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Enantioselective synthesis of the dioxabicyclo[3.2.1]octane core of the zaragozic acids *via* intramolecular Wacker-type cyclisation reactions

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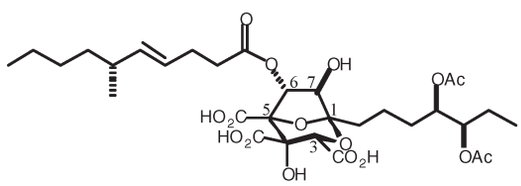
Wacker-type cyclisation reactions provide an effective entry into the dioxabicyclo[3.2.1]octane core of the zaragozic acid analogues.

Introduction

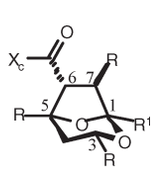
The zaragozic acids (also referred to as squalestatins) are a class of fungal metabolites that exhibit picomolar inhibition of the enzyme squalene synthase (EC 2.5.1.21) and hence, of cholesterol biosynthesis.[1,2] The highly functionalised 2,8-dioxabicyclo[3.2.1]-octane core common to all the zaragozic acids (*e.g.* zaragozic acid C, Fig. 1) presents the most significant synthetic challenge of these natural products.[3]



1

Fig. 1 Zaragozic acid C.

To date these natural products have not been successfully developed into a useful therapeutic. One reason for this is the lack of rapid means of assembling the unusual bicyclic core. In their review of this class of natural products Nadin and Nicolaou[1a] highlighted those features identified through SAR studies which are critical for biological activity. These features included the C5 carboxylic acid as well as the hydrophobic chain attached to C1 and C6. Significantly the C6 oxygen was found to be unnecessary for activity. Taking this information into account we selected **2** as a plausible target (we have reported[3o] a similar approach to C5-substituted derivatives). Hence in the first part of this report we provide full details of an earlier communication on the construction and intramolecular Wacker-type cyclisation reactions of precursors of type **5**.

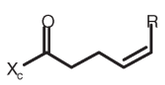


2

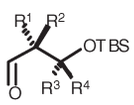
The second part of this paper describes the application of an intramolecular Wacker-type cyclisation reaction to a carbohydrate-derived precursor resulting in the synthesis of a 6,7-dioxygenated dioxabicyclo[3.2.1]octane.

Results and discussion

Initial efforts in this laboratory were directed towards the synthesis of precursors *via* asymmetric aldol coupling of **3a** with **4a–d** and **3b** to **4a**.

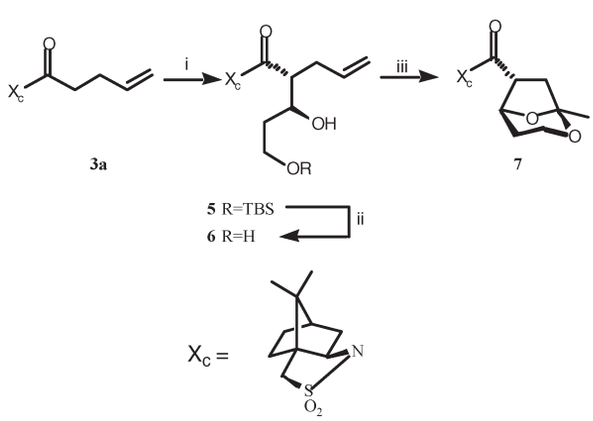


3a R=H
3b R=$(CH_2)_3OBn$



4a R^1 to R^4=H
4b R^1=CH_3, R^2 - R^4=H
4c R^1=R^2=R^4=H, R^3=CH_3
4d R^1=R^2=R^3=H, R^4=CH_3

Aldol addition of the (*Z*)-diethylboron enolate[4] of **3a** to aldehyde **4a** proceeded with essentially complete diastereoselectivity (Scheme 1). Subjection of compound **6** to a Wacker cyclisation[5] reaction, involving its treatment with a mixture of $PdCl_2$, $CuCl_2$, O_2 at 60 °C, resulted in the smooth formation of **7** incorporating the dioxabicyclo[3.2.1]octane framework. A single X-ray crystal structure of **7** provided unambiguous confirmation of its structural and stereochemical assignment.[3n] Whilst deprotection of the silylated alcohol **5** was initially effected with HCl–THF (1 : 10)[6] prior to cyclisation, the need for such a conversion was obviated since the direct ring closure of mono-silyl ether **5** proceeded as efficiently as that for **6**.



Scheme 1 *Reagents and conditions*: (i) (a) Et_2BOTf, $Et_2(i\text{-}Pr)N$, CH_2Cl_2, 0 °C, 20 min then −78 °C; (b) **4a**, −78 °C, 3 h, 95%; (ii) conc. HCl–THF (1 : 10), rt, 2 h, 74%; (iii) $PdCl_2$ (5 mol%), $CuCl_2$, DME, O_2, 65 °C, 12 h, 60%.

With these results in hand we coupled **3a** to aldehydes **4a–d** and **3b** to **4a** (see Table 1). All these aldol reactions proceeded with essentially complete diastereoselectivity.[7] Each of the adducts was then subjected to the ring closing conditions described above. In each case the bicyclic product was produced in good yield. Significantly, this process was successful with secondary as well as primary silyl ethers (entries 3 and 4) allowing the introduction of substituents at C3 and C4. Most important, ring closure of the internal alkene **14** was also successful (entry 5) although in relatively modest yields. This last example, which is not optimised at this stage, provides access to 2,8-dioxabicyclo[3.2.1]octanes bearing functionalised substituents

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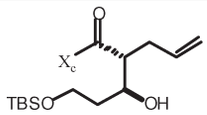
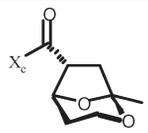
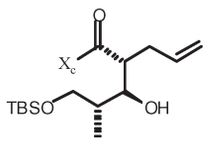
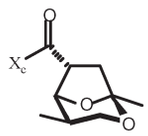
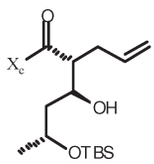
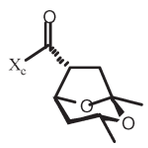
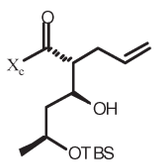
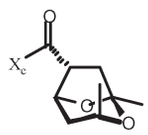
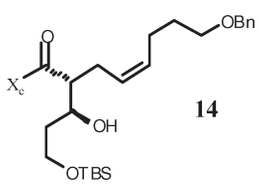
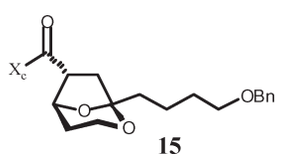
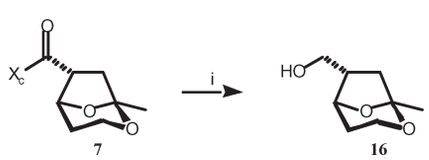
Table 1

Entry	Reactants	Aldol adduct	Yield (%)	Ring closed Product	Yield (%)
1	**3a** + **4a**	 **5**	95	 **7**	60
2	**3a** + **4b**	 **8**	94	 **9**	60
3	**3a** + **4c**	 **10**	95	 **11**	65
4	**3a** + **4d**	 **12**	95	 **13**	50
5	**3b** + **4a**	 **14**	71	 **15**	39

X_c = 

at C1, and is of great value in the design and synthesis of zaragozic acid and its analogues. To the best of our knowledge this is also the first example of an intramolecular Wacker oxidation of an internal alkene.[8] Reductive removal of the auxiliary with $LiAlH_4$ (Scheme 2), provided its corresponding primary alcohol in excellent yield.



Scheme 2 *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, 0 °C, 45 min, 87%.

Whilst the method described above delivers the bicyclic core efficiently and rapidly we were interested in preparing analogues which contained the C6 and C7 hydroxy groups with correct absolute stereochemistry. In order to achieve this the synthesis of a more highly functionalised precursor, **23**, was developed commencing with **17**, available in four steps from D-xylose.[9] The primary alcohol of **17** was selectively protected as its TBS-ether under standard silylating conditions. Hydrolysis of **18** using $HgCl_2$, HgO in acetone–water (10 : 1) at 40 °C resulted in the formation of **19** which existed predominantly in the lactol form shown.[10] Wittig methylenation next gave compound **20** in 80% yield.[11] β-Hydroxy ester **22** was obtained as a 3 : 1 mixture[12] in 96% yield over two steps *via* oxidation of the secondary alcohol with Dess–Martin periodinane,[13] followed by a zinc mediated Reformatsky reaction.[14] The stereochemistry of the newly formed quaternary centre of the major product was deduced by NOESY experiments on **24**. A 5.8% enhancement was observed as indicated in Scheme 3.

