Synthesis of the 8-Hydroxy Acid of Jasplakinolide

Saengchai Wattanasereekul, Martin E. Maier*

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
Fax: (+49)-7071-295-137; e-mail: martin.e.maier@uni-tuebingen.de

Received: January 8, 2004; Accepted: April 5, 2004

Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Abstract: The protected ω-hydroxy acid **4b** contained in the depsipeptide jasplakinolide (**1**) was prepared in a sequence of 13 steps from the silylated 3-hydroxy ester **6**. By chain extension **6** was converted to the allyl alcohol **10**. A subsequent asymmetric cyclopropanation of the allylic alcohol **10** using the Charette method provided the hydroxymethylcyclopropane **12** with excellent diastereoselectivity. This cyclopropanation was used to establish the methyl-bearing stereocenter at C-6 of the hydroxy acid **4** by reductive ring cleavage of the (iodomethyl)cyclopropane **14**. The alkene **15** was used for a cross alkene metathesis reaction with 2-methylacrylate **20** providing the enoate **19**. The derived allylic iodide **24** served as an electrophile in the final Evans alkylation step to give the ω-hydroxy acid derivative **26**.

Keywords: alkenes; alkylation; asymmetric synthesis; cyclopropanes; metathesis; natural products

Introduction

The key structural feature of cyclic depsipeptides is the replacement of an amide bond by an ester bond. Besides the presence of hydroxy acids, depsipeptides often contain unusual amino acids. The most common modifications include *N*-methylation or extension of the carbon chain. Aromatic amino acids such as tyrosine or tryptophan sometimes contain ring substituents like halides. While β-hydroxy acids can be traced back to the corresponding α-amino acids, ω-hydroxy acids present in cyclic depsipeptides are made by the polyketide machinery. Thus, these natural products are made by the combination of building blocks from different biosynthetic pathways. An illustrative example is the cyclodepsipeptide jasplakinolide (**1**) which was isolated from the marine sponge *Jaspis* sp.[1] Jasplakinolide shows potent antifungal, insecticidal and antitumor activity. It is also used as a tool in cytoskeletal research since it stabilizes F-actin which includes the reorganization of actin filaments into a layer adjacent to the plasma membrane.[2] Related compounds are the marine cyclodepsipeptides geodiamolide A and B which are reported to have weak antifungal activity.[3] These depsipeptides share the same 11-carbon polypropionate unit, the 8-hydroxy-2,4,6-trimethyl-4-nonenoic acid (**4a**). The retrosynthesis which is typical for several total syntheses dissects the macrolide **1** into a tripeptide fragment **3** and a hydroxy-protected carboxylic acid **4b**. This strategy should allow for an easy variation of the tripeptide fragment.

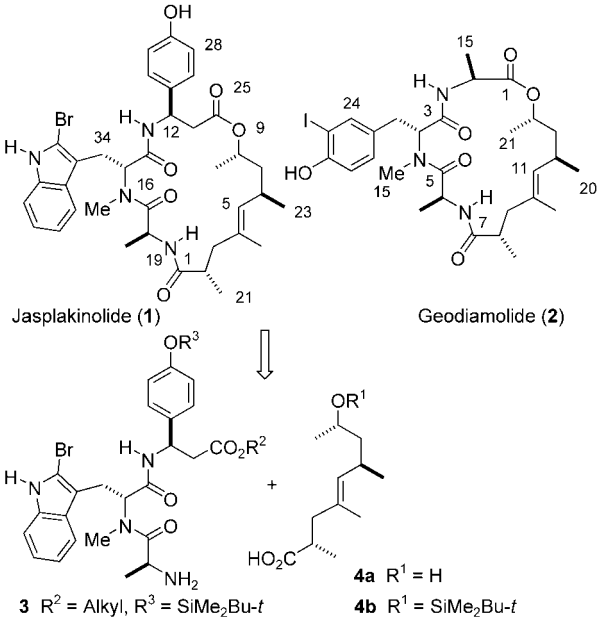


Figure 1. Structures of jasplakinolide (**1**) and geodiamolide (**2**).

The two depsipeptides differ in the tripeptide fragment. Due to the presence of the β-amino acid in jasplakinolide they also have different ring sizes (19 *vs.* 18). It is not clear what the role of the individual building blocks is. The tripeptide fragment might mimic a peptide or protein ligand. The 8-hydroxy acid could function as a conformational control element, being involved in bind-

 DOI: 10.1002/adsc.200404004

ing or not. Thus, akin to the immunosuppressives FK506 and rapamycin,[4] jasplakinolide could be a dual domain molecule. Irrespective of that, the ω-hydroxy acid is of interest from the viewpoint of conformational control. The hydroxy acid **4a** contains four methyl groups in a 1,3-distance. One can identify two *syn*-pentane interactions and one 1,3-allylic interaction. The consequence of the methyl groups is that the functional groups (carboxyl and hydroxy) at both ends of the chain point in one direction and allow bridging with a peptide fragment. Based on the work of Hoffmann et al.[5] one can assume that the conformation of the chain is largely determined by the central double bond and the three other methyl groups. While definitely several low energy conformations are possible, an arrangement such as the one depicted in Figure 2 should be accessible and still allow for an easy bridging.[6] The conformation of the central part is governed by 1,3-allylic strain. The dihedral angles of the single bonds next to the allylic system are *gauche*$^+$ (60°) and *gauche*$^-$ (300°), respectively. Since the hydroxy acid **4a** is of great interest as a controlling element for the orientation of bridging peptide fragments we developed a novel synthesis for this compound.

