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Communication

Synthesis of the C(7)-C(20) Fragment of Spirotoamides A, B and C

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This work describes the preparation of the C(7)-C(20) fragment of spirotoamides A to C in a very elegant fashion, achievement very high levels of stereocontrol. The synthesis has been accomplished by a sequence involving 14 steps (0.36% overall yield, average of 81% for each step) in high diastereo and enantioselectivity, employing, as determining steps, asymmetric Mukaiyama and boron-mediated 1,5-*anti* promoted aldol reactions between α-methyl-β-hydroxyketones and aldehydes.

Keywords: total synthesis, natural products, aldol reactions, Mukaiyama reaction, spirotoamides

Introduction

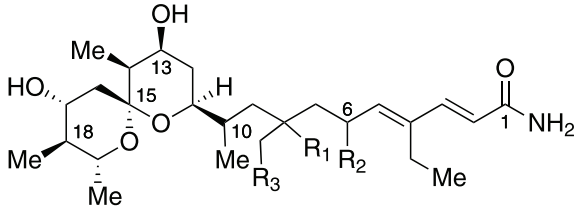
Recently, four new polyketides containing 6,6-spiroketal cores with two anomeric effects, and terminal amide were isolated. Spirotoamides A and B in 2012 by Nogawa *et al.*[1] and the spirotoamides C and D in 2017 by Yang *et al.*[2] All compounds were isolated from a fraction of the microbial metabolite of *Streptomyces griseochromogenes* JC82-1223,[3] presenting 9 or 10 stereogenic centers, in which the fragment containing the spiroketal contains 7 of them.

Having only the structural knowledge from their isolation, the high structural complexity of such compounds inspired us to prepare the C(7)-C(20) fragment, similar to spirotoamides A to C, which contains the same stereogenic centers of spiroketal (Figure 1).

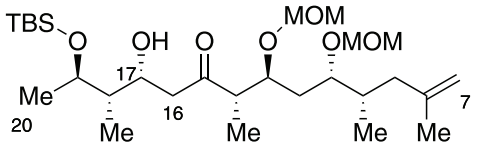
Results and Discussion

Our disconnection strategy is summarized in Scheme 1. Intermediate **4** (C(7)-C(20) fragment) can be obtained by a Mukaiyama aldol reaction (key step) between the aldehyde **5** and the enolsilane **6**. The enolsilane **6** (C(7)-C(16) fragment), in turn, can be obtained by a boron-mediated aldol reaction between α-methyl-β-hydroxyketone **9** (C(12)-C(16) fragment) and the aldehyde **10** (C(7)-C(11) fragment). Both the aldehyde **5** and the methylketone **9** can be prepared by the boron-mediated aldol reaction in good levels of 1,4-*anti* induction between α-hydroxyethylketone **8** and acetaldehyde (**7**) (Scheme 1).

Our approach to the C(7)-C(20) fragment of spirotoamides A, B and C began with the asymmetric



Spirotoamide A (1) **(R_1 = OH, R_2 = R_3 = H)**
Spirotoamide B (2) **(R_1 = H, R_2 = OH, R_3 = H)**
Spirotoamide C (3) **(R_1 = R_2 = H, R_3 = OH)**



Fragment C7-C20 (**4**)

Figure 1. Structure of spirotoamides A, B and C and fragment C7-C20.

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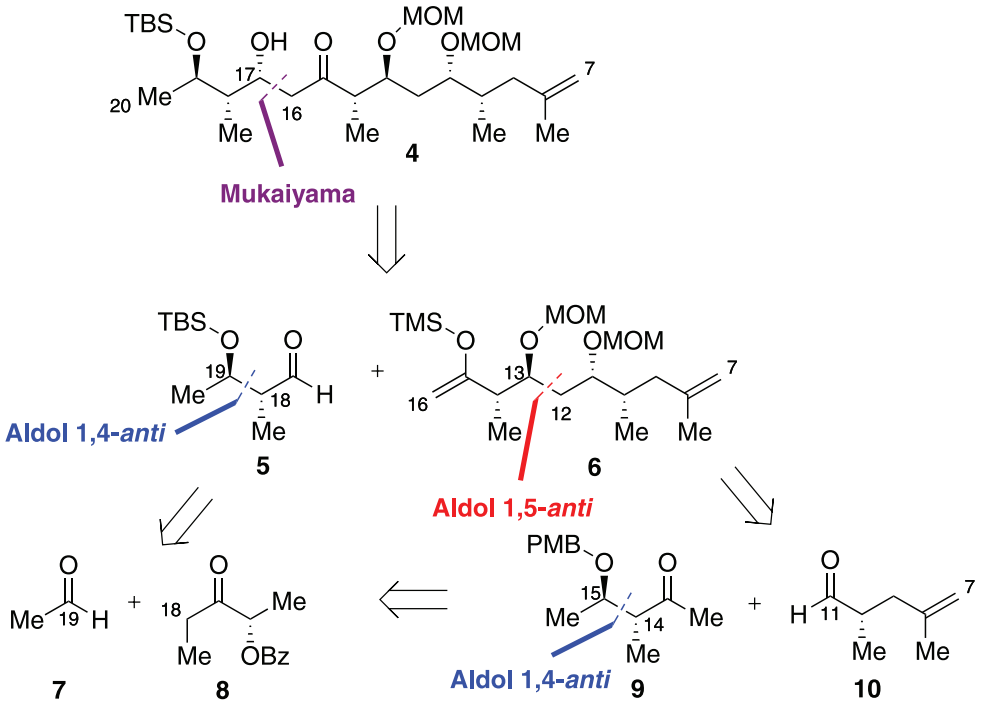


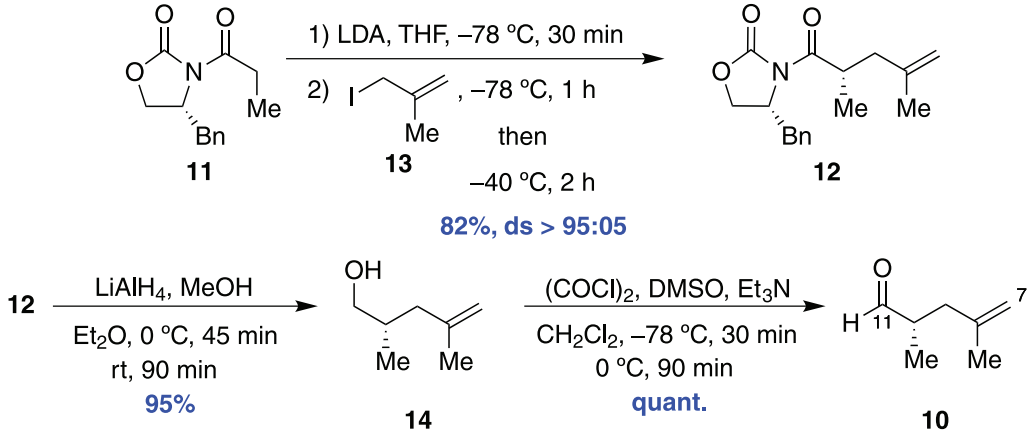
Scheme 1. Retrosynthetic analysis.

