A Formal Synthesis of 18-*O*-Methyl Mycalamide B

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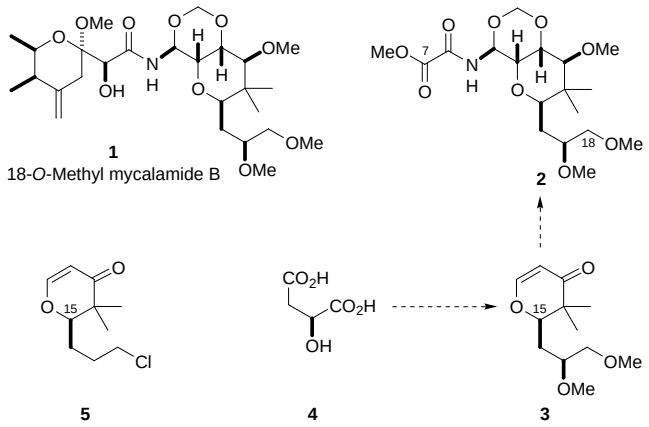
Abstract: A new approach to the C7–C18 fragment **2** of the potent antitumour agent 18-*O*-methyl mycalamide B benefits from greater flexibility in side chain construction and a more efficient synthesis of the 1,3-dioxane ring.

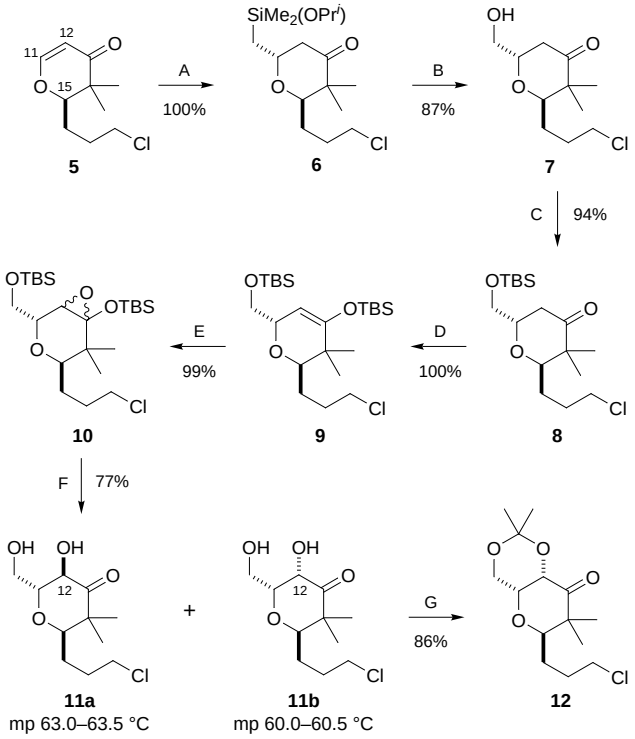
Key words: conjugate addition, Fleming–Tamao oxidation, asymmetric dihydroxylation, 1,3-dioxane synthesis, stereoselective α-hydroxylation of a ketone, addition reactions, Grignard reaction, reductions, osmium, protecting groups

18-*O*-Methyl mycalamide B (**1**, Scheme 1) is the most potent derivative of the marine antitumour agent mycalamide B[1] discovered during a structure-activity relationship study by Munro and co-workers.[2] With very limited supplies of the natural product available for study, we undertook a total synthesis which confirmed the high potency of **1**, but our synthesis was marred by two defects.[3] Firstly, construction of the dihydropyranone intermediate **3** from (*S*)-(–)-malic acid (**4**) was long and inefficient owing to low diastereoselectivity in the construction of the C15 stereogenic centre. Secondly, construction of the 1,3-dioxane in intermediate **2** from the dihydropyranone **3** was capricious and difficult to scale up. We now report an improved synthesis of C7–C18 fragment **2** from the readily available (*R*)-dihydropyranone **5**[4] which circumvents both of the aforementioned problems. An added bonus to the new route is the opportunity to vary the substitution in the side chain.



Scheme 1

The first phase of our synthesis required appendage of hydroxymethyl and hydroxyl groups to the dihydropyranone **5** as outlined in Scheme 2. The sequence began with a highly diastereoselective Cu(I)-mediated conjugate addition of Tamao's Grignard reagent, (*i*-PrO)$SiMe_2CH_2MgCl$,[5] to the dihydropyranone **5**. The reaction occurred in high yield to give the adduct **6** as a single diastereoisomer (Note 1). The latent hydroxyl group was unveiled by a Fleming–Tamao oxidation[5–7] and the nascent hydroxyl protected as its TBS ether **8** in 94%



Reagents and conditions: (7 steps, 53% overall yield)

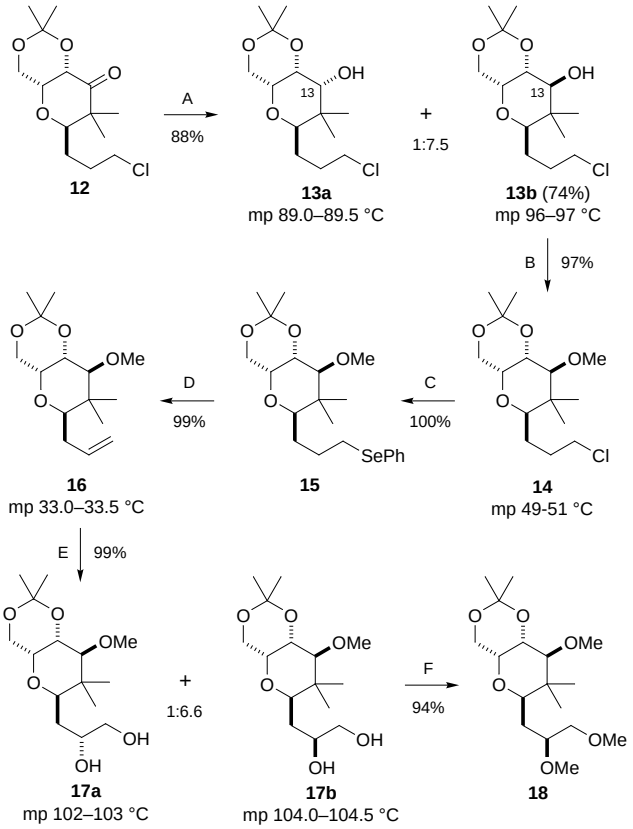
A 100% (*i*-PrO)$SiMe_2CH_2MgCl$/CuBr•SMe_2/THF, –70 to –30 °C
B 87% H_2O_2/KF•$2H_2O$/$KHCO_3$/THF-MeOH-H_2O, 0 °C, 6 h
C 94% TBSCl/Et_3N/DMAP/CH_2Cl_2, r.t., 36 h
D 100% TBSOTf/Et_3N/CH_2Cl_2, r.t., 1.5 h
E 99% oxone/$KHCO_3$/18-crown-6/toluene-acetone-H_2O, r.t., 1 h
F 77% (a) PPTS/MeOH-H_2O, reflux, 18 h; (b) column chromatographic separation
G 86% 2-methoxypropene/PPTS/CH_2Cl_2, r.t., 4.25 h

Scheme 2

yield. α-Hydroxylation of the ketone at C12 was accomplished by a three-step sequence beginning with the preparation of the enol silane **9** (Note 2). Then epoxidation with dimethyldioxirane generated in situ by phase-transfer catalysis[8,9] gave the sensitive oxirane **10** which was immediately hydrolysed to give a mixture of the diastereoisomeric crystalline α-hydroxy ketones **11a** and **11b** (dr = 1:15) which were separable by column chromatography. The major product **11b** was assigned the desired (*S*)-stereochemistry based on the doublet (J = 7.9 Hz) for the C12-H at δ = 4.61. The corresponding signal in the minor isomer appeared as a dd (J = 8.5, 3.3 Hz) at δ = 3.83. To complete the sequence, the two hydroxyl groups were protected as the isopropylidene acetal **12** in 86% yield.

The second phase of our synthesis entailed the elaboration of the side chain at C15 (Scheme 3). But first the hindered ketone **12** had to be reduced selectively to give the alcohol **13b**. Efficiency and stereoselectivity depended strongly on both the diol protecting group and the reducing agent. The di-*tert*-butylsilylene group was introduced in highest yield (99%) but it was the least reactive of the substrates tried and it only gave a modest dr (**13a**:**13b** = 1:2–3) at best in the reduction step. The benzylidene derivative gave the best dr (**13a**:**13b** = 1:14) in the reduction step but it was formed in meagre yield (30–40%) using benzaldehyde dimethylacetal and TsOH. The isopropylidene group offered the best compromise because it was introduced in good yield (86%) and reduction of the keto function was sensitive to the reducing agent. Thus, reduction of **12** with L-selectride in THF at –78 °C favoured the undesired diastereoisomer **13a** (**13a**:**13b** = 10:1) and less hindered reducing agents such as sodium borohydride in MeOH likewise favoured **13a**. However, sodium triacetoxyborohydride in the presence of cerium trichloride in MeOH favoured the desired isomer **13b**.[10] At room temperature, the reduction gave **13a**:**13b** = 1:2.5 but this improved to at least 1:7.5 by conducting the reaction at 0 °C (Note 3). At low temperature (–78 °C) the reaction was too slow to be practical. Pure **13b** obtained directly by crystallisation from the mixture, was then *O*-methylated using phase-transfer catalysis to give the methyl ether **14** in 97% yield.