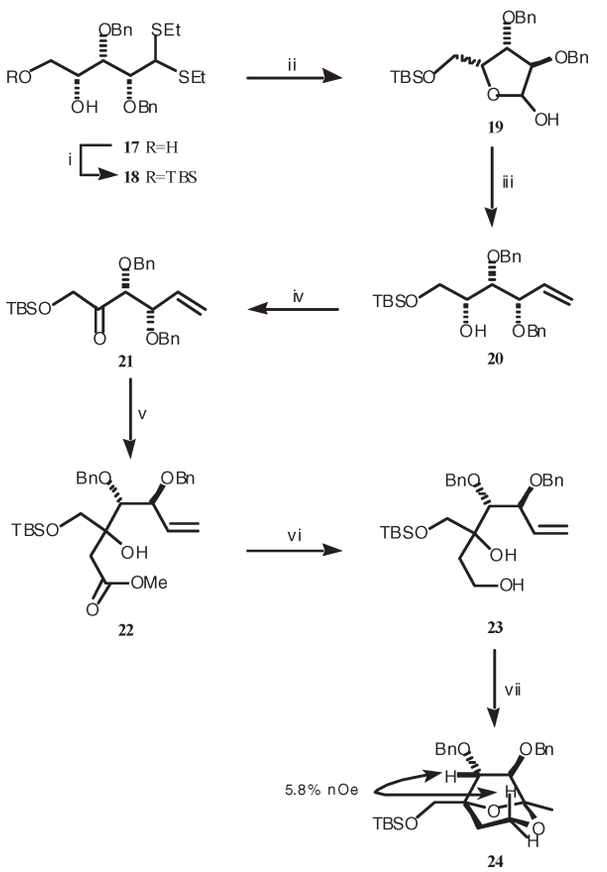
Treatment of ester **22** with DIBAL-H in CH_2Cl_2 at −78 °C resulted in the smooth formation of compound **23**.[15] Subsequently, this pivotal diol was subjected to a Wacker reaction[5] (using $PdCl_2$, $CuCl_2$, O_2 at 60 °C as before) furnishing the corresponding cyclisation product **24** in excellent yield (89%).[15]

Conclusions

The successful application of intramolecular Wacker-type cyclisation reactions to a variety of alkenediols offers a powerful technology for the preparation of functionalized dioxabicyclo[3.2.1]-octanes of relevance to the zaragozic acids.

Experimental

Melting points were conducted on a Kofler hotstage and are uncorrected. Elemental microanalyses were performed by the Australian Microanalytical Service, National Analytical Laboratories, Melbourne or the University of Otago, Dunedin, New Zealand. Optical rotations were recorded on a Perkin Elmer Model 141 Polarimeter and are reported as follows: $[\alpha]_D$, concentration, *c* (g/100 mL) and solvent. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier Transform spectrophotometer (cm^{-1} scale) and refer to thin films of liquids (neat) or paraffin (Nujol) mulls of solids between NaCl plates. High-resolution hydrogen-1 nuclear magnetic resonance (^1H NMR) spectra were recorded at 200 MHz on a Bruker AC-200 spectrometer; 300 MHz on a Varian Mercury, Bruker AM-300 spectrometer or DPX-300 spectrometer; 400 MHz on a Bruker Avance DRX 400 spectrometer. The ^1H NMR spectral data refer to deuteriochloroform solutions ($CDCl_3$) using tetramethylsilane (TMS) as internal reference (δ 0.00 ppm),



Scheme 3 *Reagents and conditions*: (i) TBSCl, DMAP, Im, DMF, rt, 5 h, 95%; (ii) $HgCl_2$, HgO, acetone–water (10 : 1), 40 °C, 3 h; (iii) $Ph_3P{=}CH_2$, THF, HMPA, 0 °C to rt, 4 h, 80% over two steps; (iv) Dess–Martin, CH_2Cl_2, rt, 2.5 h, 91%; (v) α-methyl bromoacetate, Zn, THF, 60 °C, 30 min, 96%; (vi) DIBAL, CH_2Cl_2, −78 to 0 °C, 2 h, 79%; (vii) $PdCl_2$ (5 mol%), $CuCl_2$, DME, O_2, 50 °C, 3 h, 89%.

unless otherwise stated. Each resonance was assigned according to the following convention: chemical shift (δ) measured in parts per million (ppm) downfield from TMS, multiplicity, observed coupling constant (*J* Hz), number of hydrogens, and assignment. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 50 MHz on a Bruker AC-200 spectrometer; 75 MHz on a Bruker APX-300 or Varian Mercury spectrometer; 100 MHz on a Bruker Advance DRX 400 spectrometer and refer to deuteriochloroform solutions with the central peak of the $CDCl_3$ triplet (77.0 MHz) used as the reference. The program of the spin-echo for ^{13}C nuclei coupling to proton (JMOD ^{13}C NMR) was used for most samples in order to determine the number of hydrogens attached. ^{13}C chemical shifts (δ) are reported and assignments for identifiable carbons are given where pronticity is defined as C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl; C or CH_2 = quaternary or methylene; CH or CH_3 = methine or methyl. Mass spectrometry (ESI) was performed using samples in MeOH on a Micromass Platform QMS spectrometer. High-resolution mass spectra (HRMS) for accurate mass determinations were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration (accuracy ±3 ppm). Low-resolution mass spectra were recorded on a VG micromass 70/70F or a VG TRIO-1 mass spectrometer with an ion source temperature of 200 °C and electron impact energy (70 eV). Chemical ionisation mass spectra (CI) were obtained using methane as the reagent gas. The principal ion peaks (*m*/*z*) are reported together with their intensities (in parentheses) expressed as percentages of the base peak (usually) greater than 10% and M^+ denotes the molecular ion. X-Ray crystallography was performed on a Nonius Kappa CCD. Analytical thin layer chromatography (TLC) was performed on Polygram Sil G/UV 254 plastic sheets coated with silica gel containing UV254 fluorescent indicator and inspected under ultraviolet light, stained with iodine or sprayed with ammonium molybdate/cerium sulfate solution. Preparative TLC was performed on glass plates (20 × 20 cm), coated with 0.5 mm of silica gel (Merck 70–230 mesh, No. 7747), which were activated at 100 °C for at least 1 h before use. Flash chromatography was performed using Kieselgel 60 silica gel (Merck 230–400 mesh, No. 9385). Hexane refers to the hydrocarbon fraction boiling between 40–60 °C. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium metal/benzophenone ketyl under nitrogen atmosphere prior to use. Toluene and dichloromethane were distilled from calcium hydride under nitrogen atmosphere prior to use. Methanol was distilled from magnesium methoxide under a nitrogen atmosphere prior to use. *N*,*N*-Dimethylformamide (DMF) was of analytical purity and stored over 4 Å molecular sieves. Dimethoxyethane (DME) was distilled from calcium hydride and stored over 4 Å molecular sieves. Triethylamine was distilled from and stored over potassium hydroxide pellets. Trifluoromethanesulfonic acid (triflic acid) was distilled from phosphorus pentoxide (P_2O_5) under a nitrogen atmosphere prior to use.

Preparation of aldehydes 4a–4d

General procedure for silylation of 1,*n*-diols. *tert*-Butyldimethylsilyl chloride (1 eq.) was added in portions to a cold (−25 °C) solution of diol (2.4 eq.) in dry DMF (0.25 mL/1 mmol of diol). After 1 h, the reaction mixture was warmed to 0 °C and stirred at this temperature for 4 h. The reaction mixture was diluted with *n*-pentane, washed with water (6×), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate–hexane, 1 : 9) provided the silyloxy alcohols.

General procedure for DIBAL-H reduction of esters. A stirred solution of ester (1 eq.) in dry toluene (3 mL/1 mmol of the ester) was cooled to −78 °C under a nitrogen atmosphere, DIBAL-H in toluene solution was added dropwise and the reaction mixture was stirred at this temperature until TLC analysis showed no starting material. Acetone was added dropwise to the mixture followed by the rapid addition of water, the reaction mixture then warmed to room temperature and salts were filtered off. The aldehyde was extracted with diethyl ether, and the organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation under reduced pressure or flash chromatography provided the aldehyde.

General procedure for Swern oxidation of alcohols. Dimethyl sulfoxide (2.2 eq.) was added to a solution of oxalyl chloride (1.1 eq.) in dry dichloromethane (2 mL/1 mmol of oxalyl chloride) at −70 °C under a nitrogen atmosphere and the reaction mixture was stirred at this temperature for 30 min. A solution of silyloxy alcohol (1 eq.) in dry dichloromethane (5 mL/1 mmol of alcohol) was added dropwise and stirring was continued for a further 1 h. Triethylamine (5 eq.) was then added, and the mixture was stirred for 10 min then quenched with water. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to furnish the aldehyde.

General procedure for asymmetric Aldol reactions. Freshly distilled trifluoromethanesulfonic acid (2 eq.) was added dropwise to triethylborane (1 M in hexane, 2 eq.) with strong stirring under an atmosphere of nitrogen at room temperature for 30 min (warmed to 40 °C for 30 min to effect homogeniety if necessary) and the reaction was cooled to −5 °C. Acyl sultam (1 eq.) in dry dichloromethane (4 mL/1 mmol of the acyl sultam) was added dropwise and the reaction mixture was stirred at this temperature for 5 min. Diisopropylethylamine (1 M in dichloromethane, 2.2 eq.) was added dropwise followed by stirring at −3 °C to −5 °C for 30 min. The reaction mixture was cooled to −78 °C and the required aldehyde (2 eq.) in dry dichloromethane (3 mL/1 mmol of aldehyde) was added dropwise followed by stirring at −78 °C until TLC analysis indicated no starting material. The reaction was

quenched with aqueous phosphate buffer (pH 7, 1 eq.) and allowed to warm to room temperature. The layers were partitioned and the dichloromethane layer separated. Products were extracted from the aqueous layer with dichloromethane (5×), the organic layers were combined, washed with saturated aqueous ammonium chloride solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography to provide the pure aldol adduct.

General procedure for Wacker reaction. A mixture of $PdCl_2$ (0.05 eq.) and anhydrous $CuCl_2$ (0.236 eq.) in dry DME (1 mL/1 mmol of $CuCl_2$) was stirred and heated at 65 °C. Oxygen was bubbled through the mixture, a solution of the cyclisation precursor (1 eq.) in dry DME (4 mL/1 mmol of the cyclisation precursor) was added dropwise. Oxygen bubbling was continued, the reaction mixture stirred at 65 °C and judged to be complete by TLC. The reaction mixture was cooled to room temperature, diethyl ether added, the mixture filtered (sintered glass funnel), then passed through a short column of neutral alumina and the solvent concentrated *in vacuo*. The resulting yellow residue was purified by preparative TLC or flash chromatography.

