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Synthesis of Optically Active Cyclohexenol Derivatives *via* Enzyme Catalyzed Ester Hydrolysis of 4-Acetoxy-3-methyl-2-cyclohexenone

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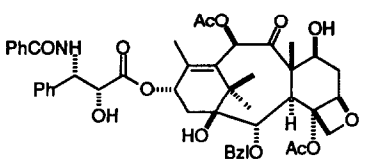
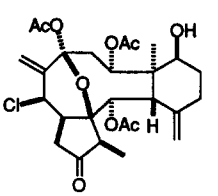
Abstract *The optically active cyclohexenol derivatives* ***9a-d*****,** *and* ***10a-c*** *are synthesized from (-)-6, which is obtained by enzymatic ester hydrolysis of racemic* ***8*** *Attempts towards the synthesis of the taxane skeleton are described*

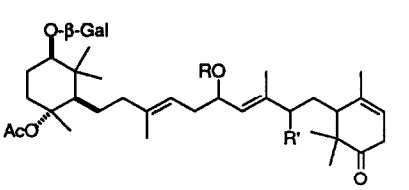
A number of natural products contain structural units related to 4-hydroxy-3-methyl-2-cyclohexenone **6** Some examples are taxol (**1**)[1], junceelloides (**2**)[2], pouoside (**3**)[3], chapinolin (**4**)[4] and a recently isolated monocyclic tripterpen from *Compositae* species (**5**)[5] An efficient synthesis of both enantiomers of **6** would therefore be desirable



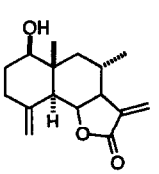
1 taxol



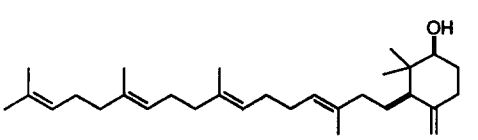
2 junceeloides



3 pouosides



4 chapinolin



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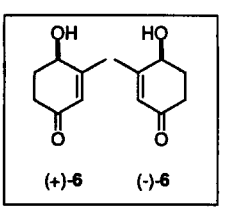
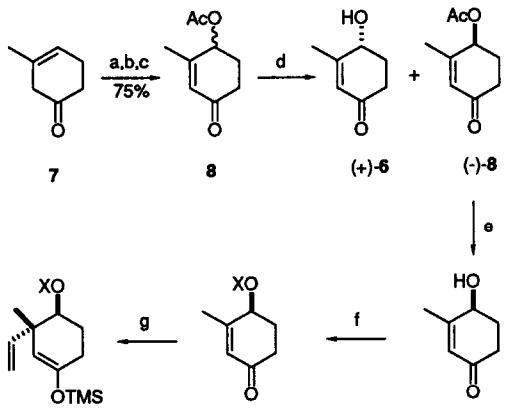


We now report a short route to (+) and (-)-**6** *via* enzymatic asymmetric hydrolysis[6] of the corresponding racemic acetate **8** (Scheme 1) Our attempts to use (-)-**6** for the synthesis of taxane related derivatives[7] (Scheme 2 and 3) are also reported

RESULTS AND DISCUSSION

Epoxidation of 3-methyl-3-cyclohexenone (**7**, Scheme 2), with peracetic acid followed by triethylamine promoted isomerization of the intermediate epoxide gave the allylic alcohol **6**,[8] which was acetylated to give **8** in 71 % overall yield from **7**. Several enzymes were then screened (0 3 M aqueous Tris-buffer at pH 7 5 and 20°C) for the hydrolysis of **8** (Table I) While a number of enzymes gave racemic material,[9] six of them (Entries 1-6) gave an optically active product, although with modest enantiomeric excess (ee)



Scheme 1 [a] CH_3CO_3H, [b] Et_3N, [c] $(Ac)_2O$, $Et(iPr)_2N$, [d] PLE, [e] Na_2CO_3, MeOH, [f] DHP, H^+ or TBDMSCl, imidazol or TBDPSCl, imidazol or BzlBr, Ag_2O, [g] CH_2=CHMgBr, CuBr SMe_2, TMSCl, TMEDA

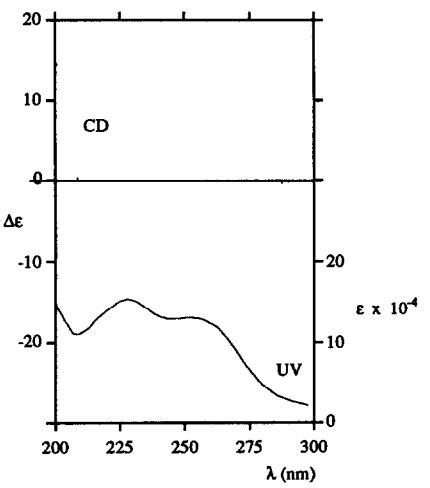


Fig 1 CD and UV spectra of the p-nitrobenzoate of (-)-**6**.

