2-aryl-3-hydroxy-4-oxo-4H-1-benzopryans or flavonols. *J. Org. Chem.* **65**, 583–586 (2000).

132. Pinto, D. C. G. A. *et al.* Synthesis of 4-Aryl-3-(2-chromonyl)-2-pyrazolines by the 1,3-dipolar cycloaddition of 2-styrylchromones with diazomethane. *J. Heterocycl. Chem.* **35**, 217–224 (1998).

133. Santos, C. M. M., Silva, A. M. S. & Cavaleiro, J. A. S. Synthesis of New Hydroxy-2-styrylchromones. *Eur. J. Org. Chem.* **2003**, 4575–4585 (2003).

134. Yu, Y. *et al.* Synthesis of Multi-Functionalized Chromeno[2,3-c]pyrrol-9(2H)-ones: Investigation and Application of Baker–Venkataraman Rearrangement Involved Reactions Catalyzed by 4-(Dimethylamino)pyridine. *Eur. J. Org. Chem.* **2011**, 4551–4563 (2011).

135. Atherton, E., Logan, C. J. & Sheppard, R. C. Peptide synthesis. Part 2. Procedures for solid-phase synthesis using Nα-fluorenylmethoxycarbonylamino-acids on polyamide supports. Synthesis of substance P and of acyl carrier protein 65–74 decapeptide. *J. Chem. Soc. [Perkin 1]* 538–546 (1981). doi:10.1039/P19810000538

136. Middleton, E., Kandaswami, C. & Theoharides, T. C. The Effects of Plant Flavonoids on Mammalian Cells:Implications for Inflammation, Heart Disease, and Cancer. *Pharmacol. Rev.* **52**, 673–751 (2000).

137. Packer, L. *Handbook of Antioxidants*. (New York, 1996).

138. Rice-Evans, C. A. & Packer, L. *Flavonoids in Health and Disease, Second Edition,*. (CRC Press, 1998).

139. Rao, K. V., Chattopadhyay, S. K. & Reddy, G. C. Flavonoids with mosquito larval toxicity. *J. Agric. Food Chem.* **38**, 1427–1430 (1990).

140. Örner, M. W. & Jha, H. C. Antifungal activity of flavonoids and their mixtures against different fungi occurring on grain. *Pestic. Sci.* **38**, 347–351 (1993).

141. Silva, A. M. S., WeidenbÖRner, M. & Cavaleiro, J. A. S. Growth control of different Fusarium species by selected flavones and flavonoid mixtures. *Mycol. Res.* **102**, 638–640 (1998).

142. Quintin, J., Roullier, C., Thoret, S. & Lewin, G. Synthesis and anti-tubulin evaluation of chromone-based analogues of combretastatins. *Tetrahedron* **62**, 4038–4051 (2006).

143. Cushman, M., Zhu, H., Geahlen, R. L. & Kraker, A. J. Synthesis and Biochemical Evaluation of a Series of Aminoflavones as Potential Inhibitors of Protein-Tyrosine Kinases p56lck, EGFr, and p60v-src. *J. Med. Chem.* **37**, 3353–3362 (1994).

144. Bois, F. *et al.* Halogenated Chalcones with High-Affinity Binding to P-Glycoprotein: Potential Modulators of Multidrug Resistance. *J. Med. Chem.* **41**, 4161–4164 (1998).

145. Boumendjel, A. *et al.* B-ring substituted 5,7-dihydroxyflavonols with high-affinity binding to P-glycoprotein responsible for cell multidrug resistance. *Bioorg. Med. Chem. Lett.* **11**, 75–77 (2001).

146. Akama, T., Ishida, H., Kimura, U., Gomi, K. & Saito, H. Structure−Activity Relationships of the 7-Substituents of 5,4‘-Diamino-6,8,3‘-trifluoroflavone, a Potent Antitumor Agent. *J. Med. Chem.* **41**, 2056–2067 (1998).

147. Costantino, L. *et al.* 1-Benzopyran-4-one Antioxidants as Aldose Reductase Inhibitors. *J. Med. Chem.* **42**, 1881–1893 (1999).

148. Tang, L. *et al.* A novel approach to the synthesis of 6-amino-7-hydroxy-flavone. *Mol. Basel Switz.* **9**, 842–848 (2004).

149. Kontogiorgis, C. & Hadjipavlou-Litina, D. Biological Evaluation of Several Coumarin Derivatives Designed as Possible Anti-inflammatory/Antioxidant Agents. *J. Enzyme Inhib. Med. Chem.* **18**, 63–69 (2003).

150. Mouri, T., Yano, T., Kochi, S., Ando, T. & Hori, M. Synthesis and Antifungal Activity of New 3,4,7-Trisubstituted Coumarins. *J. Pestic. Sci.* **30**, 209–213 (2005).

151. Mutlu, D. A. & Dilek, D. E. Synthesis and Evaluation of Antimicrobial Activity of New 3-Hydroxy-6-methyl-4-oxo-4H-pyran-2- carboxamide Derivatives. *Turk. J. Chem.* **27**, 757–764 (2003).

152. Magiatis, P. *et al.* Synthesis and Cytotoxic Activity of Pyranocoumarins of the Seselin and Xanthyletin Series. *J. Nat. Prod.* **61**, 982–986 (1998).

153. Davies, E. G. & Ashton, W. M. Coumarin and related compounds of Anthoxanthum puelii and Melilotus alba and dicoumarol formation in spoilt sweet vernal and sweet clover hay. *J. Sci. Food Agric.* **15**, 733–738 (1964).

154. Schumacher, R. W., Davidson, B. S., Montenegro, D. A. & Bernan, V. S. γ-Indomycinone, a New Pluramycin Metabolite from a Deep-Sea Derived Actinomycete. *J. Nat. Prod.* **58**, 613–617 (1995).

155. K. Eckardt. *Quinones and Other Carbocyclic Antitumor Antibiotics in Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*. **vol. II, CRC Press, Boca Raton**, (1981).

156. Séquin, U. in *Fortschritte Chem. Org. Naturstoffe Prog. Chem. Org. Nat. Prod.* (Herz, D. W., Grisebach, P. D. H., D, G. W. K. S. & Tamm, P. D. C.) 57–122 (Springer Vienna, 1986). at <http://link.springer.com/chapter/10.1007/978-3-7091-8888-0_3>

157. Nakatani, K., Okamoto, A. & Saito, I. Spezifische Alkylierung von Guanin, das einer Ausbuchtung von einem Nucleotid gegenüberliegt: eine chemische Sonde für DNA-Ausbuchtungen. *Angew. Chem.* **111**, 3581–3584 (1999).

158. Hansen, M. & Hurley, L. Altromycin B Threads the DNA Helix Interacting with Both the Major and the Minor Grooves To Position Itself for Site-Directed Alkylation and Guanine N7. *J. Am. Chem. Soc.* **117**, 2421–2429 (1995).

159. Hansen, M. R. & Hurley, L. H. Pluramycins. Old Drugs Having Modern Friends in Structural Biology. *Acc. Chem. Res.* **29**, 249–258 (1996).

160. Brockmann, H. Indomycins and Indomycinones. *Angew. Chem. Int. Ed. Engl.* **7,** 481–481 (1968).

161. Hauser, F. M. & Rhee, R. P. Anthra[1,2-b]pyran antibiotics: total synthesis of O-methylkidamycinone. *J. Org. Chem.* **45**, 3061–3068 (1980).

162. Krohn, K., Tran-Thien, H. T., Vitz, J. & Vidal, A. Total synthesis of rac-γ-indomycinone by baker-venkataraman rearrangement. *Eur. J. Org. Chem.* 1905–1911

163. Krohn, K. & Vitz, J. Total Synthesis of Premithramycinone H and Related Anthrapyran Antibiotics. *Eur. J. Org. Chem.* **2004**, 209–219 (2004).

164. Uno, H., Sakamoto, K., Honda, E. & Ono, N. Total synthesis of (S)-espicufolin and absolute structure determinaton of espicufolin. *Chem. Commun.* 1005–1106 (1999). doi:10.1039/A901602C

165. Uno, H. *et al.* Synthesis of espicufolin based on 6-endo ring closure of o-alkynoylnaphthols. *J. Chem. Soc. [Perkin 1]* 229–238 (2001). doi:10.1039/B007859J

166. Fei, Z. & McDonald, F. E. Synthesis of the Aglycones of Altromycins and Kidamycin from a Common Intermediate. *Org. Lett.* **7**, 3617–3620 (2005).

167. Krohn, K. *et al.* First enantiospecific Baker–Venkataraman-rearrangements aiming at the total synthesis of chiral anthrapyran antibiotics. *Tetrahedron Asymmetry* **17**, 3051–3057 (2006).

168. Hauser, F. M. & Rhee, R. P. 4H-Anthra[1,2-b]pyran antibiotics. Total synthesis of the methyl ether of kidamycinone. *J. Am. Chem. Soc.* **101**, 1628–1629 (1979).

169. Krohn, K., Roemer, E. & Top, M. Total synthesis of Aklanonic Acid and Derivatives by Baker–Venkataraman Rearrangement. *Liebigs Ann.* **1996**, 271–277 (1996).

170. Krohn, K., Böker, N., Flörke, U. & Freund, C. Synthesis of Angucyclines. 8. Biomimetic-Type Synthesis of Rabelomycin, Tetrangomycin, and Related Ring B Aromatic Angucyclinones. *J. Org. Chem.* **62**, 2350–2356 (1997).

171. Krohn, K. Biomimetic Synthesis of Deca- and Dodecaketide-Derived Quinone Antibiotics. *Eur. J. Org. Chem.* **2002**, 1351–1362 (2002).