4-Pentenoyl chloride. Oxalyl chloride (0.9 mL, 10.8 mmol) was added dropwise to 4-pentenoic acid (1.0 mL, 9.8 mmol) at 0 °C and the reaction was warmed to room temperature and stirred for 3 h. The acid chloride was used without purification. ^{1}H NMR and IR spectra of the acid chloride were obtained to ensure complete conversion: IR (neat): ν_{max} 2983, 1798, 1643, 1409, 1132, 1042, 958m, 920, 724 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40–2.48 (2H, m), 2.99 (2H, t, *J* 7.2 Hz), 5.05–5.16 (2H, m), 5.79 (1H, ddt, *J* 6.5, 10.2 and 16.8 Hz).

(2*R*)-*N*-(4-Pentenoyl)bornane-10,2-sultam 3a. *n*-Butyllithium (2.14 M, 7.3 mL, 15.7 mmol) was added *via* a dropping funnel to a cold (0 °C) solution of (2*R*)-*N*-(4-pentenoyl)bornane-10,2-sultam (2.74 g, 12.7 mmol) in dry toluene (34 mL). The reaction mixture was stirred for 2 h whilst warming to room temperature. Freshly prepared 4-pentenoyl chloride in dry toluene (10 mL) was added dropwise to the reaction mixture and the reaction mixture stirred at room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl solution (27 mL). The toluene layer was separated and the aqueous layer extracted with diethyl ether (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to give the crude product as a yellow solid. Dry column chromatography (diethyl ether–hexane) followed by recrystallisation (hexane) provided the title compound as colourless crystals (2.50 g, 66%): IR (Nujol): ν_{max} 2968, 2853, 2341, 1694, 1121, 1135, 806, 721 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (3H, s), 1.02 (3H, s), 1.12–1.42 (2H, m), 1.73–1.85 (3H, m), 1.86–2.02 (2H, m), 2.23–2.49 (2H, m), 2.55–2.77 (2H, m), 3.31 and 3.41 (2H, AB quartet, *J* 13.9 Hz), 3.73 (1H, dd, *J* 5.5 and 7.3 Hz), 4.82–4.98 (2H, m), 5.70 (1H, ddt, *J* 6.4, 10.3, 16.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5, 20.5, 26.1, 27.9, 32.4, 34.1, 38.1, 44.3, 47.4, 48.1, 52.5, 64.8, 115.3, 136.2, 170.7.

4-(Benzyloxy)-1-butanol. 1,4-Butanediol (8.11 g, 90 mmol) was added dropwise to NaH (2.16 g, 90 mmol) in dry DMF (56 mL) at 0 °C under a nitrogen atmosphere. Benzyl chloride (12.32 g, 97 mmol) was then added and the stirred reaction mixture allowed to warm to room temperature. The reaction mixture was stirred at room temperature for a further 2 days then poured into ethyl acetate–water (200/200 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting yellow oil was subjected to flash chromatography (ethyl acetate–hexane, 1 : 3) providing the title compound (12.2 g, 75%) as a yellow oil: IR (neat): ν_{max} 3418, 2865, 1953, 1873, 1812, 1719, 1667, 1455, 1362, 1311, 1098, 958, 737, 699, 612 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65–1.73 (4H, m), 2.48 (1H, br s), 3.52 (2H, t, *J* 5.9 Hz), 3.63 (2H, t, *J* 6.0 Hz), 4.52 (2H, s, 2H), 7.27–7.53 (5H, m); ^{13}C NMR (200 MHz, $CDCl_3$): δ 26.6, 30.0, 62.6, 70.3, 72.9, 127.6, 127.7, 128.4, 138.1.

4-(Benzyloxy)-1-butanal. Using the general Swern oxidation procedure described in general remarks, a solution of DMSO (8.60 g, 7.8 mL, 110 mmol) in dry dichloromethane (100 mL) was added to a stirred cold (−70 °C) solution of oxalyl chloride (6.98 g, 4.8 mL, 55 mmol) in dry dichloromethane (140 mL) followed by the addition of a solution of the above alcohol (9.0 g, 50 mmol) in dry dichloromethane (250 mL). The reaction mixture was stirred at −78 °C for 2 h and work-up provided the title compound (8.8 g, 99%) as a yellow liquid. The aldehyde was used in the next step without further purification: IR (neat): ν_{max} 2945, 1958, 1869, 1818, 1725, 1477, 1256, 1100, 836, 774 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–1.99 (2H, m), 2.55 (2H, dt, *J* 1.6 and 7.1 Hz), 3.51 (2H, t, *J* 6.1 Hz), 4.49 (2H, s), 7.27–7.37 (5H, m), 9.78 (1H, t, *J* 1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6, 40.9, 69.1, 72.9, 127.5, 127.6, 128.3, 128.4, 138.3, 202.1.

(3-Ethoxycarbonylprop-1-yl)triphenylphosphonium bromide. A solution of ethyl 4-bromobutyrate (19.5 g, 0.1 mol) and triphenylphosphine (26.2 g, 0.1 mol) in dry toluene (100 mL) was stirred and heated under reflux for 24 h. After cooling the reaction mixture to room temperature the insoluble white precipitate was filtered off and washed with toluene (40 mL). The filtrate and washings were combined and heated under reflux for a further 24 h then filtered and washed. The second crop was combined with the first and dried under reduced pressure (4 mmHg, 24 h) to give the title compound (33 g, 72%) as a white powder: mp 172–174 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (3H, t, *J* 7.1 Hz), 1.85–2.05 (2H, m), 2.86 (2H, t, *J* 5.5 Hz), 3.93–4.08 (2H, m), 4.09 (2H, q, *J* 7.1 Hz), 7.65–7.95 (15H, m).

Ethyl (*Z*)-8-(benzyloxy)-4-octenoate. Sodium bis(trimethylsilyl)amide (1 M, 45 mL, 45 mmol) was added dropwise to a suspension of the above phosphonium salt (20.57 g, 45 mmol) in dry THF (18 mL) under nitrogen atmosphere at 0 °C. The resulting orange solution was stirred for 20 min and cooled to −78 °C. A solution of freshly prepared 4-benzyloxy-1-butanal (5.31 g, 30 mmol) in dry THF (30 mL) was added dropwise and stirring was continued for an additional 1.5 h. The reaction mixture was warmed to 0 °C, quenched by addition of water (30 mL) and poured into ethyl acetate–water (300/90 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. Flash chromatography (ethyl acetate–hexane, 1 : 9) afforded the title compound (5.4 g, 65%) as a yellow oil: IR (Nujol): ν_{max} 3448, 2351, 2342, 1950, 1868, 1715, 1734, 1451, 1370, 1161, 736 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (3H, t, *J* 7.0 Hz), 1.61–1.72 (2H, m), 2.10–2.19 (2H, m), 2.30–2.39 (4H, m), 3.42–3.49 (2H, m), 4.12 (2H, q, *J* 7.0 Hz), 4.50 (2H, s), 5.33–5.45 (2H, m), 7.26–7.39 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 22.8, 23.9, 29.6, 34.4, 60.3, 69.7, 72.9, 127.3, 127.5, 127.9, 128.2, 130.4, 138.4, 172.9. HRMS: Calc. $C_{17}H_{24}O_3$: $[M + Na]^+$ *m*/*z* 299.1623. Found: 299.1620.

(4*Z*)-8-(Benzyloxy)-4-octenoic acid. A solution of the above ester (2.76 g, 10 mmol) in THF (20 mL) was added to a solution of NaOH (1 M, 40 mL). The reaction mixture was stirred at room temperature overnight and extracted with diethyl ether (2 × 20 mL). The aqueous layer was acidified with aqueous HCl (5 M) to pH 3 and extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure to give the title compound (2.4 g, 97%) as a colourless oil: IR (Nujol): ν_{max} 3350, 1928, 1949, 1873, 1713, 1708, 1496, 1453, 1364, 1208w, 1103, 736, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63–1.70 (2H, m), 2.15 (2H, q, *J* 6.8 Hz), 2.34–2.41 (4H, m), 3.47 (2H, t, *J* 6.5 Hz), 4.50 (2H, s), 5.32–5.48 (2H, m), 7.27–7.38 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.5, 23.9, 29.6, 33.9, 69.6, 72.9, 127.4, 127.6, 127.9, 128.3, 128.4, 138.5, 178.6. HRMS: Calc. $C_{15}H_{20}O_3$: $[M + Na]^+$ *m*/*z* 271.1310. Found: 271.1303.

(4*Z*)-8-(Benzyloxy)-4-octenoyl chloride. Oxalyl chloride (0.86 mL, 9.9 mmol) was added dropwise to the above acid (2.23 g, 9.0 mmol) at 0 °C and the reaction was warmed to room temperature and stirred at this temperature for a further 3 h. The

acid chloride was not isolated and used immediately. ^{1}H NMR and IR spectra of acid chloride were obtained to ensure complete conversion: IR (Nujol): ν_{max} 2936, 2857, 1794, 1453, 1401, 1364, 1102, 957, 735, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63–1.71 (2H, m), 2.11–2.18 (2H, m), 2.20–2.26 (2H, m), 2.89–2.94 (2H, m), 3.46 (2H, t, *J* 6.5 Hz), 4.50 (2H, s), 5.31 (1H, m), 5.44–5.62 (1H, m), 7.27–7.40 (5H, m).

