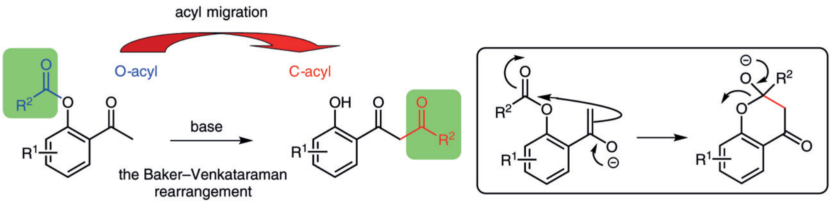
Central Lancashire Online Knowledge (CLoK)

Title	Mechanism and Application of Baker–Venkataraman O→C Acyl Migration Reactions
Type	Article
URL	https://clok.uclan.ac.uk/id/eprint/12388/
DOI	https://doi.org/10.1055/s-0034-1379498
Date	2014
Citation	Snape, Timothy James and Ameen, Dana (2014) Mechanism and Application of Baker–Venkataraman O→C Acyl Migration Reactions. Synthesis, 47 (02). pp. 141-158. ISSN 0039-7881
Creators	Snape, Timothy James and Ameen, Dana

Mechanism and Application of Baker–Venkataraman O→C Acyl Migration Reactions

Dana Ameen
Timothy J. Snape*

School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Maudland Building, Preston, Lancashire, PR1 2HE, UK
tjsnape@uclan.ac.uk



Received: 04.07.2014
Accepted after revision: 20.08.2014

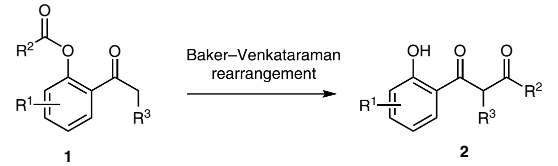
DOI: 10.1055/s-0034-1379498; Art ID: ss-2014-e0423-r

Abstract This literature review focuses on the O→C acyl migration of aryl esters to yield the corresponding 1,3-dicarbonyl products—a reaction known as the Baker–Venkataraman rearrangement—and outlines their subsequent transformations. The purpose of the review is to highlight the utility of the rearrangement which provides a key step in the synthesis of various heterocyclic motifs. The scope of the Baker–Venkataraman rearrangement is illustrated by way of numerous examples of its application, and in doing so, the review contains over 100 references and covers just over 100 years of the literature, from the first report of the rearrangement by Auwers in 1910 up to more recent examples in the past few years.

Key words acyl migrations, rearrangements, Baker–Venkataraman, heterocycles, aryl esters

1 Introduction

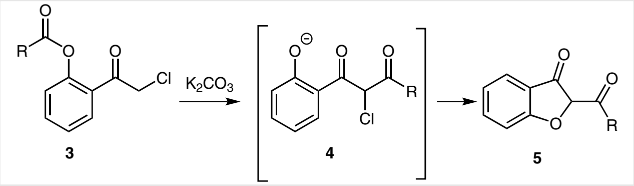
Acyl migrations permeate the chemical literature, yet most involve heteroatom → heteroatom rearrangements; for example, instances of such acyl migrations have been observed on ribonucleoside derivatives,[1] glycerol esters,[2] during the asymmetric synthesis of β-amino tertiary alcohols,[3] and on the taxane skeleton,[4] amongst many others.[5] Such migrations have also been exploited as a prodrug strategy for the preparation of taxoids[6] and HIV-1 protease inhibitors,[7] as well as occurring over increasingly long molecular distances, such as that seen in a 1,7-O,O′-intramolecular acyl migration,[8] and via 13-, 15-, and 16-membered cyclic transition states.[9] Such rearrangement reactions are powerful tools in organic synthesis because simple, readily available, suitable primed precursors can give rise to large structural changes in a single step, or they are able to exploit the inherent reactivity of a molecule under a certain set of conditions.[10] Whilst heteroatom → sp^3-carbon acyl migrations are known,[11] they are less well known than their all-heteroatom counterpart. As such, the focus of this review is the specific rearrangement which sees the O → C migration of aromatic acyl groups to sp^3-carbons—the so-called Baker–Venkataraman rearrangement (Scheme 1)—reactions which have received numerous citations in organic chemistry, especially due to their use in the regioselective formation of carbon–carbon bonds.



Scheme 1 The Baker–Venkataraman rearrangement

2 Historical Perspective

In 1910, during his work on coumaranones and 2-hydroxycoumarones, Auwers observed that esters of 2-chloro-2′-hydroxyacetophenone **3** reacted with potassium carbonate to form 2-substituted coumaran-3-ones **5**, and it was suggested that the reaction proceeded through the 1,3-diketone species **4** (Scheme 2).[12]



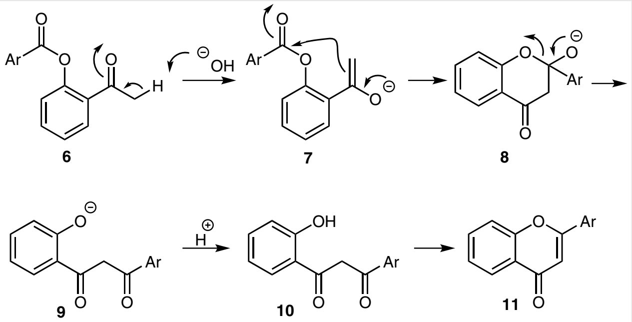
3 4 5

Scheme 2 Rearrangement of 2-chloro-2′-hydroxyacetophenone esters

Later, Venkataraman,[13] and independently Baker,[14] reported the isolation of a similar 1,3-diketone, **10** (Scheme 3), following the rearrangement of 2′-aroyloxyacetophenone **6**. Since these early examples,[15] the reaction has been exploited and is now of prime importance in the synthesis of flavones (**11**), amongst other heterocyclic ring systems (see section 4).

3 Mechanism

The currently accepted mechanism of this transformation can be regarded as an intramolecular Claisen condensation between an acetophenone derivative and a proximal ester on the aromatic ring. Whilst classical Claisen condensations between a ketone and an ester occur intermolecularly, in the Baker–Venkataraman rearrangement both functionalities are present, typically *ortho* to each other, on the same aromatic ring, and thus the reaction occurs intramolecularly (Scheme 3).[16] The reaction differs from the classical intramolecular Claisen (Dieckmann) condensation in that cyclic products are not formed.



6 7 8 9 10 11

Scheme 3 The mechanism of the Baker–Venkataraman rearrangement (**6**→**10**)

Using the example in Scheme 3 as an illustration, in a typical reaction, base abstraction of one of the α-hydrogens of the aromatic ketone **6** occurs, which results in the formation of enolate **7**. Intramolecular attack of the enolate occurs onto the ester carbonyl to form the cyclic charged hemiacetal **8**, the tetrahedral intermediate of which subsequently collapses to form the more stable phenolate **9**, which is protonated during acid workup to give the 1,3-diketone Baker–Venkataraman product **10**.

In 1933, when studying similar reactions, and attempting the O-benzylation of 4′-benzoylresacetophenone (**12**), Baker observed that an unexpected dibenzoylated product, **14**, was formed in 20% yield. Upon further investigation into its mechanism of formation, a sample of separately prepared 2′,4′-dibenzoylresacetophenone (**13**) was exposed to the same reaction conditions, wherein the same product **14** was formed. It was thus postulated that the dibenzoylated

Biographical Sketches

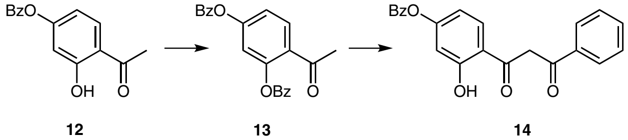
Timothy J. Snape

Tim grew up in Lancashire, England. He obtained his MSci in chemistry (University of Nottingham, 2000) and his PhD (University of Liverpool, 2003) working with Prof. Stan Roberts. Tim moved to the University of Manchester in 2005 to undertake postdoctoral research with Prof. Jonathan Clayden which was followed by a Research Fellowship with CoEBio3, where his independent research career began. Since 2008 Tim has been a Lecturer, then Senior Lecturer, in Medicinal Chemistry at UCLan where his group's research interests include developing new synthetic methods to biologically important molecules and determining the anticancer and antimicrobial activities of the compounds prepared.

Dana M. Hamad Ameen

Dana grew up in South Kurdistan, Hawler (Erbil). He obtained his BSc in pharmacy from the University of Salahaddin in 2002 and his MSc in medicinal chemistry from Hawler Medical University in 2007, after which he was employed as an assistant lecturer in medicinal chemistry. In 2014, he obtained his PhD in medicinal chemistry from the University of Central Lancashire under the supervision of Dr Tim Snape and he has since returned to his previous university as a lecturer in medicinal chemistry.

product **13** must have been an intermediate of the attempted benzylation reaction (presumably through intermolecular benzoyl transfer under the basic reaction conditions), and that once formed, the dibenzoylated product **13** must undergo an O→C acyl migration to provide the observed product **14** (Scheme 4).[14]



Scheme 4 An unexpected rearrangement during benzylation

Baker confirmed the generality of this new rearrangement by demonstrating success with a variety of related rearrangement precursors (Figure 1): 2′-benzoyloxyacetophenone (**15**), resacetophenone diveratrate (**16**), gallacetophenone tribenzoate (**17**), cinnamoylresacetophenone (**18**) and 2′,4′-dibenzoyloxyphenyl benzyl ketone (**19**), all of which were successful substrates in the rearrangement. The results suggest that the acyl migration only occurs when there is an *ortho*-aryloxy group, since it does not occur in 4′-benzoyloxyresacetophenone (**20**) or in 4′- benzoyloxyacetophenone (**21**).[14]

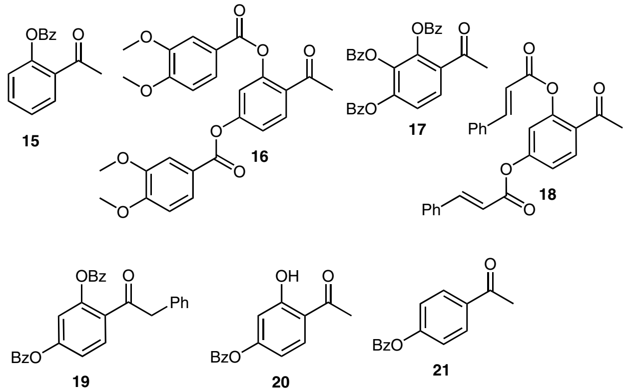


Figure 1 Early generality of the rearrangement

Furthermore, in the same year, continued attempts by Venkataraman et al. to effect the dehydration of 2-acetylnaphthalen-1-yl benzoate (**22**) to 1,4-α-naphthapyrones revealed that the action of sodium amide on an ethereal solution of **22** at room temperature, followed by decomposition of the precipitate with acid, gave the Baker–Venkataraman product, diketone **23**, instead (Figure 2).[17] Incidentally, in the context of naphthalene scaffolds, it has also been shown that the Baker–Venkataraman rearrangement can take place across *peri*-substituted naphthalenes, such as **24**, too.[18]

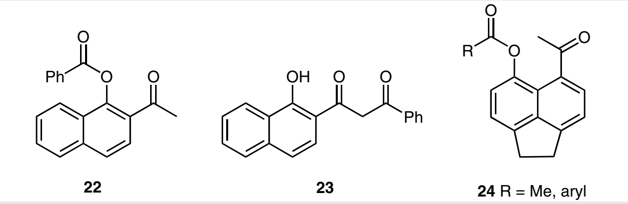
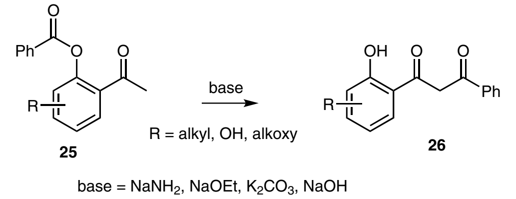


Figure 2 Naphthalene scaffolds

Continuing these early efforts, the rearrangement, by then known as the Baker–Venkataraman rearrangement, was studied and extended by a number of workers.[19–24] The rearrangement of 2′-aroyloxyacetophenones **25** to 2′-hydroxybenzoylmethanes **26** (Scheme 5), in the presence of basic reagents, is typical.[22]



Scheme 5 Typical rearrangement conditions

Whilst the 1,3-diketone products depicted throughout this review generally exist in equilibrium with their enol tautomers, they are represented here as they were depicted in the original publication. The reader should be aware of this equilibrium.