The major stereoisomer of the resulting alcohol had (R)-configuration in all cases except for the use of rabbit liver esterase (RLE) (entry 5) It is well documented that different additives or the use of mixed solvents may influence the reaction rate and the enantioselectivity of the enzymes [10-14] The effect of the addition of some organic solvents on the reactions catalyzed by pig liver esterase (PLE) and RLE are shown in Entries 7-13 These enzymes were chosen as they most rapidly gave the highest ee's of **6** The addition of t-BuOH and diisopropyl ether to the reaction mixture containing RLE caused a dramatic decrease in reaction rate while for PLE the reaction rate was essentially unaffected However, the enantioselectivity decreased

from about 60 to 40 % ee. In the PLE-catalyzed reaction the addition of 8 % DMSO increased the ee (Entry 12), while a decrease was observed in the RLE-catalyzed reaction (Entry 9) The best result (90% ee) with PLE was obtained in 25 % DMSO (Entry 13) As reported earlier, different PLE preparations may show different degrees of selectivity [13,14] Thus, when performing the hydrolysis in 25% DMSO using PLE from different sources (Fluka, Boehringer-Mannheim, and several batches from Sigma) the ee of (+)-**6** ranged from 75 to 90 %.

Table 1 Enzymatic Hydrolysis of **8** to Give **6** [9]

entry	enzyme[a]	additive	conversion (%)[b]	reaction time	ee (%)[c] of **6**	config of **6**
1	*Aspergillus niger*[d]	--	49	96 h	34	R
2	2212 F[e]	--	45	35 h	34	R
3	*Arthrobacter sp* [f]	--	45	2 weeks	54	R
4	Acetylcoline esterase[g]	--	40	72 h	60	R
5	Rabbit liver esterase[g]	-	40	24 h	66	S
6	Pig liver esterase[g]	--	48	2 h	63	R
7	Rabbit liver esterase	8% $(iPr)_2O$	--[h]	--	--	--
8	Rabbit liver esterase	8% t-BuOH	--[h]	--	--	--
9	Rabbit liver esterase	8% DMSO	47	30 h	37	S
10	Pig liver esterase	8% $(iPr)_2O$	45	2 h	42	R
11	Pig liver esterase	8% t-BuOH	45	2 h	45	R
12	Pig liver esterase	8% DMSO	41	2 h	76	R
13	Pig liver esterase	25% DMSO	45	10 h	90	R
14	Pig liver esterase	25% DMSO	62	30 h	99[1]	S[1]

a) Lipase, unless otherwise noted. b) The reactions were monitored by GC c) The enantiomeric excess was determined from ^1H NMR spectra of the esters of (-)-menthyloxyacetic acid in presence of $Eu(fod)_3$ d) Fluka e) Röhm f) Sumitomo Chemical Co g) Sigma. h) Very slow reaction i) The absolute configuration and the % ee refers to that of the alcohol obtained from hydrolysis of the remaining acetate

In cases with low selectivity it is possible to obtain the remaining enantiomer in high ee by increasing the degree of conversion [15] Hence, hydrolysis of the acetate remaining at 62 % conversion by the use of PLE (Entry 14), gave (-)-**6** in 32% yield with >99% ee [16] Enzyme catalyzed ester hydrolysis using *Arthrobacter* lipase has recently been applied to compounds structurally similar to **8**, e g the acetate of 4-hydroxy-3-methyl-2-(2-propynyl)-2-cyclopentenone (HMPC) [17,18] The hydrolysis of this acetate is very stereospecific and gives (+)-HMPC in 99 4% ee As seen in entry 3 the use of **8** as substrate results in a very slow reaction

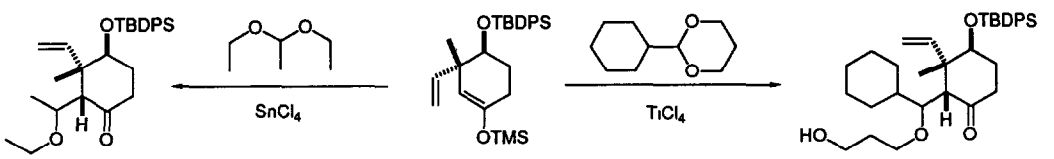
yielding (+)-**6** in only 54% ee This low selectivity is consistent with the model of the enzyme-substrate binding site presented by Mitsuda et al According to the model the substrate should carry a lipophilic side arm at C-2 to give the highest enantioselectivity, a structural feature that **8** is lacking

The absolute configuration of (–)-**6** was determined by the exciton chirality method [19-21] The CD-spectrum of its p-nitrobenzoate (Fig. 1) shows a large negative Cotton-effect ($\Delta\varepsilon_{250}$ –14 5) in the region of the p-nitrobenzoate π - π^* transition (253 nm, ε 13100) indicating that the compound has the (S)-configuration. Further support for this is obtained by comparing the experimental and the calculated CD-spectrum. The negative Cotton-effect at 250 nm is reproduced in the calculated spectrum[22,23] although the amplitude is lower than in the experimental curve

