Asymmetric synthesis of (*R*)-hexane-1,5-diol, (*R*)-hex-3-ene-1,5-diol and (*R*)-6-methylhept-5-en-2-ol (sulcatol) employing a tandem asymmetric conjugate addition and stereospecific Meisenheimer rearrangement protocol

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Highly stereoselective conjugate addition of lithium (*R*)-*N*-methyl-(α-methylbenzyl)amide to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate, followed by reduction of the ester to the corresponding alcohol, affords a substrate which undergoes, upon oxidation, a stereospecific Meisenheimer rearrangement to give a single diastereomer of the corresponding trialkylhydroxylamine. The analogous *N*-benzyl adduct gives lower yields in the oxidation–rearrangement reaction. If the ester is not reduced to the alcohol, *N*-oxidation leads to Cope elimination, not Meisenheimer rearrangement. Cleavage of the N–O bond gives (*R*)-hex-3-ene-1,5-diol, and hydrogenation of the double bond affords (*R*)-hexane-1,5-diol in high ee. This methodology has been applied to the synthesis of the insect pheromone (*R*)-6-methylhept-5-en-2-ol (sulcatol) from *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate, *via* a sequence involving conjugate addition of the lithium amide, Grignard addition to the ester, Meisenheimer rearrangement, hydrogenation of the double bond, dehydration of the tertiary alcohol and finally N–O bond cleavage.

Introduction

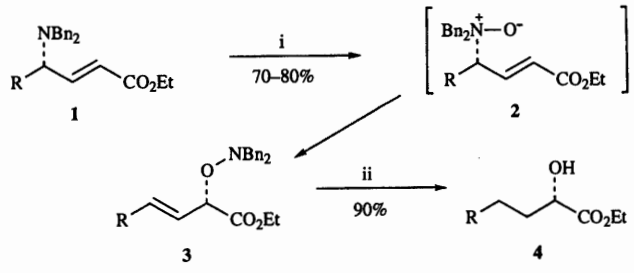
The Meisenheimer rearrangement consists of migration of one of the substituents of a tertiary amine *N*-oxide from nitrogen to oxygen, resulting in an *O*-substituted hydroxylamine.[1] In fact, the term covers two mechanistically distinct rearrangements: when the migrating group is a benzyl substituent, the reaction normally proceeds through a radical dissociation–recombination mechanism.[2] By contrast, if the migration is of an allyl group, the rearrangement is usually a [2,3]-sigmatropic shift.[3]

Examples of asymmetric Meisenheimer rearrangements of chiral allylic amine *N*-oxides are rare in the literature (in contrast to, for example, the corresponding [2,3]-rearrangement between sulfoxides and sulfenate esters[4]). After some initial investigations by Inouye *et al.*[5] (which do not represent efficient synthetic procedures, either because the starting material is not available in high enantiomeric purity, or because the cleavage of the N–O bond of the hydroxylamine product is accompanied by racemisation) there have been few pertinent studies.

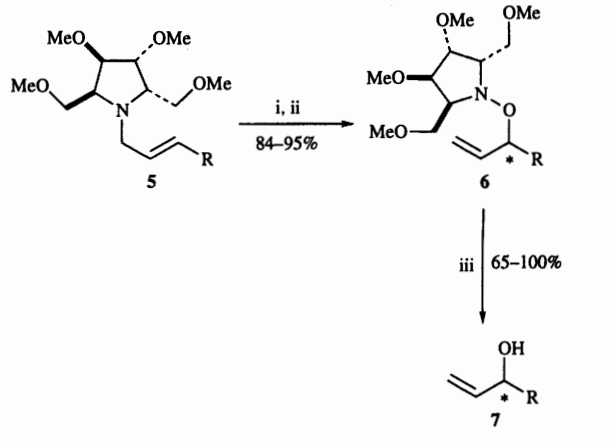
Reetz and Lauterbach[6] oxidised substrates **1** (prepared from the corresponding α-amino acids), and found that the resulting amine *N*-oxides **2** readily underwent stereospecific Meisenheimer rearrangement to afford the hydroxylamines **3** (Scheme 1). This excellent 1→3 chirality transfer is expected by analogy with other [2,3]-sigmatropic rearrangements.[7] Hydrogenation with concomitant hydrogenolysis then gave the α-hydroxy esters **4** in >95% ee. The synthetic applicability of this procedure is limited only by the availability of the α-amino acid starting materials.

Enders and Kempen[8] used a C_2-symmetric pyrrolidine chiral auxiliary in an asymmetric Meisenheimer rearrangement (Scheme 2). Oxidation of the amines **5**, followed by immediate [2,3]-rearrangement, gave hydroxylamines **6** in 65–73% de. After purification by HPLC, N–O bond cleavage gave the alcohols **7** in 93–99% ee. While this method is suitable for the synthesis of a variety of alcohols, it obviously suffers from the need to employ HPLC to obtain products of useful enantiomeric purity.

We describe herein the asymmetric synthesis of (*R*)-hexane-1,5-diol, (*R*)-hex-3-ene-1,5-diol and (*R*)-6-methylhept-5-en-2-ol (sulcatol) employing a tandem asymmetric conjugate addition and stereospecific Meisenheimer rearrangement protocol. Part of this work has been previously communicated.[9]



Scheme 1 *Reagents and conditions:* i, MCPBA, $NaHCO_3$, CH_2Cl_2, −50 °C; ii, H_2, $Pd(OH)_2$



Scheme 2 *Reagents and conditions:* i, MCPBA, CH_2Cl_2, −40 °C; ii, Et_2O solution, −8 °C; iii, Zn, AcOH, ultrasound

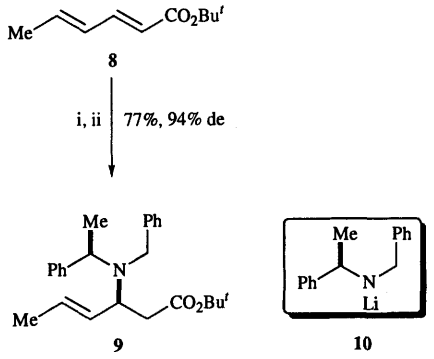
Results and discussion

Development and optimisation of the conjugate addition–Meisenheimer rearrangement strategy

The investigations of Enders and Kempen suggested that chiral auxiliaries on nitrogen were unlikely to exert very effective

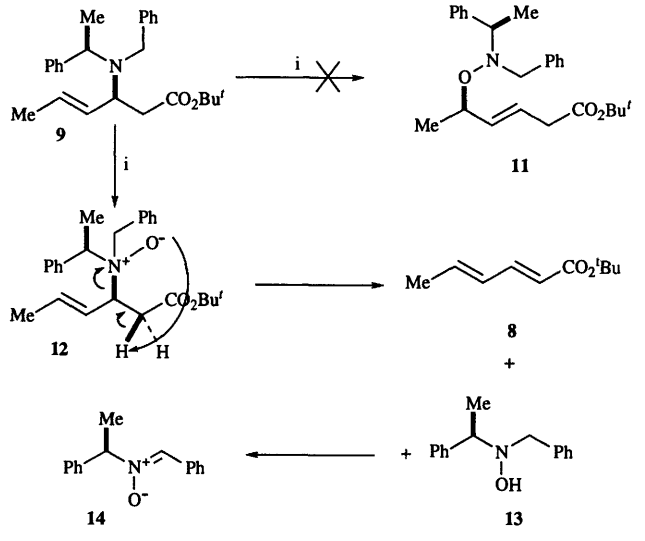
stereocontrol over a Meisenheimer rearrangement. Attention therefore turned to the preparation of chiral allylic amines suitable for undergoing a stereospecific Meisenheimer rearrangement of the type exploited by Reetz and Lauterbach. An obvious way to prepare such amines in high enantiomeric purity would be to employ the highly diastereoselective conjugate addition to α,β-unsaturated esters of secondary lithium amides derived from α-methylbenzylamine, a reaction developed in this laboratory.[10]

Accordingly, the adduct **9** was prepared by the conjugate addition of lithium (*R*)-*N*-benzyl(α-methylbenzyl)amide **10** to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **8** (Scheme 3). The reaction proceeded in 94% de to afford **9** in 77% yield.



Scheme 3 *Reagents and conditions:* i, **10**, THF, −78 °C; ii, NH_4Cl (aq.), −78 °C to 20 °C

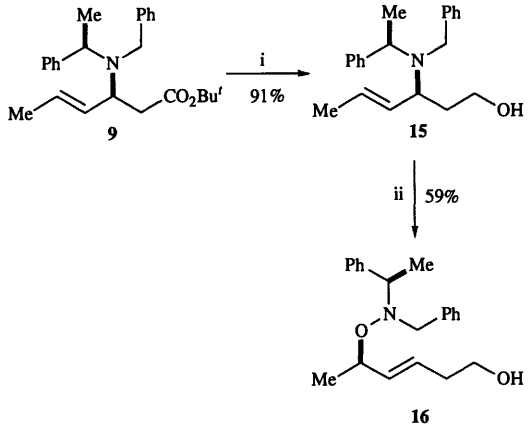
Oxidation of **9** with *m*-chloroperbenzoic acid (MCPBA), gave, after work up (passage of the reaction mixture through activated basic alumina[11]), a mixture of products containing none of the desired **11**. Instead the starting ester **8**, hydroxylamine **13** and nitrone **14** were detected, as well as some unreacted starting material **9** (Scheme 4). This was considered



Scheme 4 *Reagents and conditions:* i, MCPBA, $CHCl_3$, 20 °C

to result from Cope elimination from the *N*-oxide **12**,[12] followed by further oxidation by the peracid present in the reaction mixture of the initially formed hydroxylamine **13** to the nitrone **14**. The nitrone **14** was identified by comparison of its spectroscopic properties with those reported in the literature[13] for the enantiomer, while the hydroxylamine **13** was compared with an authentic sample prepared by oxidation of (*R*)-*N*-benzyl-(α-methylbenzyl)amine with dimethyldioxirane.[14]

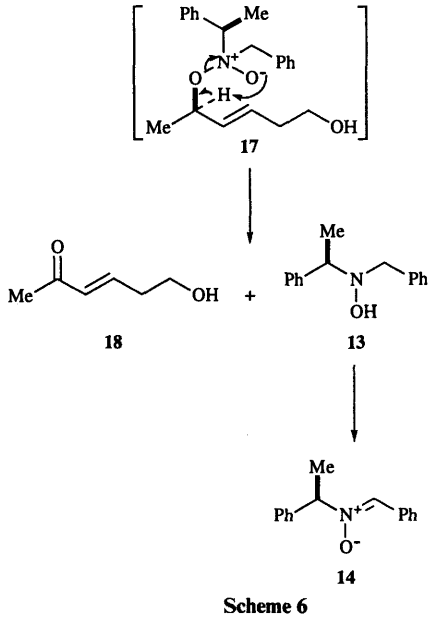
It seemed likely that the reason the Cope elimination was proceeding much faster than the desired Meisenheimer rearrangement was the acidity of the protons adjacent to the ester. This suggested that reducing the ester **9** to the corresponding alcohol **15** (which was readily achieved with lithium aluminium hydride) might cause the Meisenheimer rearrangement to prevail. Indeed, oxidation of **15** with MCPBA, with concomitant [2,3]-rearrangement, led to the formation of the desired hydroxylamine **16** as a single diastereomer (Scheme 5).