Initial attempts to convert the 3-chloropropyl side chain in **14** to its 2-propenyl analogue by dehydrohalogenation using DBU gave messy reactions as did similar experiments on the corresponding iodoalkane. A longer but efficient route via the selenide **15** gave the desired alkene **16** in 99% yield from **14**. Poor stereoselectivity in the substrate-controlled dihydroxylation of the terminal alkene with OsO_4 prompted a survey of several asymmetric variants. Best results were obtained using the hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$] ligand of Sharpless[11] whereupon the crystalline diols **17a,b** were obtained in a combined yield of 99% in the ratio **17a**:**17b** = 1:6.6. Even higher diastereoselectivity (11:1) in favour of the undesired isomer **17a** was obtained using hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PYR$] (Note 4). Phase 2 was completed by *O*-methylation of the diol **17b** to give **18** in 94% yield.

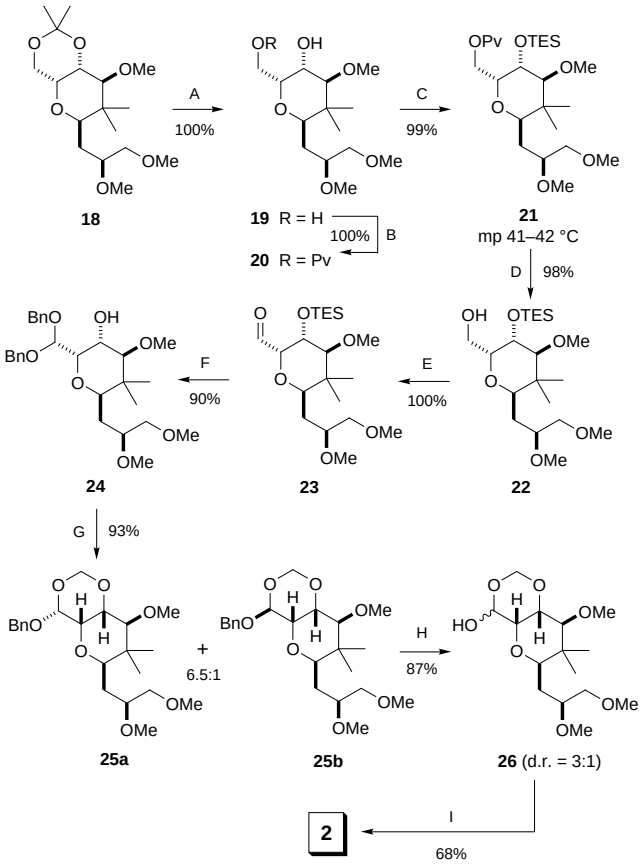


Reagents and conditions: (7 steps, 55% overall yield)

A	74%	$NaB(OAc)_3H/CeCl_3.7H_2O$/MeOH-H_2O, 0 °C, 4.25 h
B	97%	$(MeO)_2SO_2/Bu_4NHSO_4$/NaOH/toluene-H_2O, r.t., 14 h
C	100%	$(PhSe)_2/NaBH_4$/EtOH, reflux, 40 min
D	99%	(a) $NaIO_4$/MeOH-H_2O, r.t.; (b) Et_3N/toluene, reflux, 10 min
E	83%	$(DHQ)_2PYR/K_2OsO_4/K_3Fe(CN)_6/K_2CO_3$/*t*-BuOH-$H_2O$, 0 °C, 3 h
F	94%	NaH/MeI/THF, r.t., 7 h

Scheme 3

The third and final phase of the synthesis (Scheme 4) began with a series of protecting group manipulations to produce the free primary alcohol **22** whose oxidation with the Dess–Martin periodinane[12] yielded the sensitive aldehyde **23**. Conversion of the aldehyde **23** to its dibenzyl acetal **24** was accompanied by partial deprotection of the TES ether. Complete scission of the TES ether was achieved with TBAF whereupon the nascent hydroxyl group was used to initiate construction of the 1,3-dioxane ring. Treatment of **24** with paraformaldehyde in the presence of HCl[13] gave the diastereoisomeric 1,3-dioxane acetals **25a,b** (dr = 6.5:1) in 93% yield. Separation of the acetals **25a,b** by column chromatography was possibe but useless since hydrogenolysis of the benzyl group gave the same mixture of the hemiacetals **26** (dr = 3:1). To complete the synthesis, the mixture of the hemiacetals **26** was converted to the C7–C18 fragment **2** and thence to 18-*O*-methyl mycalamide B as described previously.[3]



Reagents and conditions: (11 steps, 48% overall yield)

A	~100%	PTSA/MeOH, r.t., 45 min
B	~100%	PvCl/pyr-CH_2Cl_2
C	99%	TESCl/imidazole/DMF, r.t., 2 h
D	98%	DIBALH/CH_2Cl_2, –78 °C, 30 min
E	~100%	Dess–Martin periodinane/CH_2Cl_2, r.t., 40 min
F	90%	(a) $HC(OBn)_3$/CSA/CH_2Cl_2, r.t., 5 h; (b) TBAF/THF, r. t., 11 h
G	93%	$(HCHO)_n$/HCl (gas)/CH_2Cl_2, 0 °C, 30 min
H	87%	H_2/Pd-C/EtOAc, r.t., 17 h
I	68%	2 steps (see Ref. 3)

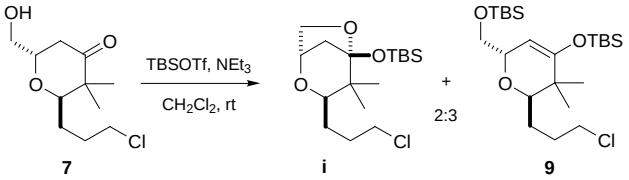
Scheme 4

In conclusion, the modifications reported herein offers a more practical and flexible route to 18-*O*-methyl mycalamide B and its relatives than the related route we reported in 1996. Key features to the new route are: (1) the ready availability of the dihydropyranone **5** on a large scale from cheap, easily available materials; (2) the potential for side chain variation offered by the chloroalkane intermediate **14** and its alkene derivative **16**; (3) the efficiency of the 1,3-dioxane ring construction step **24**→ **25**. All is not well though: the synthesis is still in need of abbreviation.

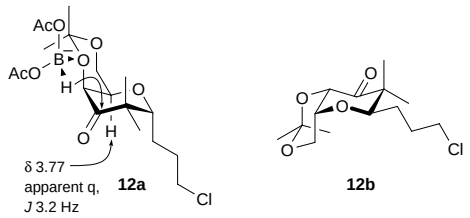
Notes

1. The efficient Cu(I)-catalysed 1,4-addition of (*i*-PrO)$SiMe_2CH_2MgCl$ to dihydropyranone was surprising because Tamao and Ishida[14] had established that the reaction was of limited synthetic value.

2. Attempts to convert the hydroxyketone **7** to the enol silane **9** in a single step was thwarted by competing formation of the bicyclic TBS ether **i**.

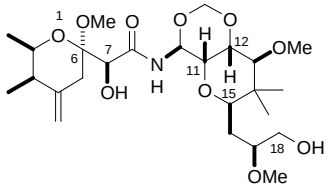


3. The favourable stereochemistry in the reduction of the ketone **12** is consistent with equatorial attack on conformer **12a** involving intramolecular delivery of hydride from a coordinated borohydride. The ^{1}H NMR data for **12** suggests **12a** is the principal conformer since the C11 proton appears as a broadened quartet at δ 3.77 with J = 3.2 Hz. By contrast, the corresponding signal from conformer **12b** would have a large *trans*-diaxial coupling.



4. Other ligands surveyed were: hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$],[15] **17a**:**17b** = 1:2; hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$],[15] 2.5:1; hydroquinine 9-phenanthryl ether,[15] 1:2; hydroquinine 4-methyl-2-quinolyl ether,[11] 1:2; hydroquinidine 2,5-pyyridazinediyl diether [$(DHQD)_2PYDZ$], [16,17] 2.1:1.

For general experimental details, see Reference 3. The NMR assignments in the following experimental section are based on the mycalamide numbering given below.



(2*S*,6*R*)-6-(3-Chloropropyl)-2-[(isopropyloxydimethylsilyl)methyl]-5,5-dimethyltetrahydro-2*H*-pyran-4-one (6)

To a suspension of Mg turnings (5.60 g, 0.23 mol) in THF (80 mL), was added 1,2-dibromoethane (250 μL) followed by chloromethylisopropoxydimethylsilane (Aldrich, 2.0 mL, 11.1 mmol). The mixture was heated gently until a strong exotherm indicated the reaction had begun whereupon the remaining portion of chloromethylisopropoxydimethylsilane (18.6 mL, 103.2 mmol) was added carefully maintaining a temperature range of 50–60 °C over a period of 20 min. After the addition was complete the mixture was left to cool to r.t. and stirred for 24 h. To a mixture of CuBr•SMe_2 (694 mg, 3.37 mmol) and SMe_2 (10.4 mL) at –78 °C was added the Grignard reagent over 30 min whilst maintaining a temperature below –60 °C. The mixture was diluted with THF (20 mL) and stirred at –70 °C for 10 min after which time the enone **5** (9.0 g, 44 mmol) was added. After a further 1 h the mixture was left to warm to –30 °C and quenched by the addition of sat. aq NH_4Cl (200 mL), 10% aq NH_3 (10 mL) and hexanes (200 mL). After stirring for 15 min the organic layer was removed and the aqueous layer extracted with hexanes (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude silane **6** (14.8 g, ~100%) which was used immediately in the next step. A sample was purified by column chromatography (silica gel, hexanes/Et_2O, 10–20% and Et_3N 1%); $[\alpha]_D^{22}$ +8.7 (*c* = 2.2, $CHCl_3$).

