The Reaction Mechanism of Spirocylization and Stereoselectivity Studies for the Calyculin C_{16}–C_{25} Fragment

Vesa Rauhala,[a] Kalle Nättinen,[b] Kari Rissanen,[c] and Ari M. P. Koskinen*[a]

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The mechanism of the double intramolecular hetero-Michael addition, a key reaction in the planned synthesis of the natural product calyculin C, has been studied by NMR. The cyclization follows Baldwin's rules and proceeds first through a six-membered ring closure (6-*endo*-*dig*), followed by a five-membered ring cyclization (5-*exo*-*trig*).

Introduction

The 1,6-dioxaspiro[4.5]decane ring system is a ubiquitous structure occurring in nearly 100 natural products.[1] It is noteworthy that the configurations of the stereogenic carbon atoms in most of these structures are dictated by double anomeric effects, placing the oxygen in the oxolane ring axial with respect to the oxane ring (Figure 1).[2] Because of the wide occurrence of such motifs, a rapid and reliable route to the spirocyclic structure is highly desirable. This was of special interest to us because of our ongoing efforts[3] towards the total synthesis of calyculin C, a potent protein phosphatase inhibitor.[4] We have recently communicated[3j] a rapid route to such spikoketals based on the use of the double intramolecular hetero-Michael addition (DIHMA) technique.[5] In this paper we report a stereoselective approach to the spiroketal model fragment of calyculin C[6] as well as our results on the study of the reaction mechanism.

Utilising the DIHMA approach for the construction of the spiroketal required the ynone **12** as the penultimate cyclization precursor (Scheme 1). This should be available through a nucleophilic addition of the alkyne **7** onto the Weinreb amide **11**, this in turn being available by the Evans aldol methodology from propionyloxazolidinone and (benzyloxy)propanal. The alkyne **7** was prepared through a Seyferth–Gilbert-type homologation[7] of lactol **4**, available enantioselectively in two steps from the enoate **1**.

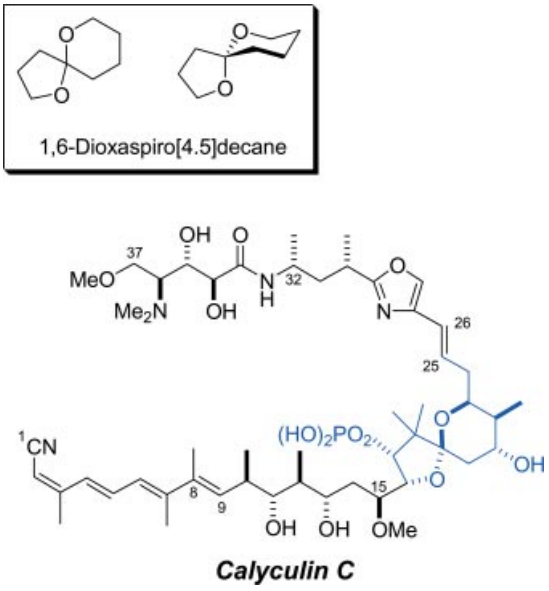

Figure 1. Spiroketal fragment of calyculin C.

Results

The stereoselective synthesis of alkyne **7** is shown in Scheme 2. Sharpless asymmetric dihydroxylation of enoate **1** resulted in spontaneous lactonization and gave the desired single enantiomer of lactone **2** in 82% yield and with 75% *ee*, which was increased to >97% *ee* by recrystallisation (Figure 2).[8] Lactonization was also tested with AD-mix α, which gave 63–67% *ee*. The free alcohol was protected as the benzyl ether (benzyl 2,2,2-trichloroacetimidate, CF_3SO_3H, 91%).[9] Reduction of **3** with DIBAL-H afforded lactol **4** in 90% yield after purification. Original Seyferth–Gilbert-type homologation requires harsher reaction conditions than the widely used Ohira's reagent **5** to transform an aldehyde into the corresponding alkyne.[7,10] The aldehyde surrogate **4** was transformed into alkyne **6** in 61%

[a] Laboratory of Organic Chemistry, Helsinki University of Technology,
P.O. Box 6100, 02015 HUT, Finland
E-mail: Ari.Koskinen@hut.fi
[b] VTT Processes,
P.O. Box 1607, 33101 VTT
E-mail: kalle.nattinen@vtt.fi
[c] Nanoscience Center, Department of Chemistry, University of Jyväskylä,
P.O. Box 35, 40014 Jyväskylä, Finland
E-mail: kari.rissanen@jyu.fi

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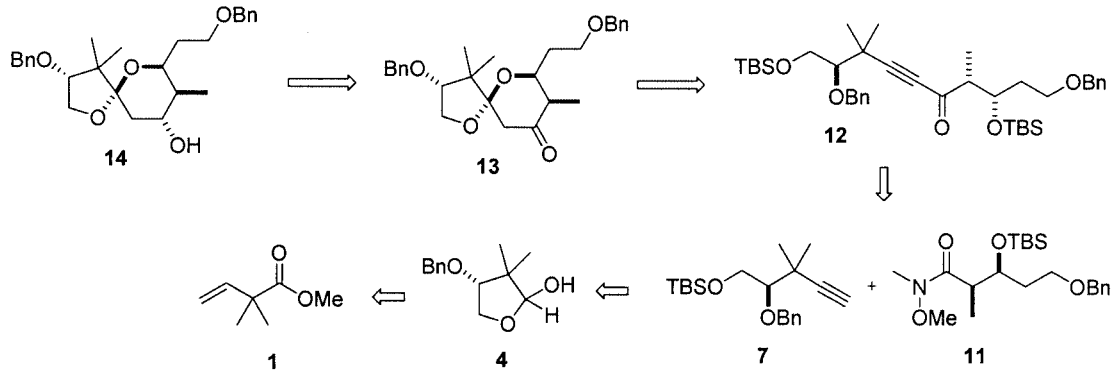
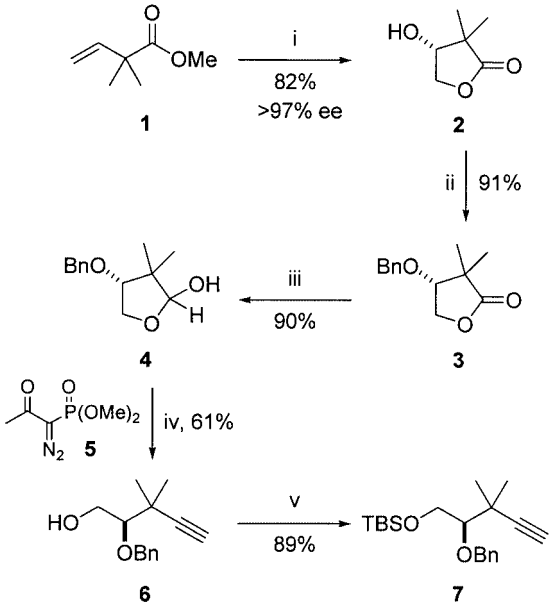