Selective protection of alcohol (–)-**6** as the benzyl ether **9d** without affecting the ketone proved to be an arduous task Both basic and acidic reaction conditions gave by-products formed *via* enolisation and aromatization The best results were obtained using Ag_2O / BzlBr in DMF [24] Benzyl ether **9d** was then formed in 30 - 40 % yield in a rather capricious reaction However, the THP, TBDMS (t-butyldimethylsilyl), and TBDPS (t-butyldiphenylsilyl) derivatives **9a-c** could be obtained in good yields, using standard procedures

The cyclohexanol ring of all the previously mentioned natural products (**1-5**) carries a tertiary center next to the alcohol group Thus, it is necessary to attach at C-3 of **6** a carbon chain or a grouping that could be transformed into various structures The vinyl moiety would be one such an alternative We therfore examined the possibility of copper mediated conjugate addition of vinylmagnesium bromide and found that the reagent formed from CuBr SMe_2 (1 equiv), vinylmagnesium bromide (2 equiv), (TMEDA) (2 equiv) and (TMSCl) (2 5 equiv) gave the silyl enol ethers **10a-c** in high yields [25] (Scheme 1) The expected anti-addition relative to the oxygen substituent at C(γ) was supported by NOESY experiments.

In conjuction with a project directed towards the synthesis of taxanes we envisaged that silyl enol ethers **10a-c** would be useful for the attachment of suitable A-ring units In this respect the results of Kende et al ,[26] who used a Lewis acid promoted coupling of an acetal and a silyl enol ether in a synthesis of a racemic taxane skeleton, seemed encouraging Thus, when silyl enol ether **10c** was treated with 1,1-diethoxyethane/$SnCl_4$ or 2-cyclohexyl-1,3-dioxane/$TiCl_4$ at -75°C, smooth reactions occurred to give mainly the axial coupling products **11** and **12**, respectively (Scheme 2)

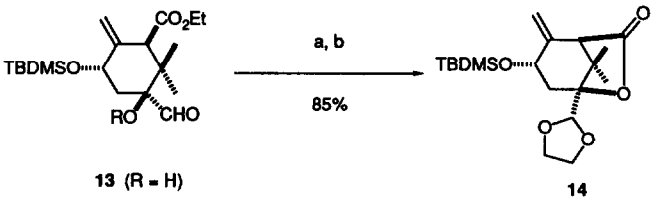


11a **10** **12**

Scheme 2

The configuration at C-2 in these derivatives is opposite to that of the corresponding position in the taxanes (C-3 in the taxane numbering system), but may be changed later in the synthesis We therefore turned

to the synthesis of A-ring acetal **14** in order to attempt the aldol-type coupling with **10c** Acetal **14** was synthesised from the known aldehyde **13**[27] by the following sequence (Scheme 3) Treatment of aldehyde **13** with 1,2-bis([trimethylsilyl]oxy) ethane and a catalytic amount of trimethylsilyl triflate[28] resulted in acetalization together with lactonization and cleavage of the TBDMS ether Compound **14** was then obtained in 85 % yield by reprotection of the hydroxyl group



13 (R = H) **14**

Scheme 3 [a] $(TMSOCH_2)_2$, TMSOTf [b] TBDMSOTf, 2,6-Lutidine

Unfortunately, no reaction was observed when acetal **14** and silyl enol ether **10c** were treated with excess $SnCl_4$, $TiCl_4$ or BF_3 OEt_2, not even at elevated temperature for several days Equally unsuccessful was the attempted aldol reaction of the metal enolates obtained by treating silyl enol ether **10a** with MeLi (alternatively followed by $ZnCl_2$ to give the ZnCl-enolate or $MgCl_2$ to give the MgCl-enolate) with aldehyde **13** (R = Li or TMS) [29]

EXPERIMENTAL.

All liquid chromatography separations were performed using Merck SiO_2 60 (0 040-0 063 mm) silica gel TLC analyses were done on Merck SiO_2 60 F_{254} precoated aluminum sheets and the spots were visualized with UV light or by charring with 5 % molybdatophosphoric acid in ethanol NMR-spectra were recorded at 23°C with a Varian XL-300 spectrometer operating at 300 MHz proton frequency (software version 6 2) using $CDCl_3$ as solvent and $CHCl_3$ as internal standard (δ 7 26 ppm as compared to TMS) Optical rotations were measured with a Perkin-Elmer 141 polarimeter Mass spectra were recorded on a Finnigan 4021 spectrometer (electron impact mode) and a Jeol JMS-SX 102 for the high resolution mass spectra CD spectra were recorded on a Jasco J-41A spectropolarimeter and UV spectra were obtained with a Varian Carry 2290 Spectrophotometer GC analyses were carried out on a Varian 3700 gas chromatograph equipped with a RSL-300 capillary column at 130°C Vinylmagnesium bromide in THF was purchased from Alfa Ventron Magnesium sulfate was used as drying reagent for organic extracts