alkylation of the Evans auxiliary[4] **11** with 3-iodo-2-methylprop-1-ene (**13**), leading to the formation of the alkylation product **12** in 82% yield and diastereoselectivity (ds) of > 95:05. Reduction of **12** in the presence of $LiAlH_4$ led to the formation of alcohol **14** in 95% isolated yield.[4] Alcohol **14** was subjected to oxidation following Swern reaction conditions,[5] resulting in the aldehyde **10** (C(7)-C(11) fragment) in quantitative yield (Scheme 2).

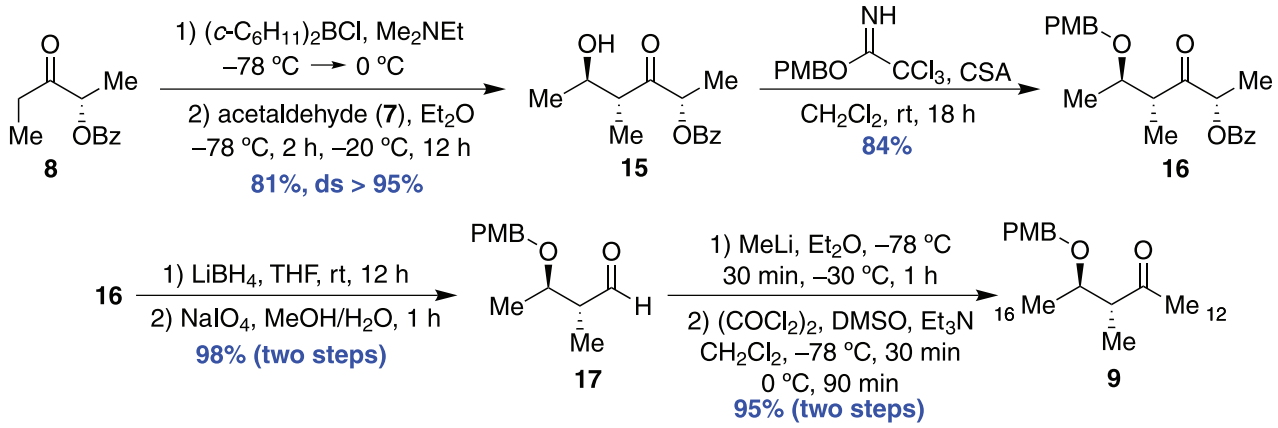
In the meantime, ethyl ketone **8** was reacted with acetaldehyde (**7**) in an asymmetric 1,4-*anti* induced aldol reaction leading to the formation of the aldol adduct **15** in 81% yield and ds > 95:05, according to literature procedure.[6] Subsequently, the alcohol **15** was subjected to reaction with *p*-methoxybenzyl (PMB) trichloroacetimidate, resulting in the PMB ether **16** in 84% yield.[6] Ketone **16** was then treated with $LiBH_4$ followed by oxidative cleavage reaction, leading to formation of the aldehyde **17** in 98% yield for two steps,[7] thereafter the aldehyde **17** was reacted with MeLi,[8] leading to a mixture of diastereoisomers which were transformed into methylketone **9** through Swern oxidation (Scheme 3).[5]

In an analogous manner, aldehyde **5** can be prepared by subjecting aldol adduct **15** to protection reaction in presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf),[6] followed by reduction with $LiBH_4$ and oxidative cleavage (Scheme 4).[7]

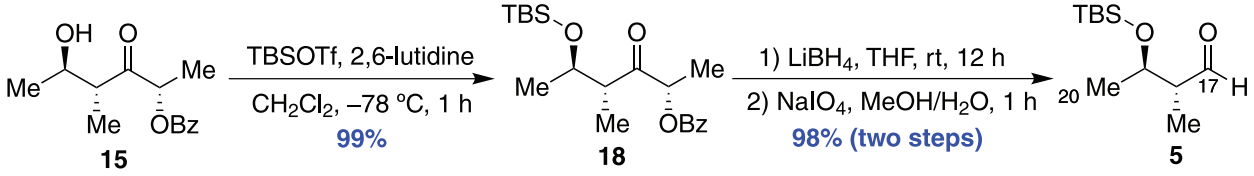
Aldehyde **10**, previously prepared (Scheme 2), was employed in the aldol reaction with the boron enolate



Scheme 2. Synthesis of aldehyde **10**.



Scheme 3. Synthesis of α-methyl-β-hydroxyketone **9**.



Scheme 4. Synthesis of α-methyl-β-hydroxyaldehyde **5**.

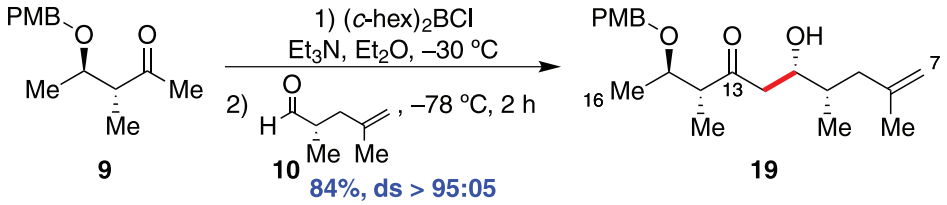
formed from methylketone **9**, leading to the formation of the aldol adduct **19** in good yield and ds > 95:05 (Scheme 5).[9]

In the next step, alcohol **19** was diastereoselectively reduced under Evans-Saksena reaction conditions, using $Me_4NHB(OAc)_3$ as a complexing agent and camphorsulfonic acid (CSA) in acetic acid, resulting in diol **20** in high yield and excellent diastereoselectivity in favor of the 1,3-*anti* isomer.[10] Subsequently, diol **20** was subjected to the protection reaction with 2,2-dimethoxypropane (DMP) catalyzed by CSA for 12 h,[10] resulting in acetonide **21** in 91% yield. The acetonide **21** made it possible to determine the relative stereochemistry of C(11) and C(13) by ^{13}C nuclear magnetic resonance (NMR) analysis according to Rychnovsky's method.[11] The observed ^{13}C NMR chemical shifts at δ 24.5, 24.4 and 100.1 ppm are characteristic of a *trans* acetonide (Scheme 6).