Scheme 1. Retrosynthetic analysis for the spiroketal fragment **14**.

recycled yield, and the primary hydroxy group was protected with TBS to give the alkyne **7** (89%) ready for coupling.[3j]



Scheme 2. Reagents: *i*) DHQ-PYR, $K_3Fe(CN)_6$, K_2CO_3, H_2O/*t*BuOH (1:1), OsO_4, 0 °C. *ii*) CH_2Cl_2/cyclohexane (1:3), benzyl 2,2,2-trichloroacetimidate, CF_3SO_3H, 35 °C. *iii*) DIBAL-H, PhMe, –78 °C. *iv*) **5**, K_2CO_3, MeOH, 36 °C. *v*) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

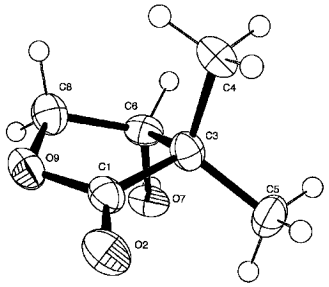
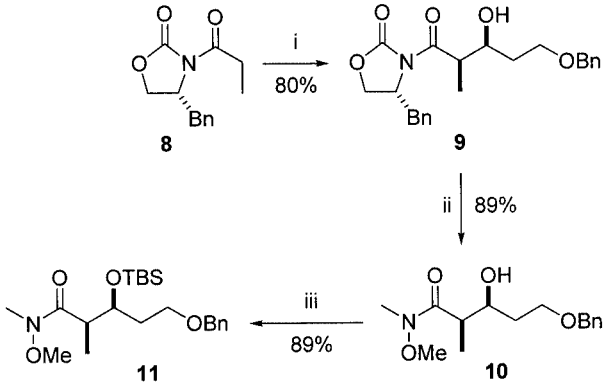


Figure 2. Crystal structure of lactone **2**.

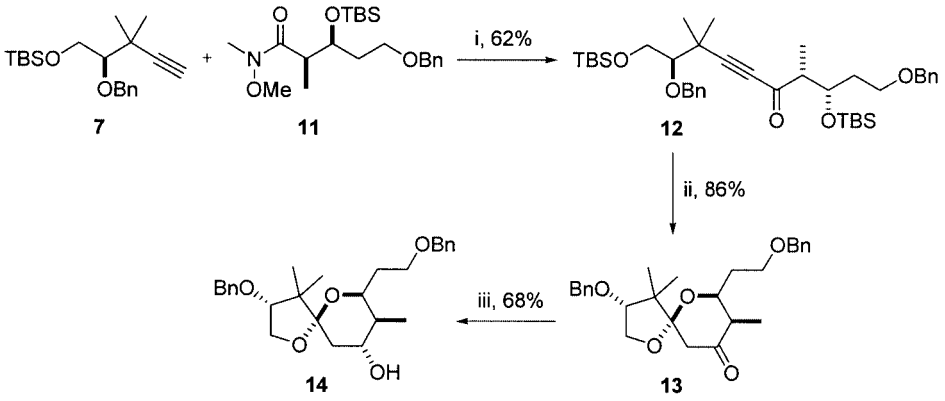
The enantiopure Weinreb amide **11** fragment was prepared as previously reported, by an Evans *syn*-selective aldol reaction[11] between (4*R*)-4-benzyl-3-propionyl-2-oxazolidinone (**8**) and 3-(benzyloxy)propionaldehyde to give the desired **9** in 80% yield and 99% *ee* (Scheme 3). Synthesis of the Weinreb amide **10** from a different propionyloxazolidinone has been reported previously in the literature.[12] In our case conversion of **9** into **10** succeeded in 89% yield, and TBS protection (TBSOTf, 2,6-lutidine, 89%) gave the desired coupling partner **11**.



Scheme 3. Reagents: *i*) **8**, Bu_2BOTf, Et_3N, CH_2Cl_2, $T < 2$ °C; then $BnOCH_2CH_2CHO$, –77 °C. *ii*) MeOMeNH·HCl, $AlMe_3$, THF, 0 °C. *iii*) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

Weinreb–Nahm-type coupling of alkyne **7** and the Weinreb amide **11** produced alkynone **12** in 62% yield (Scheme 4).[13] The yield was lower than previously reported, due to some unreacted starting materials remaining. The stepwise DIHMA[5] method afforded the spirocycle as a single enantiomer (86%). A DPFGSE-NOE experiment between C(23)H and C(22)H/C(16)H_2 ensured the correct conformation (calyculin numbering; see also Figure 3). Stereoselective reduction of spiroketal **13** with L-Selectride afforded the desired axial diastereomer **14** in 68% yield.[14]

The reaction mechanism for the cyclisation of the sterically highly hindered 1,6-dioxaspiro[4.5]decane spiroketal remained open (Scheme 5). In order to shed light on this matter, we conducted the spirocyclization, catalysed by CSA, in the NMR tube in deuterated methanol. The reaction was monitored at regular intervals. The TBS protection is cleaved from the primary alcohol group first (as evidenced by the immediate disappearance of the signals at about 4.0 and 3.8 ppm, Figure 4). After 0.5 h the first trace



Scheme 4. Reagents: *i*) BuLi, **7**, then **11**, THF –78 °C. *ii*) CSA, MeOH, then *p*TsOH, PhH, room temp. *iii*) L-Selectride, THF, –78 °C.

