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Enantioselective Deprotonation of 8-Oxabicyclo[3.2.1]octan-3-one Systems using Homochiral Lithium Amide Bases

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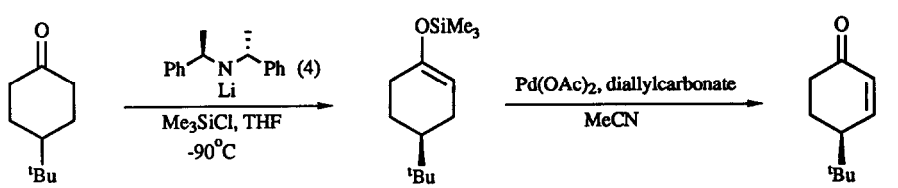
Abstract: The asymmetric transformation of oxabicyclic ketones **6** and **7** into non-racemic enol silanes **12** (88% ee) and **10** (85% ee), respectively, was achieved using the homochiral lithium amide base **4**. Conversion of **10** into a known key intermediate **15** for *C*-nucleoside synthesis was possible in a highly efficient two step sequence.

Introduction

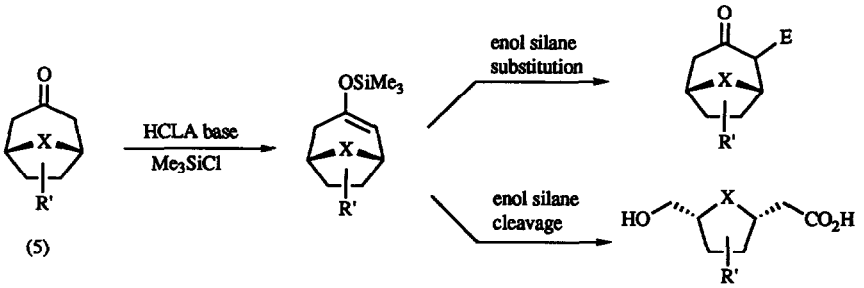
Homochiral lithium amide (HCLA) bases are emerging as useful new reagents for asymmetric synthesis.[1] These reagents have been most widely utilised in kinetically controlled deprotonations of cyclic ketones in which the base discriminates between enantiotopic α-hydrogens. This enables the direct conversion of a prochiral ketone into a chiral enolate, and hence to derived non-racemic products, particularly enol silanes. This method was first applied to conformationally anchored cyclohexanones,[2] since the stereoelectronically preferred removal of axial hydrogens in such systems should avoid complications arising due to the presence of diastereotopic α-hydrogens.[3] This chemistry allows access to a range of useful cycloalkanone-derived products in *ca.* 90% enantiomeric excess (ee), e.g. **1** → **2** → **3**, as shown in Scheme 1.[4]



(1) (2) 66% yield, 88% ee (3) 86%

Scheme 1

We have found the readily available HCLA base **4** to be very useful for preparing chiral enol silanes such as **2** in this way. In order to expand the application of this approach, and to access more highly functionalised products, we planned similar reactions of bridged azabicyclic and oxabicyclic ketones of general structure **5**, Scheme 2.



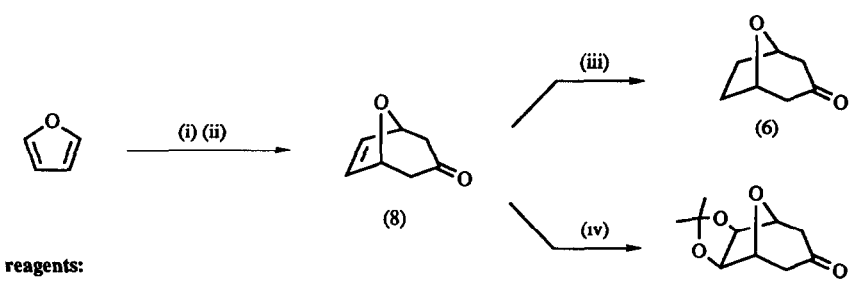
R'– indicates a symmetrical substitution pattern
X = O, S, or NR

Scheme 2

Asymmetric transformation of readily available tropinone derivatives **5** (X = NR) was anticipated to allow rapid access to chiral precursors of tropane alkaloids such as cocaine. Alternatively, cleavage of chiral enol silanes derived from **5** would lead to *cis*-disubstituted tetrahydrofuran or pyrrolidine products. Following our initial study of the HCLA base deprotonations of the tropinone system,[5] the strategy shown in Scheme 2 has been eloquently realised by two other groups, using azabicyclic ketones.[6,7] We describe here full details of our studies using the corresponding oxabicyclic ketones **5** (X = O).[8]

Results and Discussion

Two oxabicyclic ketones, **6** and **7**, suitable for this study, were readily prepared from furan following the well-established "[4+3] cycloaddition" approach. Thus, unsaturated ketone **8**, prepared using the procedure of Ansell *et al.*,[9] was either hydrogenated to give the simple saturated ketone **6**, or subjected to osmylation to furnish **7**, Scheme 3.