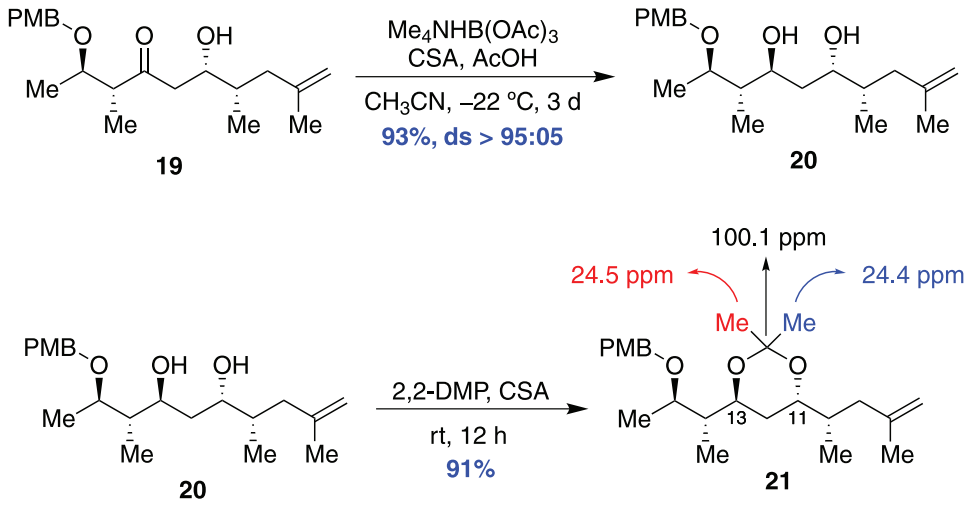
For the determination of C(14) and C(15) absolute configurations, PMB ether **20** was subjected to cyclization reaction in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and molecular sieves,[10] leading to the formation of the *p*-methoxyphenyl (PMP) acetal **22** in 79% yield. ^1H NMR analysis showed coupling between hydrogens H_b-H_d (10.2 Hz) and H_c-H_d (9.8 Hz), characteristic of hydrogens in a *trans* relationship and selective nuclear Overhauser effect (NOE) experiment showed increments of 5.61% between H_a and H_b and of 4.90% between H_a and H_c, possibly for hydrogen atoms in 1,3-diaxial positions (Scheme 7).

Subsequently, the PMP acetal **22** was subjected to cyclization under acidic conditions, leading to the formation of the hydrofuran **23** in 79% yield.[12] Compound **23** was analyzed by nuclear Overhauser effect spectroscopy (NOESY; from this experiment, two chemical shifts were selected, 1.21 and 1.31 ppm), allowing to visualize increments of 0.48% between H_a and Me_a, 0.64% between H_b and Me_a, 1.27% between H_c and Me_a and 0.72% between H_d and Me_b, according to Felkin relationship between C(10) and C(11) (Scheme 8).

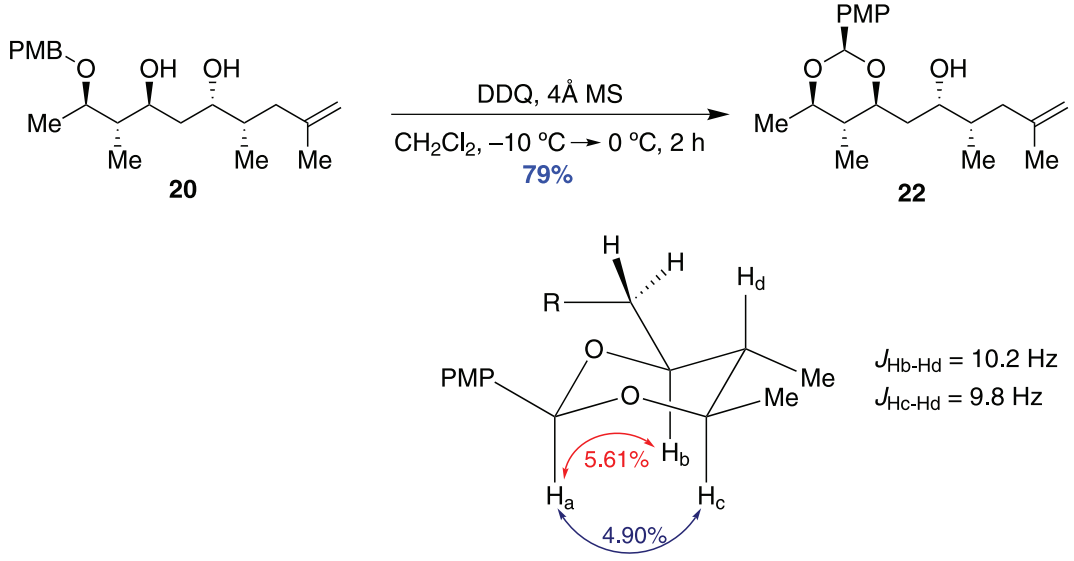
Reaction of diol **20** with chloromethyl methyl ether (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane resulted in the formation of intermediate **24**,[13] which in the presence of DDQ was transformed into alcohol **25**,[10] which after oxidation under Dess-Martin conditions afforded methylketone **26** in 97% yield.[14] Methylketone **26** was converted to the enolsilane **6** in



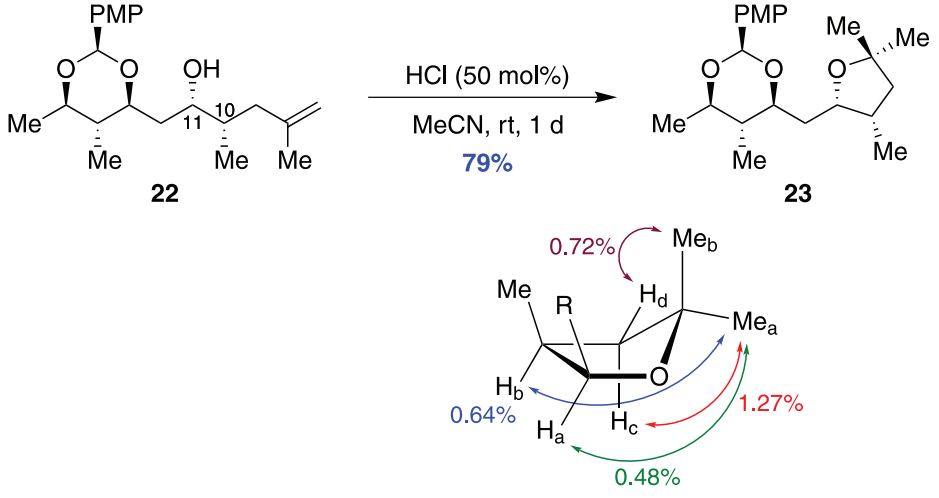
Scheme 5. Preparation of aldol adduct **19**.



