Regio- and enantio-selective enolisations of cyclic ketones using chiral lithium amide bases

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Enolisations of 3-methylcyclohexanone **16**, and of a *trans*-fused perhydroisoquinolone derivative **8**, using several chiral lithium amide bases have been examined. In reactions involving a single enantiomer of the ketone **8**, the use of a chiral base can result in enhancement or reversal of the normal regioselectivity of enolisation to give the enol silane derivatives **9** and **10**, depending on the configuration of the base used. Similar matched and mismatched results are observed when (*R*)-3-methylcyclohexanone, (*R*)-**16**, is treated with either enantiomer of the chiral base **3**. A new type of kinetic resolution, termed regiodivergent resolution, is observed when enolisation of the racemic ketones **8** or **16** is carried out using the chiral base **3**.

Although much of the asymmetric chemistry of chiral lithium amide bases has focused on the transformation of cyclic *prochiral* ketones into chiral non-racemic products, *e.g.* conversion of **1** into **2** by base **3**,[1] other related applications involving *chiral* ketones have also appeared. One such report from the group of Koga describes how the usual regiocontrol seen in the enolisation of certain steroidal ketones can be modified by use of a chiral lithium amide base, *e.g.* in reactions of **4** with base **5** to give the enol silanes **6** and **7**.[2] Several other reports have described how classical kinetic resolution of racemic substrates, including cyclic ketones, can be accomplished by reaction with a deficiency of chiral base.[3] We recently described a new type of chiral base reaction in which aspects of regiocontrol and kinetic resolution are combined, which resulted in a novel type of transformation which we have called regiodivergent resolution, the full details of which are described herein.[4]

Results and discussion

Our initial interest focused on the possible outcome of a chiral base reaction involving the racemic *trans*-fused perhydroisoquinolone derivative **8**.† In enolisations involving achiral bases such as lithium diisopropylamide (LDA) the selectivity of enolisation is poor, favouring the $\Delta^{6,7}$ isomer (ratio of $\Delta^{6,7}$ to $\Delta^{5,6}$ isomer *ca.* 2:1 with LDA).‡ Based on the known preference of chiral lithium amide **3** for one of a pair of enantiotopic hydrogens (highlighted for **1**) in deprotonations involving prochiral ketones, we expected the selectivity shown in Scheme 1 for each of the enantiomers of **8**.

Assuming that, as in the case of **4**, reagent control dominates the direction of enolisation, we predicted that the two enantiomers of **8** should be separated, each enantiomer being converted predominantly into one of the two regioisomeric enol silanes **9** and **10**. This novel type of asymmetric transformation has very little precedent and is quite different to the classical type of kinetic resolution, which relies on *partial* conversion of a starting material to a product.[5]

† We thank Lilly research for generous gifts of perhydroisoquinolone ketone precursors to **8** (the corresponding ketone with *N*-Boc replaced by *N*-Me).

‡ In all cases the ratio of regioisomeric enol silanes was determined by integration of the signals due to the alkenyl hydrogens in the two isomers (δ 4.66 and 4.81) in the ^{1}H NMR spectrum.

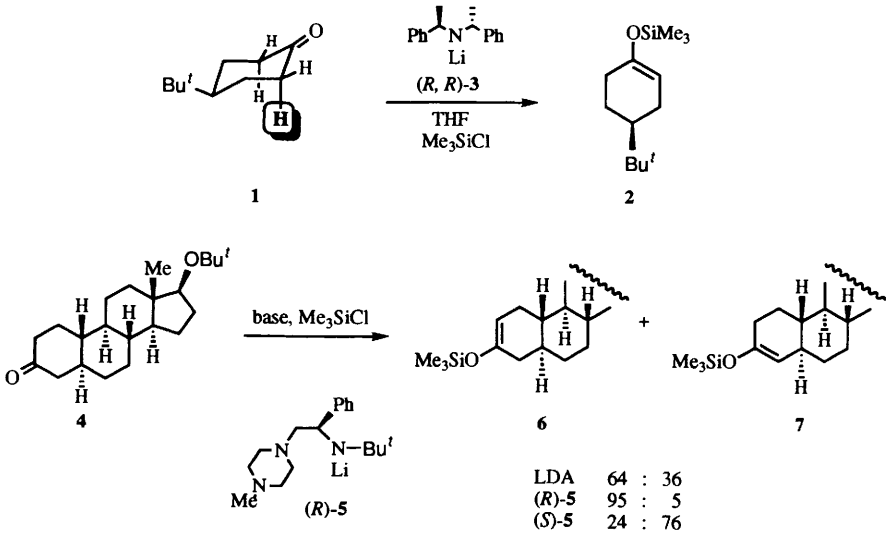


Table 1 Regiocontrol in enolisations of ketones (*R*,*R*)-**8** and (*S*,*S*)-**8**

Ketone **8**	Lithium amide base	Enol silane ratio $\Delta^{6,7}:\Delta^{5,6}$
(*R*,*R*)	(*R*,*R*)-**3**	90:10 (−73 °C)
		94:6 (−90 °C)
(*R*,*R*)	**11**	74:26 (−70 °C)
(*R*,*R*)	**12**	87:13 (−70 °C)
(*S*,*S*)	(*R*,*R*)-**3**	32:68 (−73 °C)
		21:79 (−90 °C)
(*S*,*S*)	(*S*,*S*)-**3**	94:6 (−90 °C)
(*S*,*S*)	**11**	97:3 (−70 °C)
(*S*,*S*)	**12**	87:13 (−70 °C)

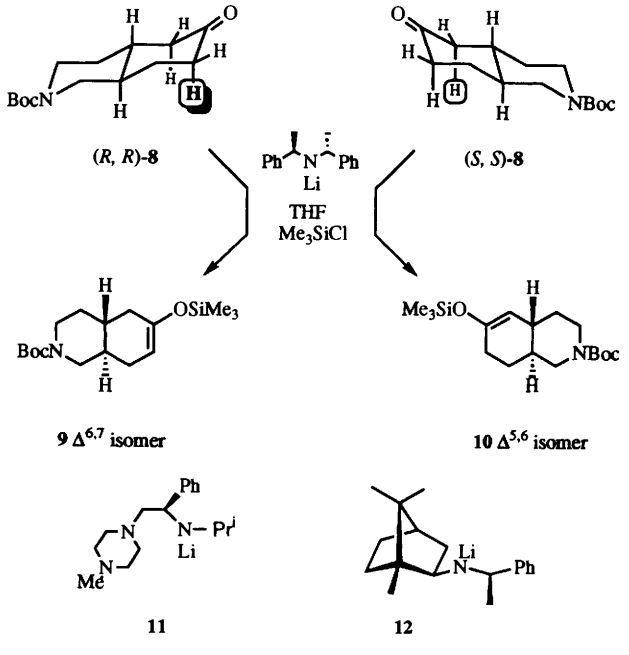
Enolisations involving single enantiomers

Before proceeding with reactions of racemic ketones we decided to examine enolisations involving individual enantiomers of ketone and chiral base, the results of which are summarised in Table 1.