4-Hydroxy-3-methyl-2-cyclohexenone (6) Peracetic acid[30] (10 0 mL, 1 M, 10 0 mmol) saturated with NaOAc, was added dropwise over 30 min to a stirred suspension of Na_2CO_3 (10 0 g, 94 3 mmol) and 7[31](0 87 g, 7 9 mmol) in CH_2Cl_2 (125 mL) After 120 min of additional stirring, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and dried Triethylamine (2 2 mL, 16 mmol) was added and the

resulting solution was stirred for 150 min. The reaction mixture was filtered, washed with brine, dried and concentrated under reduced pressure Caution! Peracids may form expolsive peroxides Chromatography of the residue (heptane-EtOAc, 1 1) gave **6** (0.75 g, 75 %) as a pale yellow oil ^{1}H NMR δ 5 85 (m, 1 H, 2-H), 4 33-4 42 (m, 1 H, 4-H), 2 52-2 62 (m, 1 H, 6-H), 2 24-2 41 (m, 2 H, 5-H, 6-H), 2 05 (m, 3 H, CH_3), 1 95-2 04 (m, 1 H, 5-H) Anal Calcd for $C_7H_{10}O_2$ C, 66 65, H, 7 99 Found C, 66 54, H, 8 02 EIMS m/e 126 (M^+)

4-Acetoxy-3-methyl-2-cyclohexenone (8) Ethyldiisopropylamine (3 3 mL, 19 mmol) was added to a solution of **6** (1 0 g, 8 0 mmol), acetic anhydride (2 0 mL, 20 mmol) and 4-pyrrolidinopyridine (0 10 g, 0 7 mmol) in CH_2Cl_2 (20 mL) After stirring for 120 min, the reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and water The organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (heptane-EtOAc, 3 1) yielded **8** (1 25 g, 93 0 %) as a pale yellow oil ^{1}H NMR δ 5 94 (m, 1 H, 2-H), 5 52-5 60 (m, 1 H, 4-H), 2 50-2 60 (m, 1 H, 6-H), 2 22-2 45 (m, 2 H, 5-H, 6-H), 2 14 (s, 3 H, $COCH_3$), 2 01-2.14 (m, 1 H, 5-H), 1 94 (t, 3 H, CH_3) HRMS Calcd for $C_9H_{12}O_3$ 168 0783, Found 168 0758 The acetate **8** was not stable and was used immediately in the following step

Screening of enzymes The appropriate enzyme (1 mg) followed by compound **8** (50 mg, 0 31 mmol) was added to a stirred solution of organic solvent (x mL) in 0 3 M aqueous tris(hydroxymethyl)amino-methane hydrochloride (Tris-HCl) (20-x mL, pH 7 5) at 20°C The reaction was monitored by GC analysis and terminated at ca 45% conversion The reaction mixture was then extracted with EtOAc (3x40 mL) and the combined organic layers were washed with brine, dried and concentrated Chromatography of the residue (heptane-EtOAc, 3 1) gave alcohol **6** as a pale yellow oil, which was esterified with (-)-menthyloxyacetic acid [32] The ee was determined by NMR analysis of the ester in the presence of $Eu(fod)_3$.

(S)-4-Acetoxy-3-methyl-2-cyclohexenone ((-)-8) PLE (~25 mg) followed by compound **8** (0 95 g, 7 6 mmol) was added to a solution of DMSO (40 mL, 25 %) in 0 3 M aqueous Tris-HCl (120 mL, pH 7 0) at 20°C The slowly decreasing pH was kept constant throughout the reaction by continuous addition of 0 1 M aqueous NaOH from a Radiometer pH-stat After stirring for 30 h (62 % conversion) the reaction mixture was extracted with EtOAc (3 x 250 mL) and the combined organic layers were washed with brine, dried and concentrated Chromatography of the residue (heptane-EtOAc, 3 1) gave (-)-**8** (0 34 g, 36 %) as a pale yellow oil $[\alpha]_D^{25}$ – 35 1° (c 0 61, $CDCl_3$), >99 % ee The spectral data are identical with those of racemic **8**

(S)-4-Hydroxy-3-methyl-2-cyclohexenone ((-)-6) Na_2CO_3 (2 0 g, 19 mmol) was added to a solution of (-)-**8** (0 34 g, 2 0 mmol) in CH_3OH (15 mL) After stirring for 120 min, the reaction mixture was filtered and concentrated under reduced pressure Flash chromatography of the residue (heptane-EtOAc, 1 3) gave (-)-**6** (0 23 g, 90 %) $[\alpha]_D^{25}$ – 48 8° (c 0 98, $CDCl_3$) The spectral data are identical with those of racemic **6**