(2*R*)-*N*-[(4*Z*)-8-Benzyloxyocten-1-oyl)bornane-10,2-sultam 3b. *n*-Butyllithium (2.5 M solution in hexane, 5.76 mL, 14.4 mmol) was added *via* a dropping funnel to a cooled (0 °C) solution of the sultam (2.52 g, 11.7 mmol) in dry toluene (30 mL). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2 h. A solution of the above acid chloride in dry toluene (9 mL) was added dropwise, the reaction mixture allowed to warm to room temperature and stirring was continued overnight. Saturated NH_4Cl solution (25 mL) was added and the toluene layer was separated. The aqueous layer was extracted with diethyl ether (3 × 8 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to afford the crude acyl sultam as a brown residue. Flash chromatography (ethyl acetate–hexane, 1 : 4) provided the title compound (3.18 g, 79%) as a yellow oil: IR (neat): ν_{max} 2958, 2360, 2341, 1952, 1870, 1716, 1697, 1454, 1330, 1272, 737, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (3H, s), 1.14 (3H, s), 1.30–1.40 (2H, m), 1.61–1.68 (2H, m), 1.85–2.10 (5H, m), 2.18–2.25 (2H, m), 2.36–2.42 (2H, m), 2.76 (2H, t, *J* 6.6 Hz), 3.41 and 3.49 (2H, AB quartet, *J* 13.8 Hz), 3.46 (1H, t, *J* 6.6 Hz), 3.86 (1H, dd, *J* 5.4 and 7.3 Hz), 4.50 (2H, s), 5.32–5.45 (2H, m), 7.24–7.35 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9, 20.8, 22.3, 23.8, 26.4, 29.6, 32.8, 35.3, 38.5, 44.6, 47.7, 48.4, 52.9, 65.2, 69.8, 72.9, 127.4, 127.6, 128.3, 130.5, 138.4, 171.1. HRMS: Calc. $C_{25}H_{35}NO_4S$: $[M + Na]^+$ *m*/*z* 468.2184. Found: 468.2192.

3-(*tert*-Butyldimethylsilyloxy)-1-propanol. Using the general procedure for silylation described in general remarks, TBSCl (7.8 g, 53 mmol) was added in portions to a cold (−25 °C) solution of 1,3-propanediol (9.7 g, 127 mmol) and imidazole (7.5 g, 110 mmol) in dry DMF (30 mL) under a nitrogen atmosphere. After 1 h, the reaction mixture was warmed to 0 °C and stirred at this temperature for 4 h. The yellow oil obtained upon work-up was subjected to flash chromatography (ethyl acetate–hexane, 1 : 9) providing the title compound as a colourless oil (7.0 g, 69%): IR (neat): ν_{max} 3356, 2930, 2858, 1471, 1388, 1362, 1256, 1097, 1006, 961, 836, 776, 718, 662 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.87 (9H, s), 1.75 (2H, quin, *J* 5.7 Hz), 2.76 (1H, br s), 3.76 (2H, t, *J* 5.7 Hz), 3.80 (2H, t, *J* 5.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.6, 18.1, 25.8, 34.2, 62.1, 62.7.

3-(*tert*-Butyldimethylsilyloxy)propanal 4a. Using the general Swern oxidation procedure described in general remarks, DMSO (3.61 g, 3.3 mL, 46 mmol) in dry dichloromethane (18 mL) was added to a stirred cold (−70 °C) solution of oxalyl chloride (2.93 g, 2.0 mL, 23 mmol) in dry dichloromethane (46 mL) followed by the addition of the above alcohol (4.0 g, 21 mmol) in dry dichloromethane (105 mL). The reaction mixture was stirred at −70 °C for a further 1 h and work-up to furnish the title compound (3.96 g, 100%) as a yellow oil. The aldehyde **4a** was used in the next reaction without purification: IR (neat): ν_{max} 2955, 2857, 2730, 1728, 1472, 1464, 1389, 1361, 1256, 1099, 1099, 1006, 971, 939, 836, 774 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.81 (9H, s), 2.52 (2H, dt, *J* 2.1 and 6.0 Hz), 3.92 (1H, t, *J* 6.0 Hz), 9.73 (1H, t, *J* 2.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.0, −5.6, 18.1, 25.7, 46.5, 57.3, 201.5.

Methyl (*R*)-3-[(*tert*-butyldimethylsilyloxy)-2-methyl]propionate. Using the general procedure for silylation described in general remarks, (2*S*)-methyl 3-hydroxy-2-methylpropionate (2.14 g, 18.0 mmol), TBSCl (2.92 g, 19.4 mmol), DMAP (0.16 g, 1.3 mmol) and imidazole (1.46 g, 21.4 mmol) in dry DMF (9 mL) was stirred under a nitrogen atmosphere at room temperature overnight. The resulting yellow oil obtained upon work-up was subjected to flash chromatography (dichloromethane–hexane, 1 : 1) provided the title compound (3.5 g, 83%) as a colourless oil. Specific rotation: $[\alpha]_D$ −23.6 (*c* 4.0, MeOH); IR (neat): ν_{max} 2954, 2771, 1747, 1471, 1435, 1389, 1362, 1257, 1198, 1096, 1025, 1006, 990, 939, 837, 777, 665 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (6H, s), 0.85 (9H, s), 1.12 (3H, d, *J* 7.0 Hz), 2.63 (1H, ddq, *J* 6.0, 6.9 and 7.0 Hz), 3.61 (1H, dd, *J* 6.0 and 9.7 Hz), 3.65 (3H, s), 3.76 (1H, dd, *J* 6.9 and 9.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 13.5, 18.3, 25.8, 42.6, 51.6, 65.3, 175.5. All spectral data compare favourably with the literature.[16]

(*R*)-3-[(*tert*-Butyldimethylsilyloxy)-2-methyl]propional 4b. Using the general DIBAL-H reduction procedure described in general remarks, DIBAL-H solution (1.5 M, 4.0 mL, 6.0 mmol) was added to a stirred cold (−78 °C) solution of the above ester (1.16 g, 5.0 mmol) in dry toluene (15 mL). The reaction mixture was stirred at this temperature for 2 h. The resulting yellow oil obtained upon work-up was subjected to flash chromatography (dichloromethane) providing the title compound (1.01 g, 62%) as a colorless oil. Specific rotation: $[\alpha]_D$ −36.7 (*c* 1.0, CH_2Cl_2); IR (neat): ν_{max} 2956, 2931, 2858, 2713, 2362, 1734, 1473, 1389, 1362, 1257, 1100, 1033, 837, 777, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.88 (9H, s), 1.09 (3H, d, *J* 7.0 Hz), 2.49–2.56 (1H, m), 3.80 (1H, dd, *J* 6.3 and 10.2 Hz), 3.86 (1H, dd, *J* 5.3 and 10.2 Hz), 9.68 (1H, d, *J* 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.6, −5.5, 10.3, 18.2, 25.7, 48.8, 63.5, 204.6. All spectral data compare favourably with the literature.[17]

Ethyl (*R*)-3-(*tert*-butyldimethylsilyloxy)butyrate. Using the general silylation procedure described in general remarks, a mixture of ethyl (*R*)-(−)-3-hydroxybutyrate (1.0 g, 7.6 mmol), TBSCl (1.22 g, 8.1 mmol), DMAP (65 mg, 0.5 mmol) and imidazole (0.61 g, 8.9 mmol) in dry DMF (4 mL) was stirred under a nitrogen atmosphere at room temperature overnight. The resulting yellow oil obtained upon work-up was subjected to flash chromatography (dichloromethane) providing the title compound (1.257 g, 68%) as a colourless oil. Specific rotation: $[\alpha]_D$ −25.5 (*c* 1.0, CH_2Cl_2); IR (neat): ν_{max} 2957, 2858, 1740, 1472, 1376, 1300, 1256, 1183, 1139, 1083, 1034, 1003, 939, 836, 776 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.19 (3H, d, *J* 6.1 Hz), 1.26 (3H, t, *J* 7.2 Hz), 2.35 (1H, dd, *J* 5.4 and 14.5 Hz), 2.47 (1H, dd, *J* 7.4 and 14.5 Hz), 4.10 (2H, q, *J* 7.2 Hz), 4.27 (1H, ddq, *J* 5.4, 6.1 and 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.0, −4.5, 14.2, 17.9, 23.9, 25.7, 45.0, 60.3, 65.9, 171.6. All spectral data compare favourably with the literature.[18]

(*R*)-3-(*tert*-Butyldimethylsilyloxy)butanal 4c. Using the general DIBAL-H reduction procedure described in general remarks, DIBAL-H solution (1.5 M in toluene, 4.0 mL, 6.0 mmol) was added to a stirred solution of the above ester (1.23 g, 5.0 mmol) in dry toluene (15 mL) at −78 °C and the reaction mixture was stirred at this temperature for 2 h. The resulting yellow oil obtained upon work-up was subjected to fractional distillation to yield the title compound (660 mg 65%) as a colourless oil. Aldehyde **4c** was used immediately in the next step. Specific rotation: $[\alpha]_D$ −11.3 (*c* 1.0, CH_2Cl_2); IR (neat): ν_{max} 2957, 2858, 1728, 1472, 1376, 1256, 1099, 1028, 1005, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.23 (3H, d, *J* 6.2 Hz), 2.46 (1H, ddd, *J* 2.1, 5.0 and 15.7 Hz), 2.55 (1H, ddd, *J* 2.8, 6.8 and 15.7 Hz), 4.25 (1H, ddq, *J* 5.0, 6.2 and 6.8 Hz), 9.80 (1H, dd, *J* 2.1 and 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.3, 17.9, 24.2, 25.7, 53.0, 64.6, 202.0. All spectral data compare favourably with the literature.[18]

Ethyl (*S*)-3-(*tert*-butyldimethylsilyloxy)butyrate. Using the general silylation procedure described in general remarks, a mixture of ethyl (*S*)-(+)-3-hydroxybutyrate (2.0 g, 15.1 mmol), TBSCl (2.24 g, 16.2 mmol), DMAP (0.13 g, 1.9 mmol) and imidazole (1.22 g, 17.9 mmol) in dry DMF (8 mL) was stirred under a nitrogen atmosphere at room temperature overnight. The resulting yellow oil obtained upon work-up was subjected to flash chromatography (dichloromethane) providing the title compound

