The Formal Total Synthesis of Epothilone A

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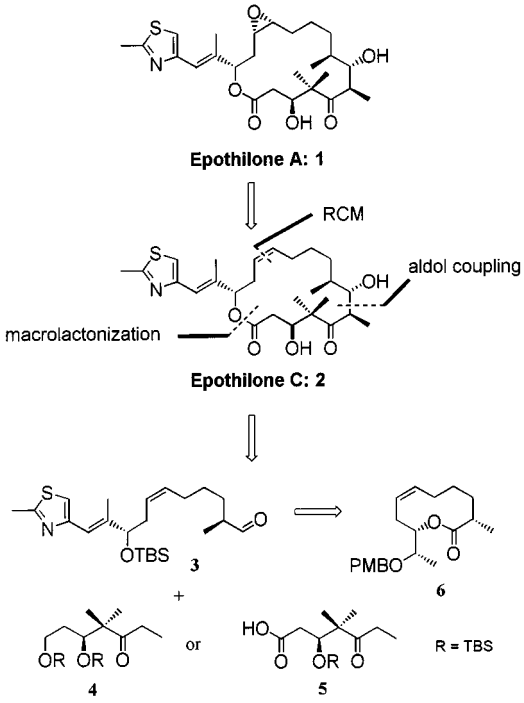
The formal total synthesis of epothilone A is described. The key steps in the synthesis of the northern hemisphere are a Z-selective ten-membered ring-closing metathesis reaction (RCM) and the diastereoselective alkylation at C8. Aldehyde **3** is formed by introduction of the thiazole moiety by a Wittig reaction and subsequent functional group transformation. An efficient route to keto acid **5** is described.

Introduction

Epothilones were isolated from the myxobacteria *Sorangium cellulosum* and were characterized by Höfle et al.[1] These compounds have drawn much attention, as their biological activity is closely related to that of Taxol® and both compounds seem to bind to the same receptor.[2] The antitumor activity of both compounds is due to the stabilization of microtubules, but because epothilones are much more active against multi-drug-resistant cells (MDR) than taxol is, epothilones are regarded as promising new agents for the treatment of ovarian and breast cancer.[3]

The important biological activity of epothilones, combined with some interesting synthetic problems initiated a variety of different research projects towards their total synthesis.[4]

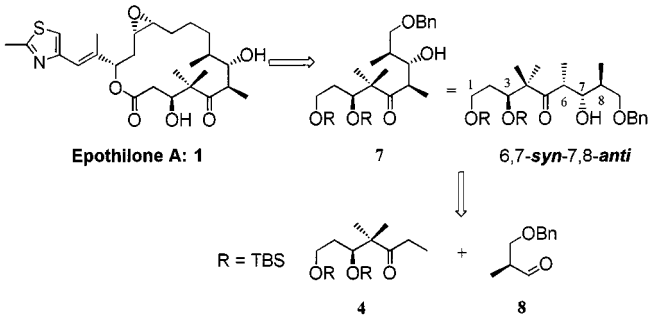
There are two regions of chemical complexity in the carbon skeleton of epothilones (Scheme 1): The northern hemisphere features an epoxide and a thiazole moiety attached by an *E*-trisubstituted double bond; the southern part of the molecule can be regarded as a polypropionate fragment (C1−C9), and an aldol reaction may possibly be used to establish the C6−C7 carbon bond. The biosynthetic precursor of a retrosynthetic disassembly, epothilone C (**2**), is constructed by macrolactonization of the aldol product which forms from aldehyde **3** and either ethyl ketone **4** or keto acid **5**. The key intermediate in our synthesis of aldehyde **3** is the ten-membered lactone **6**.



Scheme 1. Retrosynthesis of epothilone A

Results and Discussion

When we initiated our research, it was not clear if the aldol reaction between ethyl ketone **4** and an aldehyde fragment would generate the desired stereochemistry of epothilones. For this reason we began our studies with the synthesis of ketone **4** so that we could investigate this important aldol reaction. Aldehyde **8**, generated from 3-hydroxyisobutyric acid, could possibly be a suitable coupling partner towards the synthesis of epothilones (Scheme 2).



Scheme 2. Synthesis of the C1−C9 fragment of epothilones

Ethyl ketone **4** and keto acid **5** were synthesized according to the strategy employed by Masamune et al. for their synthesis of bryostatin.[5] Diol **9** was protected as a benzyl

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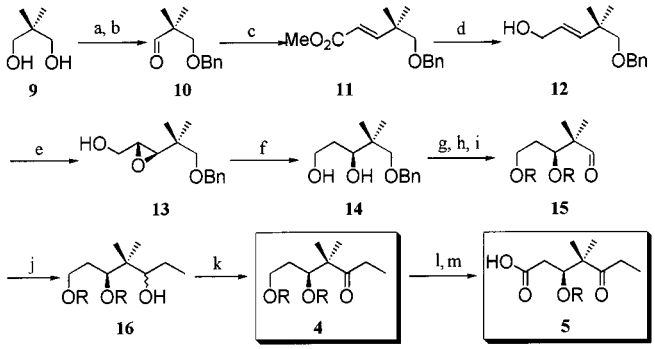
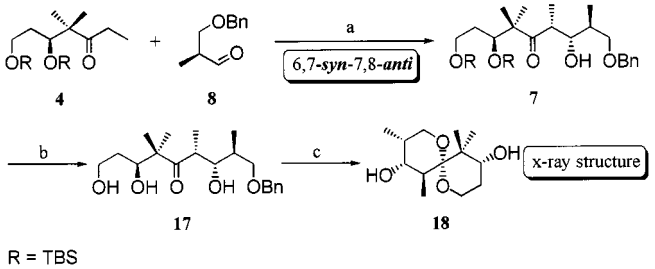
ether which was then oxidized to the corresponding aldehyde **10** (Scheme 3). Subsequent Wadsworth−Horner−Emmons reaction generated the α,β-unsaturated ester **11**, which was reduced to the allylic alcohol **12** with the aid of DIBAl−H. The hydroxyl group was introduced stereospecifically via epoxide **13**, which was generated by Sharpless asymmetric epoxidation. Reductive epoxide opening with Red-Al,[6] followed by protection of the resultant diol **14** as a bis(TBS ether), debenzylation, and Dess−Martin oxidation furnished aldehyde **15**. The addition of ethylmagnesium bromide and subsequent reoxidation gave ethyl ketone **4** which was further elaborated to keto acid **5** by TFA-catalyzed deprotection of the primary TBS ether followed by PDC oxidation.