These reactions, and all those described below were conducted under standard *in situ* quench conditions (Me_3SiCl–ISQ), which involves premixing of the lithium amide base with an excess of Me_3SiCl before addition of the ketone.[6] Reaction of each of the two enantiomers of **8** with the lithium amide (*R*,*R*)-**3** resulted in modification of the regioselectivity seen using LDA in a fashion closely analogous to that reported earlier by Koga and co-workers. Thus, in the case of (*R*,*R*)-**8** the ratio of $\Delta^{6,7}$ to $\Delta^{5,6}$ isomer is enhanced to 94:6, representing a 'matched' situation, whereas with the (*S*,*S*)-**8** ketone the usual selectivity is reversed, resulting in predominance of the $\Delta^{5,6}$ enol derivative. As was expected, the overall result obtained by reaction of (*R*,*R*)-**8** with (*R*,*R*)-**3** was identical with that observed in the complementary reaction involving (*S*,*S*)-**8** and (*S*,*S*)-**3**.

Reactions involving two other chiral bases, **11** and **12**, gave somewhat unexpected results. In the case of **11**, a close relative to base **5** mentioned above, the matched case gives very high selectivity for the $\Delta^{6,7}$ isomer (97:3), this being entirely expected and similar to the result obtained with **3**. However, with the mismatched combination, involving reaction of **11** with (*R*,*R*)-**8**, we did not observe the expected change in selectivity and again the $\Delta^{6,7}$ isomer predominates. The inability of the base **11** to override the inherent preference for **8** to enolise to form the $\Delta^{6,7}$ isomer is somewhat puzzling, given the close analogy to previous work. With base **12** both enantiomers of the ketone **8** reacted to give the same ratio of $\Delta^{6,7}$ and $\Delta^{5,6}$ enol silanes. This result indicates a complete lack of enantioselectivity for this chiral base in reaction with ketone **8**, although the regioselectivity of the enolisation is increased from 2:1 with LDA to almost 7:1 with **12**.

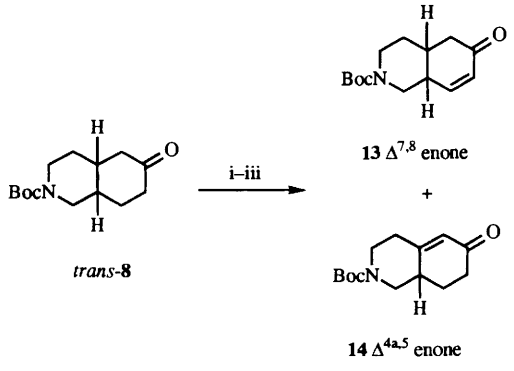
The above results allowed us to predict the outcome of the kinetic resolution shown in Scheme 1, since, provided each of the enantiomers of **8** in the racemic mixture behaved in a similar fashion as when reacted separately, we could simply average appropriate entries from Table 1. Thus for a reaction involving *racemic* **8** and the chiral base (*R*,*R*)-**3** at −90 °C the proportion of $\Delta^{6,7}$ enol silane derived from (*R*,*R*)-**8** should be 94% and the proportion derived from (*S*,*S*)-**8** should be 21%. Therefore the expected ee of the $\Delta^{6,7}$ enol silane can be calculated as (94 − 21)/(94 + 21) × 100 = 63%; a similar calculation for the $\Delta^{5,6}$ enol silane giving a value of 86% ee. From the data shown it is also possible to calculate the expected ratio of the two enol silanes, in this case (94 + 21)/2 = 58% of $\Delta^{6,7}$ isomer and (6 + 79)/2 = 42% of $\Delta^{5,6}$ isomer is expected. At this point we required methods for regioisomer separation and ee determination before proceeding with the enolisations of racemic **8**.



Scheme 1

Regioisomer separation and ee determination

Initial experiments indicated that the two enol silane derivatives are very difficult to separate by chromatography, and we were unable to devise a method for analysing the enantiomeric excess of each component in the mixture. It became clear that we needed to convert the mixture of enol silanes into some derivative in order to facilitate separation and ee determination. In this context we synthesised a range of enol derivatives, including enol carbonates, sulfonates and phosphonates and briefly examined each series for ease of separation and the possibility of ee determination. None of these compounds proved suitable; an alternative approach, involving the formation of *C*-substituted ketone products (*e.g.* α-hydroxy, α-bromo, α-phenylsulfenyl, *etc.*) in place of enol derivatives, also proved fruitless, especially since in these cases mixtures of diastereoisomers further complicated the situation. A solution was developed which involved conversion of the mixture of regioisomeric enol silanes into a corresponding mixture of α,β-unsaturated ketones (Scheme 2).



Scheme 2 *Reagents and conditions:* i LDA or chiral base, Me_3SiCl, THF (*ca.* 100%); ii PhSeCl, CH_2Cl_2, −78 °C (75–90%); iii DMDO, CH_2Cl_2, −15 °C (*ca.* 40–60%)

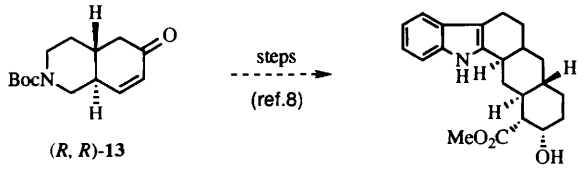
Thus, following enol silane formation in the usual way, treatment of the so-formed mixture of products with PhSeCl in CH_2Cl_2 and subsequent oxidation with dimethyldioxirane

(DMDO) resulted in the formation of the enones **13** and **14**.§ These compounds proved separable and examination of the ^{1}H NMR spectrum of each compound in the presence of the chiral solvating agent (−)-TFAE¶ provided a method of ee determination. Since the enantiomerically pure *N*-Boc ketones (*R*,*R*)-**8** and (*S*,*S*)-**8** were prepared from the corresponding *N*-methyl compounds of known absolute configuration we were also able to prepare the enones **13** and **14** of known configuration by the sequence in Scheme 2.[7] Therefore, we could now establish both the absolute configuration and enantiomeric excess of enol silane products arising from enolisation of racemic **8**.

Enolisation of racemic 8—realisation of a new type of kinetic resolution

With the appropriate analytical tools established, we next proceeded to carry out enolisation of *racemic* **8** using chiral bases **3**,**11** and **12** under standard conditions, and to convert the resulting enol silane mixtures into the corresponding enones as described above. Table 2 shows the results obtained, including the initial ratio of enol silanes and the yield, ee and configuration of the resulting enones.

Pleasingly, these results are in accord with our general prediction of the kinetic resolution in Scheme 1 and with the precise levels of regioselectivity and enantiomeric excess expected from the results in Table 1. For example, comparison of the aforementioned predictions for reaction of **8** with (*R*,*R*)-**3** of 63% ee for the $\Delta^{6,7}$ enol silane **9** and 86% ee for the $\Delta^{5,6}$ isomer **10** (Scheme 1), with the values obtained by analysis of the enones (60 and 83%, respectively—Table 2, line 2) shows good agreement. The sense of asymmetric induction was also demonstrated to be as expected from comparison with optically pure enones of known configuration prepared by us and by the group of Momose.[8] Thus, whilst this work was in progress, Momose and co-workers published an asymmetric synthesis of (+)-yohimbine employing the $\Delta^{7,8}$ enone (*R*,*R*)-**13** as a key intermediate (Scheme 3). Comparison of the published spectral



(*R*, *R*)-**13**

Scheme 3

and optical rotation data for this compound with those for our synthetic materials fully confirms our stereochemical assignments and further reinforces our estimates of ee.