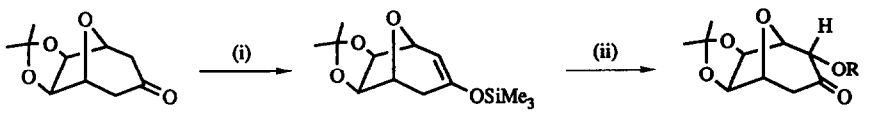


reagents:
(i) $Br_2CHCOCHBr_2$, $B(OEt)_3$, Zn (ii) Zn/Cu, NH_4Cl, MeOH
(iii) H_2, Pd/C, EtOH (37% overall) (iv) OsO_4, ^tBuOH, Et_2O, H_2O_2, acetone (66%)

Scheme 3

In our hands the osmylation step carried out with acetone as cosolvent furnished the desired isopropylidine-protected diol **7** without the need for the separate protection step described previously.[10] Both ketones **6** and **7** were found to be cleanly converted to the corresponding racemic enol silanes on treatment with a mixture of LDA and Me_3SiCl in THF (internal trapping conditions[11]).

In order to examine the asymmetric preparation of enol silanes from **6** and **7** using HCLA bases we required methods to establish both the enantiomeric excess (ee), and the absolute configuration of these products. We first established a method for the determination of the ee of products derived from **7**, which involved HPLC analysis of dinitrobenzoate derivative **9** using a chiral Pirkle column.[12] This derivative was prepared by the sequence outlined in Scheme 4.

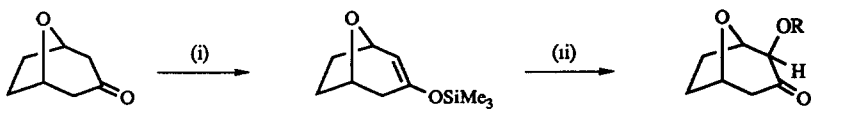


reagents:
(i) LDA, Me_3SiCl (see Table 1) (ii) PhIO, $BF_3 \cdot OEt_2$, H_2O (67%)
(iii) ArCOCl, pyridine (73%) (Ar = 3,5-dinitrophenyl)

Scheme 4

Conversion of the enol silane **10** into the α-hydroxy ketone **11** was best carried out using a mixture of PhIO and $BF_3 \cdot OEt_2$ in water.[13] This conversion is proposed to occur by initial formation of an α-iodo ketone, which undergoes *in situ* substitution to give the hydroxy ketone product. Since initial *exo*-approach of the PhIO is to be expected, and the subsequent substitution should occur with inversion, we assigned the *endo*-orientation to the resulting hydroxyl group. Alternative methods of oxidation, such as treatment with mCPBA,[14] MoOPH,[15] or Davis' sulphonyloxaziridine,[16] gave very low yields of the desired hydroxy ketone product. Reaction of **11** with 3,5-dinitrobenzoyl chloride then gave the racemic ester **9**, the two enantiomers of which were widely separated by the Pirkle column.

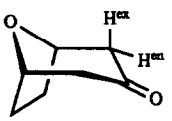
Somewhat surprisingly, the oxidation of the enol silane **12**, derived from **6**, using the conditions used for **7**, proved unreliable and low-yielding. In this case we found that the use of dimethyldioxirane (DMDO) gave good yields of α-hydroxy ketone **13**,[17] which could be derivatised to give **14** and separated on the chiral HPLC column as before, Scheme 5.



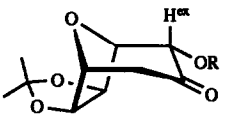
reagents:
(i) LDA, Me_3SiCl (see Table 2) (ii) DMDO, acetone (69%)
(iii) ArCOCl, pyridine (73%) (Ar = 3,5-dinitrophenyl)

Scheme 5

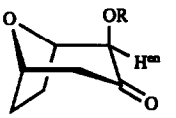
The α-hydroxy ketone **13**, obtained using DMDO, was assigned the *exo*-configuration, as shown. The stereochemical assignment of the two hydroxy ketones **11** and **13** is based on analysis of their ^{1}H NMR spectra, in comparison with that of the simple ketone **6**. In particular, characteristic chemical shifts and coupling patterns for the protons α to the hydroxyl group are seen for the two stereochemical series, as shown in Figure 1.