Results and Discussion

In most of the published syntheses[7–9] of **4**, the aldehyde **17** (**cf**. Scheme 2) serves as a key building block. Extension is done either by reaction with 2-propenylmagnesium bromide followed by Claisen rearrangement or by the tactical sequence Wittig reaction, conversion to allylic halide and asymmetric alkylation. Our synthesis started with the chiral 3-hydroxy ester **5** which is available by yeast reduction of acetoacetate.[10] Alternatively a Noyori reduction might be used.[11] The latter option is of particular interest for the synthesis of other analogues. A subsequent silylation of the hydroxy ester with *tert*-butyldimethylsilyl chloride in the presence of imidazole gave the known compound **6**.[12] Reduction with diisobutylaluminium hydride (DIBAL-H) provided the aldehyde[12a,13] **7** that was converted to the enoate[14] **9** by reaction with the stabilized Wittig reagent $(Ph)_3P{=}CHCO_2Me$ (**8**). Reaction of the enoate **9** with 2.2 equivalents of DIBAL-H furnished the allylic alcohol **10**.[15] In order to introduce a methyl group at position 6 of the target hydroxy acid we used the reductive opening of an (iodomethyl)cyclopropane. Accordingly, the allylic alcohol was converted to the hydroxymethylcyclopropane **12** using the combination of diiodomethane, diethylzinc and the chiral dioxaborolane **11** (Charette method).[16] Since a direct conversion of the primary alcohol to the corresponding iodide (I_2, imidazole, PPh_3, CH_3CN) was not a clean reaction, the pathway *via* the mesylate **13** was followed. Treatment of the mesylate **13**, obtained from the alcohol **12** with mesyl chloride and triethylamine, with NaI in acetone gave an excellent yield of the iodide **14**. The reductive ring opening[17,18] of **14** was achieved with *n*-butyllithium in THF between −78 and −30 °C providing the alkene **15** in 73% yield. According to the ^{13}C NMR spectrum, this compound is diastereomerically pure (>98%).

For the extension of the alkene to the enoate we initially used the sequence of ozonolysis and Wittig reaction of the resulting aldehyde with the stabilized ylide **18**. However, the ozonide **16** proved to be rather stable and its reductive cleavage with dimethyl sulfide (2 mL/mmol of **15**) in CH_2Cl_2 required stirring for 1 week. Also the one-pot cleavage and Wittig reaction did not work.[19] Therefore we opted for the direct conversion of the alkene **15** to the enoate **19** by alkene cross-metathesis[20] with methyl 2-methylacrylate (**20**). Using an excess of **20** (10 equivs.) and 5 mol % of the Grubbs catalyst **21** gave a good yield of the desired enoate **19**. The original Grubbs catalyst provided the enoate **19** only

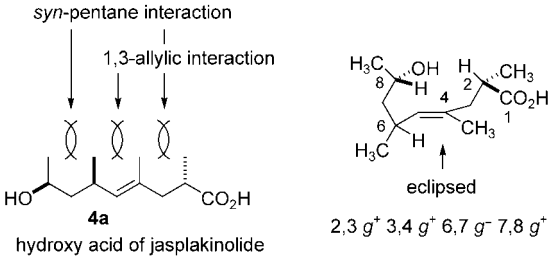
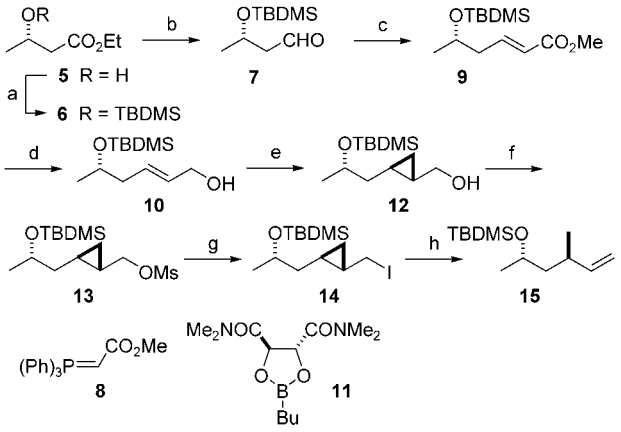


Figure 2. Possible conformation of the 8-hydroxy acid **4a** due to the avoidance of CH_3–CH_3 steric interactions.

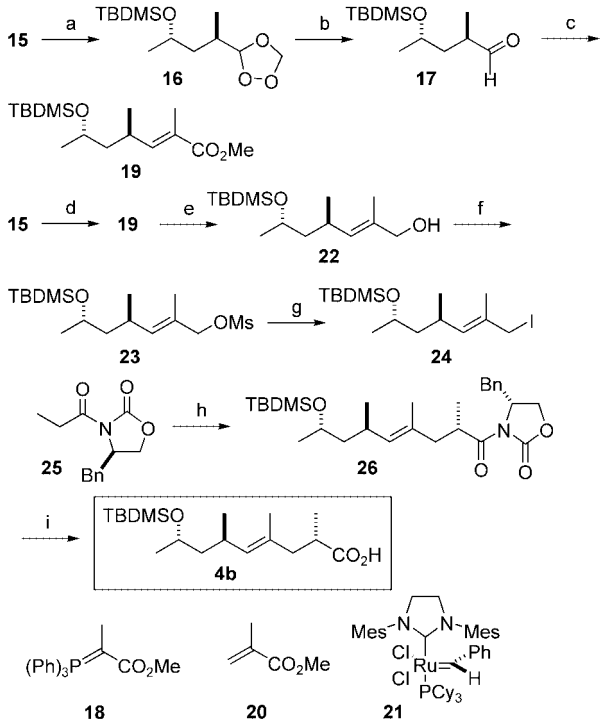


Scheme 1. Synthesis of the key building block **15** by a stereoselective Charette cyclopropanation followed by reductive cyclopropane opening of the iodomethylcyclopropane **14**. Reaction conditions: a) TBDMSCl, imidazole, CH_2Cl_2, 23 °C, 21 h, 100%; b) DIBAL-H, CH_2Cl_2, −78 to −30 °C, 0.5 h, 100%; c) $Ph_3PC{=}CHCO_2Me$ (**8**), benzene, 80 °C, 16 h, 97%; d) DIBAL-H, CH_2Cl_2, −78 to −30 °C, 1.5 h, 96%; e) Et_2Zn, CH_2Cl_2, $CH_3OCH_2CH_2OCH_3$, −10 °C, CH_2I_2, 10 min, then add **11**, −10 to 23 °C, 15.5 h, 96%; f) NEt_3, CH_3SO_2Cl, CH_2Cl_2; g) NaI, acetone, 0 to 23 °C, 3 h, 96% (from **12**); h) TMEDA, MS 4 Å, *n*-BuLi, −78 to −30 °C, 2.5 h, 73%.