Scheme 6. Synthesis of acetonide **21** and indirect determination of the stereochemistry of diol **20**.



Scheme 7. Determination of the stereochemistry of the aldol adduct **19**.



Scheme 8. Determination of the relative stereochemistry of hydrofuran **23**.

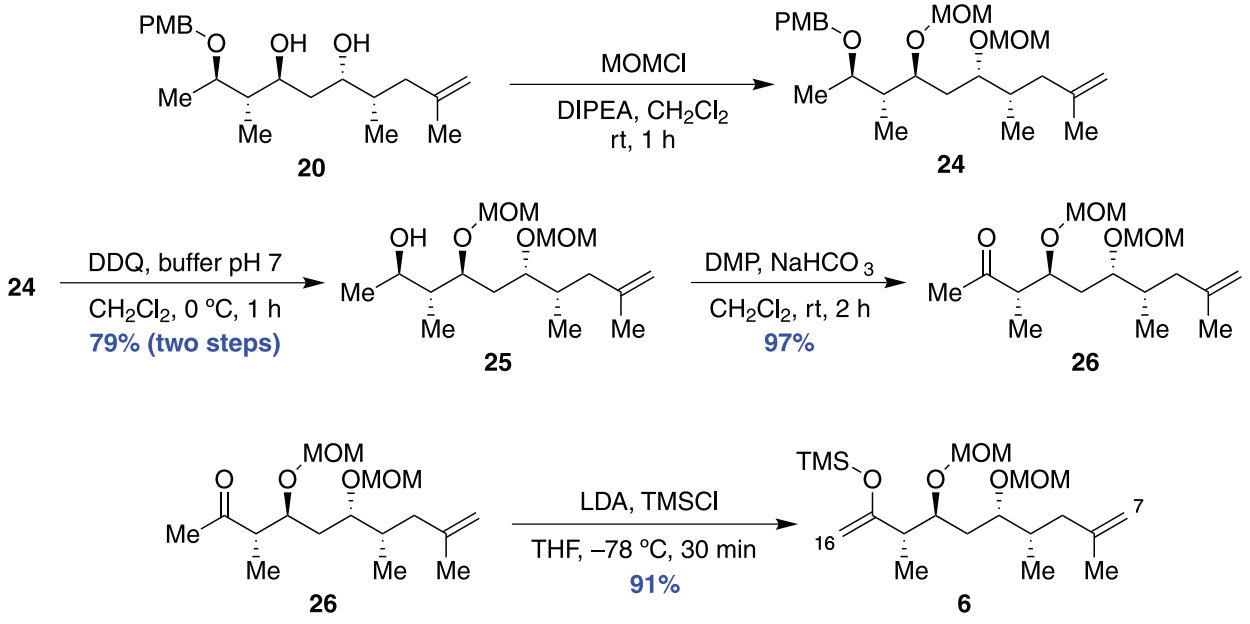
the presence of lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) in 91% isolated yield (Scheme 9).[15]

With the requisite C(7)-C(16) and C(17)-C(20) fragments in hand, their coupling (key step) was undertaken using Mukaiyama conditions,[16] with selective 1,3-*anti* induction, leading to the product of interest (**4**) in 89% yield and diastereoselectivity > 95:05 (Scheme 10).

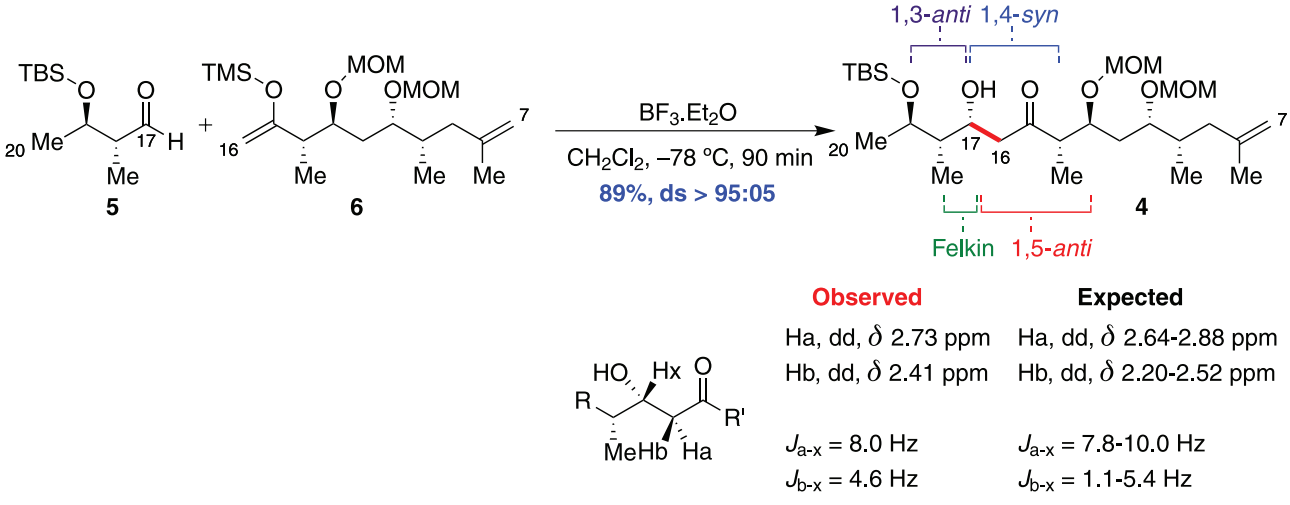
^{1}H NMR analysis following the ABX method[17] gave us indications that the relative stereochemistry between C18 methyl and C17 hydroxyl is 1,3-*anti*. It can be seen that adduct **4** has coupling constants for H_a of 8.0 Hz (expected 7.8-10.0 Hz) and H_b of 4.6 Hz (expected 1.1-5.4 Hz). The experimental values are consistent with a Felkin compound, therefore confirms the 1,3-*anti* induction (Scheme 10).

