Flexible Routes to the 5-Hydroxy Acid Fragment of the Cryptophycins

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Two solutions to establishing the *anti* stereochemistry of the vicinal stereocenters in the 5-hydroxy acid subunit of cryptophycin, based on initial Evans *syn* aldol reactions between an *N*-(propionyl)oxazolidinone **4** and a C_3 aldehyde, were developed. In the first route, the secondary hydroxy group was inverted by use of Mitsunobu reaction conditions, whereas the second route features an inversion of the methyl-bearing stereocenter, achieved by reductive removal of the chiral auxiliary, elimination to afford the terminal alkene, and *anti*-selective hydroboration. The aryl part can be attached either by Wittig–Horner olefination or by a modified Julia coupling. Both routes provide the hydroxy acid **16** in a very efficient manner. The substrate for the hydroboration, alkene **22**, could also be obtained from (*S*)-malic acid.

Introduction

Interference with microtubule assembly and disassembly during cell division by specific small molecules has emerged as a promising strategy in cancer therapy.[1−3] Some compounds − such as taxol, the epothilones, or discodermolide − stabilize microtubuli. On the other hand, compounds such as vinblastine, colchicine, or podophyllotoxin shift the microtubuli-tubulin equilibrium towards the tubulin protein. These kinds of compounds are supplemented by the cryptophycins, which encompass a family of about 20 macrocyclic depsipeptides.[4−7] The first representative of these depsipeptides, cryptophycin-1 (**1**), was isolated from the blue-green algae *Nostoc sp.* ATCC 53789 in 1990.[8] Cryptophycin-1 (**1**) stops the cell cycle at the G2/M-transition by inhibition of tubulin polymerization into microtubules.[9] However, the binding site seems to be different from the colchicine site. A further notable feature is that the cryptophycins are only minimally affected by multiple drug resistance in comparison with other antimitotic agents.

As depsipeptides, the cryptophycins are of particular interest in the context of the synthesis of natural product-like libraries. Thanks to their modular structures, they are ideally suited for structural variations. We have already demonstrated this strategy for the solid-phase assembly of hapalosin analogues.[10] Key to the solid-phase assembly of depsipeptides are the Fmoc protecting group for amino groups and acid-labile or silicon-based protecting groups for hydroxy functions. The synthesis of the more complicated subunits can be performed in solution. Retrosynthetically, the cryptophycins can be divided into four units.

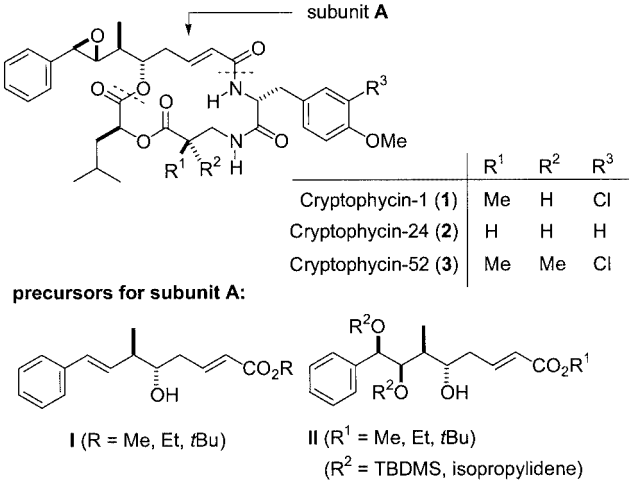

Figure 1. Structures of representative cryptophycins

Two subunits are derived from amino acids, one from an α-oxo acid, whereas the hydroxy acid (part **A**) originates from a polyketide. A synthesis of subunit **A** has to address the attachment of the aryl ring and the establishment of the *anti* stereorelationship at C-5 and C-6. The epoxide in section **A** may be derived either from the corresponding alkene (**I**) or from a *syn*-diol precursor (**II**). Depending on this, different strategies for dealing with the stereochemical issue have been developed. Thus, the *anti* stereochemistry can be set by epoxide opening,[11−13] by a *syn* aldol reaction followed by reduction of the carboxylate to a methyl group,[14,15] by crotylboration of an aldehyde,[16,17] by nucleophilic addition to a 2-methyl aldehyde,[18] by Frater alkylation of a 3-hydroxy ester,[17] or by a [2,3]-Wittig rearrangement.[19] If a diol precursor such as **II** is targeted, aldol strategies[20] or nucleophilic additions to the aldehyde derived from man-

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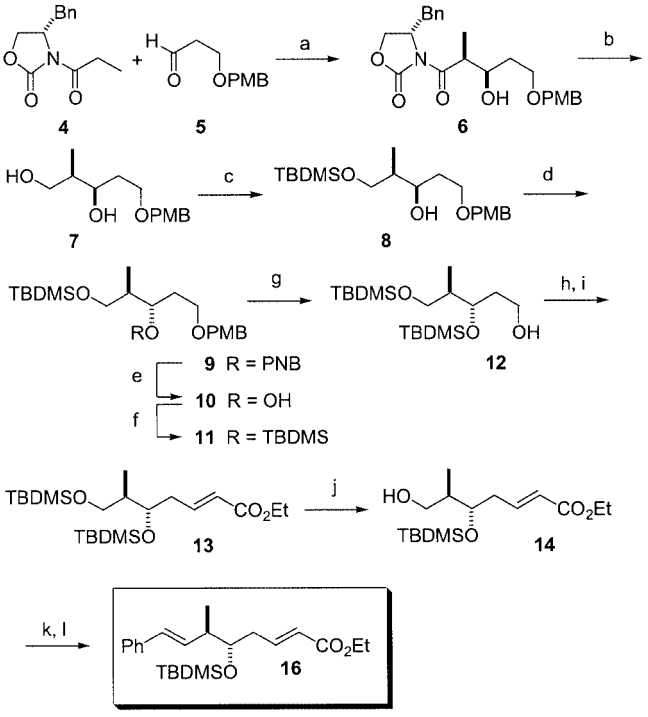
delate are possible.[21−23] In these cases the stereochemistry of one secondary alcohol is set by a directed reduction.

We sought to develop a route that is simple to perform and that allows for flexible introduction of an aryl or hetaryl group by cross-coupling and Julia or Wittig olefination. In this paper we illustrate two aldol approaches that invert either one of the stereocenters. Route 1 utilizes a Mitsunobu reaction, whereas route 2 is based on an *anti*-selective hydroboration of an alkyl 2-methylprop-2-enyl ether. In a utilization of Evans' aldol methodology,[24−26] the *N*-propionyloxazolidinone **4** was treated with the aldehyde **5** under standard conditions to give the *syn* aldol product **6**. After reductive removal of the chiral auxiliary with sodium borohydride,[27] the diol **7** was obtained, and its primary hydroxy group was temporarily protected by silylation with *tert*-butyldimethylsilyl chloride to allow the inversion of the secondary hydroxy group by treatment with *p*-nitrobenzoic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphane.[28] Basic ester hydrolysis delivered the alcohol **10**. Extension of the carbon chain on the other terminus necessitated protection of the secondary alcohol as its *tert*-butyldimethyl silyl ether, giving compound **11**, subsequent oxidative removal of the *p*-methoxybenzyl group furnishing alcohol **12**.[29,30] Two straightforward steps, first a Swern oxidation and then a Horner−Wadsworth−Emmons reaction between the resulting aldehyde and ethyl diethylphosphonoacetate, provided enoate **13** in good overall yield. Construction of the styrene part began with the selective cleavage of the primary silyl ether to afford alcohol **14**. Swern oxidation[31] and a Wittig reaction between the obtained aldehyde and the phosphonate **15** gave the target compound **16**. As can be judged from the ^1H and ^{13}C NMR spectra, the diastereomeric purity of this compound was very high.

