Mechanistic and Synthetic Aspects of the Benzilic Acid and Ester Rearrangements

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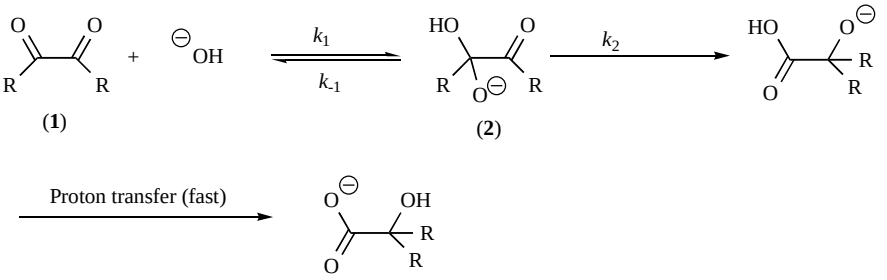
Abstract: Since its discovery the Benzilic acid rearrangement has been the subject of a number of mechanistic studies and successfully employed in key steps in the synthesis of a number of important target molecules. In this review we look at the advances that have been made over the last 20 years in understanding the mechanism of this rearrangement (including the stereochemical aspects), whilst reviewing some important syntheses where this particular rearrangement was used as a key step.

Keywords: Benzilic acid rearrangement, benzilic ester rearrangement, *retro*-benzilic acid rearrangement, [1,2] rearrangement, synthesis.

INTRODUCTION

The benzilic acid rearrangement (BAR) was discovered by Liebig in 1838 [1] and since then both this (hydroxide = nucleophile) and the analogous benzilic ester rearrangement (BER) (alkoxide = nucleophile) have been the subject of several experimental studies over the last 50 years, and to a lesser extent theoretical studies. This 1,2-rearrangement has been extensively reviewed by Selman and Eastham almost 50 years ago [2], and by Gill more than 15 years ago [3] and this review serves to fill the reader in with new developments in this field since this time. Both mechanistic developments and important applications in organic synthesis, particularly towards the synthesis of biologically active compounds, will be considered.



Scheme 1.

THE MECHANISM: STATUS REPORT

The accepted mechanism for the BAR is that shown in Scheme **1**. It is an hydroxide catalysed rearrangement, thought to proceed by reversible addition of a nucleophile such as hydroxide to one of the carbonyl groups to give the intermediate (**2**), followed by a rate determining [1,2] rearrangement (governed by the rate constant k_2) of a formally nucleophilic R group (which can be; H, alkyl, aryl, acyl, aroyl, ester, amide and acid) to the second carbonyl group [2,3]. The mechanism of the BER is similar, only the nucleophile is an alkoxide or an alcohol [2,3].

Bowden and Williams [4] conducted a series of kinetic studies to determine the rate coefficients for a series of 2,2', 3,3' and 4,4'-disubstituted benzils at different temperatures in aqueous DMSO. They observed that the biggest rate coefficients were obtained when electron-withdrawing substituents were present, being highest when the electron-withdrawing group (Cl) was present in the *meta*-position and lowest for an electron-donating group (OMe) in the *ortho*-position. A very similar trend was observed for the enthalpy of activation ($\Delta H^{\ddagger}$) and entropy of activation ($\Delta S^{\ddagger}$). A comparison of the effect of using aqueous DMSO and aqueous dioxane solvent systems on the reaction rate was also undertaken, and it was observed that the former gave the highest rate coefficients. In both cases the presence of water seemed to reduce the reaction rate, as the highest rate coefficients were obtained with only 10% water present. The ability of DMSO to increase the activity of hydroxide was the explanation given. This study also led the authors to propose the existence of the rearrangement transition state depicted in Fig. (**1**), with minor charge delocalisation about the migrating aryl group.

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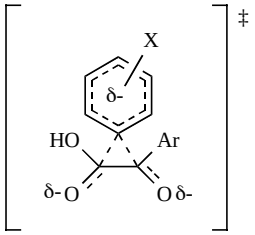


Fig. (1).

A number of decades ago Collins and Neville carried out an elegant experimental study using a radioactive labelled precursor to show that in the case of the hydroxide catalysed BAR of 1,3-diphenylpropan-1,2-dione it was the benzyl group that migrated preferentially [5]. Marques *et al.* [6], recently have shown that certain α-hydroxyketone substrates are readily oxidised *in situ* to intermediate α-diketones that subsequently undergo stereoselective benzilic ester rearrangements affording tertiary α-hydroxy esters (Scheme **2**). The *anti*-diastereomer was the major diastereomer in all cases (see below for full details).