(2.98 g, 80%) as a colourless oil. Specific rotation: $[\alpha]_D$ +23.7 (*c* 1.0, CH_2Cl_2); IR (neat): ν_{max} 2958, 2858, 1739, 1472, 1376, 1300, 1249, 1183, 1130, 1084, 1034, 1003, 939, 836, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.19 (3H, d, *J* 6.1 Hz), 1.24 (3H, t, *J* 7.2 Hz), 2.35 (2H, dd, *J* 5.4 and 14.5 Hz), 2.47 (2H, dd, *J* 7.5 and 14.5 Hz), 4.12 (1H, q, *J* 7.2 Hz), 4.27 (1H, ddq, *J* 5.4, 6.1 and 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.0, −4.5, 14.2, 17.9, 23.9, 25.7, 44.9, 60.3, 65.9, 171.7. All spectral data compare favourably with the literature.[19]

(*S*)-3-(*tert*-Butyldimethylsilyloxy)butanal 4d. Using the general DIBALH reduction procedure described in general remarks, DIBALH solution (1.5 M in toluene, 4.0 mL, 6.0 mmol) was added to a stirred cold (−78 °C) solution of the above ester (1.23 g, 5.0 mmol) in dry toluene (15 mL). The reaction mixture was stirred at this temperature for 2 h. The resulting yellow oil obtained upon work-up was subjected to fractional distillation to yield the title compound (720 mg, 71%) as a colourless oil. Aldehyde **4d** was used immediately in the next step. Specific rotation: $[\alpha]_D$ +11.0 (*c* 1.0, CH_2Cl_2); IR (neat): ν_{max} 2957, 2858, 2365, 1729, 1473, 1376, 1255, 1099, 1029, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.24 (3H, d, *J* 6.2 Hz), 2.46 (1H, ddd, *J* 2.1, 5.1 and 15.7 Hz), 2.55 (1H, ddd, *J* 2.8, 6.9 and 15.7 Hz), 4.25 (1H, ddq, *J* 5.1, 6.2 and 6.9 Hz), 9.79 (1H, dd, *J* 2.1 and 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.4, 17.9, 24.2, 25.7, 53.0, 64.6, 202.1. All spectral data compare favourably with the literature.[20]

(2*R*)-*N*-[(2*R*)-2-{(1*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-hydroxyprop-1-yl}-4-penten-1-oyl]bornane-10,2-sultam 5. Using the general aldol reaction procedure described in general remarks, aldol addition of acyl sultam **3a** (4 mmol) to aldehyde **4a** with the reaction time of 3 h afforded upon work-up crude product as a yellow residue. Purification by dry column chromatography (diethyl ether–hexane) followed by recrystallisation (hexane) provided adduct **5** (1.85 g, 95%) as colourless crystals: mp 108–109 °C. Specific rotation: $[\alpha]_D$ −59.9 (*c* 1.0, CH_2Cl_2). Analysis (%): Calc. $C_{24}H_{43}NO_5SSi$: C 59.35, H 8.93, N 2.89. Found: C 59.51, H 9.19, N 2.94; IR (Nujol): ν_{max} 3480, 2918, 2360, 2354, 1694, 1483, 1376, 1312, 1165, 1072, 973, 838, 781, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.89 (9H, s), 0.96 (3H, s), 1.16 (3H, s), 1.31–1.41 (2H, m), 1.64–1.70 (1H, m), 1.76–1.80 (2H, m), 1.81–1.91 (2H, m), 2.01–2.03 (2H, m), 2.55–2.64 (2H, m), 3.23–3.29 (1H, m), 3.42 and 3.50 (2H, AB quartet, *J* 13.8 Hz), 3.66 (1H, br s), 3.76–3.81 (1H, m), 3.83–3.89 (2H, m), 4.09–4.14 (1H, m), 4.95–5.10 (2H, m), 5.86 (1H, ddt, *J* 6.5, 10.3 and 17.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.5, 18.2, 19.9, 20.9, 25.9, 26.5, 33.0, 33.7, 36.4, 38.5, 44.7, 47.7, 48.1, 50.3, 53.3, 62.2, 64.2, 70.8, 117.3, 135.0, 174.0. HRMS: Calc. $C_{24}H_{43}NO_5SSi$: $[M + Na]^+$ *m*/*z* 486.271. Found: 486.271.

(2*R*)-*N*-[(1*S*,5*S*,6*R*)-1-Methyl-2,8-dioxabicyclo[3.2.1]octanyl-6-carbonyl]bornane-10,2-sultam 7. Using the general Wacker reaction procedure described in general remarks, Pd(II)-catalysed cyclisation of aldol adduct **5** (0.25 mmol scale) for 3 h afforded, upon work-up, a yellow residue, which was purified by preparative TLC (ethyl acetate–hexane, 1 : 1). Extraction of the major chromophoric band at R_f 0.40 followed by crystallisation (2-propanol–dichloromethane) provided the title compound (55 mg, 60%) as colourless crystals. Specific rotation: $[\alpha]_D$ −65.6 (*c* 1.4, CH_2Cl_2). Analysis (%): Calc. for $C_{18}H_{27}NO_5S$: C 58.51, H 7.37, N 3.79. Found: C 58.44, H 7.27, N 3.83; IR (Nujol): ν_{max} 2923, 2852, 1687, 1463, 1377, 1333, 1215, 1133, 1083, 949, 833, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, s), 1.16 (3H, s), 1.32–1.47 (3H, m), 1.51 (3H, s), 1.87–1.97 (3H, m), 2.05–2.20 (3H, m), 2.23 (1H, dd, *J* 4.7 and 13.7 Hz), 2.46 (1H, dd, *J* 9.1 and 13.7 Hz), 3.45 and 3.52 (2H, AB quartet, *J* 13.8 Hz), 3.62 (1H, dd, *J* 4.7 and 9.1 Hz), 3.88–4.00 (3H, m), 4.73 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 20.9, 24.0, 26.4, 29.5, 32.9, 38.5, 39.4, 44.6, 47.1, 47.8, 48.5, 53.1, 59.7, 65.7, 78.2, 105.9, 172.3. HRMS: Calc. $C_{18}H_{27}NO_5S$: $[M + Na]^+$ *m*/*z* 370.169. Found: 370.169.

(2*R*)-*N*-[(2*R*)-2-{(1*S*,2*S*)-3-*tert*-Butyldimethylsilyloxy)-1-hydroxy-2-methylprop-1-yl}-4-penten-1-oyl]bornane-10,2-sultam 8. Using the general aldol reaction procedure described in general remarks, aldol addition of acyl sultam **3a** (1 mmol) to aldehyde **4b** with the reaction time of 3 h afforded upon work-up crude product as a yellow solid. Purification by flash chromatography (ethyl acetate–hexane; 1 : 90) followed by recrystallisation (diethyl ether–hexane) provided adduct **8** (470 mg, 95%) as colourless crystals: mp 137–139 °C. Specific rotation: $[\alpha]_D$ −68.0 (*c* 1.0, CH_2Cl_2); IR (Nujol): ν_{max} 3508, 2953, 2358, 1698, 1457, 1332, 1258, 1068, 835, 721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 0.95 (3H, s), 1.00 (3H, d, *J* 7.0 Hz), 1.15 (3H, s), 1.34–1.41 (2H, m), 1.70–1.77 (1H, m), 1.83–1.94 (3H, m), 1.98–2.02 (2H, m), 2.51–2.55 (1H, m), 2.63–2.74 (1H, m), 3.32–3.39 (1H, m), 3.40 and 3.49 (2H, AB quartet, *J* 13.8 Hz), 3.66 (1H, dd, *J* 3.9 and 10.1 Hz), 3.71–3.91 (3H, m), 4.95–5.09 (2H, m), 5.85 (1H, ddt, *J* 6.5, 10.3, 17.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.7, −5.6, 14.4, 18.1, 19.9, 20.7, 25.8, 26.4, 32.3, 32.8, 36.9, 38.4, 44.5, 47.3, 47.7, 48.1, 53.1, 65.2, 65.9, 73.3, 117.3, 134.9, 174.7. HRMS: Calc. $C_{25}H_{45}NO_5SSi$: $[M + Na]^+$ *m*/*z* 522.269. Found: 522.269.

(2*R*)-*N*-[(1*S*,4*R*,5*S*,6*R*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]-octanyl-6-carbonyl]bornane-10,2-sultam 9. Using the general Wacker reaction procedure described in general remarks, Pd(II)-catalysed cyclisation of aldol adduct **8** (0.1 mmol scale) for 3 h afforded, upon work-up, a yellow residue which was purified by flash chromatography (ethyl acetate–hexane, 1 : 3) followed by crystallisation (diethyl ether) providing the title compound (23–36 mg, 60–93%) as colourless crystals: mp 190–191 °C. Specific rotation: $[\alpha]_D$ −53.1 (*c* 1.0, CH_2Cl_2). Analysis (%): Calc. for $C_{19}H_{29}NO_5S$: C 59.50, H 7.63, N 3.65. Found: C 59.22, H 7.75, N 3.57; IR (Nujol): ν_{max} 2850, 2725, 1695, 1570, 1456, 1377, 1165, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, s), 1.15 (3H, s), 1.25 (3H, d, *J* 7.0 Hz), 1.30–1.44 (2H, m), 1.50 (3H, s), 1.54–1.64 (1H, m), 1.86–1.92 (3H, m), 2.07–2.11 (2H, m), 2.18 (1H, dd, *J* 4.8 and 13.6 Hz), 2.43 (1H, dd, *J* 9.0 and 13.6 Hz), 3.45 and 3.52 (2H, AB quartet, *J* 13.8 Hz), 3.54 (1H, dd, *J* 1.3 and 12.0 Hz), 3.61 (1H, dd, *J* 4.8 and 9.0 Hz), 3.89 (1H, dd, *J* 5.5 and 5.6 Hz), 4.04 (1H, dd, *J* 4.0 and 12.0 Hz), 4.40 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 19.8, 20.9, 23.8, 26.3, 32.7, 32.8, 38.5, 38.6, 44.6, 47.7, 48.1, 48.4, 53.1, 65.4, 65.7, 82.8, 106.0, 172.3. HRMS: Calc. $C_{19}H_{29}NO_5S$: $[M + Na]^+$ *m*/*z* 406.166. Found: 406.165.