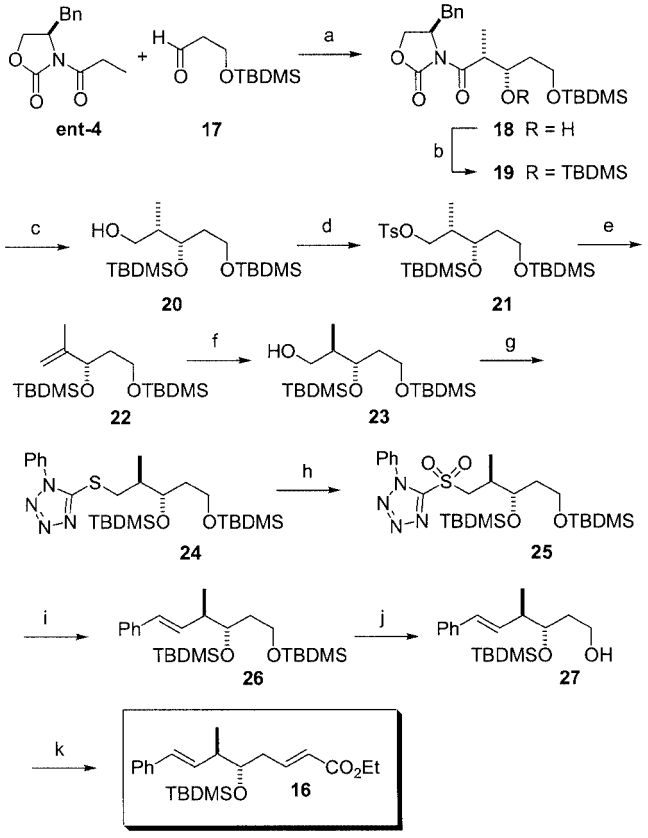


Scheme 1. Synthesis of the key building block **12** by Evans aldol reaction and inversion of the secondary alcohol by Mitsunobu reaction: a) nBu$_2$BOTf, iPr$_2$NEt, CH_2Cl_2, −78 to 23 °C, 2.5 h, 82%; b) $NaBH_4$, THF/H_2O (5:1), 0 to 25 °C, 2 h, 76%; c) TBDMSCl, NEt_3, DMAP (cat.), CH_2Cl_2, 0 to 23 °C, 12 h, 95%; d) PPh_3, iPrO$_2$CN=NCO$_2i$Pr, 4-O$_2$NC$_6$H$_4$CO$_2$H, THF, 0 to 23 °C, 12 h, 70%; e) NaOH, MeOH, 23 °C, 2 h, 94%; f) TBDMSCl, imidazole, DMF, 23 °C, 12 h, 87%; g) DDQ, CH_2Cl_2/H_2O (20:1), 0 to 23 °C, 2.5 h, 85%; h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, NEt_3, −78 to 0 °C, 2 h; i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 to 23 °C, add aldehyde, 0 °C, 1 h, 95% (2 steps); j) AcOH/H_2O/THF (1:1:2), 23 °C, 50 h, 75%; k) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, NEt_3, −78 to 0 °C, 3 h; l) $(EtO)_2P(O)CH_2Ph$ (**15**), nBuLi, THF, −78 °C, 1 h, add aldehyde, −78 to 23 °C, 7 h; 56% (2 steps)

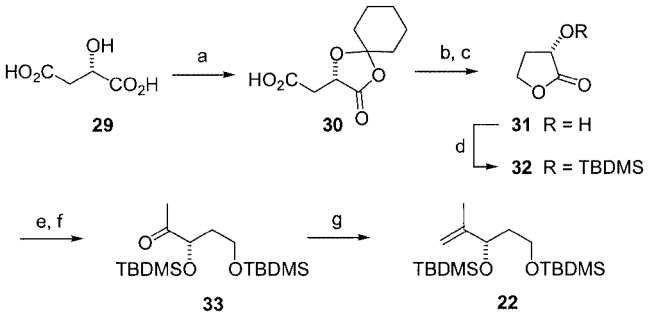
The second route started from the aldehyde **17**[32] and is also based on an Evans aldol reaction. In this case, however, the enantiomeric oxazolidinone (*ent*-**4**) derived from D-phenylalanine was used (Scheme 2). Protection of the hydroxy group in **18** with *tert*-butyldimethylsilyl triflate/lutidine was followed by reductive removal[27] of the auxiliary, affording **20**. Next, a terminal double bond had to be introduced. This was accomplished in high yield by the method we had previously described.[33] Thus, tosylation of the alcohol **20** and subsequent heating of the tosylate **21** at reflux in glyme (1,2-dimethoxyethane) in the presence of NaI (2.5 equiv.) and DBU (5.0 equiv.) effected clean elimination to provide the disubstituted allyl ether **22**. The stereocenter destroyed in this process was reintroduced by diastereoselective hydroboration,[34,35] which gave the *anti* product **23** with high diastereoselectivity (9:1). In this case, the introduction of the styrene component was performed by means of a Julia olefination.[36,37] Accordingly, the primary alcohol was converted into the sulfide **24** under Mitsunobu conditions, oxidation of **24** furnished the sulfone **25**, and deprotonation of the sulfone [KN(SiMe$_3$)$_2$, THF, −78 °C] and subsequent addition of benzaldehyde directly gave the (*E*)-alkene **26**. To conclude the synthesis, the primary trialkylsilyl ether was cleaved, the resulting primary alcohol **27** was subjected to a Swern oxidation, and the aldehyde was extended by Wittig olefination,[38] also to give the enoate **16**.

In the course of this work an alternative synthesis of alkene **22** was developed. This route started with (*S*)-malic acid (**29**), a compound featuring a secondary hydroxy group (Scheme 3). As has been described by Schinzer's group,[39] protection of **29** with cyclohexanone, selective reduction of the acid group of the lactone **30** with borane−dimethyl sulfide, and lactonization gave rise to the 2-hydroxy lactone **31**.[40] In this sequence it is very important to perform the reduction very slowly in order to assure a good chemical yield of compound **31**. After protection of the hydroxy group as its silyl ether, treatment of the lactone **32** with methyllithium yielded the known methyl ketone **33**. Finally, an olefination reaction gave the known alkene **22**.[41]

In summary, we have developed two syntheses of **16**, a protected building block for the 5-hydroxy acid fragment of the cryptophycins. Both routes feature an inversion of a stereocenter. The facile conversion of *syn* aldol products such as **6** or **18** into derivatives featuring an *anti* stereorelationship at the two stereocenters provides an easy route to this chiral moiety. In one approach the secondary hydroxy group was inverted by use of a Mitsunobu reaction, whereas