IR (neat): ν = 1712s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.19 (1 H, dddd, *J* = 13.7 7.9, 6.2, 5.0 Hz, C11-H), 3.99 (1 H, septet, *J* = 6.2 Hz, C*H*Me_2), 3.67 (1 H, dd, *J* = 10.6, 3.9 Hz, C15-H), 3.58 (2 H, t, *J* = 6.2 Hz, C18-H_2), 2.55 (1 H, 4 lines of ABX system, *J* = 14.3, 4.4 Hz, C12-H_AH_B), 2.48 (1 H, 4 lines of ABX system, *J* = 14.3, 8.3 Hz, C12-H_AH_B), 2.10–1.50 (4 H, m), 1.23 (3 H, s, C14-CH_3), 1.14 [6 H, d, *J* = 6.2 Hz, CH(CH_3)$_2$], 1.03 (3 H, s, C14-CH_3), 1.02 (2 H, m, C10-H_2), 0.16 [6 H, s, Si(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.7 (0), 80.2 (1), 69.4 (1), 65.2 (1), 49.6 (0), 45.9 (2), 45.0 (2), 29.2 (2), 25.9 (3, 2C), 25.7 (2), 25.3 (2), 24.0 (3), 19.5 (3), –0.2 (3), –0.4 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 335 [(M + H)$^+$, 15], 275 (60), 229 (100), 170 (50).

Anal. Calcd for $C_{16}H_{31}ClO_3Si$: C, 57.19; H, 9.16. Found: C, 57.40; H, 9.27.

(2*S*,6*R*)-6-(3-Chloropropyl)-2-hydroxymethyl-5,5-dimethyltetrahydro-2*H*-pyran-4-one (7)

Oxidation of a isopropoxydimethylsilyl group to a hydroxyl was accomplished by the method of Tamao et al.[18] The crude silane **6** (14.7 g, 43.3 mmol) prepared as described above was dissolved in an ice cold mixture of KF•$2H_2O$ (6.28 g, 66.7 mmol), $KHCO_3$ (8.2 g, 82.0 mmol), THF (80 mL) and MeOH (80 mL). Aq H_2O_2 (30% wt solution, 45.0 mL) was added in several portions. The mixture was stirred for 6 h at 0 °C and treated carefully with sat. aq $Na_2S_2O_3$ solution (200 mL) over 15 min whereupon the solution turned bright yellow (strong exotherm!). H_2O (200 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 20–50%) to give the alcohol **7** (9.1 g, 87% yield over 2 steps) as a clear colourless oil; $[\alpha]_D^{22}$ –8.7 (*c* = 1.2, $CHCl_3$).

IR (neat): ν = 3436s, 1701s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.00 (1 H, m, C11-H), 3.78 (1 H, dd, *J* = 11.6, 3.7 Hz, C15-H), 3.71 (1 H, 4 lines of ABX system, *J* = 11.8, 3.6 Hz, C10-H_AH_B), 3.62 (1 H, 4 lines of ABX system, *J* = 11.8, 6.0 Hz, C10-H_AH_B), 3.57 (2 H, t, *J* = 6.6 Hz, C18-H_2), 2.72 (1 H, dd, *J* = 14.7, 10.0 Hz, C12-H_AH_B), 2.28 (1 H, dd, *J* = 14.7, 4.2 Hz, C12-H_AH_B), 2.20–1.50 (5 H, m), 1.28 (3 H, s, C14-CH_3), 1.02 (3 H, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 211.8 (0), 81.8 (1), 71.5 (1), 65.1 (2), 49.7 (0), 44.8 (2), 39.2 (2), 28.8 (2), 25.3 (2), 24.7 (3), 19.5 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 235 [(M + H)$^+$, 30], 252 [(M + NH_4)$^+$, 45], 217 (10), 128 (100).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10. Found: C, 56.02; H, 7.98.

(2*S*,6*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-5,5-dimethyltetrahydro-2*H*-pyran-4-one (8)

To a solution of the alcohol **7** (12.15 g, 51.7 mmol), Et_3N (93.0 mmol, 13.0 mL) and DMAP (230 mg) in CH_2Cl_2 (120 mL) was added *t*-$BuMe_2SiCl$ (9.35 g, 62.04 mmol) and the mixture left stirring at room temperature for 36 h whereupon sat. aq $NaHCO_3$ (200 mL), H_2O (300 mL) and hexanes (200 mL) were added successively. The organic layer was removed and the aqueous layer was extracted with hexanes (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was filtered through a pad of silica eluting with hexanes/EtOAc (5:1) to give the TBS ether **8** (17.0 g, 48.8 mmol, 94%) as a pale yellow oil: $[\alpha]_D^{22}$+0.1 (*c* = 2.4, $CHCl_3$).

IR (neat): ν = 1714s, 838s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.99 (1 H, m, C11-H), 3.82 (1 H, dd, *J* = 11.2, 3.3 Hz, C15-H), 3.72 (1 H, 4 lines of ABX system, *J* = 10.8, 3.5 Hz, C10-H_AH_B), 3.69 (1 H, 4 lines of ABX system, *J* = 10.8, 5.0 Hz, C10-H_AH_B), 3.59 (2 H, t, *J* = 6.6 Hz, C18-H_2), 2.65 (1 H, dd, *J* = 14.7, 8.7 Hz, C12-H_AH_B), 2.38 (1 H, dd, *J* = 14.7, 5.0 Hz, C12-H_AH_B), 2.10–1.40 (4 H, m), 1.23 (3 H, s, C14-CH_3), 1.03 (3 H, s, C14-CH_3), 0.90 (9 H, s, *t*-C_4H_9Si), 0.08 and 0.07 [3 H each, s, $(CH_3)_2Si$].

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 212.3 (0), 81.0 (1), 72.0 (1), 66.0 (2), 49.3 (0), 44.7 (2), 39.2 (2), 28.9 (2), 25.9 (3, 3C), 25.4 (2), 23.6 (3), 19.2 (3), 18.3 (0), –5.4 (3), –5.5 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 366 [(M + NH_4)$^+$, 15], 349 [(M + H)$^+$, 50], 291 (35), 185 (100), 117 (80).

HRMS (CI mode): *m*/*z* Found: (M + H)$^+$, 349.1966. $C_{17}H_{34}ClO_3Si$ requires 349.1966.

(2*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-5,5-dimethyl-5,6-dihydro-2*H*-pyran (9)

To a solution of the ketone **8** (16.8 g, 48.2 mmol) and Et_3N (11.0 mL, 78.9 mmol) in CH_2Cl_2 (100 mL) was added dropwise *t*-$BuMe_2SiOTf$ (13.3 mL, 57. 9 mmol) over 5 min. The yellow solution turned orange with a slight exotherm which was controlled by cooling with a water bath. After 1.5 h, the reaction was quenched by adding the mixture to a mixture of sat. aq $NaHCO_3$ (200 mL) and hexanes (200 mL). The organic layer was removed, dried ($MgSO_4$) and concentrated in vacuo to give the enol silane **9** as a pale yellow oil (22.4 g, ~100%) which was used immediately in the next step. A sample (200 mg) was purified by column chromatography (silica gel, hexanes/Et_2O, 2%); $[\alpha]_D^{22}$ –24.8 (*c* = 2.0, $CHCl_3$).

IR (neat): ν = 1664s, 1471s, 1256s, 1126, 838s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.62 (1 H, d, *J* = 3.3 Hz, C12-H), 4.22 (1 H, ddd, *J* = 6.8, 5.2, 3.3 Hz, C11-H), 3.73–3.53 (3 H, m), 3.52–3.42 (2 H, m), 2.2–2.0 (1 H, m), 1.9–1.4 (3 H, m), 0.99 (3 H, s, C14-CH_3), 0.97 (3 H, s, C14-CH_3), 0.95 (9 H, s, *t*-C_4H_9Si), 0.90 (9 H, s, *t*-C_4H_9Si), 0.172 and 0.170 [3 H each, s, (CH3)Si], 0.06 [6 H, s, $(CH3)_2Si$].

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 156.7 (0), 99.0 (1), 77.6 (1), 72.9 (1), 65.2 (2), 45.4 (2), 38.9 (0), 30.2 (2), 26.5 (2), 26.1 (3, 3C), 25.9

(3, 3C), 22.3 (3), 19.6 (3), 18.4 (0, 2C), –4.2 (3), –4.7 (3), –5.2 (3, 2C).

LRMS (CI, NH_3): *m*/*z* (%) = 463 [(M + H)$^+$, 35], 347 (45), 317 (100), 157 (70).

HRMS (CI mode): *m*/*z* Found: (M + H)$^+$, 463.2827. $C_{23}H_{48}ClO_3Si_2$ requires 463.2831.