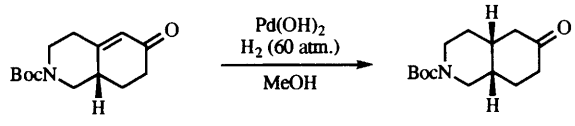
Whilst the $\Delta^{7,8}$ enone proved to be of synthetic value in the synthesis of *trans*-fused isoquinoline alkaloids, the $\Delta^{4a,5}$ enone **14** could be used to access the corresponding *cis*-fused series. Thus, in accord with previous related transformations,[9] hydrogenation of **14** gave predominantly the *cis*-fused product **15** (Scheme 4).

§ The ratio of the $\Delta^{7,8}$ and $\Delta^{4a,5}$ does not accurately reflect the initial ratio of the enol silanes owing to the difficulty in achieving complete conversion in the selenoxide elimination step.

¶ (−)-TFAE = (−)-1-(9-anthryl)-2,2,2-trifluoroethanol. Analysis of samples of enantiomerically enriched enones **13** and **14** was carried out by addition of 5 equiv. of (−)-TFAE to a solution of the enone in $CDCl_3$. Examination of the ^{1}H NMR spectrum of the resulting solution allowed estimation of the ee of the sample due to splitting of the signal at δ = *ca.* 1.5 (Bu^t) in the case of **13**, and the signal at δ = *ca.* 5.5 (C=CH) in the case of **14**.

Table 2 Results of enolisation of racemic ketone **8**

Temp (*t*/°C)	Lithium amide base	Enol silane ratio $\Delta^{6,7}$:$\Delta^{5,6}$	ee of $\Delta^{7,8}$ enone	ee of $\Delta^{4a,5}$ enone
−70	(*R*,*R*)-**3**	59:41	46 (*R*,*R*)	78 (*S*)
−90	(*R*,*R*)-**3**	55:45	60 (*R*,*R*)	83 (*S*)
−70	**11**	86:14	12 (*S*,*S*)	66 (*R*)
−70	**12**	86:14	4	3

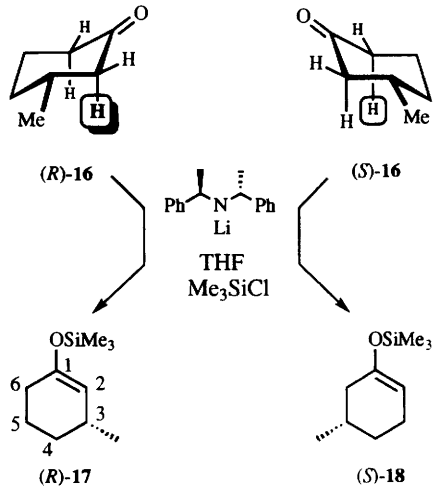


rac-**14** *rac*-**15** 66% + *rac*-**8** 14%

Scheme 4

Enolisations of 3-methylcyclohexanone

Having demonstrated a new kinetic resolution of racemic **8** we sought another system with which to verify this type of reaction and chose 3-methylcyclohexanone **16** for further study. The expected selectivity for reaction of racemic **16** with chiral base (*R*,*R*)-**3** is shown in Scheme 5.



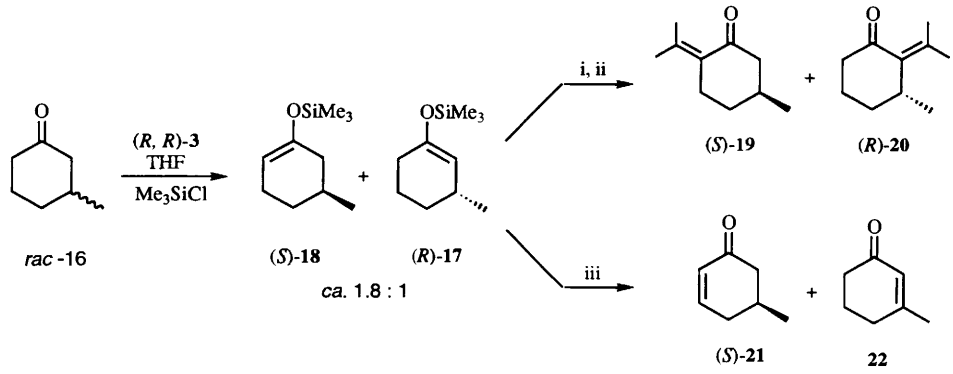
(*R*)-**17** (*S*)-**18**

Scheme 5

As in the previous example, providing that chiral base selectivity is dominant, the enantiomers are expected to be separated, with (*R*)-**16** being converted predominantly into (*R*)-**17**, and (*S*)-**16** being converted mainly into (*S*)-**18**. Results for enolisation of (*R*)-3-methylcyclohexanone (the *S*-isomer was not readily available) are shown in Table 3.

Entries in lines 2 and 3 represent mismatched and matched situations, use of the chiral base **3** allowing increased or diminished levels of regioselectivity in enol silane formation, but unlike the enolisations of **8** no overall reversal of the normal selectivity was accomplished (*i.e.* in *both* cases the $\Delta^{1,6}$ enol silane predominates).[10] As in the earlier work, separation of the product isomers and determination of enantiomeric excess proved to be difficult, the volatility of many derivatives being a serious problem. No entirely satisfactory solution to the problem was developed, although mixtures of enol silanes prepared by enolisation of racemic **16** with (*R*,*R*)-**3** could be processed in low yield to give mixtures of (*S*)-pulegone **19** and (*R*)-**20**, or (*S*)-5-methylcyclohex-2-enone **21** and 3-methylcyclohex-2-enone **22** (see Scheme 6).

Thioalkylation, using the thioketal derived from acetone and



Scheme 6 *Reagents and conditions:* i $MeC(SEt)_2Me$, CH_2Cl_2, $SnCl_4$, −78 °C; ii Bu^{t}OK, BuOH iii $Pd(OAc)_2$, diallyl carbonate, MeCN reflux

Table 3 Regiocontrol in enolisations of 3-methylcyclohexanone **16**

Ketone **16**	Lithium amide base	Enol silane ratio $\Delta^{1,2}:\Delta^{1,6}$
rac.	LDA	25:75 (−78 °C)
(*R*)	(*R*,*R*)-**3**	36:64 (−90 °C)
(*R*)	(*S*,*S*)-**3**	7:93 (−90 °C)
(*R*)	**11**	5:95 (−90 °C)
(*R*)	**12**	10:90 (−90 °C)

ethanethiol, under Lewis acidic conditions,[11] followed by elimination of EtSH under basic conditions, gave mixtures containing mainly pulegone **19** (*ca.* 10% accompanied by 16% of the corresponding β,γ-enone) and the regioisomeric product **20** (19%). Although we were unable to establish the enantiomeric excess of these materials, comparison of optical rotation data for our synthetic pulegone **19** confirmed the absolute stereochemistry expected from the analysis in Scheme 5 (*i.e.* the *S*-configuration shown) and indicated an optical purity of 17%.[12] Alternatively, conversion of the mixture of enol silanes **17** and **18** into a mixture of the enones **21** and **22** (28% unoptimised yield) was possible by treatment with diallyl carbonate under palladium catalysis, according to the method of Tsuji.[13] This gave mainly (*S*)-**21** in 17% optical purity,[14] in accord with the result for pulegone **19**, along with the regioisomer **22**.

Although the apparent levels of enantiomeric enrichment of the enol silane **18** are low, as judged by rotation data for the derived ketones **19** and **21**, this is to be expected from the selectivities observed in enolisations involving single enantiomers of base and ketone shown in Table 3. These data predict an enantiomeric excess of only 23% for **18**, but a much higher level of induction, *ca.* 67% ee, for the regioisomeric product **17**. Unfortunately, this isomer is predicted (and found) to be the minor product from the enolisation and the inefficiency of the sequence which generates **20**, combined with our inability to readily establish the ee of this product, has precluded confirmation of the higher level of ee expected for **17**.