Scheme 2. Synthesis of the enoate **16** by Evans aldol reaction and inversion of the methyl bearing stereocenter by elimination and hydroboration: a) $TiCl_4$, sparteine, CH_2Cl_2, 0 °C, 25 min, add aldehyde, 0 °C, 1 h, 87%; b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 12 h, 93%; c) $NaBH_4$, THF/H_2O (5:1), 0 to 25 °C, 2 h, 75%; d) *p*TsCl, pyridine, 0 °C, 95%; e) NaI, DBU, glyme, reflux, 3 h, 95%; f) 9-BBN, THF, 0 to 23 °C, 3 h, then H_2O_2, NaOH, 83%; g) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, *i*$PrO_2CN{=}NCO_2$*i*Pr, DMF, 0 to 23 °C, 30 min, 84%; h) *m*CPBA, CH_2Cl_2, 0 to 23 °C, 3 h, 76%; i) $KN(SiMe_3)_2$, glyme, −55 °C, 40 min, add aldehyde, −55 to 23 °C, 4 h, 70%; j) PPTS, MeOH, 50 °C, 4 h, 86%; k) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 40 min, NEt_3, −60 to 0 °C, 2 h, add $Ph_3P{=}CHCO_2Et$, 23 °C, 12 h, 78%



Scheme 3. Synthesis of the alkene **22** from (*S*)-malic acid (**29**): a) cyclohexanone (1 equiv.), $BF_3{\cdot}OEt_2$ (1.5 equiv.), Et_2O, 0.35 M, 0 °C, 1 h, 23 °C, 10 h, 98%; b) $BH_3{\cdot}SMe_2$ (2.9 equiv.), $(MeO)_3B$ (2.9 equiv.), THF, 0.2 M, 0 to 23 °C, 24 h, coevaporation with MeOH; c) CH_2Cl_2, 0.3 M, *p*TsOH H_2O (0.1 equiv.), 23 °C, 24 h (68%); d) TBDMSCl (1.1 equiv.), imidazole (2.0 equiv.), DMF, 1.4 M, 23 °C, 24 h, 92%; e) MeLi (1.1 equiv.), THF, −78 °C, 3 h; f) TBDMSCl (1.1 equiv.), imidazole (2.0 equiv.), DMF, 0.8 M, 23 °C, 24 h, 65% (2 steps); g) $Ph_3PCH_3{}^+Br^-$, *n*BuLi, THF, 0 °C, add **33**, 0 to 23 °C, 48 h, 48%

the second route features an inversion of the methyl-bearing stereocenter by hydroboration of a terminal 2,2-disubstituted double bond. Both routes are flexible enough to allow for variations in the aryl part. Studies to further elaborate building block **16** into cryptophycin analogues are underway in our laboratory.

Experimental Section

General: ^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH = 7.25 ppm, δC = 77.00 ppm). Melting points: Büchi Melting Point B-540, uncorrected values. Polarimeter: JASCO Polarimeter P-1020. IR: Jasco FT/IR-430. EI-MS: Finnigan Triple-Stage-Quadrupole (TSQ-70). HR-MS (EI): Modified AMD Intectra MAT 711 A. HPLC-MS (API-ES): Agilent 1100 Series LC/MSD. HR-MS (FT-ICR): Bruker Daltonic APEX 2 with electrospray ionization (ESI). Flash chromatography: J. T. Baker silica gel 43−60 μm. Thin-layer chromatography Macherey-Nagel Polygram Sil G/UV_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 40−60 °C was used.

(4*S*)-4-Benzyl-3-{(2*S*,3*R*)-3-hydroxy-5-[(4-methoxybenzyl)oxy]-2-methylpentanoyl}-1,3-oxazolidin-2-one (6):[42,43] Di-*n*-butylboron triflate (1 M in CH_2Cl_2, 29.5 mL, 29.5 mmol) was added at 0 °C to a solution of imide **4**[24] (6.3 g, 27 mmol) in CH_2Cl_2 (60 mL), followed by the dropwise addition of Hünig's base (5.5 mL, 31.9 mmol). After stirring at 0 °C for 1 h, the reaction mixture was cooled to −78 °C and a solution of 3-(*p*-methoxybenzyloxy)propanal[17,44,45] (**5**, 4.8 g, 24.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting pale yellow solution was stirred at −78 °C for 1.5 h, then allowed to warm to 0 °C over 30 min, and stirred at 0 °C for 30 min. The reaction was quenched by the addition of phosphate buffer (pH = 7, 33 mL) followed by methanol (120 mL), resulting in a homogeneous solution. After 5 min, 33 mL of 30% aqueous hydrogen peroxide in methanol (50 mL) was added dropwise over 30 min. After having been stirred at 0 °C for 1 h, the reaction mixture was concentrated by rotary evaporation. The resulting mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were washed with HCl (1 N, 100 mL), aqueous $NaHCO_3$ (5%, 100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (40% EtOAc in petroleum ether) to provide the aldol product **6** (9.5 g, 82% yield) as a colorless, viscous liquid. $[\alpha]_D^{23}$ = +42.4 (*c* = 1.81, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3515 (br.), 2936, 1781, 1695, 1514, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.20 (m, 7 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.69 (ddd, *J* = 3.3, 6.8, 9.8 Hz, 1 H), 4.45 (s, 2 H), 4.22−4.16 (m, 3 H), 3.85−3.78 (m, 1 H), 3.80 (s, 3 H), 3.72−3.61 (m, 2 H), 3.26 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.89 (dd, *J* = 9.5, 13.4 Hz, 1 H), 1.90−1.83 (m, 1 H), 1.78−1.72 (m, 1 H), 1.29 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 159.1, 153.0, 135.1, 130.0, 129.4, 129.3, 128.9, 127.3, 113.7, 72.8, 70.4, 68.0, 66.1, 55.18, 55.15, 42.5, 37.7, 33.6, 11.4 ppm. MS (EI): *m*/*z* (%) = 426 (2), 306 (4), 290 (15) 176 (30), 137 (80), 121 (100). HRMS (FT-ICR): calcd. for $C_{24}H_{29}NO_6Na$ 450.1887, found 450.1883.

(2*R*,3*R*)-5-[(4-Methoxybenzyl)oxy]-2-methylpentane-1,3-diol (7): $NaBH_4$ (5.4 g, 140 mmol) was added portionwise at 0 °C to a stirred solution of the aldol adduct **6** (12.0 g, 28.1 mmol) in THF and water (180 mL, 5:1). The reaction mixture was stirred at 0 °C for 5 min and was then allowed to warm to 25 °C. After having

been stirred at room temperature for 2 h, the reaction mixture was quenched with HCl solution (2 N, 70 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude product, which was purified by flash chromatography (60% EtOAc in petroleum ether) to give the diol **7** (5.41 g, 76% yield) as a colorless, viscous liquid. $[\alpha]_D^{24} = -10.4$ ($c = 0.80$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3407 (br.), 2876, 1613, 1515, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 4.46 (s, 2 H), 4.02 (dt, J = 2.7, 10.1 Hz, 1 H), 3.81 (s, 3 H), 3.73 (ddd, J = 4.8, 4.8, 9.3 Hz, 1 H), 3.68−3.62 (m, 3 H), 3.22 (s, 2 H), 1.92−1.81 (m, 2 H), 1.62 (dddd, J = 2.4, 4.8, 4.8, 14.4 Hz, 1 H), 0.9 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 129.8, 129.3, 113.8, 74.7, 73.0, 69.5, 66.6, 55.2, 39.4, 32.7, 10.9 ppm. MS (EI): m/z (%) = 254 (4) $[M]^+$, 235 (8), 177 (15), 137 (92), 121 (100). HRMS (EI): calcd. for $C_{14}H_{22}O_4$ 254.1518, found 254.1509.