(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-3,4-epoxy-5,5-dimethyltetrahydro-2*H*-pyran (10)

To a mechanically stirred solution of the enol silane **9** (22.2 g, 48 mmol), $KHCO_3$ (121.0 g, 120.0 mmol), 18-crown-6 (1.11 g, 4.21 mmol), toluene (600 mL), acetone (120 mL) and H_2O (1.20 L) was added oxone (200 g, 300 mmol) in portions over a period of 0.5 h. Beware gas evolution! After the addition was complete the mixture was stirred for 30 min and the organic layer was removed. The aqueous layer was extracted with hexanes (2 × 100 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the oxirane **10** (22.7 g, 99%) as a pale yellow oil which was used immediately in the next step. A sample (200 mg) was purified by column chromatography (silica gel, hexanes/Et_2O, 1%); $[\alpha]_D^{22}$ –8.6 (*c* = 1.0, $CHCl_3$).

IR (neat): ν = 1664s, 1471s, 1256s, 1126s, 838s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.10 (1 H, dt, *J* = 7.0, 3.3 Hz, C11-H), 3.69 (1 H, dd, *J* = 9.7, 7.5 Hz, C10-H_AH_B), 3.61 (1 H, dd, *J* = 9.7, 6.8 Hz, C10-H_AH_B), 3.54 (2 H, m, C18-H_2), 3.41 (1 H, d, *J* = 3.3 Hz, C12-H), 3.24 (1 H, dd, *J* = 10.4, 1.0 Hz, C15-H), 2.1–1.9 (1 H, m), 1.8–1.5 (2 H, m), 1.4–1.2 (1 H, m) 1.04 (3 H, s, C14-CH_3), 0.96 (3 H, s, C14-CH_3), 0.91 and 0.90 (9 H each, s, t-C_4H_9Si), 0.14, 0.09, 0.08 and 0.07 [3 H each, s, $(CH_3)_2Si$].

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 86.1 (0), 75.6 (1), 71.0 (1), 60.7 (1), 60.2 (2), 45.3 (2), 39.1 (0), 30.3 (2), 26.9 (2), 26.0 (3, 3C), 25.9 (3, 3C), 18.6 (3), 18.4 (0), 18.0 (0), 16.9 (3), –3.2 (3), –3.4 (3), –5.3 (3), –5.2 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 479 [(M + H)$^+$, 65], 443 [(M + H–HCl)$^+$, 20], 347 [(M + H – TBSOH)$^+$, 100].

HRMS (CI mode): *m*/*z* Found: (M + NH_4)$^+$, 496.3058. $C_{23}H_{51}ClO_4NSi_2$ requires 496.3045; *m*/*z* found: (M + H)$^+$, 479.2748. $C_{23}H_{48}ClO_4Si_2$ requires 479.2780.

Hydrolysis of the Oxirane 10

A mixture of the crude oxirane **10** (1.19 g, 2.48 mmol), pyridinium *p*-toluenesulfonate (PPTS, 62 mg, 0.248 mmol), MeOH (5 mL) and H_2O (0.25 mL) was heated at reflux for 18 h. The mixture was poured onto sat. aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 20 g, hexanes/EtOAc, 20–70%) to give a mixture of the diols **11a** and **11b** (537 mg, 86%) as a colourless oil. ^{1}H NMR spectroscopic analysis (C_6D_6) of the mixture revealed doublets at δ = 4.29 (major) and 4.34 (minor) attributed to the methine proton adjacent to the carbonyl corresponding to a 15:1 mixture of diastereoisomers. The diastereoisomers were separated by recrystallisation to give the pure desired diastereoisomer **11a** (335 mg, 54%) as clear colourless crystals. The mother liquor was purified by column chromatography (silica gel, 15 g, hexanes/EtOAc 20–70%) to give more of the desired diastereoisomer **11a** (137 mg, 23%) as a white solid and the pure undesired diastereoisomer **11b** (30 mg, 5%) as a white solid.

(2*R*,3*S*,6*R*)-6-(3-Chloropropyl)-3-hydroxy-2-hydroxymethyl-5,5-dimethyltetrahydro-2*H*-pyran-4-one (11a)

Mp 63–63.5 °C (hexanes:Et_2O); $[\alpha]_D^{22}$ +9.7 (*c* = 1.8, $CHCl_3$).

IR (neat): ν = 3443s, 1714s, 1048s cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.49 (1 H, dd, *J* = 9.6, 2.4 Hz, C15-H), 3.94 (1 H, dd, *J* = 11.4, 3.2 Hz, C10-H_AH_B), 3.85 (1 H, dd, *J* = 12.4, 3.3 Hz, C10-H_AH_B), 3.83 (1 H, dd, *J* = 12.4, 3.3 Hz, C11-H), 3.69 (1 H, d, *J* = 3.2 Hz, C12-OH), 3.55 (2 H, apparent t, *J* = 6.2 Hz, C18-H_2), 3.46 (1 H, ddd, *J* = 10.3, 9.5, 3.2 Hz, C11-H), 2.44 (1 H, br s, CH_2OH), 1.95–1.40 (4 H, m), 1.41 (3 H, s, C14-CH_3), 1.05 (3 H, s, C14-CH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.7 (0), 83.6 (1), 76.8 (1), 70.0 (1), 63.2 (2), 49.7 (0), 44.6 (2), 28.1 (2), 26.0 (3), 24.5 (2), 19.5 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 268 [(M + NH_4)$^+$, 100].

Anal. Calcd for $C_{11}H_{19}ClO_4$: C, 52.69; H, 7.58. Found: C, 52.61; H, 7.56.

(2*R*,3*S*,6*R*)-6-(3-Chloropropyl)-3-hydroxy-2-hydroxymethyl-5,5-dimethyltetrahydro-2*H*-pyran-4-one (11b)

Mp 60–60.5 °C (hexanes/Et_2O); $[\alpha]_D^{22}$ +90.0 (*c* = 1.5, $CHCl_3$).

IR (neat): ν = 3417s, 1714s, 1463s, 1376m cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.61 (1 H, d, *J* = 7.9 Hz, C12-H), 4.43 (1 H, ddd, *J* = 8.1, 5.2, 3.8 Hz, C11-H), 3.91 (1 H, dd, *J* = 12.6, 5.2 Hz, C10-H_AH_B), 3.80 (1 H, dd, *J* = 12.6, 3.5 Hz, C10-H_AH_B), 3.86–3.77 (2 H, m), 3.50–3.65 (2 H, complex AA'BB', C18-H_2), 2.20–1.75 (3 H, m), 1.70–1.50 (2 H, m), 1.18 (3 H, s, C14-CH_3), 1.07 (3 H, s, C14-CH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 213.3 (0), 79.0 (1), 78.1 (1), 70.7 (1), 62.4 (2), 49.0 (0), 45.1 (2), 30.0 (2), 27.0 (2), 20.3 (3), 19.4 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 268 [(M + NH_4)$^+$, 65], 251 [(M + H)$^+$, 50], 233 [(M + H – H_2O)$^+$, 25], 144 (100).

Anal. Calcd for $C_{11}H_{19}ClO_4$: C, 52.69; H, 7.58. Found: C, 52.66; H, 7.45.

(1*S*,6*R*,8*R*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-one (12)

A solution of diol the **11a** (4.2 g, 16.6 mmol), 2-methoxypropene (3.2 mL, 33.0 mmol) and PPTS (420 mg, 1.7 mmol) in CH_2Cl_2 (65 mL) was stirred at r.t. for 4.25 h. The mixture was poured onto sat. aq $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 120 g, hexanes/Et_2O, 20–50%) to give the acetonide **12** (4.2 g, 86%) as a colourless oil; $[\alpha]_D^{22}$ –1.5 (*c* = 1.4, $CHCl_3$).

IR (neat): ν = 1726s, 1090s cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.25 (1 H, dd, *J* = 11.5, 2.5 Hz, C15-H), 4.21 (1 H, d, *J* = 3.2 Hz, C12-H), 4.09 (1 H, dd, *J* = 13.0, 3.6 Hz, C10-H_AH_B), 3.90 (1 H, dd, *J* = 13.0, 2.8 Hz, C10-H_AH_B), 3.77 (1 H, apparent q, *J* = 3.2 Hz, C11-H), 3.62 (2 H, apparent t, *J* = 6.1 Hz, C18-H_2), 2.05–1.78 (2 H, m), 1.70–1.60 (1 H, m), 1.55–1.45 (1 H, m) 1.45 [3 H, s, $C(CH_3)_2$], 1.43 [3 H, s, $C(CH_3)_2$], 1.33 (3 H, s, C14-CH_3), 1.03 (3 H, s, C14-CH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 208.3 (0), 99.1 (0), 80.4 (1), 72.8 (1), 65.7 (1), 62.8 (2), 49.2 (0), 44.8 (2), 29.1 (2), 28.6 (3), 25.5 (2), 24.5 (3), 19.8 (3), 19.5 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 291 [(M + H)$^+$, 100], 275 (15), 203 (25), 132 (30), 101 (20), 73 (30).

Anal. Calcd for $C_{14}H_{23}ClO_4$: C, 57.83; H, 7.91. Found: C, 57.79; H, 7.84.