Conclusion

The results described herein highlight the usefulness of chiral bases in controlling the regiochemical outcome of the enolisation of enantiomerically pure ketones. The new type of kinetic resolution which has been discovered, which we have termed regiodivergent resolution, is unusual in converting enantiomers into separable regioisomeric products, for example the conversion of ketone **8** into isoquinolones of obvious utility for alkaloid synthesis. These results further expand the applications of chiral lithium amides and should be applicable to many other types of substrate.

Experimental

Mps for solid products were determined using a Reichert Microscope apparatus, and are uncorrected. IR spectra were recorded on a Philips PU96706, Pye Unicam SP3-100 or Perkin-Elmer 1720 FTIR instrument. NMR spectra were recorded on a Bruker AM250, Jeol FX270, Bruker AM 300 or Bruker AM400 machine, with Me_4Si as internal standard. *J* Values are recorded in Hz and multiplicities indicated for ^{13}C NMR were obtained using a DEPT sequence. Mass spectra were recorded on AEI 902 or VG micromass 70E spectrometers. Microanalyses were performed at the microanalytical laboratory at Nottingham University using a Perkin-Elmer 240B elemental analyser. Optical rotations were measured using a Jasco DIP 370 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was performed on Merck pre-coated silica gel F_{254} plates. Preparative (flash) chromatography was carried out on columns of Merck Keiselgel 60 (230–400 mesh). Solvents were purified by standard techniques.

Preparation of the racemic ketone 8 from the corresponding *N*-methyl derivative *via* an intermediate ethyl carbamate

N-Methylperhydroisoquinolone **8** (Boc replaced by Me)† (2.00 g, 11.97 mmol) was dissolved in dry toluene (40 cm^3) and ethyl chloroformate (2.28 ml, 23.95 mmol) was added dropwise to the stirred solution under nitrogen. The reaction mixture was heated under reflux for 2 h, before being cooled to room temperature, washed with water (40 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (25% ethyl acetate–75% light petroleum of the residue) yielded the ethyl carbamate derivative **8** (Boc replaced by CO_2Et) (2.03 g, 75%) as a white crystalline product, mp 43–47 °C (Found: C, 63.8; H, 8.7; N, 6.3; $C_{12}H_{19}NO_3$ requires C, 63.98; H, 8.50; N, 6.22); $\nu_{max}(CHCl_3)$/cm^{-1} 2934, 2861, 1681, 1464 and 1139; δ_H(270 MHz, $CDCl_3$) 1.27 (3 H, t, *J* 7, CH_3CH_2), 1.32–1.67 (5 H, m, 8-CH_{ax}, 4-CH_{ax}, 4-CH_{eq}, 8a-CH, 4a-CH), 2.00 (1 H, m, 8-CH_{eq}), 2.10 (1 H, dd, *J* 16, 13, 5-CH_{ax}), 2.30–2.49 (4 H, m, 1-CH_{ax}, 7-CH_{ax}, 7-CH_{eq}, 5-CH_{eq}), 2.71 (1 H, br dd, *J* 12, 12, 3-CH_{ax}) and 4.10–4.35 (4 H, m, 3-CH_{eq}, 1-CH_{eq}, CH_3CH_2); δ_C(67.8 MHz, $CDCl_3$) 14.5 (CH_3, CH_3CH_2), 29.2 (CH_2, C-8), 32.2 (CH_2, C-4), 39.7 (CH, C-4a), 40.5 (CH_2, C-7), 41.4 (CH, C-8a), 43.2 (CH_2, C-3), 47.2 (CH_2, C-5), 48.5 (CH_2, C-1), 60.7 (CH_2, CH_3CH_2), 154.8 (C, CO_2Et) and 209.3 (C, C-6); *m*/*z* (FAB) 226 (M^+ + H, 100%).

To a stirred solution of the ethyl carbamate (2.03 g, 9.02 mmol) in dry acetonitrile (40 cm^3) under a nitrogen atmosphere, was added Me_3SiCl (3.0 cm^3, 23.63 mmol) followed by NaI (3.6 g, 24.00 mmol). The reaction mixture was

† See footnote on p. 2535.

stirred for 10 min at room temperature before being heated to reflux for 48 h. The mixture was cooled to room temperature, gradually diluted with MeOH (40 cm^3) and then evaporated under reduced pressure to give the crude secondary amine (0.85 g, 63%), which was used without further purification. The crude secondary amine (0.85 g, 5.55 mmol) was dissolved in acetone (40 cm^3) and added to a solution of di-*tert*-butyl dicarbonate (3.66 g, 16.75 mmol) and DMAP (1.46 g, 11.95 mmol) in acetone at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred for 24 h. It was then evaporated under reduced pressure and the residue flash chromatographed (20% ethyl acetate–80% light petroleum) to give the pure *N*-Boc protected perhydroisoquinolone **8** (2.47 g, 81%) as a waxy solid, mp 53–57 °C. Rotamers exist in $CDCl_3$ and ^1H and ^1C NMR signals due to the 1 and 3 positions are broadened; however, at 360 K in DMSO these signals become sharper; δ_H(270 MHz, $CDCl_3$) 1.20–1.42 (2 H, m, 4-CH_{ax}, 8-CH_{ax}), 1.45–1.50 (2 H, m, 4a-CH, 8a-CH), 1.47 (9 H, s, Bu^t), 1.61 (1 H, m, 4-CH_{eq}), 1.99 (1 H, m, 8-CH_{eq}), 2.15 (1 H, dd, *J* 12, 12, 5-CH_{ax}), 2.30–2.50 (4 H, m, 1-CH_{ax}, 7-CH_{ax}, 7-CH_{eq}, 5-CH_{eq}), 2.69 (1 H, br dd, *J* 12, 3-CH_{ax}) and 4.05–4.35 (2 H, m, 1-CH_{eq}, 3-CH_{eq}); δ_H(300 MHz, DMSO, 360 K) 1.14–1.38 (2 H, m, 4-CH_{ax}, 8-CH_{ax}), 1.39–1.51 (2 H, m, 4a-CH, 8a-CH), 1.41 (9 H, s, Bu^t), 1.58 (1 H, m, 4-CH_{eq}), 1.77 (1 H, m, 8-CH_{eq}), 2.12–2.26 (3 H, m, 7-CH_{eq}, 5-CH_{ax}, 5-CH_{eq}), 2.29–2.45 (2 H, m, 7-CH_{ax}, 1-CH_{ax}), 2.66 (1 H, ddd, *J* 13, 12, 3, 3-CH_{ax}), 3.98 (1 H, m, 3-CH_{eq}) and 4.23 (1 H, m, 1-CH_{eq}); δ_C(67.8 MHz, $CDCl_3$) 28.2 (3 CH_3, Bu^t), 29.5 (CH_2, C-8), 32.74 (CH_2, C-4), 39.9 (CH, C-4a), 40.6 (CH_2, C-7), 41.6 (CH, C-8a), 43.5 (CH_2, br, C-3), 47.8 (CH_2, C-5), 48.6 (CH_2, br, C-1), 79.4 (C, Bu^t), 154.5 (C, CO_2Bu^t) and 209.9 (C, C-6); δ_C(75.5 MHz, DMSO, 360 K) 28.0 (3 CH_3, Bu^t), 28.7 (CH_2, C-8), 32.5 (CH_2, C-4), 39.1 (CH, C-4a), 40.2 (CH_2, C-7), 40.9 (CH, C-8a), 43.4 (CH_2, C-3), 46.9 (CH_2, C-5), 48.5 (CH_2, C-1), 77.9 (C, Bu^t), 153.2 (C, CO_2Bu^t) and 208.9 (C, C-6); *m/z* (EI) (Found: $M^+ - C_4H_8$, 197.1047. $C_{14}H_{23}NO_3$ requires $M^+ - C_4H_8$, 197.1052); *m/z* (FAB) 254 ($M^+ + H$, 19%) and 198 ($M^+ - C_4H_8 + H$, 100%). Enantiomerically enriched samples of (*R*,*R*)-**8** and (*S*,*S*)-**8** of *ca.* 99% ee were prepared in the same way, starting with the *N*-methylperhydroisoquinolone, resolved as described by Harden and Rackham.[7b] (*R*,*R*)-**8** was obtained as a waxy solid; $[\alpha]_D^{20}$ −40.0 (*c* 1.54, in CH_2Cl_2); (*S*,*S*)-**8** was obtained as a waxy solid; $[\alpha]_D^{20}$ +38.9 (*c* 1.41, in CH_2Cl_2). Spectral data were identical with those of the racemate.