in traces. The remaining steps to the desired acid were performed more or less according to the literature. Thus, reduction of ester **19** to the alcohol **22**, followed by conversion to the allylic mesylate **23** and substitution of the mesylate with iodide delivered the iodide[7b,9c] **24** in good overall yield for the three steps. Besides the mesylate **23**, the corresponding allylic chloride is also formed in less than 10%. For analytical purposes, the mesylate and chloride were separated. However, the mixture can be used as such for the next step. The iodide **24** was then used as the electrophile in an Evans alkylation[21] with the propionyloxazolidinone **25**. The latter was prepared from D-phenylalanine.[22] A final hydrolysis of the alkylation product **26** provided the TBDMS-protected hydroxy acid **4b**.[7,8,9]

Conclusion

The whole sequence involves 13 steps from the ester **6**. Key reactions include the Charette cyclopropanation of the allylic alcohol **10**, a reductive ring opening of the (iodomethyl)-cyclopropane **14** and an alkene metathesis to extend the alkene **15** to the enoate **19**. Since 3-hydroxy esters such as **5** are easily available by Noyori reduction, and the Evans alkylation can be done with different ester derivatives, analogues of the hydroxy acid **4** should be easily accessible by the route described in this paper.



Scheme 2. Conversion of the alkene **15** to the enoate **19** by a cross alkene metathesis reaction with the 2-methylacrylate **20** followed by chain extension *via* an Evans alkylation to yield compound **26**. Reaction conditions: a) O_3, CH_2Cl_2, $-78\,^{\circ}C$; b) Me_2S, CH_2Cl_2, $23\,^{\circ}C$, 7 d, 97%; c) $Ph_3PC{=}C(Me)CO_2Me$ (**18**), benzene, $80\,^{\circ}C$, 16 h, $E/Z = 3:1$, 82%; d) $CH_2{=}C(Me)CO_2Me$ (**20**), complex **21** (5 mol %), CH_2Cl_2, $40\,^{\circ}C$, 20 h, 73%; e) DIBAL-H, CH_2Cl_2, -78 to $-30\,^{\circ}C$, 1.5 h, 100%; f) CH_3SO_2Cl, NEt_3, CH_2Cl_2, $0\,^{\circ}C$, 30 min; g) NaI, acetone, 0 to $23\,^{\circ}C$, 3 h, 95% (from **22**); h) oxazolidinone **25**, $NaN(SiMe_3)_2$, THF, $-78\,^{\circ}C$, 2 h, add iodide **24**, $-78\,^{\circ}C$, 15 h, 61%; i) LiOH, H_2O_2, THF/H_2O, $0\,^{\circ}C$, 1.5 h, 100%.

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: $CDCl_3$ ($\delta_H = 7.25$ ppm, $\delta_C = 77.00$ ppm). Melting points: Büchi Melting Point B-540, uncorrected. 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 Machery-Nagel Polygram Sil G/UV_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used.

Ethyl (3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}butanoate (6)

To a stirred solution of alcohol **5** (38.3 g, 0.29 mol) in CH_2Cl_2 (500 mL) was added imidazole (39.5 g, 0.58 mol) at 0 °C and the mixture stirred for 5 min resulting in a homogeneous solution. Subsequently, *tert*-butyldimethylsilyl chloride (52.6 g, 0.348 mol) was added and the whole mixture stirred for 0.5 h at 0 °C and then at room temperature for 21 h. The reaction mixture was diluted with H_2O, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (4×75 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtrated, and concentrated to give **6** as colorless oil; yield: 71.4 g (100%). TLC (petroleum ether/ethyl acetate, 19:1): $R_f = 0.44$; $[\alpha]_D^{26}$: +22.0 (*c* 0.97, $CHCl_3$) {Ref.[12a] $[\alpha]_D^{23}$: +28 (*c* 1.5, $CHCl_3$)}. IR (neat): $\tilde{\nu} = 1739$, 1255, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$, 0.03 (2 s, 3H each), 0.83 [s, 9H, $SiC(CH_3)_3$], 1.17 (d, $J = 6.1$ Hz, 3H, H-4), 1.23 (t, $J = 7.1$ Hz, 3H, CH_3), 2.33 (dd, $J = 14.5$, 5.3 Hz, 1H, H-2), 2.44 (dd, $J = 14.5$, 7.6 Hz, 1H, H-2), 4.04–4.13 (m, 2H, CH_2), 4.21–4.29 (m, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.1$, −4.6, 14.2, 17.9, 23.9, 25.7, 44.9, 60.2, 65.8, 171.6.

(3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}butanal (7)

To a solution of ester **6** (123 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (1.0 M in hexane, 0.55 mL, 0.55 mmol) dropwise at $-78\,^{\circ}C$. After being stirred for 0.5 h at $-78\,^{\circ}C$, the temperature was raised to $-30\,^{\circ}C$, methanol (0.5 mL) was then added, the cooling bath removed, and the mixture warmed to 0 °C. A saturated solution of potassium sodium tar-

tarte was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O, 1:8) to afford aldehyde **7** as a colorless oil; yield: 101 mg (100%); TLC (petroleum ether/ethyl acetate, 6:1): $R_f = 0.47$; $[\alpha]_D^{27}$: +14 (*c* 1.0, $CHCl_3$) {Ref.[13] $[\alpha]_D^{23}$: +19 (*c* 2.0, $CHCl_3$)}; IR (neat): $\tilde{\nu}$ = 2930, 1715, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = −0.02, 0.00 (2 s, 3H each, $SiCH_3$), 0.79 [s, 9H, $SiC(CH_3)_3$], 1.16 (d, J = 6.2 Hz, 3H, H-4), 2.33 (dd, J = 15.9, 3.4 Hz, 1H, H-2), 2.47 (dd, J = 15.7, 2.5 Hz, 1H, H-2), 4.26–4.30 (m, H-3), 9.72 (s, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6, −4.0, 18.3, 24.6, 26.1, 53.4, 64.9, 202.7.