(6) H^{ex} δ = 2.7
H^{en} δ = 2.3



(11) R = H, H^{ex} = dd, δ = 4.3
(9) R = COAr, H^{ex} = d, δ = 5.6



(13) R = H, H^{en} = s, δ = 3.6
(14) R = COAr, H^{en} = s, δ = 5.0

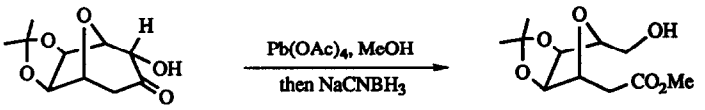
Figure 1

In particular, the *exo*-orientated hydrogen H^{ex} in compounds **9** and **11** shows coupling with the bridgehead hydrogen, whereas the *endo*-hydrogen H^{en} in **13** and **14** appears as a singlet. The chemical shift of the α-hydrogen in **9** and **11** is also about 0.6–0.7 ppm downfield of the equatorial counterpart in **13** and **14** respectively, which is to be expected from the shifts of the α-hydrogens in **6**. The coupling constants are best accommodated by a flattening of the six-membered ring, in accord with assignments made previously for related azabicyclic ketones.[18]

With an analytical procedure for ee determination established, we next examined the formation of optically active enol silane **10** using HCLA base **4** and an *in situ* Me_3SiCl quench in THF at low temperature. Under our standard conditions the enol silane **10** was produced in 86–95% yield, and in 70% ee at -78°C, and 85% ee at -94°C, as indicated by chiral HPLC analysis of the derived optically active dinitrobenzoates **9**. Ketone **6** gave comparable results when treated with HCLA base **4**, HPLC analysis indicating the formation of products in 88% ee at -95°C.

Having established that **10** could be formed in good yield and ee we next wanted to assign its absolute configuration, which was expected to be as shown in Scheme 4 based on our previous work on a related azabicyclic ketone.[5] It was decided to transform **10** into the hydroxy ester **15** of known absolute configuration. This compound had previously been utilised as a key intermediate in the synthesis of a range of *C*-nucleosides, including showdomycin.[10] An asymmetric synthesis of **15**, involving oxidative cleavage of the bicyclic enol silane **10**, would serve to establish the absolute configuration of our chiral product, and would also constitute a concise and versatile synthetic entry to the aforementioned *C*-nucleosides.

Ozonolysis of **10** under typical conditions and using a variety of work-up procedures clearly resulted in double-bond cleavage but gave mixtures of products. However, treatment of the α-hydroxy ketone **11** with lead tetraacetate in methanol, followed by reduction with $NaCNBH_3$, in the same pot, gave **15** in excellent yield, and with identical spectroscopic characteristics to those reported previously, Scheme 6.[19]



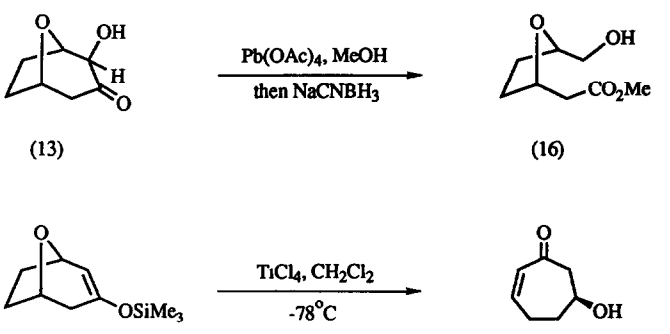
(11) (15) 93%

Scheme 6

Application of this route to non-racemic **10**, obtained as above, using base **4**, at -78°C, furnished optically active **15** in 93% overall yield, with $[\alpha]_D^{18}$ +4.32 (c 2.87, $CHCl_3$), indicating 66% optical purity (lit.[19] $[\alpha]_D^{15}$ -6.28 (c 2.33, $CHCl_3$) for enantiomer). The sign and magnitude of the rotation are consistent both with our assignment of absolute configuration of **10**, as shown in Schemes 4 and 6, and also our estimate of the level of asymmetric induction. In addition, the level and sense of asymmetric induction is similar to that achieved previously using base **4** with cyclohexanone substrates, and lends support to our expectation that "asymmetric deprotonation" of these systems should occur by removal of the more accessible pseudoaxial *exo*-orientated hydrogens.

