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Asymmetric Synthesis of (*R*)-Hexane-1,5-diol and (*R*)-Hex-3-ene-1,5-diol *via* a Tandem Asymmetric Conjugate Addition / Stereospecific Meisenheimer Rearrangement Protocol

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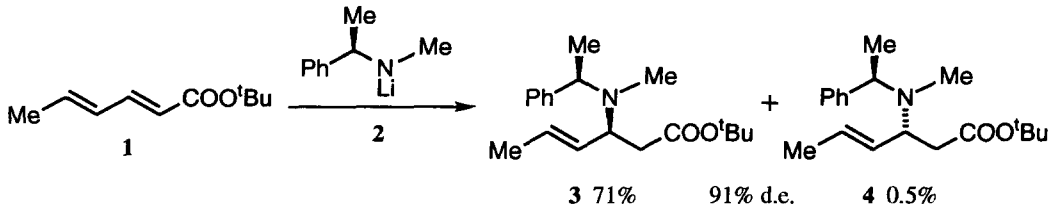
Abstract: Stereoselective conjugate addition of (*R*)-lithium *N*,α-dimethylbenzylamide to *tert*-butyl (*E,E*)-hexa-2,4-dienoate, followed by reduction of the ester to the corresponding alcohol, affords a substrate which undergoes, on oxidation, a stereospecific Meisenheimer rearrangement to give a single diastereomer of the corresponding trialkylhydroxylamine. Cleavage of the N–O bond gives (*R*)-hex-3-ene-1,5-diol and subsequent hydrogenation of the double bond affords (*R*)-hexane-1,5-diol in high e.e.

The Meisenheimer rearrangement of allylic tertiary amine *N*-oxides to the corresponding *N,N,O*-trisubstituted hydroxylamines is one of the less studied [2,3]-sigmatropic rearrangements.[1,2] In particular, reports of asymmetric versions of the reaction are rare. Since the initial investigations of Inouye *et al.*[3] (which were hampered by the low enantiomeric excesses of the substrates employed, and by epimerisation that sometimes accompanied the N–O bond cleavage of the product hydroxylamines), there have been two pertinent studies. Reetz and Lauterbach[4] homologated homochiral α-amino acids, and employed a stereospecific Meisenheimer rearrangement to afford, after N–O bond cleavage, the corresponding homologated α-hydroxy ester. As anticipated by analogy with other [2,3]-sigmatropic rearrangements,[5] excellent 1→3 chirality transfer was observed, to give the product α-hydroxy esters in high e.e. More recently, Enders and Kempen[6] have reported an asymmetric Meisenheimer rearrangement employing a C_2-symmetric pyrrolidine chiral auxiliary on the nitrogen, giving moderate asymmetric induction in the formation of the new stereogenic centre.

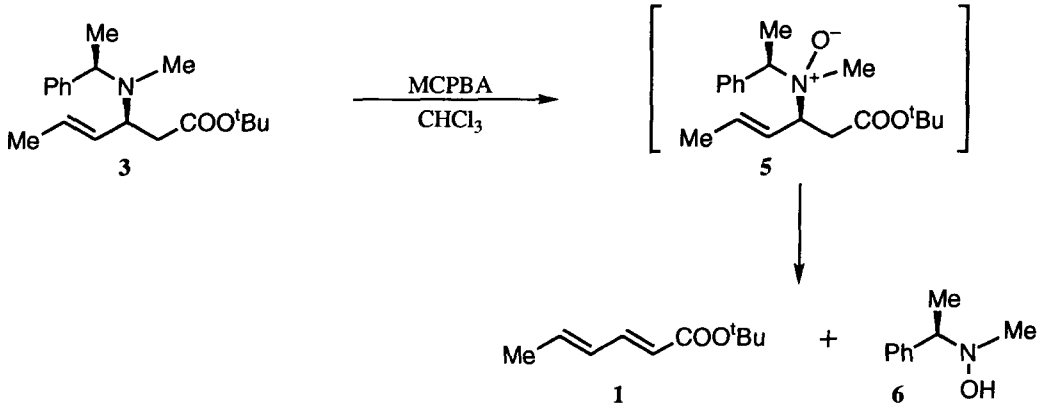
The conjugate addition of lithium amides of secondary amines derived from α-methylbenzylamine to α,β-unsaturated esters proceeds with good diastereoselectivity.[7] It seemed that application of this reaction to α,β,γ,δ-unsaturated esters would provide substrates for a stereospecific Meisenheimer rearrangement, analogous to that of Reetz and Lauterbach. Provided the N–O bond of the product hydroxylamines could be cleaved without epimerisation, this would provide a route for the preparation of alcohols in high enantiomeric excess.