Methyl (2*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-hexenoate (9)

A mixture of the aldehyde **7** (51 mg, 0.25 mmol) and methoxycarbonylmethylenetriphenylphosphorane (**8**) (92 mg, 0.28 mmol) in benzene (2 mL) was refluxed overnight (80 °C, 16 h). The resulting precipitate was removed by filtration and washed with Et_2O. The filtrate was concentrated and the residue purified by chromatography (petroleum ether/Et_2O, 15:1) to afford the enoate **9** as colorless oil; yield: 67 mg (97%; *trans/cis* = 33:1 as determined by relative peak heights in the ^1H NMR spectrum); TLC (petroleum ether/ethyl acetate, 16:1): $R_f = 0.45$; $[\alpha]_D^{26}$: +7.8 (*c* 0.98, $CHCl_3$) {Ref.[14c] $[\alpha]_D^{18}$: +8.94 (*c* 1.01, $CHCl_3$)}; IR (neat): $\tilde{\nu}$ = 2954 , 2930, 1729, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.02 (2 s, 3H each, $SiCH_3$), 0.85 [s, 9H, $SiC(CH_3)_3$], 1.13 (d, J = 6.1 Hz, 3H, H-6), 2.27–2.31 (m, 2H, H-4), 3.70 (s, 3H, OCH_3), 3.86–3.94 (m, 1H, H-5), 5.81 (d, J = 15.7 Hz, 1H, H-2), 6.93 (dt, J = 15.7, 7.7 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.6, 18.0, 23.7, 25.8, 42.4, 51.3, 67.6, 122.8, 146.3, 166.8.

(2*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-hexen-1-ol (10)

To a solution of ester **9** (17.6 g, 68 mmol) in CH_2Cl_2 (150 mL) was added DIBAL-H (1.0 M in hexane, 150 mL, 150 mmol) dropwise at −78 °C. After being stirred for 1.5 h at −78 °C, the temperature was raised to −30 °C, methanol (2 mL) was added, and the mixture allowed to reach 0 °C. Then a saturated solution of potassium sodium tartarte (100 mL) was added and the mixture extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 4:1) to afford alcohol **10** as a colorless oil; yield: 15.0 g (96%); TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.49$; $[\alpha]_D^{26}$: +6.04 (*c* 0.98, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3343 (br), 2956, 2929, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.02 (2 s, 3H, $SiCH_3$), 0.86 [s, 9H, $SiC(CH_3)_3$], 1.11 (d, J = 6.1 Hz, 3H, H-6), 1.62 (s, br, 1H, OH), 2.09–2.21 (m, 2H, H-4), 3.77–3.85 (m, 1H, H-5), 4.07 (d, J = 4.0 Hz, 1H, H-1), 5.63–5.67 (m, 2H, H-3, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6, −4.6, 18.1, 23.4, 25.8, 42.5, 63.7, 68.4, 129.6, 131.2.

[(1*S*,2*R*)-2-((2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]-oxy}propyl)cyclopropyl]methanol (12)

To a mixture of CH_2Cl_2 (300 mL) and 1,2-dimethoxyethane (DME) (10.4 mL, 100 mmol) was added a solution of diethylzinc (1 M in hexane, 100 mL, 100 mmol) at −10 °C followed by the dropwise addition of CH_2I_2 (16.1 mL, 200 mmol) over 15–20 min while maintaining the internal temperature between −8 and −12 °C. After complete addition, the resulting clear solution was stirred for 10 min at −10 °C before a solution of dioxaborolane ligand 11 (16.21 g, 60 mmol) in CH_2Cl_2 (50 mL, 1.2 M) was added via a cannula over a 15–20 min period while maintaining the internal temperature below −5 °C. This was followed by the dropwise addition of alcohol **10** (11.5 g, 50.0 mmol), dissolved in CH_2Cl_2 (50 mL) while maintaining the internal temperature below −5 °C. After being stirred for 0.5 h at −10 °C, the mixture was allowed to reach room temperature and stirred for 15 h. The reaction was quenched with saturated NH_4Cl solution (50 mL) and 10% HCl (200 mL) and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were added to a mixture of 2 N NaOH (300 mL) and H_2O_2 (30%, 50 mL). The biphasic solution was stirred for 5 min and then the layers were separated. The organic phase was washed with 10% HCl (250 mL), Na_2SO_3 (250 mL), $NaHCO_3$ (250 mL), and brine (250 mL). After drying ($MgSO_4$), filtration and concentration of the organic layer under reduced pressure, the crude product was purified by flash chromatography (petroleum ether/Et_2O, 5:1) to afford **12** as colorless oil; yield:11.73 g (96%, the diastereomeric ratio was determined in the next step); TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.47$; $[\alpha]_D^{26}$: +22.2 (*c* 0.97, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3348 (br), 2956, 2929, 2857, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.04, 0.05 (2 s, 3H each, $SiCH_3$), 0.29–0.39 (m, 2H, cyclopropane CH_2), 0.63–0.72 (m, 1H, H-2′), 0.83–0.90 (m, 2H, H-1′), 0.88 [s, 9H, $SiC(CH_3)_3$], 1.12–1.19 (m, 1H, H-1″), 1.15 (d, J = 6.1 Hz, 3H, CH_3), 1.53–1.60 (m, 1H, H-1″), 3.37–3.52 (m, 2H, CH_2OH), 3.85 (q, J = 6.1 Hz, 1H, CHOR); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.5, 9.9, 13.8, 18.1, 21.1, 23.6, 25.9, 43.5, 67.1, 68.7. HRMS: calcd. for $C_{13}H_{28}O_2SiNa$: 267.17508; found: 267.17513.

[(1*S*,2*R*)-2-((2*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)cyclopropyl]methyl Methanesulfonate (13)

Triethylamine (6.3 mL, 45 mmol) and methanesulfonyl chloride (1.75 mL, 22.5 mmol) were added to a cooled (0 °C) solution of the alcohol **12** (3.67 g, 15 mmol) in dry CH_2Cl_2 (100 mL) under a nitrogen atmosphere. After being stirred for 30 min at 0 °C, the mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give **13** as colorless oil; yield: 4.84 g.

