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Enantioselective Synthesis of α-Hydroxyketones using the DiTOX Asymmetric Building Block

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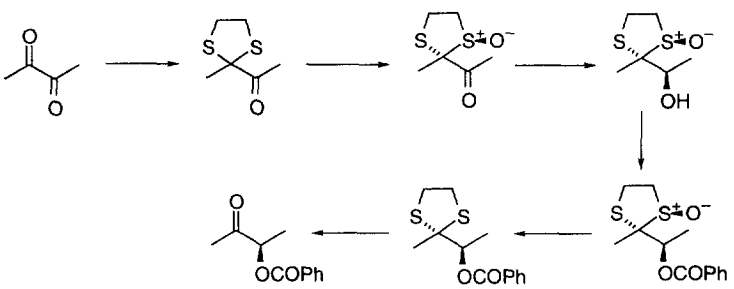
Abstract: The 2-(*R*)- and 2-(*S*)-hydroxy-1-phenylbutan-1-ones have been prepared in high enantiomeric excesses and in five steps from propanal using a dithiane oxide unit as an asymmetric building block and a modified Sharpless enantioselective sulphur oxidation as the source of chirality.

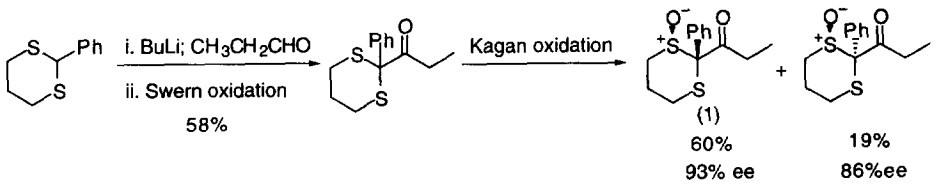
α-Hydroxy ketones are an important structural feature of many biologically active molecules.[1] Compounds containing this functionality have also been reported to control the stereochemistry for several different transformations: α-hydroxy ketones can be selectively reduced to give either the *threo* or *erythro* diols, through suitable protection of the alcohol functionality and appropriate choice of the reducing agent;[2] Maycock and Trost have each reported that silyl enol ethers of α-hydroxy ketone derivatives undergo highly diastereofacially selective Lewis acid catalysed aldol reactions,[3,4] and Paterson has used the diastereofacially selective aldol reaction of boron enolates of α-hydroxy ketone derivatives in the synthesis of bafilomycin A1.[5] A recent report by Maycock concerning the enantioselective synthesis of 3-benzoyloxybutan-2-one from butane-2,3-dione in six steps, using a derived mono-dithioacetal sulphoxide as the enantiocontrol element in a diastereoselective reduction (Scheme 1),[6] prompts us to publish our own results in this area.



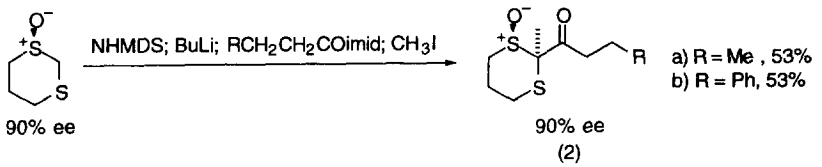
Scheme 1

The approach shown in Scheme 1 is interesting, but is of course limited to cases where the α-diketone starting material is symmetrical, and where it is readily available and reacts appropriately with ethanedithiol. Herein we report a more general approach to α-hydroxy ketone synthesis through application of our dithiane oxide methodology;[7] we have previously described the preparation in high ee,[8] and the stereocontrolled reduction,[9] of a number of 2-acyl-1,3-dithiane 1-oxides, and have reported thioacetal hydrolysis in these systems.[7,10]

Suitable acyl dithiane oxide substrates from each diastereoisomeric series were prepared using our standard methods. *anti*-2-Propanoyl-2-phenyl-1,3-dithiane 1-oxide (1) (93% ee) was generated from 2-phenyl-1,3-dithiane by deprotonation, addition of the resulting anion to propanal, oxidation to the ketone, and asymmetric sulfoxidation by a modified Sharpless protocol (Scheme 2);[8] in accordance with Kagan,[11] but in contrast to Maycock,[6] we have found that these reactions require addition of water to achieve optimum enantioselection. *syn*-2-Butanoyl-2-methyl-1,3-dithiane 1-oxide (2a) (90% ee) and *syn*-2-(3-phenylpropanoyl)-2-methyl-1,3-dithiane 1-oxide (2b) (90% ee) were produced from 1,3-dithiane 1-oxide (90% ee)[12] in one-pot reactions by reaction of the anion with an appropriate acyl imidazole in the presence of additional base, and treatment of the enolate so generated with methyl iodide (Scheme 3).[13]