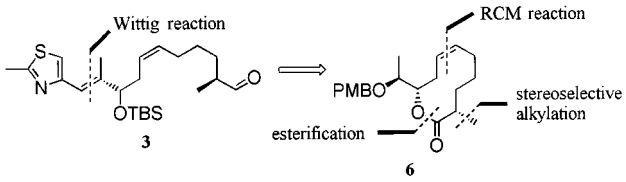
Scheme 3. (a) BnCl, KO*t*-Bu, dioxane, 2 h, 90°C, 91%; (b) Swern ox., 1 h, −78°C→0°C, 93%; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene/THF, 1 h, 0°C→room temp., 93%; (d) DIBAl-H, Et_2O, 3 h, 0°C→room temp., 99%; (e) Sharpless: molecular sieves 4A, $Ti(OiPr)_4$, (−)-diethyl tartrate, *t*BuOOH, CH_2Cl_2, −40°C→room temp., 96%; (f) Red-Al, THF, 1 h, 0°C, 96%; (g) TBSCl, imidazole, DMF, 44 h, 60°C, 98%; (h) H_2, 10% Pd/C, EtOH, 48 h, room temp., 80%; (i) Swern ox., 1 h, −78°C→0°C, 97%; − (j) EtMgBr, THF, 0°C, 15 min, 82%; (k) Jones ox. 0°C, 10 min, 80%; (l) CH_2Cl_2:TFA:H_2O (10:9:1); (m) PDC, DMF, 68% over two steps

The aldol reaction between aldehyde **8** and ethyl ketone **4** gave a single diastereomer with the desired 6,7-*syn*-7,8-*anti* stereochemistry (Scheme 4). The configurations at the newly generated carbons were confirmed by an X-ray structural analysis of spiro ketal **18**, which cyclized upon deprotection of the aldol product **7**.[4o] Even though we used this particular aldol coupling only as a model reaction, propionate fragments were used in Danishefsky's,[4d] Mulzer's[4k] and White's[4m] total syntheses to control the C7−C8 stereochemistry of epothilones.



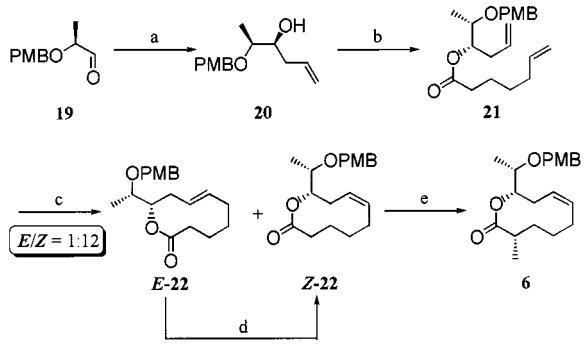
Scheme 4. (a) LDA, THF, 15 min, −78°C, 74%; (b) HF (48%), MeCN, 3 h, room temp., 96%; (c) H_2, Pd/C, MeOH, 24 h, room temp., 58%

Our retrosynthetic analysis of the northern hemisphere, i.e., aldehyde **3**, leads back to the ten-membered lactone **6** obtained by a ring-closing metathesis (RCM) reaction (Scheme 5). By synthesizing a smaller-sized lactone, we expected to circumvent the rather unsatisfying *E*/*Z*-ratio observed for 16-membered macrocycle. This completely functionalized molecule would enable us to introduce the required trisubstituted double bond and the thiazole moiety by a Wittig reaction; the C8 methyl group could be introduced by diastereoselective alkylation.



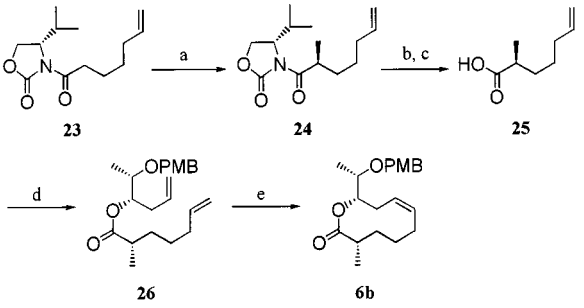
Scheme 5. Lactone **6** as the precursor of the northern hemisphere of epothilone A

The synthesis of **6** (Scheme 6) involved protection of (*S*)-ethyl lactate with PMB-trichloroacetimidate followed by reduction with $LiAlH_4$. Swern oxidation to give **19** and subsequent addition of allyltrimethylsilane (*de* = 91%) provided the desired diastereomer, alcohol **20**, as the major compound.[7] Esterification with 6-heptenoic acid according to Steglich's protocol[8] gave ester **21**, which set the stage for our selective RCM reaction with Grubbs' catalyst in refluxing dichloromethane. The *Z*-isomer (*Z*-**22**) was obtained in a reproducible excess of *Z*/*E* = 12:1 when the reaction was performed with freshly recrystallized $[RuCl_2(PCy_3)_2CHPh]$. When the separated *E*-isomer (*E*-**22**) was subjected to the same metathesis conditions, complete isomerization to the *Z*-isomer took place (Scheme 6). Computational analysis of both isomers showed the *Z*-isomer to be 9 kcal/mol lower in energy than the *E*-isomer, indicating that the *Z*-isomer is the thermodynamically controlled product. Lactone *Z*-**22** was methylated diastereoselectively with NaHMDS and methyl iodide at −78°C to introduce the biologically important methyl group at C8 (Scheme 6).[9] The configuration at C8 was assigned by comparing this product to the RCM product when (2*S*)-methyl 6-heptenoic acid was used in the esterification step.