(4S)-3-Methyl-4-[(tetrahydropyranyl)oxy]-2-cyclohexenone (9a). Compound **9a** was prepared from (-)-**6** (0 50 g, 4 0 mmol), DHP (0 60 mL, 6 6 mmol) and pyridinium tosylate (0 10 g, 0 40 mmol) in CH_2Cl_2 (20 mL) [33] Chromatography (heptane-EtOAc, 5 1) gave **9a** (0 78 g, 94%) as a clear oil $[\alpha]_D^{25}$ – 36 3° (c 0 81, $CDCl_3$) ^1H NMR δ 5 83, 5 89 (2 m, 1 H, 2-H), 4 75-4 82 (m, 1 H, THP), 4 24, 4 39 (2 m, 1 H, 4-H), 3 57, 3 92 (2 m, 2 H, THP), 2 50-2 63 (m, 1 H, 6-H), 2 09-2 40 (m, 3 H, 5-H, 6-H), 1 98, 2 08 (2 m, 3 H, CH_3), 1 50-1 90 (m, 6 H, THP) Anal Calcd for $C_{12}H_{18}O_3$ C, 68 55, H, 8 63 Found C, 68 39, H, 8 72 EIMS m/e 210 (M^+)

(S)-4-[(t-Butyldimethylsilyl)oxy]-3-methyl-2-cyclohexenone (9b). Compound **9b** was prepared from (-)-**6** (0 10 g, 0 79 mmol), TBDMSCl (09 20 g, 1 3 mmol) and imidazol (0 17 g, 2 5 mmol) in DMF (1 0 mL) [34] Chromatography (heptane-EtOAc, 10 1) gave **9b** (92%) as an oil $[\alpha]_D^{25}$ – 32 1° (c 1 16, $CDCl_3$) ^1H NMR δ 5 82, (q, 1 H, 2-H), 4 35 (dd, 1 H, 2-H), 2 50-2 60 (m, 1 H, 6-H), 2 25-2 37 (m, 1 H, 6-H), 2 11-2 22 (m, 1 H, 5-H), 1 91-2 05 (m, 1 H, 5-H), 1.98 (m, 3 H, CH_3), 0 92 (s, 9 H, t-Bu), 0 13 (2 s, 6 H, $SiMe_3$) Anal Calcd for $C_{13}H_{24}O_2Si$ C, 64 94, H, 10 06 Found C, 64 58, H, 10 29 EIMS m/e 183 (M^+ – t-Bu)

(S)-4-[(t-Butyldiphenylsilyl)oxy]-3-methyl-2-cyclohexenone (9c). Compound **9c** was prepared from (-)-**6** (0 10 g, 0 79 mmol), TBDPSCl (0 23 mL, 1 5 mmol), imidazol (0 20 g, 3 0 mmol) in DMF (1 0 mL) [34] Chromatography (heptane-EtOAc, 10 1) gave **9c** (95%) $[\alpha]_D^{25}$ + 4 7° (c 1 03, $CDCl_3$) ^1H NMR δ 7 73, 7 48 (2m, 10 H, phenyl), 5 80 (m, 1 H, 2-H), 4 35 (m, 1 H, 4-H), 2 45-2 56 (m, 1 H, 6-H), 1 87-2 17 (m, 3 H, 5-H, 6-H), 1 95 (m, 3H, CH_3), 1 09 (s, 9 H, t-Bu) Anal Calcd for $C_{23}H_{28}O_2Si$ C, 75 78, H, 7 74 Found C, 75 7, H, 8 0 EIMS m/e 307 (M^+ – t-Bu)

4-[(Benzyl)oxy]-3-methyl-2-cyclohexenone (9d). Compound **9d** was prepared from **6** (0 10 g, 0 79 mmol), BzlBr (0 50 g, 2 9 mmol)) and Ag_2O (1 0 g, 4 3 mmol) in DMF (3 mL) [24] Chromatography (heptane-EtOAc, 5 1) gave **9d** (30-40%) ^1H NMR δ 7 28-7 40 (m, 5 H, phenyl), 5 87 (s, 1 H, 2-H), 4 65 (dd, 2 H, $\underline{CH_2}C_6H_5$), 4 07 (m, 1 H, 4-H), 2 55-2 65 (m, 1 H, 6-H), 2 21-2 36 (m, 2H, 5-H, 6-H), 2 04-2 17 (m, 2 H, 5-H), 2 02 (m, 3 H, CH_3) Anal Calcd for $C_{14}H_{16}O_2Si$ C, 77 75, H, 7 46 Found C, 77 8, H, 7 4