Scheme 5 *Reagents and conditions:* i, $LiAlH_4$, Et_2O, 20 °C; ii, MCPBA, $CHCl_3$, 20 °C

The ^1H NMR spectrum of **16** showed very broad resonances at room temperature, but a satisfactory spectrum could be obtained at 70 °C, using [$^2H_8$]toluene as the solvent. This behaviour was observed in all the substituted hydroxylamines that were prepared, and is well documented for such compounds.[15]

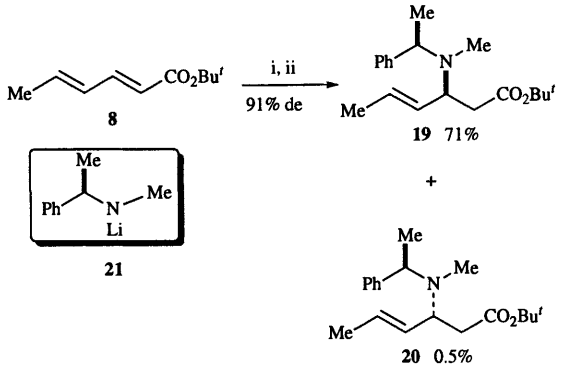
The yield of **16** was rather low, and a number of by-products were isolated (Scheme 6): hydroxylamine **13** and



Scheme 6

nitrone **14**, together with hydroxy ketone **18**. Monitoring the reaction with starch–KI paper and by TLC revealed that the oxidation of **15** was rather sluggish, taking several hours, while the rearrangement to produce **16** was comparatively quite rapid. This suggested that the low yield of **16** was due to further oxidation to give **17**, which then underwent a β-elimination reaction to give the observed by-products.

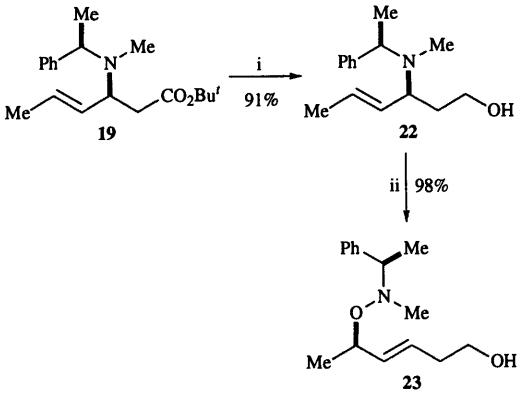
To increase the yield of the oxidation–rearrangement sequence, it seemed that it was required to accelerate the former step, and retard the latter. Reducing the steric bulk of the substituents on nitrogen should have precisely that effect. Therefore, the conjugate addition reaction of (*R*)-lithium *N*-methyl-(α-methylbenzyl)amide **21** to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **8** was examined (Scheme 7). The reaction was found to proceed in 91% de, and the two diastereomers of the product



Scheme 7 *Reagents and conditions:* i, **21**, THF, −78 °C; ii, NH_4Cl (aq.), −78 °C to 20 °C

were readily separable by column chromatography on silica gel. The major diastereomer **19** was isolated in 71% yield, and the minor diasteromer **20** in 0.5% yield. It can be seen that the diastereoselectivity of addition does decrease somewhat as the the size of the substituent on nitrogen decreases, but that the effect is not very large.

The adduct **19**, obtained diastereomerically pure, was reduced to the alcohol **22**, and treated with MCPBA (Scheme 8). After passing through activated basic alumina, the reaction

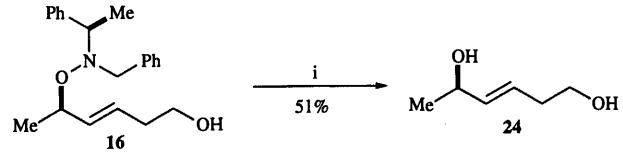


Scheme 8 *Reagents and conditions:* i, $LiAlH_4$, Et_2O, 20 °C; ii, MCPBA, $CHCl_3$, 20 °C

mixture was left for 24 h for the rearrangement to proceed to completion. As expected, the hydroxylamine **23** was obtained, as a single diastereomer, in higher yield, and no by-products were observed. Monitoring the reaction with starch–KI paper and by TLC indicated that the oxidation was complete within a few minutes, whereas rearrangement took several hours, in accordance with the rationalisation above.

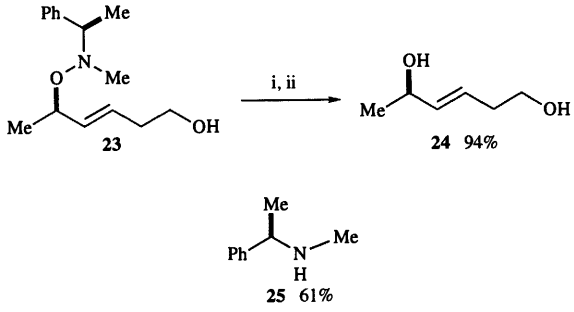
Cleavage of the N–O bond of hydroxylamines 16 and 23

Attention then turned to the cleavage of the N–O bond of the rearrangement products **16** and **23**. This turned out to be much more problematic than expected, and a variety of reagents were tried without success, including hydrogenolytic procedures (H_2, Pd/C, MeOH;[6a,c] H_2, $Pd(OH)_2$/C, HCl, MeOH[16]), Raney nickel,[17] nickel–aluminium alloy with potassium hydroxide,[18] samarium iodide,[19] sodium–mercury amalgam[20] and zinc in acetic acid.[6b,d,21] The first effective reagent found was a zinc–copper couple in acetic acid,[22] and this was used for the cleavage of the N–O bond of hydroxylamine **16** to give (*R*)-hex-3-ene-1,5-diol **24** (Scheme 9).



Scheme 9 *Reagents and conditions:* i, Zn–Cu, AcOH (aq.), 60–70 °C

However, this procedure was rather low-yielding, and did not allow recovery of the amine. Therefore, once the protocol for the Meisenheimer rearrangement had been improved, a better method for the cleavage of the N–O bond of **23** was sought (although the zinc–copper couple was effective for this substrate). Sodium naphthalenide[23] was successful, but the reaction was not very clean, and once again the amine could not be recovered. Finally, sodium in liquid ammonia was found to effect the desired bond cleavage in very high yield (Scheme 10).

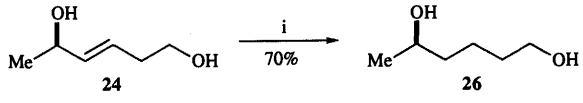


Scheme 10 *Reagents and conditions:* i, Na, NH_3 (l), THF, −78 °C; ii, NH_4Cl (s), −78 °C to 20 °C

Conveniently, when the product mixture was exposed to air, the amine reacted with atmospheric carbon dioxide to form what was assumed to be the ammonium carbamate salt[24] that was insoluble in diethyl ether, so trituration of the residue with diethyl ether extracted the diol **24** only. The residue could then be dissolved in dilute aqueous hydrochloric acid, basified and extracted with diethyl ether to allow isolation of the amine **25** (the lower yield for the amine compared with the diol is probably due to the volatility of this amine). Hence this protocol allows for recycling of the chiral auxiliary.

^1H NMR spectroscopy using (*S*)-*O*-acetylmandelic acid as a chiral shift reagent[25] indicated the starting and the recovered amine **25** to be of >95% ee, consistent with no loss of enantiomeric purity. Since (*R*)-hex-3-ene-1,5-diol **24** is derived *via* diastereomerically pure materials, it can therefore also be assigned as >95% ee.

In order to establish the absolute configuration unequivocally, **24** was hydrogenated to the known diol **26** (Scheme 11).



Scheme 11 *Reagents and conditions:* i, H_2 (6 atm), Rh/Al_2O_3, EtOH, 20 °C

The specific rotation determined for **26** $[\alpha]_D^{23} = -12.2$ (*c* 1.39 in MeOH) was in good agreement with the literature values[26] $[\alpha]_D^{26} = -11$ (*c* 0.41 in MeOH) and[27] $[\alpha]_D^{20} = +12.9$ (*c* 1 in MeOH) for the (*R*)- and (*S*)-enantiomers respectively. This confirms the (*R*)-configuration, which is consistent with that expected from a stereoselective conjugate addition and stereospecific Meisenheimer rearrangement. In order to verify the enantiomeric purity of **26**, its dibenzoyl derivative was analysed by chiral HPLC [Chiralcel OB column, hexane–propan-2-ol (4:1), detect at 220 nm]. 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%.

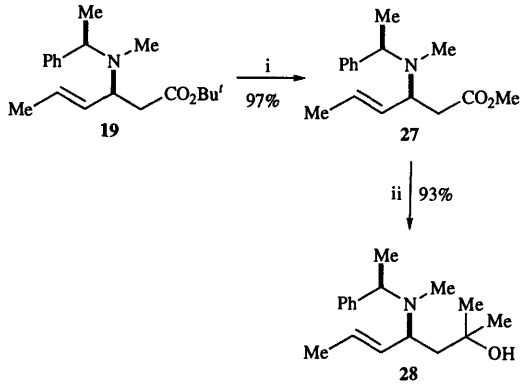
As the enantiomer of **26** has been oxidised to the corresponding δ-lactone using Fetizon's reagent,[28] while the same conversion has been achieved for other analogous 1,5-diols using tetrapropylammonium perruthenate–*N*-methylmorpholine-*N*-oxide (TPAP–NMO),[29] this procedure

represents a strategy for the preparation of δ-lactones in high enantiomeric purity.