The residue was used for the next reaction without further purification. TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.40; $[\alpha]_D^{23}$: +7.89 (*c* 0.93, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2956, 2930, 2858, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03, 0.04 (2 s, 3H each, $SiCH_3$), 0.45–0.56 (m, 2H, cyclopropane CH_2), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.95–1.02 (m, 1H, H-2′), 1.14 (d, J = 6.0 Hz, 3H, CH_3), 1.15–1.19 (m, 1H, CH_2), 1.24 (s, br, 1H, H-1′), 1.56–1.62 (m, 1H, CH_2), 2.99 (s, 3H, Ms CH_3), 3.85 (q, J = 6.1 Hz, 1H, CHOR), 4.01–4.14 (m, 2H, CH_2OMs);

^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.5, 11.0, 14.9, 17.4, 18.1, 23.6, 25.9, 37.9, 43.2, 68.3, 74.7; HRMS: calcd. for $C_{14}H_{30}O_4SSiNa$ $[M+Na]^+$: 345.15263; found: 345.15299.

(1*R*,2*R*)-1-[(2*S*)-2-[*tert*-Butyl(dimethyl)silyl]oxy]-2-(iodomethyl)cyclopropane (14)

A solution of the crude sulfonate **13** (4.84 g, 15 mmol) in dry acetone (100 mL) was treated with sodium iodide (4.84 g, 135 mmol) at 0 °C. After being stirred for 3 h at room temperature, the mixture was diluted with petroleum ether (50 mL) and washed with H_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O, 8:1) to afford the iodide **14** as a pale yellow oil which is used immediately for the next step; yield: 5.11 g (96% from **12**); TLC (petroleum ether/ethyl acetate, 60:1): R_f = 0.44; IR (neat): $\tilde{\nu}$ = 2956, 2928, 2857 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04, 0.04 (2 s, 3H each, $SiCH_3$), 0.42–0.46 (m, 1H, cyclopropane CH_2), 0.59–0.63 (m, 1H, cyclopropane CH_2), 0.68–0.76 (m, 1H, cyclopropane CH), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.03–1.10 (m, 1H, CH_2), 1.15 (d, *J* = 6.0 Hz, 3H, CH_3), 1.24 (s, br, 1H, cyclopropane CH), 1.47–1.53 (m, 1H, CH_2), 3.09–3.19 (m, 2H, CH_2I), 3.85 (q, *J* = 6.1 Hz, 1H, CHOR); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.5, 13.7, 17.9, 18.1, 22.1, 23.3, 23.6, 25.9, 43.8, 68.4; HRMS: calcd. for $C_{13}H_{27}OISiNa$ $[M+Na]^+$: 377.07681; found: 377.07665.

(3*R*,5*S*)-5-[*tert*-Butyl(dimethyl)silyl]oxy-3-methylhex-1-ene (15)

A solution of the iodide **15** (15.6 g, 44.0 mmol) in dry Et_2O (250 mL) containing 4 Å molecular sieves (7.7 g) and TMEDA (13.2 mL, 88 mmol) was treated with *n*-BuLi (2.5 M in hexane, 35.2 mL, 88 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, then the temperature was raised to −30 °C over 2 h. The reaction was quenched with H_2O (100 mL), the layers were separated and the aqueous layer extracted with Et_2O (3 × 75 mL). The combined organic layers were successively washed with 10% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), H_2O and brine, respectively. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (petroleum ether) to give the alkene **15** as a colorless oil; yield: 7.33 g (73%, >98% de); TLC (petroleum ether): R_f = 0.44; $[\alpha]_D^{26}$: +3.91 (*c* 0.98, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 2957, 2927, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.98 (d, *J* = 6.7 Hz, 3H, CH_3), 1.12 (d, *J* = 6.0 Hz, 3H, H-6), 1.24–1.29 (m, 1H, H-4), 1.49–1.56 (m, 1H, H-4), 2.23 (m, 1H, H-3), 3.78–3.85 (m, 1H, H-5), 4.90 (d, *J* = 10.3 Hz, 1H, H-1), 4.93 (d, *J* = 17.2 Hz, 1H, H-1), 5.65–5.74 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.3, 18.1, 20.1, 23.7, 25.9, 34.4, 46.7, 66.5, 112.2 144.8; HRMS: calcd. for $C_{13}H_{28}O_2Si$ $[M-1]^+$: 227.183116; found: 227.183745.

3-[(1*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylbutyl]-1,2,4-trioxolane (16)

Ozone was passed through the solution of **15** (6.85 g, 30.0 mmol) in 100 mL of CH_2Cl_2 (0.3 M) at −78 °C until a deep blue color appeared (2 h). The solution was kept at −78 °C before nitrogen gas was passed through it until the color faded (2 h). The solution was used for the next reaction without further purification. For analytical purposes, a sample was carefully concentrated under vacuum. TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.40; IR (neat): $\tilde{\nu}$ = 2957, 2930, 2886, 2858, 1463, 1255, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.05 (s, 6H, $SiCH_3$), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.97 (dd, *J* = 6.8, 2.3 Hz, 3H, CH_3), 1.14 (d, *J* = 6.1 Hz, 3H, H-4′), 1.32–1.71 (m, 1H, H-2′), 2.04–2.12 (m, 1H, H-2′), 3.86–3.96 (m, 1H, H-1′), 4.93–4.96 (m, 1H, H-3), 5.00 (d, *J* = 3.8 Hz, 1H, H-5), 5.20 (d, *J* = 2.0 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.1, 13.5, 13.7, 18.2, 24.4, 25.8, 31.3, 31.6, 41.2, 41.4, 65.6, 94.2, 94.3, 106.8; HRMS: calcd. for $C_{13}H_{28}O_4SiNa$ $[M+Na]^+$: 299.16491; found: 299.16494.