(2*R*,3*R*)-1-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-[(4-methoxybenzyl)-oxy]-2-methylpentan-3-ol (8): Et_3N (3.3 mL, 25.2 mmol), TBSCl (2.3 g, 15.1 mmol), and 4-(dimethylamino)pyridine (DMAP, 77 mg, 0.63 mmol) were added to a cooled (0 °C) solution of the diol **7** (3.2 g, 12.6 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred at room temperature overnight and was then quenched with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude product, which was purified by flash chromatography (20% EtOAc in petroleum ether) to provide the silyl ether **8** (4.4 g, 95% yield) as a colorless oil. $[\alpha]_D^{26} = -0.82$ ($c = 1.84$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3504, 2954, 2857, 1513, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 4.47 (s, 2 H), 3.98−3.94 (dt, J = 2.9, 9.8 Hz, 1 H), 3.81 (s, 3 H), 3.73−3.62 (m, 4 H), 1.83−1.79 (m, 1 H), 1.74−1.66 (m, 2 H), 0.93 (d, J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.3, 129.2, 113.7, 72.7, 72.3, 68.3, 67.5, 55.2, 39.6, 34.0, 25.8, 18.1, 10.6, −5.63, −5.67 ppm. MS (API-ES, 90 V): m/z (%) = 391 (95) $[M + Na]^+$, 277 (12), 121 (100). HRMS (FT-ICR): calcd. for $C_{20}H_{36}O_4SiNa$ 391.2275, found 391.2273.

(1*S*,2*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-{2-[(4-methoxybenzyl)-oxy]ethyl}-2-methylpropyl 4-Nitrobenzoate (9): Triphenylphosphane (6.6 g, 25 mmol), diisopropyl azodicarboxylate (4.95 mL, 25 mmol), and then *p*-nitrobenzoic acid (4.18 g, 25 mmol) were added with stirring to a cooled (0 °C) solution of compound **8** (4.6 g, 12.5 mmol) in THF (50 mL). The reaction mixture was then stirred at room temperature overnight, diluted with diethyl ether (100 mL), and quenched with saturated $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in petroleum ether) to provide the benzoate **9** (4.53 g, 70% yield) as a light yellow liquid. $[\alpha]_D^{26} = -14.5$ ($c = 1.58$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2955, 2857, 1724, 1528, 1276 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 9.1 Hz, 2 H), 8.11 (d, J = 9.1 Hz, 2 H), 7.15 (d, J = 8.6 Hz, 2 H), 6.74 (d, J = 8.6 Hz, 2 H), 5.39 (ddd, J = 3.8, 5.9, 9.0 Hz, 1 H), 4.33 (s, 2 H), 3.73 (s, 3 H), 3.61 (dd, J = 5.7, 10.1 Hz, 1 H), 3.59−3.49 (m, 3 H), 2.09 (m, 1 H), 2.04−1.98 (m, 2 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.00 and −0.01 (2 s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 159.0, 150.3, 136.0, 130.5, 130.1, 129.3, 123.3, 113.5, 75.0, 72.7, 66.6, 64.5, 55.1, 39.3, 31.0, 25.8, 18.2, 12.8, −5.55, −5.59 ppm. MS (API-ES, 90 V): m/z (%) = 540 (100) $[M + Na]^+$, 391 (20), 121 (60). HRMS (FT-ICR): calcd. for $C_{27}H_{39}NO_7SiNa$ 540.2388, found 540.2385.

(2*R*,3*S*)-1-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-[(4-methoxybenzyl)-oxy]-2-methylpentan-3-ol (10): A solution of the ester **9** (2.34 g, 4.52 mmol) in MeOH (15 mL) was treated with NaOH (0.9 g, 22.58 mmol) and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was treated with water (50 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (20% EtOAc in petroleum ether) to give the pure *anti* isomer **10** (1.57 g, 94% yield) as a colorless liquid. $[\alpha]_D^{25} = -9.7$ ($c = 0.78$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3498 (br.), 2955, 2857, 1513, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.6 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 4.46 (s, 2 H), 3.80 (s, 3 H), 3.76−3.60 (m, 5 H), 1.87−1.80 (m, 1 H), 1.78−1.68 (m, 2 H), 0.90 (s, 9 H), 0.88 (d, J = 7.1 Hz, 3 H), 0.80 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.4, 129.3, 113.7, 74.2, 72.8, 68.1, 67.5, 55.2, 40.2, 34.6, 25.8, 18.1, 13.4, −5.58, −5.64 ppm. MS (EI): m/z (%) = 369 (5) $[M]^+$, 261 (15), 137(20), 121 (100). HRMS (EI): calcd. for $C_{20}H_{36}O_4Si$ 368.2392, found 368.2383.

(2*R*,3*S*)-1,3-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-5-[(4-methoxybenzyl)oxy]-2-methylpentane (11): TBSCl (0.82 g, 5.4 mmol) and imidazole (0.55 g, 8.1 mmol) were added to a solution of alcohol **10** (1.0 g, 2.7 mmol) in DMF (5 mL) and the reaction mixture was stirred at room temperature overnight. It was then treated with saturated aqueous NH_4Cl solution (10 mL) and partitioned between Et_2O (50 mL) and water (50 mL). The diethyl ether layer was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in petroleum) to give the pure product **11** (1.14 g, 87% yield) as a colorless liquid. $[\alpha]_D^{25} = -8.6$ ($c = 1.16$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2955, 2857, 1514, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 4.40 (ABq, J = 11.6, 2 H), 3.87 (ddd, J = 4.3, 4.3, 7.5 Hz, 1 H), 3.78 (s, 3 H), 3.55−3.45 (m, 3 H), 3.38 (dd, J = 6.3, 10.1 Hz, 1 H), 1.81 (dddd, J = 6.8, 6.8, 11.6, 13.6 Hz, 1 H), 1.74−1.61 (m, 2 H), 0.86−0.85 (2 s, 18 H), 0.82 (d, J = 6.8 Hz, 3 H), 0.02−0.00 (4 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 67.2, 65.1, 55.2, 41.5, 32.3, 25.90, 25.87, 18.2, 18.1, 11.7, −4.5, −4.7, −5.4, −5.5 ppm. MS (EI): m/z (%) = 337 (4), 281 (6), 221 (10), 147 (100), 121 (90). HRMS (FT-ICR): calcd. for $C_{26}H_{50}O_4Si_2Na$ 505.3140, found 505.3143.

(3*S*,4*R*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-4-methylpentan-1-ol (12): DDQ (0.730 g, 3.2 mmol) was added at 0 °C to a stirred solution of diethyl ether **11** (1.4 g, 2.9 mmol) in a mixture of CH_2Cl_2 and water (21 mL, 20:1). After the mixture had been stirred for 30 min at 0 °C, the cooling bath was removed and the mixture was stirred for an additional 2 h. It was then diluted with CH_2Cl_2 (20 mL), and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (15% EtOAc in petroleum ether) to give the alcohol **12** (0.895 g, 85% yield) as a colorless, viscous liquid. $[\alpha]_D^{25} = -7.6$ ($c = 0.59$, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3267 (br.), 2885, 1462, 1051 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.97 (dd, J = 5.1, 6.6 Hz, 1 H), 3.79−3.70 (m, 2 H), 3.47 (dABq, ^3J = 7.1, J_{AB} = 10.1 Hz, 2 H), 2.27 (s, 1 H), 1.97−1.87 (m, 1 H), 1.73−1.63 (m, 2

H), 0.88 and 0.87 (2 s, 18 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.08−0.02 (4 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.4, 65.1, 60.7, 40.9, 33.7, 25.88, 25.84, 18.2, 18.0, 11.6, −4.54, −4.59, −5.41, −5.53 ppm. MS (EI): m/z (%) = 189 (45), 173 (85), 131 (45), 73 (100). HRMS (EI): calcd. for $C_{18}H_{41}O_2Si_2$ 345.2668, found 345.2645.