(2*R*)-*N*-[(2*R*,3*S*,5*R*)-2-Allyl-5-(*tert*-butyldimethylsilyloxy)-hexan-1-oyl]bornane-10,2-sultam 10. Using the general aldol reaction procedure described in general remarks, aldol addition of acyl sultam **3a** (1 mmol) to aldehyde **4c** with the reaction time of 3 h afforded upon work-up crude product as a yellow residue. Purification by flash chromatography (ethyl acetate–hexane, 1 : 9) followed by recrystallisation (diethyl ether–hexane) provided adduct **10** (475 mg, 95%) as colourless crystals: mp 138–140 °C. Specific rotation: $[\alpha]_D$ −69.0 (*c* 1.18, CH_2Cl_2); IR (Nujol): ν_{max} 3487, 3077, 2957, 2856, 1694, 1463, 1333, 1210, 1133, 1065, 836, 775 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 0.95 (3H, s), 1.14 (3H, s), 1.19 (3H, d, *J* 6.3 Hz), 1.27–1.38 (2H, m), 1.43–1.54 (1H, m), 1.65–1.78 (1H, m), 1.81–1.92 (3H, m), 1.98–2.01 (2H, m), 2.46–2.66 (2H, m) 3.16–3.31 (1H, m), 3.40 and 3.50 (2H, AB quartet, *J* 13.8 Hz), 3.74 (1H, br s), 3.88 (1H, t, *J* 6.3 Hz) 4.08–4.47 (2H, m), 4.93–5.10 (2H, m), 5.86 (1H, ddt, *J* 6.5, 10.3, 17.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.1, −4.6, 17.9, 19.9, 20.8, 22.9, 25.8, 26.4, 32.9, 33.8, 38.4, 42.0, 44.6, 47.7, 48.0, 50.4, 53.3, 65.3, 67.0, 67.7, 117.3, 135.1, 174.2. HRMS: Calc. $C_{25}H_{45}NO_5SSi$: $[M + Na]^+$ *m*/*z* 522.269. Found: 522.268.

(2*R*)-*N*-[(1*S*,3*R*,5*S*,6*R*)-1,3-Dimethyl-2,8-dioxabicyclo[3.2.1]-octanyl-6-carbonyl]bornane-10,2-sultam 11. Using the general Wacker reaction procedure described in general remarks, Pd(II)-catalysed cyclisation of aldol adduct **10** (0.1 mmol scale) for 3 h afforded, upon work-up, a yellow residue which was purified

by flash chromatography (ethyl acetate–hexane, 1 : 4) followed by crystallisation (diethyl ether) providing the title compound (25–34 mg, 65–89%) as colourless crystals: mp 147–148 °C. Specific rotation: $[\alpha]_D$ −61.0 (*c* 1.0, CH_2Cl_2). Analysis (%): Calc. for $C_{19}H_{29}NO_5S$: C 59.5, H 7.63, N 3.65. Found: C 59.50, H 7.85, N 3.57; IR (Nujol): ν_{max} 2852, 2360, 1686, 1460, 1377, 1329, 1211, 1162, 1136, 1069, 953, 770, 722, 653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, s), 1.13 (3H, s), 1.17 (3H, d, *J* 6.1 Hz), 1.23–1.44 (2H, m), 1.50 (3H, s), 1.56 (1H, ddd, *J* 2.0, 3.8 and 13.3 Hz), 1.68 (1H, ddd, *J* 3.6, 10.9 and 13.3 Hz), 1.80–1.96 (3H, m), 2.03–2.12 (2H, m), 2.17 (1H, dd, *J* 4.8 and 13.6 Hz), 2.42 (1H, dd, *J* 9.1 and 13.6 Hz), 3.44 and 3.51 (2H, AB quartet, *J* 13.8 Hz), 3.55 (1H, dd, *J* 4.8 and 9.1 Hz), 3.87 (1H, dd, *J* 5.4 and 7.2 Hz), 3.91–3.98 (1H, m), 4.69 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 20.9, 21.7, 24.1, 26.3, 32.9, 37.3, 38.5, 39.8, 44.6, 47.5, 47.7, 48.5, 53.1, 65.2, 65.7, 77.9, 105.7, 172.3. HRMS: Calc. $C_{19}H_{29}NO_5S$: $[M + Na]^+$ *m*/*z* 406.166. Found: 406.165.

(2*R*)-*N*-[(2*R*,3*S*,5*S*)-2-Allyl-5-(*tert*-butyldimethylsilyloxy)-hexan-1-oyl]bornane-10,2-sultam 12. Using the general aldol reaction procedure described in general remarks, aldol addition of acyl sultam **3a** (1 mmol) to aldehyde **4d** with the reaction time of 3 h afforded upon work-up crude product as a yellow residue. Purification by flash chromatography (ethyl acetate–hexane) followed by recrystallisation (diethyl ether–hexane) provided adduct **12** (467 mg, 94%) as colourless crystals: mp 138–141 °C. Specific rotation: $[\alpha]_D$ −61.0 (*c* 1.0, CH_2Cl_2); IR (Nujol): ν_{max} 3499, 2960, 1699, 1462, 1335, 1265, 1210, 1133, 1065, 990, 836, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (3H, s), 0.09 (3H, s), 0.85 (9H, s), 0.95 (3H, s), 1.15 (3H, s), 1.16 (3H, d, *J* 6.0 Hz), 1.21–1.42 (2H, m), 1.54 (1H, ddd, *J* 2.0, 4.6 and 14.3 Hz), 1.69 (1H, ddd, *J* 8.7, 9.6 and 14.3 Hz), 1.82–1.96 (3H, m), 1.99–2.09 (2H, m), 2.53–2.69 (2H, m), 3.17–3.24 (1H, m), 3.42 and 3.50 (2H, AB quartet, *J* 13.8 Hz), 3.88 (1H, t, *J* 6.3 Hz), 4.00–4.11 (2H, m), 4.94–5.09 (2H, m), 5.58 (1H, ddt, *J* 6.2, 10.0 and 16.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.1, 17.9, 19.9, 20.8, 24.0, 25.0, 26.4, 32.9, 33.8, 38.4, 43.7, 44.6, 47.7, 48.0, 50.6, 53.3, 65.2, 69.6, 70.3, 117.3, 135.0, 174.2. HRMS: Calc. $C_{25}H_{45}NO_5SSi$: $[M + Na]^+$ *m*/*z* 522.269. Found: 522.268.

(2*R*)-*N*-[(1*S*,3*S*,5*S*,6*R*)-1,3-Dimethyl-2,8-dioxabicyclo[3.2.1]-octanyl-6-carbonyl]bornane-10,2-sultam 13. Using the general Wacker reaction procedure described in general remarks, Pd(II)-catalysed cyclisation of aldol adduct **12** (0.1 mmol scale) overnight afforded, upon work-up, a yellow residue which was purified by flash chromatography (ethyl acetate–hexane, 1 : 4) providing the title compound (19 mg, 50%) as a white solid: IR (Nujol): ν_{max} 2932, 2359, 1688, 1460, 1377, 1326, 1159, 1133, 953, 770, 722, 653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, s), 1.12 (3H, s), 1.16 (3H, d, *J* 6.1 Hz), 1.22–1.42 (2H, m), 1.50 (3H, s), 1.57 (1H, ddd, *J* 2.0, 3.7 and 13.3 Hz), 1.69 (1H, ddd, *J* 3.6, 10.9 and 13.3 Hz), 1.83–1.95 (3H, m), 2.02–2.12 (2H, m), 2.16 (1H, dd, *J* 4.8 and 13.6 Hz), 2.40 (1H, dd, *J* 9.1 and 13.6 Hz), 3.45 and 3.50 (2H, AB quartet, *J* 13.8 Hz), 3.54 (1H, dd, *J* 4.7 and 9.1 Hz), 3.81–3.89 (1H, m), 3.90–3.96 (1H, m), 4.69 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 20.8, 21.5, 24.0, 26.4, 32.8, 37.4, 38.4, 40.4, 44.6, 47.4, 47.7, 48.5, 53.2, 65.0, 65.6, 78.1, 105.9, 172.3. HRMS: Calc. $C_{19}H_{29}NO_5S$: $[M + Na]^+$ *m*/*z* 406.166. Found: 406.165.