Although the level of asymmetric induction in the HCLA base reactions described above is reasonably high, enantiomerically pure products are generally required in asymmetric synthesis. We found that the hydroxy ketone **11** could be recrystallised (from Et_2O) to provide optically enriched material, which, when derivatised and subjected to chiral HPLC as before, proved to be of >98% ee.

Some additional transformations of the products derived from the simpler ketone **6** were also carried out, as shown in Scheme 7.



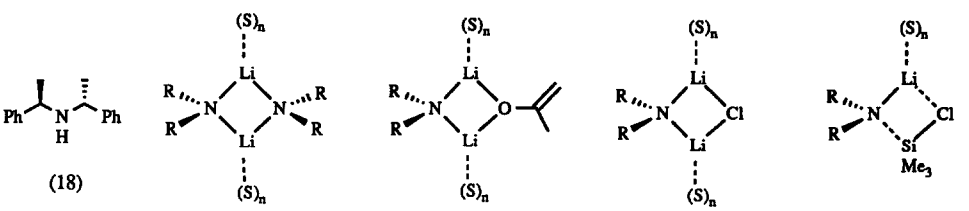
(13) (16)

(12) (17)

Scheme 7

Oxidative cleavage of the α-hydroxy ketone **13** using lead tetraacetate occurred smoothly to give **16** in 89% yield, following the procedure used previously, and further demonstrates the versatility of this strategy for the asymmetric synthesis of *cis*-substituted tetrahydrofuran products. In addition we found that exposure of the enol silane **12** to $TiCl_4$ in CH_2Cl_2 at -78°C for three hours resulted in opening of the bicyclic system to give the hydroxycycloheptenone **17** in 76% yield.[20] The synthesis of **16** and **17** in non-racemic form was also carried out using enol silane **12** prepared using the HCLA base **4**. The ee of these materials has not been independently determined, but is assumed to be comparable to that indicated by the HPLC results for **14**.

Considering the synthetic potential of these HCLA base deprotonations little is known about the dependence of the product ee on the reaction conditions. The reactions are complicated by the fact that a number of ionic and neutral species that could influence the outcome of the reaction are simultaneously present, depending on the way the reaction is carried out. In addition to the obvious reactants, the homochiral amine **18** and LiCl are generated as the deprotonation of the ketone, and the quenching of the enolate with Me_3SiCl, proceed. Another complication is that the lithium amide **4** may not actually be the reactive species responsible for the ketone deprotonation, since lithium amide dimers (and in some cases higher aggregates) such as **19** are very well established,[21] and may be in dynamic equilibrium with solvated monomeric species in THF solution. Mixed aggregates **20** and **21** involving either a lithium enolate or lithium halide also have recent literature precedent,[22] and we also considered that some kind of silicon-modified lithium amide species, represented here as **22**, might also be implicated in the *in situ* quench reactions. Therefore it is important to consider the possible intervention of a range of aggregates **19–22** as reactive species in the "asymmetric deprotonation". In order to probe some of these features of the HCLA base deprotonations we conducted a range of reactions under the conditions shown in Table 1 using the ketones **6** and **7**.



e.g. R_2NLi = (4), S = THF, (18), etc., n = 1 or 2

Table 1. Enantioselectivities in Deprotonations of Ketone **6** and **7**[a]

entry (ketone)	**4** (eq.)	Me_3SiCl (eq.)	additive	temp °C[b]	yield **10** or **12** (%)	ee (%)
1 (**6**)	1.5	5	-	-95	79	88
2 (**6**)	1.5	5	-	-78	78	82
3 (**6**)	1.5	5(ex)	-	-78	81	33
4 (**6**)	1.5	5(ex)	LiCl 0.1 eq.	-78	75	84
5 (**7**)	2.0	5	-	-94	88	85
6 (**7**)	1.2	5	-	-78	86	70
7 (**7**)	1.5	5(ex)	-	-78	98	27

Yields refer to crude silyl enol ether (estimated >95% pure by ^1H NMR), ee values were obtained by HPLC.

(a) Reactions carried out using *in situ* quench technique, except entries 3, 4 and 7 which involved the external quench method with the Me_3SiCl added after 10–15 min deprotonation time.

(b) Bath temperature (dry ice–acetone) for -78°C, otherwise an internal thermometer was employed.

Reactions of both of the ketones give slightly enhanced levels of enantioselectivity at temperatures of about -95°C, compared to -78°C. Secondly, a comparison of entries 2 and 3, and 6 and 7, shows that, in the absence of other additives, the use of an internal Me_3SiCl quench is vital for optimal selectivity. Significantly, the inclusion of LiCl in the reaction of **6** under external trapping conditions leads to a dramatic increase in the ee compared to the reaction in the absence of added salt (entry 3 versus 4). Indeed, in the presence of added LiCl the ee obtained under the external quench conditions is comparable to that obtained using the internal trap technique.