Ethyl (2*E*,5*S*,6*R*)-5,7-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-6-methylhept-2-enoate (13)

Step 1: (3*S*,4*R*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-4-methylpentanal: DMSO (0.308 mL, 4.36 mmol), dissolved in CH_2Cl_2 (1 mL), was added at −78 °C to a stirred solution of oxalyl chloride (0.204 mL, 2.37 mmol) in CH_2Cl_2 (5 mL). After 5 min, alcohol **12** (0.715 g, 1.98 mmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was stirred at −78 °C for 1 h. Et_3N (1 mL, 9.99 mmol) was then added dropwise, and the reaction mixture was allowed to come to 0 °C over 2 h. Water (5 mL) was then added and the layers were separated. The organic layer was washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde, which was used for the next reaction without any further purification.

Step 2: Ethyl (2*E*,5*S*,6*R*)-5,7-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-6-methylhept-2-enoate: The phosphonate $(EtO)_2P(O)CH_2CO_2Et$ (1.81 mL, 10.5 mmol) was added dropwise at 0 °C to a slurry of NaH (0.21 g, 8.75 mmol) in THF (10 mL). After 30 min at 0 °C, the mixture was stirred at room temperature for an additional 30 min and recooled to 0 °C, after which the aldehyde (from the previous reaction), dissolved in THF (3 mL), was added. The reaction mixture was stirred at 0 °C for 1 h, and was then quenched with a saturated aqueous solution of NH_4Cl (5 mL), diluted with water (15 mL), and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in petroleum ether) to provide the enoate **13** (0.806 g, 95% yield) as a colorless liquid. $[\alpha]_D^{26}$ = −2.95 (c = 0.65, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2928, 2857, 1725, 1472, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03−6.95 (m, 1 H), 5.82 (dt, J = 1.3, 15.4 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.83 (ddd, J = 4.8, 4.8, 6.6 Hz, 1 H), 3.50 (dABq, ^3J = 6.8, J_{AB} = 10.1 Hz, 2 H), 2.38−2.25 (m, 2 H), 1.81 (ddd, J = 6.8, 12.9, 19.2 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.88 and 0.87 (2 s, 18 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.02 (br. s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 146.8, 123.1, 72.2, 64.9, 60.1, 41.2, 36.0, 25.9, 25.8, 18.2, 18.1, 14.3, 12.0, −4.5, −4.7, −5.4, −5.5 ppm. MS (API-ES, 70 V): m/z (%) = 453 (10) $[M + Na]^+$, 431 (100) $[M + 1]^+$, 299 (40), 167 (35). HRMS: calcd. for $C_{22}H_{46}O_4Si_2Na$ 453.2827, found 453.2830.

Ethyl (2*E*,5*S*,6*R*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-7-hydroxy-6-methylhept-2-enoate (14): A solution of enoate **13** (0.806 g, 1.87 mmol) in AcOH and aqueous THF (AcOH/H_2O/THF 1:1:2, 16 mL) was stirred at room temperature for 50 h. The reaction mixture was neutralized to pH = 7 with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (20% EtOAc in petroleum ether) to provide the alcohol **14** (0.445 g, 75% yield) as a colorless, viscous liquid. $[\alpha]_D^{26}$ = +15.1 (c = 0.32, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3469 (br.), 2929, 2857, 1722, 1471, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (ddd, J = 7.6, 7.6, 15.4 Hz, 1 H), 5.85 (dt, J = 1.5, 15.4 Hz, 1 H), 4.17 (q, J = 7.3 Hz, 2 H), 3.81 (q, J = 5.6 Hz, 1 H), 3.73 (d of A of ABq, ^3J = 4.0, J_{AB} = 11.1 Hz, 1 H), 3.55 (d of B of ABq, ^3J = 5.6, J_{AB} = 11.1 Hz, 1 H), 2.52−2.39 (m, 2 H), 2.12 (br. s, 1 H), 1.78−1.69 (m, 1 H), 1.27 (t, J = 7.3 Hz, 3 H), 0.97 (d, J = 3 H), 0.89 (s, 9 H), 0.08 and 0.07 (2 s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 144.9, 123.8, 75.5, 65.1, 60.3, 38.9, 37.8, 25.8, 17.9, 14.23, 14.18, −4.4, −4.8 ppm. MS (API-ES, 70 V): m/z (%) = 339 (45) $[M + Na]^+$, 317 (95) $[M]^+$, 185 (100), 139 (70). HRMS (FT-ICR): calcd. for $C_{16}H_{32}O_4SiNa$ 339.1962, found 339.1962.

Ethyl (2*E*,5*S*,6*R*,7*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-8-phenylocta-2,7-dienoate (16)

(a) From Alcohol 14. Step 1: Ethyl (2*E*,5*S*,6*S*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-7-oxohept-2-enoate: Dimethyl sulfoxide (0.05 mL, 0.7 mmol), dissolved in CH_2Cl_2 (1 mL), was added at −78 °C to a solution of oxalyl chloride (0.033 mL, 0.38 mmol) in CH_2Cl_2 (2 mL). After 5 min, alcohol **14** (0.1 g, 0.32 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture and stirring was continued at −78 °C for 1 h. Et_3N (0.207 mL, 1.6 mmol) was then added dropwise, and the mixture was allowed to come to room temperature over 3 h and then treated with water (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde, which was used for the next step without any further purification.

Step 2: Ethyl (2*E*,5*S*,6*R*,7*E*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-8-phenylocta-2,7-dienoate (16): *n*BuLi (2.5 M in hexane, 0.168 mL, 0.42 mmol) was added at −78 °C to a solution of diethyl benzylphosphonate[18] (0.133 mL, 0.64 mmol) in THF (3 mL). Stirring was continued at −78 °C for 1 h, after which a solution of the aldehyde (from the previous reaction), dissolved in THF (2 mL), was added. After having been stirred at −78 °C for 1 h, the mixture was allowed to warm gradually to room temperature over 6 h. Aqueous NH_4Cl solution (5 mL) was then added, and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (20% EtOAc in petroleum ether) to provide the pure dienoate **16** (0.068 g, 56% yield) as a colorless, viscous liquid. $[\alpha]_D^{26}$ = +58.5 (c = 0.63, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2927, 2856, 1723, 1655, 1462, 1259 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.19 (m, 5 H), 6.96 (ddd, J = 7.6, 7.6, 15.4 Hz, 1 H), 6.38 (d, J = 16.2 Hz, 1 H), 6.17 (dd, J = 8.1, 15.9 Hz, 1 H), 5.83 (dt, J = 1.3, 15.9 Hz, 1 H), 4.19 (q, J = 7.3 Hz, 2 H), 3.76 (ddd, J = 4.0, 6.3, 6.3 Hz, 1 H), 2.48−2.44 (m, 1 H), 2.38−2.34 (m, 2 H), 1.28 (t, J = 7.3 Hz, 3 H), 1.11 (d, J = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.07 and 0.06 (2 s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 146.1, 137.6, 131.9, 130.4, 128.5, 127.0, 126.0, 123.3, 75.0, 60.1, 42.8, 37.5, 25.8, 18.1, 16.2, 14.2, −4.4, −4.5 ppm. MS (API-ES, 90 V): m/z (%) = 411 (75) $[M + Na]^+$, 389 (10) $[M]^+$, 257 (50), 183 (100). HRMS (FT-ICR): calcd. for $C_{23}H_{36}O_3SiNa$ 411.2326, found 411.2324.