Enolisation of (*R*,*R*)-8 using the chiral base (*R*,*R*)-3 to give a mixture of regioisomeric enol silanes

A solution of the base (*R*,*R*)-**3** was prepared by treatment of the corresponding (*R*,*R*)-bisphenethylamine (0.33 g, 1.5 mmol), in THF (20 cm^3) at −90 °C (±2 °C) under a nitrogen atmosphere, with BuLi (0.94 cm^3, 1.5 mmol). The reaction mixture was allowed to warm to room temperature to ensure complete formation of the lithium amide, and then after 5 min was recooled to −90 °C (±2 °C). Chlorotrimethylsilane (0.61 g, 4.92 mmol) was added slowly to the mixture and, after 2 min, was followed by a solution of the ketone (*R*,*R*)-**8** (0.25 g, 0.98 mmol) in THF (20 cm^3), added dropwise over a period of 5 min to maintain a constant temperature of −90 °C (±2 °C). After the mixture had been held at this temperature for 15 min, triethylamine (6 cm^3) was added to it, followed by saturated aqueous $NaHCO_3$ (45 cm^3). The mixture was extracted with light petroleum (2 × 60 cm^3), and the combined extracts were washed with saturated aqueous NH_4Cl (60 cm^3) and saturated aqueous $NaHCO_3$ (45 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to afford the crude enol silanes in a 94:6 ratio of $\Delta^{6,7}$ to $\Delta^{5,6}$ isomers (0.31 g, 97%); δ_H(300 MHz; $CDCl_3$, major isomer) 0.16 (9 H, s, $SiMe_3$), 1.11–1.43 (2 H, m, 4-CH_{ax}, 8-CH_{ax}), 1.45 (9 H, s, Bu^t), 1.58–1.66 (2 H, m, 4a-CH, 8a-CH), 1.78 (1 H, m, 4-CH_{eq}), 1.94–2.04 (2 H, m, 8-CH_{eq}, 5-CH_{ax}), 2.23 (1 H, m, 5-CH_{eq}), 2.30 (1 H, dd, *J* 13, 11, 1-CH_{ax}), 2.66 (1 H, ddd, *J* 13, 13, 3, 3-CH_{ax}), 4.03–4.14 (2 H, m, 1-CH_{eq}, 3-CH_{eq}) and 4.81 (1 H, ddd, *J* 2, 2, 5, 7-CH); δ_C(75.5 MHz, $CDCl_3$, major isomer) 0.30 (CH_3, $SiMe_3$), 27.8 (CH_2), 28.5 (CH_3, Bu^t), 36.6 (CH_2), 37.3 (CH_2), 43.9 (CH_2, br, C-3), 49.0 (CH_2, br, C-1), 79.3 (C Bu^t, 102.6 (CH), 149.3 (C) and 154.7 (C, CO_2Bu^t).

Enolisation of (*S*,*S*)-8 using the chiral base (*R*,*R*)-3 to give a mixture of regioisomeric enol silanes

Enolisation of (*S*,*S*)-**8** (0.25 g) was carried out as described above to afford the crude enol silanes as a 21:79 ratio of $\Delta^{6,7}$ to $\Delta^{5,6}$ isomers (0.30 g, 95%); spectroscopic data for this mixture of products was consistent with the data for the mixture of enol silanes derived by enolisation of racemic **8**, described below.

Enolisation of enantiomerically pure ketone **8** with other chiral bases, or at different temperatures, gave the enol silane products in the ratios indicated in Table 1.

Enolisation of racemic 8 using chiral base (*R*,*R*)-3 to give a mixture of regioisomeric enol silanes

A solution of chiral base (*R*,*R*)-**3** (2.32 mmol) in THF (30 cm^3) and chlorotrimethylsilane (7.74 mmol) at −70 °C (±2 °C) was prepared, as described above. A solution of racemic *N*-Boc protected perhydroisoquinolone **8** (0.40 g, 1.55 mmol) in THF 15 cm^3 was added to the mixture dropwise over a period of 10 min to maintain a constant temperature of −70 °C (±2 °C). After 15 min at this temperature the reaction mixture was worked up as described above, and flash chromatography (20% ethyl acetate–80% light petroleum) gave an inseparable mixture of enol silanes in a 59:41 ratio of $\Delta^{6,7}$ to $\Delta^{5,6}$ isomers as a colourless oil (0.42 g, 85%) (Found: C, 62.7; H, 9.8; N, 4.2 $C_{17}H_{31}NO_3Si$ requires C, 62.93; H, 9.60; N, 4.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3624, 2929, 1671, 1367, 1162, 1127, 892 and 863; δ_H(300 MHz; $CDCl_3$) 0.16 (9 H, s, $SiMe_3$, $\Delta^{6,7}$), 0.17 (9 H, s, $SiMe_3$, $\Delta^{5,6}$) 1.11–1.43 (4 H, m, 4-CH_{ax}, 8-CH_{ax}, $\Delta^{6,7}$ and $\Delta^{5,6}$), 1.45 (9 H, s Bu^t, $\Delta^{6,7}$), 1.47 (9 H, s Bu^t, $\Delta^{5,6}$) 1.58–1.66 (4 H, m, 4a-CH, 8a-CH, $\Delta^{6,7}$ and $\Delta^{5,6}$), 1.78 (2 H, m, 4-CH_{eq}, $\Delta^{6,7}$ and $\Delta^{5,6}$), 1.94–2.04 (2 H, m, 8-CH_{eq}, 5-CH_{ax}, $\Delta^{6,7}$), 1.99 (1 H, m, 8-CH_{eq}, $\Delta^{5,6}$), 2.17–2.28 (2 H, m, 7-CH_{eq}, 7-CH_{ax}, $\Delta^{5,6}$), 2.23 (1 H, m, 5-CH_{eq} $\Delta^{6,7}$), 2.30 (1 H, dd, *J* 13, 11, 1-CH_{ax}, $\Delta^{6,7}$), 2.33 (1 H, dd, *J* 13, 11, 1-CH_{ax}, $\Delta^{5,6}$), 2.66 (1 H, ddd, *J* 13, 13, 3, 3-CH_{ax}, $\Delta^{6,7}$), 2.69 (1 H, ddd, *J* 13, 13, 3, 3-CH_{ax}, $\Delta^{5,6}$), 4.03–4.14 (4 H, m, 1-CH_{eq}, 3-CH_{eq}, $\Delta^{6,7}$ and $\Delta^{5,6}$), 4.66 (1 H, br s, 5-CH, $\Delta^{5,6}$) and 4.81 (1 H, ddd, *J* 2, 2, 5, 7-CH, $\Delta^{6,7}$); δ_C(75.5 MHz, $CDCl_3$), 0.30 (CH_3, $SiMe_3$, $\Delta^{6,7}$ and $\Delta^{5,6}$), 26.5 (CH_2, $\Delta^{5,6}$), 27.8 (CH_2, $\Delta^{6,7}$), 28.5 (CH_3 Bu^t, $\Delta^{6,7}$ and $\Delta^{5,6}$), 29.8 (CH_2, $\Delta^{5,6}$), 32.4 (CH_2, $\Delta^{5,6}$), 36.6 (CH_2, $\Delta^{6,7}$), 37.3 (CH, $\Delta^{6,7}$), 39.4 (CH, $\Delta^{5,6}$), 39.6 (CH, $\Delta^{5,6}$), 43.9 (CH_2, br, C3, $\Delta^{6,7}$ and $\Delta^{5,6}$), 49.0 (CH_2, br, Cl, $\Delta^{6,7}$ and $\Delta^{5,6}$), 79.3 (C, $\Delta^{6,7}$ and $\Delta^{5,6}$), 102.6 (CH, $\Delta^{6,7}$), 108.1 (CH, $\Delta^{5,6}$), 149.3 (C, $\Delta^{6,7}$ and $\Delta^{5,6}$), and 154.7 (C, COBu^t, $\Delta^{6,7}$ and $\Delta^{5,6}$); *m/z* (EI) (Found: $M^+ - C_4H_9$, 269.1437. $C_{17}H_{31}NO_3Si$ requires $M^+ - C_4H_9$, 269.1447).