172. Williams, J. G. *Chem Abstr* **131**, 322537m (1999).

173. Ruchirawat, S. & Thasana, N. The First Synthesis of Wrightiadione. *Synth. Commun.* **31**, 1765–1769 (2001).

174. Lin, L.-J. *et al.* Wrightiadione from Wrightia tomentosa. *Phytochemistry* **31**, 4333–4335 (1992).

175. Thasana, N. & Ruchirawat, S. The application of the Baker–Venkataraman rearrangement to the synthesis of benz[b]indeno[2,1-e]pyran-10,11-dione. *Tetrahedron Lett.* **43**, 4515–4517 (2002).

176. Nagarathnam, D. & Cushman, M. A short and facile synthetic route to hydroxylated flavones. New syntheses of apigenin, tricin, and luteolin. *J. Org. Chem.* **56**, 4884–4887 (1991).

177. Prasad, K. J. R., Periasamy, P. A. & Vijayalakshmi, C. S. A Facile Synthesis of Isopongaflavone, Atalantoflavone Dimethylether, Racemoflavone Dimethyleter, and Methylenedioxy Isopongaflavone. *J. Nat. Prod.* **56**, 208–214 (1993).

178. Ares, J. J. *et al.* Synthesis and Biological Evaluation of Substituted Flavones as Gastroprotective Agents. *J Med Chem* **38**, 4937–4943 (1995).

179. Tanaka, H., Stohlmeyer, M. M., Wandless, T. J. & Taylor, L. P. Synthesis of flavonol derivatives as probes of biological processes. *Tetrahedron Lett.* **41**, 9735–9739 (2000).

180. OKi, T. in *Aclacinomycin Anthracyclines Curr. Status New Dev.* 323–342 (1980).

181. Krohn, K. & Schafer, G. SYNTHESIS OF PROTECTED 4-DEOXYAKLANONIC ACID VIA NAPHTHALENE-SUBSTITUTED OLIGOKETIDES. *Liebigs Ann.* 265–270

182. Bella, M., Kobbelgaard, S. & Jorgensen, K. A. Organocatalytic regio- and asymmetric C-selective SNAr reactions-stereoselective synthesis of optically active spiro-pyrrolidone-3,3'-oxoindoles. *J. Am. Chem. Soc.* **127**, 3670–3671 (2005).

183. Liu, Y., Ma, Y., Zhan, C., Huang, A. & Ma, C. One-pot synthesis of fused pyridazino[4,5-b][1,4]oxazepine-diones via smiles rearrangement. *Synlett* 255–258 (2012). doi:10.1055/s-0031-1290073

184. Dey, C., Katayev, D., Ylijoki, K. E. O. & Kündig, E. P. Aza-oxindole synthesis via base promoted Truce–Smiles rearrangement. *Chem. Commun.* **48**, 10957–10959 (2012).

185. Alemán, J., Richter, B. & Jorgensen, K. A. Organocatalytic Highly enantioselective alpha-arylation of beta-ketoesters. *Angew. Chem. Int. Ed Engl.* **46**, 5515–5519 (2007).

186. Corey, E. J., Bo, Y. & Busch-Petersen, J. Highly Enantioselective Phase Transfer Catalyzed Alkylation of a 3-Oxygenated Propionic Ester Equivalent; Applications and Mechanism. *J. Am. Chem. Soc.* **120**, 13000–13001 (1998).

187. Dolling, U. H., Davis, P. & Grabowski, E. J. J. Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-indacrinone via chiral phase-transfer catalysis. *J. Am. Chem. Soc.* **106**, 446–447 (1984).

188. Zaheer Akbar, UCLAN, Aluffield Bursary, 2009.

189. Gnas, Y. & Glorius, F. Chiral auxiliaries - Principles and recent applications. *Synth.-Stuttg.* 1899–1930 (2006).

190. Evans, D. A., Bartroli, J. & Shih, T. L. Enantioselective aldol condensations. 2. Erythro-selective chiral aldol condensations via boron enolates. *J. Am. Chem. Soc.* **103**, 2127–2129 (1981).

191. Evans, D. A., Ennis, M. D. & Mathre, D. J. Asymmetric alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of .alpha.-substituted carboxylic acid derivatives. *J. Am. Chem. Soc.* **104**, 1737–1739 (1982).

192. Evans, D. A., Chapman, K. T. & Bisaha, J. New asymmetric Diels-Alder cycloaddition reactions. Chiral .alpha.,.beta.-unsaturated carboximides as practical chiral acrylate and crotonate dienophile synthons. *J. Am. Chem. Soc.* **106**, 4261–4263 (1984).

193. Evans, D. A., Chapman, K. T., Hung, D. T. & Kawaguchi, A. T. Transition State π-Solvation by Aromatic Rings: An Electronic Contribution to Diels–Alder Reaction Diastereoselectivity. *Angew. Chem. Int. Ed. Engl.* **26**, 1184–1186 (1987).

194. Matsumura, Y., Kanda, Y., Shirai, K., Onomura, O. & Maki, T. A Convenient Method for Synthesis of Optically Active Methylphenidate from N-Methoxycarbonylpiperidine by Utilizing Electrochemical Oxidation and Evans Aldol-type Reaction. *Tetrahedron* **56**, 7411–7422 (2000).

195. Eberlein, T. H., West, F. G. & Tester, R. W. The Stevens [1,2]-shift of oxonium ylides: a route to substituted tetrahydrofuranones. *J. Org. Chem.* **57**, 3479–3482 (1992).

196. Truce, W. E. & Hampton, D. C. *J Org Chem* **28**, 2276 (1963).

197. Masson, C. Substituted compounds derived from N-(benzyl)phenylacetamide, preparation and uses. *U. S. Pat. Appl. 0060079696*

198. Corey, E. J. & Enders, D. Applications of N,N-dimethylhydrazones to synthesis. Use in efficient, positionally and stereochemically selective C-C bond formation; oxidative hydrolysis to carbonyl compounds. *Tetrahedron Lett.* **17**, 3–6 (1976).

199. Jozwiak, K., Lough, W. J. & Wainer, I. W. *Chapter 14: Stereochemically Pure Drugs: An Overview". Drug stereochemistry: analytical methods and pharmacology*. (Informa Healthcare, 2012).

200. Enders, D. & Kipphardt, H. Asymmetric Synthesis Using the SAMP-/RAMP- Hydrazone Method: (S)-(+)-4-Methyl-3-Heptanoe. *Org. Synth.* **65**, 183 (1987).

201. Enders, D., Eichenauer, H., Baus, U., Schubert, H. & Kremer, K. A. M. Asymmetric syntheses via metalated chiral hydrazones : Overall enantioselective α-alkylation of acyclic ketones. *Tetrahedron* **40**, 1345–1359 (1984).

202. Enders, D. *et al.* Structure of a Chiral Lithium Azaenolate: Monomeric, Intramolecular Chelated Lithio-2-acetylnaphthalene-SAMP-hydrazone. *Angew. Chem. Int. Ed. Engl.* **27**, 1522–1524 (1988).

203. Ahlbrecht, H., Düber, E. O., Enders, D., Eichenauer, H. & Weuster, P. NMR-spektroskopische untersuchungen an deprotonierten iminen und hydrazonen. *Tetrahedron Lett.* **19**, 3691–3694 (1978).

204. Enders, D. & Baus, U. Asymmetrische Synthese beider Enantiomere von (E)-4,6-Dimethyl-6-octen-3-on – Abwehrsubstanz der Weberknechte Leiobunum vittatum und L. calcar (Opiliones). *Liebigs Ann. Chem.* **1983**, 1439–1445 (1983).

205. Bauer, W. & Seebach, D. Degree of Aggregation of Organolithium Compounds by Means of Cryoscopy in Tetrahydrofuran. *Helv. Chim. Acta* **67**, 1972–1988 (1984).

206. Martens, J. & Lübben, S. (1S,3S,5S)-2-Amino-3-methoxymethyl-2-azabicyclo [3.3.0]octan: SAMBO — ein neuer chiraler Hilfsstoff. *Liebigs Ann. Chem.* **1990**, 949–952 (1990).

207. Wilken, J. *et al.* Utilization of Industrial Waste Materials, 11. Synthesis of New, Chiral β-sec-Amino Alcohols – Diastereodivergent Addition of Grignard Reagents to α-Amino Aldehydes Based on the (all-R)-2-Azabicyclo[3.3.0]octane System. *Liebigs Ann.* **1997**, 2133–2146 (1997).

208. Wengryniuk, S. E., Lim, D. & Coltart, D. M. Regioselective Asymmetric α,α-Bisalkylation of Ketones via Complex-Induced Syn-Deprotonation of Chiral N-Amino Cyclic Carbamate Hydrazones. *J. Am. Chem. Soc.* **133**, 8714–8720 (2011).

209. Luengo, J. I., Konialian-Beck, A. & Holt, D. A. Ionization of the c7 methoxy group in rapamycin by 5 M lithium perchlorate-diethyl ether. *Tetrahedron Lett.* **36**, 7823–7824 (1995).

210. Enders, D., Wortmann, L. & Peters, R. Recovery of Carbonyl Compounds from N,N-Dialkylhydrazones. *Acc. Chem. Res.* **33**, 157–169 (2000).

211. Nicolaou, K. C. *et al.* Total Synthesis of Swinholide A, Preswinholide A, and Hemiswinholide A. *Chem. – Eur. J.* **2**, 847–868 (1996).

212. Nicolaou, K. C., Härter, M. W., Boulton, L. & Jandeleit, B. Synthesis of the Bicyclic Core of CP-225,917 and CP-263,114 by an Intramolecular Diels–Alder Reaction. *Angew. Chem. Int. Ed. Engl.* **36**, 1194–1196 (1997).