(1*R*,6*R*,8*S*,10*S*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (13)

Solid $CeCl_3.7H_2O$ (1.25 g, 3.35 mmol) was added to a stirred solution of the ketone **12** (718 mg, 2.47 mmol) in MeOH (45 mL) at 0 °C. The solution was stirred for 20 min and $NaB(OAc)_3H$ (2.0 g, 9.43 mmol) was added. The mixture was stirred at 0–5°C for 3.5 h, then sat. aq $NaHCO_3$ (100 mL) was carefully added and the MeOH

was removed on the rotary evaporator. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (40 g, hexanes/Et_2O, 20–70%) to give the diastereoisomeric alcohols **13a,b** (643 mg, 88%) as a white solid. ^{1}H NMR spectroscopic analysis of the mixture (C_6D_6) revealed singlets at δ = 0.78 (major) and 0.88 (minor) corresponding to a dr = 1:7.5. Crystallisation from hexanes/Et_2O gave the diastereoisomerically pure alcohol **13a** (535 mg, 74%) as colourless needles; mp 96–97 °C (hexanes/Et_2O); $[\alpha]_D^{22}$ +30.4 (*c* = 1.2, $CHCl_3$). On a larger scale (14.3 mmol of ketone **12**) the ratio of **13a**:**13b** was better (1:11) but the yield was lower (72% of the mixture).

IR (neat): ν = 3437 (br), 1462s, 1377s cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 3.77 (1 H, dd, *J* = 12.4, 3.3 Hz, C10-H_AH_B), 3.67 (1 H, dd, *J* = 12.4, 3.7 Hz, C10-H_AH_B), 3.60 (1 H, dd, *J* = 3.7, 3.1 Hz, C12-H), 3.44 (1 H, apparent q, *J* = 3.5 Hz, C11-H), 3.35 (1 H, d, *J* = 3.9 Hz, OH), 3.34 (1 H, dd, *J* = 3.8, 2.9 Hz, C13-H), 3.25 (3 H, t, *J* = 6.8 Hz, C18-H_2, C15-H), 2.10–1.90 (1 H, m), 1.85–1.80 (1 H, m), 1.60–1.40 (1 H, m), 1.45 [3 H, s, $C(CH_3)_2$], 1.40–1.25 (1 H, m), 1.24 and 1.23 [3 H each, s, $C(CH_3)_2$ and C14-CH_3], 0.80 (3 H, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.5 (0), 80.3 (1), 75.0 (1), 70.5 (1), 62.9 (2), 60.3 (1), 45.2 (2), 36.4 (0), 29.8 (2), 28.9 (3), 27.1 (3), 24.6 (2), 21.2 (3), 19.8 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 293 [(M + H)$^+$, 100], 277 (20), 217 (20).

Anal. Calcd for $C_{14}H_{25}ClO_4$: C, 57.43; H, 8.55. Found: C, 57.42; H, 8.55.

Column chromatography (silica gel, hexanes/Et_2O, 50–70%) of the mother liquor gave a pure sample of the minor isomer **13b**.

(1*R*,6*R*,8*S*,10*R*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (13b)

Mp 89–90°C (hexanes/Et_2O); $[\alpha]_D^{22}$ +47.0 (*c* = 1.0, $CHCl_3$).

IR (neat): ν = 3516m, 1461s, 1377s cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 3.66 (1 H, dd, *J* = 12.7, 1.9 Hz, C10-H_AH_B), 3.59 (1 H, dd, *J* = 4.2, 2.1 Hz, C12-H), 3.53 (1 H, dd, *J* = 12.6, 2.9 Hz, C10-H_AH_B), 3.39 (1 H, dd, *J* = 11.5, 3.1 Hz, C15-H), 3.37–3.30 (1 H, m, C13-H), 3.28–3.10 (2 H, m, C18-H_2), 2.72 (1 H, apparent q, *J* = 2.1 Hz, C11-H), 2.31 (1 H, d, *J* = 10.6 Hz, OH), 1.65–1.15 (4 H, m), 1.37 and 1.27 [3 H each, s, $C(CH_3)_2$], 1.13 and 0.88 (3 H each, s, C14-CH_3).

^{13}C NMR (90 MHz, $CHCl_3$): δ = 98.9 (0), 81.8 (1), 71.6 (1), 67.5 (1), 63.2 (2), 62.7 (1), 45.1 (2), 37.7 (0), 29.4 (3), 29.1 (2), 24.6 (3), 22.6 (3), 22.6 (2), 18.7 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 310 [(M + NH_4)$^+$, 60], 293 [(M + H)$^+$, 55].

Anal. Calcd for $C_{14}H_{25}ClO_4$: C, 57.43; H, 8.55. Found: C, 57.36; H, 8.47.

(1*R*,6*R*,8*R*,10*S*)-8-(3-Chloropropyl)-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decane (14)

Dimethyl sulfate (4.0 g, 3.0 mL, 32.0 mmol) was added to a vigorously stirred mixture of the alcohol **13a** (2.42 g, 8.27 mmol), Bu_4NHSO_4 (573 mg, 1.70 mmol), toluene (32 mL) and 50% aq NaOH (21 mL). The mixture was stirred vigorously for 14 h whereupon MeOH (9 mL) was added and after 15 min the mixture was treated with H_2O (220 mL). The mixture was extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 80 g, hexanes/Et_2O, 10–25%) to give the methyl ether **14** (2.47 g, 97%) as a colourless oil which solidified; mp 49–50 °C (MeOH/H_2O); $[\alpha]_D^{22}$ –1.9 (*c* = 1.2, $CHCl_3$).

IR (neat): ν = 1454s, 1381s, 1276s, 1094s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.08 (1 H, dd, *J* = 12.7, 2.5 Hz, C10-H_AH_B), 3.90 (1 H, apparent t, *J* = 2.3 Hz, C12-H), 3.86 (1 H, dd, *J* = 12.7, 1.7 Hz, C10-H_AH_B), 3.59 (2 H, t, *J* = 6.6 Hz, C18-H_2), 3.55–3.45 (2 H, m, C11-H and C15-H), 3.39 (3 H, s, OCH_3), 2.84 (1 H, d, *J* = 2.7 Hz, C13-H), 2.20–2.05 (1 H, m), 1.95–1.45 (3 H, m), 1.47 and 1.45 [3 H each, s, $C(CH_3)_2$], 1.25 and 0.93 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.6 (0), 85.8 (1), 80.5 (1), 67.3 (1), 63.6 (2), 60.7 (1), 59.3 (3), 45.6 (2), 36.9 (0), 30.5 (2), 29.6 (3), 28.3 (3), 25.1 (2), 22.3 (3), 19.6 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 307 [(M + H)$^+$, 100].

Anal. Calcd for $C_{15}H_{27}ClO_4$: C, 58.73; H, 8.81. Found: C, 57.80; H, 8.74.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-3,3,9,9-tetramethyl-8-(3-phenylselenylpropyl)-2,4,7-trioxabicyclo[4.4.0]decane (15)

$NaBH_4$ (208 mg) was added portionwise to a stirred suspension of Ph_2Se_2 (773 mg, 2.47 mmol) in anhyd EtOH (11.5 mL). Addition of $NaBH_4$ was continued until the solution of NaPhSe formed became colourless. A solution of the chloride **14** (990 mg, 3.23 mmol) in anhyd EtOH (3 × 2.5 mL) was transferred via cannula to the solution of NaPHSe. The resulting mixture was stirred at reflux for 40 min. After cooling to r.t. the mixture was diluted with Et_2O (160 mL) and extracted with 2 M aq solution of NaOH (2 × 35 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, 10 g, hexanes/Et_2O, 0–30%) to give the selenide **15** (1.40 g, ~100%) as a colourless oil; $[\alpha]_D^{22}$+17.9 (*c* = 1.4, $CHCl_3$).

IR (neat): ν = 1579s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.52–7.45 (2 H, m), 7.29–7.21 (3 H, m), 4.01 (1 H, dd, *J* = 12.7, 2.5 Hz, C10-H_AH_B), 3.87 (1 H, t, *J* = 2.3 Hz, C12-H), 3.76 (1 H, dd, *J* = 12.7, 1.7 Hz, C10-H_AH_B), 3.46 (1 H, dd, *J* = 12.2, 2.9 Hz, C15-H), 3.42 (1 H, apparent q, *J* = 2.3 Hz, C11-H), 3.38 (3 H, s, OCH_3), 3.01 (1 H, ddd, *J* = 11.8, 7.9, 6.0 Hz, C18-H_AH_B), 2.88 (1 H, ddd, *J* = 12.0, 7.9, 7.1 Hz, C18-H_AH_B), 2.81 (1 H, d, *J* = 2.7 Hz, C13-H), 2.11 (1 H, dddd, *J* = 14.1, 12.2, 9.1, 4.6 Hz, C16-H), 1.90–1.60 (3 H, m), 1.46 and 1.44 [3 H each, s, $C(CH_3)_2$], 1.22 and 0.89 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 132.7 (1, 2C), 130.5 (0), 129 (1, 2C), 126.7 (1), 98.3 (0), 84.9 (1), 80.6 (1), 66.5 (1), 63.4 (2), 59.4 (3), 59.3 (1), 36.3 (0), 29.4 (3), 27.9 (3), 27.8 (2), 27.0 (2), 26.9 (2), 22.4 (3), 18.8 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 446 [(M + NH_4)$^+$, 17], 429 [(M + H)$^+$, 9].