Synthesis of (*R*)-sulcatol 37

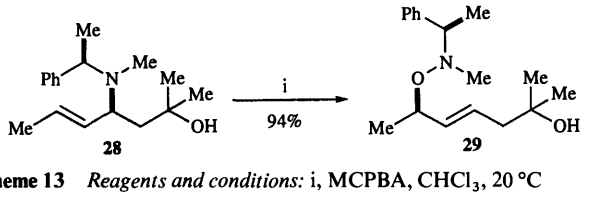
This protocol of a tandem asymmetric conjugate addition reaction and stereoselective Meisenheimer rearrangement should provide the basis for an asymmetric synthesis of the insect pheromone sulcatol **37** [(*R*)-6-methylhept-5-en-2-ol]. This is an aggregation pheromone of the beetles *Gnathotricus sulcatus*[30] and *Gnathotricus retusus*,[31] and there has been much interest in its synthesis in enantiomerically pure form[32] (many syntheses employing biochemical reduction of the corresponding ketone[33]), for biological studies and as a potential agent for the trapping of the beetles in pest control programmes. Also, sulcatol has served as an intermediate in the synthesis of other natural products.[32c,33g]

It was envisaged that the dimethyl group in sulcatol would be introduced by a Grignard reaction on the ester **19**, followed by a dehydration to introduce the double bond. In fact, the *tert*-butyl ester was resistant to reaction with methylmagnesium bromide, and so was transesterified to the methyl ester **27**, which readily underwent the desired addition to afford the tertiary alcohol **28** (Scheme 12).



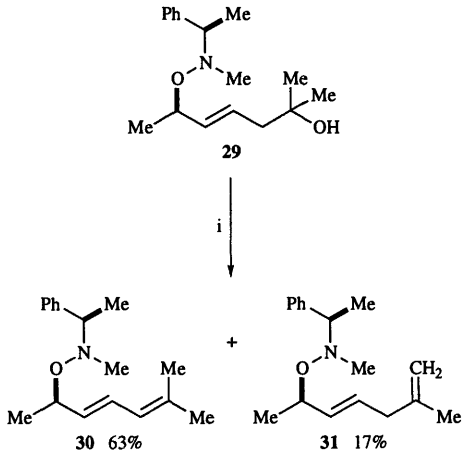
Scheme 12 *Reagents and conditions:* i, HCl, MeOH, 20 °C; ii, MeMgBr, Et_2O, THF, 20 °C

Oxidation of **28**, with concomitant Meisenheimer rearrangement to give **29**, proceeded readily under the same conditions as optimised for **22** (Scheme 13). To avoid the possibility of by-products from further oxidation of the rearranged product (given the difficulties in precisely estimating the purity of the MCPBA used), the reaction was run with slightly under one equivalent of oxidant, resulting in recovery of 7% starting material. The yield quoted is therefore based on consumed starting material.



Scheme 13 *Reagents and conditions:* i, MCPBA, $CHCl_3$, 20 °C

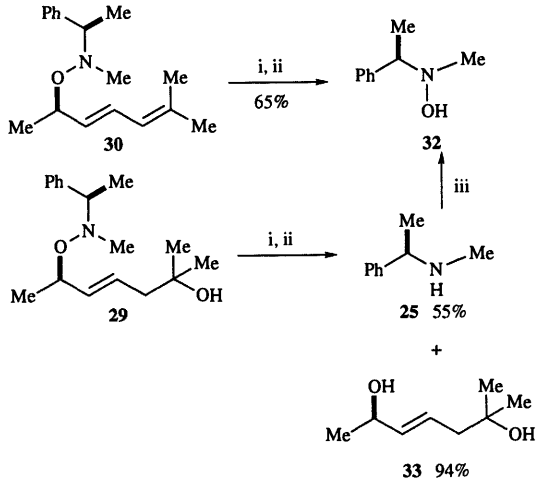
It was hoped that the double bond present in **29** might help direct the dehydration to give the desired regiochemistry, and so dehydration of this substrate was examined first (even though this would require good regiochemical control over the hydrogenation to remove selectively the unwanted 3,4-double bond). However, dehydration with methanesulfonyl chloride and triethylamine proceeded with rather low selectivity, giving the two regioisomers **30** and **31** in a ratio of *ca* 2:1 (Scheme 14). Similar results were obtained using phosphorus oxychloride–pyridine or the Martin sulfurane,[34] while the substrate was resistant to dehydration with camphorsulfonic acid or iodine. The two regioisomers **30** and



Scheme 14 *Reagents and conditions:* i, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 20 °C

31 could be separated by chromatography on silica gel doped with silver nitrate, and were isolated in 63% and 17% yields respectively.

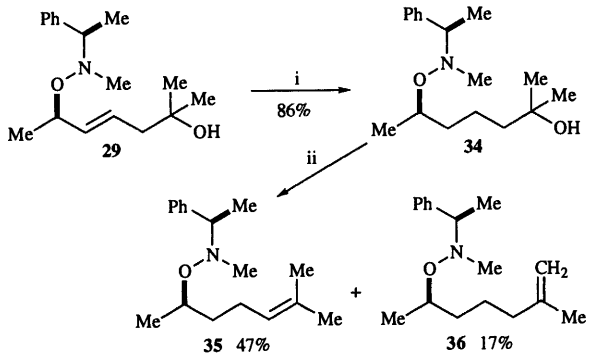
When **30** was subjected to the conditions developed for N–O bond cleavage, no products from that cleavage reaction were observed. Instead, hydroxylamine **32** was isolated, suggesting that O–allyl cleavage was occurring. This was clearly due to the presence of the additional 3,4-double bond, since N–O bond cleavage of **29** to give **33** took place without mishap (Scheme 15). To confirm the identity of hydroxylamine **32**, an authentic sample was prepared by oxidation of amine **25** with dimethyldioxirane.[14]



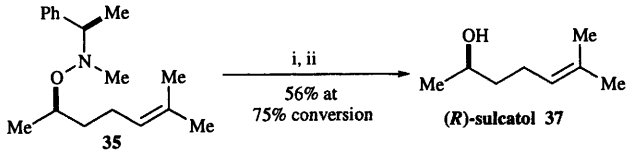
Scheme 15 *Reagents and conditions:* i, Na, NH_3 (l), THF, −78 °C; ii, NH_4Cl (s), −78 °C to 20 °C; iii, Me_2CO_2

Because of the low selectivity in the dehydration of **29**, and then the problems encountered attempting to cleave the N–O bond, the alternative strategy of hydrogenating the unwanted double bond before the dehydration step was investigated. Accordingly, **29** was subjected to catalytic hydrogenation over a rhodium/alumina catalyst to afford **34**, whose dehydration with a number of reagents was examined. Reaction with phosphorus oxychloride in pyridine afforded the two regioisomers of product, **35** and **36**, in a ratio of *ca.* 2:1 (Scheme 16). The ratio was slightly lower if methanesulfonyl chloride–triethylamine or the Martin sulfurane was employed. Once again, the two isomers could be separated by column chromatography on silica gel doped with silver nitrate, and two isomers **35** and **36** were isolated in yields of 47% and 17% respectively.

The major regioisomer **35** was then subjected to N–O bond cleavage with sodium in liquid ammonia. Unfortunately, this reaction did not proceed to completion, but even so, (*R*)-sulcatol was obtained in reasonable yield (Scheme 17).



Scheme 16 *Reagents and conditions:* i, H_2 (6 atm), Rh/Al_2O_3, EtOH, 20 °C; ii, $POCl_3$, pyridine, 20 °C



Scheme 17 *Reagents and conditions:* i, Na, NH_3 (l), THF, −78 °C; ii, NH_4Cl (s), −78 °C to 20 °C

The specific rotation obtained for this synthetic material, $[\alpha]_D^{23} = -16.3$ (*c* 1.26 in EtOH), was in good agreement with the value reported,[32c] $[\alpha]_D^{24.5} = -16.0$ (*c* 1.1 in EtOH).

Thus a sequence consisting of a highly stereoselective conjugate addition followed by a stereospecific Meisenheimer rearrangement has been developed, which affords alcohols in high enantiomeric excess. This methodology has been applied to the asymmetric synthesis from *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate of (*R*)-hexane-1,5-diol, (*R*)-hex-3-ene-1,5-diol and (*R*)-6-methylhept-5-en-2-ol (sulcatol).

Experimental

Optical rotations were determined using a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell, and are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were recorded using either a Gallenkamp capillary apparatus or a Leica Galen III heated stage apparatus, and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1750 FT spectrometer. Solution spectra were recorded using 1.0 mm sodium chloride cells. Selected diagnostic peaks only are quoted. Elemental analyses were performed by the Dyson Perrins analytical department. ^{1}H NMR spectra were recorded on a Bruker AM250 instrument (high temperature spectra), and on Bruker WH300, AM500 or AMX500 instruments. ^{13}C NMR spectra were recorded on Bruker AC200, Varian Gemini 200, Bruker AM500 or AMX500 instruments. All spectra were referenced internally using the solvent signal (^{13}C spectra; or added dioxane for spectra recorded in D_2O) or the residual protonated solvent signal (^{1}H spectra). Chemical shifts (δ) are quoted in ppm downfield from tetramethylsilane. Coupling constants (*J*) are quoted in Hz. First order approximations are employed throughout. The multiplicities of the ^{13}C signals were determined by DEPT editing. The ^{13}C NMR spectra of many of the trisubstituted hydroxylamines and non-cyclic carbamates prepared contained peaks that were very broad. These are identified by an asterisk (*). Furthermore, often a very broad signal for one methyl group lay underneath a much sharper signal for another, so that the chemical shift for only the sharp peak is quoted. Mass spectra were obtained using chemical ionisation (CI, NH_3) on a V.G. TRIO-1 GCMS instrument; using chemical ionisation (CI, NH_3) or desorption chemical ionisation (DCI) on a V.G. Masslab 20–250 instrument; using electrospray on a V.G. BIO-Q instrument, and using atmospheric pressure chemical ionisation (APCI) on a Platform instrument. Column chromatography was performed on silica gel (Kieselgel 60), neutral alumina (BDH, Brockman grade 3), or silver nitrate-doped silica gel (prepared by adding a solution of 10% by weight of silver nitrate in acetonitrile to a suspension of silica in the same solvent and then removing the solvent *in vacuo* at 50 °C). THF and diethyl ether were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Dichloromethane was distilled from calcium hydride under an atmosphere of dry nitrogen. Petrol refers to the fraction of light petroleum boiling in the range 40–60 °C, and was redistilled before use. All reaction diastereoselectivities were estimated by peak integration in the ^{1}H NMR spectrum of the crude reaction products.