Two very significant questions are presented by the above observations. Firstly, why is a much lower ee obtained using an external quench than with an internal quench? And secondly, why does added LiCl improve the ee of the external quench procedure?

Enolate equilibration is unlikely to occur in reactions carried out at very low temperature over such short reaction times,[23] and therefore does not explain the lower selectivity seen in the external quench reactions. More likely is the intervention of reagents of improved selectivity in the *in situ* quench reactions. It is possible that the lithium amide **4** and/or the dimer **19** are responsible for the low ee observed under the external quench reactions whilst, with Me_3SiCl present, a more stereoselective species such as **21** or **22** gives improved results. The remarkable effect of LiCl on the enantioselective enolisation of **6** is analogous to the effect of LiCl on the *E:Z* selectivities in certain ketone enolisations,[24] and to salt effects in other systems.[25]

In a previous study of the reactions of certain types of HCLA bases it was possible to make some correlation between the aggregation state of the base and the optimal conditions for asymmetric deprotonations (i.e. best yield and ee).[26] The conclusion was that a solvated monomeric form of the base, such as that found in THF or in the presence of HMPA, gave better results than a dimeric form, present in less polar solvents such as diethyl ether or toluene. However, the crucial nature of the *in situ* quench procedure for optimal enantioselectivity was not addressed in this study.

The new results described above highlight the importance of the *in situ* quench protocol, and indicate that LiCl may be implicated in such reactions, possibly resulting in the formation of highly reactive mixed aggregates which show improved enantioselectivity compared with "simple" lithium amide solutions. The finding that the addition of lithium salts to HCLA enolisations can dramatically improve the enantioselectivities obtained under external quench conditions should be useful in extending the scope and synthetic utility of this chemistry.

Acknowledgements

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Experimental

Melting points for solid products were determined using a Reichert Microscope apparatus, and are uncorrected. Products without melting points are colourless oils. Infra-red spectra were recorded on a Perkin-Elmer 298, Philips PU96706 or Pye Unicam SP3-100 grating spectrophotometer. NMR spectra were recorded on a Bruker WP80SY, Bruker WM250, Bruker AM400 or Jeol EX270 machine, with Me_4Si as internal standard; *J* values are given in Hz. Mass spectra were recorded on AEI 902 or VG micromass 70E spectrometers. Microanalyses were performed at the microanalytical laboratory at Nottingham University.

HPLC was carried out on a Pirkle column (covalent D-naphthylalanine, 250 x 4.6mm, supplied by Regis Chemical Company) with a Waters 600E controller/pump system and Waters 484 detector (254nm). Isopropanol/hexane was used as eluant (50:50 mixture for **9**, 40:60 mixture for **14**) at a flow rate of 1.5 ml/min.

Analytical TLC was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Kieselgel 60 (230–400 mesh). Solvents were purified by standard techniques before use.

Enol Silane 10

To a solution of chiral amine **18** (395mg, 1.8 mmol) in dry THF (40ml) at -78°C under N_2 was added, dropwise, ^nBuLi (1.1 ml of a 1.6M solution in pentane, 1.8 mmol). After 5 min the mixture was allowed to warm to room temperature (*ca.* 30 min) and then recooled to -78°C. Me_3SiCl (0.93ml, 7.3 mmol) was added, and after 2 min the ketone **7** (290mg, 1.5 mmol) in THF (5ml) was added over 10–15 min, whilst maintaining the reaction mixture at -78°C. After stirring for an additional 20 min at -78°C $NaHCO_3$ (sat. aq., 10ml) was added and the mixture allowed to warm to room temperature. The two phases were separated and the aqueous layer extracted with petroleum ether (2 x 30ml). The combined organic extract was washed with $CuSO_4$ (sat. aq., 5 x 40ml) and then dried (Na_2SO_4), before concentrating to give **10** as a clear colourless oil which slowly crystallised under vacuum (336mg, 85%); δ_H(250MHz; $CDCl_3$) 0.20 (9H, s), 1.31 (3H, s), 1.50 (3H, s), 1.76 (1H, d, *J* 16.5), 2.59 (1H, ddd, *J* 16.5, 6 and 1), 4.35 (1H, d, *J* 6), 4.42 (1H, d, *J* 5), 4.55 (1H, d, *J* 5.5), 4.63 (1H, d, *J* 5.5) and 4.93 (1H, dt, *J* 5 and 1).