213. Schwaebe, M. & Little, R. D. Asymmetric Reductive Cyclization. Total Synthesis of (−)-C10-Desmethyl Arteannuin B. *J. Org. Chem.* **61**, 3240–3244 (1996).

214. Ziegler, F. E. & Becker, M. R. Total synthesis of (-)-denticulatins A and B: marine polypropionates from Siphonaria denticulata. *J. Org. Chem.* **55**, 2800–2805 (1990).

215. Nadin, A. & Nicolaou, K. C. Chemistry and Biology of the Zaragozic Acids (Squalestatins). *Angew. Chem. Int. Ed. Engl.* **35**, 1622–1656 (1996).

216. Nicolaou, K. C. *et al.* Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy. *J. Am. Chem. Soc.* **119**, 7974–7991 (1997).

217. Erickson, W. & McKennon, M. Unexpected Truce-Smiles type rearrangement of 2-(2 ’-pyridyloxy)phenylacetic esters: synthesis of 3-pyridyl-2-benzofuranones. *Tetrahedron Lett.* **41**, 4541–4544 (2000).

218. Munoz-Muniz, O. & Juaristi, E. Enantioselective Alkylation and Protonation of Prochiral Enolates in the Asymmetric Synthesis of β-Amino Acids. *Tetrahedron* 4223 (2003). doi:10.1002/chin.200340183

219. Muñoz-Muñiz, O. & Juaristi, E. Increased Enantioselectivity in the Addition of Diethylzinc to Benzaldehyde by the Use of Chiral Ligands Containing the α-Phenylethylamino Group in Combination with Achiral Ligands. *J Org Chem* **68**, 3781–3785 (2003).

220. Liu, Z. *et al.* Thio-Claisen Rearrangement Used in Preparing Anti-β-Functionalized γ,δ-Unsaturated Amino Acids: Scope and Limitations. *J. Org. Chem.* **77**, 1289–1300 (2012).

221. Hauser, C. R. & Crowther, G. P. *J Org Chem* **33**, 2228 (1968).

222. Xiao Tian, R.-M. W. Smiles Rearrangement for the Synthesis of Diarylamines. *ARKIVOC* 118–126 (2011).

223. Al-Kaysi, R. O., Gallardo, I. & Guirado, G. Stable spirocyclic Meisenheimer complexes. *Mol. Basel Switz.* **13**, 1282–1302 (2008).

224. CCDC 960190 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

225. Whitesell, J. K. C2 symmetry and asymmetric induction. *Chem. Rev.* **89**, 1581–1590 (1989).

226. Gouverneur, V. & Ghosez, L. Asymmetric amination of carboxylic acids via a diels-alder strategy. *Tetrahedron Lett.* **32**, 5349–5352 (1991).

227. Kawanami, Y., Fujita, I., Taniguchi, Y., Katsuki, T. & Yamaguchi, M. Diastereoselective Reduction of α-Keto Amides Having trans-2,5-Disubstituted Pyrrolidines as Chiral Auxiliaries. *Chem. Lett.* **16**, 2021–2024 (1987).

228. Kawanami, Y., Katsuki, T. & Yamaguchi, M. Asymmetric Diels–Alder Reaction of Acrylamides Having trans-2,5-Disubstituted Pyrrolidines as Chiral Auxiliaries. *Bull. Chem. Soc. Jpn.* **60**, 4190–4192 (1987).

229. Kitagawa, O., Hanano, T., Kikuchi, N. & Taguchi, T. Asymmetric synthesis of α-amino acids through α-iodination of chiral unsaturated carboxamides and stereoselective iodolactonization. *Tetrahedron Lett.* **34**, 2165–2168 (1993).

230. Kaoru, F., Manabu, N., Yoshimitsu, N. & Takeo, K. Enantioselective iodolactonization through diastereotopic group differentiation. *Tetrahedron Lett.* **31**, 3175–3178 (1990).

231. Zhang, Z., Tang, J., Wang, X. & Shi, H. Chiral ketone- or chiral amine-catalyzed asymmetric epoxidation of cis-1-propenylphosphonic acid using hydrogen peroxide as oxidant. *J. Mol. Catal. Chem.* **285**, 68–71 (2008).

232. Enomoto, M., Ito, Y., Katsuki, T. & Yamaguchi, M. A highly effective asymmetric synthesis of α-hydroxy acids by alkylation of chiral n-(benzyloxyacetyl)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine. *Tetrahedron Lett.* **26**, 1343–1344 (1985).

233. Hilmersson, G. & Malmros, B. Mixed Dimer and Mixed Trimer Complexes of nBuLi and a Chiral Lithium Amide. *Chem. – Eur. J.* **7,** 337–341 (2001).

234. Andrews, P. C., Duggan, P. J., Maguire, M. & Nichols, P. J. Crystal structures of (R,R)-{[Ph(Me)CH]2NLi·pmdeta} and {[PhC(CH2)NH]Na·pmdeta}2: alkali metal amides derived from (R,R)-bis(α-methylbenzyl)amine. *Chem. Commun.* 53–54 (2001). doi:10.1039/B007482I

235. Johansson, A., Pettersson, A. & Davidsson, Ö. Internal coordination and solvent effects upon hetero- and homocomplexation of chiral lithium amides: structure reactivity effects. *J. Organomet. Chem.* **608**, 153–163 (2000).

236. Pache, S., Botuha, C., Franz, R., Kündig, E. P. & Einhorn, J. Asymmetric Synthesis of Planar Chiral (Arene)tricarbonylchromium Complexes via Enantioselective Deprotonation by Conformationally Constrained Chiral Lithium-Amide Bases. *Helv. Chim. Acta* **83**, 2436–2451 (2000).

237. Sun, C. & Williard, P. G. Mixed Aggregates: Lithium Enolate of 3-Pentanone and a Chiral Lithium Amide. *J. Am. Chem. Soc.* **122**, 7829–7830 (2000).

238. Armstrong, D. R. *et al.* Structural studies of the chiral lithium amides [{PhC(H)Me}2NLi] and [PhCH2{PhC(H)Me}NLi·THF] derived from α-methylbenzylamine. *J. Chem. Soc. Dalton Trans.* 4063–4068 (1999). doi:10.1039/A904725E

239. Arvidsson, P. I. & Davidsson, Ö. 6Li and 15N NMR Data as a Probe for the Influence of Solvent and Intramolecular Solvation on the Solution-State Structures of Chiral Lithium Amides. *Angew. Chem. Int. Ed.* **39**, 1467–1470 (2000).

240. Davies, S. G., Fletcher, A. M., Roberts, P. M. & Thomson, J. E. The conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents part II: 2005−2011. *Tetrahedron Asymmetry* **23**, 1111–1153 (2012).

241. Davies, S. G. *et al.* Homochiral lithium amides for the asymmetric synthesis of β-amino acids. *Tetrahedron Asymmetry* **17**, 1793–1811 (2006).

242. Majewski, M. & Gleave, D. M. Reduction with lithium dialkylamides. *J. Organomet. Chem.* **470**, 1–16 (1994).

243. Takeda, K., Ohnishi, Y. & Koizumi, T. Enantioselective Reduction of α,β-Unsaturated Acylsilanes by Chiral Lithium Amides. *Org. Lett.* **1**, 237–240 (1999).

244. Brun, E. M., Gil, S. & Parra, M. Enantioselective α-alkylation of unsaturated carboxylic acids using a chiral lithium amide. *Tetrahedron Asymmetry* **12**, 915–921 (2001).

245. Toriyama, M., Sugasawa, K., Motohashi, S., Tokutake, N. & Koga, K. Stereoselective Reactions. XXXIV.¹⁾ Enantioselective Deprotonation of Prochiral 4-Substituted Cyclohexanones Using Chiral Bidentate Lithium Amides Having a Bulky Group Instead of a Phenyl Group on the Chiral Carbon. *Chem. Pharm. Bull. (Tokyo)* **49**, 468–472 (2001).

246. Hodgson, D. M., Gibbs, A. R. & Drew, M. G. B. Mechanism and applications of lithium amide-induced asymmetric rearrangements of 4-substituted and 4,4-disubstituted cyclopentene oxides to cyclopentenols. *J. Chem. Soc. [Perkin 1]* 3579–3590 (1999). doi:10.1039/A907522D

247. Aggarwal, V. K., Humphries, P. S. & Fenwick, A. Enantioselective deprotonation of 4-tert-butylcyclohexanone by conformationally constrained chiral lithium amide bases. *J. Chem. Soc. [Perkin 1]* 2883–2889 (1999). doi:10.1039/A905947D

248. Clayden, J., Johnson, P. & Pink, J. H. Asymmetric synthesis of enantiomerically enriched atropisomeric amides by desymmetrisation of N,N-dialkylmesitamides. *J. Chem. Soc. [Perkin 1]* 371–375 (2001). doi:10.1039/B008678I

249. Simpkins, N. S. Enantioselective Proton Transfer Chemistry: Asymmetric Synthesis with Chiral Lithium Amide Bases. *Chimia* **54**, 53 (2000).

250. Asami, M., Sato, S., Honda, K. & Inoue, S. Kinetic Resolution of cis-3-Alkylcyclohexene Oxide by a Chiral Lithium Amide - An Application to a Synthesis of Both Enantiomers of Isomenthon -. *HETEROCYCLES* **52**, 1029 (2000).

251. Bigi, A. *et al.* Kinetic resolution of racemic alkoxy oxiranes by chiral lithium amides. *Tetrahedron Asymmetry* **9**, 2293–2299 (1998).

252. Kim, B. H., Lee, H. B., Hwang, J. K. & Kim, Y. G. Asymmetric induction in the conjugate addition of thioacetic acid to methacrylamides with chiral auxiliaries. *Tetrahedron Asymmetry* **16**, 1215–1220 (2005).