Preparation of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 9

Butyllithium (1.50 M; 17.8 cm^3, 26.7 mmol) was added to a solution of (*R*)-*N*-benzyl-(α-methylbenzyl)amine (6.0 g, 28.4 mmol) in anhydrous THF (30 cm^3) under nitrogen at 0 °C. The resultant deep claret solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **8** (3.0 g, 17.8 mmol) in anhydrous THF (15 cm^3) was added by cannula over 1 min, whereupon the reaction mixture turned rapidly dark yellow. After stirring at −78 °C for 2 h (during which time the solution darkened to nearly the original claret colour) the reaction was quenched by the dropwise addition of saturated aqueous ammonium chloride (15 cm^3), and the mixture warmed to 20 °C, giving a pale yellow organic layer. Water (15 cm^3) and diethyl ether (50 cm^3) were added, the layers separated, and the aqueous layer extracted with diethyl ether (3 × 20 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel [petrol–diethyl ether (20:1)] to give (3S,αR)-(E)-tert-*butyl* 3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*hex*-4-*enoate* **9** as a clear pale yellow oil (5.2 g, 77%) (Found: C, 79.40; H, 8.88; N, 3.59. $C_{25}H_{33}NO_2$ requires C, 79.11; H, 8.76; N 3.69%); $[\alpha]_D^{24} = -23.3$ (*c* 2.04 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1729 (s, ester C=O); *m*/*z* (electrospray) 380 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.36 (9 H, s, $OCMe_3$), 1.37 [3 H, partially obscured d, C(α)Me], 1.69 [3 H, d, *J* 4, C(6)H_3], 2.22 [1 H, dd, $J_{2A.2B}$ 14, $J_{2A.3}$ 9, C(2)H_A], 2.35 [1 H, dd, $J_{2A.2B}$ 14, $J_{2B.3}$ 5, C(2)H_B], 3.66 (2 H, s, NCH_2Ph), 3.71–3.79 [1 H, m, C(3)H], 4.00 [1 H, q, *J* 7, C(α)H], 5.46–5.59 [2 H, m, C(4)H and C(5)H], 7.16–7.40 (10 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.7 and 18.0 [C(6) and C(α)*Me*], 28.0 ($OCMe_3$), 39.5 [C(2)], 50.5 (NCH_2Ph), 57.2 and 57.4 [C(3) and C(α)], 79.9 ($OCMe_3$), 126.4 [C(5)], 126.6 and 126.9 (*p*-Ph), 127.8, 127.9, 128.0 and 128.2 (*o*- and *m*-Ph), 131.2 [*C*(4)], 141.7 and 144.5 (*i*-Ph), 171.3 [C(1)].

Oxidation of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 9

A solution of MCPBA (60% pure; 0.17 g, 0.59 mmol) in chloroform (5 cm^3) was added to a solution of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **9** (0.20 g, 0.59 mmol) in chloroform (10 cm^3) at 0 °C. The resulting solution was stirred at 0–20 °C for 3 h, before being loaded onto a column of activated basic alumina (10 g). The column was eluted with chloroform until further elution produced no more material (about 100 cm^3). After concentration *in vacuo*, the residue was examined by ^{1}H NMR spectroscopy. It was found to consist of unreacted starting material **9**, together with *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **8**, (*R*)-*N*-benzyl-*N*-hydroxy(α-methylbenzyl)amine **13** (prepared and characterised below), and (*R*)-*N*-benzylidene-(α-methylbenzyl)amine *N*-oxide **14** (isolated and characterised below).

Preparation of (*R*)-*N*-benzyl-*N*-hydroxy(α-methylbenzyl)amine 13

An acetone solution of dimethyldioxirane[14] (*ca.* 0.1 M; 5.0 cm^3) was added in one portion to a stirred solution of (*R*)-*N*-

benzyl(α-methylbenzyl)amine (0.422 g, 2.0 mmol) in acetone (5 cm^3). After 15 min, the solvents were removed *in vacuo*, and the residue subjected to column chromatography on silica gel [petrol–diethyl ether (5:1)] to give (R)-N-*benzyl*-N-*hydroxy*-(α-*methylbenzyl*)*amine* **13** as a white solid (0.080 g), mp 70–74 °C (*Found: C*, 79.40; H, 7.91; N, 6.29. $C_{15}H_{17}NO$ requires C, 79.26; H, 7.54; N, 6.16%); $[\alpha]_D^{22} = +3.0$ (*c* 1.72 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3581 (m, free OH), 3223 (br, H-bonded OH); *m/z* (CI, NH_3) 228 (MH^+, 30%), 212 (100, $MH^+ - O$), 210 (70, $MH^+ - H_2O$); δ_H(300 MHz; $CDCl_3$) 1.49 (3 H, d, *J* 7, NCH*Me*), 3.62 (1 H, d, *J* 13, NCH_AH_BPh), 3.74 (1 H, d, *J* 13, NCH_AH_BPh), 3.84 (1 H, q, *J* 7, NC*H*Me), 5.10 (1 H, br s, OH), 7.24–7.41 (10 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.5 (NCH*Me*), 61.1 (NCH_2Ph), 66.8 (NCHMe), 127.1 and 127.3 (*p*-Ph), 127.9, 128.2, 128.4 and 129.5 (*o*- and *m*-Ph), 138.2 and 142.7 (*i*-Ph).

Preparation of (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]hex-4-en-1-ol 15

Lithium aluminium hydride (0.105 g, 2.63 mmol) was suspended in anhydrous diethyl ether (5 cm^3) under nitrogen, and cooled to 0 °C. A solution of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **9** (1.0 g, 2.64 mmol) in anhydrous diethyl ether (10 cm^3) was added by cannula over 10 min, and the reaction mixture stirred at 20 °C for 2 h. Water (0.105 cm^3), aqueous sodium hydroxide (15% w/v; 0.105 cm^3), then more water (0.315 cm^3) were added cautiously dropwise with vigorous stirring, causing the grey suspension to turn white. Ethyl acetate (30 cm^3) was added, and the mixture stirred for 30 min, before being filtered through Celite, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [petrol–diethyl ether (2:1)] to give (3S,αR)-(E)-3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*hex-4-en-1-ol* **15** as a clear colourless oil (0.74 g, 91%) (Found: C, 81.67; H, 8.92; N, 4.55. $C_{21}H_{27}NO$ requires C, 81.51; H, 8.79; N 4.53%); $[\alpha]_D^{24} = -62.3$ (*c* 2.73 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3582 (m, free OH), 3267 (br, H-bonded OH); *m/z* (APCI) 310 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.42 [3 H, d, *J* 7, C(α)Me], 1.38–1.48 [1 H, m, $C(2)H_A$], 1.74 [3 H, d, *J* 6, $C(6)H_3$], 1.79–1.91 [1 H, m, $C(2)H_B$], 2.71 (1 H, br s, OH), 3.27–3.41 and 3.53–3.58 [3 H, m, $C(1)H_2$ and C(3)H], 3.63 (1 H, d, *J* 14, NCH_AH_BPh), 3.89 (1 H, d, *J* 14, NCH_AH_BPh), 4.06 [1 H, q, *J* 7, C(α)H], 5.53 [1 H, dq, $J_{4,5}$ 15, $J_{5,6}$ 6, C(5)H], 5.67 [1 H, dd, $J_{4,5}$ 15, $J_{3,4}$ 8, C(4)H], 7.20–7.36 (10 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 14.6 and 18.1 [C(6) and C(α)*Me*], 35.2 [C(2)], 50.3 (NCH_2Ph), 55.9 and 57.3 [C(3) and C(α)], 61.4 [C(1)], 126.8 [C(5)], 126.9 and 127.0 (*p*-Ph), 128.0, 128.1, 128.4 and 129.0 (*o*- and *m*-Ph), 131.9 [C(4)], 140.5 and 144.1 (*i*-Ph).

Preparation of (5*R*,α*R*)-(*E*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)-aminooxy]hex-3-en-1-ol 16

A solution of MCPBA (50% pure; 0.67 g, 1.94 mmol) in chloroform (20 cm^3) was added to a solution of (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol **15** (0.60 g, 1.94 mmol) in chloroform (10 cm^3) at 0 °C. The resulting solution was stirred at 0 °C for 4 h, before being loaded onto a column of activated basic alumina (25 g). The column was eluted with chloroform–methanol (10:1) until further elution produced no more material (about 50 cm^3). After concentration *in vacuo*, the residue was subjected to column chromatography on silica gel [petrol–diethyl ether (5:1)].

The least polar fraction was identified by ^1H NMR spectroscopy as (*R*)-*N*-benzyl-*N*-hydroxy(α-methylbenzyl)-amine **13** (0.01 g, 2%). The assignment was confirmed by synthesis of an authentic sample (*vide supra*).

The next fraction contained some unreacted starting material **15** (0.03 g, 5%).

The next fraction gave the desired product (5R,αR)-(E)-5-[N-*benzyl*-N-(α-*methylbenzyl*)*aminooxy*]*hex*-3-*en*-1-*ol* **16** as a clear colourless oil (0.37 g, 59%) (Found: C, 77.36; H, 8.72; N, 4.05. $C_{21}H_{27}NO_2$ requires C, 77.50; H, 8.36; N, 4.30%); $[\alpha]_D^{22} = +38.3$ (*c* 3.05 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3619 (m, free OH); *m/z* (CI, NH_3) 326 (MH^+, 100%); δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 0.75 (1 H, br s, OH), 1.02 [3 H, d, *J* 6, $C(6)H_3$], 1.43 [3 H, d, *J* 7, C(α)Me], 1.99 [2 H, app. dq, *J* 6.5 and 1.5, $C(2)H_2$], 3.45 [2 H, t, *J* 6, $C(1)H_2$], 3.59 (1 H, app. d, *J* 13, NCH_AH_BPh), 3.77 (1 H, app. d, *J* 13, NCH_AH_BPh), 3.84 [1 H, app. quintet, *J* 6.5, C(5)H], 3.93 [1 H, q, *J* 7, C(α)H], 5.22 [1 H, dd, $J_{3,4}$ 15.5, $J_{4,5}$ 7, C(4)H], 5.34 [1 H, dt, $J_{3,4}$ 15.5, $J_{2,3}$ 6.5, C(3)H], 6.97–7.36 (10 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.8* and 19.6 [C(6) and C(α)*Me*], 35.6 [C(2)], 59.6* and 61.8 [C(1) and NCH_2Ph], 64.9* and 79.2 [C(5) and C(α)], 127.3, 127.4, 128.0, 128.2, 128.4, 128.5 and 130.2 [C(3) and Ph], 135.4 [C(4)], 138.7 and 143.1* (*i*-Ph).

The following fraction contained (*R*)-*N*-benzylidene-(α-methylbenzyl)amine *N*-oxide **14** (0.09 g, 22%); $[\alpha]_{578}^{22} = -77.0$ (*c* 1.32 in CH_2Cl_2) {lit.,[13] $[\alpha]_{578}^{20} = +83.6$ (*c* 1 in CH_2Cl_2) for enantiomer}; δ_H(300 MHz; $CDCl_3$) 1.90 (3 H, d, *J* 7, NCH*Me*), 5.19 (1 H, q, *J* 7, NC*H*Me), 7.28–7.55 (9 H, m, N=C*H*Ph and Ph), 8.21–8.24 (2 H, m, Ph).