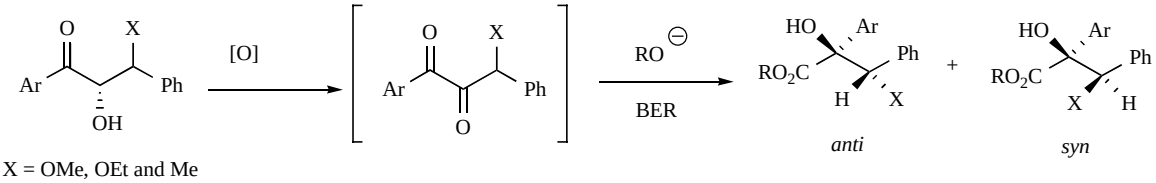
It was of interest to determine which of the carbonyl substituents present in the α-diketone intermediate, the phenyl or the α-methoxybenzyl group, migrated and if there was a preference for just one to migrate. Thus Burke and coworkers [7] carried out a labelling study using 1,3-diphenyl-2(^{13}C)-hydroxy-3-methoxypropan-1-one (**3**) as substrate to give the corresponding ester (**4**) as a mixture of diastereomers in 50% yield (Scheme **3**). Analysis of this mixture of diastereomers by ^{13}C NMR spectroscopy showed conclusively that the ^{13}C label was incorporated into the ester carbonyl function. This conclusively confirmed that it was the α-methoxybenzyl group that exclusively migrated in this BER.

Only a few theoretical studies have been carried out on the BAR over the last 20 years. Of note is the recent DFT study by Yamabe *et al.* [8] that has shed some light on the mechanism of this rearrangement and confirmed some of the previous "allegations" pertaining to this mechanism.

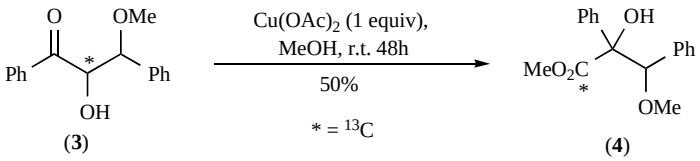
In their study, Yamabe *et al.* investigated the BAR reaction of biacetyl and benzil with hydroxide using DFT at the B3LYP level with 6-31G* as the basis set. They found that in these two cases the rate determining step was the carbanion [1,2] rearrangement, which had the highest ΔE. They claimed that although on the basis of FMO theory this rearrangement was forbidden, it is allowed with α-diketone substrates because it is in fact a 4 + 2 π electron system where the α-diketone substrate has nodeless LUMOs with large lobes.

Several years earlier, Screttas *et al.* [9] suggested that a SET (single electron transfer) mechanism may be operative in the BAR, after studying this rearrangement in benzil and 9,10-phenanthrenoquinone with lithium *tert*-butoxide as nucleophile in THF-benzene, they noticed in the former reaction an intense violet colour appeared and in the latter a brownish red colour, indicating the presence of radical intermediates. An ESR study of the benzil, *tert*-butoxide in THF-benzene solution showed that the semi-dione of benzil was an intermediate. Rajyagura and Rzepa [10], carried out a MNDO SCF-MO study and they claimed that a SET mechanism was a distinct possibility for the benzilic acid and related rearrangements (Scheme **4**, shows the most probable pathways, path a (classical) and paths b and c (SET processes). Their calculations were carried out on glyoxal and phenylglyoxal. In the case of phenylglyoxal (**5**) (Scheme **4**, R = H, R^1 = Ph) it was calculated on the basis of the classical mechanism that the Ph group should migrate preferentially, which is contrary to the experimental evidence [5]. To surmount this difficulty Rajyagura and Rzepa [10] proposed an intramolecular SET mechanism (Scheme **4**, pathway b and c) in which hydrogen migration was preferred over phenyl migration due to the ability of the phenyl group to stabilise the adjacent radical centre in intermediates (**II**) and (**III**) (Scheme **4**, R = Ph). Further studies into the mechanism for this particular system are currently underway in our group.