Conclusions

In conclusion, we have described an efficient asymmetric synthesis of the C(7)-C(20) fragment of spirotoamides A, B and C. This approach required 14 steps for the longest linear sequence (0.36% overall yield, average of 81% for each step). The determinant steps of this work involved the boron-mediated 1,5-*anti* aldol reaction between α-methyl-β-hydroxyketone **9** and aldehyde **10** and the induction promoted by the Mukaiyama aldol reaction between α-methyl-β-hydroxyaldehyde **5** and enolsilane **6**. As a result, the C(7)-C(20) fragment can be obtained in highly diastereoselective form and all the stereocenters could be determined during the synthesis or by derivatization. Extension of this work toward completion on the synthesis



Scheme 9. Synthesis of the enolsilane **6**.



Scheme 10. Mukaiyama aldol reaction (key step) for the preparation of the C(7)-C(19) fragment.

of spirotoamides A, B, and C is underway and results will be described in due course.

Experimental

All reactions were carried out under an atmosphere of argon with dry solvents under anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone prior to use. Triethylamine (Et_3N), 2,6-lutidine, *N*,*N*-dimethylethylamine (DMEA), DIPEA, dichloromethane (CH_2Cl_2), and acetonitrile (MeCN) were distilled from calcium hydride prior to use. Acetic acid (AcOH) was fractionally distilled from acetic anhydride and chromium (VI) oxide prior to use. CSA was recrystallized from ethyl acetate. All other reagents were used without further purification, unless otherwise stated. The purification of reaction products was performed by flash column chromatography using silica gel (230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator R-215, B-491. Reactions were monitored by thin layer chromatography carried out on silica-gel 60 and GF (5-40 μm thickness) plates with fluorescent indicator, and visualization was accomplished using UV light, phosphomolybdic acid (PMA), $KMnO_4$ or vanillin followed by heating. Optical rotations were measured on a PerkinElmer 341 polarimeter with a sodium lamp using a 1.0 cm cell and are reported as follows: $[\alpha]_D^{T(°C)}$ (*c* (g *per* 100 mL), solvent). Melting points were measured with a Buchi M-565 equipment and are uncorrected. ^{1}H and proton-decoupled ^{13}C NMR spectrum were acquired on a Bruker DPX250 (250 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR), Bruker Avance 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR), Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C NMR), or Bruker Avance 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C NMR). Chemical shifts (δ) are reported in ppm using residual undeuterated solvent as an internal standard ($CHCl_3$ at 7.26 ppm and TMS at 0.00 ppm for ^{1}H NMR spectrum and $CDCl_3$ at 77.0 ppm for ^{13}C NMR spectrum). Multiplicity data are reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddt = doublet of doublets of triplets, td = triplet of doublets, tt = triplet of triplets, tq = triplet of quartets, qdd = quartet of doublets of doublets, and m = multiplet. The multiplicity is followed by the coupling constant(s) in Hz and integration. Infrared spectrum (IR) was recorded on PerkinElmer Spectrum Two spectrometer. Wavelengths of maximum absorbance (max) are quoted in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) were measured using electrospray ionization (ESI) (Thermo Scientific LTQ, FT Ultra).

Synthesis, characterization and spectra data of aldehyde **10** (C(7)-C(11) fragment)

(*R*)-4-Benzyl-3-((*S*)-2,4-dimethylpent-4-enoyl)oxazolidin-2-one (**12**)

To a 250 mL flask containing *n*-BuLi (47.7 mmol, 19.0 mL, 2.5 M in hexane) in THF (50 mL) at –78 °C was added diisopropylamine (DIPA) (47.7 mmol, 4.82 g, 6.7 mL). The reaction mixture was stirred for 1 h at –78 °C. Subsequently, a solution containing the oxazolidinone **11** (44.6 mmol, 10.40 g in 20 mL of THF) was added via cannula and the mixture was stirred at –78 °C for a further 30 min. Thereafter, the alkyl iodide **13** (90 mmol, 17.00 g, 10.4 mL) was added dropwise. The reaction was stirred at –78 °C for 1 h and at –40 °C for 2 h. The reaction was warmed to 0 °C, then the mixture was washed with saturated aqueous ammonium chloride solution (50 mL), which was extracted with dichloromethane (CH_2Cl_2) (4 × 50 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/ethyl acetate (17:3) as the eluent to afford the corresponding alkylation product **12** (yellow oil) in 10.40 g, 82% yield (36.6 mmol). Rf: 0.30, UV/PMA (Hex:EtOAc, 17:3); $[\alpha]_D^{20}$ –54.2 (*c* 1.0, CH_2Cl_2); IR (attenuated total reflectance (ATR)) ν / cm^{-1} 3074, 3030, 2975, 2936, 1775, 1697, 1455, 1385, 1207, 1195, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.22-7.20 (m, 2H), 4.81 (br s, 1H), 4.76 (br s, 1H), 4.69 (ddt, *J* 7.4, 6.6, 3.2 Hz, 1H), 4.19 (dd, *J* 8.9, 7.8 Hz, 1H), 4.15 (dd, *J* 9.1, 3.1 Hz, 1H), 4.03 (apparent sextet, *J* 7.1 Hz, 1H), 3.27 (dd, *J* 13.4, 3.2 Hz, 1H), 2.71 (dd, *J* 13.4, 9.7 Hz, 1H), 2.57 (dd, *J* 13.8, 7.0 Hz, 1H), 2.09 (dd, *J* 13.8, 7.5 Hz, 1H), 1.78 (s, 3H), 1.16 (d, *J* 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.9, 153.1, 142.9, 135.3, 129.4, 128.9, 127.3, 112.5, 65.9, 55.3, 41.8, 37.9, 35.5, 22.2, 16.6.

(*S*)-2,4-Dimethylpent-4-en-1-ol (**14**)

To a flask containing compound **12** (1 equiv., 28.0 mmol, 8.00 g), it was added methanol (1.1 equiv., 32 mmol, 1.3 mL) in Et_2O (mL). The mixture was cooled to 0 °C, $LiBH_4$ (1 equiv., 28.0 mmol, 16.0 mL, 2 M in tetrahydrofuran) was added and the mixture stirred at 0 °C for 45 min. The reaction was then warmed to room temperature and was stirred for 90 min, then the reaction was quenched in the presence of NaOH (4.50 g in 50 mL

of water) and extracted with ethyl ether (Et_2O) (3 × 80 mL). The organic phase was dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and pentane/ethyl ether (2:1) as eluent, resulting in alcohol **14** (colorless oil) in 3.46 g, 95% yield (26.6 mmol). Rf: 0.34, PMA (Hex:Et_2O, 2:1); $[\alpha]_D^{20}$ –5.7 (*c* 2.0, CH_2Cl_2); IR (ATR) ν / cm^{-1} 3338, 3075, 2956, 2918, 2873, 1651; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 4.71 (br s, 1H), 3.50 (dd, *J* 10.6, 5.5 Hz, 1H), 3.43 (dd, *J* 10.6, 5.6 Hz, 2H), 2.18-2.10 (m, 1H), 1.97 (s, 1H), 1.90-1.80 (m, 1H), 1.72 (s, 3H), 0.90 (d, *J* 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 111.6, 68.2, 42.2, 33.5, 22.1, 16.5.