Hydroxy ketone 11

Boron trifluoride diethyl etherate (0.33ml, 2.7mmol) was added to an ice-cooled mixture of enol silane **10** (336mg, 1.25mmol) and iodosylbenzene (288mg, 1.3mmol) in deionised water (5ml). The resulting suspension was allowed to warm to room temperature and stirred until the mixture became clear (2–3h). Solid $NaHCO_3$ was then added to neutralise the solution, which was then extracted with CH_2Cl_2 (5 x 50ml). The organic extract was dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue subjected to column chromatography on silica gel (30% EtOAc in petroleum ether) to give **11** as a colourless solid (180mg, 67%); m.p. 140–142°C (from Et_2O) (Found: C, 56.14; H, 6.69. $C_{10}H_{14}O_5$ requires C, 56.05; H, 6.59%); ν_{max}(film)/cm^{-1} 3403 and 1718; δ_H(250MHz; $CDCl_3$) 1.28 (3H, s), 1.50 (3H, s), 2.52 (1H, dt, *J* 15 and 0.5), 2.84 (1H, ddd, *J* 15, 6, and 1.5), 3.69 (1H, br.s), 4.30 (1H, dd, *J* 6 and 1.5), 4.41 (1H, d, *J* 6), 4.45 (1H, d, *J* 6), 4.59 (1H, d, *J* 6) and 4.62 (1H, d, *J* 6); δ_C(100MHz; $CDCl_3$) 24.51 (CH_3), 25.93 (CH_3), 43.84 (CH_2), 75.46 (CH), 79.77 (CH), 80.74 (CH), 82.97 (CH), 83.73 (CH), 112.12 (C) and 206.51 (C=O); *m/z* 214 (M^+, 2%) and 199 (100). Optically active **11** of 63% ee gave $[\alpha]_D^{22}$ -6.9 (c 2.02, $CHCl_3$), optically enriched material (>98% ee) gave $[\alpha]_D^{24}$ -12.9 (c 0.87, $CHCl_3$).

3, 5-Dinitrobenzoate Derivative 9[27]

To a solution of the hydroxy ketone **11** (18mg, 0.08mmol) in pyridine (2ml) at 0°C was added 3,5-dinitrobenzoyl chloride (37mg, 0.16mmol). The stirred solution was then allowed to warm to room temperature over 1h after which time the pyridine was removed under reduced pressure. Column chromatography on silica gel (30% to 50% EtOAc in petroleum ether) gave **9** as a colourless solid (24mg, 73%); m.p. 165–167°C (from EtOAc/petroleum ether) (Found: C, 49.83; H, 3.88; N, 6.58. $C_{17}H_{16}O_{10}N_2$ requires C, 49.99; H, 3.95; N, 6.86%); ν_{max}(film)/cm^{-1} 1751 and 1724; δ_H(250MHz; $CDCl_3$) 1.34 (3H, s), 1.52 (3H, s), 2.58 (1H, d, *J* 15.5), 2.92 (1H, dd, *J* 15.5 and 6), 4.57 (1H, d, *J* 6), 4.69 (1H, d, *J* 5.5), 4.71 (1H, d, *J* 5), 4.78 (1H, d, *J* 6), 5.62 (1H, d, *J* 6), 9.15 (2H, d, *J* 5) and 9.26 (1H, t, *J* 2); δ_C(100MHz; $CDCl_3$) 24.73 (CH_3), 25.97 (CH_3), 44.93 (CH_2), 76.56 (CH), 80.42 (CH), 80.72 (CH), 81.93 (CH), 83.25 (CH), 112.84 (C), 123.08 (CH), 129.75 (CH), 132.57 (C), 148.82 (C), 161.17 (C) and 198.27 (C=O); *m/z* 393 (M^+ - CH_3, 78%). Material of 72% ee gave $[\alpha]_D^{20}$ -20.8 (c 1.46, $CHCl_3$), optically enriched material (>98% ee) gave $[\alpha]_D^{18}$ -25.5 (c 1.74, $CHCl_3$).