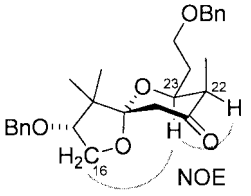
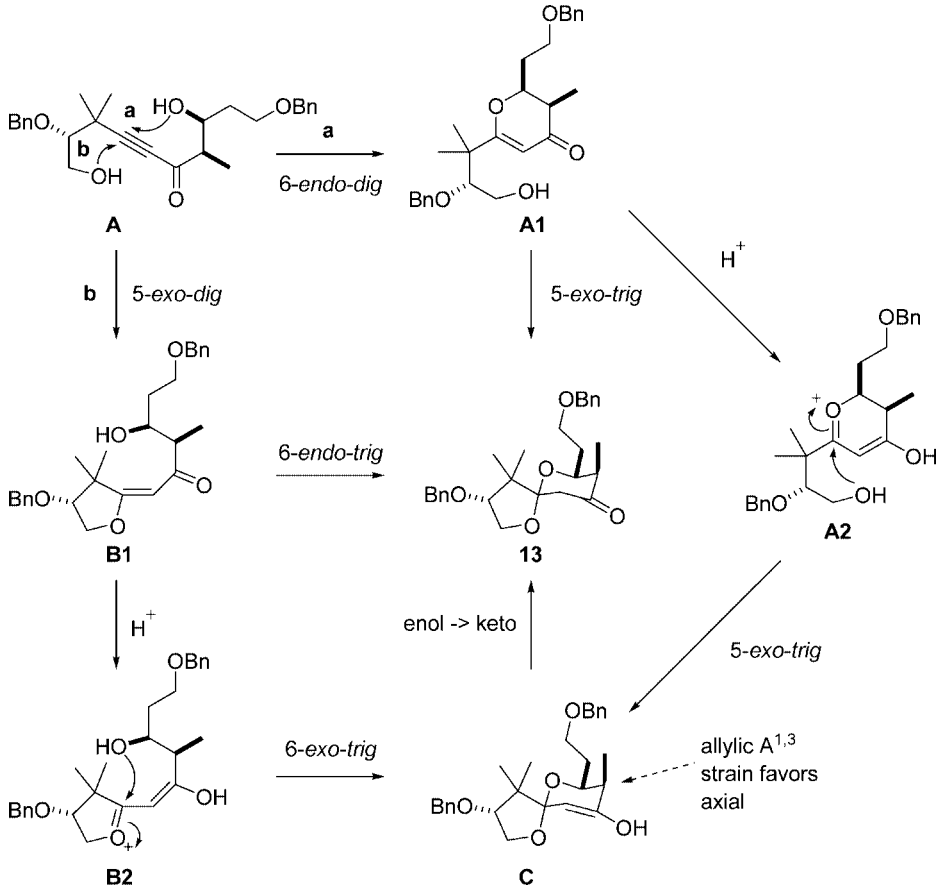


Figure 3. Double-pulsed field-gradient spin-echo (DPFGSE) NOE experiment.

of the six-membered ring in H(22) at 4.2 ppm can be seen, and signals around 3.95 and 3.75 ppm start to appear (CH_2-16), disappearing later and being replaced by the signals of the final spirocycle at ca. 3.75 and 3.80 ppm. In accordance with Baldwin's rules for ring-closure,[15] the 6-*endo-dig* cyclisation is clearly favourable, whereas the 5-*exo-dig* process is less favoured.[16]

The suggested reaction path is therefore path **a** (Scheme 5). However, it is impossible to distinguish whether



Scheme 5. Possible reaction pathways.

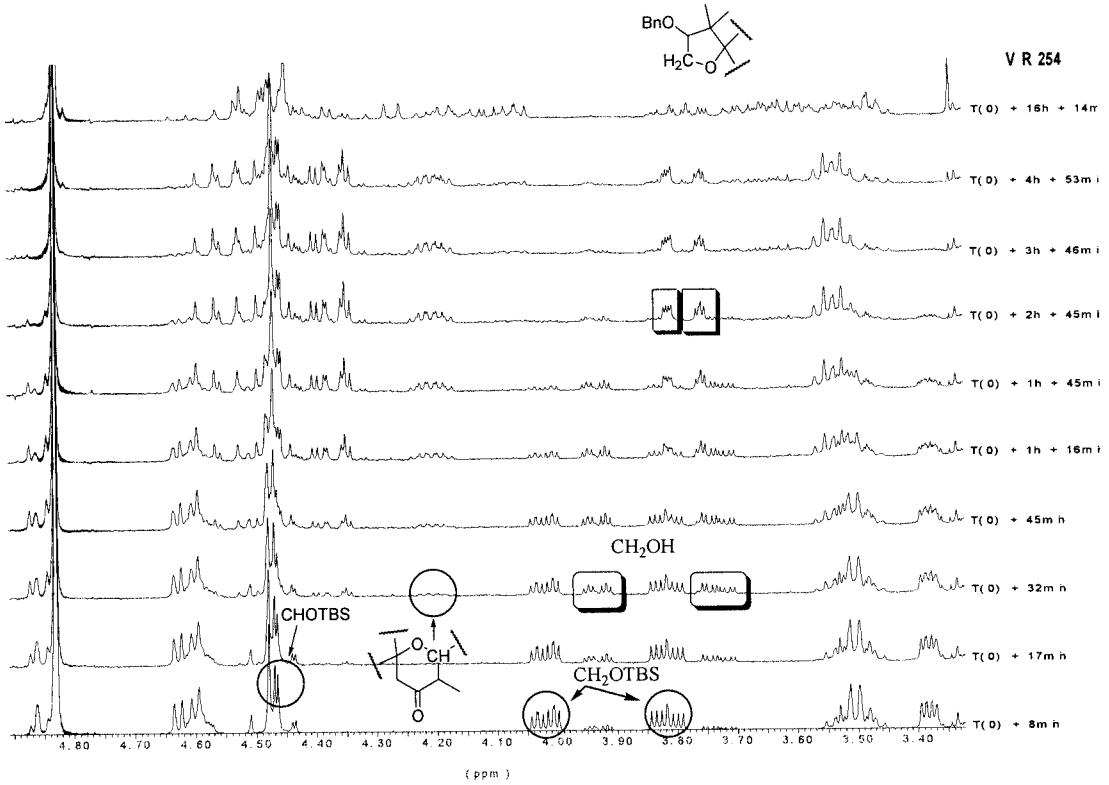


Figure 4. Reaction *T*(0) + 8 min to *T*(0) +16 h 14 min.

the spirocyclization occurs directly from **A1** or through the intermediates **A2** and **C**.