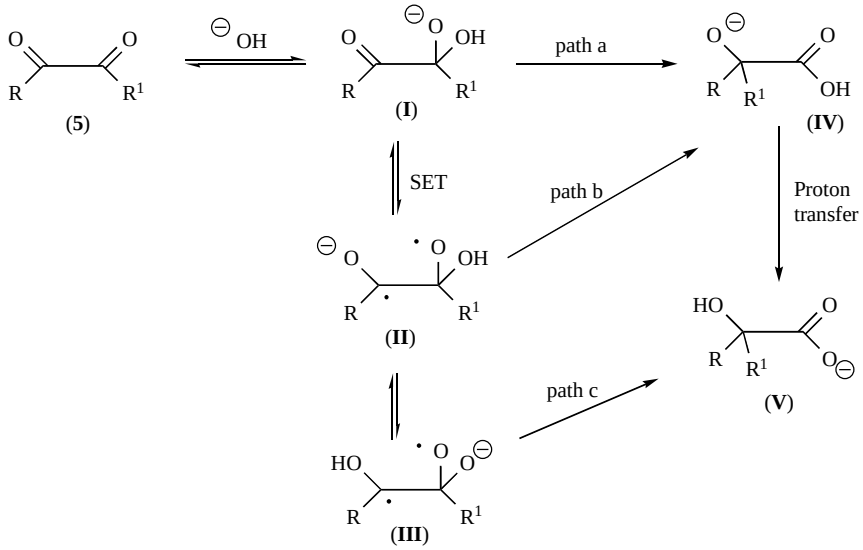
This mechanism (SET) may be an alternative way of explaining the preferential migration of the CH(OMe)Ph group in the reaction recently studied by Marques *et al.* [7] who hypothesised that the α-diketone (**6**) generated from the hydroxyketone (**3**), would selectively be attacked at the harder carbonyl-carbon 2 by the hard methoxide nucleophile (Scheme **5**) on the basis of Pearson's HSAB theory. A theoretical study into the mechanism for this particular system is currently under way.



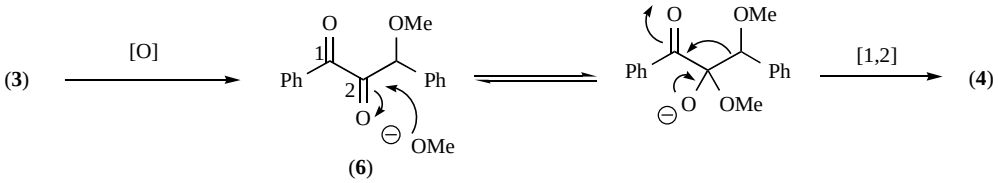
Scheme 2.



Scheme 3.



Scheme 4.



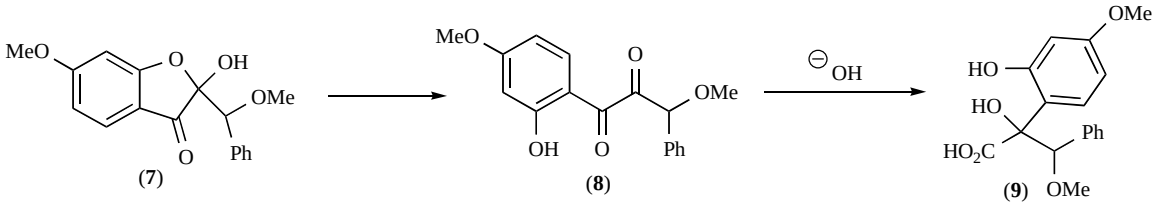
Scheme 5.

Very recently Comisar and Savage reported the very first non-catalysed benzil-benzilic acid rearrangement in high-temperature water (HTW) [11]. This particular medium was chosen owing to the elevated levels of hydroxide present, and its increased solubility for small organic compounds over water at room temperature.

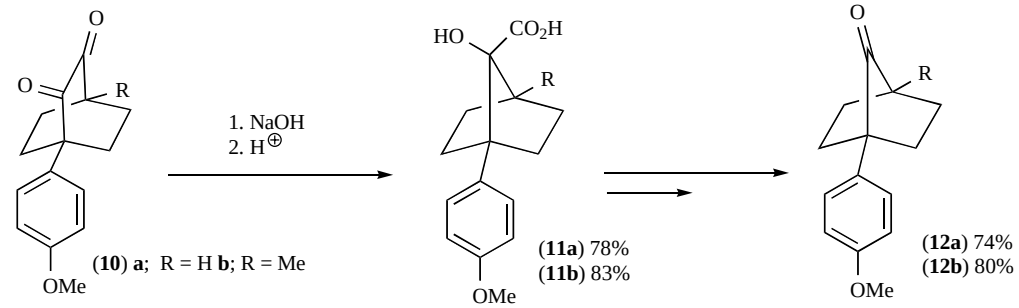
With regards to the stereochemistry of this rearrangement, it was predicted by Deslongchamps [12] that it should occur with stereoelectronic control, and this has already been borne out by experiment (see refs. 6 and 7, and the discussion below).