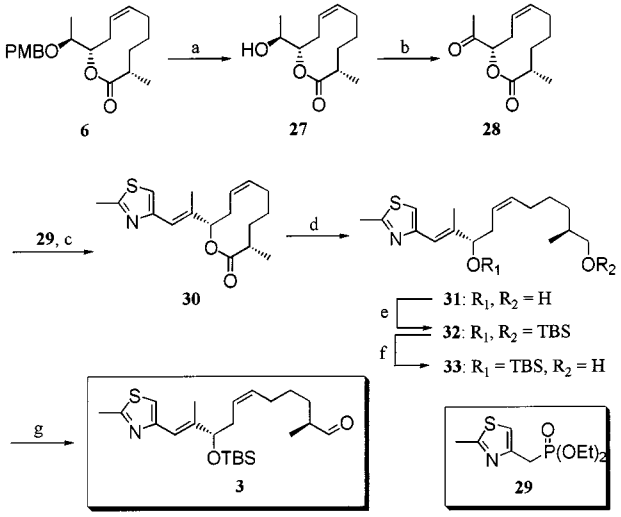
Scheme 6. (a) allyltrimethylsilane, $SnCl_4$, CH_2Cl_2, −78°C, 88%; (b) 6-heptenoic acid, DCC, DMAP, CH_2Cl_2, room temp., 94%; (c) $RuCl_2(PCy_3)_2CHPh$ (20 mol%), CH_2Cl_2, reflux, 63%, *Z*:*E* = 12:1; (d) $RuCl_2(PCy_3)_2CHPh$ (20 mol%), CH_2Cl_2, reflux, 60%; (e) NaHMDS, THF, MeI, −78°C, 82%

Acid **25** was synthesized according to the Evans protocol (Scheme 7). *N*-(6-Heptenoyl)-oxazolidinone **23** was selectively methylated to give **24**, thus establishing the desired stereochemistry. Reduction with $LiAlH_4$[10] and subsequent oxidation generated the required (2*S*)-methyl-6-heptenoic acid **25**. Esterification with alcohol **20** and RCM of the resultant ester **26** gave lactone **6b**, whose NMR spectrum is identical to that of the product obtained when methylation is the last step.



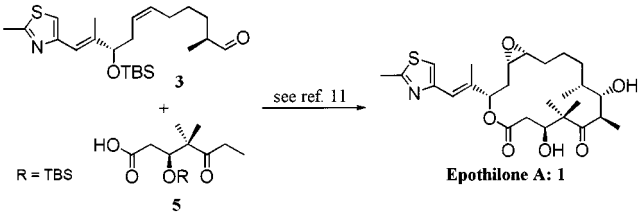
Scheme 7. (a) NaHMDS, THF, −78°C, MeI, 73%; (b) $LiAlH_4$, Et_2O, 0°C, 76%. (c) PDC, CH_2Cl_2, room temp., 61%; (d) **20**, DCC, DMAP, CH_2Cl_2, room temp., 92%; (e) $RuCl_2(PCy_3)_2CHPh$ (20 mol%), high dilution, CH_2Cl_2, reflux, 53%

Further elaboration to aldehyde **3** involved deprotection of the PMB group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in aqueous dichloromethane (Scheme 8). Oxidation with tetra-*n*-propylammonium perruthenate (TPAP) generated ketone **28** which was then subjected to a Horner−Emmons reaction with thiazole phosphonate **29** to produce the 10-membered epothilone analog **30** in 65% yield. $LiAlH_4$ reduction of lactone **30** generated diol **31**, which was protected as the corresponding TBS ether (**32**) with 3 equiv. TBS triflate and 2,6-lutidine in dichloromethane. Selective deprotection of the primary ether with CSA[11] in methanol followed by Dess−Martin oxidation of the resultant alcohol **33** completed the synthesis of aldehyde **3**.



Scheme 8. (a) DDQ, CH_2Cl_2/H_2O 18:1, room temp., 1 h, 98%; (b) TPAP, NMO, molecular sieves 3A, CH_2Cl_2, room temp., 1 h, 83%; (c) **29**, n-BuLi, −78°C → room temp. 2 h, 65%; (d) $LiAlH_4$, Et_2O, 0°C, 1 h, 95%; (e) TBS triflate, lutidine, CH_2Cl_2, −78°C, 91%; (f) CSA, CH_2Cl_2/MeOH 1:1, 0°C, 92%; (g) Dess−Martin periodinane, CH_2Cl_2, 0°C, 1 h, 93%

It is noteworthy, that our strategy to aldehyde **3** does not require any additional chiral auxiliary besides (*S*)-ethyl lactate. The final coupling steps follow the procedure employed by Nicolaou et al.[11] in their total synthesis of epothilone A (**1**) (Scheme 9).



Scheme 9. Final steps in the synthesis of epothilone A

Conclusion

Our convergent route, which represents a formal total synthesis of epothilone A (**1**) in connection with Nicolaou′s work, features a practicable synthesis of keto acid **5**, which may be prepared in multigram quantities from achiral starting material, and a completely new approach to aldehyde **3**.

We employed a rare ten-membered ring-closing metathesis reaction that gave a good *E*/*Z* ratio as the key step in the northern hemisphere of epothilone A. The remarkable *Z*-selectivity of this reaction can be explained by an isomerization in favor of the thermodynamically stable *Z*-olefin under metathesis conditions. The use of the rigid ten-membered lactone facilitates the diastereoselective introduction of the methyl group at C8 without the need for any additional chiral auxiliary. The thiazole moiety is introduced at the end of this reaction sequence, to make this sequence suitable for the introduction of different heterocyclic side chains in a combinatorial manner.