(2*R*,4*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpentanal (17)

The ozonide **16** was reduced to aldehyde by the addition of dimethyl sulfide (60 mL, 2 mL/mmol). The solution was allowed to warm to room temperature and stirred for 7 days, then washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), respectively. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O, 15:1) to afford aldehyde **17** as a colorless oil; yield: 6.71 g (97%, over 2 steps from alkene **15**); TLC (petroleum ether/ethyl acetate, 16:1): R_f = 0.47; $[\alpha]_D^{24}$: +6.20 (*c* 0.89, $CHCl_3$) {Ref.[9b] $[\alpha]_D^{25}$: +23.2 (*c* 0.06, $CHCl_3$)}; IR (neat): $\tilde{\nu}$ = 2957, 2930, 2858, 1728, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.05 (s, 6H, $SiCH_3$), 0.87 [s, 9H, $SiC(CH_3)_3$], 1.09 (d, *J* = 6.0 Hz, 3H, CH_3), 1.16 (d, *J* = 6.1 Hz, 3H, H-5), 1.47–1.54 (m, 1H, H-3), 1.80–1.87 (m, 1H, H-3), 2.47–2.57 (m, 1H, H-4), 3.83–3.96 (m, 1H, H-4), 9.61 (s, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8, −4.1, 13.4, 18.0, 24.3, 25.8, 40.4, 43.5, 66.1, 205.2.

Methyl (2*E*,4*R*,6*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylhept-2-enoate (19)

Methyl methacrylate (20) (222 μL 2.0 mmol) and alkene **15** (46 mg 0.2 mmol) were added to a solution of Grubbs catalyst 21 (8 mg, 10^{-2} mmol, 5 mol %) in CH_2Cl_2 (1 mL). The mixture was refluxed at 40 °C under nitrogen for 20 h. The reaction mixture was then concentrated to about 0.5 mL and purified directly by flash chromatography (petroleum ether/Et_2O, 20:1) to afford the enoate **19** as a colorless oil; yield: 42 mg (73%, only *trans* was detected by ^{1}H NMR spectroscopy); TLC (petroleum ether/ethyl acetate, 20:1): R_f = 0.52; $[\alpha]_D^{26}$: −6.98 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 2956, 2929, 2857, 1719, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.98 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10 (d, *J* = 6.0 Hz, 3H, H-7), 1.32–1.38 (m, 1H, H-5), 1.46–1.53 (m, 1H, H-5), 1.83 (s, 3H, CH_3), 2.58–2.69 (m, 1H, H-4), 3.72 (s, 3H, OCH_3), 3.75–3.79 (m, 1H, H-6), 6.57 (d, *J* = 9.9 Hz, 1H, H-3);

^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8, −4.2, 12.4, 18.0, 19.5, 24.0, 25.8, 29.7, 46.5, 51.7, 66.2, 125.7, 148.2, 168.9; HRMS: calcd. for $C_{16}H_{32}O_3SiNa$: 323.20129; found: 323.20125.

(2*E*,4*R*,6*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylhept-2-en-1-ol (22)

A solution of ester **19** (990 mg, 3.3 mmol) in CH_2Cl_2 (100 mL) was treated with DIBAL-H (1.0 M in hexane, 7.3 mL, 7.3 mmol) in a dropwise fashion at −78 °C. After stirring for 1.5 h at −78 °C, the temperature was raised to −30 °C, methanol (0.5 mL) was added, and the mixture warmed up to 0 °C. The other work-up manipulations were carried out as described for the synthesis of **10**. The crude product was used without further purification; yield: 898 mg (100%), colorless oil; TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.50; $[\alpha]_D^{25}$: −1.94 (*c* 0.25, $CHCl_3$) {Ref.[9c] $[\alpha]_D^{24}$: −1.6 (*c* 0.91, $CHCl_3$)}; IR (neat): $\tilde{\nu}$ = 3336 (br), 2957, 2928, 2857, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.93 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10 (d, *J* = 6.0 Hz, 3H, CH_3), 1.26 (s, br, 1H, OH), 1.26–1.32 (m, 1H, H-5), 1.41–1.48 (m, 1H, H-5), 1.66 (s, 3H, CH_3), 2.47–2.54 (m, 1 H, H-4), 3.73–3.81 (m, 1H, H-6), 3.97 (s, 2H, C*H*$_2$OH), 6.57 (d, *J* = 9.9 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.2, 13.7, 18.1, 20.5, 24.0, 25.9, 28.6, 47.5, 66.5, 69.0, 132.8, 133.0.

(2*E*,4*R*,6*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylhept-2-enyl Methanesulfonate (23)

Triethylamine (340 μL, 1.25 mmol) and methanesulfonyl chloride (97 μL, 1.25 mmol) were added to a cooled (0 °C) solution of the alcohol **22** (221 mg, 0.81 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere. After being stirred for 30 min at 0 °C, the mixture was diluted with Et_2O (10 mL), washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated under vacuum providing the crude mesylate **23** as a colorless oil; yield: 275 mg (97%). The crude product, containing around 10% of the corresponding chloride was used for the next step without further purification. TLC (petroleum ether/ethyl acetate, 8:1): R_f = 0.54; $[\alpha]_D^{24}$: −1.04 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2956, 2930, 1353, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $SiCH_3$), 0.89 [s, 9H, $SiC(CH_3)_3$], 0.98 (d, *J* = 6.8 Hz, 3H, H-4a), 1.39 (d, *J* = 6.3 Hz, 3H, H-7), 1.50–1.55 (m, 1H, H-5), 1.59 (s, 3H, H-2a), 1.71–1.78 (m, 1H, H-5), 2.46–2.54 (m, 1H, H-4), 2.97 (s, 3H, Ms CH_3), 3.98 (s, 2H, H-1), 4.73–4.78 (m, 1H, H-6), 5.18 (dd, *J* = 9.6, 2.6 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3, 13.5, 18.4, 20.8, 21.3, 25.9, 28.6, 38.6, 44.2, 68.3, 78.8, 129.0, 134.1; HRMS: calcd. for $C_{16}H_{34}O_4SSiNa$ $[M+Na]^+$: 373.18393; found: 373.18381.