(3S,4S)-3-Methyl-4-[(tetrahydropyranyl)oxy]-1-[(trimethylsilyl)oxy]-3-vinylcyclohexene (10a). Vinylmagnesium bromide (1 92 mL of a 1 0 M solution in THF, 1 92 mmol) was added dropwise during 20 min to CuBr SMe_2 (196 mg, 0 960 mmol) in THF (4 mL) at -75°C under nitrogen The mixture was stirred at -75°C for 20 min Then TMEDA (0 28 mL, 1 9 mmol) was added, followed by TMSCl (0 30 mL, 2 4 mmol) and a solution of **9a** (0 10 g, 0 48 mmol) in THF (0 5 mL) The reaction mixture was stirred at -75°C for 180 min whereafter the cooling bath was allowed to warm slowly to room temperature After stirring for 16 h, the reaction mixture was diluted with hexane, washed successively with water and saturated aqueous $NaHCO_3$, dried and concentrated under reduced pressure to give crude **10a** (0 150 g, 100%) A small amount

of the compound was purified by short column flash chromatography (hexane) for characterization ^{1}H NMR δ 5 77-5 93 (m, 1 H, vinyl), 4 95-5 06 (m, 2 H, vinyl), 4.64, 4 77 (2 m, 1 H, THP), 4 53, 4.57 (2 m, 1 H, 2-H), 3 87-3 97 (m, 1 H, THP), 3 44-3 62 (2 m, 3 H, 4-H, THP), 1 50-2 28 (m, 10 H), 1 08, 1 16 (2 s, 3 H, CH_3), 0 20 (s, 9 H, TMS) Anal Calcd for $C_{17}H_{30}O_3Si$ C, 65 76; H, 9 74 Found C, 65 82, H, 9 78. EIMS m/e 311 (M^+)

(3S,4S)-4-[(t-Butyldimethylsilyl)oxy]-3-methyl-1-[(trimethylsilyl)oxy]-3-vinylcyclohexene (10b) was prepared in a quantitative crude yield as above using **9b** ^{1}H NMR data for crude **10b** δ 5 80 (dd, 1 H, vinyl), 5 00 (dd, 2 H, vinyl), 4.95 (dd, 1 H, vinyl), 3 54 (dd, 1 H, 4-H), 2.07-2 19 (m, 1 H, 6-H), 1 89-2 01 (m, 1H, 6-H), 1 62-1 75 (m, 2 H, 5-H), 1 04 (s, 3 H, CH_3), 0 89 (s, 9 H, t-Bu), 0 19 (s, 9 H, TMS), 0 04 (2s, 6 H, $Si(CH_3)_2$) HRMS calcd for $C_{18}H_{36}O_2Si_2$ 340 2244 Found 340 2289.

The crude enol ether could not be purified further but was instead hydrolyzed to give the corresponding ketone for characterization Thus, crude **10b** (0 16 g, 0.48 mmol) was added to a mixture of silica gel (ca 10 mg) and CH_3OH /water (10 1, 1 mL) After stirring for 16 h the reaction mixture was diluted with EtOAc and washed with water The organic phase was dried and concentrated at reduced pressure Chromatography of the residue (heptane-EtOAc, 3 1) gave (3S,4S)-4-[(t-butyldimethylsilyl)oxy]-3-methyl-3-vinylcyclohexanone (0 10 g, 81%) as an oil ^{1}H NMR δ 5 67 (dd, 1 H, vinyl), 5 02 (2 dd, 2 H, vinyl), 3 69 (m, 1 H, 4-H), 2 44 (dd, 2 H, 2-H), 2 53 (m, 1 H, 6-H), 2 15 (m, 1 H, 6-H), 1 93-2 06 (m, 1 H, 5-H), 1 78-1 88 (m, 1 H, 5-H), 1 07 (s, 3 H, CH_3), 0 93 (s, 9 H, t-Bu), 0 12 (2 s, 6 H, $Si(CH_3)_2$) Anal Calcd for $C_{15}H_{28}O_2Si$ C, 67 10, H, 10 51 Found C, 67 30; H, 10 27 EIMS m/e 211 (M^+ – t-Bu)

(3S,4S)-4-[(t-butyldiphenylsilyl)oxy]-3-Methyl-1-[(trimethylsilyl)oxy]-3-vinylcyclohexene (10c) was prepared in a quantitative crude yield as above using **9c** ^{1}H NMR data for crude **10c** δ 7 69, 7 39 (2 m, 10 H, phenyl), 5 78 (dd, 1 H, vinyl), 4 97 (dd, 1 H, vinyl), 4 92 (dd, 1 H, vinyl), 4 52 (s (broad), 1 H, 2-H), 3 70 (dd, 1 H, 4-H), 1 92-2 03 (m, 1 H, 6-H), 1 47-1 83 (m, 3 H, 5-H, 6-H), 1 14 (s, 3 H, CH_3), 1 05 (s, 9 H, tBu), 0 17 (s, 9 H, TMS) HRMS calcd for $C_{28}H_{40}O_2Si_2$ 464 2556 Found 464 2574

The crude enol ether could not be purified further but was instead hydrolyzed as above to give the corresponding ketone for characterization Thus, crude **10c** (0 22 g, 0 48 mmol) gave (3S,4S)-4-[(t-butyldiphenylsilyl)oxy]-3-methyl-3-vinylcyclohexanone (0 17 g, 90%) after hydrolysis, work-up and chromatography (hexane EtOAc, 10 1) ^{1}H NMR δ 7 70, 7 41 (2 m, 10 H, phenyl), 5 61 (dd, 1 H, vinyl), 4 96 (2 dd, 2 H, vinyl), 3 85 (dd, 1 H, 4-H), 2 47 (dd, 2 H, 2-H), 2 41-2 53 (m, 1 H, 6-H), 1 99-2 09 (m, 1 H, 6-H), 1 65-1 83 (m, 2 H, 5-H), 1 11 (s, 9 H, t-Bu), 1 06 (s, 3 H, CH_3) Anal Calcd for $C_{25}H_{33}O_2Si$ C, 76 48, H, 8 22 Found C, 76 37, H, 8 35 EIMS m/e 307 (M^+ – t-Bu)