Experimental Section

General Remarks: All reagents were of analytical grade quality. Solvents were distilled in glass apparatus. Anhydrous reactions were performed under argon in flame-dried (under vacuum) glassware. − IR: Perkin−Elmer FT 1710. − NMR: Bruker WP 200, AM 400. ^{13}C NMR spectra were measured with ^1H-broadband decoupling. − High-resolution and FAB mass spectra: VG Autospec. − Elemental analysis of oils was not possible in Hannover. − Thin layer chromatography (TLC): Merck TLC Aluminium sheets Silica gel 60 F_{254}, precoated. − Flash chromatography: J. T. Baker silica gel (0.03−0.06 mm). − Anhydrous solvents: Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), Hünig′s base (diisopropylethylamine) and triethylamine were distilled from CaH_2 under argon. THF and diethyl ether were distilled from sodium under argon.

(*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-ol (16): Aldehyde **15** (28.8 g, 76.8 mmol) was dissolved in Et_2O (100 mL), and a freshly prepared solution of ethylmagnesium bromide (108 mL, 1M, 108 mmol) was added to it over 1 h. The reaction mixture was stirred for an additional 30 min and was then quenched at 0°C with saturated aq NH_4Cl. The layers were separated and the aqueous layer was extracted with MTB ether

(2 × 100 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. Flash chromatography (silica gel, PE/EtOAc 9:1) gave 24.74 g (62.98 mmol, 82%) of a colorless oil: $[\alpha]_D^{20} = -17.12$ (*c* = 1.25, $CHCl_3$, mixture of diastereomers). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3496, 2956, 2928, 2856, 1472, 1388, 1256 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 4.35 (s, 0.5 H), 3.69 (m, 3.5 H), 3.33 (m, 0.5 H), 2.82 (d, *J* = 4 Hz, 0.5 H), 1.71−1.95 (m, 2 H), 1.32−1.49 (m, 2 H), 0.74−1.15 (m, 27 H), 0.04−0.12 (m, 12 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.94, 77.36, 77.31, 75.49, 61.90, 60.10, 42.77, 40.63, 36.46, 35.95, 26.08, 26.06, 25.94, 25.87, 24.45, 24.17, 23.52, 20.52, 18.69, 18.49, 18.36, 18.27, 18.22, 18.17, 11.70, 11.26, −3.58, −3.92, −4.35, −4.40, −5.29, −5.32, −5.40, −5.41. − HRMS ($C_{21}H_{48}O_3Si_2$) *m/z*: calcd. 404.3142, found 404.3148.

(*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-one (4): The secondary alcohol **16** (22.7 g, 56.08 mmol) was dissolved in glacial acetic acid (500 mL). The solution was cooled to 0°C and Jones reagent (10 mL, 2 M CrO_3, 3.3 M H_2SO_4) was added over 30 min. The reaction mixture was stirred for an additional 2 h and then quenched with aqueous ammonia. The mixture was extracted with ethyl acetate (5 × 100 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography (PE/EtOAc 9:1) provided a colorless oil (16.56 g, 80%): $[\alpha]_D^{20} = -9.7$ (*c* = 1.04, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2928, 2856, 1708, 1472, 1388, 1256, 1024 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (dd, *J* = 3 Hz, *J* = 7.7 Hz, 1 H), 3.54−3.64 (m, 2 H), 2.55 (dq, *J* = 18.5 Hz, *J* = 7.1 Hz, 1 H), 2.45 (dq, *J* = 18.5 Hz, *J* = 7.1 Hz, 1 H), 1.40−1.56 (m, 2 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.12, 73.34, 60.02, 52.99, 37.20, 31.50, 26.03, 25.87, 22.13, 19.94, 18.30, 18.18, 7.69, −4.06, −4.09, −5.36. − HRMS ($C_{21}H_{30}O_4$) *m/z*: calcd. 402.2985, found 402.2985.

(2*S*,3*S*,4*R*,7*S*)-1-Benzyloxy-7,9-bis(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4,6,6-tetramethylnonan-5-one (7): Diisopropylamine (392 µL, 2.79 mmol) was dissolved in THF (16 mL) and cooled to 0°C. A solution of *n*BuLi in hexanes (1.6 M, 1.74 mL, 2.79 mmol) was added. The solution was stirred for 15 min and then cooled to −78°C. A solution of ketone **4** (749 mg, 1.86 mmol) in THF (4 mL) was added over 15 min. The reaction mixture was stirred for an additional 15 min and aldehyde **8** (332 mg, 1.86 mmol), dissolved in 4 mL THF, was added. The reaction was quenched at −78°C with saturated aq. NH_4Cl. The layers were separated, and the aqueous layer was extracted (2 × 30 mL) with MTB ether. The organic layers were separated, dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc/PE 1:11) provided the desired compound as a colorless liquid (802 mg, 1.38 mmol, 74%): $[\alpha]_D^{20} = -25.7$ (*c* = 1.0, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2928, 2884, 2856, 1472, 1256, 1100, 776 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.24 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.88 (dd, *J* = 7.5 Hz, *J* = 2.8 Hz, 1 H), 3.69−3.60 (m, 2 H), 3.59−3.51 (m, 2 H), 3.49−3.43 (m, 1 H), 3.24 (dq, *J* = 6.9 Hz, *J* = 1.8 Hz, 1 H), 1.90−1.80 (m, 1 H), 1.67−1.56 (m, 1 H), 1.51−1.40 (m, 1 H), 1.19 (s, 3 H), 1.07 (s, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 6 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.58, 138.65, 128.28, 127.54, 127.42, 74.18, 73.22, 72.90, 72.75, 60.50, 53.92, 41.56, 37.86, 36.33, 26.08, 25.92, 23.02, 20.36, 18.32, 18.26, 14.02, 9.68, −3.76, −4.08, −5.29. − HRMS ($C_{28}H_{51}O_5Si_2$) *m/z* [$M^+ - C(CH_3)_3$]: calcd. 523.3275 found 523.3277.