Elution with diethyl ether then gave the most polar fraction, which was further purified by column chromatography on silica gel (diethyl ether) to give 6-*hydroxyhex*-3-*en*-2-*one* **18** as a clear colourless oil (0.033 g, 15%) (Found: C, 63.02; H, 9.01. $C_6H_{10}O_2$ requires C, 63.14; H, 8.83%); ν_{max}($CHCl_3$ solution)/cm^{-1} 3621 (m, free OH), 3489 (br, H-bonded OH), 1674 (α,β-unsaturated ketone C=O); *m/z* (CI, NH_3) 115 (MH^+, 10%), 97 (100, $MH^+ - H_2O$); δ_H(300 MHz; $CDCl_3$) 1.79 (1 H, br s, OH), 2.26 [3 H, s, C(1)H], 2.49 [2 H, app. dq, *J* 6 and 1, $C(5)H_2$], 3.79 [2 H, t, *J* 6, C(6)H], 6.16 [1 H, d, *J* 16, C(3)H], 6.82 [1 H, dt, $J_{3,4}$ 16, $J_{4,5}$ 7, C(4)H]; δ_C(50.3 MHz; $CDCl_3$) 26.9 [C(1)], 35.6 [C(5)], 60.8 [C(6)], 132.9 [C(3)], 144.9 [C(4)], 198.9 [C(2)].

Preparation of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 19

Butyllithium (1.50 M; 47.5 cm^3, 71.3 mmol) was added over 15 min to a solution of (*R*)-*N*-methyl(α-methylbenzyl)amine **25** (10.3 g, 76.1 mmol) in anhydrous THF (50 cm^3) under nitrogen at 0 °C. The resultant orange solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **8** (8.0 g, 47.5 mmol) in anhydrous THF (30 cm^3) was added by cannula over 10 min, whereupon the reaction mixture turned yellow. After stirring at −78 °C for 2 h (during which time the solution darkened somewhat) the reaction was quenched by the dropwise addition of saturated aqueous ammonium chloride (50 cm^3), and the mixture warmed to room temperature, giving a pale orange organic layer. Water (50 cm^3) and diethyl ether (150 cm^3) were added, the layers separated, and the aqueous layer extracted with diethyl ether (2 × 50 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [petrol–diethyl ether (9:1)] to give (3S,αR)-(E)-tert-*butyl* 3-[N-*methyl*-N-(α-*methylbenzyl*)*amino*]*hex*-4-*enoate* **19** as a clear pale yellow oil (10.2 g, 71%) (Found: C, 75.26; H, 9.62; N, 4.82. $C_{19}H_{29}NO_2$ requires C, 75.21; H, 9.63; N, 4.62%); $[\alpha]_D^{24} = +27.5$ (*c* 2.08 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1730 (s, ester C=O); *m/z* (APCI) 304 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.33 [3 H, d, *J* 6.5, C(α)Me], 1.42 (9 H, s, $OCMe_3$), 1.70 [3 H, d, *J* 6, $C(6)H_3$], 2.05 (3 H, s, NMe), 2.29 [1 H, dd, $J_{2A,2B}$ 14, $J_{2A,3}$ 8, $C(2)H_A$], 2.52 [1 H, dd, $J_{2A,2B}$ 14, $J_{2B,3}$ 7, $C(2)H_B$], 3.61 [1 H, q, *J* 6.5, C(α)H], 3.78 [1 H, app. q, *J* 7, C(3)H], 5.46 [1 H, dd, $J_{4,5}$ 15.5, $J_{3,4}$ 7, C(4)H], 5.58 [1 H, dq, $J_{4,5}$ 15.5, $J_{5,6}$ 6, C(5)H], 7.17–7.34 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.9 and 20.1 [C(6) and C(α)*Me*], 28.0 ($OCMe_3$), 33.2 (NMe), 38.5 [C(2)], 58.2 and 61.2 [C(3) and C(α)], 80.0 ($OCMe_3$), 126.8 [C(5)], 127.6 (*o*- or *m*-Ph), 127.9 (*p*-Ph), 128.4 (*o*- or *m*-Ph), 129.2 [C(4)], 146.2 (*i*-Ph), 171.9 [C(1)].

A more polar fraction was also isolated off the column, which, after further purification by column chromatography on silica gel [petrol–diethyl ether (5:1)] gave (3R,αR)-(E)-tert-*butyl* 3-[N-*methyl*-N-(α-*methylbenzyl*)*amino*]*hex*-4-*enoate* **20** as a clear colourless oil (0.07 g, 0.5%) (Found: C, 75.19; H, 9.95; N, 4.55. $C_{19}H_{29}NO_2$ requires C, 75.21; H, 9.63; N, 4.62%); $[\alpha]_D^{24} = +50.8$ (*c* 1.21 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1730 (s, ester C=O); *m*/*z* (APCI) 304 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.32 [3 H, d, *J* 7, C(α)Me], 1.40 (9 H, s, $OCMe_3$), 1.68 [3 H, d, *J* 4, C(6)H_3], 2.17 (3 H, s, NMe), 2.26 [1 H, dd, $J_{2A,2B}$ 13.5, $J_{2A,3}$ 9, C(2)H_A], 2.46 [1 H, dd, $J_{2A,2B}$ 13.5, $J_{2B,3}$ 6.5, C(2)H_B], 3.57–3.64 [2 H, m, C(3)H and C(α)H], 5.37–5.48 [2 H, m, C(4)H and C(5)H], 7.18–7.31 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.8 and 21.1 [C(6) and C(α)*Me*], 28.0 ($OCMe_3$), 32.6 (NMe), 39.1 [C(2)], 59.1 and 61.6 [C(3) and C(α)], 80.0 ($OCMe_3$), 126.9 [C(5)], 127.7 and 128.4 (*o*- and *m*-Ph), 128.6 (*p*-Ph), 128.7 [C(4)], 146.8 (*i*-Ph), 171.7 [C(1)].

Inspection of the ^1H NMR spectrum of the crude reaction mixture, and integration of the two singlets at 2.05 and 2.17 ppm (corresponding to the major and minor diastereomer of addition, **19** and **20**, respectively), showed the addition to have occurred in 91% de.

Preparation of (3*S*,α*R*)-(*E*)-3-[*N*-methyl-*N*-(α-methylbenzyl)-amino]hex-4-en-1-ol 22

Lithium aluminium hydride (0.658 g, 16.5 mmol) was suspended in anhydrous diethyl ether (20 cm^3) under nitrogen, and cooled to 0 °C. A solution of (3*S*,α*R*)-(*E*)-*tert*-butyl 3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **19** (5.0 g, 16.5 mmol) in anhydrous diethyl ether (25 cm^3) was added by cannula over 5 min, and the reaction mixture stirred at 0 °C for 2.5 h. Water (0.66 cm^3), aqueous sodium hydroxide (15% w/v; 0.66 cm^3), then more water (2.0 cm^3) were added cautiously dropwise with vigorous stirring, causing the grey suspension to turn white. The mixture was then filtered through Celite, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [petrol–diethyl ether (1:2)] to give (3S,αR)-(E)-3-[N-*methyl*-N-(α-*methylbenzyl*)*amino*]*hex*-4-*en*-1-*ol* **22** as a clear colourless oil, which solidified upon standing (3.5 g, 91%). An analytical sample was prepared by recrystallisation from diethyl ether–petrol to give white plates, mp 42–45 °C (Found: C, 77.48; H, 10.03; N, 5.97. $C_{15}H_{23}NO$ requires C, 77.21; H, 9.93; N, 6.00%); $[\alpha]_D^{22} = +88.6$ (*c* 2.06 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3200 (br, OH); *m*/*z* (APCI) 234 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.42 [3 H, d, *J* 7, C(α)Me], 1.45–1.53 [1 H, m, C(2)H_A], 1.74 [3 H, d, *J* 6, C(6)H_3], 1.95–2.09 [1 H, m, C(2)H_B], 2.00 (3 H, s, NMe), 3.56 [1 H, q, *J* 7, C(α)H], 3.74–3.95 [3 H, m, C(1)H_2 and C(3)H], 5.49 [1 H, dd, $J_{4,5}$ 15, $J_{3,4}$ 8, C(4)H], 5.61 [1 H, dq, $J_{4,5}$ 15, $J_{5,6}$ 6, C(5)H], 5.99 (1 H, br s, OH), 7.20–7.33 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 18.0 and 20.6 [C(6) and C(α)*Me*], 32.4 [C(2)], 33.5 (NMe), 61.5 and 62.2 [C(3) and C(α)], 63.5 [C(1)], 127.0 [C(5)], 127.2 (*o*- or *m*-Ph), 127.6 (*p*-Ph), 128.3 [C(4)], 128.5 (*o*- or *m*-Ph), 144.9 (*i*-Ph).

Preparation of (5*R*,α*R*)-(*E*)-5-[*N*-methyl-*N*-(α-methylbenzyl)-aminooxy]hex-3-en-1-ol 23

A solution of MCPBA (50% pure; 2.96 g, 8.57 mmol) in chloroform (50 cm^3) was added to a solution of (3*S*,α*R*)-(*E*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol **22** (2.0 g, 8.57 mmol) in chloroform (50 cm^3) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, before being loaded onto a column of activated basic alumina (150 g). The column was eluted with chloroform–methanol (5:1) until further elution produced no more material (about 200 cm^3). The solution was left at room temperature for 48 h until the rearrangement was complete. After concentration *in vacuo*, the residue was subjected to column chromatography on silica gel [petrol–diethyl ether (1:2)] to give (5R,αR)-(E)-5-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hex*-3-*en*-1-*ol* **23** (2.1 g, 98%) as a clear colourless oil (Found: C, 72.58; H, 9.45; N, 5.54. $C_{15}H_{23}NO_2$ requires C, 72.25; H, 9.30; N 5.62%); $[\alpha]_D^{22} = +30.3$ (*c* 2.06 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3620 (m, free OH); *m*/*z* (CI, NH_3) 250 (MH^+, 100%); δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 0.86 (1 H, br s, OH), 1.18 [3 H, d, *J* 6, C(6)H_3], 1.37 [3 H, d, *J* 7, C(α)Me], 2.00–2.07 [1 H, m, C(2)H_2], 2.37 (3 H, s, NMe), 3.37 [2 H, t, *J* 6, C(1)H_2], 3.60 [1 H, q, *J* 7, C(α)H], 4.02–4.12 [1 H, m, C(5)H], 5.35–5.44 [2 H, m, C(3)H and C(4)H], 6.97–7.27 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.7 [C(6) and C(α)*Me*], 35.6 [C(2)], 44.3 (NMe), 61.5 [C(1)], 68.5 and 76.5 [C(5) and C(α)], 127.1 and 128.1 [C(3) and Ph], 134.9 [C(4)], 143.1 (*i*-Ph).