(b) From Alcohol 27: Dimethyl sulfoxide (0.033 mL, 0.47 mmol) was added dropwise at −60 °C to a stirred solution of oxalyl chloride (0.022 mL, 0.234 mmol) in CH_2Cl_2 (2 mL). After 10 min, a solution of alcohol **27** (60 mg, 0.187 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture. After 30 min, the reaction mixture was treated with triethylamine (0.13 mL, 0.936 mmol) and allowed to warm to 0 °C. At this point ethyl (triphenylphosphoranylidene)-acetate (196 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) was added. After the reaction mixture had been stirred at room temperature overnight, it was poured into half-saturated NaCl solution (20 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic

layers were dried with Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 5:95) gave dienoate **16** as a colorless oil (57 mg, 78%). $[\alpha]_D^{25}$ = +66.6 (c = 0.73, $CHCl_3$).

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-5-{[(*tert*-butyl)dimethylsilyl]oxy}-3-hydroxy-2-methylpentanoyl]-1,3-oxazolidin-2-one (18): Titanium(IV) chloride (0.49 mL, 4.50 mmol) was added dropwise to a cooled (0 °C) solution of the oxazolidinone[24] *ent*-**4** (1.0 g, 4.29 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred for 5 min. Subsequently, (−)-sparteine (2.51 g, 10.72 mmol) was added to the yellow slurry. The dark-red enolate solution was stirred at 0 °C for 20 min, after which aldehyde **17**[46] (0.89 g 4.72 mmol), dissolved in CH_2Cl_2 (10 mL), was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then quenched with half-saturated NH_4Cl (10 mL). After separation of the layers, the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (20% EtOAc in petroleum ether) afforded 1.58 g (87%) of **18**, colorless oil. $[\alpha]_D^{24}$ = −42.0 (c = 0.98, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1209, 1241, 1697, 1737, 1782, 2857, 2954, 3504 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.3−7.05 (m, 5 H), 4.65−4.55 (m, 1 H), 4.17−4.01 (m, 3 H), 3.82−3.66 (m, 3 H), 3.51 (d, J = 1.8 Hz, 1 H), 3.18 (dd, J = 8.3, 13.1 Hz, 1 H), 2.70 (dd, J = 9.4, 13.4 Hz, 1 H), 1.75−1.63 (m, 1 H), 1.61−1.51 (m, 1 H), 1.21 (d, J = 7.1 Hz, 3 H), 0.82 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 152.9, 135.1, 129.3, 128.8, 127.2, 71.0, 65.9, 61.7, 55.2, 42.7, 37.6, 35.8, 25.8, 18.1, 11.2, −5.6 ppm. MS (EI): *m*/*z* (%) = 364 (22), 346 (5), 290 (4), 272 (12), 252 (61), 234 (29), 187 (46), 131 (100), 91 (35), 57 (7). HRMS (FT-ICR): calcd. for $C_{22}H_{35}NO_5SiNa$ $[M + Na]^+$ 444.21767, found 444.21793.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3,5-bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpentanoyl]-1,3-oxazolidin-2-one (19): *tert*-Butyldimethylsilyl triflate (0.407 g, 0.35 mL, 1.54 mmol) was added to a solution of compound **18** (0.50 g, 1.18 mmol) and 2,6-lutidine (0.32 g, 0.34 mL, 2.96 mmol) in CH_2Cl_2 (10 mL) and the solution was stirred overnight. Water (5 mL) was added, the mixture was stirred for 20 min, and the organic layer was separated. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (10% EtOAc in petroleum ether) afforded silyl ether **19** (0.593 g, 93%) as a colorless, gummy product, which solidified on standing; m.p. 52−53 °C. $[\alpha]_D^{25}$ = −56.5. IR (neat): $\tilde{\nu}$ = 1209, 1252, 1383, 1703, 1784, 2857, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.10 (m, 5 H), 4.60−4.51 (m, 1 H), 4.17−4.01 (m, 3 H), 3.89−3.80 (m, 1 H), 3.71−3.56 (m, 2 H), 3.22 (dd, J = 3.0, 13.4 Hz, 1 H), 2.71 (dd, J = 9.6, 13.4 Hz, 1 H), 1.88−1.68 (m, 2 H), 1.18 (d, J = 6.8 Hz, 3 H), 0.84 (s, 18 H), 0.02, 0.00, 0.00, −0.03 (4 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 152.9, 135.3, 129.4, 128.9, 127.3, 70.4, 65.9, 59.4, 55.6, 43.1, 38.2, 37.6, 25.9, 18.2, 17.9, 12.3, −4.5, −4.9, −5.4 ppm. MS (EI): *m*/*z* (%) = 478 (9), 422 (6), 346 (3), 290 (11), 234 (14), 171 (7), 117 (8), 91 (8), 84 (100), 73 (24). HRMS (FT-ICR): calcd. for $C_{28}H_{49}NO_5Si_2Na$ $[M + Na]^+$ 558.30415, found 558.30402.

(2*S*,3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpentan-1-ol (20): A solution of $NaBH_4$ (261 mg, 6.9 mmol) in H_2O (3 mL) was added at 0 °C to a stirred solution of **19** (925 mg, 1.72 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C for 5 min and then at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution and the mixture was stirred for 1 h, after which it was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL), H_2O (20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc in petroleum ether) to give 471 mg (75%) of alcohol **20** as a colorless oil. $[\alpha]_D^{25}$ = −19.0 (c = 0.72, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3394, 2955, 2930, 2858, 1470, 1254, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.95−3.88 (m, 1 H), 3.72−3.56 (m, 3 H), 3.52 (dd, J = 5.1, 10.6 Hz, 1 H), 2.87 (br. s, 1 H), 2.02−1.91 (m, 1 H), 1.68 (q, J = 6.31 Hz, 1 H), 0.87 (s, 18 H), 0.78 (d, J = 7.1 Hz, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.7, 65.9, 59.8, 39.8, 35.1, 25.8, 18.2, 17.9, 12.5, −4.8, −5.3 ppm. MS (EI): *m*/*z* (%) = 305 (10), 289 (3), 261 (4), 189 (14), 173 (100), 147 (70), 133 (33), 115 (27), 105 (40), 89 (96), 73 (93). HRMS (FT-ICR): calcd. for $C_{18}H_{42}O_3Si_2Na$ $[M + Na]^+$ 385.25647, found 385.25582.