(3*S*,6*R*,7*S*,8*S*)-9-Benzyloxy-1,3,7-trihydroxy-4,4,6,8-tetramethylnonan-5-one (17): Compound **7** (275 mg, 0.473 mmol) was dissolved in acetonitrile (3 mL) in a polyethylene vial. The solution was cooled to 0°C and an aqueous solution of HF was added (48% H_2O, 34 µL, 0.946 mmol). The same amount was added after stirring for 1.5 h. The mixture was stirred for an addditional 30 min at room temp. The solution was neutralized with saturated aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted with MTB ether (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc/PE 1:1) yielded a colorless liquid (160 mg, 0.454 mmol, 96%): $[\alpha]_D^{20} = -32.2$ (*c* = 1.0, MeOH). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2972, 2934, 2860, 1687, 1495, 1454, 1365, 1323, 1255, 1230, 1096, 1018, 994 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.22 (m, 5 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.06−4.00 (m, 1 H), 3.80−3.69 (m, 2 H), 3.67 (dd, *J* = 8.9 Hz, *J* = 3.7 Hz, 1 H), 3.64−3.58 (m, 1 H), 3.42 (dd, *J* = 8.9 Hz, *J* = 6.9 Hz, 1 H), 3.35 (dq, *J* = 6.8 Hz, *J* = 2.8 Hz, 1 H), 2.88 (br. s, 1 H), 1.85−1.74 (m, 1 H), 1.64−1.55 (m, 1 H), 1.55−1.44 (m, 1 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.69, 140.07, 128.98, 128.21, 128.03, 75.33, 73.57, 73.49, 73.41, 61.17, 53.65, 42.46, 37.42, 34.86, 21.30, 19.40, 14.80, 11.09. − HRMS ($C_{20}H_{32}O_5$) *m/z*: calcd. 352.2249, found 352.2255.

(4*S*,7*R*,8*S*,9*S*)-5,5,7,9-Tetramethyl-1,7-dioxa-6-spiro[5.5]-undecane-4,8-diol (18): Alcohol **17** (160 mg, 0.454 mmol) was dissolved in MeOH (4 mL). A round-bottom flask was charged with argon and Pd/C (5.0 mg, 4.54 µmol, 10%) was added. The mixture was then flushed several times with H_2. Hydrogenation with H_2 proceeded at room temp. over 12 h. The solid was filtered off and washed with MeOH. The filtrate was concentrated and purified by flash chromatography (EtOAc/PE 1:1) to yield the desired compound (64 mg, 0.262 mmol, 55%) as a colorless oil: $[\alpha]_D^{20} = +82.0$ (*c* = 1.0, MeOH). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3352, 2956, 2916, 2880, 1156, 1132, 1112, 1076, 1004, 964, 924 cm^{-1}. − ^1H NMR (400 MHz, [D$_4$]MeOH, TMS): δ = 3.91 (dd, *J* = 11.9 Hz, *J* = 4.8 Hz, 1 H), 3.58−3.53 (m, 3 H), 3.48 (dd, *J* = 9.8 Hz, *J* = 4.9 Hz, 1 H), 3.31 (dd, *J* = 11.1 Hz, *J* = 2.3 Hz, 1 H), 1.87 (dq, *J* = 9.8 Hz, *J* = 6.5 Hz, 1 H), 1.80−1.72 (m, 1 H), 1.72−1.60 (m, 1 H), 1.50−1.44 (ddt, *J* = 12.6 Hz, *J* = 4.7 Hz, *J* = 2.3 Hz, 1 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 1.02 (s, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.93 (s, 3 H). − ^{13}C NMR (100 MHz, [D$_4$]MeOH, TMS): δ = 105.34, 74.68, 71.53, 64.59, 59.89, 45.85, 37.17, 35.77, 31.38, 22.23, 18.09, 14.81, 11.07. − HRMS ($C_{13}H_{24}O_4$) *m/z*: calcd. 244.1674, found 244.1675.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptenoic Acid (5): Ketone **4** (1.0 g, 2.48 mmol) was dissolved in CH_2Cl_2 (40 mL), cooled to 0°C and a mixture of CH_2Cl_2/TFA/H_2O (2 mL, 10:9:1) was added. The reaction mixture was quenched after 45 min with aq. saturated $NaHCO_3$ solution, extracted with MTB ether (2 × 40 mL), dried over Na_2SO_4 and concentrated. The crude product was dissolved in DMF (5 mL) and oxidized with the aid of PDC (2.3 g). The reaction mixture was stirred for 12 h and quenched with water. The aqueous layer was extracted with MTB ether (3 × 50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (PE/EtOAc 6:1→ 100% EtOAc) provided acid **5** (490 mg, 1.6 mmol, 68%) as a colorless liquid: $[\alpha]_D^{20} = -20.12$ (*c* = 0.79, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2932, 2884, 2736, 2680, 1712, 1572, 1144, 1004 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 4.48 (dd, *J* = 3.6 Hz, *J* = 7.0 Hz, 1 H), 2.44−2.62 (m, 2 H), 2.5 (dd, *J* = 16.3 Hz, *J* = 3.6 Hz, 1 H), 2.33 (dd, *J* = 16.3 Hz, *J* = 7.0 Hz, 1 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.0 (t, *J* = 7.1 Hz, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). − ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 215.15, 177.88, 73.47, 52.55, 39.20, 31.75, 25.86, 21.01, 20.53, 18.10, 7.68, −4.41, −4.91. − HRMS ($C_{15}H_{30}O_4Si$) *m/z*: calcd. 302.1913, found 302.1920.