253. Silverman, R. B. *The organic chemistry of drug design and drug action*. (Elsevier Academic Press, 1992).

254. Dandia, A., Singh, R., Singh, D., Laxkar, A. & Sivpuri, A. Regioselective Synthesis of Diltiazem Analogue Pyrazolo[4,3-c][1,5]benzothiazepines and Antifungal Activity. *Phosphorus Sulfur Silicon Relat. Elem.* **185**, 2472–2479 (2010).

255. Kano, T. & Maruoka, K. Unique properties of chiral biaryl-based secondary amine catalysts for asymmetric enamine catalysis. *Chem. Sci.* **4**, 907–915 (2013).

256. Muñoz-Muñiz, O. & Juaristi, E. Enantioselective alkylation and protonation of prochiral enolates in the asymmetric synthesis of β-amino acids. *Tetrahedron* **59**, 4223–4229 (2003).

257. Melgar-Fernández, R., González-Olvera, R. & Juaristi, E. Corrigendum to 'Enantioselective alkylation and protonation of prochiral enolates in the asymmetric synthesis of β-amino acids' [Tetrahedron 59 (2003) 4223]. *Tetrahedron* **61**, 4329–4333 (2005).

258. Eagon, S. *et al.* Enantioselective reduction of α-substituted ketones mediated by the boronate ester TarB-NO2. *Tetrahedron Lett.* **51**, 6418–6421 (2010).

259. Buu-Hoï, N. P. & Lavit, D. The bromination of o- and p-hydroxyaryl ketones. *J Chem Soc* 18–20 doi:10.1039/JR9550000018

260. Yu, W. *et al.* Discovery and SAR of hydantoin TACE inhibitors. *Bioorg. Med. Chem. Lett.* **20**, 1877–1880 (2010).

261. Bruneau, P., Delvare, C., Edwards, M. P. & McMillan, R. M. Indazolinones, a new series of redox-active 5-lipoxygenase inhibitors with built-in selectivity and oral activity. *J. Med. Chem.* **34**, 1028–1036 (1991).

262. Ameen, D. & Snape, T. J. Developing the Scope of O→C Aryl Migrations: Exploring Amide Substrates as Potential Precursors for Asymmetric Reactions. *Eur. J. Org. Chem.* **2014**, 1925–1934 (2014).

263. Bordwell, F. G. & Harrelson Jr, J. A. Acidities and homolytic bond dissociation energies of the αC—H bonds in ketones in DMSO. *Can. J. Chem.* **68**, 1714–1718 (1990).

264. Gómez-Bombarelli, R., Calle, E. & Casado, J. Mechanisms of Lactone Hydrolysis in Neutral and Alkaline Conditions. *J. Org. Chem.* **78**, 6868–6879 (2013).

265. Simon, C., Constantieux, T. & Rodriguez, J. Utilisation of 1,3-Dicarbonyl Derivatives in Multicomponent Reactions. *Eur. J. Org. Chem.* **2004**, 4957–4980 (2004).

266. Kozikowski, A. P. & Tückmantel, W. Chemistry, Pharmacology, and Clinical Efficacy of the Chinese Nootropic Agent Huperzine A. *Acc. Chem. Res.* **32**, 641–650 (1999).

267. Ahmad, N. M., Rodeschini, V., Simpkins, N. S., Ward, S. E. & Blake, A. J. Synthesis of Polyprenylated Acylphloroglucinols Using Bridgehead Lithiation: The Total Synthesis of Racemic Clusianone and a Formal Synthesis of Racemic Garsubellin A. *J. Org. Chem.* **72**, 4803–4815 (2007).

268. Moseley, J. D. Alternative esters in the synthesis of ZD0947. *Tetrahedron Lett.* **46**, 3179–3181 (2005).

269. Cotterill, I. C. *et al.* Microwave assisted combinatorial chemistry synthesis of substituted pyridines. *Tetrahedron Lett.* **39**, 1117–1120 (1998).

270. Tietze, L. F., Rackelmann, N. & Müller, I. Enantioselective Total Syntheses of the Ipecacuanha Alkaloid Emetine, the Alangium Alkaloid Tubulosine and a Novel Benzoquinolizidine Alkaloid by Using a Domino Process. *Chem. – Eur. J.* **10**, 2722–2731 (2004).

271. Goss, J. M. & Schaus, S. E. Enantioselective Synthesis of SNAP-7941: Chiral Dihydropyrimidone Inhibitor of MCH1-R. *J. Org. Chem.* **73**, 7651–7656 (2008).

272. Noël, R., Fargeau-Bellassoued, M.-C., Vanucci-Bacqué, C. & Lhommet, G. Convenient One-Pot Synthesis of Chiral Tetrahydropyridines via a Multicomponent Reaction. *Synthesis* **2008**, 1948–1954 (2008).

273. Mahling, J.-A., Jung, K.-H. & Schmidt, R. R. Glycosyl imidates, 69. Synthesis of flavone C-glycosides vitexin, isovitexin, and isoembigenin. *Liebigs Ann.* **1995**, 461–466 (1995).

274. Davis, B. R. & Garatt, P. J. *Comprehensive Organic Synthesis*. **2**.

275. Claisen, L. & Claparède, A. Condensationen von Ketonen mit Aldehyden. *Berichte Dtsch. Chem. Ges.* **14**, 2460–2468 (1881).

276. Claisen, L. Ueber die Einführung von Säureradicalen in Ketone. *Berichte Dtsch. Chem. Ges.* **20**, 655–657 (1887).

277. Jukic, M., Sterk, D. & Casar, Z. Recent Advances in the Retro-Claisen Reaction and Its Synthetic Applications. *Curr. Org. Synth.* **9**, 488–512 (2012).

278. Heath, R. J. & Rock, C. O. The Claisen condensation in biology. *Nat. Prod. Rep.* **19**, 581–596 (2002).

279. Grogan, G. Emergent mechanistic diversity of enzyme-catalysed β-diketone cleavage. *Biochem. J.* **388**, 721 (2005).

280. Grogan, G. β-Diketone hydrolases. *J. Mol. Catal. B Enzym.* **19–20**, 73–82 (2002).

281. Hamed, R. B., Batchelar, E. T., Clifton, I. J. & Schofield, C. J. Mechanisms and structures of crotonase superfamily enzymes – How nature controls enolate and oxyanion reactivity. *Cell. Mol. Life Sci.* **65**, 2507–2527 (2008).

282. Kutz, W. M. & Adkins, H. THE ALCOHOLYSIS OF CERTAIN 1,3-DIKETONES AND BETA-KETONIC ESTERS. *J. Am. Chem. Soc.* **52**, 4391–4399 (1930).

283. Johnson, D. A., Waugh, A. B., Hambley, T. W. & Taylor, J. C. Synthesis and crystal structure of 1,1,1,5,5,5-hexafluoro-2-aminopentan-4-one (HFAP). *J. Fluor. Chem.* **27**, 371–378 (1985).

284. Connor, R. & Adkins, H. ALCOHOLYSIS AND HYDROLYSIS OF 1,3-DIKETONES AND BETA-KETO ESTERS. *J. Am. Chem. Soc.* **54**, 3420–3427 (1932).

285. Gupta, S. K. Exceptionally facile reaction of .alpha.,.alpha.-dichloro-.beta.-keto esters with bases. *J. Org. Chem.* **38**, 4081–4082 (1973).

286. Burdett, J. L. & Rogers, M. T. Keto-Enol Tautomerism in β-Dicarbonyls Studied by Nuclear Magnetic Resonance Spectroscopy.1 I. Proton Chemical Shifts and Equilibrium Constants of Pure Compounds. *J. Am. Chem. Soc.* **86**, 2105–2109 (1964).

287. Pearson, R. G. & Mayerle, E. A. Mechanism of the Hydrolytic Cleavage of Carbon—Carbon Bonds. I. Alkaline Hydrolysis of β-Diketones1. *J. Am. Chem. Soc.* **73**, 926–930 (1951).

288. Hauser, C. R., Swamer, F. W. & Ringler, B. I. Alkaline Cleavage of Unsymmetrical β-Diketones. Ring Opening of Acylcylohexanones to Form ε-Acyl Caproic Acids1. *J. Am. Chem. Soc.* **70**, 4023–4026 (1948).

289. Rouchaud, J., Neus, O., Bulcke, R., Cools, K. & Eelen, H. Sulcotrione Soil Metabolism in Summer Corn Crops. *Bull. Environ. Contam. Toxicol.* **61**, 669–676 (1998).

290. Bedos-Belval, F., Rouch, A., Vanucci-Bacqué, C. & Baltas, M. Diaryl ether derivatives as anticancer agents – a review. *MedChemComm* **3**, 1356–1372 (2012).

291. Sriram, D., Yogeeswari, P. & Devakaram, R. V. Synthesis, in vitro and in vivo antimycobacterial activities of diclofenac acid hydrazones and amides. *Bioorganic Amp Med. Chem.* **14**, 3113–3118 (2006).

292. Inoue, T. *et al.* Inhibition of COX-2 expression by topical diclofenac enhanced radiation sensitivity via enhancement of TRAIL in human prostate adenocarcinoma xenograft model. *BMC Urol.* **13**, 1 (2013).

293. S., S., P., M. & S., V. Design, molecular docking, synthesis and evaluation of some heterocyclic analogues of diclofenac as potent analgesic and anti-inflammatory agents with less ulcerogenicity. *Pharma Chem.* **3**, 443–455 (2011).

294. Nugteren, D. H. & Hazelhof, E. Isolation and properties of intermediates in prostaglandin biosynthesis. *Biochim. Biophys. Acta* **326**, 448–461 (1973).