Anal. Calcd for $C_{21}H_{32}O_4Se$: C, 59.02; H, 7.49. Found: C, 59.27; H, 7.61.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-3,3,9,9-tetramethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4.4.0]decane (16)

$NaIO_4$ (1.01 g, 4.70 mmol) was added in several portions to a stirred mixture of the selenide **15** (1.31 mg, 3.23 mmol), H_2O (18 mL) and MeOH (45 mL) at r.t. The mixture was stirred for 15 min and then diluted with H_2O (55 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was treated with toluene (4.5 mL) and Et_3N (4.5 mL) and heated at reflux for 10 min. The yellow mixture was cooled to r.t., poured onto sat. aq $NaHCO_3$ .and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, 30 g, hexanes/Et_2O, 0–20%) to give the alkene **16** (780 mg, 99%) as a colourless oil which solidified on storage in the refrigerator; mp 33–33.5 °C (MeOH/H_2O); $[\alpha]_D^{22}$ –11.2 (*c* = 1.1, $CHCl_3$).

IR (neat): ν = 1651m 1463m, 1390s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.82 (1 H, dddd, *J* = 17.6, 10.2, 7.5, 6.0 Hz, C17-H), 5.03 (1 H, dq, *J* = 16.9, 1.7 Hz, C18-H_{trans}), 4.98 (1 H, dm, *J* = 10.2 Hz, C18-H_{cis}), 4.05 (1 H, dd, *J* = 12.7, 2.7 Hz, C10-H_AH_B), 3.90 (1 H, t, *J* = 2.5 Hz, C12-H), 3.82 (1 H, dd, *J* = 12.7, 2.1 Hz, C10-H_AH_B), 3.59 (1 H, dd, *J* = 12.0, 3.7 Hz, C15-H), 3.53 (1 H, apparent q, *J* = 2.3 Hz, C11-H), 3.40 (3 H, s, OCH_3), 2.84 (1 H, d, *J* = 2.7 Hz, C13-H), 2.79 (1 H, dddt, *J* = 15.0, 11.4, 7.3, 1.1 Hz, C16-H_AH_B), 2.17 (1 H, dddt, *J* = 15.5, 5.4, 3.5, 1.5 Hz, C16-H_AH_B), 1.47 and 1.44 [3 H each, s, $C(CH_3)_2$], 1.25 and 0.93 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.7 (1), 115.2 (2), 98.1 (0), 84.8 (1), 80.7 (1), 66.3 (1), 63.2 (2), 59.3 (3), 59.1 (1), 36.2 (0), 32.2 (2), 29.2 (3), 27.6 (3), 22.4 (3), 18.7 (3).

LRMS (CI, NH_3): *m*/*z* = 271 [$(M + H)^+$, 30], 229 (80), 171 (70), 101 (55), 85 (80), 71 (100).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.66; H, 9.62. Found: C, 66.64; H, 9.61.

Dihydroxylation of Alkene 16

The asymmetric dihydroxylation was performed according to the procedure of Sharpless et al.[19] The alkene **16** (918 mg, 3.4 mmol) and $(DHQ)_2PYR$ (34 mg, 0.039 mmol) were stirred in warm *t*-BuOH (21 mL) until the ligand dissolved (ca 30 min). After cooling to r.t., H_2O (21 mL), $K_3Fe(CN)_6$ (3.4 g, 10.32 mmol) and K_2CO_3 (1.43 g, 10.36 mmol) were added and the mixture was cooled to 0°C. Potassium osmate dihydrate (12.5 mg, 0.034 mmol) was then added. The mixture was stirred for 3 h at 0 °C, treated with sat. aq Na_2SO_3 (42 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a 1:6.6 mixture of the diols **17a,b** according to integration of the singlets at δ = 0.86 (major) and 0.92 (minor) revealed in the ^1H NMR spectrum (C_6D_6) of the mixture. The diastereoisomers were separated by column chromatography (silica gel, 20 g, CH_2Cl_2/MeOH, 0–4%) to afford the pure major diol **17b** (860 mg, 83%) and a mixture of diols **17a,b** (165 mg, 16%).

(1*R*,6*R*,8*R*,10*S*)-8-[(2*S*)-2,3-Dihydroxypropyl]-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decane (17b)

Recrystallised from hexanes/Et_2O to form thick colourless needles; mp 102–103 °C (Et_2O/hexanes); $[\alpha]_D^{17}$ –19.1 (*c* = 1.0, $CHCl_3$).

IR (CCl_4): ν = 3441 (br) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.09 (1 H, dd, *J* = 12.9, 2.5 Hz, C10-H_AH_B), 3.93 (1 H, t, *J* = 2.5 Hz, C12-H), 3.88 (1 H, m, C17-H), 3.86–3.73 (3 H, m), 3.64 [1 H, m (in presence of D_2O appears as dd, *J* = 11.2, 3.7 Hz), C18-H_AH_B], 3.50 [1 H, m (in presence of D_2O appears as dd, *J* = 11.2, 6.0 Hz, C18-H_AH_B], 3.40 (3 H, s, OCH_3), 2.86 (1 H, d, *J* = 2.9 Hz, C13-H), 2.20 (1 H, br, OH), 2.19 (1 H, ddd, *J* = 15.1, 12.0, 8.9 Hz, C16-H_AH_B), 1.67 (1 H, br, OH), 1.56 (1 H, ddd, *J* = 3.5, 2.1 Hz, C16-H_AH_B), 1.47 and 1.45 [3 H each, s, $C(CH_3)_2$], 1.23 and 0.93 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.4 (0), 84.5 (1), 81.1 (1), 72.5 (1), 66.5 (1), 66.0 (2), 63.2 (2), 60.3 (1), 59.3 (3), 36.5 (0), 30.0 (2), 29.2 (3), 27.4 (3), 21.9 (3), 18.8 (3).

LRMS: (CI, NH_3): *m*/*z* (%) = 305 [$(M + H)^+$, 50], 289 (25), 273 (15), 247 (55), 87 (100).

Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.21; H, 9.21. Found: C, 59.31; H, 9.11.

A sample of the undesired diastereoisomer **17a** was obtained by further column chromatography.

(1*R*,6*R*,8*R*,10*S*)-8-[(2*R*)-2,3-Dihydroxypropyl]-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decane (17a)

Mp 104–104.5 °C (Et_2O/hexanes); $[\alpha]_D^{17}$ +6.9 (*c* = 0.9, $CHCl_3$).

IR (CCl_4): ν = 3441 (br) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.09 (1 H, dd, *J* = 12.7, 2.2 Hz, C10-H_AH_B), 3.93–3.81 (4 H, m), 3.64–3.48 (2 H, m), 3.39 (3 H, s, OCH_3), 2.85 (1 H, d, *J* = 2.8 Hz, C13-H), 2.86 (1 H, d, *J* = 2.7 Hz, C13-H) 2.76 (1 H, d, *J* = 4.3 Hz, OH), 2.29 (1 H, dd, *J* = 8.1, 4.1 Hz, OH), 2.13 (2 H, ddd, *J* = 17.9, 12.2, 2.9 Hz, C16-H_AH_B), 1.50 and 1.46 [3 H each, s, $C(CH_3)_2$], 1.27 and 0.92 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.5 (0), 84.5 (1), 77.7 (1), 68.9 (1), 67.7 (2), 66.4 (1), 63.3 (2), 59.5 (1, 2, 2C), 36.0 (0), 30.3 (2), 29.3 (3), 27.8 (3), 22.5 (3), 18.6 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 305 [$(M + H)^+$, 5], 289 (20), 273 (10), 231 (15), 87 (100).

Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.21; H, 9.21. Found: C, 59.23; H, 9.29.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(*S*)-2,3-dimethoxypropyl]-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4.4.0]decane (18)

NaH (500 mg, 60% in oil, 12.5 mmol) was added to a stirred solution of the diol **17b** (1.65 g, 4.96 mmol) and MeI (1.0 mL, 16.7 mmol) in THF (18 mL) at 0 °C. After 5 min the cooling bath was removed and the mixture was stirred at r.t. for 7 h and then poured onto brine and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 20 g, hexanes/EtOAc, 10–50%) to give the methyl ether **18** (1.55 g, 94%) as a colourless oil; $[\alpha]_D^{23}$ +7.6 (*c* = 1.1, $CHCl_3$).

IR (neat): ν = 2878s, 2821s, 1455s, 1380s, 1094s, 850s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.09 (1 H, dd, *J* = 12.6, 2.5 Hz, C10-H_AH_B), 3.93 (1 H, t, *J* = 2.1 Hz, C12-H), 3.85 (1 H, dd, *J* = 12.7, 1.7 Hz, C10-H_AH_B), 3.63 (1 H, apparent q, *J* = 1.9 Hz, C11-H), 3.57 (1 H, dd, *J* = 12.3, 3.0 Hz, C15-H), 3.51 (1 H, 4 lines of ABX system, *J* = 10.2, 3.5 Hz, C18-H_AH_B), 3.46 (1 H, 4 lines of ABX system, *J* = 10.2, 5.0 Hz, C12-H_AH_B), 3.42–3.32 (1 H, m, C17-H), 3.37 (6 H, s, OCH_3), 3.36 (3 H, s, OCH_3), 2.83 (1 H, d, *J* = 2.5 Hz, C13-H), 2.35 (1 H, ddd, *J* = 14.8, 12.4, 4.6 Hz, C16-H_AH_B), 1.57 (1 H, ddd, *J* = 14.9, 7.9, 3.1 Hz, C16-H_AH_B), 1.47 and 1.44 [3 H each, s, $C(CH_3)_2$], 1.23 and 0.91 (3 H each, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.3 (0), 84.8 (1), 78.7 (1), 78.6 (1), 73.2 (2), 66.5 (1), 63.5 (2), 59.7 (1), 59.4 (3), 59.2 (3), 57.2 (3), 36.3 (0), 29.4 (3), 28.2 (2), 27.7 (3), 22.3 (3), 18.7 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 350 [$(M + NH_4)^+$, 55], 333 [$(M + H)^+$, 100].