SYNTHETIC APPLICATIONS OF THE BAR AND BER

In 1989 Brady *et al.* [13] reported the occurrence of a BAR on the α-diketone intermediate (**8**) (resulting from ring-opening of the benzofuranone (**7**)), giving the corresponding glycolic acid product (**9**) as a single diastereomer (Scheme



Scheme 6.

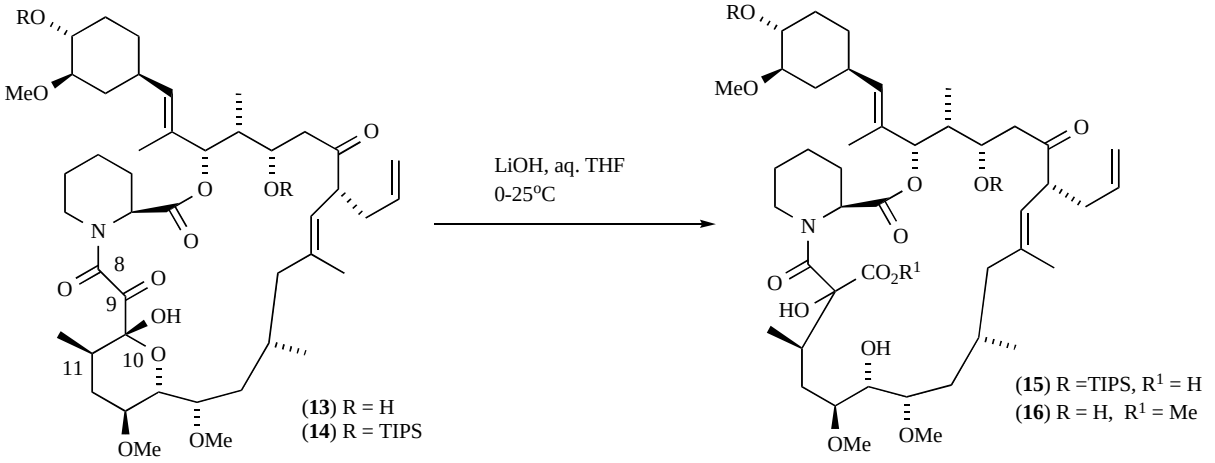


Scheme 7.