Conclusions

We have presented a stereoselective route to obtain the spiroketal fragment of calyculin C. We also succeeded in discovering that cyclization mechanism follows Baldwin's rules and proceeds first through a six-membered ring (6-*endo*-*dig*) followed by a five-membered ring cyclization (5-*exo*-*trig*). Application in the total synthesis of calyculin C is under investigation.

Experimental Section

General: All reactions were conducted under positive pressure of argon. THF was distilled prior to use from sodium-benzophenone, MeOH from $Mg(OMe)_2$ and toluene from sodium. Other solvents were p.a. grade. Melting points, determined on a Gallenkamp MFB-595 melting point apparatus, were not corrected. TLC was conducted on Merck 0.25 mm silica gel 60 F plates and samples were viewed with UV light, anisaldehyde, PMA and ninhydrin staining. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh) as a stationary phase. HPLC was performed with a Waters 501 pump, a Waters 486 tuneable absorbance detector and a Waters 746 data module with the following columns: Shandon Hypersil Silica Column with Waters Guard-Pak™ precolumn fitted with Resolve™ silica inserts for normal phase chromatography and Daicel Chiralcel OD 25 cm × 0.46 cm with Daicel Chiracel OD 5 cm × 0.46 cm precolumn for chiral chromatography. Optical rotations were measured at 20 °C on a Perkin–Elmer 343 polarimeter. IR spectra were measured with a Perkin–Elmer Spectrum One instrument. Elemental analyses were performed with a Perkin–Elmer 2400 CHN Elemental Analyzer. HRMS spectra were measured with Jeol JMS-DX 303 and Micromass LCT instruments. NMR spectra were measured with a Bruker AMX 400 (^{1}H 400.13 MHz, ^{13}C 100.61 MHz). The single-crystal X-ray diffraction for lactone **2** was done with a Nonius KappaCCD diffractometer with graphite-monochromatized Mo-*Kα* (λ = 0.71073 Å) radiation. Collect software was used in the measurement and DENZO-SMN[17] in the processing of the data. The structure was solved and refined by full-matrix least-squares on F^2 with the WinGX software package utilizing SHELXS97 and SHELXL97 modules.[18–20] Hydrogen atoms were refined by a riding model. Absorption correction was not performed for the compound.

CCDC-255366 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam-.ac.uk].

(*R*)-4-Hydroxy-3,3-dimethyl-4,5-dihydro-3*H*-furan-2-one (2): DHQ-PYR (0.264 g, 0.30 mmol, 1.0 mol%), $K_3Fe(CN)_6$ (29.6 g, 90 mmol, 300 mol%) and K_2CO_3 (12.4 g, 90 mmol, 300 mol%) were dissolved in a mixture of H_2O (140 mL) and *t*BuOH (140 mL), followed by OsO_4 (1.5 mL of 2.5 wt.-% in 2-methylpropan-2-ol). The reaction mixture was cooled to 0 °C, and compound **1** (3.85 g, 30 mmol, 100 mol%) in a mixture of H_2O (10 mL) and *t*BuOH (10 mL) was added. This mixture was stirred overnight at 0 °C and after 18.5 h was quenched by addition of Na_2SO_3 (37.9 g) and H_2O (50 mL). The phases were separated, the aqueous phase

was extracted five times with EtOAc (50 mL), and the combined organic phases were then extracted once with brine (50 mL) and dried with $MgSO_4$. The crude product was filtered through a silica pad with 50% EtOAc/hexane and pure EtOAc. The product was purified by crystallizing it twice from a mixture of pentane (10 mL) and EtOAc (2.8 mL) to afford **2** (3.2 g, 82%, 97.5% *ee*) as white needle-like crystals; m.p. 59–60 °C; R_f (50% EtOAc/hexane, UV/permanganate) = 0.20; R_t (GC, cyclodextrin beta, inj. temp. 270 °C, vel. 28, 100–220 °C 4 °C·min^{-1}, 220 °C 30 min, det. temp. 270 °C) = 20.61 min. $[\alpha]_D^{20}$ = –5.1 (*c* = 1.0; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 6 H, C*H*$_3$), 2.51 (d, *J* = 4.4 Hz, 1 H, O*H*), 4.13 (dd, *J* = 3.2, 10.0 Hz, 1 H, CH$_a$*H*$_b$), 4.20 (ddd, *J* = 3.2, 4.4, 4.4 Hz, 1 H, C*H*), 4.45 (dd, *J* = 4.4, 10.0 Hz, 1 H, C*H*$_a$H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 22.7, 43.6, 71.9, 75.5, 181.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 1760, 3459 cm^{-1}. $C_6H_{10}O_3$ (130.1418): C 55.37, H 7.74; found C 55.13, H, 7.83.

(*R*)-4-(Benzyloxy)-3,3-dimethyl-4,5-dihydro-3*H*-furan-2-one (3): Lactone **2** (0.105 g, 0.807 mmol, 100 mol%) was dissolved in a mixture of CH_2Cl_2 (2 mL) and cyclohexane (6 mL). Benzyl 2,2,2-trichloroacetimidate (0.360 mL, 1.94 mmol, 240 mol%) and CF_3SO_3H (17 μL, 0.192 mmol, 24 mol%) were added, and the reaction mixture was heated to 35 °C. White, solid trichloroacetamide appeared in the yellow reaction mixture, and was filtered off after three hours and washed through twice with cyclohexane (5 mL). The combined organic phases were extracted with sat. $NaHCO_3$ (2 × 10 mL) and once with brine (10 mL) and were dried with $MgSO_4$. Product **3** was purified by step gradient column chromatography (10%, 15% and 25% MTBE/hexane in 100 mL portions) affording the light yellow oil 0.163 g (91%). R_f (50% EtOAc/hexane, UV/PMA) = 0.46. $[\alpha]_D^{20}$ = –5.3 (*c* = 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, C*H*$_3$), 1.28 (s, 3 H, C*H*$_3$), 3.90 (dd, *J* = 4.0, 5.2 Hz, 1 H, C*H*), 4.15 (dd, *J* = 4.0, 10.0 Hz, 1 H, CH$_a$*H*$_b$), 4.31 (dd, *J* = 5.2, 10.0 Hz, 1 H, CH$_a$*H*$_b$), 4.58 (d, J_{AB} = = 12.1 Hz, 2 H, C*H*$_2$Ph), 7.29–7.38 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 23.4, 42.9, 68.9, 72.1, 81.9, 127.5, 128.0, 128.5, 137.4, 180.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 1773 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{13}H_{16}O_3Na$: 243.0997; found 243.0979.