295. Hamberg, M. & Samuelsson, B. Detection and Isolation of an Endoperoxide Intermediate in Prostaglandin Biosynthesis. *Proc. Natl. Acad. Sci.* **70**, 899–903 (1973).

296. Chandrasekharan, N. V. & Simmons, D. L. The cyclooxygenases. *Genome Biol.* **5**, 241 (2004).

297. Mattia, C. & Coluzzi, F. COX-2 inhibitors: pharmacological data and adverse effects. *Minerva Anestesiol.* **71**, 461–470 (2005).

298. Garavito, R. M. & DeWitt, D. L. The cyclooxygenase isoforms: structural insights into the conversion of arachidonic acid to prostaglandins. *Biochim. Biophys. Acta* **1441**, 278–287 (1999).

299. Cipollone, F., Cicolini, G. & Bucci, M. Cyclooxygenase and prostaglandin synthases in atherosclerosis: recent insights and future perspectives. *Pharmacol. Ther.* **118**, 161–180 (2008).

300. Blobaum, A. L. & Marnett, L. J. Structural and functional basis of cyclooxygenase inhibition. *J. Med. Chem.* **50**, 1425–1441 (2007).

301. Xie, W. L., Chipman, J. G., Robertson, D. L., Erikson, R. L. & Simmons, D. L. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc. Natl. Acad. Sci. U. S. A.* **88**, 2692–2696 (1991).

302. Bagga, D., Wang, L., Farias-Eisner, R., Glaspy, J. A. & Reddy, S. T. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 1751–1756 (2003).

303. Calder, P. C. Dietary modification of inflammation with lipids. *Proc. Nutr. Soc.* **61**, 345–358 (2002).

304. Bell-Parikh, L. C. *et al.* Biosynthesis of 15-deoxy-delta12,14-PGJ2 and the ligation of PPARgamma. *J. Clin. Invest.* **112**, 945–955 (2003).

305. Funk, C. D. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* **294**, 1871–1875 (2001).

306. Taketo, M. M. Cyclooxygenase-2 inhibitors in tumorigenesis (Part II). *J. Natl. Cancer Inst.* **90**, 1609–1620 (1998).

307. Jm, L. *et al.* Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J. Biol. Chem.* **272**, (00:00:00.0).

308. Wolfe, M. M., Lichtenstein, D. R. & Singh, G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N. Engl. J. Med.* **340**, 1888–1899 (1999).

309. Yan, H., Kermouni, A., Abdel-Hafez, M. & Lau, D. C. W. Role of cyclooxygenases COX-1 and COX-2 in modulating adipogenesis in 3T3-L1 cells. *J. Lipid Res.* **44**, 424–429 (2003).

310. Brinton, R. D. & Yamazaki, R. S. Advances and Challenges in the Prevention and Treatment of Alzheimer's Disease. *Pharm. Res.* **15**, 386–398 (1998).

311. Eikelenboom, P., Rozemuller, A. J., Hoozemans, J. J., Veerhuis, R. & van Gool, W. A. Neuroinflammation and Alzheimer disease: clinical and therapeutic implications. *Alzheimer Dis. Assoc. Disord.* **14 Suppl 1**, S54–61 (2000).

312. Michaela A. A Blom, M. G. H. van T. NSAIDS inhibit the IL1 β-induced IL6 release from human post-mortem astrocytes: the involvement of prostaglandin E 2. *Brain Res. - BRAIN RES* **777**, 210–218 (1997).

313. Andersen, K. *et al.* Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. *Neurology* **45**, 1441–1445 (1995).

314. Galasko, D. *et al.* Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. *Neurology* **48**, 632–635 (1997).

315. Flynn, B. L. & Theesen, K. A. Pharmacologic management of Alzheimer disease part III: nonsteroidal antiinflammatory drugs--emerging protective evidence? *Ann. Pharmacother.* **33**, 840–849 (1999).

316. Sugaya, K., Uz, T., Kumar, V. & Manev, H. New anti-inflammatory treatment strategy in Alzheimer's disease. *Jpn. J. Pharmacol.* **82**, 85–94 (2000).

317. Hensley, K. Neuroinflammation in Alzheimer's disease: mechanisms, pathologic consequences, and potential for therapeutic manipulation. *J. Alzheimers Dis. JAD* **21**, 1–14 (2010).

318. Aisen, P. S. Development of antiinflammatory therapy for Alzheimer's disease. *Drug Dev. Res.* **56**, 421–427 (2002).

319. Fiebich, B. L., Lieb, K., Kammerer, N. & Hüll, M. Synergistic inhibitory effect of ascorbic acid and acetylsalicylic acid on prostaglandin E2 release in primary rat microglia. *J. Neurochem.* **86**, 173–178 (2003).

320. Chan, F. K. L. *et al.* Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* **376**, 173–179 (2010).

321. McKenna, F. Efficacy of diclofenac/misoprostol vs diclofenac in the treatment of ankylosing spondylitis. *Drugs* **45 Suppl 1**, 24–30; discussion 36–37 (1993).

322. Bandgar, B. P., Sarangdhar, R. J., Ahamed, F. A. & Viswakarma, S. Synthesis, Characterization, and Biological Evaluation of Novel Diclofenac Prodrugs. *J. Med. Chem.* **54**, 1202–1210 (2011).

323. Moser, P., Sallmann, A. & Wiesenberg, I. Synthesis and quantitative structure-activity relationships of diclofenac analogues. *J. Med. Chem.* **33**, 2358–2368 (1990).

324. Ferreira, S. H., Moncada, S. & Vane, J. R. Prostaglandins and the mechanism of analgesia produced by aspirin-like drugs. *Br. J. Pharmacol.* **120**, 401–412 (1997).

325. Cryer, B. NSAID-associated deaths: the rise and fall of NSAID-associated GI mortality. *Am. J. Gastroenterol.* **100**, 1694–1695 (2005).

326. James, M. W. & Hawkey, C. J. Assessment of non-steroidal anti-inflammatory drug (NSAID) damage in the human gastrointestinal tract. *Br. J. Clin. Pharmacol.* **56**, 146–155 (2003).

327. Naesdal, J. & Brown, K. NSAID-associated adverse effects and acid control aids to prevent them: a review of current treatment options. *Drug Saf. Int. J. Med. Toxicol. Drug Exp.* **29**, 119–132 (2006).

328. Penning, T. D. *et al.* Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benze nesulfonamide (SC-58635, celecoxib). *J. Med. Chem.* **40**, 1347–1365 (1997).

329. Talley, J. J. *et al.* 4-[5-Methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J. Med. Chem.* **43**, 775–777 (2000).

330. Picot, D., Loll, P. J. & Garavito, R. M. The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. *Nature* **367**, 243–249 (1994).

331. Antman, E. M. *et al.* Use of Nonsteroidal Antiinflammatory Drugs An Update for Clinicians: A Scientific Statement From the American Heart Association. *Circulation* **115**, 1634–1642 (2007).

332. Kearney, P. M. *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* **332**, 1302–1308 (2006).

333. Cannon, C. P. & Cannon, P. J. COX-2 Inhibitors and Cardiovascular Risk. *Science* **336**, 1386–1387 (2012).

334. Sloan, K. B., Selk, S., Haslam, J., Caldwell, L. & Shaffer, R. Acyloxyamines as prodrugs of anti-inflammatory carboxylic acids for improved delivery through skin. *J. Pharm. Sci.* **73**, 1734–1737 (1984).

335. Yano, T., Nakagawa, A., Tsuji, M. & Noda, K. Skin permeability of various non-steroidal anti-inflammatory drugs in man. *Life Sci.* **39**, 1043–1050 (1986).

336. Ettmayer, P., Amidon, G. L., Clement, B. & Testa, B. Lessons learned from marketed and investigational prodrugs. *J. Med. Chem.* **47**, 2393–2404 (2004).

337. Beaumont, K., Webster, R., Gardner, I. & Dack, K. Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. *Curr. Drug Metab.* **4**, 461–485 (2003).

338. Wallace, J. L. The 1994 Merck Frosst Award. Mechanisms of nonsteroidal anti-inflammatory drug (NSAID) induced gastrointestinal damage--potential for development of gastrointestinal tract safe NSAIDs. *Can. J. Physiol. Pharmacol.* **72**, 1493–1498 (1994).

339. Kim, H. *et al.* A molecular mechanism for the anti-inflammatory effect of taurine-conjugated 5-aminosalicylic acid in inflamed colon. *Mol. Pharmacol.* **69**, 1405–1412 (2006).

340. N, G., D, N., S, D., S, D. & S, C. Synthesis, Hydrolysis Kinetics And Pharmacodynamic Profile Of Novel Prodrugs Of Flurbiprofen. *Indian J. Pharm. Sci.* **67**, 369 (2005).

341. Sagara, K. *et al.* Biovavailability Study of Commercial Sustained-Release Preparations of Diclofenac Sodium in Gastrointestinal Physiology Regulated-Dogs. *Chem. Pharm. Bull. (Tokyo)* **40**, 3303–3306 (1992).

342. Iqbal, Z. *et al.* Preparation and in-vitro in-vivo evaluation of sustained release matrix diclofenac sodium tablets using PVP-K90 and natural gums. *Pak. J. Pharm. Sci.* **24**, 435–443 (2011).

343. Mohammad, H. N. T., Soodabeh, D. & Ali Akbar, E. Synthesis of Diclofenac Polymeric Prodrugs and Their Hydrolysis Reactivity. *Iran. Polym. J.* **5**, 243–249 (1996).