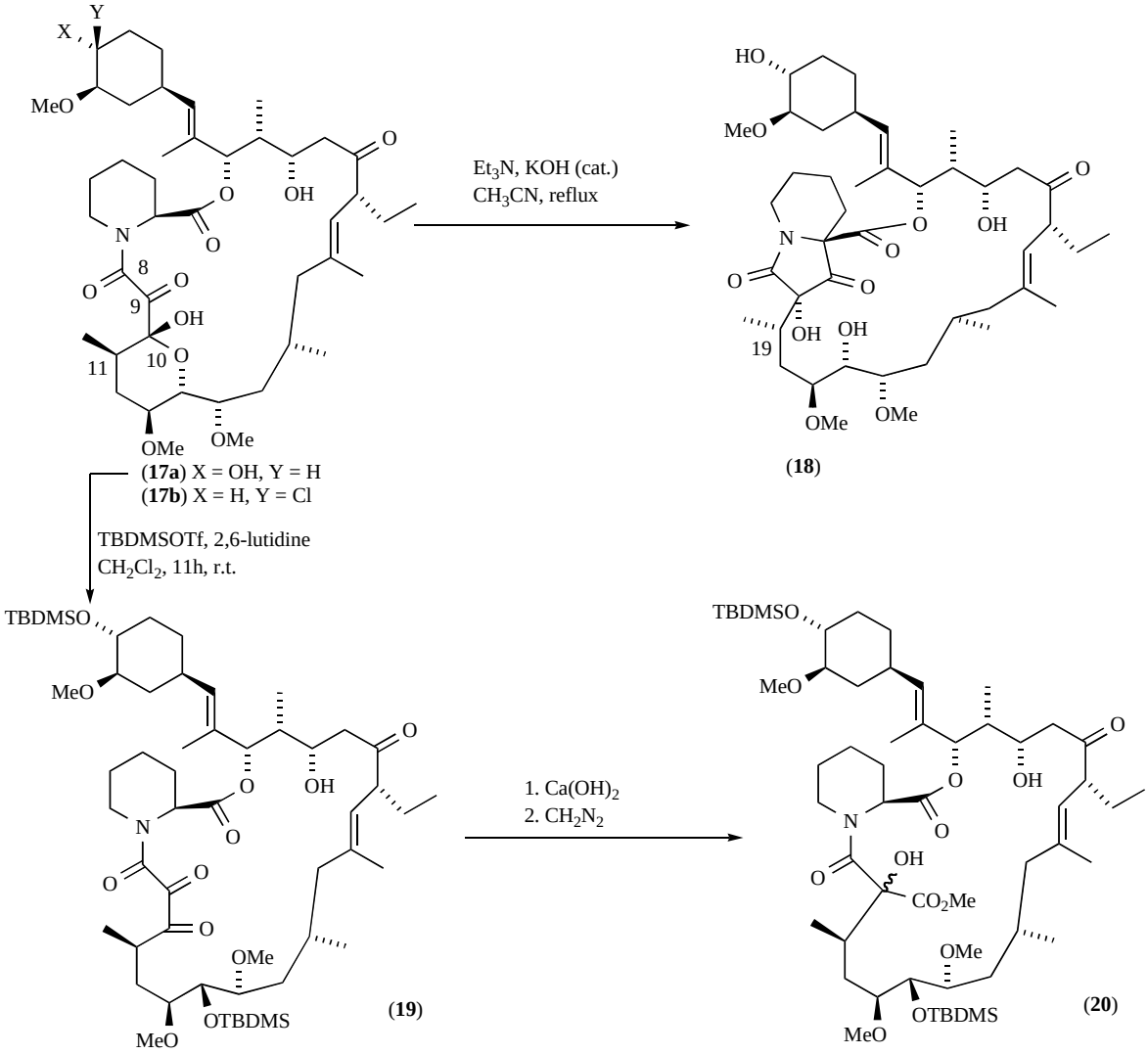
6). This product was later confirmed to have the (2*R*,3*R*;2*S*,3*S*) configuration [14], however, the actual mechanism is still under evaluation.

As an approach to oxonorbornanes, in 1993 Deb *et al*. [15] used a BAR to convert the bicyclic α-diones (**10a,b**) to the corresponding bicyclic hydroxy acids (**11a**,**b**) in good yields and afforded the oxonorbornane products (**12a**, **b**) after further synthetic manipulation (Scheme **7**).

Vicinal tricarbonyl compounds undergo facile benzilic acid rearrangement under basic conditions [16]. The immunosupressor FK-506 (**13**), extensively studied by Ashin [17,18] and others [19,20], contains a masked tricarbonyl



Scheme 8.



Scheme 9.

unit (C-10 is actually a masked carbonyl). Askin and coworkers [17] transformed silylated FK-506 (**14**) to the corresponding silylated α-hydroxy ester derivative (**15**), *via* a BAR using an aqueous THF solution of LiOH (Scheme **8**). In this case it was the *N*-acyl group that migrated to the C-10, after hydroxide addition at C9 and de-acetalation of the hemiacetal group. This research group then discovered that on repeating this reaction and conducting an esterification with diazomethane followed by desilylation, they got compound (**16**) (Scheme **8**) [17]. They also established that it was in fact predominantly an acyl(C8) migration, when a study using C9-^{13}C (**13**) revealed that after the rearrangement most of the ^{13}C-label was found in the acid carboxyl group. This mechanism was supported by later mechanistic studies carried out by Baumann's group [19].

In 1991 Danishefsky's group reported that upon refluxing FK-506 (**13**) in methanol for 3h a BER occurred giving a single diastereomeric hydroxy ester (**16**) in 82% yield (Scheme **8**) [20]. Two years later Luengo *et al.* [21] showed that if methanolic $ZnCl_2$ was used in this reaction at room temperature, the same hydroxy ester product (**16**) was obtained in almost quantitative yield after only three hours. None of these groups have established the configuration of the new quaternary carbon centre.