4 Applications: General Routes to Heterocycles

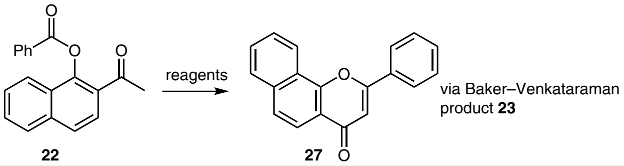
Since this early work, the Baker–Venkataraman rearrangement has become an extremely reliable reaction in organic synthesis allowing for the rapid construction of 1,3-diketones in high yield, and such compounds are known as important synthetic intermediates that are widely used as a route to biologically active heterocycles.

In the context of total synthesis, the rearrangement 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 anthracyclins, anthrapyrans, benzopyrans, chromones, coumarins, flavones, flavanones and xanthones, and applications of each class are outlined below.

4.1 Flavones and Flavanones

The flavone nucleus is an important scaffold used in the preparation of pharmaceutical agents, since both natural and synthetic derivatives are known to be responsible for a large variety of biological and pharmacological activities, including antitumour, anti-inflammatory, antiviral, and antioxidant properties.[25] The presence of hydroxyl groups in the flavone skeleton is important for their capacity to act as antioxidants,[26] as exemplified by quercetin (3,3′,4′,5,7-pentahydroxyflavone), a well-known antioxidant and important compound with wide-ranging biological activities.[27] Another important structural feature of the flavone class 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,[28–30] whilst more recently, it has been reported that certain 3-aroylflavones possess tubulin binding activity as well.[31]

The first application of the Baker–Venkataraman rearrangement towards the synthesis of flavones was by Venkataraman himself, when he attempted the synthesis of α-naphthaflavone **27** from naphthyl derivative **22** (Scheme 6).[17]



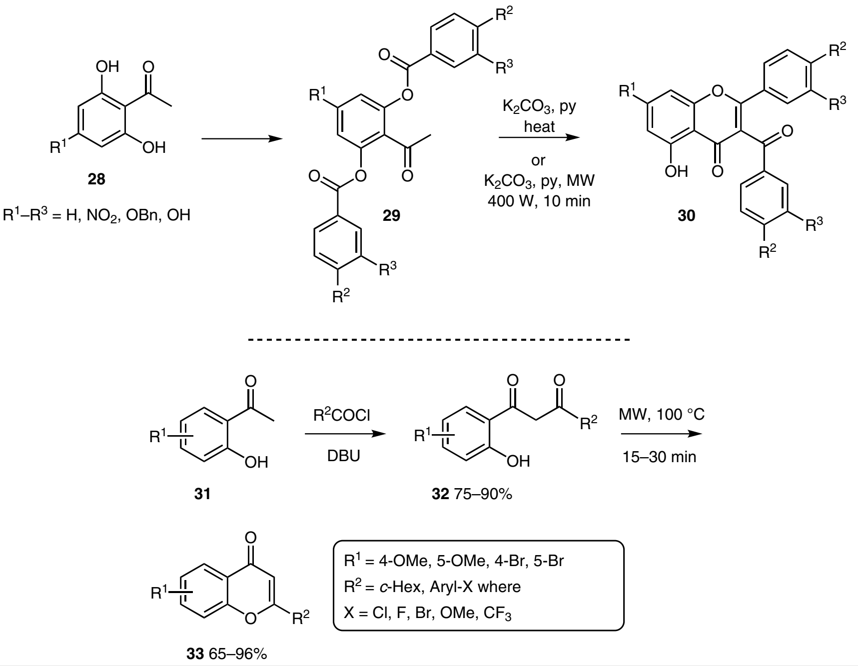
Scheme 6 Synthesis of flavones

Subsequently, a variety of flavones have been synthesized which exploit the rearrangement. For example, nine aroyl-5-hydroxyflavones have been synthesized under a microwave-assisted Baker–Venkataraman transposition (Scheme 7).[32]

In their work, a new and successful method was established wherein microwave irradiation was shown to selectively induce a Baker–Venkataraman rearrangement of 2′,6′-diaroyloxyacetophenones **29** to give the corresponding 3-aroyl-5-hydroxyflavones **30**, in very short reaction times (10 min) and good yields (68–72%). Conversely, under classical thermal conditions these reactions afforded 5-hydroxyflavones **30** only as by-products.[32]

The scope of the reaction 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, exemplified by the rearrangement of 2′,6′-diaroyloxyacetophenones **29** ($R^2 = NO_2$) under their preferred microwave experimental conditions, led to 3-aroyl-5-hydroxyflavones **30** ($R^2 = NO_2$) in good yield.[32]

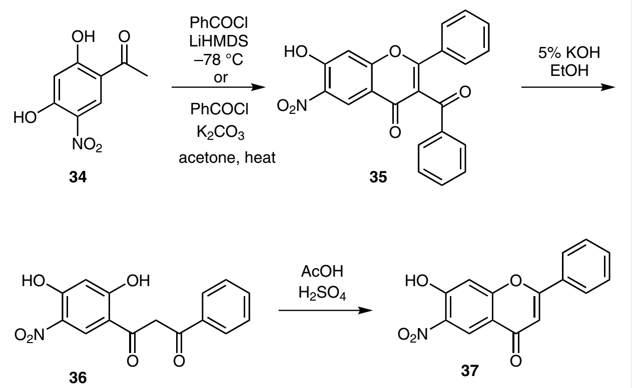
In addition, a practical and economical method has been developed by Brown and co-workers for the synthesis of eleven flavonoid derivatives (compounds **33**) from 2′-hydroxyacetophenones **31** using a modified Baker–Venkataraman rearrangement, followed by microwave-assisted condensation of the diones **32** to close the heterocycle.[33] All of the synthetic flavonoids displayed antifungal activity against *Aspergillus niger* and *Fusarium oxysporium*, and two of the analogues exhibited significant activity against methicillin-resistant *Staphylococcus aureus*.[33]



R^1 = 4-OMe, 5-OMe, 4-Br, 5-Br
R^2 = *c*-Hex, Aryl-X where
X = Cl, F, Br, OMe, CF_3

Scheme 7 The Baker–Venkataraman rearrangement under classical thermal and microwave conditions

It had been observed that the presence of hydroxyl groups at position 5 or 7 is frequently required for satisfactory biological activity to exist,[34,35] whilst the analogous aminoflavones are known tyrosine kinase inhibitors[36] and antimitotic agents.[37] In light of this, interest in the synthesis of flavones bearing both hydroxyl and amino groups began to grow (Scheme 8). For example, the synthesis of flavone **37** by a modified Baker–Venkataraman method was reported.[38] In this process, the 1,3-diketone intermediate **36** was apparently prepared in one step by the reaction of **34** and benzoyl chloride using lithium bis(trimethylsilyl)amide (LiHMDS) as base, at low temperature (–78 °C), but compound **36** was neither isolated nor fully characterised. In an effort to avoid the inconvenient low temperature preparation of the 1,3-diketone, the rearrangement was reinvestigated,[39] and the synthesis of **35** was achieved from 2′,4′-dihydroxy-5′-nitroacetophenone (**34**) using benzoyl chloride in refluxing dry acetone in the presence of anhydrous potassium carbonate (Scheme 8). Under these conditions, yields of the separated compounds, 3-benzoyl-7-hydroxy-6-nitroflavone (**35**) and 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenylpropane-1,3-dione (**36**), were 43% and 13%, respectively.[39]

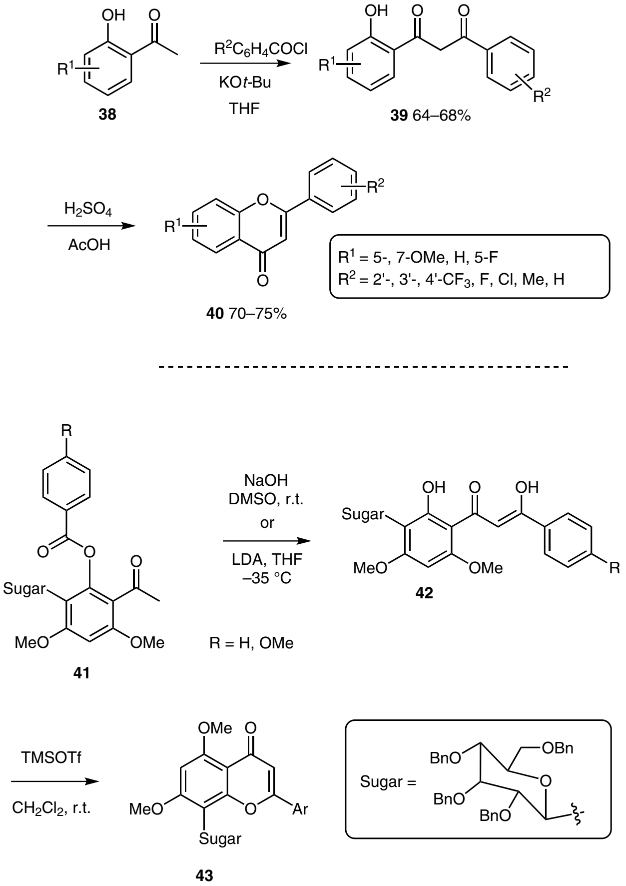


Scheme 8 The Baker–Venkataraman rearrangement applied to the synthesis of aminoflavones

These improved results also demonstrated that the hydroxyl group *para* to the ketone in **34** is not acylated under the selected reaction conditions; this lack of reactivity can be attributed to resonance deactivation caused by the *ortho*-nitro group and *para*-ketone.