(4*R*)-4-(Benzyloxy)-3,3-dimethyl-tetrahydrofuran-2-ol (4): Lactone **3** (0.342 g, 1.55 mmol, 100 mol%) in toluene (15 mL) was cooled to –78 °C. DIBAL-H (1 M in toluene, 2.64 mL, 2.64 mmol, 170 mol%) was added over 10 min. After 11 min, the reaction was quenched by addition of MeOH (1.0 mL) and allowed to warm up to room temp. The solution was partitioned between HCl (1 M, 25 mL) and EtOAc (25 mL) and was stirred for an hour. The phases were separated and the aqueous phase was extracted three times with EtOAc (15 mL). The combined organic phases were washed once with sat. $NaHCO_3$ (10 mL) and brine (10 mL) and were dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (15%, 20%, 25%, and 30% EtOAc/hexane in 200 mL portions), affording pure **4** (0.310 g, 90%) as a slightly yellow oil. R_f (50% EtOAc/hexane, UV/PMA) = 0.41. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, C*H*$_3$), 1.23 (s, 3 H, C*H*$_3$), 3.56 (d, *J* = 12.0 Hz, 1 H, CHO*H*), 3.61 (d, *J* = 3.8 Hz, 1 H, C*H*OBn), 4.05 (dd, *J* = 10.2, 3.8 Hz, 1 H, C*H*$_a$H$_b$), 4.22 (d, *J* = 10.2 Hz, 1 H, CH$_a$*H*$_b$), 4.43 (d, J_{AB} = 11.9 Hz, 1 H, C*H*$_a$H$_b$Ph), 4.64 (d, J_{AB} = 11.9 Hz, 1 H, CH$_a$*H*$_b$Ph), 4.80 (d, *J* = 11.0 Hz, 1 H, C*H*OH), 7.29–7.38 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 24.0, 46.5, 70.9, 72.1, 85.3, 105.2, 127.6, 127.9, 128.5, 137.4 ppm. IR (film): $\tilde{\nu}_{max}$ = 1725, 3435 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{13}H_{18}O_3Na$: 245.1154; found 245.1171.

(*R*)-2-(Benzyloxy)-3,3-dimethylpent-4-yn-1-ol (6): Lactol **4** (0.148 g, 0.666 mmol, 100 mol%) was dissolved in dry MeOH (7 mL), and dimethyl (1-diazo-2-oxopropyl)phosphonate (**5**) (0.264 g, 1.332 mmol, 200 mol%) and K_2CO_3 (0.184 g, 1.332 mmol, 200 mol%) were added. The reaction mixture was warmed to 33 °C and allowed to stir for five days, during which more phosphonate **5** (0.066 g, 0.33 mmol, 50 mol%) and K_2CO_3 (0.046 g, 0.33 mmol, 50 mol%) were added (five times, once a day). The blue-green reaction mixture was evaporated to dryness and dissolved in EtOAc and H_2O (1:1 mixture, 20 mL). The phases were separated and the aqueous one was extracted four times with EtOAc (10 mL) and once with brine (10 mL) and dried with $MgSO_4$. Crude **6** was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc/hexane in 250 mL portions), affording a slightly yellow oil (0.088 g, 61%). R_f (50% EtOAc/Hex, UV/anisaldehyde) = 0.48; R_t (GC, cyclodextrin beta, inj. temp. 270 °C, vel. 28, 100–220 °C 4 °C·min^{-1}, 220 °C 30 min, det. temp. 270 °C) = 27.63 min. $[\alpha]_D^{20}$ = 0.58 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, C*H*$_3$), 1.30 (s, 3 H, C*H*$_3$), 1.88 (dd, *J* = 7.4, 5.3 Hz, 1 H, O*H*), 2.19 (s, 1 H, C(CH$_3$)$_2$CC*H*), 3.40 (dd, *J* = 6.6, 3.8 Hz, 1 H, C*H*OBn), 3.77 (ddd, *J* = 11.8, 6.6, 5.3 Hz, 1 H, C*H*$_a$H$_b$OH), 3.92 (ddd, *J* = 11.8, 7.4, 3.8 Hz, 1 H, CH$_a$*H*$_b$OH), 4.72 (d, J_{AB} = 11.5 Hz, 1 H, C*H*$_a$H$_b$Ph), 4.78 (d, J_{AB} = 11.5 Hz, 1 H, CH$_a$*H*$_b$Ph), 7.30–7.39 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 26.7, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.8, 128.5, 138.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 1029, 1102, 3295, 3436 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{14}H_{18}O_2NaSi$ 241.1204; found 241.1206.

[(*R*)-2-(Benzyloxy)-3,3-dimethylpent-4-ynyloxy]-*tert*-butyldimethylsilane (7): The alcohol **6** (0.073 g, 0.334 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (4 mL) and cooled to 0 °C. 2,6-Lutidine (0.156 mL, 1.34 mmol, 400 mol%) was added, and the reaction mixture was allowed to stir for 1 h 13 min, after which TBSOTf (0.154 mL, 0.67 mmol, 200 mol%) was added. After 20 min the reaction was quenched with sat. K_2CO_3 (2 mL). The mixture was partitioned between water and Et_2O (20 mL, 1:1) and the phases were separated. The aqueous phase was extracted four times with Et_2O (10 mL) and the combined organic phase was dried with $MgSO_4$. Crude **7** was purified by column chromatography (10% EtOAc/hexane), affording pure product (0.099 g, 89%) as a slightly yellow oil. R_f (50% EtOAc/hexane, UV/PMA) = 0.72. $[\alpha]_D^{20}$ = –1.1 (*c* = 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, C*H*$_3$), 0.08 (s, 3 H, C*H*$_3$), 0.92 (s, 9 H, C(C*H*$_3$)$_3$), 1.20 (s, 3 H, C*H*$_3$), 1.27 (s, 3 H, C*H*$_3$), 2.14 (s, 1 H, C(CH$_3$)$_2$CC*H*), 3.36 (dd, *J* = 7.3, 2.7 Hz, 1 H, C*H*), 3.80 (dd, *J* = 10.8, 7.3 Hz, 1 H, OC*H*$_a$H$_b$), 4.10 (dd, *J* = 10.8, 2.7 Hz, 1 H, OCH$_a$*H*$_b$), 4.65 (d, J_{AB} = = 11.5 Hz, 1 H, PhC*H*$_a$H$_b$), 4.92 (d, J_{AB} = 11.5 Hz, 1 H, PhCH$_a$*H*$_b$), 7.24–7.38 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –5.3, 18.2, 24.4, 25.9, 27.0, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.1, 139.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 837, 1069, 1256, 3309 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{20}H_{32}O_2NaSi$ 355.2069; found 355.2079.