HRMS (CI mode): *m*/*z* Found: $(M + H)^+$, 333.2270. $C_{17}H_{33}O_6$ requires 333.2277.

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyltetrahydro-2*H*-pyran-3-ol (20)

A solution of the acetal **18** (1.38g, 4.15 mmol) and *p*-TsOH (16 mg, 0.083 mmol) in MeOH (14 mL) was stirred at r.t. for 45 min. Then solid $NaHCO_3$ (0.4 g) was added and the mixture was concentrated. The residue was treated with CH_2Cl_2, filtered through a pad of Celite and concentrated to give the crude diol **19** which was converted to the pivalate ester **20** (1.58 g, ~100% for the two steps) using pivaloyl chloride and pyridine as described previously.[3]

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-(triethylsilyloxy)tetrahydro-2*H*-pyran (21)

A solution of the alcohol **20** (1.58 g, 4.21 mmol), imidazole (331 mg, 5.0 mmol) and Et_3SiCl (0.81 mL, 4.72 mmol) in anhyd DMF (6 mL) was stirred at r.t. for 2 h. The mixture was poured onto H_2O (60

mL) and extracted with hexanes (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 15 g, hexanes/EtOAc, 0–10%) to give the silyl ether **21** (1.96 g, 99%) as colourless crystals; mp 41–42 °C (MeOH/H_2O); $[\alpha]_D^{23}$ +70.9 (*c* = 1.2, $CHCl_3$).

IR (CCl_4): ν = 1730s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.52 (1 H, dd, *J* = 12.4, 9.5 Hz, C10-H_AH_B), 4.27 (1 H, dd, *J* = 12.4, 2.3 Hz, C10-H_AH_B), 4.12 (1 H, ddd, *J* = 9.5, 6.9, 4.3 Hz, C11-H), 3.93 (1 H, dd, *J* = 9.5, 6.8 Hz, C12-H), 3.50 (3 H, s, OCH_3), 3.50–3.30 (4 H, m), 3.361 (3 H, s, OCH_3), 3.359 (3 H, s, OCH_3), 2.78 (1 H, d, *J* = 9.6 Hz, C13-H), 1.68 (2 H, m, C16-H_2), 1.23 (9 H, s, *t*-C_4H_9), 0.973 (3 H, t, *J* = 8.1 Hz, CH_3CH_2), 0.971 (6 H, t, *J* = 8.1 Hz, CH_3CH_2), 0.94 (3 H, s, C14-CH_3), 0.87 (3 H, s, C14-CH_3), 0.633 (4 H, q, *J* = 7.9 Hz, CH_3CH_2), 0.629 (2 H, q, *J* = 7.9 Hz, CH_3CH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 178.6 (0), 86.5 (1), 77.9 (1), 75.3 (1), 73.8 (1), 73.4 (2), 70.2 (1), 62.3 (3), 60.1 (2), 59.3 (3), 56.9 (3), 41.1 (0), 38.8 (0), 29.8 (2), 27.3 (3, 3C), 23.4 (3), 14.0 (3), 6.8 (3, 2C), 6.7 (3), 5.9 (2), 4.9 (2, 2C).

LRMS (CI, NH_3): *m*/*z* (%) = 508 [(M + NH_4)$^+$, 30], 491 [(M + H)$^+$, 20].

Anal. Calcd for $C_{25}H_{50}O_7Si$: C, 61.22; H, 10.20. Found: C, 61.08; H, 10.10.

(2*R*,3*R*,4*S*,6*R*)-2-Hydroxymethyl-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-[(triethylsilyl)oxy]tetrahydro-2*H*-pyran (22)

DIBALH (neat, 2 mL, 11.2 mmol) was added dropwise to a stirred solution of the ester **21** (3.03 g, 6.17 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The mixture was stirred for 30 min before being treated with sat. aq Na_2SO_4 (2 mL) and CH_2Cl_2 (50 mL). After stirring for a further 1 h at r.t., the resulting milky suspension was filtered through a pad of Celite and concentrated to give the alcohol **22** (2.47 g, 98%) as a colourless oil: $[\alpha]_D^{20}$ +57.8 (*c* = 1.0, $CHCl_3$).

IR (neat): ν = 3476 (br) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.02–3.88 (3 H, m), 3.69 (1 H, br, C10-H), 3.62 (1 H, dd, *J* = 9.5, 4.6 Hz, C12-H), 3.58–3.32 (3 H, m, C17-H and C18-H_2), 3.51 (3 H, s, OCH_3), 3.41 (3 H, s, OCH_3), 3.38 (3 H, s, OCH_3), 2.79 (1 H, d, *J* = 9.3 Hz, C13-H), 1.70–1.50 (1 H, br, OH), 1.68 (2 H, t, *J* = 6.4 Hz, C16-H_2), 0.972 (3 H, t, *J* = 8.3 Hz, CH_3CH_2), 0.970 (6 H, t, *J* = 8.0 Hz, CH_3CH_2), 0.92 (3 H, s, C14-CH_3), 0.87 (3 H, s, C14-CH_3), 0.626 (4 H, q, *J* = 7.9 Hz, CH_3CH_2), 0.623 (2 H, q, *J* = 8.0 Hz, CH_3CH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 86.7 (1), 78.3 (1), 76.7 (1), 75.8 (2), 72.3 (1), 71.0 (1), 62.5 (3), 59.1 (3), 57.3 (3), 57.1 (2), 41.3 (0), 31.2 (2), 23.2 (3), 13.7 (3), 6.8 (3, 3C), 6.0 (2), 4.9 (2, 2C).

LRMS (CI, NH_3): *m*/*z* (%) = 407 [(M + H)$^+$, 80], 377 (50), 345 (30), 213 (100).

Anal. Calcd for $C_{20}H_{42}O_6Si$: C, 59.11; H, 10.34. Found: C, 59.06; H, 10.17.

(2*S*,3*R*,4*S*,6*R*)-2-Formyl-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-(triethylsilyloxy)tetrahydro-2*H*-pyran (23)

Dess–Martin periodinane[12] was added in one portion to a solution of the alcohol **22** (200 mg, 0.49 mmol) in CH_2Cl_2 (8 mL) at r.t. After 40 min the reaction was quenched by the addition of sat. aq $NaHCO_3$ (20 mL). After stirring for 10 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the crude aldehyde **23** as a colourless oil (~100%). Due to the instability of the aldehyde it was used immediately in the next step. The analytical and spectral data were collected without further purification; $[\alpha]_D^{20}$ +29.2 (*c* = 1.7, $CHCl_3$).

IR (neat): ν = 1729s, 1604s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 10.1 (1 H, s, C10-H), 4.31 (1 H, d, *J* = 7.3 Hz, C11-H), 4.14 (1 H, dd, *J* = 9.7, 7.1 Hz, C12-H), 3.72–3.56 (3 H, m, C17-H, C18-H_2), 3.52 (3 H, s, OCH_3), 3.51 (1 H, dd, *J* = 9.6, 2.7 Hz, C15-H), 3.43 (3 H, s, OCH_3), 3.40 (3 H, s, OCH_3), 2.64 (1 H, d, *J* = 9.7 Hz, C13-H), 1.70–1.50 (2 H, m, C16-H_2), 1.00 (9 H, t, *J* = 8.3 Hz, CH_3CH_2), 0.89 (3 H, s, C14-CH_3), 0.85 (3 H, s, C14-CH_3), 0.696 (4 H, q, *J* = 7.9 Hz, CH_3CH_2), 0.692 (2 H, q, *J* = 7.9 Hz, CH_3CH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 202.8 (1), 88.1 (1), 80.7 (1), 77.8 (1), 77.0 (1), 72.6 (2), 71.1 (1), 62.3 (3), 59.1 (3), 57.8 (3), 41.4 (0), 29.7 (2), 22.9 (3), 13.6 (3), 6.7 (3, 3C), 4.8 (2, 3C).

LRMS (CI): *m*/*z* (%) = 405 [(M + H)$^+$, 100].

HRMS (CI mode): *m*/*z* Found: (M + H)$^+$, 405.2668. $C_{20}H_{41}O_6Si$ requires 405.2672.

(2*S*,3*R*,4*S*,6*R*)-2-Dibenzyloxymethyl-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyltetrahydro-2*H*-pyran-3-ol (24)

A solution of the aldehyde **23** (891 mg, 2.19 mmol), benzyl orthoformate[20] (2.22 g, 6.6 mmol) and camphorsulfonic acid (109 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. for 5 h. Solid K_2CO_3 (138 mg) was added and the solvent removed in vacuo. The residue was treated with THF (20 mL) and TBAF (3.15 g, 10 mmol) and stirred at r.t. After 11 h, the mixture was concentrated. The residue was taken into Et_2O (150 mL), washed with H_2O (2 × 50 mL) and brine. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 30 g, hexanes/Et_2O, 10–80%) to give the hydroxy acetal **24** (908 mg, 90%) as a yellow oil; $[\alpha]_D^{20}$ +89.6 (*c* = 1.6, $CHCl_3$).