The addition of (*R*)-lithium *N*,α-dimethylbenzylamide **2** to *tert*-butyl (*E,E*)-hexa-2,4-dienoate **1** proceeded in 91% d.e., giving the pure adduct **3** in 71% yield after isolation (Scheme 1): the more polar minor diastereomer **4** could be removed by column chromatography on silica gel, and was isolated in 0.5% yield.[8]



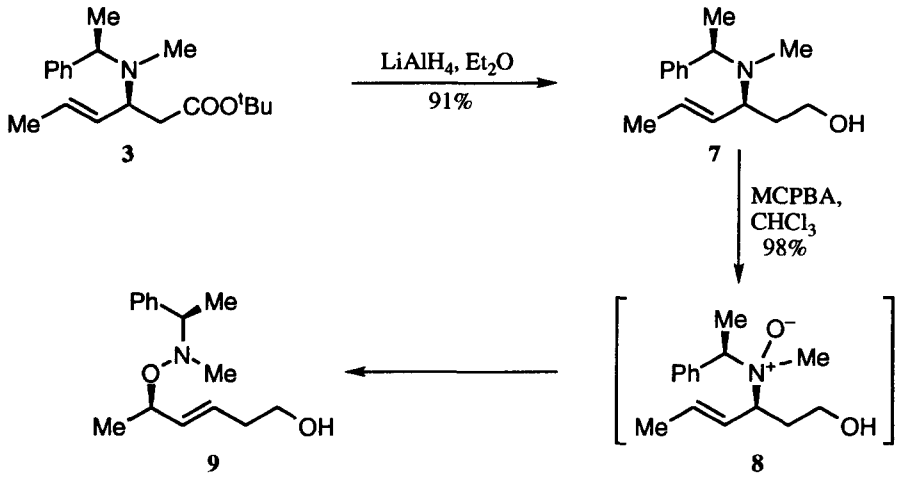
Scheme 1

Treatment of β-amino ester **3** with MCPBA, gave, after workup (passage of the reaction mixture through deactivated basic alumina[9]) a mixture of the hydroxylamine **6**, and the starting dienoate ester **1** (Scheme 2). This is consistent with Cope elimination of the expected intermediate amine *N*-oxide **5** occurring more rapidly than the alternative Meisenheimer rearrangement. This can be attributed to the relatively high acidity of the α-protons, and suggested that reduction of the ester to the corresponding alcohol might reverse this chemoselectivity. On the other hand, this protocol represents an interesting variant on a known strategy[10] for the controlled generation of *N,N*-dialkylhydroxylamines from the corresponding secondary amine.



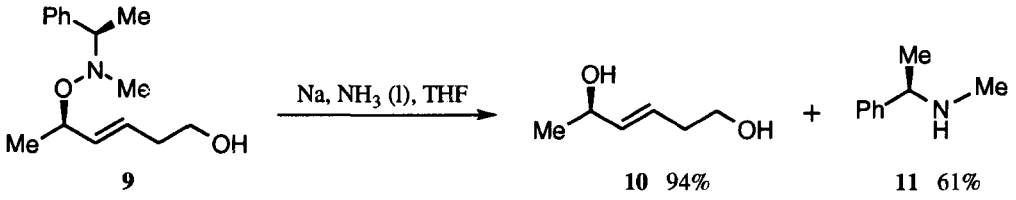
Scheme 2

The ester **3** was readily reduced to the alcohol **7** in high yield, using $LiAlH_4$. The alcohol **7** was treated with MCPBA, and, after passage through a column of deactivated basic alumina, the chloroform solution was left at room temperature for 24h for rearrangement to proceed to completion. As anticipated, the rearrangement occurred in high yield, only one diastereomer of product **9** was detected, and no products from Cope elimination were observed (Scheme 3). A new stereogenic centre at nitrogen is formed during the oxidation step, but the rearrangement proceeds too fast to observe whether or not it is formed stereoselectively.