Synthesis of enantiomerically pure $\Delta^{7,8}$ enone (*R*,*R*)-13 starting with the ketone (*R*,*R*)-8 *via* selenylation–selenoxide *syn*-elimination

The crude mixture of $\Delta^{6,7}$ and $\Delta^{5,6}$ enol silanes, produced in a ratio of 94:6 by enolisation of enantiomerically pure perhydroisoquinolone (*R*,*R*)-**8** (0.98 mmol) with base (*R*,*R*)-**3**, as described above, was dissolved in dichloromethane (20 cm^3) under a nitrogen atmosphere and the solution cooled to −78 °C. Phenylselenanyl chloride (0.19 g, 0.98 mmol) was added in dichloromethane (10 cm^3) to the reaction mixture which was then stirred at −78 °C for 1 h before being quenched with water (10 cm^3). The aqueous layer was extracted with dichloromethane (2 × 20 cm^3) and the combined extracts were

dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (20% ethyl acetate–80% light petroleum) of the residue afforded a mixture of stereoisomeric selenides (0.31 g, 76%), which was used for the next step. The mixture of selenides (0.31 g, 0.84 mmol) was dissolved in dichloromethane (20 cm^3) and the solution cooled to −15 °C under a nitrogen atmosphere. Dimethyldioxirane (0.1 mol dm^{-3} solution in acetone; 16 cm^3, 1.6 mmol) was added slowly to the reaction mixture which was then stirred for 1 h before being diluted with water (10 cm^3) and extracted with dichloromethane (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure and flash chromatography (20% ethyl acetate–80% light petroleum) of the residue gave firstly, recovered starting material (0.07 g, 19%), followed by $\Delta^{7,8}$ enone (*R,R*)-**13** as a white solid, mp 108–110 °C (lit.,[8] 106–108 °C) $[\alpha]_D^{22}$ −56.5 (*c* 1.56 in $CHCl_3$) {lit.,[9] $[\alpha]_D^{26}$ −55.6 (*c* 1.2 in $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 1702, 1697, 1412, 1366, 1267, 1255 and 1159; δ_H(300 MHz, DMSO, 300 K) 1.30 (1 H, m, 4-CH_{ax}), 1.42 (9 H, s, Bu^t), 1.60 (1 H, m, 4-CH_{eq}), 1.81 (1 H, m, 4a-CH), 2.16 (1 H, m, 8a-CH), 2.19 (1 H, dd, *J* 13, 16, 5-CH_{ax}), 2.14 (1 H, dd, *J* 16, 6, 5-CH_{eq}), 2.47 (1 H, dd, *J* 12, 12, 1-CH_{ax}), 2.65 (1 H, ddd, *J* 13, 12, 3, 3-CH_{ax}), 4.14 (1 H, dddd, *J* 12, 4, 4, 2, 3-CH_{eq}), 4.12 (1 H, ddd, *J* 14, 4, 2, 1-CH_{eq}), 5.91 (1 H, ddd, *J* 10, 3, 1, 7-CH) and 6.80 (1 H, dd, *J* 10, 3, 8-CH); δ_C(67.8 MHz, $CDCl_3$) 28.4 (3 CH_3, Bu^t), 31.54 (CH_2, C-4), 40.4 (CH, C-8a), 40.9 (CH, C-4a), 43.7 (CH_2, C-3), 44.9 (CH_2, C-5), 47.3 (CH_2, C-1), 80.0 [C, $C(CH_3)_3$], 130.9 (CH, C-7), 150.2 (CH, C-8), 154.8 (C, CO_2-Bu^t) and 197.0 (C, C-6).

Synthesis of enantiomerically pure $\Delta^{4a,5}$ enone (S)-14 starting with the ketone (*S,S*)-8 *via* selenylation–selenoxide *syn*-elimination

The crude mixture of $\Delta^{6,7}$ and $\Delta^{5,6}$ enol silanes, produced in a ratio of 21:79 by enolisation of enantiomerically pure perhydroisoquinolone (*S,S*)-**8** (0.98 mmol) with base(*R,R*)-**3**, as described above, was dissolved in dichloromethane (20 cm^3) under a nitrogen atmosphere and the solution cooled to −78 °C. Phenylselenanyl chloride (0.19 g, 0.98 mmol) was added in dichloromethane (10 cm^3) to the reaction mixture which was then stirred at −78 °C for 1 h before being quenched with water (10 cm^3). The aqueous layer was extracted with dichloromethane (2 × 20 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (20% ethyl acetate–80% light petroleum) afforded a mixture of isomeric phenylselenides as a bright yellow oil (0.36 g, 88%) which was used for the next step.