(*S*)-2,4-Dimethylpent-4-enal (**10**)

To a flask of 15 mL containing oxalyl chloride (3 equiv., 3 mmol, 0.5908 g, 0.40 mL) in dichloromethane (5 mL) was added dimethyl sulfoxide (DMSO; 5.5 equiv., 5.5 mmol, 0.4297 g, 0.39 mL). The mixture was stirred at −78 °C for 30 min. Then the alcohol **14** (1 equiv., 1 mmol, 0.1142 g) was added and the mixture stirred at −78 °C for a further 30 min. The mixture was warmed to 0 °C followed by addition of triethylamine (12 equiv., 12 mmol, 1.1673 g, 1.6 mL) while stirring at 0 °C for 90 min. The reaction was washed with saturated aqueous ammonium chloride solution (NH_4Cl) (20 mL), which was extracted with ethyl ether (Et_2O) (3 × 30 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, giving aldehyde **10** (yellowish oil) in 0.1122 g, in quantitative yield (1 mmol). Rf: 0.50, PMA (Hex:EtOAc, 9:1); $[\alpha]_D^{20}$ +3.7 (*c* 2.0, CH_2Cl_2); IR (ATR) ν / cm^{-1} 3074, 2955, 2920, 2871, 2855, 1724, 1650, 1457; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, *J* 1.9 Hz, 1H), 4.82 (br s, 1H), 4.73 (br s, 1H), 2.58-2.51 (m, 1H), 2.17 (d, *J* 16.3 Hz, 1H), 2.03 (dd, *J* 14.3, 8.0 Hz, 1H), 1.73 (s, 3H), 1.08 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 142.2, 112.8, 44.2, 38.8, 22.2, 13.4.

Synthesis, characterization and spectra data of ketone **9** (C(12)-C(16) fragment)

(2*S*,4*R*,5*R*)-5-Hydroxy-4-methyl-3-oxohexan-2-yl benzoate (**15**)

To a 100 mL flask containing dicyclohexylborane chloride ($(c\text{-}C_6H_{11})_2BCl$) (1.5 equiv., 7.2 mmol, 1.5270 g, 1.60 mL) in 20 mL of diethyl ether at −78 °C dimethylethylamine (Me_2NEt) (11.8 equiv., 8.6 mmol, 0.2632 g, 0.38 mL) and ethylketone **8** (4.8 mmol, 1.00 g in 20 mL of Et_2O, via cannula) were added dropwise. The mixture was warmed to 0 °C and was stirred for 2 h. The reaction mixture was then cooled to −78 °C, followed by a dropwise addition of the acetaldehyde (5 equiv., 24.0 mmol, 1.0570 g, 1.3 mL in 20 mL of Et_2O, via cannula). After 1 h at −78 °C the mixture was warmed to −20 °C (freezer) and stirred for 14 h. The temperature was raised to 0 °C, followed by the slow addition of MeOH (20 mL), phosphate buffer pH 7 (20 mL) and H_2O_2 30% solution (20 mL). The reaction was stirred at 0 °C for 1 h, then the mixture was extracted with dichloromethane (CH_2Cl_2) (3 × 50 mL). The organic phase was dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and dichloromethane/ethyl ether (4:1) as the eluent to give the aldol adduct **15** (off-white solid) in 0.9720 g, 81% yield (3.9 mmol) and ds > 95:05. Rf: 0.49, PMA (CH_2Cl_2:Et_2O, 4:1); $[\alpha]_D^{20}$ +38.1 (*c* 1.4, $CHCl_3$); mp 85.2-86.7 °C; IR (ATR) ν / cm^{-1} 3348, 2976, 2935, 2880, 1732, 1719, 1602, 1585, 1485, 1451, 1264, 1111, 1006, 706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* 8.4, 1.3 Hz, 2H), 7.59 (t, *J* 7.4, 1.3 Hz, 1H), 7.46 (t, *J* 7.7 Hz, 2H), 5.44 (q, *J* 7.1 Hz, 1H), 3.98 (pentet, *J* 6.4 Hz, 1H), 2.81 (pentet, *J* 7.2 Hz, 1H), 2.51 (br s, 1H), 1.57 (d, *J* 7.1 Hz, 3H), 1.25 (d, *J* 7.2 Hz, 3H), 1.23 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 165.8, 133.3, 129.7, 129.4, 128.4, 74.5, 69.4, 49.9, 20.8, 15.8, 14.4.

(2*S*,4*R*,5*R*)-5-((4-Methoxybenzyl)oxy)-4-methyl-3-oxohexan-2-yl benzoate (**16**)

To a mixture with *p*-methoxybenzyl alcohol (1.5 equiv., 36.0 mmol, 4.9740 g, 4.4 mL) in diethyl ether (19 mL) at room temperature under an inert atmosphere, it was added sodium hydride in mineral oil (0.15 equiv., 3.6 mmol, 0.1440 g of NaH). The suspension was stirred for 1 h. The mixture was cooled to 0 °C followed by addition of trichloroacetonitrile (1.5 equiv., 36.0 mmol, 5.1980 g, 3.6 mL) over 15 min. The mixture was maintained at 0 °C for 5 min and at room temperature for a further 1 h. The reaction was washed with saturated $NaHCO_3$ (20 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. To the residue, it was added the alcohol **15** (1 equiv., 24.0 mmol, 6.00 g), CSA (0.2 equiv., 4.8 mmol, 1.12 g) and CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 18 h. Subsequently, the reaction was washed with saturated aqueous $NaHCO_3$ solution (200 mL), which was extracted with Et_2O (4 × 100 mL). The organic phase was dried with $MgSO_4$. The product was purified by flash column chromatography on hexane/ethyl acetate (9:1) as eluent, providing a colorless oil (**16**) in 7.4683 g, 84% yield (20.2 mmol). Rf: 0.12, PMA (Hex:EtOAc, 9:1);

$[\alpha]_D^{20}$ –26.6 (*c* 2.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3064, 3034, 2975, 2937, 2909, 2879, 2837, 1716, 1613, 1513, 1451, 1246, 1114, 1028, 823, 712; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* 7.2 Hz, 2H), 7.57 (t, *J* 7.4 Hz, 1H), 7.44 (t, *J* 7.7 Hz, 2H), 7.16 (d, *J* 8.6 Hz, 2H), 6.83 (d, *J* 8.6 Hz, 2H), 5.37 (q, *J* 7.0 Hz, 1H), 4.42 (d, *J* 10.8 Hz, 1H), 4.27 (d, *J* 10.8 Hz, 1H), 3.78 (s, 3H), 2.94 (dq, *J* 14.2, 7.1 Hz, 1H), 1.47 (d, *J* 7.0 Hz, 3H), 1.18 (d, *J* 6.2 Hz, 3H), 1.14 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 165.8, 159.0, 133.1, 130.5, 129.8, 129.3, 128.3, 113.6, 76.8, 75.1, 71.1, 55.2, 49.0, 16.7, 15.2, 13.6.