In a similar manner, Ares et al. developed a convenient, large-scale preparation of 5-methoxyflavone (**40**; R^1 = 5-OMe, R^2 = H) using potassium *tert*-butoxide, via diketone **39**, as the key step (Scheme 9, top), and the method was successfully applied to the synthesis of a number of further flavone analogues.[40]

During their studies it was found that the conventional Baker–Venkataraman approach[14,17] was not appropriate for synthesising large amounts of their desired products, since low yields and product isolation complications were encountered in both the benzoylation and condensation steps.[40] In addition, the alternate conditions that had been developed for directly converting hydroxyacetophenones into the required diketones (i.e., potassium carbonate,[41] organolithium reagents,[42,43] or phase-transfer catalysis[44]) proved to be ineffective or impractical for large-scale use. Therefore, a convenient large-scale preparation of 5-methoxyflavone (**40**; R^1 = 5-OMe, R^2 = H) was developed using a further set of conditions (KO*t*-Bu, THF, reflux) in the key step.[40]



Scheme 9 Alkoxy- and C-glycoside-derived flavones

The developed method was successfully applied to the convenient synthesis of a number of flavone analogues, substituted on either aromatic ring, as well as flavones substituted on both rings. The conditions have also been successfully combined with a phenolic alkylation step, thereby providing a short and efficient means of transforming dihydroxyacetophenones into alkoxyflavones.[40]

Despite the utility of all the known conditions for the one-step acylation and rearrangement process, the overall isolated yields tend to be slightly lower than those of the conventional Baker–Venkataraman sequence (i.e., separate acylation and migration steps); nevertheless, the method is practically simple, scalable, quick and efficient.[40]

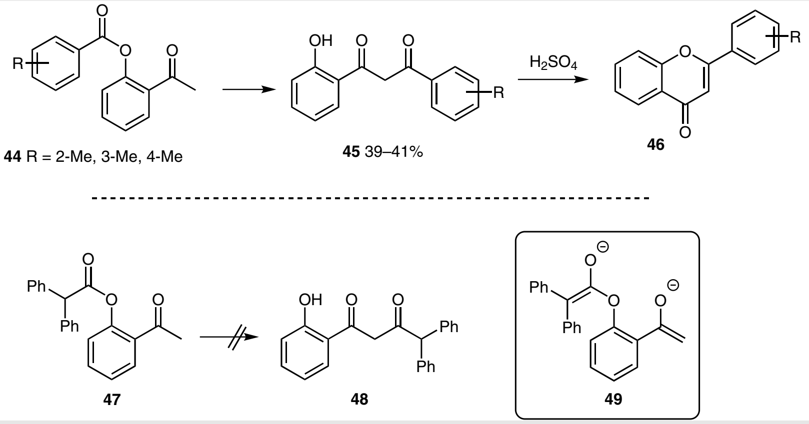
Despite such precedent, until the reaction had been firmly established, there were scant reports of the Baker–Venkataraman rearrangement used on complex molecules. Nevertheless, the O-benzoyl ester of C-glycoside **41** (R = H) was observed to undergo the rearrangement to 1,3-dicarbonyl compound **42**, a product which was formed as a keto–enol mixture in 48% yield (Scheme 9, bottom).[45] Treatment of the **42** with trimethylsilyl triflate, at room temperature in dichloromethane, then yielded the desired C-glycoside flavone **43**.

This approach was extended slightly when it was shown that the *p*-anisoyl ester **41** (R = OMe) could also rearrange when treated with lithium diisopropylamide in tetrahydrofuran at –35 °C (Scheme 9).[45]

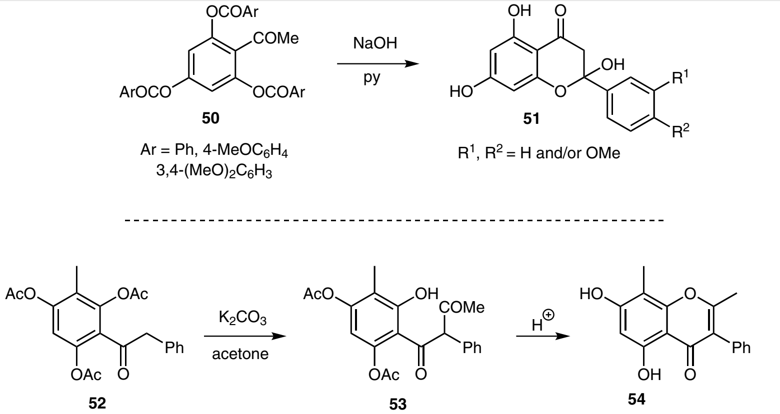
For a number of decades (1930s–1950s), the exact conditions required for a successful Baker–Venkataraman rearrangement to take place and form flavones (**44**→**46**) were investigated by numerous authors (Scheme 10).[46] Ultimately, it was found that, on the substrates studied, sodium ethoxide in benzene was the best solvent and reagent combination for this reaction. However, from a mechanistic point of view at least, it was also demonstrated that the rearrangement failed in the case of ester **47**. Presumably, owing to the availability of an additional acidic proton in this substrate, a competing enolate (i.e., **49**) can be formed upon reaction with base, therefore, once formed, the enolate derived from the methyl ketone will not attack the enolate of the α,α-diphenyl ester due to charge repulsion. In addition, the α,α-diphenyl ester is large and may be too sterically hindered to react.

The Baker–Venkataraman rearrangement has also been used as a key step in the synthesis of trihydroxyflavanones **51**[47] as well as isoflavones **54**[48] (Scheme 11).

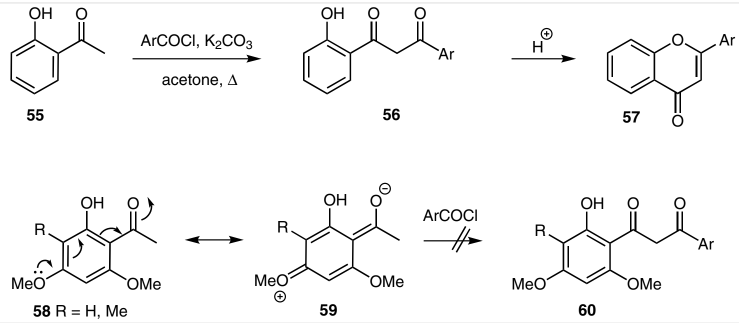
Other examples of the Baker–Venkataraman rearrangement, that offer the rearranged 1,3-diketone products directly from the acetophenone starting material, are those published by Seshadri and Gupta in 1957. In their work, 2′-hydroxyacetophenone (**55**) and aroyl chlorides were heated to reflux in acetone containing anhydrous potassium carbonate, to give the dibenzoylmethane products **56** directly. These were subsequently cyclized to flavones **57** in good yields (Scheme 12).[49] However, this simplified procedure was reported to have its limitations, whereby 2′-hydroxy-4′,6′-dimethoxyacetophenone (**58**, R = H) and 2′-hydroxy-3′-methyl-4′,6′-dimethoxyacetophenone (**58**, R = Me) failed to undergo conversion into the corresponding dibenzoyl-



Scheme 10 Limitations of the early Baker–Venkataraman rearrangement



Scheme 11 The synthesis of trihydroxyflavanones (**51**) and isoflavones (**54**)



Scheme 12 Deactivated substrates

methanes **60** (Scheme 12).[44] The lack of reactivity of these acetophenones was attributed to the resonance effect of the methoxy groups deactivating the ketone to enolate formation (**58**↔**59**), an effect which has been reported on similar substrates in the mechanisticallyrelated Truce–Smiles rearrangement.[50]

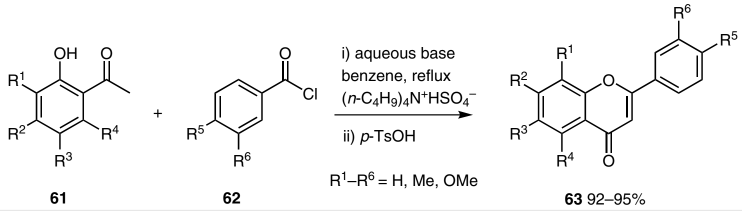
Later, research published in 1982 by Makrandi and coworkers presented a related process which was able to overcome the limitation above, in which an extremely facile one-step procedure was developed. They found that, when the 2′-hydroxyacetophenone starting materials **61**, containing either methoxy or methyl groups at various positions, were subjected to reaction with an aroyl chloride **62** and either aqueous potassium carbonate or potassium hydroxide solution, in benzene, under phase-transfer-catalysis conditions (*n*-tetrabutylammonium hydrogen sulfate), the reaction resulted in the formation of the corresponding dibenzoylmethanes in near quantitative yields.[44] The benzene solution, upon treatment with *p*-toluenesulfonic acid, then afforded cyclized flavones **63** in excellent yields (Scheme 13). The method was of general applicability, and even 2′-hydroxy-4′,6′-dimethoxyacetophenones and 2′-hydroxy-3′-methyl-4′,6′-dimethyoxyacetophenones **58** were found to undergo smooth conversion under these amended conditions.[44]

With their newly developed conditions, the authors were able to use this modified Baker–Venkataraman rearrangement to synthesize a variety of hydroxyflavones too.[51]

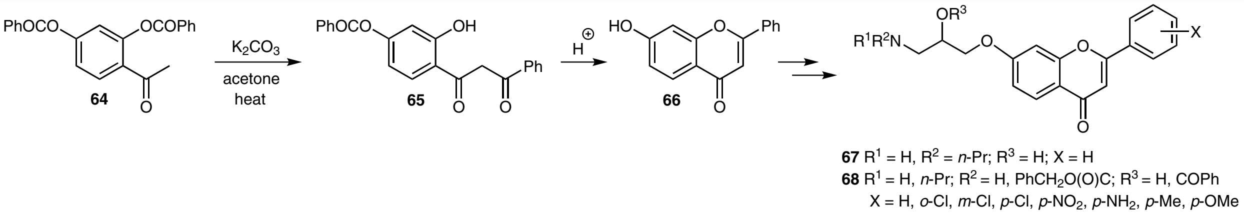
Finally, in an approach towards the synthesis of a novel class of antihypertensive agents with catecholamine-depleting properties [e.g., flavodilol (**67**) and its analogues **68**], Wu et al. demonstrated that the modified Seshadri protocol[49] (potassium carbonate in refluxing acetone) could offer the key diketone intermediate **65** directly, which, following cyclization, afforded the desired 7-hydroxyflavone **66** in good yield (85%), ready for further manipulation to **67** and **68** (Scheme 14).[41]

4.2 Xanthones

Xanthones are a particular class of oxygenated heterocycle that occur widely as secondary metabolites in some higher plant families, such as gentianaceae, guttiferae, fungi and lichens.[52] These natural derivatives are found with



Scheme 13 Phase-transfer-catalyzed rearrangements



Scheme 14 Synthesis of a novel class of antihypertensive agent

varying substitution patterns around the carbon skeleton, with methoxy, hydroxyl and glycosyl groups being the most frequently occurring.[53,54]

The pharmacological properties of both natural and synthetic xanthone derivatives have been reported extensively in the literature, reflecting the growing interest in this class of compound.[55] These properties include antiallergic,[56] antifungal,[57] anti-inflammatory,[58] antimalarial,[59] and antitumor activities,[60] as well as antioxidant behavior,[61] and there are currently two formulations of oxygenated and prenylated xanthones on the market being used as antioxidants.[62] The aromatic character and the presence of hydroxyl groups and/or catechol moieties at certain positions of the xanthone core appear to be crucial requirements for strong antioxidant activity to exist.[58]

Investigations by Silva and co-workers led to an extension of the substrate scope of the Baker–Venkataraman rearrangement to include precursors that contain α,β-unsaturated esters. The authors demonstrated an efficient and general route towards the synthesis of hydroxylated 2,3-diarylxanthones **73**, in which the key intermediate of this synthesis (3-bromo-2-styrylchromone **72**), is obtained via a Baker–Venkataraman rearrangement of the appropriate 2′-cinnamoyloxyacetophenone **70** (Scheme 15).[63] The key step consisted of a cinnamoyl group transposition from the phenyl 2-position to the acetyl group's methyl carbon (**70**→**71**). The reaction was performed by treatment of **70** with potassium hydroxide in dimethylsulfoxide to afford 5-aryl-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-ones **71** in good yields (73–95%); products **71** were then cyclized into the desired 3-bromo-2-styrylchromones **72** (53–67%). After two more steps, the hydroxylated 2,3-diarylxanthones **73** were obtained in good yields (70–94%).[63]