(2*S*,3*S*)-2-(*p*-Methoxybenzyloxy)-3-(hept-6-enoyl)hex-5-ene (21): To a solution of DCC (1.24 g, 6.0 mmol, 1.5 equiv.) and 4-DMAP (98 mg, 0.8 mmol, 0.2 equiv.) in CH_2Cl_2 (24 mL), a solution of alcohol **20** (945 mg, 4 mmol) in CH_2Cl_2 (8 mL) was added. Hept-6-enoic acid (0.54 mL, 4 mmol, 1 equiv.) was added neat. After stirring for 16 h at room temp. the suspension was diluted with MTB ether and washed with saturated aq $NaHCO_3$ solution. The aqueous layer was re-extracted with MTB ether. The combined organic extracts were dried ($MgSO_4$) and freed from solvent to give, after column chromatography (silica gel, PE/EtOAc 30:1), 1.30 g (3.76 mmol, 94%) of a colorless liquid: $[\alpha]_D^{20}$ = +11.3 (*c* = 1.13, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3080, 2980, 2936, 1728, 1612, 1512, 1248 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.28 (m, 2 H), 6.85−6.90 (m, 2 H), 5.64−5.85 (m, 2 H), 4.91−5.09 (m, 5 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 4.43 (d, *J* = 11.5 Hz, 1 H), 3.80 (s, 3 H), 3.60 (m, H2), 2.27−2.47 (m, 4 H), 2.01−2.09 (m, 2 H), 1.58−1.70 (m, 2 H), 1.37−1.45 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 3 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.23, 159.15, 138.36, 133.96, 130.51, 129.25, 117.49, 114.59, 113.70, 74.56, 73.95, 70.71, 55.20, 34.38, 34.21, 33.31, 28.29, 24.45, 15.32. − HRMS ($C_{21}H_{30}O_4$) *m/z*: calcd. 346.2144, found 346.2149.

(10*S*)-[(1*S*)-(*p*-Methoxybenzyloxy)ethyl]-3,4,5,6,9,10-hexahydrooxecin-2-one (22): To a refluxing solution of $RuCl_2(PCy_3)_2CHC_6H_5$ (95 mg, 0.115 mmol, 20 mol%) in CH_2Cl_2 (160 mL) was added, dropwise, a solution of diene **21** (200 mg, 0.577 mmol) in CH_2Cl_2 (20 mL) over a period of 1 h. After refluxing for 3 h the mixture was concentrated in vacuo. The crude product was purified by column chromatography (PE/EtOAc 60:1) to provide a colorless oil (99 mg, 0.312 mmol, 63%): $[\alpha]_D^{20}$ = −14.8 (*c* = 1.0, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2932, 2860, 1720, 1612, 1512 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22−7.28 (m, 2 H). − 6.84−6.89 (m, 2 H), 5.38−5.50 (m, 2 H), 4.90 (dd, *J* = 10.7, 6.0 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 3.80 (s, 3 H), 3.65 (m, 1 H), 2.07−2.46 (m, 6 H), 1.86−2.00 (m, 1 H), 1.58−1.78 (m, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.44, 159.08, 134.57, 130.66, 129.21, 124.07, 113.73, 75.58, 74.38, 70.96, 55.20, 35.27, 26.81, 25.49, 25.25, 23.49, 16.15. − HRMS ($C_{19}H_{26}O_4$) *m/z* [M^+ + 1]: calcd. 318.1831, found 318.1821.

(3*S*,10*S*)-10-[(1*S*)-(*p*-Methoxybenzyloxy)ethyl]-3-methyl-3,4,5,6,9,10-hexahydrooxecin-2-one (6): To a solution of lactone **22** (78 mg, 0.245 mmol) in THF (0.25 mL) was added, dropwise, NaHMDS (0.35 mL, 1 M in THF, 0.35 mmol, 1.4 equiv.) at −78°C. After stirring for 1 h at −78°C, CH_3I (0.1 mL, 1.6 mmol, 6.5 equiv.) was added. Stirring was continued for 5 h. After addition of water at −78°C the mixture was allowed to warm to room temp. Extraction with MTB ether, drying ($MgSO_4$), evaporation, and column chromatography on silica gel (PE/EtOAc 80:1) gave a colorless oil (67 mg, 0.201 mmol, 82%): $[\alpha]_D^{20}$ = −11.3 (*c* = 1.0, $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3000, 2972, 2936, 2856, 1720, 1612, 1512 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22−7.28 (m, 2 H), 6.84−6.89 (m, 2 H), 5.38−5.53 (m, 2 H), 4.85 (dt, *J* = 7.2, 4.7 Hz), 4.59 (d, *J* = 11.4 Hz, 1 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.69 (m, 1 H), 2.31−2.42 (m, 1 H), 1.99−2.26 (m, 3 H), 1.86−1.99 (m, 1 H), 1.69−1.82 (m, 1 H), 1.54−1.68 (m, 2 H), 1.45−1.54 (m, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.19 (d, *J* = 7.02 Hz, 3 H). − HRMS ($C_{20}H_{28}O_4$) *m/z*: calcd. 332.1987, found 332.1991.

(2*S*,3*S*,2′*S*)-2-(*p*-Methoxybenzyloxy)-3-(2′-methylhept-6′-enoyl)-hex-5-ene (26): Acid **25** (50 mg, 0.352 mmol) and alcohol **20** (92 mg, 0.389 mmol, 1.1 equiv.) were allowed to react according to the synthesis of diene **21**. Flash chromatography on silica gel (PE/EtOAc 30:1) furnished 117 mg of the ester **26** as colorless liquid (0.324 mmol, 92%): FTIR ($CHCl_3$): $\tilde{\nu}$ = 2976, 2936, 2860, 1724, 1612, 1512 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24−7.28 (m, 2 H), 6.85−6.90 (m, 2 H), 5.65−5.84 (m, 2 H), 4.91−5.10 (m, 5 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.46 (d, *J* = 11.6 Hz, 1 H), 3.80 (s, 3 H), 3.61 (m, 1 H), 2.37−2.50 (m, 2 H), 2.27−2.39 (m, 1 H), 1.98−2.06 (m, 2 H), 1.60−1.74 (m, 1 H), 1.33−1.45 (m, 3 H), 1.15 (d, *J* = 1.4 Hz, 3 H), 1.13 (d, *J* = 1.8 Hz, 3 H). − HRMS ($C_{22}H_{32}O_4$) *m/z* [M^+ + 1]: calcd. 360.2300, found 360.2303.