344. Perera, P., Bohlin, L., Vasänge, M. & Huss, U. in *Bioact. Compd. Nat. Sources* 433–472 (Taylor & Francis, 2001).

345. Pairet, M. *et al.* in *Sel. COX-2 Inhib.* (Vane, S. J. & Botting, D. J.) 27–46 (Springer Netherlands, 1998). at <http://link.springer.com/chapter/10.1007/978-94-011-4872-6_3>

346. Battistini, B., Botting, R. & Bakhle, Y. COX-1 and COX-2: Toward the developpement of more selective NSAIDs. *Drug News Perspect.* **7**, 501–512 (1994).

347. Kim, Y. P. *et al.* Inhibition by tectorigenin and tectoridin of prostaglandin E2 production and cyclooxygenase-2 induction in rat peritoneal macrophages. *Biochim. Biophys. Acta* **1438**, 399–407 (1999).

348. Kase, Y., Saitoh, K., Ishige, A. & Komatsu, Y. Mechanisms by which Hange-shashin-to reduces prostaglandin E2 levels. *Biol. Pharm. Bull.* **21**, 1277–1281 (1998).

349. Noreen, Y., Serrano, G., Perera, P. & Bohlin, L. Flavan-3-ols isolated from some medicinal plants inhibiting COX-1 and COX-2 catalysed prostaglandin biosynthesis. *Planta Med.* **64**, 520–524 (1998).

350. Subbaramaiah, K. *et al.* Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. *J. Biol. Chem.* **273**, 21875–21882 (1998).

351. Sittampalam, G. S., Kahl, S. D. & Janzen, W. P. High-throughput screening: advances in assay technologies. *Curr. Opin. Chem. Biol.* **1**, 384–391 (1997).

352. Wang, H. *et al.* Antioxidant and antiinflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. *J. Nat. Prod.* **62**, 294–296 (1999).

353. Vlietnick, A. & Apers, S. in *Bioact. Compd. Nat. Sources* 3–29 (Taylor & Francis, 2000).

354. COX Fluorescent Inhibitor Screening Assay Kit; Cyclooxygenase Fluorescent Inhibitor Screening Assay Kit Cayman Chemical Supplier. at <https://www.caymanchem.com/app/template/Product.vm/catalog/700100>

355. Shen, T. Perspectives in Nonsteroidal Antiinflammatory Agents. *Angew. Chem.-Int. Ed.* **11**, 460–& (1972).

356. Northover, B. J. The action of anti-inflammatory drugs on the permeability of mesenteric mesothelium to plasma protein. *J. Pharm. Pharmacol.* **15**, (1963).

357. Shen, T. Y. *et al.* Non-Steroid Anti-Inflammatory Agents. *J. Am. Chem. Soc.* **85**, 488–489 (1963).

358. Adams, S. S., Cliffe, E. E., Lessel, B. & Nicholson, J. S. Some Biological Properties of 'ibufenac', a New Anti-Rheumatic Drug. *Nature* **200**, (1963).

359. Durant, G. J., Smith, G. M., Spickett, R. G. W. & Szarvasi, E. Nonsteroidal Antiinflammatory Agents. Some Arylacetic Acids. *J. Med. Chem.* **8**, 598–603 (1965).

360. Esser, R. *et al.* Preclinical pharmacology of lumiracoxib: a novel selective inhibitor of cyclooxygenase-2. *Br. J. Pharmacol.* **144**, 538–550 (2005).

361. Abdou, W. M., Ganoub, N. A. & Sabry, E. Synthesis and quantitative structure–activity relationship study of substituted imidazophosphor ester based tetrazolo[1,5- *b*]pyridazines as antinociceptive/anti-inflammatory agents. *Beilstein J. Org. Chem.* **9**, 1730–1736 (2013).

362. Hadjipavlou-Litina, D. Quantitative structure--activity relationship (QSAR) studies on non steroidal anti-inflammatory drugs (NSAIDs). *Curr. Med. Chem.* **7**, 375–388 (2000).

363. Flower, R. J. The development of COX2 inhibitors. *Nat. Rev. Drug Discov.* **2**, 179–191 (2003).

364. Dannhardt, G. & Kiefer, W. Cyclooxygenase inhibitors - current status and future prospects. *Eur. J. Med. Chem.* **36**, 109–126 (2001).

365. Kalgutkar, A. S., Crews, B. C., Saleh, S., Prudhomme, D. & Marnett, L. J. Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors. *Bioorg. Med. Chem.* **13**, 6810–6822 (2005).

366. Atkinson, D. C., Godfrey, K. E., Meek, B., Saville, J. F. & Stillings, M. R. Substituted (2-phenoxyphenyl)acetic acids with antiinflammatory activity. 1. *J. Med. Chem.* **26**, 1353–1360 (1983).

367. Atkinson, D. C. *et al.* Substituted (2-phenoxyphenyl)acetic acids with antiinflammatory activity. 2. *J. Med. Chem.* **26**, 1361–1364 (1983).

368. El-Sayrafi, S. & Rayyan, S. Intramolecular Acylation of Aryl- and Aroyl-Aliphatic Acids by the Action of Pyrophosphoryl Chloride and Phosphorus Oxychloride. *Molecules* **6**, 279–286 (2001).

369. Zagorevskij et al. *J. Org. Chem. USSR Engl. Transl.* **3**, 544 (1967).

370. Krayushkin, M. M. *et al.* Synthesis and reactivity of 1-aryl-9H-thieno[3,4-b]chromon-9-ones. *New J. Chem.* **33**, 2267–2277 (2009).

371. Mason, H. L. α-Oximino and α-Amino Derivatives of o-Hydroxypropiophenone. *J. Am. Chem. Soc.* **56**, 2499–2500 (1934).

372. Kalinin, A. V., da Silva, A. J. M., Lopes, C. C., Lopes, R. S. C. & Snieckus, V. Directed ortho metalation - cross coupling links. Carbamoyl rendition of the baker-venkataraman rearrangement. Regiospecific route to substituted 4-hydroxycoumarins. *Tetrahedron Lett.* **39**, 4995–4998 (1998).

373. Kraus, G. A., Fulton, B. S. & Wood, S. H. Aliphatic acyl transfer in the Baker-Venkataraman reaction. *J. Org. Chem.* **49**, 3212–3214 (1984).

374. Stahmann, M. A., Wolff, I. & Link, K. P. Studies on 4-Hydroxycoumarins. I. The Synthesis of 4-Hydroxycoumarins1. *J. Am. Chem. Soc.* **65**, 2285–2287 (1943).

375. Yang, K., Li, Z., Wang, Z., Yao, Z. & Jiang, S. Highly Efficient Synthesis of Phenols by Copper-Catalyzed Hydroxylation of Aryl Iodides, Bromides, and Chlorides. *Org. Lett.* **13**, 4340–4343 (2011).

376. King, L. C., McWhirter, M. & Barton, D. M. The Reactions of Acetophenols with Iodine and Pyridine and the Preparation of Hydroxybenzoic Acids. *J. Am. Chem. Soc.* **67**, 2089–2092 (1945).

377. Ghasemnejad-Bosra, H., Ramzanian-Lehmali, F. & Jafari, S. Simple and improved regioselective brominations of aromatic compounds using N-benzyl-N,N-dimethylanilinium peroxodisulfate in the presence of potassium bromide under mild reactions conditions. (2011). at <http://core.kmi.open.ac.uk/display/954679>

378. Yang, C.-C., Tai, H.-M. & Sun, P.-J. Conversion of α-Anilino Alkenenitriles to Amides by Chemoselective Palladium-Catalyzed Arylations. *Synlett* **1997**, 812–814 (1997).

379. Lee, J. *et al.* 2-Benzyl and 2-phenyl-3-hydroxypropyl pivalates as protein kinase C ligands. *Bioorg Med Chem* **14**, 2022–2031 (2006).

380. Stillings, M. R. *et al.* Substituted 5H-dibenz[b,g]-1,4-oxazocines and related amino acids with antiinflammatory activity. *J. Med. Chem.* **28**, 225–233 (1985).

381. Aitken, H. R. M., Furkert, D. P., Hubert, J. G., Wood, J. M. & Brimble, M. A. Enantioselective access to benzannulated spiroketals using a chiral sulfoxide auxiliary. *Org. Biomol. Chem.* **11**, 5147–5155 (2013).

APPENDIX

APPENDIX

Table 1. Crystal data and structure refinement.

Identification code	**2013ncs0352 / DA1.81(38-45)**	
Empirical formula	$C_{28}H_{24}N_2O_4$	
Formula weight	452.49	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 7.3807(14) Å	α = 90°
	b = 13.547(3) Å	β = 90.834(10)°
	c = 22.864(5) Å	γ = 90°
Volume	2285.8(8) Å^3	
Z	4	
Density (calculated)	1.315 Mg / m^3	
Absorption coefficient	0.717 mm^{-1}	
F(000)	952	
Crystal	Blade; Orange	
Crystal size	0.250 × 0.120 × 0.080 mm^3	
θ range for data collection	3.793 – 68.242°	
Index ranges	$-8 \le h \le 8$, $-16 \le k \le 15$, $-27 \le l \le 27$	
Reflections collected	19910	
Independent reflections	4140 [R_{int} = 0.0397]	
Completeness to θ = 67.687°	99.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.843	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4140 / 0 / 308	

Goodness-of-fit on F^2	1.049
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0471, *wR2* = 0.1287
R indices (all data)	*R1* = 0.0487, *wR2* = 0.1309
Extinction coefficient	n/a
Largest diff. peak and hole	0.294 and –0.207 e $Å^{-3}$

Diffractometer: *Rigaku AFC11* quarter chi goniometer equipped with an enhanced sensitivity (HG) *Saturn944+* detector mounted at the window of *007 HF* copper rotating anode generator with *Varimax optics.*

Cell determination and data collection: *CrystalClear-SM Expert 3.1 b26* (Rigaku, 2012).