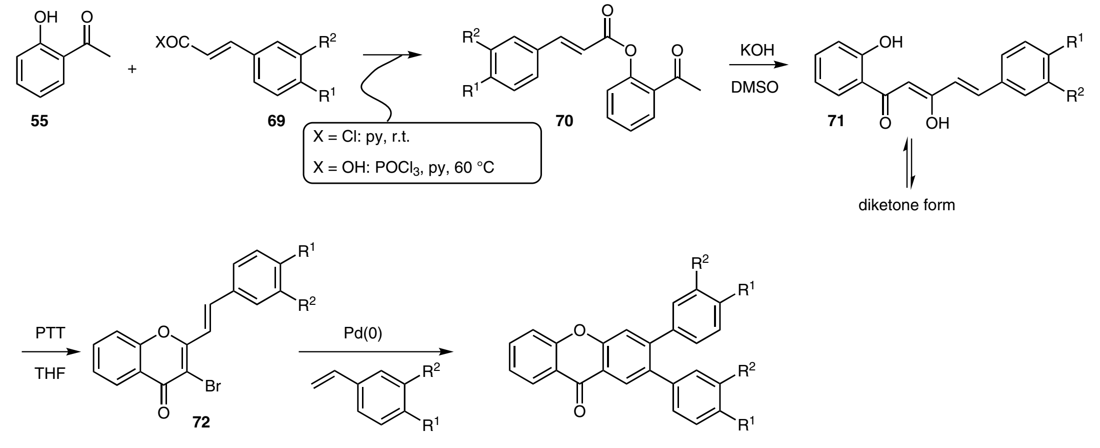
4.3 Chromones

Chromones are one of the most abundant classes of naturally occurring oxygen heterocycles,[64] and they are found in a wide variety of synthetic products as well. 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,[64] anticancer,[65–67] anticardiovascular,[68] and anti-inflammatory activities.[69] Some of the more successful candidates are also marketed as drugs.[70]

Their interest in the synthesis of biologically active compounds with heterocyclic skeletons, especially polyhydroxy-2-styrylchromones, led Pinto et al. to develop a simple and successful research program that was aimed at the synthesis of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **75** (Scheme 16).[71]

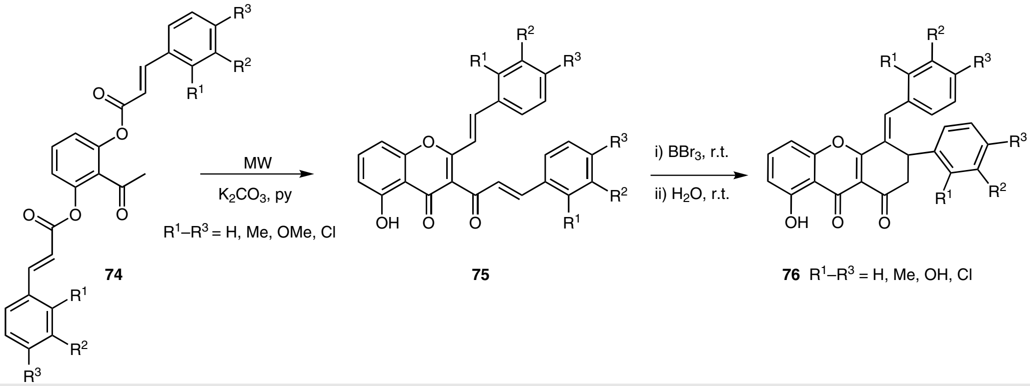
During their research, in efforts to both utilize inexpensive reagents and create shorter reaction times, they applied a two-step approach, namely, double esterification of the appropriate 2,6-dihydroxyacetophenone with cinnamoyl chloride derivatives, followed by the Baker–Venkataraman rearrangement of the resulting (2*E*,2′*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylate)s **74** in 86% yield.[72] In the event, great improvements in the yield of the rearrangement were achieved when microwave irradiation (400 W) was used (Scheme 16),[32] whilst the notable beneficial effects of using microwave irradiation also saw the shortening of the reaction time from 1 hour to 17 minutes.

Other work in this area includes Nishinaga and co-workers successfully achieving the synthesis of ten different chromone derivatives through a process involving a Baker–Venkataraman rearrangement followed by cyclization promoted by a metal complex.[73] In their approach, the



PTT = phenyltrimethylammonium tribromide

Scheme 15 The synthesis of xanthones



Scheme 16 The synthesis of chromones

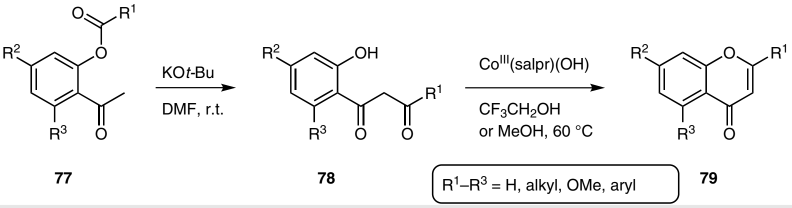
rearrangement products **78** were prepared conveniently by the potassium *tert*-butoxide induced Baker–Venkataraman rearrangement of 2′-acyloxyacetophenones **77** in *N*,*N*-dimethylformamide at room temperature in good yields (54–89%). The 1-(2-hydroxyaryl)-1,3-diketones **78** were subsequently cyclized in methanol, or trifluoroethanol, containing a cobalt(salen) complex [Co^{III}(salpr)(OH)][74] at 60 °C, to offer the chromones **79** in 70–100% yields (Scheme 17).[73]

Other chromones, less widely occurring in nature, also exhibit important biological activities. For example, 2-styrylchromones have shown potent in vitro cytotoxicity against human leukaemia cells.[75,76] Prior to the isolation of these natural 2-styrylchromones, studies had been carried out on numerous structurally related synthetic analogues that also showed promising antitumor and antiallergic activities.[77] Moreover, it was demonstrated by Desideri et al. that certain synthetic derivatives are inhibitors of replication of the human anti-rhinovirus,[78] while other authors have found that 3′-allyl-5,7,4′-trimethoxy-2-styrylchromone inhibits oxidative phosphorylation,[79] and that hydroxy-substituted 2-styrylchromones also act as potent xanthine oxidase inhibitors.[80]

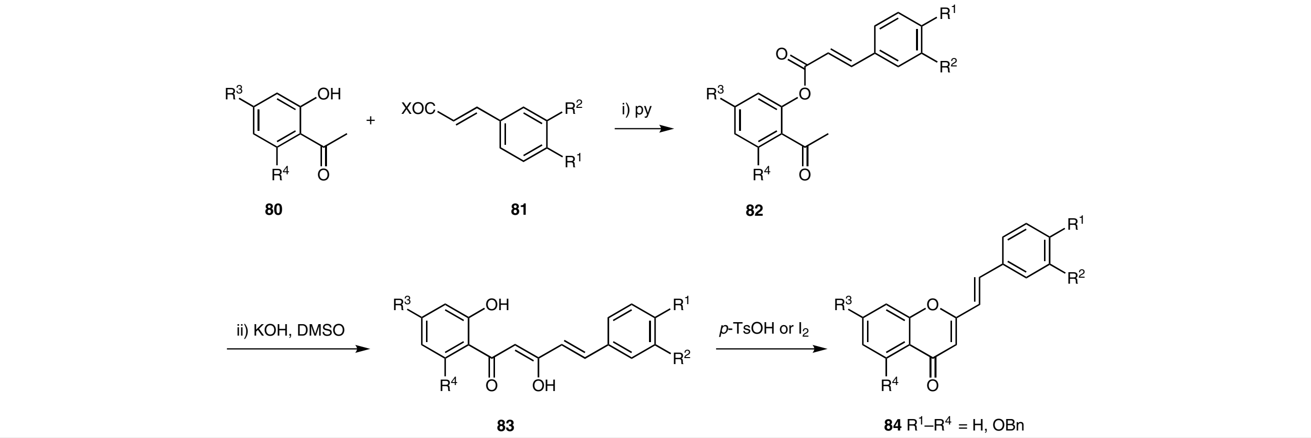
Based on these precedents, Silva and co-workers prepared several hydroxy-2-styrylchromone derivatives **84** by the Baker–Venkataraman method,[81] in which the transformation of compounds **82** into 5-aryl-3-hydroxy-1-(2-hydroxyaryl)penta-2,4-dien-1-ones **83** was carried out by treatment with an excess of potassium hydroxide in dimethylsulfoxide (Scheme 18). Compound **83** was subjected to cyclodehydration to offer the corresponding benzyloxy-substituted 2-styrylchromones **84**, whilst subsequent debenzylation of **84** was achieved by treatment with a solution of hydrogen bromide in acetic acid at reflux, to give the corresponding hydroxy-substituted 2-styrylchromones in moderate yields.

Similar rearrangements to those shown in Schemes 17 and 18 have also been carried out under solvent-free conditions, where the authors employed a solid-phase grinding of reagents to accomplish the Baker–Venkataraman reaction.[82]

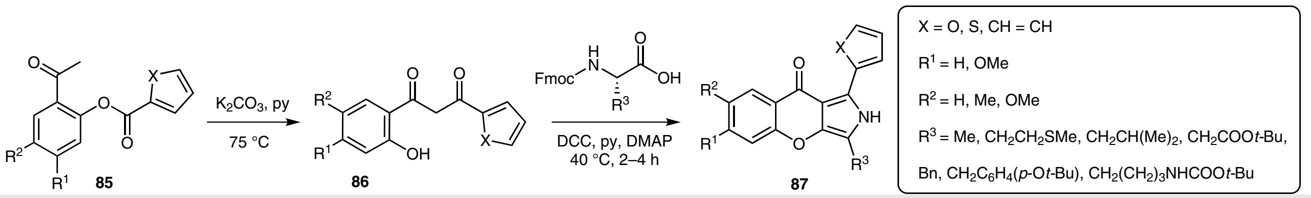
Further applications of the Baker–Venkataraman rearrangement in the formation of chromones include examples that combine oxidative or acidic catalytic cyclization,[81,83,84] conditions which have been exploited by Bu and co-workers (Scheme 19).[85] For example, in their search for potent anticancer molecules, these researchers developed an efficient one-pot synthesis of multifunctionalized chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **87**.[85] Their process realizes the synthesis of 1,3-diaryl-1,3-diketones **86** from aromatic esters **85** via a Baker–Venkataraman rearrangement (K_2CO_3 in pyridine at 75 °C), in good yields (70–83%).[85] The β-diketone intermediates **86** were esterified with various protected amino acids (lysine, aspartic acid, alanine, leucine, phenylalanine, tyrosine, and methionine) to offer the final products, 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones **87**, in 44–89% yields, a sequence which involves a second Baker–Venkataraman rearrangement (Scheme 20).[85] Under these conditions the method was successful in increasing the substrate diversity of the Baker–Venkataraman rearrangement towards this valued product class.