Enol Silane 12 by Internal Quench Procedure

To a solution of the chiral amine **18** (581mg, 2.58mmol) in THF (20ml) at -78°C under N_2 was added, dropwise, ^{n}BuLi (1.61 ml of a 1.6M solution in hexanes, 2.58mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to -78°C. Me_3SiCl (1.09ml, 8.56mmol) was added, and after 2 min the ketone **6** (217mg, 1.72mmol) in THF (2ml) was added, keeping the temperature at -78°C. After 45 min at -78°C the reaction was quenched with $NaHCO_3$ (sat. aq., 50ml), the two phases separated and the aqueous layer extracted with petroleum ether (3 x 50ml). The organic phase was washed with $CuSO_4$ (sat. aq., 5 x 50ml), dried ($MgSO_4$), and evaporated to give enol silane **12** as a colourless oil (270mg, 79%); ν_{max}(film)/cm^{-1} 2955, 1656 and 891; δ_H(250 MHz; $CDCl_3$) 0.19 (9H, s), 1.60–1.75 (2H, m), 1.80–2.20 (3H, m), 2.67 (1H, dd, *J* 4 and 17), 4.47–4.58 (2H, m) and 5.04 (1H, dt, *J* 0.7 and 5); δ_C (67.5 MHz; $CDCl_3$) 0.27 (CH_3), 29.03 (CH_2), 35.77 (CH_2), 39.58 (CH_2), 72.23 (CH), 73.04 (CH), 108.26 (CH) and 147.36 (C); *m/z* 105 (M^+ - $OSiMe_3$, 17%). Optically active **12** of 88% ee gave $[\alpha]_D^{24}$ -14.9 (c 1.27, EtOAc).

Enol Silane 12 by External Quench Procedure

To a solution of the chiral amine **18** (645mg, 2.86mmol) in THF (20ml) at -78°C under N_2 was added dropwise ^{n}BuLi (1.79 ml of a 1.6M solution in hexanes, 2.86mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to -78°C (at this point the amount of HMPA (neat) or LiCl (as a solution in THF) indicated in Table 2 was added if required; in this case 8.1mg of LiCl (0.1 eq.) was added in 2ml of THF). The ketone **6** (241mg, 1.91mmol) in THF (2ml) was then added, and the mixture stirred for 15 min before the addition of Me_3SiCl (1.21ml, 9.5mmol). The reaction was stirred at -78°C for a further 30 min and then worked up as above to give **12** (283mg, 75%) in 84% ee, identical spectroscopically to that obtained previously.

Hydroxy Ketone 13

To a solution of enol silane **12** (200mg, 1.01mmol) in CH_2Cl_2 (3 ml) at room temperature under N_2 was added a solution of dimethyldioxirane in acetone (1.1mmol, 11.1ml).[28] The solution was stirred for 2 h at room temperature and the solvent removed under reduced pressure to give an oil. This was subjected to

column chromatography (30 to 50% EtOAc in petroleum ether) to give the hydroxy ketone **13** as a colourless oil (99mg, 69%); ν_{max}(film)/cm^{-1} 3415, 2961, 1720 and 1035; δ_H(250 MHz; $CDCl_3$) 1.60–1.80 (2H, m), 2.00–2.20 (2H, m), 2.16 (1H, d, *J* 15), 3.06 (1H, ddd, *J* 15, 5 and 1), 3.60 (1H, s), 4.54 (1H, d, *J* 7) and 4.67 (1H, t, *J* 6); δ_C(67.5 MHz; $CDCl_3$) 24.31 (CH_2), 28.21 (CH_2), 46.21 (CH_2), 75.16 (CH), 77.86 (CH), 79.40 (CH) and 206.37 (C=O); (Found M$^+$, 142.0631. $C_7H_{10}O_3$ requires *M*, 142.0630). Material of 88% ee gave $[\alpha]_D^{25}$ -79 (c 0.15, EtOAc).

3,5-Dinitrobenzoate Derivative 14

To a solution of the hydroxy ketone **13** (100mg, 0.70mmol) in pyridine (2ml) at O°C was added 3,5-dinitrobenzoylchloride (162mg, 0.77mmol). The stirred solution was allowed to warm to room temperature, and after 3h the solvent was removed under reduced pressure. The residue was subjected to column chromatography (30% EtOAc in petroleum ether) to give the ester **14** as a yellow solid (171mg, 73%); m.p. 135°C (Found: C, 49.47; H, 3.64; N, 8.23. $C_{14}H_{12}O_8N_2$ requires C, 50.00; H, 3.60; N, 8.33%); ν_{max}($CHCl_3$)/cm^{-1} 1734, 1545, 1345 and 1271; δ_H (250 MHz; $CDCl_3$) 1.70–1.90 (2H, m), 2.10–2.30 (2H, m), 2.47 (1H, d, *J* 15), 3.13 (1H, dd, *J* 15 and 5), 4.85 (2H, m), 5.01 (1H, s), 9.16 (1H, d, *J* 2) and 9.26 (2H, t, *J* 2); δ_C(67.5 MHz; $CDCl_3$) 24.94 (CH_2), 28.27 (CH_2), 47.86 (CH_2), 75.18 (CH), 77.00 (CH), 79.69 (CH), 122.90 (CH), 129.69 (CH), 132.99 (C), 148.75 (C), 161.46 (C) and 200.91 (C=O); *m/z* 212 (43%), 195 (100), 166 (31), 149 (63) and 75 (95). Material of 88% ee gave $[\alpha]_D^{27}$ -36.5 (c 0.14, EtOAc).