Data reduction, cell refinement and absorption correction: *CrystalClear-SM Expert 3.1 b26* (Rigaku, 2012).

Structure solution: *SHELXS97* (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122).

S**tructure refinement**: *SHELXL-2012* (G Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.).

Graphics: *ORTEP3 for Windows* (L. J. Farrugia, J. Appl. Crystallogr. 1997, 30, 565

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	3998(2)	2203(1)	869(1)	26(1)	1
C2	5299(2)	2757(1)	466(1)	26(1)	1
C3	4232(2)	3473(1)	82(1)	28(1)	1
C4	3214(2)	4265(1)	301(1)	30(1)	1
C5	2284(2)	4923(1)	–58(1)	37(1)	1
C6	2314(2)	4804(1)	–655(1)	41(1)	1
C7	3282(2)	4032(1)	–887(1)	41(1)	1

C8	4224(2)	3385(1)	–524(1)	34(1)	1
C9	6412(2)	2012(1)	127(1)	27(1)	1
C10	8306(2)	2076(1)	127(1)	29(1)	1
C11	9322(2)	1382(1)	–178(1)	34(1)	1
C12	8474(2)	629(1)	–479(1)	35(1)	1
C13	6608(2)	557(1)	–482(1)	34(1)	1
C14	5596(2)	1243(1)	–182(1)	30(1)	1
C15	6464(2)	1943(1)	1609(1)	32(1)	1
C16	7380(2)	991(1)	1788(1)	34(1)	1
C17	8183(2)	912(1)	2338(1)	47(1)	1
C18	9080(3)	54(2)	2503(1)	57(1)	1
C19	9149(2)	–732(2)	2129(1)	53(1)	1
C20	8348(2)	–667(1)	1578(1)	49(1)	1
C21	7496(2)	199(1)	1407(1)	41(1)	1
C22	3345(2)	1279(1)	1751(1)	33(1)	1
C23	2657(2)	1936(1)	2236(1)	38(1)	1
C24	3095(2)	1730(1)	2816(1)	48(1)	1
C25	2412(3)	2329(2)	3261(1)	60(1)	1
C26	1297(3)	3111(2)	3128(1)	60(1)	1
C27	853(3)	3318(1)	2555(1)	54(1)	1
C28	1532(2)	2737(1)	2109(1)	44(1)	1
N1	4637(2)	1786(1)	1364(1)	29(1)	1
N2	3078(2)	4451(1)	932(1)	37(1)	1
O1	2390(1)	2106(1)	717(1)	32(1)	1
O2	9107(1)	2822(1)	433(1)	34(1)	1
O3	4156(1)	4071(1)	1270(1)	39(1)	1
O4	1863(2)	4992(1)	1099(1)	73(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.2384(17)	C15–N1	1.4682(18)
C1–N1	1.3450(18)	C15–C16	1.510(2)
C1–C2	1.5364(18)	C15–H15A	0.9900
C2–C3	1.5210(18)	C15–H15B	0.9900
C2–C9	1.5201(18)	C16–C21	1.385(2)
C2–H2	1.0000	C16–C17	1.387(2)
C3–C8	1.390(2)	C17–C18	1.387(3)
C3–C4	1.4061(19)	C17–H17	0.9500
C4–C5	1.386(2)	C18–C19	1.367(3)
C4–N2	1.4694(19)	C18–H18	0.9500
C5–C6	1.377(2)	C19–C20	1.386(3)
C5–H5	0.9500	C19–H19	0.9500
C6–C7	1.377(2)	C20–C21	1.386(2)
C6–H6	0.9500	C20–H20	0.9500
C7–C8	1.387(2)	C21–H21	0.9500
C7–H7	0.9500	C22–N1	1.4782(17)
C8–H8	0.9500	C22–C23	1.516(2)
C9–C14	1.3906(19)	C22–H22A	0.9900
C9–C10	1.4007(19)	C22–H22B	0.9900
C10–O2	1.3594(17)	C23–C24	1.389(2)
C10–C11	1.395(2)	C23–C28	1.394(2)
C11–C12	1.376(2)	C24–C25	1.401(3)
C11–H11	0.9500	C24–H24	0.9500
C12–C13	1.381(2)	C25–C26	1.373(3)
C12–H12	0.9500	C25–H25	0.9500
C13–C14	1.383(2)	C26–C27	1.375(3)
C13–H13	0.9500	C26–H26	0.9500
C14–H14	0.9500	C27–C28	1.388(2)

C27–H27	0.9500	N2–O4	1.2231(17)
C28–H28	0.9500	O2–H2A	0.8400
N2–O3	1.2161(17)		

O1–C1–N1	120.95(12)	C7–C8–H8	118.8
O1–C1–C2	119.24(11)	C3–C8–H8	118.8
N1–C1–C2	119.72(11)	C14–C9–C10	118.11(12)
C3–C2–C9	114.11(11)	C14–C9–C2	121.47(12)
C3–C2–C1	109.58(10)	C10–C9–C2	120.41(12)
C9–C2–C1	109.17(11)	O2–C10–C11	121.68(12)
C3–C2–H2	107.9	O2–C10–C9	118.15(12)
C9–C2–H2	107.9	C11–C10–C9	120.16(13)
C1–C2–H2	107.9	C12–C11–C10	120.35(13)
C8–C3–C4	115.25(13)	C12–C11–H11	119.8
C8–C3–C2	120.98(12)	C10–C11–H11	119.8
C4–C3–C2	123.76(12)	C11–C12–C13	120.12(13)
C5–C4–C3	122.83(14)	C11–C12–H12	119.9
C5–C4–N2	115.47(13)	C13–C12–H12	119.9
C3–C4–N2	121.70(12)	C12–C13–C14	119.72(13)
C6–C5–C4	119.83(14)	C12–C13–H13	120.1
C6–C5–H5	120.1	C14–C13–H13	120.1
C4–C5–H5	120.1	C13–C14–C9	121.54(13)
C5–C6–C7	119.07(14)	C13–C14–H14	119.2
C5–C6–H6	120.5	C9–C14–H14	119.2
C7–C6–H6	120.5	N1–C15–C16	112.61(12)
C6–C7–C8	120.58(14)	N1–C15–H15A	109.1
C6–C7–H7	119.7	C16–C15–H15A	109.1
C8–C7–H7	119.7	N1–C15–H15B	109.1
C7–C8–C3	122.43(14)	C16–C15–H15B	109.1

H15A–C15–H15B	107.8	C24–C23–C28	119.00(15)
C21–C16–C17	118.75(15)	C24–C23–C22	120.34(15)
C21–C16–C15	121.51(13)	C28–C23–C22	120.63(14)
C17–C16–C15	119.70(15)	C23–C24–C25	119.73(18)
C16–C17–C18	120.49(18)	C23–C24–H24	120.1
C16–C17–H17	119.8	C25–C24–H24	120.1
C18–C17–H17	119.8	C26–C25–C24	120.44(18)
C19–C18–C17	120.29(17)	C26–C25–H25	119.8
C19–C18–H18	119.9	C24–C25–H25	119.8
C17–C18–H18	119.9	C25–C26–C27	120.18(17)
C18–C19–C20	119.99(16)	C25–C26–H26	119.9
C18–C19–H19	120.0	C27–C26–H26	119.9
C20–C19–H19	120.0	C26–C27–C28	120.04(19)
C21–C20–C19	119.73(17)	C26–C27–H27	120.0
C21–C20–H20	120.1	C28–C27–H27	120.0
C19–C20–H20	120.1	C27–C28–C23	120.60(17)
C16–C21–C20	120.71(15)	C27–C28–H28	119.7
C16–C21–H21	119.6	C23–C28–H28	119.7
C20–C21–H21	119.6	C1–N1–C15	124.66(12)
N1–C22–C23	112.99(12)	C1–N1–C22	118.51(11)
N1–C22–H22A	109.0	C15–N1–C22	115.88(11)
C23–C22–H22A	109.0	O3–N2–O4	122.06(13)
N1–C22–H22B	109.0	O3–N2–C4	119.89(12)
C23–C22–H22B	109.0	O4–N2–C4	118.06(13)
H22A–C22–H22B	107.8	C10–O2–H2A	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	25(1)	27(1)	27(1)	–2(1)	1(1)	4(1)
C2	24(1)	29(1)	26(1)	–2(1)	–1(1)	1(1)
C3	25(1)	28(1)	31(1)	0(1)	–1(1)	–1(1)
C4	26(1)	30(1)	36(1)	–1(1)	0(1)	–1(1)
C5	27(1)	30(1)	53(1)	3(1)	–2(1)	1(1)
C6	36(1)	36(1)	50(1)	11(1)	–11(1)	–2(1)
C7	47(1)	43(1)	33(1)	6(1)	–9(1)	–3(1)
C8	37(1)	34(1)	31(1)	0(1)	–1(1)	1(1)
C9	28(1)	28(1)	26(1)	2(1)	2(1)	3(1)
C10	28(1)	29(1)	29(1)	2(1)	–1(1)	2(1)
C11	28(1)	37(1)	37(1)	0(1)	2(1)	7(1)
C12	38(1)	34(1)	35(1)	–2(1)	5(1)	7(1)
C13	39(1)	30(1)	32(1)	–4(1)	2(1)	–1(1)
C14	29(1)	33(1)	30(1)	–1(1)	2(1)	–1(1)
C15	30(1)	39(1)	28(1)	1(1)	–4(1)	0(1)
C16	29(1)	44(1)	31(1)	7(1)	1(1)	2(1)
C17	51(1)	58(1)	33(1)	10(1)	–6(1)	2(1)
C18	57(1)	70(1)	45(1)	22(1)	–6(1)	11(1)
C19	43(1)	59(1)	59(1)	27(1)	12(1)	16(1)
C20	45(1)	47(1)	55(1)	6(1)	15(1)	11(1)
C21	37(1)	48(1)	36(1)	3(1)	2(1)	8(1)
C22	34(1)	35(1)	31(1)	2(1)	6(1)	–2(1)
C23	39(1)	41(1)	33(1)	–2(1)	9(1)	–6(1)
C24	50(1)	60(1)	34(1)	2(1)	7(1)	–7(1)
C25	64(1)	85(2)	32(1)	–4(1)	12(1)	–15(1)
C26	68(1)	64(1)	48(1)	–19(1)	24(1)	–12(1)