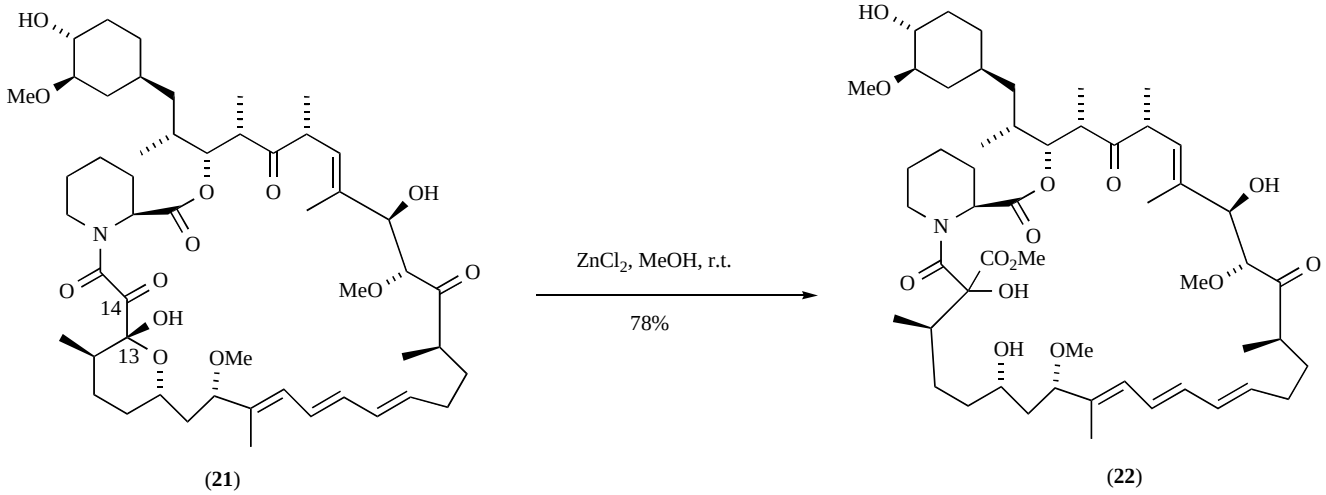
Both Koch's [22] and Baumann's groups [19] have conducted extensive research on the FK-506 type compound, ascomycin (**17a**), a macrolactam, whose 33-epi-chloro derivative, known as Pimecrolimus (**17b**) (commercially known as Elidel® or SDZ ASM) has been recently commercialised for inflammatory skin diseases. Hock and coworkers [22] have developed a large scale process for converting ascomycin (**17a**) to the analogue SCZ ASD732 (**18**) in moderate yield *via* a one pot tandem process that involves a BAR (Scheme **9**). Baumann *et al.* [19a] also discovered that upon treating the tricarbonyl derivative (**19**) (Scheme **9**) with $Ca(OH)_2$, an instantaneous BAR occurred to give the corresponding hydroxy ester (**20**) as a 96 : 4 mixture of diastereomers in favour of the 10(*S*) epimer, after esterification with diazomethane.

Rapamycin (**21**) is a potent immunosuppressive antibiotic like FK506. It was first synthesised by Nicolaou and his team in 1993 [23]. Luengo *et al.* [21] studied the chemistry of Rapamycin under lewis catalysis. They found that rapamycin (**21**) underwent a facile BER using methanolic zinc chloride (20 equiv.) to give the hydroxy ester (**22**) as a single diastereomer (Scheme **10**) in a very good yield. These authors didn't allude to the absolute configuration of this newly created quaternary centre. Although other lewis acids (e.g. ZnI_2, and $MgCl_2$) could be used, the reactions were not as clean as the first reaction. The use of protic acids (e.g. AcOH, DowexH$^+$ resin) gave no reaction.

In 1996 Stoltz and Wood [24] reported the unexpected application of an efficient, highly stereoselective BER on the pyranosylated indolocarbazole (**23**) to give the K252a carbohydrate moiety (**24**) *via* a putative α-diketone intermediate using methanolic $CuCl_2$ (Scheme **11**).