(2S, 3S, 4S)-4-[(t-butyldiphenylsilyl)oxy]-2-(1-ethoxyethyl)-3-Methyl-3-vinyl cyclohexanone (11a) and (2R, 3S, 4S)-4-[(t-butyldiphenylsilyl)oxy]-2-(1-ethoxyethyl)-3-Methyl-3-vinylcyclohexanone (11b). $SnCl_4$ (0 12 mL of a 1.0 M solution in CH_2Cl_2, 0.12 mmol) was added dropwise to a solution of compound **10c** (56 mg, 0.12 mmol) and 1,1-diethoxyethane (16 μL, 0.12 mmol) in CH_2Cl_2 (1 0 mL) at -75°C under nitrogen After stirring for 90 min, the reaction mixture was diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$ The organic phase was dried and concentrated at reduced pressure Chromatography of the residue (heptane-EtOAc, 10 1) gave **11a** (39 mg, 71 %) and **11b** (8 mg, 14 %)

11a ^{1}H NMR δ 7 72, 7 38 (2 m, 10 H, phenyl), 5 76 (dd, 1 H, vinyl), 4 99 (dd, 1 H, vinyl), 4 93 (dd, 1 H, vinyl), 3 78 (dd, 1 H, 4-H), 3.58-3 66 (m, 1 H), 3 47-3 57 (m, 1 H), 3 20-3 30 (m, 1 H), 2 95 (dd, 1 H, 2-H), 2 54-2 64 (m, 1 H, 6-H), 2 05-2 14 (m, 1 H, 6-H), 1 72-1 91 (m, 2 H, 5-H), 1.24 (s, 3 H, CH_3), 1 18 (d, 3 H, CH_3), 1 11 (t, 3 H, CH_3), 1 10 (s, 9 H, t-Bu)

11b· ^{1}H NMR δ 7 80, 7 42 (2 m, 10 H, phenyl), 5 69 (dd, 1 H, vinyl), 4 98 (dd, 1 H, vinyl), 4 96 (dd, 1 H, vinyl), 3 87 (dd, 1 H, 4-H), 3 65-3 74 (m, 1 H), 3 43-3 55 (m, 1 H), 3 17-3 27 (m, 1 H), 2 47 (d, 1 H, 2-H), 2 02-2 22 (m, 2 H, 6-H), 1 73-1 84 (m, 2 H, 5-H), 1 14 (s, 3 H, CH_3), 1.06-1 16 (m, 6 H, 2 CH_3), 1 03 (s, 9 H, t-Bu) Anal Calcd for $C_{29}H_{40}O_3Si$ C, 74 95, H, 8 68 Found. C, 74 58, H, 8 60 CIMS m/e 464 (M^+)

(2S, 3S, 4S)-4-[(t-butyldiphenylsilyl)oxy]-2-(cyclohexyl-[(3-hydroxypropyl)oxy] methyl)-3-Methyl--3-vinylcyclohexanone (12). $TiCl_4$ (82 μL of a 1 0 M solution in CH_2Cl_2, 82 μmol) was added dropwise to a solution of compound **10c** (38 mg, 82 μmol) and 2-cyclohexyl-1,3-dioxane (14 mg, 82 μmol) in CH_2Cl_2 (1 0 mL) at -75°C under nitrogen After stirring for 60 min, the reaction mixture was diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$ The organic phase was dried and concentrated at reduced pressure Chromatography of the residue (hexane-EtOAc, 5 1) gave **12** (28 mg, 60 %) ^{1}H NMR δ 7 70, 7 41 (2 m, 10 H, phenyl), 5 71 (dd, 1 H, vinyl), 4 93 (dd, 1 H, vinyl), 4 83 (dd, 1 H, vinyl), 3 85 (dd, 1 H, 4-H), 3 54-3 79 (m, 5 H), 3 34 (d, 1 H, 2-H), 2 61-2 72 (m, 1 H, 6-H), 1 10-2 35 (m, 17 H), 1 27 (s, 3 H, CH_3), 1 16 (s, 9 H, t-Bu) Anal Calcd for $C_{35}H_{50}O_4Si$ C, 74 68, H, 8 95 Found C, 74 34, H, 9 38 CIMS m/e 563 (M^++ H)