C27	57(1)	48(1)	59(1)	–9(1)	23(1)	–2(1)
C28	45(1)	45(1)	42(1)	–3(1)	12(1)	2(1)
N1	27(1)	34(1)	26(1)	1(1)	2(1)	2(1)
N2	32(1)	37(1)	41(1)	–8(1)	2(1)	4(1)
O1	24(1)	37(1)	35(1)	1(1)	0(1)	2(1)
O2	25(1)	34(1)	45(1)	–7(1)	–4(1)	2(1)
O3	42(1)	39(1)	36(1)	–6(1)	–1(1)	4(1)
O4	67(1)	95(1)	58(1)	–22(1)	2(1)	47(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	6150	3150	718	32	1
H5	1628	5454	109	44	1
H6	1675	5249	–905	49	1
H7	3305	3942	–1299	49	1
H8	4889	2862	–696	41	1
H11	10606	1430	–177	41	1
H12	9174	158	–685	42	1
H13	6022	37	–690	40	1
H14	4312	1189	–186	37	1
H15A		6386	2381	1954	39	1
H15B		7213	2280	1314	39	1
H17	8118	1450	2604	57	1
H18	9649	13	2878	69	1
H19	9746	–1322	2247	64	1
H20	8383	–1215	1319	59	1
H21	6986	251	1025	49	1
H22A		3946	694	1926	40	1
H22B		2301	1043	1513	40	1
H24	3854	1185	2911	57	1

H252723	2193	3658	72	1	
H26832	3510	3433	72	1	
H2780	3859	2465	65	1	
H281228	2886	1714	53	1	
H2A	10205	2688	492	51	1

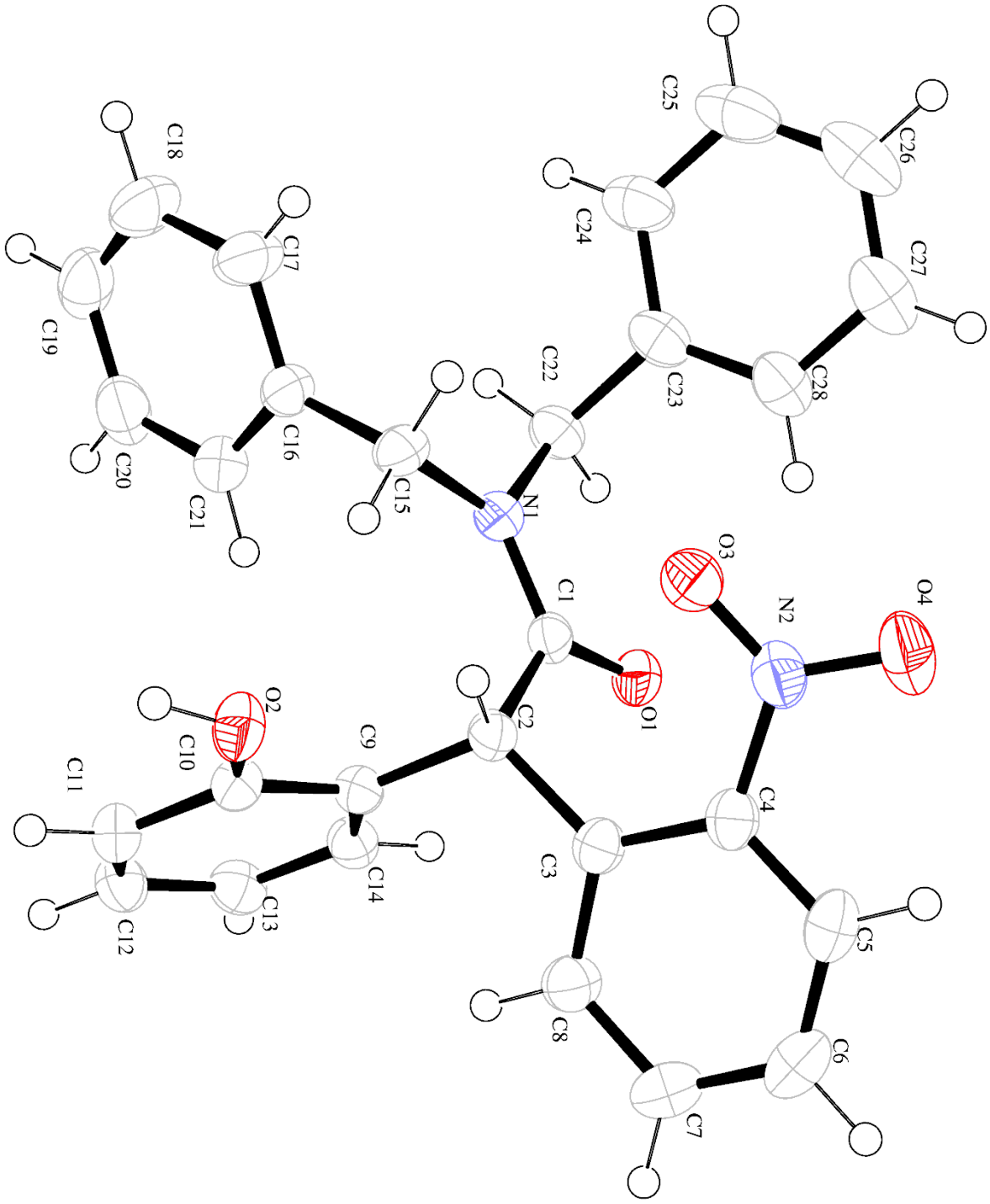
Table 6. Torsion angles [°].

O1–C1–C2–C3	25.20(16)
N1–C1–C2–C3	–158.31(12)
O1–C1–C2–C9	–100.44(14)
N1–C1–C2–C9	76.05(15)
C9–C2–C3–C8	3.94(18)
C1–C2–C3–C8	–118.82(13)
C9–C2–C3–C4	–175.35(12)
C1–C2–C3–C4	61.90(16)
C8–C3–C4–C5	–0.8(2)
C2–C3–C4–C5	178.52(13)
C8–C3–C4–N2	179.52(12)
C2–C3–C4–N2	–1.2(2)
C3–C4–C5–C6	1.0(2)
N2–C4–C5–C6	–179.34(13)
C4–C5–C6–C7	–0.3(2)
C5–C6–C7–C8	–0.4(2)
C6–C7–C8–C3	0.5(2)
C4–C3–C8–C7	0.1(2)
C2–C3–C8–C7	–179.28(13)
C3–C2–C9–C14	–71.63(16)
C1–C2–C9–C14	51.35(16)
C3–C2–C9–C10	109.42(14)

C1–C2–C9–C10	–127.60(13)
C14–C9–C10–O2	–179.43(12)
C2–C9–C10–O2	–0.45(18)
C14–C9–C10–C11	0.1(2)
C2–C9–C10–C11	179.06(12)
O2–C10–C11–C12	179.36(13)
C9–C10–C11–C12	–0.1(2)
C10–C11–C12–C13	0.1(2)
C11–C12–C13–C14	0.0(2)
C12–C13–C14–C9	0.0(2)
C10–C9–C14–C13	0.0(2)
C2–C9–C14–C13	–178.98(12)
N1–C15–C16–C21	51.70(18)
N1–C15–C16–C17	–130.61(15)
C21–C16–C17–C18	–0.2(2)
C15–C16–C17–C18	–177.93(15)
C16–C17–C18–C19	–1.4(3)
C17–C18–C19–C20	1.1(3)
C18–C19–C20–C21	0.7(3)
C17–C16–C21–C20	2.0(2)
C15–C16–C21–C20	179.73(14)
C19–C20–C21–C16	–2.3(2)
N1–C22–C23–C24	–114.06(16)
N1–C22–C23–C28	67.94(18)
C28–C23–C24–C25	–0.3(3)
C22–C23–C24–C25	–178.39(15)
C23–C24–C25–C26	0.7(3)
C24–C25–C26–C27	–0.5(3)
C25–C26–C27–C28	–0.1(3)
C26–C27–C28–C23	0.5(3)

C24–C23–C28–C27	–0.2(2)
C22–C23–C28–C27	177.79(15)
O1–C1–N1–C15	–173.48(12)
C2–C1–N1–C15	10.09(19)
O1–C1–N1–C22	–5.09(19)
C2–C1–N1–C22	178.49(11)
C16–C15–N1–C1	–133.07(13)
C16–C15–N1–C22	58.27(16)
C23–C22–N1–C1	–94.72(15)
C23–C22–N1–C15	74.68(16)
C5–C4–N2–O3	–162.92(13)
C3–C4–N2–O3	16.8(2)
C5–C4–N2–O4	17.1(2)
C3–C4–N2–O4	–163.18(15)

Symmetry transformations used to generate equivalent atoms:


C25
C26
C24
C27
C18
C17
C22
C23
C28
C19
C16
C20
C15
N1
C21
O3
C1
N2
O4
O2
C2
O1
C10
C9
C11
C4
C14
C3
C13
C12
C5
C8
C6
C7