Cleavage of (5*R*,α*R*)-(*E*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)-aminooxy]hex-3-en-1-ol 16

Copper(II) acetate monohydrate (0.030 g, 0.15 mmol) and zinc dust (0.975 g, 14.9 mmol) were suspended in glacial acetic acid (2.5 cm^3) and the suspension stirred for 10 min, until the blue colour disappeared. A solution of (5*R*,α*R*)-(*E*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)aminooxy]hex-3-en-1-ol **16** (0.312 g, 0.959 mmol) in acetic acid–water (4:1; 4.5 cm^3) was added, and the mixture was stirred at 60–70 °C for 3 h. After cooling to 20 °C, the mixture was neutralised to pH 8 with aqueous sodium hydroxide (6 M; about 15 cm^3), causing formation of a white gelatinous precipitate. This mixture was extracted with ethyl acetate (5 × 25 cm^3), and the combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate) to give (*R*)-hex-3-ene-1,5-diol **24** (0.057 g, 51%); data as below.

Cleavage of (5*R*,α*R*)-(*E*)-5-[*N*-methyl-*N*-(α-methylbenzyl)-aminooxy]hex-3-en-1-ol 23

Liquid ammonia (30 cm^3) was dried with sodium (until the blue colour persisted), recondensed, and stirred at −78 °C under nitrogen. Freshly cut sodium (0.166 g, 7.22 mmol) was added in small pieces, causing a blue colour to appear. After stirring for 20 min, a solution of (5*R*,α*R*)-(*E*)-5-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hex-3-en-1-ol **23** (0.60 g, 2.41 mmol) in anhydrous THF (5 cm^3) was added by cannula, and the solution stirred for 1.5 h. Solid ammonium chloride (0.5 g, 9.3 mmol) was added in one portion, causing the blue colour to disappear. The flask was opened to air through a calcium chloride drying tube, and left for 24 h at 20 °C for the solvents to evaporate. The residue was extracted with diethyl ether (3 × 10 cm^3), and the combined extracts were filtered and concentrated *in vacuo*. Column chromatography on silica gel [diethyl ether then diethyl ether–methanol (20:1)] gave (R)-*hex*-3-*ene*-1,5-*diol* **24** as a clear colourless oil (0.264 g, 94%) (Found: C, 62.31; H, 10.80. $C_6H_{12}O_2$ requires C, 62.04; H, 10.41%); $[\alpha]_D^{26} = -11.2$ (*c* 2.20 in $CHCl_3$), $[\alpha]_D^{26} = -1.4$ (*c* 2.22 in MeOH); ν_{max}($CHCl_3$ solution)/cm^{-1} 3609 (m, free OH), 3430 (br, H-bonded OH); *m*/*z* (CI, NH_3) 134 (MNH_4^+, 20%), 116 (100, $MNH_4^+ - H_2O$), 99 (40, $MH^+ - H_2O$), 98 (70, $MNH_4^+ - 2H_2O$), 81 (80, $MH^+ - 2H_2O$); δ_H(300 MHz; $CDCl_3$) 1.26 [3 H, d, *J* 6, C(6)H_3], 2.10 (2 H, br s, 2 × OH), 2.25–2.31 [2 H, m, C(2)H_2], 3.62–3.70 [2 H, m, C(1)H_2], 4.23–4.32 [1 H, m, C(5)H], 5.56–5.69 [2 H, m, C(3)H and C(4)H]; δ_C(50.3 MHz; $CDCl_3$) 23.1 [C(6)], 35.3 [C(2)], 61.4 [C(1)], 68.5 [C(5)], 127.1 [C(3)], 137.0 [C(4)].

The solid residue was dissolved in dilute hydrochloric acid (1 M; 10 cm^3) and basified (pH 11) by the addition of solid sodium hydroxide. This solution was extracted with diethyl ether (3 × 10 cm^3), and the organic extracts dried (magnesium sulfate), filtered and concentrated *in vacuo* to give (*R*)-*N*-methyl(α-methylbenzyl)amine **25** as a clear colourless oil (0.20 g, 61%). ^1H NMR chiral shift studies using (*S*)-*O*-acetylmandelic acid [25] showed this amine, and the starting amine, to both be of >95% ee. The chemical shifts of the peaks corresponding to the (*S*)-amine were established by doping with authentic (*S*)-*N*-methyl-α-methylbenzylamine.

Preparation of (*R*)-hexane-1,5-diol 26 and determination of enantiomeric purity

A solution of (*R*)-hex-3-ene-1,5-diol **24** (0.056 g, 0.48 mmol) in ethanol (10 cm^3) was placed in a Fischer–Porter bottle under argon and 5% rhodium on alumina (3.0 mg) was added. The suspension was stirred rapidly under hydrogen (5 atm†) at 20 °C for 18 h. After removal of the catalyst by filtration through Celite, the solution was concentrated *in vacuo*, and the residue purified by column chromatography on silica gel [diethyl ether then diethyl ether–methanol (20:1)] to give the title compound **26** as a clear colourless oil (0.040 g, 70%); $[\alpha]_D^{23} = -12.2$ (*c* 1.39 in MeOH) {lit.,[26] $[\alpha]_D^{26} = -11$ (*c* 0.41 in MeOH); and [27] $[\alpha]_D^{20} = +12.9$ (*c* 1 in MeOH) for enantiomer}; δ_H(300 MHz; $CDCl_3$) 1.20 [3 H, d, *J* 6 CH(OH)*Me*], 1.39–1.65 [8 H, m, C(2)H_2, C(3)H_2, C(4)H_2 and 2 × OH], 3.67 [2 H, t, *J* 6, C(1)H_2], 3.82 [1 H, app. sextet, *J* 6, C(5)H].

A sample of the diol **26** was converted into the dibenzoyl derivative under standard conditions [benzoyl chloride (6 equiv.), 4-dimethylaminopyridine (8 equiv.), dichloromethane, 20 °C, 8 h], and chiral HPLC was used to assess the enantiomeric purity. A Waters 600E HPLC system was employed, with 250 mm × 4.6 mm CHIRALCEL OB column (Daicel Chemical Industries, Ltd.), Waters 484 tunable absorbance detector set to 220 nm, and Hewlett Packard HP 3394A integrator. The eluent was hexane–isopropanol (4:1), and the sample (5–15 μl) was injected as a solution in hexane (10 mg ml^{-1}). Retention times of the two enantiomers (determined using the dibenzoyl derivative of racemic hexane-1,5-diol) were 9.4 min [(*R*)-enantiomer] and 16.3 min [(*S*)-enantiomer]. The minor enantiomer corresponded to the second, broader peak, which was therefore hard to integrate with accuracy. The enantiomeric excess was determined as 95%, but with an uncertainty of at least ± 5%.

Preparation of (3*S*,α*R*)-(*E*)-methyl 3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 27

(3*S*,α*R*)-(*E*)-*tert*-Butyl 3-[*N*-methyl-*N*-(α-methylbenzyl)-amino]hex-4-enoate **19** (1.2 g, 3.95 mmol) was dissolved in anhydrous methanol (5 cm^3) and a saturated solution of hydrogen chloride in anhydrous methanol (50 cm^3) was added. The resulting solution was stirred at 20 °C for 1 h, and the solvents removed *in vacuo*. The residue was treated again with methanolic hydrogen chloride in the same manner, and stirring continued overnight. After concentration *in vacuo*, the residue was partitioned between saturated aqueous sodium hydrogen carbonate (50 cm^3) and dichloromethane (100 cm^3). The aqueous phase was further extracted with dichloromethane (50 cm^3), and the combined organic extracts dried (magnesium sulfate), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica gel [petrol–diethyl ether (4:1)] to give (3S,αR)-(E)-*methyl* 3-[N-*methyl*-N-(α-*methylbenzyl*)*amino*]*hex*-4-*enoate* **27** as a clear pale yellow oil (1.0 g, 97%) (Found: C, 73.80; H, 8.71; N, 5.63. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%); $[\alpha]_D^{26} = +31.9$ (*c* 2.67 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1741 (s, ester C=O); *m*/*z* (electrospray) 262 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.33 [3 H, d, *J* 7, C(α)Me], 1.70 [3 H, dd, $J_{5,6}$ 6, $J_{4,6}$ 1, C(6)H_3], 2.05 (3 H, s, NMe), 2.42 [1 H, dd, $J_{2A,2B}$ 14, $J_{2A,3}$ 8, C(2)H_A], 2.63 [1 H, dd, $J_{2A,2B}$ 14, $J_{2B,3}$ 7, C(2)H_B], 3.61 [1 H, q, *J* 7, C(α)H], 3.67 (3 H, s, OMe), 3.87 [1 H, app. q, *J* 7.5, C(3)H], 5.47 [1 H, ddq, $J_{4,5}$ 15, $J_{3,4}$ 7.3, $J_{4,6}$ 1, C(4)H], 5.59 [1 H, dq, $J_{4,5}$ 15, $J_{5,6}$ 6, C(5)H], 7.18–7.30 (5 H, m, Ph); δ_C(50.3 MHz, $CDCl_3$) 17.9 and 20.3 [C(6) and C(α)*Me*], 33.2 (NMe), 37.5 [C(2)], 51.4 (OMe), 57.8 and 61.3 [C(3) and C(α)], 126.8 [C(5)], 127.4 (*o*- or *m*-Ph), 128.0 (*p*-Ph), 128.4 (*o*- or *m*-Ph), 129.0 [C(4)], 146.3 (*i*-Ph), 173.0 [C(1)].

† 1 atm = 101 325 Pa.

Preparation of (4*S*,α*R*)-(*E*)-2-methyl-4-[*N*-methyl-*N*-(α-methylbenzyl)amino]hept-5-en-2-ol 28

Methylmagnesium bromide solution (3 M; 8.8 cm^3, 26.4 mmol) was added by syringe over 5 min to a stirred solution of (3*S*,α*R*)-(*E*)-methyl 3-[*N*-methyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **27** (1.15 g, 4.40 mmol) in anhydrous THF (30 cm^3) under nitrogen at 20 °C. Stirring was continued for 3 h, and the reaction was then quenched by the dropwise addition of saturated aqueous ammonium chloride (10 cm^3) with cooling (ice-bath). Water (10 cm^3) was added to redissolve the white precipitate which formed, and then the mixture was extracted with diethyl ether (40 + 2 × 20 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Purification by column chromatography on neutral alumina [petrol–diethyl ether (1:1)] gave (4S,αR)-(E)-2-*methyl*-4-[N-*methyl*-N-(α-*methylbenzyl*)*amino*]*hept*-5-*en*-2-*ol* **28** as a clear colourless oil which solidified upon protracted standing (1.07 g, 93%), mp 36–43 °C (Found: C, 78.15; H, 10.73; N, 5.01. $C_{17}H_{27}NO_2$ requires C, 78.11; H, 10.41; N, 5.36%); $[\alpha]_D^{26} = +78.8$ (*c* 1.15 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3167 (br, OH); *m*/*z* (electrospray) 262 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.22 [3 H, s, C(2)Me_A], 1.26–1.35 [1 H, partially obscured dd, C(3)H_A], 1.35 [3 H, s, C(2)Me_B], 1.47 [3 H, d, *J* 7, C(α)Me], 1.74 [3 H, dd, $J_{6,7}$ 6, $J_{5,7}$ 1, C(7)H_3], 1.92–2.01 [1 H, partially obscured dd, C(3)H_B], 1.97 (3 H, s, NMe), 3.49 [1 H, q, *J* 7, C(α)H], 4.08 [1 H, ddd, $J_{3A,4}$ 11.5, $J_{4,5}$ 8, $J_{3B,43}$, C(4)H], 5.44 [1 H, ddq, $J_{5,6}$ 15, $J_{4,5}$ 8.1, $J_{5,7}$ 1, C(5)H], 5.62 [1 H, dq, $J_{5,6}$ 15, $J_{6,7}$ 6, C(6)H], 7.19–7.31 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.9 and 21.4 [C(7) and C(α)*Me*], 28.7 and 31.8 [C(2)Me_2], 33.2 (NMe), 41.7 [C(3)], 56.6 and 63.0 [C(4) and C(α)], 70.5 [C(2)], 127.3, 128.7 and 128.8 [C(5), C(6) and Ph], 145.1 (*i*-Ph).