(1S, 3S, 5S)-1-([t-Butyldimethylsilyl]oxy)-5-(1, 3-dioxa-2-cyclopentyl)-2-methylene-4, 4-dimethyl-3, 5-cyclohexanecarbolactone (14) Bis([trimethylsilyl]oxy)ethane (22 μL, 88 μmol) and a solution of compound **13** (R = H)[27] (30 mg, 81μmol) in CH_2Cl_2 (0 5 mL) was added successively to a solution of trimethylsilyltriflate (1 6 μL, 9 μmol) in CH_2Cl_2 (3 mL) at -75°C under nitrogen The reaction mixture was stirred at -75°C for 300 min, whereafter the cooling bath was allowed to warm slowly to room temperature After stirring for 48 h, the reaction mixture was diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$. The organic phase was dried and concentrated Short column flash chromatography of the residue (hexane-EtOAc, 1 1) gave (1S, 3S, 5S)-5-(1, 3-dioxa-2-cyclopentyl)-1-hydroxy-2-methylene-4, 4-dimethyl-3, 5-cyclohexanecarbolactone (18 mg, 87 %) ^{1}H NMR δ 5 32 (d, 1 H, methylene), 5 05 (d, 1 H, methylene), 5 03 (s, 1 H, acetal), 4 43 (m, 1 H, 3-H), 3 87-4 03 (m, 4 H, acetal), 2 85 (s, 1 H, 5-H), 2 64 (dd, 1 H, 2-H),

2 02 (d, 1H, OH), 1 68 (dd, 1 H, 2-H), 1 20 (s, 3 H, CH_3), 1 11 (s, 3 H, CH_3) CIMS m/e 255 (M^++ H)

t-Butyldimethylsilyltriflate (24 µL, 0 10 mmol) was added to a solution of the lactone (18 mg, 68 µmol) and 2,6-lutidine (16 µL, 0.14 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 60 min, the reaction mixture was diluted with diethyl ether and washed successively with 1 M aqueous HCl and saturated aqueous $NaHCO_3$ The organic phase was dried and concentrated under reduced pressure Short column flash chromatography of the residue (hexane-EtOAc, 10 1) gave **14** (25 mg, 98 %) as a white solid. Mp 113°C, $[\alpha]_D^{25}$ 119 8° (c 0.28, $CDCl_3$), ^{1}H NMR δ 5 27 (d, 1 H, = CH_2), 5 01 (s, 1 H, acetal), 4.96 (d, 1 H, = CH_2), 4.34 (m, 1 H, 3-H), 3 85-4.04 (m, 4 H, acetal), 2 85 (s, 1 H, 5-H), 2 46 (dd, 1 H, 2-H), 1 66 (dd, 1 H, 2-H), 1 09 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 0 92 (s, 9 H, t-Bu), 0 08 (s, 6 H, $Si(CH_3)_2$) Anal Calcd for $C_{19}H_{32}O_5Si$ C, 61 92, H, 8 75 Found C, 61 65, H, 8 63 CIMS m/e 369 (M^++ H)

Attempted reaction between acetal **14** *and silyl enol ether* **10c** $TiCl_4$ (27µL of a 0 8 M solution in CH_2Cl_2, 22 µmol) was added to a solution of **14** (5 mg, 14 µmol) and **10c** (10 mg, 21 µmol) in CH_2Cl_2 (0 5 mL) at -75°C under argon The reaction mixture was stirred for 120 min followed by 48 h additional stirring at room temperature The reaction was also performed with the following modifications a) $SnCl_4$ or BF_3 OEt_2 were used instead of $TiCl_4$, b) 2 equiv of $TiCl_4$ was used instead of 1 0 equiv , c) the reaction mixture was heated at reflux for 24 h In no case was any coupling product observed.

Attempted aldol reaction between aldehyde **13** *and metal enolates of* **10a** The metal enolates were prepared as follows MeLi (38 µL of a 1 6 M solution in diethyl ether, 60 µmol) was added to a solution of **10a** (67 mg, 60 µmol) in diethyl ether (0 3 mL) The reaction mixture was stirred for 30 min at room temperature to give the lithium enolate of **10a** Subsequent addition of anhydrous $ZnCl_2$ (8 4 mg, 60 µmol) or $MgCl_2$ (6 6 mg, 60 µmol) followed by 15 min of additional stirring gave the ZnCl- and MgCl-enolates, respectively.

A solution of **13** (R = H, 20 mg, 54 µmol) in diethyl ether (0 2 mL) was added to a solution of LDA (54 µmol) in diethyl ether (0 1 mL) The reaction mixture was coled to -50°C and the appropriate metal enolate solution was added dropwise during 5 min Stirring was continued for 240 min at -50°C followed by 24 h at room temperature Saturated aqueous NH_4Cl or 1 M aqueous HCl was then added, the mixture was extracted with diethyl ether and the collected organic phases were dried, concentrated and analyzed by NMR The reaction was also performed with the following modifications a) THF was used as solvent instead of diethyl ether, b) compound **13** (R = TMS) was used instead of aldehyde **13** (R = Li), c) the reaction was quenched at -50°C instead of room temperature No aldol product could be detected in any of these experiments

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