Scheme 17 The synthesis of chromone derivatives



Scheme 18 Hydroxy-substituted 2-styrylchromone derivatives

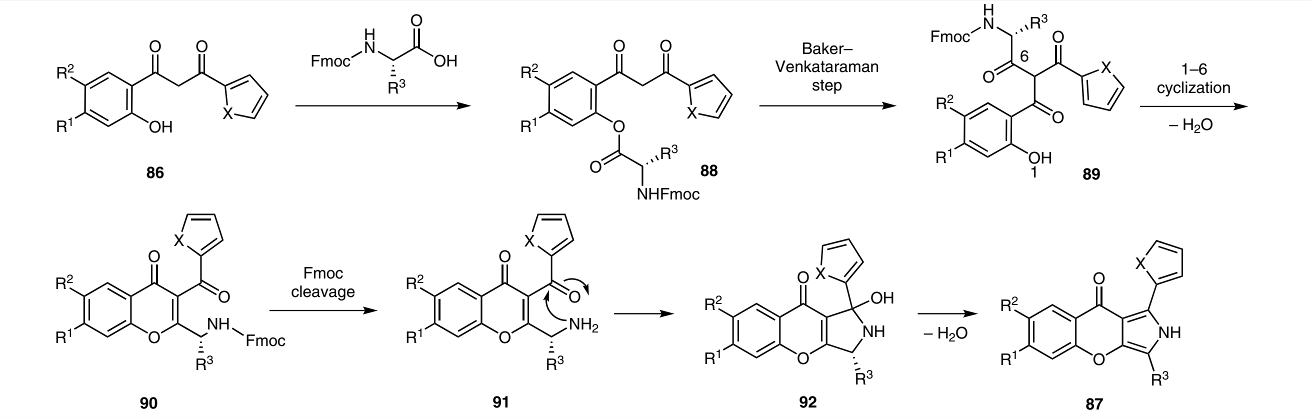


Scheme 19 A heterocyclic Baker–Venkataraman rearrangement

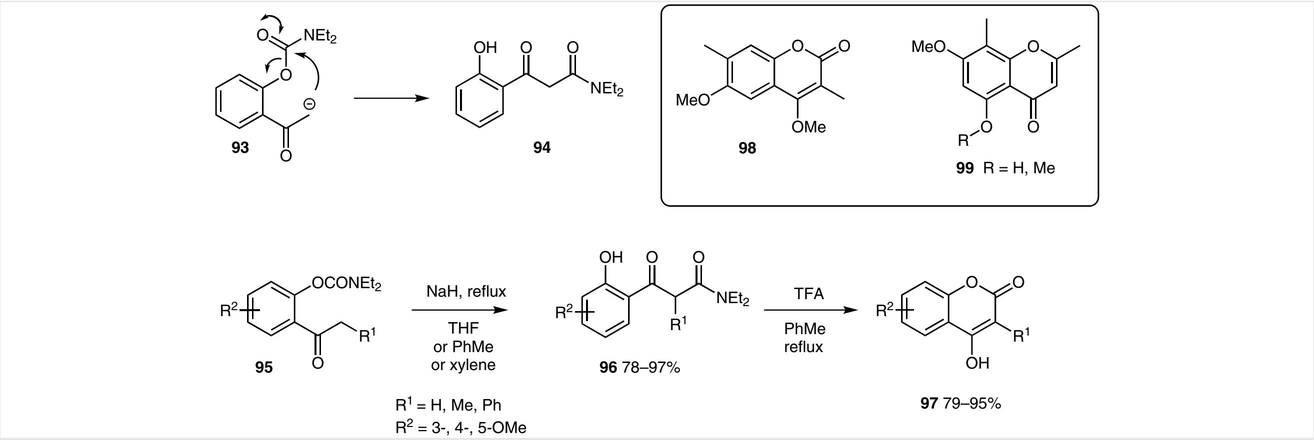
The proposed mechanism for the formation of **87** from **86** involves two steps, one of which is a second Baker–Venkataraman rearrangement (Scheme 20). Firstly, a 4-dimethylaminopyridine-catalyzed Baker–Venkataraman rearrangement occurs immediately after the esterification of **86** with the amino acid, giving the chromone intermediate **90**. Secondly, the 9-fluorenylmethyloxycarbonyl (Fmoc) group is removed by 4-dimethylaminopyridine under the same conditions.[86] The liberated amino group of **91** then undergoes intramolecular attack of the proximal carbonyl which is followed by elimination to afford the final products **87**.[85]

4.4 Coumarins

Coumarin (2*H*-1-benzopyran-2-one) is a plant-derived natural product that possesses an assortment of pharmacological activities, including anti-inflammatory,[87] antifungal,[88] antimicrobial[89] and anti-HIV activities.[90] Furthermore, examples of isolated naturally occurring coumarins (specifically, dicoumarol and umbelliferone) are well known for their anticoagulant properties.[91] Given their importance, Snieckus and co-workers documented a novel and general method for the synthesis of substituted 4-hy-



Scheme 20 A sequential Baker–Venkataraman rearrangement on rearrangement product **86**



Scheme 21 The synthesis of coumarins and isoeugenetin methyl ether (**99**)

droxycoumarins **97** (10 derivatives in 79–95% overall yields) using his carbamoyl variant of the Baker–Venkataraman rearrangement (Scheme 21).[92]

This was the first major variant of the Baker–Venkataraman rearrangement and was reported in 1998.[92] In it, *ortho*-acyl arylcarbamates **93** are rapidly and efficiently converted into substituted 4-hydroxycoumarins **97**, a large and highly diverse class of natural products that exhibits a broad spectrum of biological activity.[93–95] Furthermore, the authors demonstrated the application of this carbamoyl Baker–Venkataraman strategy to the construction of a putative coumarin natural product and provided its structural revision.[92]

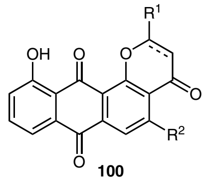
In their prototype study of the Baker–Venkataraman rearrangement on **93** (Scheme 21), an exploration of conditions gave varying results (LDA, THF, 0 °C: complex mixture; LDA, toluene, r.t.: 54% yield; $BrMgN(i\text{-}Pr)_2$, toluene, r.t. to 70 °C: 62% yield; K_2CO_3, 18-crown-6, toluene, reflux: no reaction). However, sodium hydride was found to be effective in several solvents, such that 2.5 equivalents of sodium hydride in tetrahydrofuran, toluene or xylene (at 0.2 M) at reflux for approximately two hours were the optimal conditions to afford 2-hydroxyarylacetamide **94** in high yield, and whose subsequent conversion into **97** was effected smoothly with trifluoroacetic acid (3 equiv) in refluxing toluene at 0.25 M concentration.[92]

The absence of side products in this carbamoyl migration reaction, even at relatively high (0.2 M) concentrations, suggests that, as demonstrated in the ester Baker–Venkataraman equivalent,[96] an intramolecular mechanism is taking place. For this reason, this route is regarded as a convenient, efficient approach to 4-hydroxycoumarins **97** that has particular preparative advantages in that 3-aryl- or 3-alkyl-substituted coumarins are obtained directly.[92]

Using this strategy, the authors further demonstrated the total synthesis of 4,6-dimethoxy-3,7-dimethylcoumarin (**98**), the putative natural product isolated from *Colchicum decaisnei*, and isoeugenetin methyl ether (**99**, R = Me), a synthetic derivative of isoeugenetin (**99**, R = H), isolated from *Eugenia carvophyllata*, as well as a variety of the coumarins exemplified by the general structure **97** (Scheme 21).[97]

4.5 Anthrapyran and Anthracyclin Antibiotics

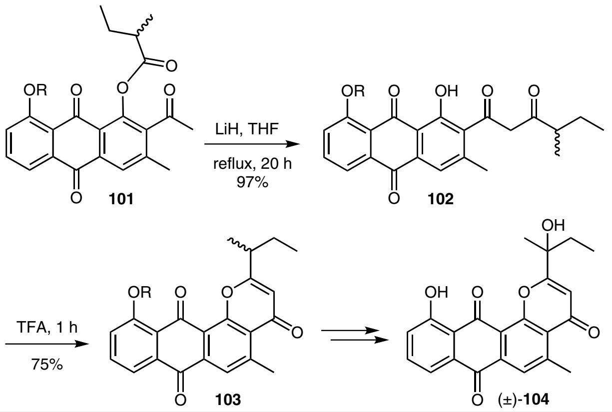
Indomycinones[98] (Figure 3) belong to the anthrapyran antibiotic family and occur mainly as their C-glycosides (e.g., pluramycines, hedamycines, riboflavines, altromycines and indomycines).[99,100] Due to their selective binding to DNA and their specific alkylation of guanine,[101,102] they have been the focus of renewed interest in the context of structural biology.[103] Additionally, a number of aglycones with the anthra[*b*]pyran nucleus have also been found in nature. For example, β-indomycinone [**100**, $R^1 = C(OH)(Me)C_4H_7$, $R^2 = Me$][104] and δ-indomycinone [**100**, $R^1 = C(OH)(Me)C_4H_9O$, $R^2 = Me$][104] have a six-carbon side chain at C-2, while γ-indomycinone [**100**, $R^1 = C(OH)(Me)C_2H_5$, $R^2 = Me$],[98] kidamycinone [**100**, $R^1 = C(Me){=}CHMe$, $R^2 = Me$],[105] the anti-hepatitic antibiotic AH-1763 IIa [**100**, $R^1 = CH(Me)C_3H_7$, $R^2 = Me$], and the neuroprotective espicufolin [**100**, $R^1 = CH(Me)C_2H_5$, $R^2 = Et$] have a four-carbon side chain.[106] Recently, several researchers have attempted the synthesis of espicufolin [**100**, $R^1 = CH(Me)C_2H_5$, $R^2 = CH_2OH$],[107,108] kidamycinone,[109] and AH-1763 IIa,[106] and this remarkable interest is attributed to their potent biological properties.



R^1 = alkyl, alkenyl
R^2 = Me, CH_2OH

Figure 3 The synthesis of anthrapyran antibiotics

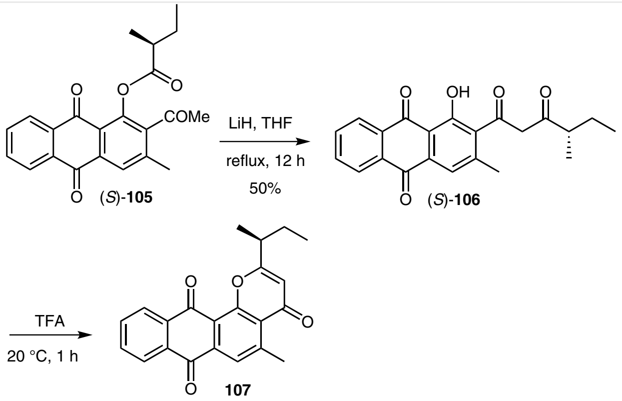
In one approach by Krohn et al. towards the synthesis of (±)-γ-indomycinones, the Baker–Venkataraman rearrangement was employed as a chain-elongation strategy to avoid the often necessary reduction and/or oxidation steps connected with the typically utilised organometallic reactions on the anthraquinone skeleton to achieve this transformation.[110,111] The key Baker–Venkataraman rearrangement was induced by heating ester **101** at reflux in tetrahydrofuran with lithium hydride to offer the β-diketo anthraquinone **102** in 97% yield (Scheme 22).[106] Acid-catalyzed cyclization to anthrapyranone **103** gave the carbon skeleton of the target compound (±)-**104**, the total synthesis of which was achieved following further minor elaboration. A similar protocol was used to prepare the corresponding 11-methyl ether of γ-indomycinone **104** as well.[106]



Scheme 22 The synthesis of (±)-γ-indomycinone

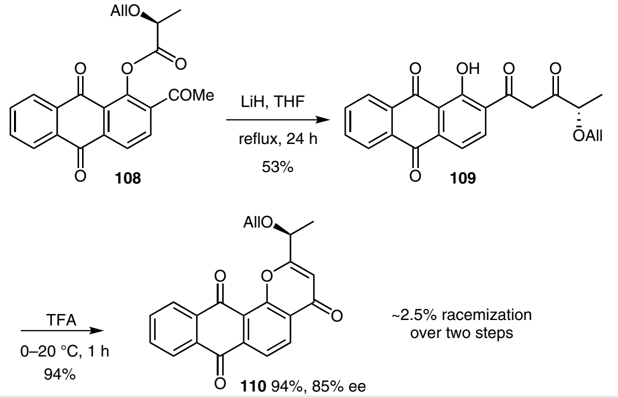
In addition, the Baker–Venkataraman reaction has been widely employed in the synthesis of a large group of anthrapyran antibiotics.[105,110,112] Similarly, the synthesis of aromatic-polyketide-derived natural products and the biomimetic-type synthesis of anthracyclines[113] and angucyclines[114] includes the construction of β-diketo side chains on an aromatic or quinoid nucleus.[115] In efforts to produce such β-diketo products, Krohn et al. attempted an enantioselective acyl-transfer reaction with α-oxygenated esters under Baker–Venkataraman conditions (Scheme 23).[111]

In their efforts to achieve this, the base-catalyzed Baker–Venkataraman rearrangement of (*S*)-2-acetyl-1-hydroxyanthraquinone ester **105** proceeded, with virtually no racemization, to the β-diketo anthraquinone product (*S*)-**106** (50%). The subsequent cyclization step offered the enantiomerically enriched (>97% ee) anthra[1,2-*b*]pyran **107**, a close derivative of the neuroprotective compound espicufolin (**100**; Figure 3), in quantitative yield.