IR (neat): ν = 3452 (br) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, 333K): δ = 7.45–7.25 (10 H, m), 5.11 (1 H, d, *J* = 5.3 Hz, C10-H), 4.78 (1 H, d, *J* = 11.6 Hz), 4.77 (1 H, d, *J* = 11.6 Hz), 4.72 (1 H, d, *J* = 11.6 Hz), 4.65 (1 H, d, *J* = 11.6 Hz), 4.16 (1 H, t, *J* = 5.5 Hz, C11-H), 4.0 (1 H, m, C12-H), 3.57 (1 H, dd, *J* = 10.5, 2.2 Hz, C15-H) 3.52–3.36 (3 H, m, C17-H, C18-H_2), 3.50 (3 H, s, OCH_3), 3.31 (3 H, s, OCH_3), 3.29 (3 H, s, OCH_3), 2.99 (1 H, d, *J* = 8.1 Hz, C13-H), 2.80 (1 H, d, *J* = 4.6 Hz, OH), 1.76 (1 H, ddd, *J* = 14.5, 10.5, 3.1 Hz, C16–H_AH_B), 1.66 (1 H, ddd, *J* = 14.3, 8.8, 2.2 Hz, C16–H_AH_B), 0.97 (3 H, s, C14-CH_3), 0.90 (3 H, s, C14-CH_3).

^{13}C NMR (90 MHz, $CDCl_3$, 333K): δ = 138.2 (0), 137.5 (0), 128.8 (1), 128.6 (1), 128.3 (1, 2C), 128.2 (1, 2C), 127.9 (1, 4C), 101.4 (1), 87.3 (1), 78.3 (1), 77.5 (1), 73.6 (2), 72.6 (1), 70.4 (2), 69.8 (1), 68.3 (2), 61.7 (3), 59.3 (3), 57.0 (3), 40.1 (0), 30.1 (2), 24.8 (3), 16.0 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 506 [(M + NH_4)$^+$, 2], 489 [(M + H)$^+$, 0.4], 398 (0.8), 381 (0.8).

HRMS (CI mode): *m*/*z* Found: (M + H)$^+$, 489.2859. $C_{28}H_{41}O_7$ requires 489.2852.

Formation of 1,3-Dioxanes 25a,b

HCl gas was passed through a stirred mixture of the hydroxy acetal **24** (908 mg, 1.97 mmol) and paraformaldehyde (635 mg, 21.2 mmol) in CH_2Cl_2 (80 mL) at 0 °C for 30 min. The white suspension of paraformaldehyde disappeared to give a colourless solution. Then a stream of N_2 was passed through the reaction mixture for 1 h to form a white suspension. The mixture was poured onto sat. aq $NaHCO_3$ and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 13 g, hexanes/Et_2O, 5–40%) to give the acetals **25a,b** (740 mg, 93%) as a 6.5:1 mixture of diastereoisomers according to integration of the C-10 methine doublets at δ = 5.15 (major) and 5.25 (minor) revealed in the ^1H NMR spectrum ($CDCl_3$). The acetals were separated by column chromatography

(silica gel, hexanes/Et_2O, 5–30%) to give to give **25a**; $[\alpha]_D^{20}$ +32.3 (*c* = 0.7, $CHCl_3$).

(1*R*,5*S*,6*S*,8*R*,10*S*)-6-benzyloxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,6-trioxabicyclo[4.4.0]decane (25a)
IR (neat): ν = 2879s, 1455s, 1178s, 1101s, 1044s, 981s, 821s, 735s, 700s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.40–7.27 (5 H, m), 5.15 (1 H, d, *J* = 6.0 Hz, OCH_AH_BO), 4.86 (1 H, d, *J* = 6.0 Hz, OCH_AH_BO), 4.85 (1 H, s, C10-H), 4.81 (1 H, d, *J* = 12.0 Hz, $PhCH_2$), 4.58 (1 H, d, *J* = 11.8 Hz, $PhCH_2$), 3.94 (1 H, t, *J* = 2.7 Hz, C12-H), 3.71 (1 H, t, *J* = 1.7 Hz, C11-H), 3.57 (1 H, dd, *J* = 12.2, 3.1 Hz, C15-H), 3.56–3.40 (2 H, m, C18-H_2), 3.40–3.30 (1 H, m, C17-H), 3.38 (3 H, s, OCH_3), 3.33 (3 H, s, OCH_3), 3.30 (3 H, s, OCH_3), 2.89 (1 H, d, *J* = 3.1 Hz, C13-H), 2.28 (1 H, ddd, *J* = 15.3, 12.4, 4.6 Hz, C16-H_AH_B), 1.59 (1 H, ddd, *J* = 14.9, 7.7, 3.1 Hz, C16-H_AH_B), 1.22 (3 H, s, C14-CH_3), 0.91 (3H, s, C14-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 137.2 (0), 128.6 (1, 2C), 128.2 (1, 2C), 128.0 (1), 96.7 (1), 85.3 (2), 83.8 (1), 78.7 (1), 78.5 (1), 73.5 (2), 70.1 (1), 69.1 (2), 63.1 (1), 59.6 (3), 59.3 (3), 57.2 (3), 37.0 (0), 28.4 (2), 27.4 (3), 21.8 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 411 [$(M + H)^+$, 45], 307 (50), 345 (25), 277 (65), 126 (100).

Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.39; H, 8.29. Found: C, 64.16; H, 8.47.

(1*R*,5*R*,6*S*,8*R*,10*S*)-6-Benzyloxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,6-trioxabicyclo[4.4.0]decane (25b)
$[\alpha]_D^{20}$ +11.4 (*c* = 0.8, $CHCl_3$).

IR (neat): ν = 2879s, 1455s, 1178s, 1101s, 1044s, 981s, 821s, 735s, 700s cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, 333 K): δ = 7.40–7.27 (5 H, m), 5.24 (1 H, d, *J* = 6.3 Hz, OCH_AH_BO), 5.00 (1 H, d, *J* = 3.6 Hz, C10-H), 4.89 (1 H, d, *J* = 11.8 Hz, $PhCH_2$), 4.63 (1 H, d, *J* = 6.3 Hz, OCH_AH_BO), 4.60 (1 H, d, *J* = 11.8 Hz, $PhCH_2$), 4.11 (1 H, dd, *J* = 6.1, 3.6 Hz, C12-H), 4.03 (1 H, dd, *J* = 10.2, 2.5 Hz), 3.98 (1 H, dd, *J* = 18.8, 6.1 Hz), 3.50–3.20 (3 H, m), 3.50 (3 H, s, OCH_3), 3.39 (1 H, d, *J* = 2.4 Hz, C13-H), 3.34 (3 H, s, OCH_3), 3.20 (3 H, s, OCH_3), 1.74–1.56 (2 H, m, C16-H_2), 0.99 (3 H, s, C14-CH_3), 0.87 (3 H, s, C14-CH_3).

^{13}C NMR (90 MHz, $CDCl_3$, 333 K): δ = 137.5 (0), 128.7 (1, 2C), 128.1 (1, 2C), 128.0 (1), 99.0 (1), 82.2 (2), 81.9 (1), 78.5 (1), 76.8 (1), 74.2 (2), 73.6 (1), 70.4 (2), 67.3 (1), 61.2 (3), 59.2 (3), 57.1 (3), 40.2 (0), 30.4 (2), 24.5 (3), 15.2 (3).

LRMS (CI, NH_3): *m*/*z* (%) = 411 [$(M + H)^+$, 45], 307 (15), 294 (20), 277 (35), 126 (100), 91 (70).

Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.39; H, 8.29. Found: C, 64.22; H, 8.41.

(1*R*,5*RS*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-5-ol (26)
A solution of the acetals **25a,b** (400 mg, 0.97 mmol) in EtOAc (30 mL) was hydrogenated (1 atmosphere) with 5% Pd/C (760 mg) for 17 h. The mixture was filtered through a pad of Celite and concentrated. The residue was passed through a pad of silica gel (7 g, hexanes/EtOAc, 50%) to give a 3:1 mixture of the hemiacetals **26** (271 mg, 87%) according to integration of the C14-CH_3 singlets at δ = 0.91 (major) and 0.94 (minor) revealed in the ^1H NMR spectrum ($CDCl_3$) of the mixture. ^1H and ^{13}C NMR spectroscopic data were identical to those previously reported.[3]

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References

(1) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.
(2) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B.; Pannell, L. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1335.
(3) Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797.
(4) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869.
(5) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth. Coll. Vol. VIII* **1993**, 315.
(6) Tamao, K. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; Jai Press Inc:55 Old Post Road/ No 2/Greenwich/CT 06836, 1996; Vol. 3; p 1.
(7) Fleming, I. *Chemtracts: Organic Chemistry* **1996**, *9*, 1.
(8) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1989**, *30*, 6497.
(9) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
(10) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(11) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4157.
(13) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242.
(14) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.
(15) Sharpless, B. K.; Amberg, W.; Bennani, G. A. C.; Martung, J.; Heong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, X. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
(16) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828.
(17) Corey, E. J.; Noe, M. C.; Ting, A. Y. *Tetrahedron Lett.* **1996**, *37*, 1735.
(18) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1649.
(19) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
(20) Alexander, E. R.; Busch, H. M. *J. Am. Chem. Soc.* **1952**, *74*, 554.

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