(2*S*,3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpentyl 4-Methylbenzenesulfonate (21): *p*-Toluenesulfonyl chloride (420 mg, 2.2 mmol) was added at 0 °C to a stirred solution of alcohol **20** (400 mg 1.10 mmol) in pyridine (3 mL). After having been stirred for 2 h, the reaction mixture was quenched by addition of water (10 mL), diluted with Et_2O (50 mL), and washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Filtration of the residue through a short pad of silica gel (5% EtOAc in petroleum ether) and evaporation of the solvent gave the pure tosylate **21** as a slightly yellow oil (543 mg, 95%). $[\alpha]_D^{25}$ = −15.7 (c = 1.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 7.8 Hz, 2 H), 4.02 (dd, J = 5.8, 9.1 Hz, 1 H), 3.86−3.75 (m, 2 H), 3.6−3.47 (m, 2 H), 2.42 (s, 3 H), 1.97−1.83 (m, 1 H), 1.65−1.53 (m, 1 H), 1.50−1.41 (m, 1 H), 0.85 (s, 9 H), 0.77 (s, 9 H), 0.00 (s, 6 H), −0.01 (s, 3 H), −0.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 133.0, 129.7, 127.9, 72.6, 69.2, 59.5, 37.9, 36.4, 25.8, 25.7, 21.6, 18.1, 17.9, 11.1, −4.5, −4.9, −5.4 ppm. MS (EI), *m*/*z* (%) = 459 (2), 361 (19), 345 (6), 303 (6), 287 (7), 271 (3), 229 (100), 213 (53), 173 (32), 133 (15), 91 (30), 73 (60), 57 (10). HRMS (FT-ICR): calcd. for $C_{25}H_{48}O_5SSi_2Na$ $[M + Na]^+$ 539.26532, found 539.26623.

(3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpent-1-ene (22)

(a) From Tosylate 21: A mixture of the tosylate **21** (400 mg, 0.81 mmol), NaI (365 mg, 2.44 mmol), and DBU (371 mg, 2.44 mmol) in glyme (10 mL) was heated at reflux with stirring for 3 h. After the reaction mixture had cooled to room temperature, Et_2O (50 mL) and H_2O (50 mL) were added and the layers were separated. The combined organic layers were washed with saturated $NaHCO_3$ solution, 1 N HCl, and brine, dried (Na_2SO_4), filtered, and concentrated. Filtration of the residue through a short pad of silica gel (petroleum ether) gave the pure alkene **22** (266 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$ = −14.2 (c = 0.88, $CHCl_3$) {ref.[47] $[\alpha]_D^{20}$ = −10.0 (c = 1.0, $CHCl_3$)}. IR (neat): $\tilde{\nu}$ = 2954, 2930, 2857, 1471, 1254, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (s, 1 H), 4.74 (s, 1 H), 4.20 (dd, J = 5.3, 7.3 Hz, 1 H), 3.68−3.55 (m, 2 H), 1.17−1.57 (m, 5 H), 0.88 (s, 18 H), 0.03 (s, 9 H), −0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ = 147.8, 110.4, 73.4, 59.7, 39.5, 25.8, 18.2, 17.1, −4.8, −5.2, −5.3 ppm. MS (EI): *m*/*z* (%) = 287 (48), 259 (72), 219 (24), 189 (67), 147 (100), 133 (24), 73 (58).

(b) From Ketone 33: *n*BuLi (1.00 mL, 2.5 M in hexane, 2.5 mmol) was added dropwise at 0 °C to a stirred suspension of (methyl)triphenylphosphonium bromide (1.10 g, 3.08 mmol) in THF (10 mL). The resulting red ylide solution was stirred at 0 °C for 30 min, after which a solution of ketone **33** (500 mg, 1.44 mmol) in THF (5 mL) was added dropwise at 0 °C over 10 min. The cooling bath was removed and the reaction mixture was stirred at ambient tempera-

ture for 48 h. Et_2O (20 mL) and H_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (petroleum ether) gave the olefin **22** (237 mg, 48%) as a colorless oil. $[\alpha]_D^{25} = -13.5$ (c = 1.09, $CHCl_3$).

(2*R*,3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methyl-1-pentanol (23): A solution of 9-BBN in THF (0.5 M, 4.3 mL, 2.17 mmol) was added dropwise at 0 °C to a solution of alkene **22** (250 mg, 0.72 mmol) in THF (2 mL). After the addition, the mixture was stirred at ambient temperature for 3 h and was then treated with EtOH (1.35 mL), aqueous NaOH (3 N, 0.9 mL), and 30% aqueous H_2O_2 (0.9 mL) and stirred at room temperature for 2 h. The mixture was saturated with solid K_2CO_3 and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (10% EtOAc in petroleum ether) gave alcohol **22** (218 mg, 83%) as a colorless oil. $[\alpha]_D^{25} = -4.0$ (c = 0.89, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3394, 2955, 2930, 2858, 1470, 1254, 1095, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (dd, J = 6.1, 10.1 Hz, 1 H), 3.73 (dd, J = 4.3, 10.9 Hz, 1 H), 3.62 (t, J = 6.6 Hz, 2 H), 3.49 (dd, J = 5.3, 10.9 Hz, 1 H), 2.68 (br. s, 1 H), 1.90−1.79 (m, 0.5 H), 1.78−1.69 (m, 2 H), 1.56−1.45 (m, 0.5 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.85, 0.86 (2 s, 18 H), 0.05, 0.00 (2 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.2, 65.2, 56.7, 38.5, 37.5, 25.8, 18.2, 18.0, 14.3, 4.5, −4.7, −5.4 ppm. MS (EI), m/z (%) = 305 (8), 289 (2), 261 (3), 189 (13), 173 (100), 147 (70), 133 (34), 115 (27), 105 (40), 89 (98), 73 (93). HRMS (FT-ICR): calcd. for $C_{18}H_{42}O_3Si_2Na$ [M + Na]$^+$ 385.25647, found 385.25613.

5-{[(2*S*,3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpentyl]-sulfanyl}-1-phenyl-1*H*-tetrazole (24): A premixed solution of 1-phenyl-1*H*-tetrazole-5-thiol (167 mg, 0.94 mmol) and diisopropyl azodicarboxylate (190 mg, 0.94 mmol) in DMF (3.5 mL) was added to a solution of alcohol **23** (210 mg, 0.58 mmol) and triphenylphosphane (246 mg, 0.94 mmol) in DMF (2.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, after which water (10 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (5% EtOAc in petroleum ether) gave the sulfide **24** (255 mg, 84%) as a colorless oil. $[\alpha]_D^{25} = +0.48$ (c = 0.92, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2954, 2930, 2857, 1500, 1469, 1387, 1253, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63−7.43 (m, 5 H), 3.99−3.81 (m, 1 H), 3.79−3.60 (m, 2 H), 3.51 (dd, J = 5.3, 13.1 Hz, 1 H), 3.17 (dd, J = 8.1, 12.9 Hz, 1 H), 2.19−2.02 (m, 1 H), 1.76−1.54 (m, 2 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.86 (s, 18 H), 0.05, 0.04, 0.01, 0.00 (4 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 133.8, 130.0, 129.7, 123.8, 71.8, 59.6, 37.7, 36.1, 36.0, 25.9, 18.0, 15.3, −4.5, −4.6, −5.4 ppm. MS (EI): m/z (%) = 466 (2), 277 (7), 235 (10), 213 (36), 173 (30), 147 (64), 133 (28), 89 (97), 73 (100). HRMS (FT-ICR): calcd. for $C_{25}H_{46}N_4O_2SSi_2Na$ [M + Na]$^+$ 545.27722, found 545.27773.