(2*E*,4*R*,6*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-iodo-2,4-dimethylhept-2-ene (24)

A solution of the crude mesylate **23** (274 mg, 0.78 mmol) in dry acetone (5 mL) was treated with sodium iodide (1.05 g, 7.0 mmol) at 0 °C. After being stirred for 3 h at room temperature, the mixture was diluted with petroleum ether (10 mL) and washed with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by short flash chromatography (petroleum ether/Et_2O, 1:1) to yield the iodide **24** as pale yellow oil; yield: 292 mg (94% from **22**); TLC (petroleum ether/ethyl acetate, 100:1): R_f = 0.40; IR (neat): $\tilde{\nu}$ = 2957, 2928, 2857, 1361, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.90 (d, *J* = 4.0 Hz, 3H, H-4a), 1.10 (d, *J* = 6.1 Hz, 3H, H-7), 1.26–1.33 (m, 1H, H-5), 1.39–1.46 (m, 1H, H-5), 1.76 (s, 3H, H-2a), 2.37–2.46 (m, 1H, H-4), 3.71–3.77 (m, 1H, H-6), 3.92 (s, 2H, H-1), 5.44 (d, *J* = 9.6 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8, −4.3, 15.5, 17.0, 18.1, 19.8, 23.8, 25.9, 29.6, 47.0, 66.3, 131.3, 136.2; HRMS: calcd. for $C_{15}H_{31}OISiNa$: 405.10867; found: 405.10812.

(4*R*)-4-Benzyl-3-((2*S*,4*E*,6*R*,8*S*)-8-{[*tert*-butyl(dimethyl)silyl]oxy}-2,4,6-trimethylnon-4-enoyl)-1,3-oxazolidin-2-one (26)

To a solution of propionyl-1,3-oxazolidin-2-one **25** (173 mg, 0.74 mmol) in THF (20 mL) was added sodium hexamethyldisilazide (0.4 mL, 2 M in THF, 0.8 mmol) at −78 °C. The solution was then stirred at −78 °C for 2 h before a solution of iodide 24 (264 mg, 0.64 mmol) in THF (3 mL) was added. The reaction was allowed to proceed at −78 °C for 15 h, then the mixture was allowed to reach 0 °C. Thereafter, the mixture was partitioned between saturated NH_4Cl (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to yield a white amorphous solid. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 6:1) to afford the alkylation product **26** as a sticky colorless oil (yield: 190 mg, 61%) and recovered iodide 24 (24%). TLC petroleum ether/ethyl acetate, 6:1): R_f = 0.54; $[\alpha]_D^{25}$: −30.0 (*c* 0.94, $CHCl_3$) {Ref.[9c] $[\alpha]_D^{24}$: −35.2 (*c* 0.94, $CHCl_3$)}; IR (neat): $\tilde{\nu}$ = 2956, 2929, 1783, 1387 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H, $SiCH_3$), 0.89 (d, *J* = 6.6 Hz, 3H, CH_3), 0.90 [s, 9H, $SiC(CH_3)_3$], 1.11 (d, *J* = 5.8 Hz, 3H, H-9′), 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 1.27–1.34 (m, 1H, H-7′), 1.43–1.50 (m, 1H, H-7′), 1.68 (s, 3H, CH_3), 1.97–2.03 (m, 1H, H-3′), 2.46–2.50 (m, 1H, H-6′), 2.52 (m, 1H, H-3′), 2.69–2.75 (m, 1H, benzylic H), 3.26–3.30 (m, 1H, benzylic H), 3.75–3.82 (m, 1H, H-8′), 3.92–4.01 (m, 1H, H-2′), 4.13–4.20 (m, 2H, H-5), 4.66–4.72 (m, 1H, H-4), 5.03 (d, *J* = 9.4 Hz, 1H, H-5′), 7.21–7.35 (m, 5H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.5, 15.4, 16.0, 18.0, 20.8, 23.6, 25.8, 29.0, 35.4, 38.0, 43.9, 47.5, 55.2, 68.5, 66.6, 127.2, 128.8, 129.3, 130.1, 134.4, 135.3, 153.0, 177.0.

(2*S*,4*E*,6*R*,8*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4,6-trimethylnon-4-enoic Acid (4b)

A cooled (0 °C) solution of the oxazolidinone **26** (73 mg, 0.15 mmol) in THF (2.5 mL) was treated with H_2O_2 (35% by weight, 68 μL, 0.60 mmol), then with a solution of $LiOH \cdot H_2O$ (13 mg, 0.30 mmol) in H_2O (1 mL). The solution was stirred at 0 °C for 1.5 h. After TLC indicated completion of the hydrolysis, a mixture of saturated Na_2SO_3 (2 mL) and saturated $NaHCO_3$ (2 mL) was added at 0 °C. The mixture was partially

concentrated and then diluted with H_2O (2 mL). The aqueous solution was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 6:1) to afford the acid **4b** as a colorless oil; yield: 49 mg (100%); TLC (petroleum ether/ethyl acetate, 6:1): $R_f = 0.57$; $[\alpha]_D^{22}$: -9.0 (*c* 0.23, CH_2Cl_2) {Ref.[9c] $[\alpha]_D^{24.5}$: -9.2 (*c* 1.1, $CHCl_3$)}; IR (neat): $\tilde{\nu} = 2957$, 2929, 2857, 1709, 1255 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6H, $SiCH_3$), 0.87 (s, 3H, CH_3), 0.87 [s, 9H, $SiC(CH_3)_3$], 1.08 (d, $J = 6.3$ Hz, 3H, CH_3), 1.10 (d, $J = 7.3$ Hz, 3H, CH_3), 1.25–1.31 (m, 1H, H-7), 1.39–1.45 (m, 1H, H-7), 1.59 (s, 3H, CH_3), 1.98–2.04 (m, 1H, H-3), 2.35–2.41 (m, 1H, H-3), 2.38–2.46 (m, 1H, H-6), 2.56–2.65 (m, 1H, H-2), 3.70–3.78 (m, 1H, H-8), 4.96 (d, $J = 9.5$ Hz, 1H, H-5), 11.43 (s, br, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.8$, -4.4, 15.6, 16.1, 18.3, 20.9, 23.6, 25.9, 29.1, 37.8, 43.8, 47.5, 66.7, 129.9, 134.3, 183.0.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (grant Ma 1012/13–1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