Scheme 23 An enantiomerically enriched Baker–Venkataraman rearrangement

In a related manner, the same reaction procedure was applied to transform enantiomerically pure *O*-allyl lactic ester **108** into anthrapyranone **110** by way of ketide **109** (Scheme 24). The Baker–Venkataraman rearrangement of ester **108** afforded a 53% yield of (β-diketo)alkyl-substituted anthraquinone **109** and the cyclization of phenol **109** to 2-allyloxy-substituted anthrapyranone **110** was excellent (94% yield), since no cleavage and no isomerization of the allyl protecting group was observed.[111] This model reaction opened the way to synthesize the enantiomerically pure 10-hydroxyanthrapyranone moiety of the indomycinones, rubiflavinones **111**, pluramycines **112**, or hedamycines **113** (Figure 4).[100]



Scheme 24 The Baker–Venkataraman rearrangement of an *O*-allyl lactic ester to a ketide

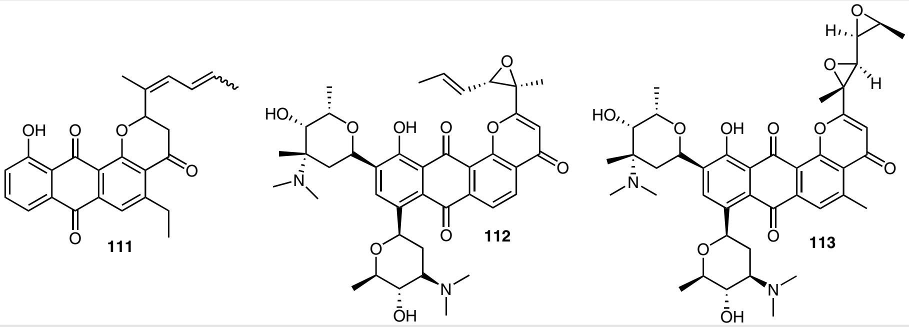
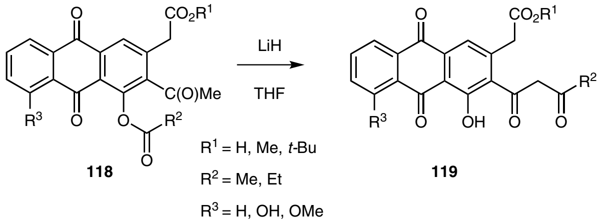


Figure 4 Enantiomerically pure 10-hydroxyanthrapyranones

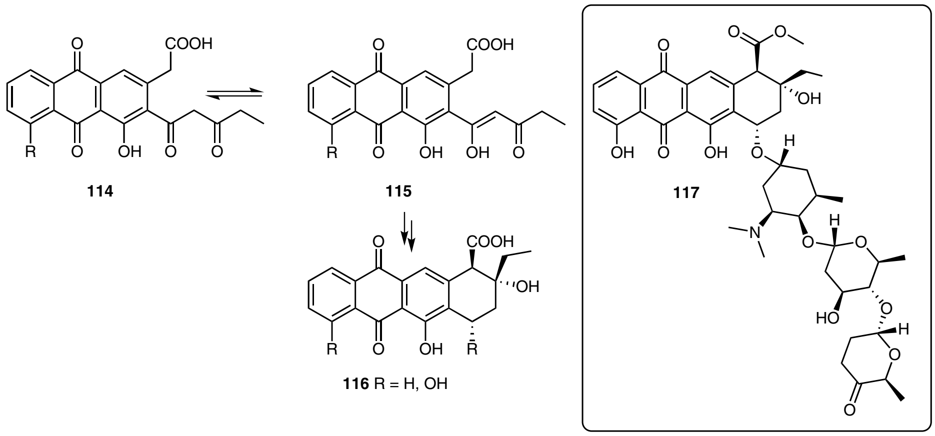
Aklanonic acid **114** (which exists in equilibrium with the enol form **115** when R = OH) and its derivatives are starting materials of great interest in studies concerning the microbial conversion of the antitumor agent aclacinomycin A (**117**), since they are suitable precursors for the preparation of the anthracycline scaffold **116** (Scheme 25).[116]

Studies on their synthesis by Krohn et al. began with a Baker–Venkataraman rearrangement (lithium hydride in tetrahydrofuran) on anthraquinones **118**, thus providing a flexible and general method for the introduction of ketide side chains on these substrates to produce derivatives **119** in high yield (Scheme 26).[113]

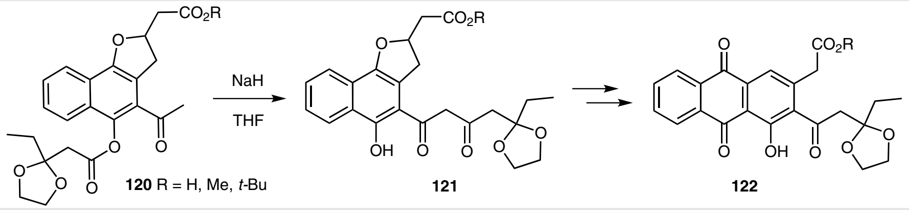


Scheme 26 Introduction of ketide side chains on anthraquinones

Moreover, in a similar manner, the attachment of different oligoketide side chains to the naphthoquinone nucleus have been carried out by Krohn and Schafer.[117] In such cases, and after a number of trials, they proved that the Baker–Venkataraman rearrangement of ester **120** was the best protocol for side-chain elongation (Scheme 27). Sodium hydride in tetrahydrofuran was found to give the best results for the transformation of **120** into the rearranged product **121** (66% yield); the corresponding naphthoquinone precursors **121** were then successfully treated with base to initiate a cascade to yield the 4-deoxyaklanonic acids **122**.



Scheme 25 Aklanonic acid derivatives



120 R = H, Me, *t*-Bu

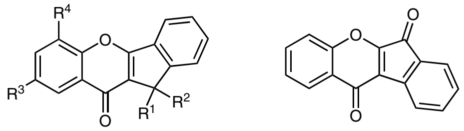
121

122

Scheme 27 Side-chain elongation

4.6 Benzopyrans

Benz[*b*]indeno[2,1-*e*]pyran-10,11-diones **123**–**125** (Figure 5) 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.[118] 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) and Ruchirawat and Thasana showed that this effect was due to wrightiadione (**126**),[119] a rare and unusual oxygen heterocycle.[120] This finding, and the reported interesting biological activity of diones **123**–**125**, motivated the authors to undertake a study of the synthesis of these compounds.[121]



123 $R^1 = R^2 = O$, $R^3 = R^4 = Me$
124 $R^1 = OH$, $R^2 = H$, $R^3 = R^4 = Me$
125 $R^1 = R^2 = O$, $R^3 = R^4 = H$

126

Figure 5 Synthesis of benzopyrans

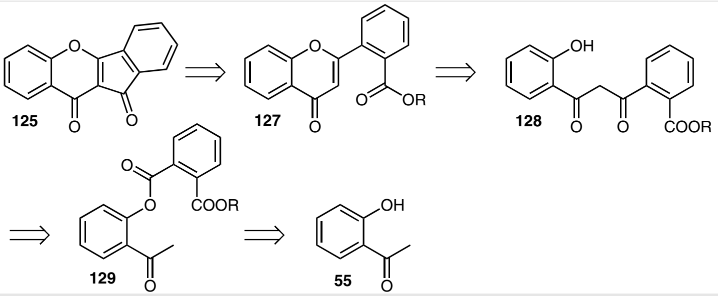
In their efforts to develop an operationally simple, highly efficient reaction for the synthesis of diones **123**–**125**, the authors envisaged that benz[*b*]indeno[2,1-*e*]pyran-10,11-dione **125** (isowrightiadione) could be obtained via the route highlighted by the retrosynthetic analysis in Scheme 28. It was expected that flavone **127** could be obtained by application of the Baker–Venkataraman rearrangement (**129**→**128**) followed by cyclization,[40,83,122–125] whilst further cyclization would lead directly to the required compounds **125**.[121]

In the investigation of this route as a practical method to prepare this class of compound, the acylation of 2-hydroxyacetophenone (**55**) with mono-methyl phthalate (**130**), using a Steglich esterification procedure, gave **131** in 68% yield (Scheme 29). The intramolecular Baker–Venkataraman acylation of **131** was successfully achieved with potassium hydroxide in pyridine, under reflux for 30 minutes, to give the desired 1,3-diketone **132**. Acidification of a solution of **132**/**133** then led to the precipitation of the desired product **125** in 72% yield.[121]

The elucidated structure of the recrystallized product was not the expected flavone **127** (R = Me, Scheme 28), but instead the final target compound **125**. The authors rationalized that the mechanism for the formation of **125** could involve diketone **132** intramolecularly cyclizing to afford the 1,3-indanedione **134**. Subsequently, the formed hemiketal **135** could dehydrate to give the obtained product **125** as shown in Scheme 29.[121]

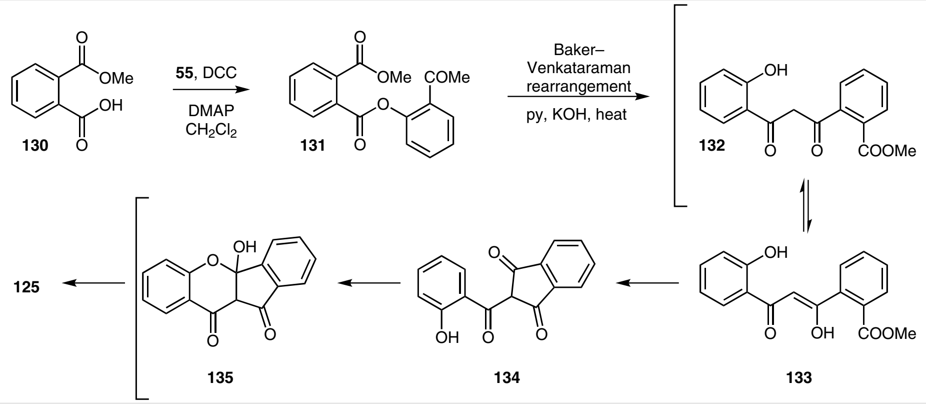
5 The Retro-Baker–Venkataraman Rearrangement

In 1979, Donnelly and Maloney reported that when reacted with base, 2-bromo-1,3-diketone **136** formed 2,3-diphenylchromone epoxide **139**,[126] a transformation that suggested an intermediate such as the conjugate base **138**.