Lactone 6b: Diene **26** (70 mg, 0.194 mmol) was reacted analogously to the RCM reaction of diene **21** to give, after chromatography (silica gel PE/EtOAc 40:1), lactone **6b** (34 mg, 0.103 mmol, 53%).

Alcohol 27: DDQ (33 mg, 145 μmol, 1.2 equiv.) was added in one portion to a solution of compound **6** (38 mg, 114 μmol) in CH_2Cl_2 (0.6 mL)/H_2O (34 μL) at room temp. After stirring for 1 h the resulting suspension was freed from solvent and chromatographed on silica gel (PE/EtOAc 35:1) to afford a colorless oil (24 mg, 114 μmol, 98%): $[\alpha]_D^{20}$ = +31.4 (*c* = 1.2 in $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3604, 2972, 2924, 2856, 1724 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 5.36−5.57 (m, 2 H), 4.58 (dt, *J* = 6.9, 4.6 Hz, 1 H), 3.94 (quin, *J* = 6.5 Hz, 1 H), 2.32−2.53 (m, 1 H), 1.48−2.30 (m, 8 H), 1.24 (d, *J* = 6.4 Hz, 3 H), 1.20 (d, *J* = 7.2 Hz, 3 H). − ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 177.03 (+), 134.85 (−), 123.26 (−), 77.70 (−), 68.13 (−), 41.79 (−), 31.77 (+), 26.93 (+), 26.33 (+), 25.13 (+), 19.18 (−), 18.59 (−). − HRMS ($C_{12}H_{20}O_3$) *m/z*: calcd. 212.1412, found 212.1414.

Ketone 28: To a solution of alcohol **27** (23 mg, 108 μmol) in CH_2Cl_2 (0.7 mL) was added, in one portion, a mixture of crushed molecular sieves (3 Å, 82 mg), NMO (97%, 20 mg, 162 μmol, 1.5 equiv.) and TPAP (2 mg, 5.4 μmol, 0.05 equiv.) at room temp. After stirring for 1 h the mixture was evaporated and chromatographed on silica gel (PE/EtOAc 15:1) to furnish 19 mg (91 μmol, 83%) of a colorless liquid: $[\alpha]_D^{20}$ = −86.0 (*c* = 1.0 in $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 3000, 2972, 2920, 2856, 1724 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 5.51 (dt, *J* = 10.6, 5.6 Hz, 1 H), 5.31−5.41 (m, 1 H), 5.03−5.56 (m, 1 H), 2.48−2.58 (m, 1 H), 2.40−2.50 (m, 1 H), 2.22 (s, 3 H), 2.10−2.25 (m, 1 H), 1.86−2.04 (m, 2 H), 1.50−1.81 (m, 4 H), 1.24 (d, *J* = 7.13 Hz, 3 H). − ^{13}C NMR (100 MHz, APT, $CDCl_3$): δ = 206.52, 176.16, 135.70, 123.35, 76.85, 41.43, 31.61, 29.67, 27.53, 26.22, 24.94, 18.52. − HRMS ($C_{12}H_{18}O_3$) *m/z*: calcd. 210.1256, found 210.1251.

Thiazole 30: A solution of diethyl (2-methylthiazole-4-yl)methanephosphonate **29** (24 mg, 96 μmol, 1.35 equiv.) in THF (0.5 mL) was cooled to −78°C and *n*BuLi (15% in hexanes, 60 μL, 96 μmol, 1.35 equiv.) was added. After stirring for 45 min a solution of ketone **28** (15 mg, 71 μmol) in THF (0.3 mL) was added dropwise. The mixture was allowed to reach room temp. and stirring was continued for 2 h. After addition of saturated aq NH_4Cl solution the suspension was evaporated to dryness. Column chromatography (PE/EtOAc 50:1) gave 12 mg (39 μmol, 65%) of a slightly yellowish oil: $[\alpha]_D^{20}$ = −88.0 (*c* = 0.6 in $CHCl_3$). − FTIR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2856, 1720 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.59 (d, *J* = 0.5 Hz, 1 H), 5.40−5.55 (m, 2 H), 5.37 (t, *J* = 4.2 Hz, 1 H), 2.73 (s, 3 H), 2.33−2.43 (m, 1 H), 2.20−2.33 (m, 2 H), 2.11 (s, 3 H), 1.96−2.08 (m, 2 H), 1.55−1.80 (m, 4 H), 1.22 (d, *J* = 7.2 Hz, 3 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.30, 164.64, 152.74, 136.77, 135.03, 123.24, 119.00, 115.80, 77.20, 42.45, 32.06, 31.91, 29.68, 27.55, 19.34, 19.22, 16.47. − HRMS ($C_{17}H_{23}NO_2S$) *m/z*: calcd. 305.1449, found 305.1449.

Diol 31: To a solution of $LiAlH_4$ (16 mg, 0.413 mmol) in diethyl ether was added lactone **30** (63 mg, 0.21 mmol), also dissolved in diethyl ether (1 mL); the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aq NH_4Cl solution (20 mL). The organic phase was washed with brine (2 × 30 mL), dried ($MgSO_4$), and the solvents were removed under reduced pressure. Flash chromatography (PE/EtOAc 2:1) furnished diol **31** (58 mg, 95%, 0.374 mmol): $[\alpha]_D^{20} = -14.2$ (c = 1.0, $CHCl_3$). – FTIR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2872, 1264 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.51 (s, 1 H), 5.45–5.54 (m, 1 H), 5.32–5.41 (m, 1 H), 4.10–4.18 (m, 1 H), 3.40–3.47 (m, 1 H), 3.34–3.40 (m, 1 H), 2.66 (s, 3 H), 2.33–2.42 (m, 3 H), 1.98–2.10 (m, 4 H), 1.98 (d, J = 1.1 Hz, 3 H), 1.50–1.64 (m, 1 H), 1.20–1.45 (m, 4 H), 1.0–1.12 (m, 1 H), 0.86 (d, J = 7 Hz, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.63, 152.71, 141.67, 132.94 125.02, 119.02, 115.44, 77.13, 68.16, 35.64, 33.37, 32.75, 27.65, 26.81, 19.10, 16.57, 14.39. – FAB MS ($C_{17}H_{27}NO_2S$) m/z [M^++Na]: calcd. 332.2470, found 332.2470.