(2*R*)-*N*-[(4*Z*)-{(1*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-hydroxyprop-1-yl)-8-benzyloxyocten-1-oyl]bornane-10,2-sultam 14. Using the general aldol reaction procedure described in general remarks, acyl sultam **3b** (223 mg, 0.5 mmol) in dry dichloromethane (2 mL) was reacted with freshly prepared diethylboron triflate (1 mmol) at −10 °C to give the corresponding diethylboron enolate which was cooled to −78 °C. Aldehyde **4a** (188 mg, 1 mmol) was added and the reaction mixture stirred at this temperature for 5 h. The resulting yellow residue obtained upon work-up was subjected to flash chromatography (ethyl acetate–hexane, 1 : 3) to provide the title compound (225 mg, 71%) as a yellow oil: IR (neat): ν_{max} 3490, 2954, 1950, 1870, 1717, 1694, 1454, 1335, 1267, 1210, 1134, 838, 776, 735, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.88 (9H, s), 0.93 (3H, s), 1.12 (3H, s), 1.19–1.40 (2H, m), 1.56–1.69 (4H, m), 1.79–1.96 (3H, m), 1.99–2.04 (2H, m), 2.07–2.30 (2H, m), 2.38–2.56 (1H, m), 2.61–2.75 (1H, m), 3.19–3.30 (1H, m), 3.35–3.52 (4H, m), 3.70–3.88 (3H, m), 4.05–4.13 (1H, m), 4.48 (2H, s), 5.32–5.52 (2H, m), 7.13–7.33 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.6, 18.0, 19.8, 20.7, 23.6, 25.8, 26.3, 26.8, 29.4, 32.8, 36.2, 38.3, 44.5, 47.5, 47.9, 50.2, 53.1, 62.0, 65.0, 69.7, 70.7, 72.7, 125.9, 127.3, 127.5, 127.6, 128.2, 130.5, 131.4, 138.5, 171.2. HRMS: Calc. $C_{34}H_{55}NO_6SSi$: $[M + Na]^+$ *m*/*z* 656.342. Found: 656.339.

(2*R*)-*N*-[(1*S*,5*S*,6*R*)-1-{4-Benzyloxybut-1-yl}-2,8-dioxabicyclo-[3.2.1]octanyl-6-carbonyl]bornane-10,2-sultam 15. Using the general Wacker reaction procedure described in general remarks, Pd(II)-catalysed cyclisation of aldol adduct **14** (0.1 mmol scale) for 8 h afforded, upon work-up, a yellow residue which was purified by flash chromatography (ethyl acetate–hexane, 1 : 1) providing the title compound (20 mg, 39%) as colourless oil: IR (neat): ν_{max} 2945, 1949, 1872, 1715, 1690, 1268, 1210, 1130, 774, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, s), 1.16 (3H, s), 1.25–1.42 (2H, m), 1.43–1.60 (6H, m), 1.69–1.90 (5H, m), 2.02–2.12 (2H, m), 2.24 (1H, dd, *J* 4.6 and 13.7 Hz), 2.38 (1H, dd, *J* 9.0 and 13.7 Hz), 3.42–3.55 (4H, m), 3.60 (1H, dd, *J* 4.6 and 9.0 Hz), 3.87–3.96 (3H, m), 4.49 (2H, s), 4.72 (1H, br s), 7.27–7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9, 19.5, 19.9, 25.4, 28.8, 28.9, 31.9, 36.5, 36.9, 37.6, 43.6, 45.7, 46.8, 47.5, 52.2, 58.6, 64.8, 69.3, 71.8, 77.2, 106.6, 126.4, 126.6, 127.3, 137.7, 171.4. HRMS: Calc. $C_{28}H_{39}NO_6S$: $[M + Na]^+$ *m*/*z* 540.240. Found: 540.238.

(1*R*,3*S*,5*R*,6*S*)-1,3-Dimethyl-6-hydroxymethyl-2,8-dioxabicyclo[3.2.1]octane 16. A solution of $LiAlH_4$ (4 mg, 0.1 mmol) in diethyl ether (1 mL) was stirred under a nitrogen atmosphere and cooled to 0 °C while a solution of **7** (82 mg, 0.21 mmol) in diethyl ether (2 mL) was added dropwise. The reaction mixture was stirred at this temperature for 45 min and water (20 μL) was added. The mixture was warmed to room temperature, filtered through a bed of $MgSO_4$ and the filtrate concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (ethyl acetate–dichloromethane, 1 : 4) to afford the title compound (32 mg, 87%) as a colourless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, d, *J* 6.1 Hz), 1.23–1.42 (2H, m), 1.46 (3H, s), 1.67–1.76 (1H, m), 2.02 (1H, br s), 2.21–2.34 (2H, m), 3.52 (2H, d, *J* 5.7 Hz), 3.91–4.08 (1H, m) and 4.35 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 24.6, 37.9, 38.0, 44.5, 65.3, 65.6, 77.4, 105.4. HRMS: Calc. $C_9H_{16}O_3$: $[M + Na]^+$ *m*/*z* 195.0997. Found: 195.0993.

2,3-Bis(phenylmethyloxy)-5-[(1,1-dimethylethyl)dimethylsilyloxy]-D-xylose 18. *tert*-Butyldimethylsilyl chloride (7.25 g, 48 mmol) was added to a magnetically stirred solution of 2,3-di-*O*-benzyl-D-xylose diethyl dithioacetal **17** (17.5 g, 40 mmol) and imidazole (3.55 g, 52 mmol) in anhydrous DMF (50 mL) maintained at rt under an atmosphere of nitrogen. After 12 h the reaction mixture was poured into water (500 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic phases were washed with water (400 mL) and brine (400 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil. Flash chromatography (5–25% v/v ethyl acetate–hexane elution) gave the title compound (20.9 g, 95%) as a yellow oil. Specific rotation: $[\alpha]_D$ −5.1 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3450, 3063, 2949, 1497, 1454, 1389, 1254, 1121, 842 cm^{-1}; ^1H NMR (300 MHz): δ 0.05 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.22 (6H, m), 2.72 (4H, m), 3.51 (1H, d, *J* 9.8), 3.53 (1H, d, *J* 9.8), 3.65 (1H, d, *J* 9.7), 3.77 (1H, ddd, *J* 8.5, 6.6 and 2.0 Hz), 4.04 (2H, m), 4.14 (1H, d, *J* 3.0 Hz), 4.62 (1H, d, *J* 11.1 Hz), 4.83 (1H, d, *J* 11.1 Hz), 4.87 (2H, AB system, *J* 11 Hz), 7.24–7.37 (10H, m); ^{13}C NMR (75 MHz): δ −5.1 (2 × CH_3, coincident), 14.6 (CH_3), 14.7 (CH_3), 25.4 (C), 26.1 (3 × CH_3, coincident), 26.2 (2 × CH_2, coincident), 53.6 (CH), 64.1 (CH_2), 71.7 (CH), 75.5 (CH_2), 75.7 (CH_2), 79.7 (CH), 83.7 (CH), 127.7 (CH), 128.0 (2 × CH, coincident), 128.2 (2 × CH, coincident), 128.4 (2 × CH,

coincident), 128.5 (2 × CH, coincident), 128.6 (CH), 138.6 (C), 138.8 (C). HRMS: Calc. $C_{29}H_{46}O_4S_2Si$: $[M + Na]^+$ *m*/*z* 573.2504. Found: 573.2485.

(2*R*,3*S*,4*S*)-3,4-Bis(phenylmethyloxy)-1-[(1,1-dimethylethyl)-dimethylsilyloxy]hex-5-en-2-ol 20. Compound **18** (5.47 g, 9.9 mmol) was dissolved in acetone–water (40 mL of a 10 : 1 solution) and HgO (4.98 g, 23.0 mmol) was added in one portion, followed by $HgCl_2$ (2.96 g, 10.5 mmol). The reaction mixture was heated to 60 °C for 3 h, then filtered through a bed of Celite™. The solvent was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (100 mL), then washed with potassium iodide (3 × 70 mL of a 1 M aqueous solution) and brine (1 × 100 mL), before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2,3-di-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-xylose (**18**) as a pale yellow oil. This material was used, without purification, in the next step of the reaction sequence. *n*-BuLi (50.04 mL of a 1.6 M solution in hexane, 80.76 mmol) was added, dropwise, to a solution of methyltriphen ylphosphonium bromide (27.41 g, 76.72 mmol) in anhydrous THF (85 mL) containing HMPA (30 mL) maintained at 0 °C under an atmosphere of nitrogen. The resulting yellow solution was allowed to warm to rt over 1 h then re-cooled to 0 °C. A solution of lactol **19** (3.42 g, 7.67 mmol) in THF (25 mL) was then added, dropwise, to the reaction mixture. After 4 h at rt the reaction mixture was treated sequentially with $NaHCO_3$ (100 mL of a saturated aqueous solution) and water (200 mL). The resulting mixture was extracted with diethyl ether (3 × 200 mL) and the combined organic extracts were washed with water (2 × 200 mL) and brine (2 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light brown oil. Flash chromatography (5–15% v/v ethyl acetate–hexane elution) gave the title compound (2.74 g, 80%) as a clear colourless oil. Specific rotation: $[\alpha]_D$ −1.0 (*c* 1.75, $CHCl_3$); IR (neat): ν_{max} 3465, 3031, 2953, 1654, 1253, 1096, 836, 777, 734, 697 cm^{-1}; ^1H NMR (300 MHz): δ 0.03 (6H, s), 0.88 (9H, s), 3.55 (2H, m), 3.65 (1H, dd, *J* 6.0 and 2.3 Hz), 3.74 (1H, br s), 4.13 (1H, AB system, *J* 7.0 Hz), 4.42 (1H, d, *J* 11.7 Hz), 4.65 (2H, d, *J* 11.4 Hz), 4.91 (1H, d, *J* 11.1 Hz), 5.29–5.42 (2H, complex m), 5.87 (1H, m), 7.26–7.41 (10H, m) (signal due to OH not observed); ^{13}C NMR (75 MHz): δ −5.1 (2 × CH_3, coincident), 26.1 (3 × CH_3, coincident), 29.9 (C), 64.1 (CH_2), 70.9 (CH_2), 71.6 (CH), 75.3 (CH_2), 79.9 (CH), 82.5 (CH), 119.5 (CH_2), 127.7 (2 × CH, coincident), 127.9 (2 × CH, coincident), 128.1 (2 × CH, coincident), 128.4 (2 × CH, coincident), 128.5 (2 × CH, coincident), 135.6 (CH), 138.7 (2 × C, coincident). HRMS: Calc. $C_{26}H_{38}O_4Si$: $[M + Na]^+$ *m*/*z* 465.2437. Found: 465.2421.