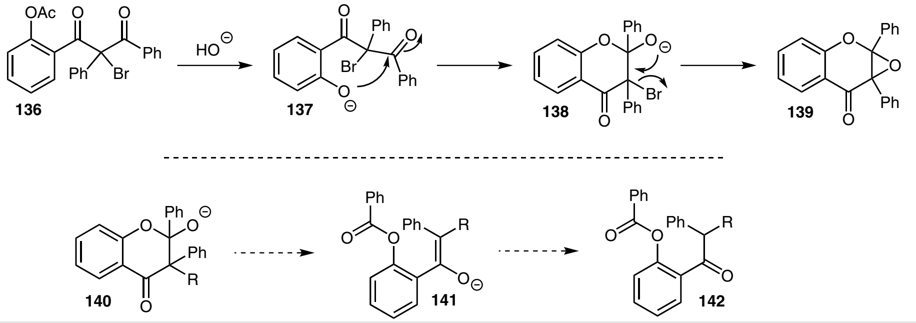


125 **127** **128** **129** **55**

Scheme 28 Retrosynthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones



Scheme 29 Rearrangement of a mono-methyl phthalate derivative

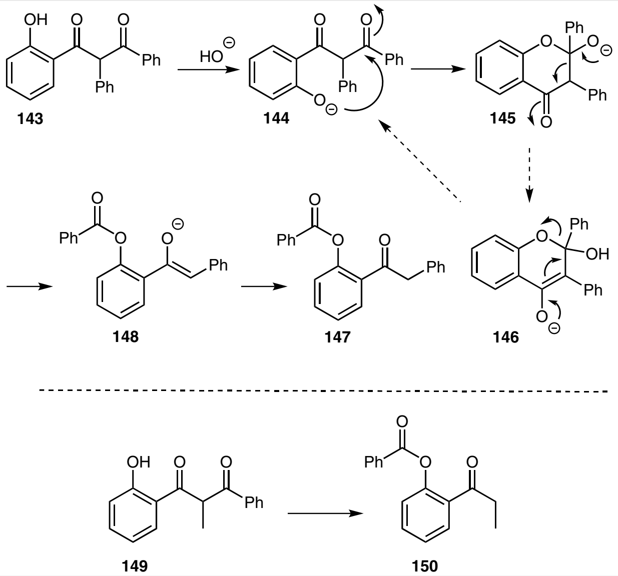


Scheme 30 A proposed retro-Baker–Venkataraman rearrangement

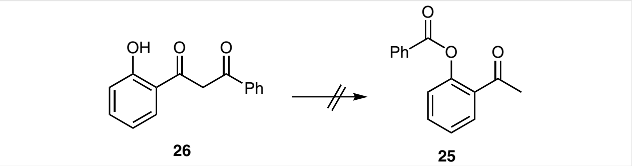
However, this also suggested that in the absence of a suitable leaving group (e.g., the bromide ion in **138**) fragmentation may occur to offer 2′-aroyloxyacetophenone **142** (Scheme 30).[126]

With this in mind, the unbrominated analogue **143** was treated with potassium carbonate at 0 °C in chloroform to afford the deoxybenzoin ester **147**, via a retro-Baker–Venkataraman rearrangement (Scheme 31, top).[127] When the 2-phenyl substituent of the 1,3-diketone **143** was exchanged for a methyl group (i.e., **149**; Scheme 31, bottom), a retro-Baker–Venkataraman rearrangement also occurred, though much more slowly. Heating at reflux under the same reaction conditions for several days gave 2′-benzoyloxypropiophenone (**150**) in 54% yield, whilst treatment of the 1,3-diketone **149** with potassium hydroxide at room temperature afforded the decomposed products, 2′-hydroxypropiophenone and propiophenone.[127]

Moreover, different conditions failed to force diketone **26** to undergo the reverse rearrangement (Scheme 32). It was thus concluded that the rate of retro-Baker–Venkataraman rearrangement depends on the 2-substituent of the 1,3-diketone. A rapid decrease in rate is seen, such that the order of reactivity is Ph > Me > H.[127]

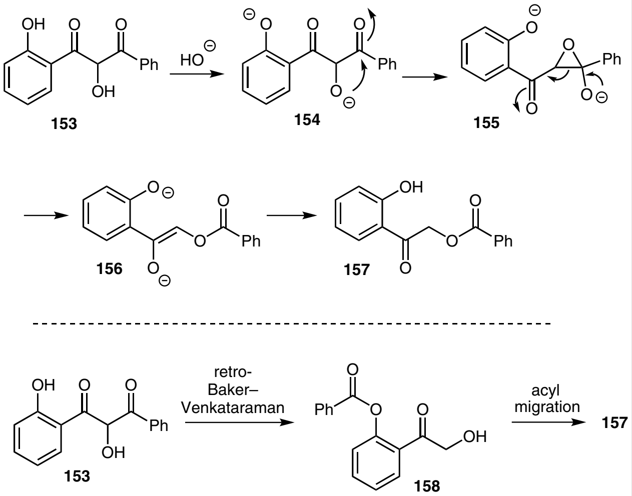


Scheme 31 The retro-Baker–Venkataraman rearrangement



Scheme 32 A limitation of the retro reaction

Occupying the 2-position of a propane-1,3-dione with a hydroxyl group, as in **153**, led to retro-Baker–Venkataraman failure, at least in terms of the isolation of the retro-product. Instead, an alternative ester-forming transformation was demonstrated. For example, reaction of 2-hydroxy-1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (**153**) with potassium carbonate offered 2-benzoyloxy-2′-hydroxyacetophenone (**157**), and the mechanism proposed is shown in Scheme 33 (top).[127] Nevertheless, although not considered originally, we suggest that the retro-transformation **153**→**158** could occur, but that the aromatic ester produced (**158**) is subsequently attacked (i.e., $O_{aryl} \rightarrow O_{alkyl}$ acyl transfer) to give the observed product **157** (Scheme 33, bottom).



Scheme 33 An unexpected rearrangement on a 2-hydroxypropane-1,3-dione derivative

6 Summary and Outlook

As we hope has become evident from this review, the introduction to the chemical community in 1910 of a general thermal rearrangement of aromatic acyl groups from oxygen to carbon to generate the corresponding 1,3-dicarbonyl compounds has provided an important set of synthetic routes to aromatic heterocycles and other products. The rearrangement has enjoyed extensive application in both academic and industrial environments, and it provides general routes to the preparation of new medicines and other molecules of biological interest. Only a couple of examples of an enantiospecific Baker–Venkataraman rearrangement are known, and these simply employ enantiopure rearrangement precursors which undergo little or no racemization during the rearrangement. However, an enantioselective Baker–Venkataraman rearrangement is yet to be developed, presumably because of the ready racemization of the resulting 1,3-dicarbonyl products of the reaction. As such, there is scope for preparing enantiomerically pure 1,3-dicarbonyl-bearing quaternary centres using this reaction. With the importance that is imparted to carbon–carbon bond-forming reactions, the Baker–Venkataraman rearrangement could see an upsurge in its use and development and thus feature more heavily in synthesis in the future.

Acknowledgment

The authors thank Hawler Medical University, Kurdistan, Iraq for financial support (to D.A.).

References

(1) Reese, C. B.; Trentham, D. R. *Tetrahedron Lett.* **1965**, 2467.
(2) Cockman, S.; Joll, C.; Mortimer, B.; Redgrave, T.; Stick, R. *Aust. J. Chem.* **1990**, *43*, 2093.
(3) March-Cortijos, A.; Snape, T. J. *Org. Biomol. Chem.* **2009**, *7*, 5163.
(4) Zamir, L. O.; Balachandran, S.; Zheng, Y. F.; Nedea, M. E.; Caron, G.; Nikolakakis, A.; Vishwakarma, R. A.; Sauriol, F.; Mamer, O. *Tetrahedron* **1997**, *53*, 15991.
(5) Skwarczynski, M.; Kiso, Y. *Curr. Med. Chem.* **2007**, *14*, 2813.
(6) Skwarczynski, M.; Sohma, Y.; Kimura, M.; Hayashi, Y.; Kimura, T.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4441.
(7) Hamada, Y.; Matusumoto, H.; Kimura, T.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2727.
(8) Victory, P.; Borrell, J. I.; Batllori, X.; Teixidó, J.; Civit, P.; Alvarez-Larena, A. *Chem. Lett.* **1993**, 705.
(9) Ha, K.; Chahar, M.; Monbaliu, J.-C. M.; Todadze, E.; Hansen, F. K.; Oliferenko, A. A.; Ocampo, C. E.; Leino, D.; Lillicotch, A.; Stevens, C. V.; Katritzky, A. R. *J. Org. Chem.* **2012**, *77*, 2637.
(10) Harwood, L. M. *Oxford Chemistry Primers: Polar Rearrangements*; Oxford University Press: Oxford, **1992**.
(11) Kells, K. W.; Ncube, A.; Chong, J. M. *Tetrahedron* **2004**, *60*, 2247.
(12) Auwers, K. *Chem. Ber.* **1910**, *43*, 2192.
(13) Mahal, H. S.; Venkataraman, K. *Curr. Sci.* **1933**, *2*, 214.
(14) Baker, W. *J. Chem. Soc.* **1933**, 1381.
(15) Wheeler, T. S. *Org. Synth.* **1952**, *32*, 72.
(16) Dahlbom, R.; Smith, B.; Sillén, L. G. *Acta Chem. Scand.* **1949**, *3*, 247.
(17) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1933**, 1767.
(18) Mezheritskii, V. V.; Pikus, A. L.; Tregub, N. G. *Zh. Org. Khim.* **1991**, *27*, 2198.
(19) Anand, N.; Patel, D. M.; Venkataraman, K. *Proc. Indian Acad. Sci., Sect. A* **1948**, *28*, 545.
(20) Baker, W. *J. Chem. Soc.* **1939**, 956.
(21) Doyle, B. G.; Gogan, F.; Gowan, J. E.; Keane, J.; Wheeler, T. S. *Sci. Proc. R. Dublin Soc.* **1948**, *24*, 291.
(22) Gulati, K. C.; Venkataraman, K. *J. Chem. Soc.* **1936**, 267.
(23) Horri, *J. Pharm. Soc. Jpn.* **1940**, 81.
(24) Appel, H.; Baker, W.; Hagenbach, H.; Robinson, R. *J. Chem. Soc.* **1937**, 738.