Preparation of (6*R*,α*R*)-(*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-4-en-2-ol 29

A solution of MCPBA (50% pure; 2.03 g, 5.89 mmol) in chloroform (50 cm^3) was added to a solution of (4*S*,α*R*)-(*E*)-2-methyl-4-[*N*-methyl-*N*-(α-methylbenzyl)amino]hept-5-en-2-ol **28** (1.54 g, 5.88 mmol) in chloroform (50 cm^3) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, before being loaded onto a column of activated basic alumina (100 g). The column was eluted with chloroform–methanol (10:1) until further elution produced no more material (about 500 cm^3). The solution was left at room temperature for 24 h until the rearrangement was complete. After concentration *in vacuo*, the residue was subjected to column chromatography on neutral alumina [petrol–diethyl ether (1:1), then diethyl ether]. The less polar fraction contained unreacted starting material **28** (0.103 g, 7%), while the more polar fraction gave (6R,αR)-(E)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hept*-4-*en*-2-*ol* **29** as a clear colourless oil [1.44 g, 88% (94% based on consumed starting material)] (Found: C, 73.76; H, 9.86; N, 5.48. $C_{17}H_{27}NO_2$ requires C, 73.61; H, 9.81; N, 5.05%); $[\alpha]_D^{26} = +33.6$ (*c* 0.73 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3401 (br, OH); *m*/*z* (electrospray) 278 (MH^+); δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 0.99 (1 H, br s, OH), 1.06 [3 H, s, C(2)Me_A], 1.07 [3 H, s, C(2)Me_B], 1.19 [3 H, d, *J* 6, C(7)H_3], 1.38 [3 H, d, *J* 7, C(α)Me], 2.01 [2 H, d, *J* 7, C(3)H_2], 2.37 (3 H, s, NMe), 3.60 [1 H, q, *J* 7, C(α)H], 4.10 [1 H, app. quintet, *J* 6.5, C(6)H], 5.41 [1 H, dd, $J_{4,5}$ 15.5, $J_{5,6}$ 7, C(5)H], 5.58 [1 H, dt, $J_{4,5}$ 15.5, $J_{3,4}$ 7, C(4)H], 6.97–7.27 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.8 [C(7) and C(α)*Me*], 29.0 and 29.1 [C(2)Me_2], 44.5 (NMe), 46.6 [C(3)], 68.6 [C(α)], 70.4 [C(2)], 78.7 [C(6)], 127.1, 127.3, 127.9 and 128.1 [C(4) and Ph], 136.4 [C(5)], 143.3 (*i*-Ph).

Dehydration of (6*R*,α*R*)-(*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-4-en-2-ol 29

(6*R*,α*R*)-(*E*)-2-Methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)amino-oxy]hept-4-en-2-ol **29** (0.60 g, 2.16 mmol) was dissolved in

anhydrous dichloromethane (30 cm^3) and stirred in a flask protected from moisture (calcium chloride drying tube). Methanesulfonyl chloride (0.743 g, 6.49 mmol), followed by triethylamine (1.31 g, 13.0 mmol), were added dropwise by syringe, and the resulting solution stirred at 20 °C for 1 h, during which time a yellow colour developed. The solvents were removed *in vacuo*, and the residue extracted with diethyl ether (2 × 50 + 2 × 15 cm^3). The organic extracts were filtered and concentrated *in vacuo*, and the residue purified by column chromatography on neutral alumina [petrol–diethyl ether (5:1)], to give a mixture of two regioisomeric dehydration products. Separation of these was achieved by column chromatography on silver nitrate-doped silica gel [petrol–diethyl ether (1:1) followed by diethyl ether].

The less polar fraction gave (6R,αR)-(4E)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hepta*-2,4-*diene* **30** as a clear colourless oil (0.355 g, 63%) (Found: C, 78.38; H, 10.10; N, 5.55. $C_{17}H_{25}NO$ requires C, 78.72; H, 9.71; N, 5.40%); $[\alpha]_D^{21} = +8.9$ (*c* 1.94 in $CHCl_3$); *m/z* (CI, NH_3) 260 (MH^+, 50%), 109 (100, $C_8H_{13}^+$); δ_H(250 MHz; $C_6D_5CD_3$; 90 °C) 1.24 [3 H, d, *J* 6, C(7)H_3], 1.39 [3 H, d, *J* 7, C(α)Me], 1.61 [3 H, s, C(2)Me_A], 1.63 [3 H, s, C(2)Me_B], 2.39 (3 H, s, NMe), 3.64 [1 H, q, *J* 7, C(α)H], 4.20 [1 H, app. quintet *J* 6.5, C(6)H], 5.49 [1 H, dd, $J_{4,5}$ 15, $J_{5,6}$ 7.2, C(5)H], 5.79 [1 H, br d, *J* 11, C(3)H], 6.36 [1 H, dd, $J_{4,5}$ 15, $J_{3,4}$ 11, C(4)H], 6.97–7.28 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 18.2 [C(2)Me_A], 19.8 [C(7) and C(α)*Me*], 25.9 [C(2)Me_B], 44.4 (NMe), 68.5 and 78.8 [C(α) and C(6)], 124.9 [C(3)], 127.3, 127.9 and 128.3 [C(4) and Ph], 132.5 [C(5)], 135.6 [C(2)], 143.6 (*i*-Ph).

The more polar fraction gave (6R,αR)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hepta*-1,4-*diene* **31** as a clear colourless oil (0.095 g, 17%) (Found: C, 78.96; H, 10.04; N, 5.44. $C_{17}H_{25}NO$ requires C, 78.72; H, 9.71; N, 5.40%); $[\alpha]_D^{21} = +21.7$ (*c* 0.92 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 890 (m, =CH_2); *m/z* (CI, NH_3) 260 (MH^+, 20%), 109 (80, $C_8H_{13}^+$), 105 (100, $PhCHMe^+$); δ_H(250 MHz; $C_6D_5CD_3$; 90 °C) 1.20 [3 H, d, *J* 6, C(7)H_3], 1.38 [3 H, d, *J* 7, C(α)Me], 1.63 [3 H, s, C(2)Me], 2.37 (3 H, s, NMe), 2.61 [2 H, d, *J* 6, C(3)H_2], 3.62 [1 H, q, *J* 7, C(α)H], 4.12 [1 H, app. quintet, *J* 6.5, C(6)H], 4.72–4.75 [2 H, m, C(1)H_2], 5.42 [1 H, ddt, $J_{4,5}$ 15, $J_{5,6}$ 7, $J_{3,5}$ 1.0, C(5)H], 5.56 [1 H, dt, $J_{4,5}$ 15, $J_{3,4}$ 6, C(4)H], 6.97–7.27 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.6 [C(7) and C(α)*Me*], 22.3 [C(2)*Me*], 40.8 [C(3)], 44.4 (NMe), 68.7 and 78.7 [C(α) and C(6)], 110.8 [C(1)], 127.3, 128.2 and 128.3 (*o*-, *m*-, and *p*-Ph), 129.8 [C(4)], 133.9 [C(5)], 143.8 (*i*-Ph), 144.9 [C(2)].

Attempted cleavage of (6*R*,α*R*)-(4*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hepta-2,4-diene 30

Liquid ammonia (30 cm^3) was dried with sodium (until the blue colour persisted), recondensed and stirred at −78 °C under nitrogen. Freshly cut sodium (0.050 g, 2.14 mmol) was added in small pieces, causing a blue colour to appear. After stirring for 20 min, a solution of (6*R*,α*R*)-(4*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hepta-2,4-diene **30** (0.185 g, 0.713 mmol) in anhydrous THF (5 cm^3) was added by cannula. Stirring was continued for 1 h, during which time the blue solution turned dark brown. Solid ammonium chloride (0.5 g, 9.3 mmol) was then added in one portion, causing a lightening of the brown colour. The flask was opened to air through a calcium chloride drying tube, and left for 24 h at 20 °C for the solvents to evaporate. The residue was extracted with diethyl ether (3 × 10 cm^3), and the combined extracts were filtered and concentrated *in vacuo*. None of the expected unsaturated alcohol could be detected in the crude ^1H NMR spectrum. The major product was the hydroxylamine resulting from O–allyl cleavage rather than N–O cleavage. This was purified by column chromatography on silica gel [petrol–diethyl ether (1:1)] to give (R)-N-*hydroxy*-N-*methyl*(α-*methylbenzyl*)*amine* **32** as a white solid (0.070 g, 65%), mp 45–50 °C (Found: C, 71.25; H, 8.39; N, 9.04. $C_9H_{13}NO$ requires C, 71.49; H, 8.67; N, 9.26%); $[\alpha]_D^{22} = +39.9$ (*c* 1.53 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3583 (m, free OH), 3212 (br, H-bonded OH); *m/z* (electrospray) 152 (MH^+); δ_H(300 MHz, $CDCl_3$) 1.45 (3 H, d, *J* 7, NCHMe), 2.55 (3 H, s, NMe), 3.63 (1 H, q, *J* 7, NC*H*Me), 6.0 (1 H, br s, OH), 7.23–7.36 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.9 (NCH*Me*), 45.8 (NMe), 69.4 (N*C*HMe), 127.6 (*p*-Ph), 128.0 and 128.7 (*o*- and *m*-Ph), 142.7 (*i*-Ph).