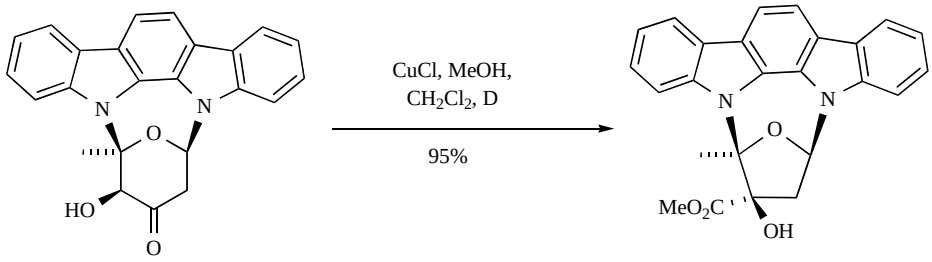
Recently, Burke and coworkers [6] have used a one pot Cu(II) oxidation/BER, with $Cu(OAc)_2$ as the copper source, to transform in a stereoselective manner, certain simple α-hydroxyketone substrates to tertiary α-hydroxy esters (Table **1**). $CuCl_2$ could also be used. Later studies using the α-hydroxyketone substrate (**28**) (Table **1**) have shown that catalytic quantities of $Cu(OAc)_2$ as low as 1 mol% can be used to form the corresponding α-hydroxy ester (**34**) [7]. Taking into consideration the results obtained by Luengo *et al.* [21] and the observation that as the loading of $Cu(OAc)_2$ was lowered the diastereoselectivity of the reaction increased, it seems that the copper ion catalyses, or at least promotes this reaction. In fact, metal catalysis has been demonstrated previously for this reaction [25].

Fleet's group [26] has very recently proposed the existence of a BAR in the $Ca(OH)_2$ conversion of *D*-glucose (**36**) to the branched ribonic acid (**38**) (which was invariably isolated as the crystalline lactone (**39**)) *via* the α-diketone intermediate (**37**) (Scheme **12**). However, it is not certain if indeed the α-diketone (**37**) undergoes the BAR to form (**38**) that then cyclises to the lactone (**39**) (Pathway a) or that it cyclises to the α-oxylactone (**40**) which subsequently suffers a tertiary ketol rearrangement (pathway b) [2, 27]. In fact, in the case of the BAR studied by Brady *et al.* [13] a tertiary ketol rearrangement on the benzofuranone (**7**) (Scheme **6**) is a possibility and we are currently investigating this.



(**21**) (**22**)

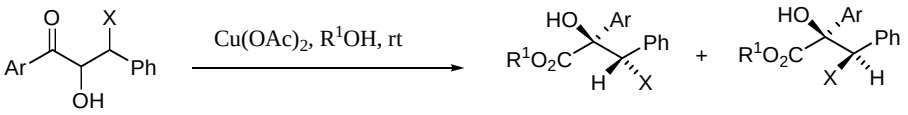
Scheme 10.



(**23**) (**24**)

Scheme 11.

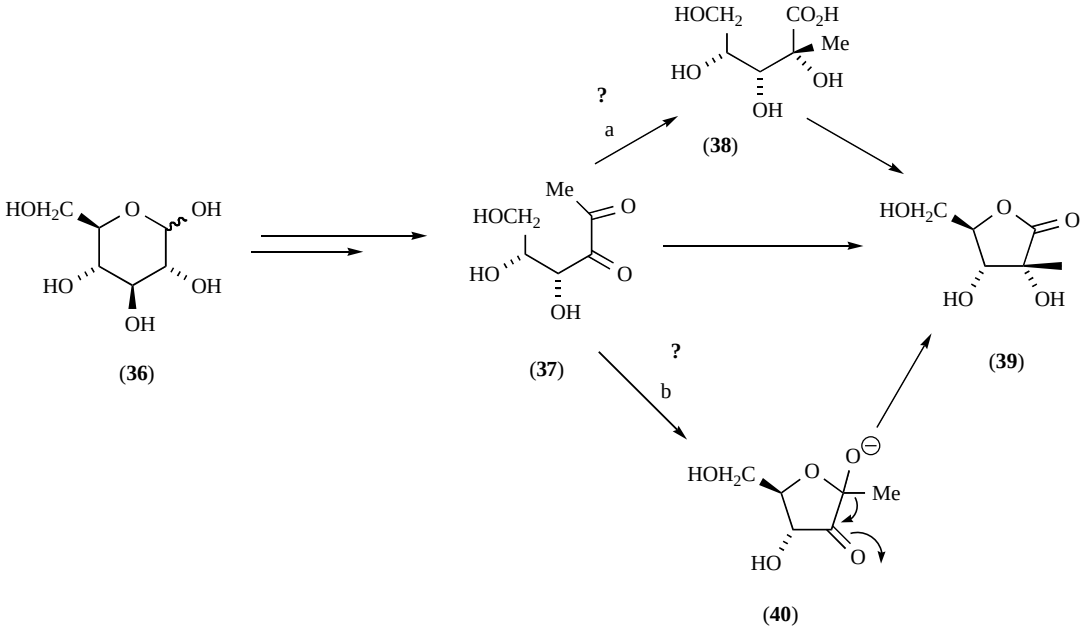
Table 1.