(25) Middleton, E.; Kandaswami, C.; Theoharides, T. C. *Pharmacol. Rev.* **2000**, *52*, 673.
(26) Packer, L. *Handbook of Antioxidants*; Marcel Dekker: New York, **1996**.
(27) Rice-Evans, C. A.; Packer, L. *Flavonoids in Health and Disease*, 2nd ed.; CRC Press/Marcel-Dekker: New York, **1998**.
(28) Rao, K. V.; Chattopadhyay, S. K.; Reddy, G. C. *J. Agric. Food Chem.* **1990**, *38*, 1427.
(29) Örner, M. W.; Jha, H. C. *Pestic. Sci.* **1993**, *38*, 347.
(30) Silva, A. M. S.; Weidenbörner, M.; Cavaleiro, J. A. S. *Mycol. Res.* **1998**, *102*, 638.
(31) Quintin, J.; Roullier, C.; Thoret, S.; Lewin, G. *Tetrahedron* **2006**, *62*, 4038.
(32) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett* **2007**, 1897.
(33) Abdel Ghani, S. B.; Weaver, L.; Zidan, Z. H.; Ali, H. M.; Keevil, C. W.; Brown, R. C. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 518.
(34) Cushman, M.; Zhu, H.; Geahlen, R. L.; Kraker, A. J. *J. Med. Chem.* **1994**, *37*, 3353.
(35) Bois, F.; Beney, C.; Boumendjel, A.; Mariotte, A.-M.; Conseil, G.; Di Pietro, A. *J. Med. Chem.* **1998**, *41*, 4161.
(36) Boumendjel, A.; Bois, F.; Beney, C.; Mariotte, A.-M.; Conseil, G.; Di Pietro, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 75.
(37) Akama, T.; Ishida, H.; Kimura, U.; Gomi, K.; Saito, H. *J. Med. Chem.* **1998**, *41*, 2056.
(38) Costantino, L.; Rastelli, G.; Gamberini, M. C.; Vinson, J. A.; Bose, P.; Iannone, A.; Staffieri, M.; Antolini, L.; Del Corso, A.; Mura, U.; Albasini, A. *J. Med. Chem.* **1999**, *42*, 1881.
(39) Tang, L.; Zhang, S.; Yang, J.; Gao, W.; Cui, J.; Zhuang, T. *Molecules* **2004**, *9*, 842.
(40) Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.; Geiger, J. C. *J. Org. Chem.* **1993**, *58*, 7903.
(41) Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Dailey, M. A.; Doring, K. G.; Fedorchuk, M.; Loch, J. T.; Thomas, T. L.; Blosser, J. C. *J. Med. Chem.* **1989**, *32*, 183.
(42) Banerji, A.; Goomer, N. C. *Synthesis* **1980**, 1980, 874.
(43) Cushman, M.; Nagarathnam, D. *Tetrahedron Lett.* **1990**, *31*, 6497.
(44) Jain, P. K.; Makrandi, J. K.; Grover, S. K. *Synthesis* **1982**, 221.
(45) Mahling, J.-A.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann.* **1995**, 461.
(46) Cramer, F.; Elschnig, G. H. *Chem. Ber.* **1956**, *89*, 1.
(47) Hauteville, M.; Chadenson, M.; Chopin, M. J. *C. R. Acad. Sci. Paris, Ser. C* **1974**, *278*, 471.
(48) Rahman, W.; Nasim, K. T. *J. Org. Chem.* **1962**, *27*, 4215.
(49) Gupta, V. N.; Seshadri, T. R. *J. Sci. Ind. Res., Sect. B* **1957**, *16*, 116.
(50) Snape, T. *Synlett* **2008**, 2689.
(51) Saxena, S.; Makrandi, J.; Grover, S. *Synthesis* **1985**, 697.
(52) Gales, L.; Damas, A. M. *Curr. Med. Chem.* **2005**, *12*, 2499.
(53) Vieira, L. M. M.; Kijjoa, A. *Curr. Med. Chem.* **2005**, *12*, 2413.
(54) Roberts, J. C. *Chem. Rev.* **1961**, *61*, 591.
(55) Pinto, M.; Sousa, M.; Nascimento, M. *Curr. Med. Chem.* **2005**, *12*, 2517.
(56) Pfister, J. R.; Ferraresi, R. W.; Harrison, I. T.; Rooks, W. H.; Fried, J. H. *J. Med. Chem.* **1978**, *21*, 669.
(57) Habsah, M.; Amran, M.; Mackeen, M. M.; Lajis, N. H.; Kikuzaki, H.; Nakatani, N.; Rahman, A. A.; Ghafar, ; Ali, A. M. *J. Ethnopharmacol.* **2000**, *72*, 403.
(58) Park, K. H.; Park, Y.-D.; Han, J.-M.; Im, K.-R.; Lee, B. W.; Jeong, I. Y.; Jeong, T.-S.; Lee, W. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5580.
(59) Riscoe, M.; Kelly, J. X.; Winter, R. *Curr. Med. Chem.* **2005**, *12*, 2539.
(60) Zhang, H.-Z.; Kasibhatla, S.; Wang, Y.; Herich, J.; Guastella, J.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem.* **2004**, *12*, 309.
(61) Merza, J.; Aumond, M.-C.; Rondeau, D.; Dumontet, V.; Le Ray, A.-M.; Séraphin, D.; Richomme, P. *Phytochemistry* **2004**, *65*, 2915.
(62) Núñez Sellés, A. J.; Vélez Castro, H. T.; Agüero-Agüero, J.; González-González, J.; Naddeo, F.; De Simone, F.; Rastrelli, L. *J. Agric. Food Chem.* **2002**, *50*, 762.
(63) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett* **2007**, 3113.
(64) *Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; Wiley: New York, **1977**.
(65) Recanatini, M.; Bisi, A.; Cavalli, A.; Belluti, F.; Gobbi, S.; Rampa, A.; Valenti, P.; Palzer, M.; Palusczak, A.; Hartmann, R. W. *J. Med. Chem.* **2001**, *44*, 672.
(66) Gobbi, S.; Rampa, A.; Bisi, A.; Belluti, F.; Valenti, P.; Caputo, A.; Zampiron, A.; Carrara, M. *J. Med. Chem.* **2002**, *45*, 4931.
(67) Palmer, B. D.; Henare, K.; Woon, S.-T.; Sutherland, R.; Reddy, C.; Wang, L.-C. S.; Kieda, C.; Ching, L.-M. *J. Med. Chem.* **2007**, *50*, 3757.
(68) Matin, A.; Gavande, N.; Kim, M. S.; Yang, N. X.; Salam, N. K.; Hanrahan, J. R.; Roubin, R. H.; Hibbs, D. E. *J. Med. Chem.* **2009**, *52*, 6835.
(69) Carvalho, J. C. T.; Ferreira, L. P.; da Silva Santos, L.; Corrêa, M. J. C.; de Oliveira Campos, L. M.; Bastos, J. K.; Sarti, S. J. *J. Ethnopharmacol.* **1999**, *64*, 173.
(70) Manthey, J. A.; Grohmann, K.; Guthrie, N. *Curr. Med. Chem.* **2001**, *8*, 135.
(71) Pinto, D. C. G. A.; Seca, A. M. L.; Leal, S. B.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett* **2011**, 2005.
(72) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *New J. Chem.* **2000**, *24*, 85.
(73) Nishinaga, A.; Ando, H.; Maruyama, K.; Mashino, T. *Synthesis* **1992**, 839.
(74) Nishinaga, A.; Kondo, T.; Matsuura, T. *Chem. Lett.* **1985**, *14*, 905.
(75) Gerwick, W. H.; Lopez, A.; Van Duyne, G. D.; Clardy, J.; Ortiz, W.; Baez, A. *Tetrahedron Lett.* **1986**, *27*, 1979.
(76) Gerwick, W. H. *J. Nat. Prod.* **1989**, *52*, 252.
(77) Brion, J. D.; Le Baut, G.; Zammattio, F.; Pierre, A.; Atassi, G.; Belachmi, L. Eur. Pat. Appl. EP 454587, **1991**; *Chem. Abstr.* **1992**, *116*, 106092k.
(78) Desideri, N.; Conti, C.; Mastromarino, P.; Mastropaolo, F. *Antivir. Chem. Chemother.* **2000**, *11*, 373.
(79) Hatakeyama, M.; Zou, E.; Matsumura, F. *J. Biochem. Mol. Toxicol.* **2002**, *16*, 209.
(80) Fernandes, E.; Carvalho, F.; Silva, A. M. S.; Santos, C. M. M.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; de Lourdes Bastos, M. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 45.
(81) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2003**, 4575.
(82) Sharma, D.; Kumar, S.; Makrandi, J. K. *Green Chem. Lett. Rev.* **2009**, *2*, 53.
(83) Fougerousse, A.; Gonzalez, E.; Brouillard, R. *J. Org. Chem.* **2000**, *65*, 583.
(84) Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M.; Cavaleiro, J. A. S.; Lévai, A.; Patonay, T. *J. Heterocycl. Chem.* **1998**, *35*, 217.
(85) Yu, Y.; Hu, Y.; Shao, W.; Huang, J.; Zuo, Y.; Huo, Y.; An, L.; Du, J.; Bu, X. *Eur. J. Org. Chem.* **2011**, 4551.
(86) Atherton, E.; Logan, C. J.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 538.
(87) Kontogiorgis, C.; Hadjipavlou-Litina, D. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 63.
(88) Mouri, T.; Yano, T.; Kochi, S.; Ando, T.; Hori, M. *J. Pestic. Sci.* **2005**, *30*, 209.
(89) Mutlu, D. A.; Dilek, D. E. *Turk. J. Chem.* **2003**, *27*, 757.

(90) Magiatis, P.; Melliou, E.; Skaltsounis, A.-L.; Mitaku, S.; Léonce, S.; Renard, P.; Pierré, A.; Atassi, G. *J. Nat. Prod.* **1998**, *61*, 982.
(91) Davies, E. G.; Ashton, W. M. *J. Sci. Food Agric.* **1964**, *15*, 733.
(92) Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995.
(93) Gorelik, E. *Cancer Res.* **1987**, *47*, 809.
(94) Wang, S.; Milne, G. W. A.; Yan, X.; Posey, I. J.; Nicklaus, M. C.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1996**, *39*, 2047.
(95) Pauli, R. M. *Anticoagulants*, In *Drug Toxicity in Embryonic Development II, Handbook of Experimental Pharmacology*; Vol. 124 (II); Springer: Berlin, **1997**, 191.
(96) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 90.
(97) Kalinin, A. V.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4999.
(98) Schumacher, R. W.; Davidson, B. S.; Montenegro, D. A.; Bernan, V. S. *J. Nat. Prod.* **1995**, *58*, 613.
(99) Eckardt, K. *Quinones and Other Carbocyclic Antitumor Antibiotics in Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; Vol. II; Aszalos, A., Ed.; CRC Press: Boca Raton, **1981**.
(100) Herz, W.; Kirby, G. W.; Steglich, W.; Tamm, C. H. *Prog. Chem. Org. Nat. Prod.* **1991**, *57*, 71.
(101) Nakatani, K.; Okamoto, A.; Saito, I. *Angew. Chem.* **1999**, *111*, 3581.
(102) Hansen, M.; Hurley, L. *J. Am. Chem. Soc.* **1995**, *117*, 2421.
(103) Hansen, M. R.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *29*, 249.
(104) Brockmann, H. *Angew. Chem. Int. Ed.* **1968**, *7*, 481.
(105) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.
(106) Krohn, K.; Tran-Thien, H. T.; Vitz, J.; Vidal, A. *Eur. J. Org. Chem.* **2007**, 1905.
(107) Uno, H.; Sakamoto, K.; Honda, E.; Ono, N. *Chem. Commun.* **1999**, *22*, 1005.
(108) Uno, H.; Sakamoto, K.; Honda, E.; Fukuhara, K.; Ono, N.; Tanaka, J.; Sakanaka, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 229.
(109) Fei, Z.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617.
(110) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, 209.
(111) Krohn, K.; Vidal, A.; Vitz, J.; Westermann, B.; Abbas, M.; Green, I. *Tetrahedron: Asymmetry* **2006**, *17*, 3051.
(112) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628.
(113) Krohn, K.; Roemer, E.; Top, M. *Liebigs Ann.* **1996**, 271.
(114) Krohn, K.; Böker, N.; Flörke, U.; Freund, C. *J. Org. Chem.* **1997**, *62*, 2350.
(115) Krohn, K. *Eur. J. Org. Chem.* **2002**, 1351.
(116) Oki, T. *Aclacinomycin A*, In *Anthracyclines: Current Status and New Developments*; Crooke, S. T.; Reich, S., Eds.; Academic Press: New York, **1980**, 323.
(117) Krohn, K.; Schafer, G. *Liebigs Ann.* **1996**, 265.
(118) Williams, J. G.; Houck, D. R.; Smith, D. E.; Rathbone, D. L.; Billington, D. C.; Golding, B. T.; Collington, E. W.; Kitchin, J.; Rich, N. US Patent US 5985913 A 19991116, **1999**.
(119) Ruchirawat, S.; Thasana, N. *Synth. Commun.* **2001**, *31*, 1765.
(120) Lin, L.-J.; Topcu, G.; Lotter, H.; Ruangrungsi, N.; Wagner, H.; Pezzuto, J. M.; Cordell, G. A. *Phytochemistry* **1992**, *31*, 4333.
(121) Thasana, N.; Ruchirawat, S. *Tetrahedron Lett.* **2002**, *43*, 4515.
(122) Nagarathnam, D.; Cushman, M. *J. Org. Chem.* **1991**, *56*, 4884.
(123) Prasad, K. J. R.; Periasamy, P. A.; Vijayalakshmi, C. S. *J. Nat. Prod.* **1993**, *56*, 208.
(124) Ares, J. J.; Outt, P. E.; Randall, J. L.; Murray, P. D.; Weisshaar, P. S.; O'Brien, L. M.; Ems, B. L.; Kakodkar, S. V.; Kelm, G. R. *J. Med. Chem.* **1995**, *38*, 4937.
(125) Tanaka, H.; Stohlmeyer, M. M.; Wandless, T. J.; Taylor, L. P. *Tetrahedron Lett.* **2000**, *41*, 9735.
(126) Donnelly, J. A.; Maloney, D. E. *Tetrahedron* **1979**, *35*, 2875.
(127) Claffey, P. J.; Donnelly, J. A.; Maloney, D. E. *Proc. R. Ir. Acad., Sect. B* **1989**, *89*, 119.