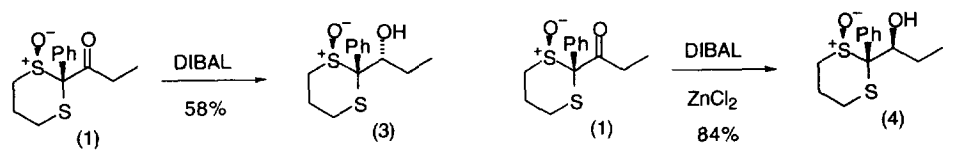


Scheme 2

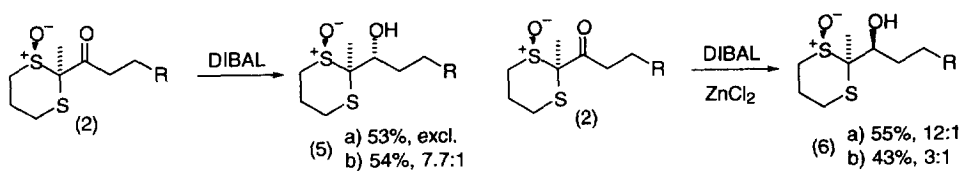


Scheme 3

We have previously described the stereoselective reduction of 2-acyl-2-alkyl-1,3-dithiane 1-oxides with DIBAL,[9] and normally observe a reversal of selectively upon addition of zinc chloride, in accordance with Solladié.[14] Treatment of substrate (1), in tetrahydrofuran solution at –78 °C, with an excess of DIBAL gave exclusively one diastereoisomer, (3), of the alcohol product after work-up. Addition of zinc chloride to the solution of (1) at room temperature, prior to cooling to –78 °C and treatment with DIBAL, also gave exclusively one diastereoisomer, (4), of the alcohol product, and the sense of induced stereoselectivity was indeed reversed (Scheme 4). Similar treatment of substrate (2a) with DIBAL again gave exclusively one diastereoisomer, (5a), of the alcohol product, and again gave a reversal of the sense of induced stereoselectivity upon addition of zinc chloride, although the diastereoselectivity, in favour of (6a), was then reduced to 12:1 (Scheme 5). Reduction of substrate (2b) proceeded analogously, although with reduced stereoselectivity.

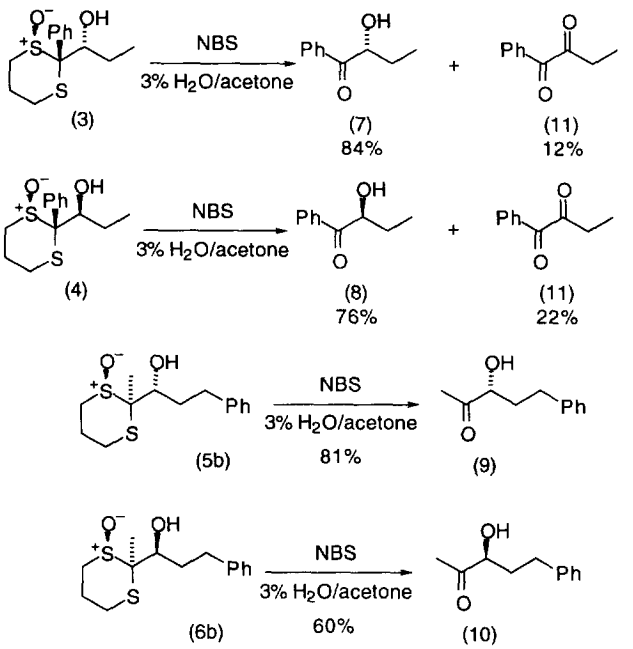


Scheme 4



Scheme 5

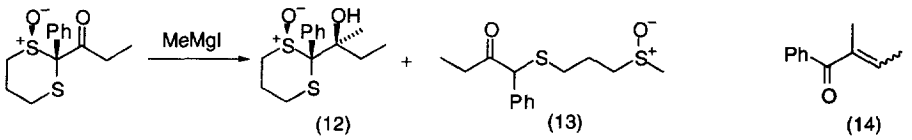
Hydrolysis of the dithiane 1-oxide moieties of alcohols (3)-(6) under our standard conditions using NBS/acetone/water gave the corresponding α-hydroxy ketones (7)-(10) in excellent yields (Scheme 6), except for alcohols (5a) and (6a), which gave poorer recovery of material, perhaps because of difficulties in product isolation.[7,10] It is interesting that a small degree of alcohol oxidation also occurred in the case of the 2-phenyl substrates, to give the corresponding 1,2-diketone (11). We have previously observed concomitant hydrolysis and oxidation phenomena in related 2-(1-hydroxyalkyl)-2-aryl-1,3-dithianes.[15] It is evident however that thioacetal hydrolysis is generally faster than alcohol oxidation in these systems, and is very rapid, the reaction for the (*R*)-α-hydroxy ketone (7), for example, being complete within one minute.



Scheme 6

The two α-hydroxy ketones (7) and (8), derived from the 2-phenyl derivatives (3) and (4) respectively, have specific rotations of opposite signs and identical numerical values within experimental error. If no racemization occurred, the ee of the two products would be 93%, identical to that of the starting material. Enders has reported a specific rotation for the (*R*)-hydroxy ketone (7), and this figure is indeed consistent with an ee of 93% for our material.[16] The *anti* substrate (1) has previously been recrystallized to optical purity.[17] In the case of the 2-methyl derivatives (5) and (6), a degree of racemization is observed, such that (9) and (10) are isolated with ees of 65% and 45% respectively.

In an extension of this methodology, diastereoselective addition of methyl Grignard reagent to the ketone (1) at room temperature gave the desired product (12) in 77% yield with a diastereoselectivity of 10:1, together with the ring opened material (13), derived from attack at the sulphoxide sulphur atom, in 11% yield (Scheme 7). Treatment of (12) with NBS/acetone however induced both hydrolysis and elimination to give a 3:1 mixture of the *cis* and *trans* α,β-unsaturated ketones (14).



Scheme 7

The 2-(*R*)- and 2-(*S*)-hydroxy-1-phenylbutan-1-ones (7) and (8) have thus been prepared in five steps and in high enantiomeric excesses from propanal, and the 3-(*R*)- and 3-(*S*)-hydroxy-5-phenylpentan-2-ones (9) and (10) in three steps from 3-phenylpropanoyl imidazole, using dithiane oxide units as asymmetric building blocks and modified Sharpless enantioselective sulphur oxidation reactions as the source of chirality.

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