(*R*)-4-Benzyl-3-[(2*R*,3*S*)-5-(benzyloxy)-3-hydroxy-2-methylpentanoyl]-2-oxazolidinone (9): (*R*)-4-Benzyl-3-propionyl-2-oxazolidinone (**8**) (1.0 g, 4.3 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C, after which dibutylboron triflate (1 M in CH_2Cl_2, 6.75 mL, 6.8 mmol, 157 mol%) was added dropwise, with the internal temperature being maintained under 2 °C. The colour in the reaction mixture changed to brown, but when Et_3N (1.02 mL, 7.3 mmol, 171 mol%) was added ($T \leq 2$ °C) it turned from transparent to yellow and shortly afterwards to burgundy. After 40 minutes the reaction mixture was cooled to –77 °C and 3-(benzyloxy)propionaldehyde (1.02 g, 6.2 mmol, 144 mol%), dissolved in dry CH_2Cl_2 (2 mL), was added slowly (35 min), with the internal temperature being kept stable. Stirring was continued for a further 3 h at –77 °C and then for 30 min at 0 °C. Phosphate

buffer (10 mL, pH 7.0) and methanol (8 mL) were added, and the mixture was cooled to –10 °C, before slow (15 min) addition of H_2O_2 (30%) and MeOH (1:1, 20 mL). The mixture was then stirred for 30 min at 0 °C, after which the organic solvents were evaporated, Et_2O was added and reaction mixture was cooled to –10 °C. Sat. aqueous $Na_2S_2O_3$ (17 mL) was added slowly (20 min) and the phases were separated. The aqueous phase was extracted three times with Et_2O (10 mL) and the combined organic phases were washed once with sat. $NaHCO_3$ (12 mL) and brine (8 mL) and dried with $MgSO_4$. Crude **9** was purified by gradient flash column chromatography (15%, 20% and 25% EtOAc/Hex in 200 mL portions), affording pure **9** (1.36 g, 80%, 99% *ee*). R_f (50% EtOAc/Hex, UV/acid-PMA) = 0.31. $[\alpha]_D^{20}$ = –44.7 (*c* = 1.0; $CHCl_3$); R_t (HPLC, Daicel, Chiracel^R OD, 250 mm, 4.6 mm, 20% IPA/Hex, 254 nm, 1.0 mL·min^{-1}) = 17.52 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.71–1.80 (m, 1 H, CH(OH)CH_aH$_b$), 1.83–1.92 (m, 1 H, CH(OH)CH$_a$*H*$_b$), 2.77 (dd, *J* = 13.4, 9.5 Hz, 1 H, PhCH_aH$_b$), 3.25 (dd, *J* = 13.4, 3.3 Hz, 1 H, PhCH$_a$*H*$_b$), 3.34 (d, *J* = 2.4 Hz, 1 H, O*H*), 3.63–3.73 (m, 2 H, CH_2OBn), 3.82 (dq, *J* = 7.0, 3.8 Hz, 1 H, C*H*Me), 4.13–4.20 (m, OCH_2CH(Bn)N, 3 H, C*H*OH), 4.51 (s, 2 H, OCH_2Ph), 4.67 (m, 1 H, OCH$_2$C*H*(Bn)N), 7.19–7.34 (m, 10 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 33.7, 37.7, 42.5, 55.2, 66.1, 68.3, 70.4, 73.2, 127.3, 127.6, 128.4, 128.4, 128.9, 129.4, 135.1, 138.0, 153.0, 176.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 1111, 1694, 1780, 3480 cm^{-1}. HRMS (EI$^+$) calcd. for $C_{23}H_{27}NO_5Na$ 420.1787; found 420.1815.

(2*R*,3*S*)-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide (10): A 25 mL two-necked flask was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (0.54 g, 5.5 mmol, 220 mol%) and THF (4 mL). The suspension was cooled to –10 °C in a NaCl/ice bath and $AlMe_3$ (2 M in Hexane, 2.64 mL, 5.3 mmol, 210 mol%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at room temp., after which it was cooled again to –10 °C. Oxazolidinone **9** (1.0 g, 2.5 mmol, 100 mol%) dissolved in a mixture (4:5) of CH_2Cl_2 (2.9 mL) and THF (4 mL) was slowly added. The mixture was stirred for 3 h 15 min at 0 °C and at room temp. for another 1 h 30 min, after which it was poured into a pre-cooled 0 °C mixture (1:1, 32 mL) of HCl [0.5 M] and CH_2Cl_2. This was stirred for 2 h at 0 °C and the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2 (30 mL) and the combined organic phases were washed once with H_2O (40 mL) and dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (30%, 40%, 50% EtOAc/hexane and pure EtOAc in 700 mL fractions), affording **10** as a yellow oil (0.617 g, 89%). R_f (50% EtOAc/Hex, UV/PMA) = 0.16. $[\alpha]_D^{20}$ = –1.8 (*c* = 0.5; $CHCl_3$) (ref.[12] $[\alpha]_D^{26}$ = –11.1 (*c* = 1.65; $CHCl_3$)). NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$), 1.67–1.74 (m, 1 H, CH(OH)CH_aH$_b$), 1.80–1.89 (m, 1 H, CH(OH)CH$_a$*H*$_b$), 2.93 (br. s, 1 H, C*H*Me), 3.18 (s, 3 H, C*H*$_3$N), 3.63–3.71 (m, 2 H, CH_2OBn), 3.66 (s, 3 H, NOC*H*$_3$), 3.87 (s, 1 H, O*H*), 4.05 (dtd, *J* = 9.0, 3.7, 1.6 Hz, 1 H, C*H*OH), 4.52 (s, 2 H, OCH_2Ph), 7.26–7.34 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 31.9, 34.0, 39.5, 61.5, 68.4, 70.4, 73.3, 127.6, 127.7, 128.4, 138.2, 177.8 ppm. IR (liq. $CHCl_3$): $\tilde{\nu}_{max}$ = 1637, 3480 cm^{-1}. ^{1}H HRMS (TOF MS EI$^+$) calcd. for $C_{15}H_{23}NO_4Na$ 304.1525; found 304.1519.