[1] a) T. M. Zabriskie, J. A. Klocke, C. M. Ireland, A. H. Marcus, T. F. Molinski, D. J. Faulkner, C. Xu, J. C. Clardy, *J. Am. Chem. Soc.* **1986**, *108*, 3123–3124; b) P. Crews, L. V. Manes, M. Boehler, *Tetrahedron Lett.* **1986**, *27*, 2797–2800.
[2] a) S. C. Posey, B. E. Bierer, *J. Biol. Chem.* **1999**, *274*, 4259–4265; b) M. R. Bubb, I. Spector, B. B. Beyer, K. M. Fosen, *J. Biol. Chem.* **2000**, *275*, 5163–5170; c) A. Holzinger, *Meth. Mol. Biol.* **2001**, *161*, 109–120.
[3] W. R. Chan, W. F. Tinto, P. S. Manchand, L. J. Todaro, *J. Org. Chem.* **1987**, *52*, 3091–3093.
[4] a) A. B. Smith, III, S. M. Condon, J. A. McCauley, *Acc. Chem. Res.* **1998**, *31*, 35–46; b) S. L. Schreiber, *Bioorg. Med. Chem.* **1998**, *6*, 1127–1152.
[5] a) R. W. Hoffmann, M. Stahl, U. Schopfer, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 559–566; b) R. W. Hoffmann, D. Stenkamp, T. Trieselmann, R. Göttlich, *Eur. J. Org. Chem.* **1999**, 2915–2927; c) R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134–2150; *Angew. Chem. Int. Ed.* **2000**; *39*, 2054–2070; d) R. W. Hoffmann, R. Göttlich, U. Schopfer, *Eur. J. Org. Chem.* **2001**, 1865–1871.
[6] A conformational search (Macromodel) on a derivative of **4a** (methyl ester, 8-*O*-acetyl) revealed 6 low energy conformations (within 1 kcal of the minimum). In 4 of these, the conformation corresponds to the one depicted in Figure 2.
[7] For syntheses of the acid **4**, see: a) U. Schmidt, W. Siegel, K. Mundinger, *Tetrahedron Lett.* **1988**, *29*, 1269–1270; b) S.-K. Kang, D.-H. Lee, *Synlett* **1991**, 175–176; c) A. V. Rama Rao, M. K. Gurjar, B. R. Nallaganchu, A. Bhandari, *Tetrahedron Lett.* **1993**, *34*, 7081–7084.
[8] For total syntheses of jasplakinolide (**1**), see: a) P. A. Grieco, Y. S. Hon, A. Perez-Medrano, *J. Am. Chem. Soc.* **1988**, *110*, 1630–1631; b) K. S. Chu, G. R. Negrete, J. P. Konopelski, *J. Org. Chem.* **1991**, *56*, 5196–5201; c) A. V. Rama Rao, M. K. Gurjar, B. R. Nallaganchu, A. Bhandari, *Tetrahedron Lett.* **1993**, *34*, 7085–7088; d) Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994**, *39*, 603–612; e) P. Ashworth, B. Broadbelt, P. Jankowski, P. Kocienski, A. Pimm, R. Bell, *Synthesis* **1995**, 199–206.
[9] For total syntheses of geodiamolide (**2**), see: a) P. A. Grieco, A. Perez-Medrano, *Tetrahedron Lett.* **1988**, *29*, 4225–4228; b) Y. Hirai, K. Yokota, T. Yamazaki, T. Momose, *Heterocycles* **1990**, *30*, 1101–1119; c) T. Shioiri, T. Imaeda, Y. Hamada, *Heterocycles* **1997**, *46*, 421–442.
[10] D. Seebach, M. A. Sutter, R. H. Weber, M. F. Züger, *Org. Synth., Coll. Vol.* **1990**, *7*, 215–220.
[11] M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1992**, *71*, 1–13.
[12] a) K. Mori, Z.-H. Qian, *Bull. Soc. Chim. Fr.* **1993**, *130*, 382–387; b) D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, J. O. Liu, *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254; c) K. Marukawa, K. Mori, *Eur. J. Org. Chem.* **2002**, 3974–3978.
[13] G. Solladié, F. Somny, F. Colobert, *Tetrahedron: Asymmetry* **1997**, *8*, 801–810.
[14] a) B. Ernst, B. Wagner, *Helv. Chim. Acta* **1989**, *72*, 165–171; b) J. Sakaki, Y. Sugita, M. Sato, C. Kaneko, *Tetrahedron* **1991**, *47*, 6197–6214; c) K. Ohta, O. Miyagawa, H. Tsutsui, O. Mitsunobu, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 523–535; d) H. Nakamura, M. Ono, Y. Shida, H. Akita, *Tetrahedron: Asymmetry* **2002**, *13*, 705–713.
[15] a) G. E. Keck, A. Palani, S. F. McHardy, *J. Org. Chem.* **1994**, *59*, 3113–3122; b) K. B. Jorgensen, T. Suenaga, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 8855–8858; c) K. B. Jorgensen, H. Koshino, T. Nakata, *Heterocycles* **1998**, *47*, 679–683.
[16] a) A. B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952; b) A. B. Charette, S. Francoeur, J. Martel, N. Wilb, *Angew. Chem.* **2000**, *112*, 4713–4716; *Angew. Chem. Int. Ed.* **2000**, *39*, 4539–4542; c) A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001**, *123*, 12168–12175.
[17] A. Charette, J. Naud, *Tetrahedron Lett.* **1998**, *39*, 7259–7262.
[18] A. K. Ghosh, C. Liu, *Org. Lett.* **2001**, *3*, 635–638.
[19] a) Y. S. Hon, L. Lu, *Tetrahedron* **1995**, *51*, 7937–7942; b) Y. S. Hon, L. Lu, R. C. Chang, S. W. Lin, P. P. Sun, C. F. Lee, *Tetrahedron* **2000**, *56*, 9269–9279.
[20] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
[21] D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
[22] a) J. R. Gage, D. A. Evans, *Org. Synth.* **1989**, *68*, 77–82; b) J. R. Gage, D. A. Evans, *Org. Synth.* **1989**, *68*, 83–91.