Hydroxy Ester 15

To a stirred solution of the hydroxy ketone **11** (Table 1 entry 2) (61mg, 0.3mmol) in MeOH (5ml) at 0°C was added $Pb(OAc)_4$ (140mg, 0.32mmol). The cooling bath was removed and the mixture stirred for 15 min, after which time $NaCNBH_3$ (95mg, 1.5mmol) was added. After 30 min the MeOH was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (30ml) before washing with water. The organic extract was dried (Na_2SO_4), and the solvent evaporated under reduced pressure to give a residue which was subjected to column chromatography (1:1 EtOAc petroleum ether) to give **15** as a colourless oil (65mg, 93%); $[\alpha]_D^{18}$ +4.32 (c 2.87, $CHCl_3$), lit. $[\alpha]_D^{15}$ -6.28 (c 2.33, $CHCl_3$). This compound gave ^{1}H and ^{13}C NMR spectra identical with the literature.[19]

Tetrahydrofuran Ester 16

To a solution of the hydroxy ketone **13** (29mg 0.2mmol) in dry methanol (2.6ml) at 0°C was added $Pb(OAc)_4$ (99mg, mmol). The cooling bath was removed and the mixture stirred for 15 min, after which time $NaCNBH_3$ (63mg, 1.0mmol) was added. After 30 min the methanol was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (5ml) before washing with water. The organic extract was dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give **16** as an oil (31mg, 89%); (Found: C, 54.80; H, 8.12. $C_8H_{14}O_4$ requires C, 55.16; H, 8.10); ν_{max}(film)/cm^{-1} 3550, 3000 and 1710; δ_H(250 MHz; $CDCl_3$) 1.60–2.20 (4H, m), 2.30 (1H, br.s), 2.52 (1H, dd, *J* 15 and 6), 2.61 (1H, dd, *J* 15 and 7), 3.46 (1H, dd, *J* 12 and 5), 3.70 (3H, s), 3.75 (1H, dd, *J* 12 and 3), 4.08 (1H, m) and 4.33 (1H, m); δ_C(100 MHz; $CDCl_3$), 26.43 (CH_2), 31.28 (CH_2), 40.52 (CH_2), 51.67 (CH_3), 64.55 (CH_2), 75.76 (CH), 79.93 (CH) and 171.70 (C=O); *m/z* 143 (M$^+$ - CH_2=OH, 100%), 111 (67), 101 (52), 83 (37) and 55 (39). Material derived from hydroxy ketone of 85% ee gave $[\alpha]_D^{28}$ -10.4 (c 0.31, $CHCl_3$).

Enone 17

To a solution of enol silane **12** (53mg, 0.26 mmol) in CH_2Cl_2 (1ml) at -78°C under N_2 was added $TiCl_4$ (0.26 ml of a 1M solution in CH_2Cl_2, 0.26mmol). After stirring at -78°C for 3 h $NaHCO_3$ (sat. aq., 10ml) was added and the reaction extracted with CH_2Cl_2 (3 x 10ml). The organic extract was dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue subjected to column chromatography (30% EtOAc in petroleum ether) to give the product as an oil (25mg, 76%); ν_{max}(film)/cm^{-1} 3393, 2923, 1652 and 1057; δ_H(250 MHz; $CDCl_3$) 1.60 (1H, br.s), 1.90–2.10 (2H, m), 2.40–2.75 (2H, m), 2.84 (1H, dd, *J* 14 and 7), 2.95 (1H, dd, *J* 14 and 5), 4.30 (1H, m), 6.05 (1H, d, *J* 12) and 6.73 (1H, dt, *J* 12 and 6); δ_C(67.5 MHz; $CDCl_3$), 25.73 (CH_2), 35.97 (CH_2), 52.28 (CH_2), 66.42 (CH), 133.00 (CH), 147.94 (CH) and 200.22 (C=O) (Found: M^+ 126.0643. $C_7H_{10}O_2$ requires *M*, 126.0651). Material derived from enol silane of 82% ee gave $[\alpha]_D^{24}$ -4.0 (c 1.30, CH_2Cl_2). Material derived from enol silane of 82% ee gave $[\alpha]_D^{24}$ -4.0 (c 0.13, CH_2Cl_2).

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