The mixture of selenides (0.36 g, 0.88 mmol) was dissolved in dichloromethane (20 cm^3) and the solution cooled to −15 °C under a nitrogen atmosphere and treated with dimethyldioxirane as described above, to give a mixture of two enone products containing mainly the $\Delta^{4a,5}$ enone (*S*)-**14**. Flash chromatography (20% ethyl acetate–80% light petroleum) of the product separated the pure enones as a white crystalline solid. First to be eluted was the $\Delta^{7,8}$ enone (*S,S*)-**13** (0.02 g, 12%) with data consistent with those of the enantiomer obtained in the previous experiment. The $\Delta^{4a,5}$ enone (*S*)-**14** was then obtained (0.06 g, 27%), $[\alpha]_D^{22}$ +68.9 (*c* 0.97 in $CHCl_3$) (Found C, 66.9; H, 8.6; N, 5.3. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42 and N, 5.57.); ν_{max}(KBr)/cm^{-1} 1697, 1687, 1679, 1425, 1241, 1166 and 120; δ_H(300 MHz, DMSO, 300 K) 1.43 (9 H, s, Bu^t, 1.53 (1 H, m, 8-CH_{ax}), 2.02 (1 H, m, 8-CH_{eq}), 2.24–2.46 (4 H, m, 4-CH_{ax}, 4-CH_{eq}, 7-CH_{ax}, 7-CH_{eq}), 2.51 (1 H, m, 8a-CH), 2.55 (1 H, dd, *J* 10, 10, 1-CH_{ax}), 2.86 (1 H, ddd, *J* 14, 12, 4, 3-CH_{ax}), 3.99 (1 H, m, 3-CH_{eq}), 4.05 (1 H, m, 1-CH_{eq}) and (1 H, s, 5-CH); δ_C(300 MHz, DMSO, 300 K) 24.3 (CH_2, C-8), 2.71 (3 CH_3, Bu^t, 32.2 (CH_2, C-4), 34.9 (CH_2, C-7), 35.3 (CH, C-8a), 42.34 (CH_2, C-3), 47.8 (CH_2, C-1), 78.1 [C, $C(CH_3)_3$], 123.9 (CH, C-5), 152.8 (C), 161.4 (C, C-4a) and 196.5 (C, C-6); *m/z* (EI) (Found: $M^+ - C_4H_8$, 195.0869. $C_{14}H_{21}NO_3$ requires $M^+ - C_4H_8$, 195.0895).

Synthesis of the enantiomerically enriched enones (*R,R*)-13 and (*S*)-14 starting with the racemic ketone 8 *via* selenylation–selenoxide *syn*-elimination

The mixture of enantiomerically enriched regioisomeric enol silanes (1.55 mmol) prepared from the racemic perhydroisoquinolone 8 by enolisation with base (*R,R*)-**3**, was treated with phenylselenanyl chloride to give a mixture of enantiomerically enriched selenides, as described above for the single enantiomer series. Flash chromatography (20% ethyl acetate–80% light petroleum) afforded the purified mixture of selenides (0.57 g, 91%); *m/z* (FAB) 409 ($M^+\{^{80}Se\}$ + H, 27%) and 407 ($M^+\{^{78}Se\}$ + H, 16%) ($C_{20}H_{27}NO_3Se$ requires $M^+\{^{80}Se\}$ + H 409 and $M^+\{^{78}Se\}$ + H 407).

Treatment of this mixture of enantiomerically enriched phenyl selenides with dimethyldioxirane in the same way as described above gave, after chromatography, firstly the $\Delta^{7,8}$ enone (0.12 g, 34%), which had an ee of 46% according to chiral shift NMR results using TFAE; comparison of the optical rotation also gave an optical purity of 40% $[\alpha]_D^{25}$ −22.5 (*c* 0.4 in $CHCl_3$) {lit.,[8] $[\alpha]_D^{26}$ −55.6 (*c* 1.2 in $CHCl_3$)}. The $\Delta^{4a,5}$ enone was then obtained (0.06 g, 16%), which had an ee of 78% according to chiral shift NMR measurements; comparison of the optical rotation gave an optical purity of 75% $[\alpha]_D^{25}$ +52.0 (*c* 0.3 in $CHCl_3$), compared to the optically pure material $[\alpha]_D^{22}$ +68.9 (*c* 0.97 in $CHCl_3$). The spectral data obtained for the two enones were consistent with those described above. Mixtures of enol silanes prepared using different bases were processed in the same way to give the separable enone products with the enantiomeric excesses indicated in Table 2.

Hydrogenation of 14 to give the *cis*-fused ketone 15

To a solution of the racemic $\Delta^{4a,5}$ enone **14** (11 mg, 0.05 mmol) in methanol (2 cm^3) was added palladium hydroxide 10% Pd-on-carbon; *ca.* 1 mg) and the mixture was then hydrogenated at 60 atm overnight. The catalyst was removed by filtration through Celite and the filtrate evaporated under reduced pressure to give a residue which was subjected to flash chromatography (20% ethyl acetate–80% light petroleum) to give firstly the *cis* fused ketone **15** (7.6 mg, 66%); ν_{max}(film)/cm^{-1} 2973, 2930, 1692, 1425 and 1168; δ_H(250 MHz, $CDCl_3$) 1.20–1.60 (2 H, m, 8-CH_{eq}, 8-CH_{ax}), 1.44 (9 H, s, Bu^t), 1.81–2.05 (2 H, m, 4-CH_{ax}, 4-CH_{eq}), 2.16 (1 H, m, 4a-CH), 2.26–2.41 (4 H, m, 8a-CH, 7-CH_{eq}, 5-CH_{ax}, 7-CH_{ax}), 2.56 (1 H, dd, *J* 14, 6, 5-CH_{eq}), 2.83 (1 H, m, 3-CH_{ax}), 3.05 (1 H, dd, *J* 10 3, 1-CH_{ax}) and 3.91–4.01 (2 H, m, 1-CH_{eq}, 3-CH_{eq}); δ_C(67.8MHz, $CDCl_3$) 25.1 (CH_2, C-8), 26.7 (CH_2, C-4), 28.2 (3CH_3, Bu^t), 34.5 (CH, C-4a), 37.1 (CH, C-8a), 39.7 (CH_2, C-7), 43.5 (CH_2, br, C-3), 45.9 (CH_2, C-5), 47.8 (CH_2, br, C-1), 79.3 [C, $C(CH_3)_3$, 154.79 (C, CO_2 Bu^t) and 210.8 (C, C-6); followed by a minor amount of *trans* fused ketone **8** (2 mg, 14%) identical with that described above.

Enolisation of racemic 3-methylcyclohexanone 16 using chiral base (*R,R*)-3 to give a mixture of regioisomeric enol silanes

A solution of the base (*R,R*)-**3** (12.44 mmol) in THF was prepared as described above and the solution then cooled to −70 °C (±2 °C) before addition of chlorotrimethylsilane (5.2 cm^3, 40.74 mmol). After 2 min (±)-3-methylcyclohexanone (1.0 cm^3, 8.15 mmol) was added dropwise to the mixture to maintain a temperature of −70 °C (±2 °C) after which it was stirred for 15 min and then worked up to provide a mixture of crude enol silanes **18** and **17** in a ratio of 64:36. This residue was dissolved in light petroleum (10 cm^3) and washed with aqueous $CuSO_4$ (6 × 20 cm^3) to remove most of the chiral secondary amine

impurity prior to flash column chromatography (2% ethyl acetate–98% light petroleum) to give a mixture of the pure enol silanes **17** and **18** (0.93 g, 62%) as a colourless oil; δ_H(250 MHz, $CDCl_3$) 0.15 (9 H, s, $SiMe_3$, **17**), 0.18 (9 H, s, $SiMe_3$, **18**), 0.92 (3 H, d, *J* 7, CH_3, **17**), 0.94 (3 H, d, *J* 7, CH_3, **18**), 1.09–2.40 (14 H, m, **18** and **17**), 4.71 (1 H, br s, 2-CH, **17**) and 4.82 (1 H, br s, 5-CH, **18**); δ_C(67.8 MHz, $CDCl_3$) 0.2 (6 CH_3, $SiMe_3$, **18** and **17**), 21.2 (CH_2, **18**), 21.5 (CH_2, **17**), 22.2 (CH_3, **17**), 23.1 (CH_3, **18**), 29.0 (CH, **18**), 29.3 (CH, **17**), 30.3 (CH_2, **18**), 30.9 (CH_2, **17**), 38.1 (CH_2, **18**), 45.6 (CH_2, **17**), 103.2 (CH, **18**), 110.7 (CH, **17**), 149.5 (C, **18**) and 149.7 (C, **17**); *m/z* (EI) (Found: M^+, 184.1289. $C_{10}H_{20}OSi$ requires M^+, 184.1283).