(2*R*,3*R*)-3-((4-Methoxybenzyl)oxy)-2-methylbutanal (**17**)

To a 500 mL flask containing the benzoate ester **16** (1 equiv., 20.0 mmol, 5.3670 g) in THF (20 mL) at −78 °C and argon atmosphere, lithium borohydride ($LiBH_4$) (10 equiv., 200.0 mmol, 100.0 mL, 2 M in THF) was added. The mixture was stirred at −78 °C for 10 min, then warmed to room temperature and stirred for a further 12 h. The reaction was cooled to 0 °C, then 100 mL of water was added and the mixture was washed with saturated aqueous ammonium chloride solution (NH_4Cl) (100 mL), then extracted with Et_2O (4 × 100 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under pressure. To the mixture of diols, methanol (200 mL), water (100 mL) and sodium periodate ($NaIO_4$) (5 equiv., 100.0 mmol, 21.4877 g) were added. The reaction mixture was stirred for 1 h at room temperature. Subsequently, distilled water (100 mL) was added to the reaction, which was extracted with Et_2O (3 × 100 mL). The organic phase was dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (4:1) as eluent to afford a colorless oil (**17**) in 4.3567 g, 98% yield (19.6 mmol). Rf: 0.32, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –46.7 (*c* 2.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 2974, 2936, 2876, 2831, 2718, 1722, 1612, 1513, 1245, 1033, 819; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* 2.4 Hz, 1H), 7.23 (d, *J* 8.6 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 4.54 (d, *J* 11.3 Hz, 1H), 4.37 (d, *J* 11.3 Hz, 1H), 3.79 (s, 3H), 3.78-3.74 (m, 1H), 2.53 (apparent pentet, *J* 7.1 and 2.4 Hz, 1H), 1.23 (d, *J* 6.3 Hz, 3H), 1.06 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 159.1, 130.2, 129.2, 113.7, 74.8, 70.3, 55.2, 51.7, 16.8, 10.0.

(3*R*,4*R*)-4-((4-Methoxybenzyl)oxy)-3-methylpentan-2-one (**9**)

To a 250 mL flask containing the aldehyde **17** (1 equiv., 20.0 mmol, 4.4456 g) in Et_2O (80 mL) at −78 °C and argon atmosphere was added methyllithium (MeLi) (3 equiv., 45.0 mmol, 28.1 mL, 1.6 M in THF) dropwise. The mixture was stirred at −78 °C for 30 min, subsequently warmed to −30 °C and stirred for an additional 1 h. Then, buffer solution pH 7 (120 mL) was added. The mixture was extracted with Et_2O (4 × 80 mL), washed with saturated sodium chloride (NaCl) solution (100 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, and the mixture of alcohols was used in the next step without purification. To a 250 mL flask containing oxalyl chloride (1.5 equiv., 30.0 mmol, 3.8079 g, 2.4 mL) in dichloromethane (120 mL, 0.25 M) at −78 °C, it was added DMSO (3.0 equiv., 60.0 mmol, 4.6878 g, 4.3 mL). The mixture was stirred at −78 °C for 30 min. Thereafter, the pre-prepared mixture of the alcohols was added and stirred at −78 °C for 30 min. The mixture was warmed to 0 °C followed by addition of triethylamine (Et_3N) (5 equiv., 100.0 mmol, 10,1190 g, 14.0 mL), and stirred at 0 °C for 90 min. The reaction was washed with saturated aqueous NH_4Cl solution (100 mL) and extracted with Et_2O (3 × 100 mL). The organic phase was washed with water (100 mL), saturated aqueous NaCl solution (100 mL), and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording a yellowish oil (**9**) in 4.4899 g, 95% yield over two steps (19.0 mmol), and was used in the next step without purification. Rf: 0.32, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –37.9 (*c* 2.4, $CHCl_3$); IR (ATR) ν / cm^{-1} 2973, 2936, 2911, 2878, 2837, 1711, 1613, 1513, 1456, 1377, 1355, 1245, 1033, 821; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* 8.7 Hz, 2H), 6.86 (d, *J* 8.7 Hz, 2H), 4.48 (d, *J* 11.0 Hz, 1H), 4.32 (d, *J* 11.0 Hz, 1H), 3.79 (s, 3H), 3.71 (dq, *J* 8.2, 6.1 Hz, 1H), 2.73 (pentet, *J* 7.2, 1H), 2.15 (s, 3H), 1.17 (d, *J* 6.2 Hz, 3H), 1.02 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 159.0, 130.4, 129.2, 113.7, 76.7, 70.6, 55.2, 52.6, 30.0, 16.6, 12.6.

Synthesis, characterization and spectra data of aldehyde **5** (C(17)-C(19) fragment)

(2*S*,4*R*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-3-oxohexan-2-yl benzoate (**18**)

To a flask, it was added the alcohol **15** (1 equiv., 5.0 mmol, 1.2515 g) in dichloromethane (50 mL). The reaction mixture was cooled to −78 °C, 2,6-lutidine (2.0 equiv., 10.0 mmol, 1.15 mL) and TBSOTf (1.5 equiv., 7.5 mmol, 1.70 mL) were added. The reaction was stirred for 1 h at −78 °C. Then, the reaction was washed with saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with Et_2O (3 × 100 mL). The organic phase was dried with $MgSO_4$. The product was purified by flash column chromatography on hexane/dichloromethane (1:1)

as eluent to provide aldol **18** (colorless oil) adduct in 1.80 g, 99% yield (4.9 mmol). Rf: 0.41, PMA (Hex:CH_2Cl_2, 1:1); $[\alpha]_D^{20}$ –15.5 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3065, 2956, 2930, 2886, 2858, 1721, 1603, 1586, 1472, 1452, 1380, 1266, 1116, 711; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (dt, *J* 7.0, 1.5 Hz, 2H), 7.57 (tt, *J* 7.3, 2.0 Hz, 1H), 7.45 (tt, *J* 6.4, 1.5 Hz, 2H), 5.41 (q, *J* 7.0 Hz, 1H), 4.06 (dq, *J* 8.4, 6.1 Hz, 1H), 2.85 (dq, *J* 14.1, 7.1 Hz, 1H), 1.52 (d, *J* 7.0 Hz, 3H), 1.15 (d, *J* 6.1 Hz, 3H), 1.09 (d, *J* 7.1 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 165.7, 133.2, 129.8, 129.7, 128.4, 75.1, 70.1, 50.5, 25.8, 21.1, 17.9, 15.2, 13.8, –4.7, –4.9; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 387.19621, found: 387.19548.