(2*R*,3*S*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpentanamide (11): The alcohol **10** (0.697 g, 2.5 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. 2,6-Lutidine (1.16 mL, 10 mmol, 400 mol%) was added, and the reaction mixture was allowed to stir for 22 min, after which TBSOTf (1.72 mL, 7.5 mmol, 200 mol%) was added dropwise. After 15 min the reaction was quenched with sat. K_2CO_3 (20 mL). The phases were separated and the organic phase was washed five times with aq. H_3PO_4 (0.5 M) and once with H_2O (20 mL). The combined organic phases were dried with $MgSO_4$. Crude **11** was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc/hexane in 500 mL portions), affording pure **11** (0.512 g, 89%) as a yellow oil. R_f (50% EtOAc/Hex, UV/PMA) = 0.45. $[\alpha]_D^{20}$ = +2.3 (*c* = 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, C*H*$_3$), 0.06 (s, 3 H, C*H*$_3$), 0.88 (s, 9 H, C(C*H*$_3$)$_3$), 1.13 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH), 1.82–1.88 (m, 2 H, CH(OTBS)CH_2), 2.98 (br. s, 1 H, C*H*Me), 3.13 (s, 3 H, C*H*$_3$N), 3.49–3.62 (m, 2 H, CH_2OBn), 3.59 (s, 3 H, NOC*H*$_3$), 4.04 (td, *J* = 7.8, 5.0 Hz, 1 H, C*H*OTBS), 4.45 (d, J_{AB} = 12.1 Hz, 1 H, OCH_aH$_b$Ph), 4.49 (d, J_{AB} = 12.1 Hz, 1 H, OCH$_a$*H*$_b$Ph), 7.23–7.34 (m, 5 H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.4, 14.4, 18.1, 25.9, 32.1, 35.4, 41.3, 61.2, 66.5, 71.4, 72.9, 127.4, 127.7, 128.3, 138.6, 176.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 836, 1103, 1663 cm^{-1}. HRMS (EI$^+$) calcd. for $C_{21}H_{37}NO_4NaSi$ 418.2390; found 418.2397.

(3*S*,4*R*,9*R*)-1,9-Bis(benzyloxy)-3,10-bis(*tert*-butylsilyloxy)-4,8,8-trimethyldec-6-yn-5-one (12): The alkyne **7** (0.057 g, 0.172 mmol, 200 mol%) was dissolved in dry THF (1.7 mL) and cooled to –78 °C. BuLi (2.25 M, 84 μL, 0.189 mmol, 220 mol%) was added, and the reaction mixture was allowed to stir for 1 h, after which the Weinreb amide **11** (0.034 g, 0.086 mmol, 100 mol%) in dry THF (0.9 mL) was added. After 55 min, the reaction mixture was allowed to warm up to room temp. and after another 3 h 21 min it was quenched with H_2O (5 mL). Et_2O (10 mL) and brine (5 mL) were added and the phases were separated. The aqueous phase was extracted three times with Et_2O (10 mL) and the combined organic phases were dried with $MgSO_4$. The crude product was purified by step gradient chromatography (5%, 10% and 15% EtOAc/hexane in 15 mL portions), affording **12** (0.035 g, 62%) as a yellow oil. R_f (50% EtOAc/Hex, UV/PMA) = 0.73. $[\alpha]_D^{20}$ = –1.1 (*c* = 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, C*H*$_3$Si), 0.03 (s, 3 H, C*H*$_3$Si), 0.06 (s, 3 H, C*H*$_3$Si), 0.07 (s, 3 H, C*H*$_3$Si), 0.84 (s, 9 H, C(C*H*$_3$)$_3$), 0.91 (s, 9 H, C(C*H*$_3$)$_3$), 1.13 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CH), 1.24 (s, 3 H, C*H*$_3$C), 1.28 (s, 3 H, C*H*$_3$C), 1.77–1.92 (m, *J* = 14.0, 6.4 Hz, 2 H, CH(OTBS)CH_2), 2.57 (qd, *J* = 6.9, 3.8 Hz, 1 H, C*H*Me), 3.38 (dd, *J* = 7.1, 3.0 Hz, 1 H, C*H*OBn), 3.49 (t, *J* = 6.4 Hz, 2 H, CH_2OBn), 3.78 (dd, *J* = 10.8, 7.1 Hz, 1 H, CHCH_aH$_b$OTBS), 4.00 (dd, *J* = 10.8, 3.0 Hz, 1 H, CHCH$_a$*H*$_b$OTBS), 4.46–4.50 (m, 1 H, C*H*OTBS), 4.52 (d, J_{AB} = 12.0 Hz, 1 H, OCH_aH$_b$Ph), 4.48 (d, J_{AB} = 12.0 Hz, 1 H, OCH$_a$*H*$_b$Ph), 4.60 (d, J_{AB} = 11.5 Hz, 1 H, CHOCH_aH$_b$Ph), 4.88 (d, J_{AB} = 11.5 Hz, 1 H, CHOCH$_a$*H*$_b$Ph), 7.25–7.33 (m, 10 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –5.4, –4.5, –4.4, 9.6, 18.1, 18.2, 23.9, 25.8, 25.9, 26.1, 35.5, 35.7, 53.5, 65.1, 66.7, 70.0, 73.0, 74.5, 81.3, 85.5, 85.5, 99.3, 127.4, 127.5, 127.5, 127.7, 128.2, 128.3, 138.4, 138.8, 190.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 836, 1095, 1256, 1677, 2209 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{39}H_{62}O_5NaSi_2$ 689.4034; found 689.4040.