Cleavage of (6*R*,α*R*)-(*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-4-en-2-ol 29

Liquid ammonia (30 cm^3) was dried with sodium (until the blue colour persisted), recondensed and stirred at −78 °C under nitrogen. Freshly cut sodium (0.149 g, 6.49 mmol) was added in small pieces, causing a blue colour to appear. After stirring for 20 min, a solution of (6*R*,α*R*)-(*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-4-en-2-ol **29** (0.60 g, 2.16 mmol) in anhydrous THF (5 cm^3) was added by cannula, and the solution stirred for 1.5 h. Solid ammonium chloride (0.5 g, 9.3 mmol) was added in one portion, causing the blue colour to disappear. The flask was opened to air through a calcium chloride drying tube, and left for 24 h at 20 °C for the solvents to evaporate. The residue was extracted with diethyl ether (3 × 10 cm^3), and the combined extracts were filtered and concentrated *in vacuo*. Column chromatography on silica gel [diethyl ether then diethyl ether–methanol (20:1)] gave (R)-2-*methylhept*-4-*ene*-2,6-*diol* **33** as a clear colourless oil (0.292 g, 94%) (Found: C, 66.84; H, 11.28. $C_8H_{16}O_2$ requires C, 66.63; H, 11.18%); $[\alpha]_D^{26} = -2.2$ (*c* 2.50 in $CHCl_3$), $[\alpha]_D^{26} = +0.9$ (*c* 1.60 in MeOH); ν_{max}($CHCl_3$ solution)/cm^{-1} 3606 (m, free OH), 3436 (br, H-bonded OH); *m/z* (CI, NH_3) 162 (MNH_4^+, 20%), 144 (70, $MNH_4^+ - H_2O$), 109 (100, $MH^+ - 2H_2O$); δ_H(300 MHz; $CDCl_3$) 1.21 [6 H, s, C(2)Me_2], 1.27 [3 H, d, *J* 6, C(7)H_3], 1.83 (2 H, br s, 2 × OH), 2.19 [2 H, d, *J* 7, C(3)H_2], 4.30 [1 H, app. quintet, *J* 6, C(6)H], 5.60 [1 H, dd, $J_{4,5}$ 15.5, $J_{5,6}$ 6, C(5)H], 5.71 [1 H, dt, $J_{4,5}$ 15.5, $J_{3,4}$ 7, C(4)H]; δ_C(50.3 MHz; $CDCl_3$) 23.3 [C(7)], 28.8 and 29.4 [C(2)Me_2], 46.2 [C(3)], 68.5 [C(6)], 70.6 [C(2)], 125.8 [C(4)], 138.3 [C(5)].

(*R*)-*N*-Methyl-(α-methylbenzyl)amine **25** (0.16 g, 55%) could be recovered from the solid residue in the manner described above.

Preparation of (6*R*,α*R*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]heptan-2-ol 34

A solution of (6*R*,α*R*)-(*E*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-4-en-2-ol **29** (0.77 g, 0.25 mmol) in ethanol (10 cm^3) was placed in a Fischer–Porter bottle under argon and 5% rhodium on alumina (70 mg) was added. The suspension was stirred rapidly under hydrogen (6 atm) at 20 °C for 20 h. After removal of the catalyst by filtration through Celite, the solution was concentrated *in vacuo*, and the residue purified by column chromatography on neutral alumina [petrol–diethyl ether (1:1), then diethyl ether] to give (6R,αR)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*heptan*-2-*ol* **34** as a clear colourless oil (0.67 g, 86%) (Found: C, 73.28; H, 10.67; N, 5.10. $C_{17}H_{29}NO_2$ requires C, 73.07; H, 10.46; N, 5.01%); $[\alpha]_D^{24} = -1.4$ (*c* 1.55 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3383 (br, OH); *m/z* (electrospray) 280 (MH^+); δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 0.65 (1 H, br s, OH), 1.04 [6 H, s, C(2)Me_2], 1.18 [3 H, d, *J* 6, C(7)H_3], 1.21–1.51 [6 H, m, C(3)H_2, C(4)H_2 and C(5)H_2], 1.36 [3 H, d, *J* 7, C(α)Me], 2.38 (3 H, s, NMe), 3.56–3.67 [2 H, m, C(6)*H* and C(α)H], 6.97–7.29 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.7 [C(7) and C(α)*Me*], 20.3 [C(4)], 29.1 and 29.2 [C(2)Me_2], 36.0 [C(5)], 44.0 [C(3)], 44.5 [NMe], 68.7* [C(α)], 70.9 [C(2)], 77.5* [C(6)], 127.0, 127.9 and 128.1 (*o*-, *m*- and *p*-Ph), 143.3 (*i*-Ph).

Dehydration of (6*R*,α*R*)-2-methyl-6-[*N*-(α-methylbenzyl)-aminooxy]heptan-2-ol 34

(6*R*,α*R*)-2-Methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)amino-

oxy]heptan-2-ol **34** was dissolved in pyridine (10 cm^3) and stirred in a flask protected from moisture (calcium chloride drying tube). Phosphorus oxychloride (4.39 g, 28.6 mmol) was added dropwise with cooling (ice-bath), and the reaction mixture stirred at 20 °C before being worked up by the cautious dropwise addition of water (20 cm^3) with cooling (ice-bath). Diethyl ether (50 cm^3) was added, and the mixture was washed with dilute hydrochloric acid (1 M; 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate (20 cm^3) and brine (20 cm^3). The organic layer was then dried (magnesium sulfate), filtered and concentrated *in vacuo* and the residue purified by column chromatography on silica gel [petrol–diethyl ether (20:1)], to give a mixture of two regioisomeric dehydration products. Separation of these was achieved by column chromatography on silver nitrate-doped silica gel [petrol–diethyl ether (20:1 then 5:1)].

The less polar fraction gave (6R,αR)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hept*-2-*ene* **35** as a clear colourless oil (0.354 g, 47%) (Found: C, 78.01; H, 10.69; N, 5.59. $C_{17}H_{27}NO$ requires C, 78.11; H, 10.41; N, 5.36%); $[\alpha]_D^{22}$ = −12.8 (*c* 2.12 in $CHCl_3$); *m*/*z* (CI, NH_3) 262 (MH^+, 15%), 136 [80, $PhCH(Me)NH_2Me^+$]; 134 [100, $PhCHMeNH(OH)Me^+ - H_2O$]; δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 1.17 [3 H, d, *J* 6, C(7)H_3], 1.25–1.60 [2 H, m, C(5)H_2], 1.36 [3 H, d, *J* 7, C(α)Me], 1.54 [3 H, s, C(2)Me_A], 1.63 [3 H, s, C(2)Me_B], 1.86–2.05 [2 H, m, C(4)H_2], 2.36 (3 H, s, NMe), 3.56–3.71 [2 H, m, C(α)H and C(6)H], 5.08–5.14 [1 H, m, C(3)H], 6.97–7.28 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 17.7 [C(2)Me_A], 19.5 and 20.2* [C(7) and C(α)*Me*], 24.1 [C(4)], 25.7 [C(2)Me_B], 35.6 [C(5)], 44.2 (NMe), 68.6* and 77.2* [C(6) and C(α)], 124.5 [C(3)], 127.0, 127.9 and 128.1 (*o*-, *m*-, and *p*-Ph), 131.1 [C(2)], 143.4 (*i*-Ph).

The more polar fraction gave (6R,αR)-2-*methyl*-6-[N-*methyl*-N-(α-*methylbenzyl*)*aminooxy*]*hept*-1-*ene* **36** as a clear colourless oil (0.128 g, 17%) (Found: C, 78.27; H, 10.65; N, 6.62. $C_{17}H_{27}NO$ requires C, 78.11; H, 10.41; N, 5.36%); $[\alpha]_D^{21}$ = −6.7 (*c* 0.78 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 887 (m, =CH_2); *m*/*z* (CI, NH_3) 262 (MH^+, 10%), 136 [60, $PhCH(Me)NH_2Me^+$]; 134 [100, $PhCHMeNH(OH)Me^+ - H_2O$]; δ_H(250 MHz; $C_6D_5CD_3$; 70 °C) 1.16 [3 H, d, *J* 6, C(7)H_3], 1.20–1.57 [4 H, m, C(4)H_2 and C(5)H_2], 1.35 [3 H, d, *J* 7, C(α)Me], 1.62 [3 H, s, C(2)Me], 1.89 [2 H, t, *J* 7, C(3)H_2], 2.36 (3 H, s, NMe), 3.55–3.68 [2 H, m, C(α)H and C(6)H], 4.71–4.72 [2 H, m, C(2)H_2], 6.97–7.27 (5 H, m, Ph); δ_C(50.3 MHz; $CDCl_3$) 19.6 [C(7) and C(α)*Me*], 22.3 [C(2)*Me*], 23.5 [C(4)], 35.1 and 37.8 [C(3) and C(5)], 44.3 [NMe], 68.7* and 77.4* [C(α) and C(6)], 109.7 [C(1)], 127.0, 127.9 and 128.1 (*o*-, *m*- and *p*-Ph), 143.7 (*i*-Ph), 146.0 [C(2)].

Synthesis of (*R*)-sulcatol 37

Liquid ammonia (20 cm^3) was dried with sodium (until the blue colour persisted), recondensed and stirred at −78 °C under nitrogen. Freshly cut sodium (0.042 g, 6.49 mmol) was added in small pieces, causing a blue colour to appear. After stirring for 20 min, a solution of (6*R*,α*R*)-2-methyl-6-[*N*-methyl-*N*-(α-methylbenzyl)aminooxy]hept-2-ene **35** (0.160 g, 0.612 mmol) in anhydrous THF (1 cm^3) was added by syringe, and the solution stirred for 1.5 h. The blue colour did not persist, so further portions of sodium (3 × 0.010 g) were added at intervals during this period, at the end of which the solution was yellow. Solid ammonium chloride (0.25 g, 4.7 mmol) was added in one portion, causing the yellow colour to disappear. The flask was opened to air through a calcium chloride drying tube, and left for 24 h at 20 °C for the solvents to evaporate. The residue was extracted with diethyl ether (3 × 10 cm^3), and the combined extracts were filtered and concentrated *in vacuo*. Column chromatography on silica gel [dichloromethane–diethyl ether (10:1 then 1:1)] gave some unreacted starting material **35** (0.040 g, 25%), followed by (*R*)-sulcatol **37** as a clear colourless oil [0.044 g, 56% (75% based on consumed starting material)]; $[\alpha]_D^{23}$ = −16.3 (*c* 1.26 in EtOH) {lit.,[32c] $[\alpha]_D^{24.5}$ = −16.0 (*c* 1.1 in EtOH)}; δ_H(300 MHz; $CDCl_3$) 1.20 [3 H, d, *J* 6 CH(OH)*Me*], 1.40 (1 H, br s, OH), 1.46–1.54 [2 H, m, $MeCH(OH)CH_2$], 1.64 (3 H, s, =CMe), 1.70 (3 H, s, =CMe), 2.01–2.18 (2 H, m, =$CHCH_2$), 3.82 [1 H, app. sextet, *J* 6, C*H*(OH)Me], 5.12–5.17 (1 H, m, =CH).

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