TBS Ether 32: Diol **31** (30 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (5 mL), the solution was cooled to −78°C, and TBS triflate (66 µL, 0.3 mmol) and 2,6-lutidine (34 µL, 0.3 mmol) were added. The reaction mixture was stirred for 1 h and quenched at −78°C with saturated aq $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was washed with MTB ether (2 × 20 mL), dried ($MgSO_4$), and the solvents were removed under reduced pressure. Flash chromatography (PE/EtOAc 2:1) furnished compound **32** (49 mg, 91%, 0.094 mmol): $[\alpha]_D^{20} = +6.1$ (c = 1.0, $CHCl_3$). – FTIR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2856, 1472, 1388, 1256, 1080 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1 H), 6.43 (s, 1 H), 5.29–5.44 (m, 2 H), 4.10 (tr, J = 6.6 Hz, 1 H), 3.41 (dd, J = 6 Hz, J = 10 Hz, 1 H), 3.32 (dd, J = 7 Hz, J = 10 Hz, 1 H), 2.68 (s, 1 H), 2.31 (dd, J = 6.24 Hz, J = 3 Hz, 1 H), 2.26 (dd, J = 6.2 Hz, J = 3 Hz, 1 H), 1.98 (d, J = 1.2 Hz, 3 H), 1.50–1.60 (m, 1 H), 1.20–1.40 (m, 4 H), 1.0–1.10 (m, 2 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.83 (d, J = 7 Hz, 3 H), 0.04 (s, 3 H), 0.01 (s, 6 H), −0.01 (s, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.34, 153.27, 142.25, 131.48 125.70, 118.82, 114.91, 78.78, 68.44, 35.72, 34.76, 32.93, 27.88, 27.13, 25.96, 25.66, 19.2,0 18.34, 18.29, 16.72, 13.94, −4.62, −4.98, −5.35. – HRMS ($C_{29}H_{55}NO_2SSi_2$) m/z: calcd. 537.3492, found 537.3486.

TBS Ether 33: Compound **32** (47 mg, 90 µmol) was dissolved in CH_2Cl_2/MeOH (2 mL, v/v 1:1) at 0°C and CSA (8 mg, 30 µmol) was added. The reaction was stirred for 30 min and quenched with saturated aq $NaHCO_3$ solution. The organic phase was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvents were removed under reduced pressure. Flash chromatography (PE/EtOAc 3:1) furnished compound **33** (25 mg, 92%): $[\alpha]_D^{20} = +1.8$ (c = 1.0, $CHCl_3$). – FTIR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2856, 1460, 1388, 1256, 1184, 1076, 836 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 6.90 (s, 1 H), 6.43 (s, 1 H), 5.30–5.44 (m, 2 H), 4.07–4.13 (m, 1 H), 3.42–3.49 (m, 1 H), 3.37 (dd, J = 6.5 Hz, J = 10.4 Hz, 1 H), 2.68 (s, 3 H), 2.32 (dd, J = 14.0 Hz, J = 6.0 Hz, 1 H), 2.25 (dd, J = 6.2 Hz, J = 3.0 Hz, 1 H), 1.96–2.04 (m, 2 H), 1.96 (s, 3 H), 1.65–1.75 (s, br, 1 H), 1.50–1.64 (m, 1 H), 1.20–1.45 (m, 3 H), 0.98–1.13 (m, 1 H), 0.87 (s, 9 H), 0.83 (d, J = 7.0 Hz, 3 H), 0.03 (s, 3 H), 0.02 (s, 6 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.46, 153.03, 142.37, 131.32 125.92, 118.99, 114.94, 78.80, 68.22, 35.77, 34.7, 32.8, 27.6, 26.9, 25.8, 19.1, 18.2, 16.5, 13.8, −4.7, −4.9. – HRMS ($C_{23}H_{41}NO_2SSi$) m/z: calcd. 423.2627, found 423.2613.

Aldehyde 3: Alcohol **33** (21 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (5 mL) at 0°C. Dess–Martin periodinane (30 mg, 0.075 mmol) was added. The reaction was quenched after 50 min with saturated aq $NaHCO_3$ solution. The organic phase was washed with brine (2 × 30 mL), dried ($MgSO_4$) and the solvents were removed under reduced pressure. Flash chromatography (PE/EtOAc 3:1) furnished aldehyde **3** (20 mg, 93%, 0.047 mmol): $[\alpha]_D^{20} = +11.1$ (c = 0.7, $CHCl_3$). – FTIR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2856, 1460, 1388, 1256, 1184, 1076, 836 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, J = 2 Hz, 1 H), 6.90 (s, 1 H), 6.43 (s, 1 H), 5.34–5.42 (m, 2 H), 4.07–4.13 (m, 1 H), 2.68 (s, 3 H), 2.22–2.34 (m, 3 H), 1.90–2.07 (m, 2 H), 1.97 (d, J = 1.2 Hz, 3 H), 1.57–1.73 (m, 2 H), 1.27–1.42 (m, 3 H), 1.05 (d, J = 9 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), −0.02 (s, 6 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.13, 164.47, 153.12, 142.10, 130.65 126.58, 118.92, 115.04, 78.64, 46.27, 34.73, 30.17, 27.34, 26.94, 25.88, 19.22, 18.23, 13.97, 13.39, −4.73, −5.06. – HRMS ($C_{23}H_{39}NO_2SSi$) m/z: calcd. 421.2470, found 421.2470.

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