(**25**-**29**) *anti*-(**30a**-**35a**) *syn*-(**30b**-**35b**)

Entry	α-hydroxyketone	R^1	X	Ar	Product	Reaction Time (h)	Yield (2 steps)[a] (%)	*anti* : *syn*[b,c]
1	(**25**)	Me	OEt	Ph	(**30**)	72	37	2.8 : 1
2	(**26**)	Me	Me	Ph	(**31**)	45	42	2 : 1
3	(**27**)	Me	OMe	2-$MeOC_2H_4$	(**32**)	44	35	2.9 : 1
4	(**27**)	Et	OMe	2-$MeOC_2H_4$	(**33**)	48	63	2.6 : 1
5	(**28**)	Me	OEt	2-$MeOC_2H_4$	(**34**)	48	49	2.1 : 1
6	(**29**)	Me	OMe	2,4-$(MeO)_2C_2H_4$	(**35**)	94	49	2.9 : 1

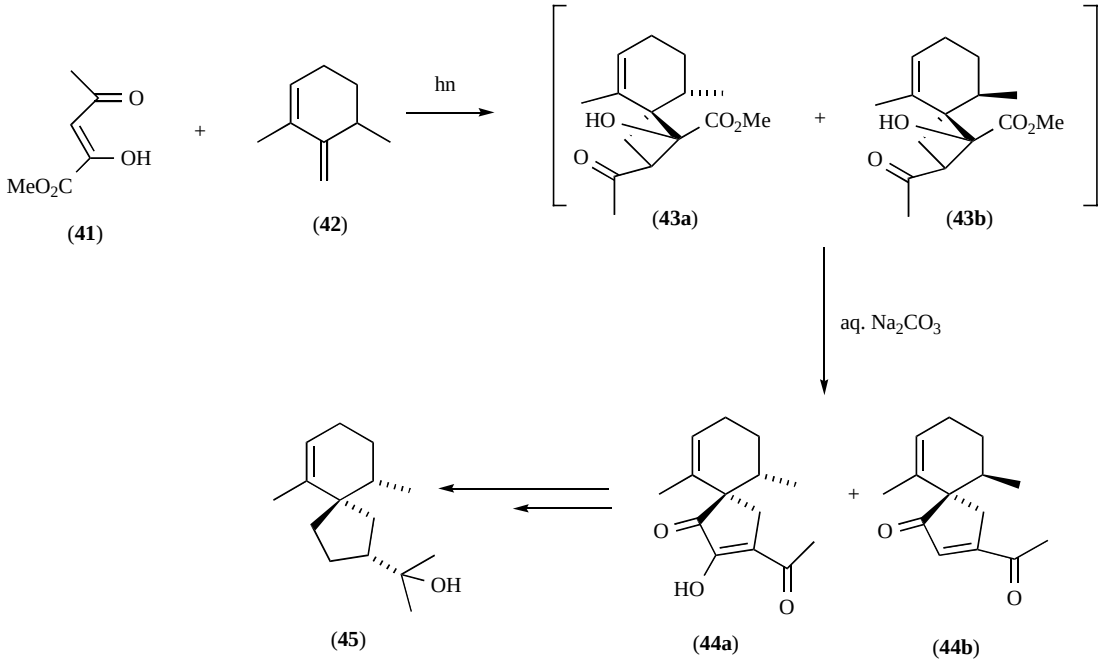
[a]For both diastereomers. [b]Determined by ^1H NMR spectroscopy. [c] The assignment of the *anti*-isomer as the major isomer was made on the basis of literature precedent [6].



(**40**)

Scheme 12.

Most important synthetic processes have a retro counterpart that is synthetically quite useful (e.g. *retro*-aldol, *retro*-Claisen, *retro*-Diels-Alder, etc). In 1995 Hatsui *et al.* [28] reported the first *retro*-BAR. Methyl 2,4-dioxopentanoate (**41**) was reacted photochemically with 1,5-dimethyl-6-methylenecyclohexene (**42**) to afford two unstable diasteromeric *proto*-[2+2] α-hydroxy ester photocycloadducts (**43a**) and (**43b**) that underwent the *retro*-BAR to give spiro-tricarbonyl diastereomers (**44a**) and (**44b**), the former of which was used as a precursor to give hinesol (**45**) (Scheme **13**).



Scheme 13.

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