(3*R*,4*S*)-3,4-Bis(phenylmethyloxy)-1-[(1,1-dimethylethyl)-dimethylsilyloxy]hex-5-en-2-one 21. Dess–Martin periodinane (7.84 g, 18.47 mmol) was added, in portions, to a stirred solution of alcohol **20** (2.74 g, 6.15 mmol) in CH_2Cl_2 (62 mL) at rt under an atmosphere of nitrogen. After 2.5 h the reaction mixture was treated with sodium thiosulfate (60 mL of a 1 M aqueous solution) and $NaHCO_3$ (60 mL of a saturated aqueous solution). After being stirred vigorously for 20 min, the reaction mixture was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil. Flash chromatography (5–15% v/v ethyl acetate–hexane elution) gave the title compound (2.47 g, 91%) as a clear colorless oil. Specific rotation: $[\alpha]_D$ +12.1 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3031, 2928, 2856, 1736, 1655, 1497, 1455, 1254, 1115, 838, 779, 697 cm^{-1}; ^1H NMR (300 MHz): δ 0.007 (s, 6H), 0.86 (s, 9H), 4.09 (d, 1H, *J* 3.5 Hz), 4.20 (dd, 1H, *J* 7.7 and 3.6 Hz), 4.30 (d, 1H, *J* 12 Hz), 4.40 (s, 2H), 4.52 (d, 1H, *J* 12 Hz), 4.60 (d, 1H, *J* 12 Hz), 4.65 (d, 1H, *J* 12 Hz), 5.28–5.40 (complex m, 2H), 5.91 (m, 1H), 7.24–7.36 (m, 10H); ^{13}C NMR (75 MHz): δ −5.3 (2 × CH_3, coincident), 26.0 (3 × CH_3, coincident), 69.3 (CH_2), 70.9 (CH_2), 74.3 (CH_2), 80.7 (CH), 85.4 (CH), 119.8 (CH_2), 127.9 (CH), 128.0 (3 × CH, coincident), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 134.5 (CH), 137.2 (C), 137.9 (C) (signal due to CO and C not observed). HRMS: Calc. $C_{26}H_{36}O_4Si$: $[M + Na]^+$ *m*/*z* 463.2281. Found: 465.2283.

(3*R*,4*R*,5*S*)-4,5-Bis(phenylmethyloxy)-3-[(1,1-dimethylethyl)-dimethylsilyloxy]-3-hydroxyhept-6-enoic acid methyl ester 22. A solution of **21** (2.47 g, 5.61 mmol) and methyl bromoacetate (1.28 g, 8.42 mmol) in THF (2 mL) were added, dropwise, to Zn dust (550 mg, 8.42 mmol) and heated to reflux under a nitrogen atmosphere. The reaction mixture was refluxed for a further 20 min then allowed to warm to rt over 1 h before being treated with H_2SO_4 (20 mL of a 2 M aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (5–15% v/v ethyl acetate–hexane elution) gave the title compound (2.69 g, 96%) as a clear colorless oil. Spectroscopic data for the major diastereomer: IR (neat) 3465, 2925, 2858, 1763, 1740, 1642, 1350, 1254, 1110, 814, 762 cm^{-1}; ^1H NMR (300 MHz): δ −0.002 (3H, s), 0.01 (3H, s), 0.86 (9H, s), 2.68 (2H, AB system, *J* 15.2 Hz), 3.60 (3H, s), 3.71 (2H, AB system, *J* 1.8 Hz), 4.05 (1H, d, *J* 4.4 Hz), 4.14 (1H, dd, *J* 7.9 and 3.1 Hz), 4.31 (1H, d, 11.8 Hz), 4.63 (1H, d, *J* 11.9 Hz), 4.71 (2H, s), 5.27–5.36 (2H, m), 5.95–6.07 (1H, m), 7.25–7.34 (10H, m) (signal due to OH not observed); ^{13}C NMR (75 MHz): δ −5.5 (2 × CH_3), 18.2 (C), 25.8 (3 × CH_3), 38.3 (CH_2), 51.4 (CH_3), 66.1 (CH), 70.1 (CH), 75.8 (CH), 76.87 (C), 80.2 (CH), 83.4 (CH), 118.2 (CH_2), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.1 (2 × CH), 128.2 (2 × CH), 128.3 (2 × CH), 136.4 (CH), 137.7 (C), 138.3 (C), 172.8 (C). HRMS: Calc. $C_{29}H_{42}O_6Si$: $[M + Na]^+$ *m*/*z* 537.2648. Found: 537.2641.

(3*R*,4*R*,5*S*)-4,5-Bis(phenylmethyloxy)-3-[(1,1-dimethylethyl)dimethylsilyloxy]hept-6-ene-1,3-diol 23. DIBAL-H (2.87 mL of a 1 M solution in toluene, 2.87 mmol) was added, dropwise, to a solution of ester **22** (740 mg, 1.43 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to 0 °C over 2 h, then treated with tartaric acid (75 mL of a 1 M aqueous solution) and allowed to warm to rt. The resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (1 × 75 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil. Flash chromatography (5–25% v/v ethyl acetate–hexane elution) gave the title compound (550 mg, 79%) as a clear colourless oil. Spectroscopic data for the major diastereomer: IR (neat) 3465, 3340, 1654, 1254, 1105, 821, 754 cm^{-1}; ^1H NMR (300 MHz): δ 0.04 (s, 6H), 0.97 (s, 9H), 1.75 (AB system, 1H, *J* 3.8 Hz), 1.81 (dd, 1H, *J* 8.9 and 4.4 Hz), 3.22 (dd, 1H, *J* 7.7 and 3.1 Hz), 3.55 (m, 1H), 3.56 (d, 1H, *J* 10.0 Hz), 3.69 (d, 1H, *J* 10.0 Hz), 3.87 (s, 2H), 4.20 (dd, 1H, *J* 8.1 and 3.2 Hz), 4.34 (d, 1H, 11.7 Hz), 4.65 (d, 1H, 11.7 Hz), 4.71 (d, 2H, *J* 2.4 Hz), 5.31–5.36 (m, 2H), 5.96–6.08 (m, 1H), 7.25–7.37 (m, 10H) (signal due to OH not observed); ^{13}C NMR (75 MHz): δ −5.6 (CH_3), −5.4 (CH_3), 18.0 (C), 25.8 (3 × CH_3), 35.2 (CH_2), 59.0 (CH_2), 64.1 (CH_2), 70.1 (CH_2), 75.9 (CH_2), 78.5 (C), 80.7 (CH), 82.6 (CH), 118.9 (CH_2), 127.6 (CH), 127.8 (2 × CH), 127.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 136.0 (CH), 137.3 (C), 138.1 (C). HRMS: Calc. $C_{28}H_{42}O_5Si$: $[M + Na]^+$ *m*/*z* 509.2699. Found: 509.2695.

(3*R*,6*R*,7*R*)-(6,7-Bis(phenylmethyloxy)-1-methyl-2,8-dioxabicyclo[3.2.1]oct-5-ylmethoxy)(1,1-dimethylethyl)dimethylsilyloxy 24. A solution of **23** (40 mg, 0.08 mmol) in DME (2 mL) was added, dropwise, to a stirred suspension of $PdCl_2$ (0.73 mg, 4.11 × 10^{-3} mmol), $CuCl_2$ (2.6 mg, 0.02 mmol) in DME (2 mL) maintained at 50 °C under a stream of oxygen. After 3 h the reaction mixture was cooled and filtered through a short pad of silica, which was subsequently washed with diethyl ether (15 mL). The combined filtrates were concentrated under reduced pressure to afford a light brown oil. Flash chromatography (5–15% v/v ethyl acetate–hexane elution) gave the title compound (34 mg, 89%) as a

clear colorless oil. Spectroscopic data for the major diastereomer: IR (neat) 2943, 1648, 1267, 1138, 818, 746 cm^{-1}; ^1H NMR (300 MHz): δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.45 (3H, s), 1.69 (1H, dd, *J* 13.2 and 3.9 Hz), 2.01 (1H, app. dt, *J* 13.2 and 6.9 Hz), 3.53 (1H, d, *J* 9.8 Hz), 3.90 (1H, d, *J* 2.4 Hz), 3.96 (1H, m), 4.01 (1H, d, *J* 9.8 Hz), 4.30 (1H, app. dt, *J* 12.6 and 3.9 Hz), 4.00 (1H, d, *J* 2.1 Hz), 4.55 (1H, d, *J* 11.6 Hz), 4.58 (1H, d, *J* 11.8 Hz), 4.63 (1H, d, *J* 11.6 Hz), 4.71 (1H, d, *J* 11.8 Hz), 7.29–7.35 (10H, m); ^{13}C NMR (75 MHz): δ −5.2 (2 × CH_3), 18.4 (C), 24.2 (CH_3), 26.1 (3 × CH_3), 31.5 (CH_2), 60.4 (CH_2), 64.0 (CH_2), 72.6 (CH_2), 72.7 (CH_2), 83.5 (C), 86.5 (CH), 91.3 (CH), 102.8 (C), 127.5 (2 × CH), 127.6 (2 × CH), 127.7 (2 × CH), 127.8 (2 × CH), 128.3 (CH), 128.4 (CH), 138.0 (C), 138.4 (C). HRMS: Calc. $C_{28}H_{40}O_5Si$: $[M + Na]^+$ *m*/*z* 507.2543 Found: 507.2541.

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