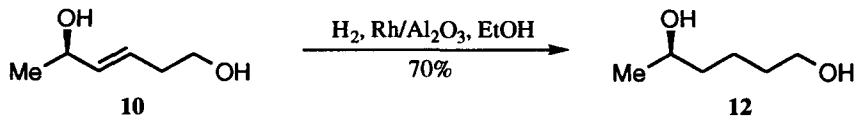
Scheme 3

N–O bond cleavage to give the diol **10** could be achieved by treatment with a zinc-copper couple in aqueous acetic acid,[11] but was much more conveniently carried out with sodium in liquid ammonia. The latter procedure also allowed recovery of the amine **11** (Scheme 4). Under these conditions, (*R*)-hex-3-ene-1,5-diol **10** $[\alpha]_D^{26}$ = -11.2 (*c* 2.20 in $CHCl_3$), $[\alpha]_D^{26}$ = -1.4 (*c* 2.22 in MeOH) was obtained in 94% yield.[12] ^{1}H NMR spectroscopy using (*S*)-*O*-acetylmandelic acid as a chiral shift reagent[13] indicated the starting and the recovered amine **11** to be of >95% e.e., consistent with no loss of enantiomeric purity. Since (*R*)-hex-3-ene-1,5-diol **10** is derived *via* diastereomerically pure materials it can therefore be assigned as >95% e.e.



Scheme 4

In order to establish the absolute configuration unequivocally, allylic alcohol **10** was hydrogenated to the known diol **12**[14] (Scheme 5). The specific rotation determined for **12** $[\alpha]_D^{23}$ = -12.2 (*c* 1.39 in MeOH) was in good agreement with the literature values[15] $[\alpha]_D^{26}$ = -11 (*c* 0.41 in MeOH) and[16] $[\alpha]_D^{20}$ = +12.9 (*c* 1 in MeOH) for the (*R*)- and (*S*)-enantiomers respectively. This confims the (*R*)-configuration, which is consistent with that expected from a stereoselective conjugate addition and stereospecific Meisenheimer rearrangement.



Scheme 5

In order to verify the enantiomeric purity of **12**, its dibenzoyl derivative was analysed by chiral HPLC [Chiralcel OB column, hexane/isopropanol (4:1), detect at 220nm]. Retention times were determined using the dibenzoyl derivative of commercially available racemic hexane-1,5-diol. The (*S*)-isomer gave the longer retention time and a rather broad peak, so the enantiomeric excess could only be determined as 95±5%.

Thus a sequence involving a highly stereoselective conjugate addition followed by a completely stereospecific Meisenheimer rearrangement has been developed, which affords alcohols in high enantiomeric excess. The application of this methodology to the asymmetric synthesis of the insect pheromone (*R*)-sulcatol is described in the following communication.

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12. Selected data for **10**: δ_H (300MHz, $CDCl_3$) 1.26 [3H, d, *J* 6.2, C(6)H_3], 2.10 [1H, br s, O*H*], 2.25-2.31 [2H, m, C(2)H_2], 3.62-3.70 [2H, m, C(1)*H*], 4.23-4.32 [1H, m, C(5)*H*], 5.56-5.69 [2H, m, C(3)*H* and C(4)*H*]; δ_C (50.3MHz, $CDCl_3$) 23.1 [*C*(6)], 35.3 [*C*(2)], 61.4 [*C*(1)], 68.5 [*C*(5)], 127.1 [*C*(3)], 137.0 [*C*(4)].
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14. Selected data for **12**: δ_H (300MHz, $CDCl_3$) 1.20 [3H, d, *J* 6.1 CH(OH)*Me*], 1.39-1.65 [8H, m, C(2)H_2, C(3)H_2, C(4)H_2 and O*H*], 3.67 [2H, t, *J* 6.3, C(1)H_2], 3.82 [1H, app sxt, *J* 6, C(5)*H*]; δ_C (50.3MHz, $CDCl_3$) 21.8 [*C*(3)], 23.4 [*C*(6)], 32.3 and 38.7 [*C*(2) and *C*(4)], 62.3 [*C*(1)], 67.7 [*C*(5)].
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