5-{[(2*S*,3*S*)-3,5-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-2-methylpentyl]-sulfonyl}-1-phenyl-1*H*-tetrazole (25): A solution of the sulfide **24** (250 mg, 0.48 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C, was treated with *m*CPBA (247 mg, 1.43 mmol), followed by stirring at room temperature for 3 h. The reaction mixture was treated with 10% aqueous sodium sulfite solution (20 mL), diluted with CH_2Cl_2 (30 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:9) gave 200 mg (76%) of **25** as a white gum. $[\alpha]_D^{25} = -1.93$ (c = 0.66, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2954, 2930, 1497, 1343, 1255, 1153, 1096 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71−7.64 (m, 2 H), 7.63−7.54 (m, 3 H), 3.95 (dd, J = 2.8, 14.9 Hz, 1 H), 3.89−3.83 (m, 1 H), 3.64 (t, J = 6.2 Hz, 2 H), 3.44 (dd, J = 9.1, 14.91 Hz, 1 H), 2.48−2.38 (m, 2 H), 1.77−1.53 (m, 2 H), 1.19 (d, J = 6.8 Hz, 3 H), 0.87, 0.86 (2 s, 18 H), 0.06, 0.04, 0.03, 0.02 (4 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 133.1, 131.4, 129.7, 125.1, 72.5, 59.25, 58.0, 36.8, 32.6, 25.9, 18.2, 18.0, 17.0, −4.4, −4.7, −5.5 ppm. MS (EI): m/z (%) = 498 (3), 439 (2), 249 (8), 189 (13), 175 (28), 147 (53), 117 (84), 84 (89), 49 (100). HRMS (FT-ICR): calcd. for $C_{25}H_{46}N_4O_4SSi_2Na$ [M + Na]$^+$ 577.26705, found 577.26660.

{(1*E*,3*R*,4*S*)-4,6-Bis{[(*tert*-butyl)dimethylsilyl]oxy}-3-methylhex-1-enyl}benzene (26): Potassium bis(trimethylsilyl)amide (1 mL, 0.5 M in toluene, 0.5 mmol) was added dropwise at −55 °C to a solution of sulfone **25** (185 mg, 0.33 mmol) in dry DME (3 mL). The resulting bright yellow-orange solution was stirred at the same temperature for 40 min, after which freshly distilled benzaldehyde (46 mg, 0.43 mmol) in DME (1 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and then allowed to warm to 0 °C over 1 h. After stirring at room temperature for 2 h, the reaction mixture was partitioned between H_2O and Et_2O, the phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/petroleum ether, 5:95) to provide the styrene **26** (102 mg, 70%) as a colorless oil. $[\alpha]_D^{25} = +17.8$ (c = 1.00, $CHCl_3$) {ref.[18] $[\alpha]_D^{22} = +24.6$ (c = 1.84, $CHCl_3$); ref.[17] $[\alpha]_D^{20} = +23$ (c = 0.77, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 2955, 2928, 1471, 1463, 1256, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.05 (m, 5 H), 6.26 (d, J = 15.9 Hz, 1 H), 6.07 (dd, J = 7.8, 15.9 Hz, 1 H), 3.79−3.67 (m, 1 H), 3.65−3.47 (m, 2 H), 2.45−2.31 (m, 1 H), 1.56 (q, J = 6.6 Hz, 2 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.82, 0.79 (2 s, 18 H), 0.02, −0.06 (2 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 132.8, 129.8, 128.4, 126.9, 126.0, 72.7, 60.2, 42.7, 36.7, 25.9, 18.3, 18.1, 15.5, −4.5, −5.3 ppm. MS (EI): m/z (%) = 323 (3), 303 (14), 261 (20), 189 (30), 173 (9), 147 (100), 131 (22), 115 (14), 89 (38), 73 (58).

(3*S*,4*R*,5*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-methyl-6-phenyl-5-hexen-1-ol (27): A mixture of pyridinium toluene-4-sulfonate (17 mg, 0.067 mmol) and silyl ether **26** (100 mg, 0.23 mmol) was stirred at 50 °C in methanol (5 mL) for 4 h. Most of the methanol was then removed under reduced pressure and the mixture was partitioned between H_2O and Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:9) gave the alcohol **27** (63 mg, 86%) as a colorless oil. $[\alpha]_D^{25} = +44.4$ (c = 0.75, $CHCl_3$) {ref.[18] $[\alpha]_D^{22} = +28.8$ (c = 2.59, $CHCl_3$); ref.[17] $[\alpha]_D^{20} = +28.3$ (c = 0.675, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 3352, 2955, 2929, 1469, 1376, 1254, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.02 (m, 5 H), 6.36−6.19 (m, 1 H), 6.12−5.91 (m, 1 H), 3.87−3.72 (m, 1 H), 3.70−3.53 (m, 2 H), 2.53−2.36 (m, 1 H), 1.88 (br. s, 1 H), 1.62 (q, J = 6.3 Hz, 2 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.80 (s, 18 H), 0.00, −0.02 (2 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 132.6, 130.0, 128.5, 127.0, 126.0, 74.6, 60.5, 42.7, 34.9, 25.9, 18.0, 14.8, −4.46, −4.6 ppm. MS (EI): m/z (%) = 263 (2), 189 (78), 147 (41), 91 (27), 89 (90), 75 (100), 73 (80).

(3*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}dihydrofuran-2(3*H*)-one (32):[39] Imidazole (2.2 g, 32.32 mmol) and TBSCl (2.44 g,

16.16 mmol) were added to a solution of lactone **31**[39] (1.5 g, 14.7 mmol) in DMF (10 mL). The mixture was stirred for 24 h at room temperature. Subsequently, the reaction was quenched with saturated $NaHCO_3$ solution and the mixture was extracted with Et_2O. The ethereal layer was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (EtOAc/petroleum ether, 1:9) afforded silyl ether **32** (2.95 g, 92%) as a colorless oil. $[\alpha]_D^{25} = +31.9$ ($c = 0.92$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2931, 2859, 1790, 1473, 1362, 1254, 1154, 1022, 840, 781 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.43−4.31 (m, 2 H), 4.22−4.12 (m, 1 H), 2.49−2.39 (m, 1 H), 2.26−2.16 (m, 1 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 68.2, 64.7, 32.3, 25.6, 18.2, 4.8, 5.3 ppm.

(3*S*)-3,5-Bis[*tert*-butyl(dimethyl)silyloxy]pentan-2-one (33):[39] MeLi (1.6 mL, 2.56 mmol, 1.6 M solution in Et_2O) was added dropwise at −78 °C to a stirred solution of silyl ether **32** (500 mg, 2.3 mmol) in THF (10 mL). After having been stirred at −78 °C for 3 h, the reaction mixture was quenched by the addition of glacial acetic acid (0.17 mL, 2.97 mmol). Et_2O (40 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) were added. The organic layer was separated after stirring for 5 min, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give crude (3*S*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-2-methyltetrahydrofuran-2-ol. The crude hydroxy ketone was dissolved in DMF (3 mL), imidazole (313 mg, 4.6 mmol) and TBSCl (350 mg, 2.32 mmol) were added, and the mixture was stirred at room temperature for 24 h. The mixture was partitioned between Et_2O (40 mL) and water (40 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 5:95) afforded ketone **33** (516 mg, 65%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 2957, 2859, 1720, 1473, 1361, 1256, 1106, 838, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13 (dd, J = 5.3, 6.8 Hz, 1 H), 3.74−3.60 (m, 2 H), 2.13 (s, 3 H), 1.86−1.69 (m, 2 H), 0.89, 0.85 (2 s, 18 H), 0.03, 0.01, 0.00 (3 s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.83, 75.71, 58.33, 37.75, 25.87, 25.69, 25.34, 18.24, 18.08, −5.02, −5.48 ppm.

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