(3*R*,5*S*,7*S*,8*R*)-3-(Benzyloxy)-7-[2-(benzyloxy)ethyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one (13): The ynone **12** (21.7 mg, 32.5 μmol, 100 mol%) was dissolved in dry MeOH (0.5 mL), and camphorsulfonic acid (1.4 mg, 6.0 μmol, 18 mol%) was added. The reaction mixture was allowed to stir at room temp. for 2 h 30 min, after which the solvent was evaporated. The residue was dissolved in dry benzene (1 mL) and the reaction mixture was stirred for 15 min, after which *p*TsOH (2.7 mg, 14 μmol, 44 mol%) was added. Stirring was continued for another 18 h. The reaction was quenched by addition of TEA (0.02 mL), followed by sat. $NaHCO_3$ (1 mL). H_2O (1 mL) and toluene (3 mL) were added, the phases were separated, and the aqueous one was extracted three times with toluene (3 mL). The combined organic phases were extracted once

with brine (5 mL) and dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (5%, 10%, 15% and 20% EtOAc/hexane in 50 mL portions), affording **13** (12.3 mg, 86%) as a light yellow oil. R_f (50% EtOAc/Hex, UV/PMA) = 0.61. $[\alpha]_D^{20}$ = –5.7 (*c* = 0.5; $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3 H, CH_3), 1.07 (d, *J* = 7.1 Hz, 3 H, CHCH_3), 1.16 (s, 3 H, CH_3), 1.64–1.72 (m, 1 H, CH_aH$_b$CH$_2$OBn), 1.81–1.90 (m, 1 H, CH$_a$$H_bCH_2$OBn), 2.28–2.34 (m, 1 H, C*H*Me), 2.30 (d, J_{AB} = 14.9 Hz, 1 H, CH$_2$OCH_aH$_b$Ph), 2.56 (d, J_{AB} = 14.9 Hz, 1 H, CH$_2$OCH$_a$$H_b$Ph), 3.46–3.55 (m, 2 H, CH_2OBn), 3.59 (dd, *J* = 8.7, 6.7 Hz, 1 H, CH(OBn)CH_aH$_b$O), 3.82 (dd, *J* = 8.7, 7.9 Hz, 1 H, CH(OBn)CH$_a$$H_b$O), 4.10 (dd, *J* = 7.6, 6.7 Hz, 1 H, C*H*OBn), 4.22 (td, *J* = 9.8, 3.0 Hz, 1 H, C*H*CH$_2$CH$_2$OBn), 4.43 (dd, J_{AB} = 11.9 Hz, 1 H, CHOCH$_a$$H_b$Ph), 4.44 (d, J_{AB} = 11.8 Hz, 1 H, CCH_aH$_b$C(O)CH), 4.47 (dd, J_{AB} = 11.8 Hz, 2 H, CCH$_a$$H_b$C(O)CH), 4.54 (d, J_{AB} = 11.9 Hz, 1 H, CHOCH_aH$_b$Ph), 7.28–7.37 (m, 10 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 17.2, 20.3, 31.7, 40.9, 47.6, 48.4, 67.0, 67.2, 69.3, 73.0, 73.1, 84.6, 110.1, 127.4, 127.7, 127.7, 128.4, 128.4, 138.2, 138.4, 209.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 1102, 1719 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{27}H_{34}O_5Na$ 461.2304; found 461.2306.

(3*R*,5*S*,7*S*,8*R*,9*R*)-3-(Benzyloxy)-7-[2-(benzyloxy)ethyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-ol (14): The spiroketal **13** (6 mg, 13.7 μmol, 100 mol%) was dissolved in dry THF (0.1 mL) and cooled to –78 °C. L-Selectride (41 μL, 41 μmol, 300 mol%) was added dropwise, and the reaction mixture was allowed to stir for 1 h 23 min before quenching by addition of MeOH (0.2 mL), NaOH (2.0 M, 0.1 mL), H_2O_2 (30%, 0.1 mL) and THF (2 mL). The reaction mixture was allowed to stir for 37 min at 0 °C and 38 min at room temp., after which H_2O (1 mL) and Et_2O (3 mL) were added. The phases were separated and the aqueous one was extracted five times with Et_2O (3 mL). The combined organic phases were extracted once with brine (5 mL) and dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (10%, 20%, 30%, 40% and 50% EtOAc/hexane in 20 mL portions), affording **14** (4.1 mg, 68%) as a colourless oil. R_f (50% EtOAc/Hex, UV/PMA) = 0.51. $[\alpha]_D^{20}$ = –9.8 (*c* = 0.31; $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.2 Hz, 3 H, CHCH_3), 0.93 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.61–1.67 (m, 3 H, C*H*Me, CH_aH$_b$CH$_2$OBn, CCH_aH$_b$CH(OH)CH), 1.72–1.79 (m, 2 H, CH$_a$$H_bCH_2OBn, CCH_a$$H_b$CH(OH)CH), 3.45–3.54 (m, 2 H, CH_2OBn), 3.60 (dd, *J* = 8.6, 6.5 Hz, 1 H, CH(OBn)CH_aH$_b$O), 3.65 (d, *J* = 9.7 Hz, 1 H, O*H*), 3.79 (qd, *J* = 9.7, 3.1 Hz, 1 H, C*H*OH), 3.86 (dd, *J* = 8.6, 7.8 Hz, 1 H, CH(OBn)CH$_a$$H_b$O), 4.05 (dd, *J* = 7.7, 6.5 Hz, 1 H, C*H*OBn), 4.22 (td, *J* = 9.9, 2.9 Hz, 1 H, C*H*CH$_2$CH$_2$OBn), 4.43 (d, J_{AB} = 11.8 Hz, 1 H, OCH_aH$_b$Ph), 4.46 (d, J_{AB} = 12.0 Hz, 1 H, OCH_aH$_b$Ph), 4.50 (d, J_{AB} = 12.0 Hz, 1 H, OCH$_a$$H_b$Ph), 4.54 (d, J_{AB} = 11.8 Hz, 1 H, OCH$_a$$H_b$Ph), 7.28–7.38 (m, 10 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 17.3, 20.4, 28.3, 29.7, 32.6, 37.9, 47.8, 63.4, 67.5, 69.5, 71.0, 73.0, 84.7, 109.5, 127.4, 127.6, 127.7, 128.4, 138.5, 138.5 ppm. IR (liq): $\tilde{\nu}_{max}$ = 1248, 3608 cm^{-1}. HRMS (TOF MS EI$^+$) calcd. for $C_{27}H_{36}O_5Na$ 463.2460; found 463.2469.

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