Similar enolisations involving other bases, or (*R*)-3-methylcyclohexanone, gave the enol silanes in the ratios given in Table 3.

Conversion of the mixture of the enol silanes 17 and 18 into a mixture of (*S*)-pulegone 19 and the enone (*R*)-20

To a solution of tin(IV) chloride (0.59 cm^3, 5.04 mmol) in dichloromethane (10 cm^3) under nitrogen at −60 °C was added 2,2-di(ethylsulfanyl)propane (0.82 g, 4.99 mmol) in dichloromethane (3 cm^3). A solution of the enol silanes **17** and **18** (0.92 g, 4.99 mmol), prepared from racemic ketone **16** as described above, in dichloromethane (3 cm^3) was added over 1 min to the reaction mixture which was then stirred for 1 h. Ice–water (10 cm^3) was then added to the mixture after which it was extracted with dichloromethane (2 × 30 cm^3). The combined organic extracts were washed with 10% aq. $NaHCO_3$ (20 cm^3), extracted with dichloromethane (2 × 20 cm^3), washed again with water (10 cm^3) and then dried (Na_2SO_4) and concentrated. A mixture of inseparable regioisomeric sulfides was isolated by flash chromatography (10% ethyl acetate–90% light petroleum), as a pungent colourless oil (0.62 g, 57%) (Found: C, 67.5; H, 10.6. $C_{12}H_{22}OS$ requires C, 67.24; H, 10.34); ν_{max}(film)/cm^{-1} 2969, 2928, 2867, 1697, 1694, 1438, 1423, 1366, 1242 and 1160; *m/z* (EI) (Found: M^+, 214.1383. $C_{12}H_{22}OS$ requires, M^+, 214.1391). This mixture was taken on to the next step.

To a solution of the keto sulfides (0.36 g, 1.68 mmol) in *tert*-butyl alcohol (10 cm^3) under nitrogen was added potassium *tert*-butoxide (0.28 g, 2.52 mmol) dissolved in *tert*-butyl alcohol (5 cm^3). The reaction mixture was stirred vigorously for 12 h, after which the *tert*-butyl alcohol was removed under reduced pressure. The crude residue was dissolved in water (10 cm^3), and the solution extracted with dichloromethane (3 × 20 cm^3); the organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The regioisomers could be partially separated by chromatography (50% dichloromethane–50% light petroleum) to give firstly deconjugated pulegone (the β,γ-isomer related to **19**) (40 mg, 16%); δ_H(300 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 7, CH_3), 1.00–1.53 (2 H, m, 4-CH_{ax}, 5-CH_{ax}), 1.71 (3 H, d, *J* 1 CH_3), 1.72–2.50 (5 H, m), 2.67 (1 H, d, *J* 14, 2-CH), 4.71 (1 H, s, C=CH_2), 4.98 (1 H, dd, *J* 2, 1, C=CH_2); followed by (*S*)-pulegone **19** (25 mg, 10%) with an optical purity of 17%, $[\alpha]_D^{23}$ −4.2 (*c* 0.3 in $CHCl_3$) {lit.,[12] (*S*)-pulegone $[\alpha]_D^{23}$ −22.5 (neat)}; δ_H(300 MHz, $CDCl_3$) 0.99 (3 H, d, *J* 7, CH_3), 1.30 (1 H, m, 4-CH_{ax}), 1.78 (3 H, s, CH_3), 1.90 (1 H, m, 4-CH_{eq}), 1.93 (1 H, m, 5-CH), 1.98 (3 H, s, CH_3), 2.00 (1 H, m, 6-CH_{ax}), 2.22 (1 H, m, 3-CH_{ax}), 2.50 (1 H, m, 6-CH_{eq}) and 2.70 (1 H, m, 3-CH_{eq}); δ_C(70 MHz, $CDCl_3$) 21.7 (CH_3), 22.0 (CH_3), 22.9 (CH_3), 28.5 (CH_2), 31.4 (CH), 32.7 (CH_2), 50.7 (CH_2), 131.8 (C), 141.8 (C) and 204.0 (C); followed by the enone **20** (obtained slightly contaminated with pulegone) (50 mg, 19%); δ_H(250 MHz, $CDCl_3$) a) 0.99 (3 H, d, *J* 7, CH_3), 1.10 (1 H, m), 1.78 (3 H, s, CH_3), 1.88 (3 H, s, CH_3), 1.85–2.00 (2 H, m), 2.20–2.48 (3 H, m) and 3.16 (1 H, m, 3-CH); δ_C(67.8 MHz, $CDCl_3$) 19.4 (CH_3), 20.5 (CH_2), 20.8 (CH_3), 22.6 (CH_3), 31.4 (CH_2), 33.6 (CH), 43.0 (CH_2), 138.5 (C), 138.5 (C) and 206.0 (C).

Preparation of (*S*)-5-methylcyclohex-2-enone 21 and 3-methylcyclohex-2-enone 22

To a suspension of palladium(II) acetate (0.56 g, 0.30 mmol) in refluxing acetonitrile (10 cm^3) under a nitrogen atmosphere was added a mixture of the enol silanes **17** and **18** (0.56 g, 3.05 mmol), prepared from the racemic ketone **16** as described above, followed by diallyl carbonate (0.92 cm^3, 6.41 mmol) in acetonitrile (6 cm^3). After being heated to reflux for 1 h, the reaction mixure was cooled to room temperature, and then diluted with ether (5 cm^3), washed with brine, and extracted with ether (3 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (5% ethyl acetate–95% light petroleum) gave firstly (*S*)-5-methylcyclohexenone **21** as a colourless oil (55 mg, 16%); $[\alpha]_D^{23}$ +17.7 (*c* 1.7 in $CHCl_3$) corresponding to an optical purity of 17% {lit.,[14] $[\alpha]_D^{25}$ +90.2 (*c* 0.8 in $CHCl_3$)}; δ_H(250 MHz, $CDCl_3$) 1.08 (3 H, s, CH_3), 1.97–2.28 (3 H, m, 5-CH, 4-CH_{eq}, 6-CH_{eq}), 2.40 (1 H, m, 6-CH_{ax}), 2.47 (1 H, dd, *J* 13, 13, 4-CH_{ax}), 6.02 (1 H, ddd, *J* 10, 1.5, 1.5, 2-CH) and 6.97 (1 H, dddd, *J* 13, 10, 6, 2, 5-CH); δ_C(67.8 MHz, $CDCl_3$) 21.20 (CH_3), 30.35 (CH), 34.02 (CH_2), 46.23 (CH_2), 129.59 (CH), 149.95 (CH) and 200.18 (C); followed by 3-methylcyclohexenone **22** as a colourless oil (42 mg, 12%); δ_H(250 MHz, $CDCl_3$) 1.96 (3 H, s, CH_3), 1.98–2.03 (2 H, m, 5-CH_2), 2.25–2.36 (4 H, m, 4-CH_2, 6-CH_2) and 5.87 (1 H, s, 2-CH).

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