(2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylbutanal (**5**)

The aldehyde **5** was prepared under the same conditions as showed for the preparation of compound **17**, resulting in a colorless oil in 0.5302 g, 98% yield. Rf: 0.40, PMA (Hex:EtOAc, 9:1); $[\alpha]_D^{20}$ –48.1 (*c* 1.0, benzene); IR (ATR) ν / cm^{-1} 2957, 2931, 2886, 2858, 2711, 1727, 1473, 1463, 1253, 1115, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* 2.6 Hz, 1H), 4.02 (pentet, *J* 6.2 Hz, 1H), 2.36 (qdd, *J* 7.0, 5.8, 2.6 Hz, 1H), 1.21 (d, *J* 6.3 Hz, 3H), 1.06 (d, *J* 7.0 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 69.8, 53.6, 26.0, 21.7, 17.9, 10.6, 8.9, –4.2, –5.0.

Synthesis and characterization, spectra data and stereochemistry determination of diol **20**

(2*R*,3*R*,6*S*,7*S*)-6-Hydroxy-2-((4-methoxybenzyl)oxy)-3,7,9-trimethyldec-9-en-4-one (**19**)

To a flask containing methyl ketone **9** (1.0 equiv., 8.5 mmol, 2.0086 g) in Et_2O (170 mL, 0.05 M) at –30 °C, it was added slowly (*c*-hex)$_2$BCl (2.0 equiv., 17.0 mmol, 3.6066 g, 3.7 mL) and Et_3N (2.1 equiv., 17.8 mmol, 1.7996 g, 2.5 mL), resulting in a white solution. After the addition of Et_3N, the mixture was cooled to –78 °C. Subsequently, the aldehyde **17** (3.0 equiv., 25.5 mmol, 2.8603 g) was added dropwise. The reaction mixture was stirred at –78 °C. After 1 h, methanol (MeOH) (170 mL) was added to the reaction, which was warmed to room temperature. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/ethyl acetate (4:1) as eluent to provide aldol **19** (colorless oil) adduct in 2.4881 g, 84% yield (7.1 mmol) and ds > 95:05. Rf: 0.23, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –32.1 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3485, 3073, 2967, 2931, 2879, 1708, 1614, 1514, 1378, 1249, 1104, 1036, 824; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* 8.6 Hz, 2H, Ar*H*), 6.85 (d, *J* 8.6 Hz, 2H, Ar*H*), 4.76 (s, 1H, H-7), 4.68 (s, 1H, H-7), 4.48 (d, *J* 10.8 Hz, 1H), 4.25 (d, *J* 10.8 Hz, 1H), 3.95 (ddd, *J* 9.5, 3.6, 2.7 Hz, 1H, H-11), 3.79 (s, 3H, OC*H*$_3$), 3.68 (dq, *J* 8.7, 6.1 Hz, 1H, H-15), 2.98 (br s, 1H, O*H*), 2.72 (dq, *J* 8.7, 7.0 Hz, 1H, H-14), 2.64 (dd, *J* 17.6, 2.4 Hz, 1H, H-12), 2.55 (dd, *J* 17.6, 9.6 Hz, 1H, H-12), 2.15 (dd, *J* 13.4, 5.3 Hz, 1H, H-9), 1.80 (dd, *J* 13.5, 9.3 Hz, 1H, H-9), 1.68 (s, 1H, H-22), 1.66-1.60 (m, 1H, H-10), 1.20 (d, *J* 6.1 Hz, 3H, H-16), 1.01 (d, *J* 7.0 Hz, 3H, H-23), 0.80 (d, *J* 6.8 Hz, 3H, H-24); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 159.2, 144.1, 130.2, 129.4, 113.7, 111.9, 77.6, 70.8, 70.0, 55.2, 52.2, 47.8, 41.4, 35.4, 22.1, 16.9, 13.8, 13.0; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 371.21983, found: 371.21912.

(2*R*,3*S*,4*S*,6*S*,7*S*)-2-((4-Methoxybenzyl)oxy)-3,7,9-trimethyldec-9-ene-4,6-diol (**20**)

To a flask containing tetramethylammonium triacetoxyborohydride (4.0 equiv., 28.0 mmol, 7.3563 g) in acetonitrile (MeCN) (21.0 mL), it was added glacial acetic acid (AcOH) (21.0 mL). The mixture was stirred for 30 min. Then, the reaction was cooled to –40 °C, followed by the addition of a solution of the alcohol **19** (1.0 equiv., 7.0 mmol, 2.4394 g) in AcOH (21.0 mL), dropwise via the cannula and a mixture of CSA (0.5 equiv., 3.5 mmol, 0.8131 g), anhydrous MeCN (21.0 mL) and glacial AcOH (21.0 mL). The reaction mixture was stirred at –20 °C for 48 h. Subsequently, the mixture was transferred to an Erlenmeyer flask under stirring with saturated aqueous solution of $NaHCO_3$ (250 mL). After the total gas evolution, a saturated solution of Rochelle's salt ($KNaC_4H_4O_6$) (250 mL) and CH_2Cl_2 (250 mL) was added. The resulting mixture was stirred at room temperature for 3 h. Thereafter, the mixture was extracted with CH_2Cl_2 (4 × 100 mL). The organic phase was dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using stationary phase silica gel and hexane/ethyl acetate (3:2) as eluent to provide diol **20** (yellow oil) at 2.2817 g, 93% yield (6.5 mmol) and ds > 95:05. Rf: 0.31, UV/PMA (Hex:EtOAc, 3:2); $[\alpha]_D^{20}$ –8.1 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3403, 3073, 2967, 2934, 2912, 2838, 1613, 1514, 1455, 1376, 1248, 1036, 888, 821; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* 8.6 Hz, 2H), 6.87 (d, *J* 8.6 Hz, 2H), 4.75 (s, 1H), 4.69 (s, 1H), 4.59 (d, *J* 11.1 Hz, 1H), 4.52 (s, 1H), 4.36 (d, *J* 11.1 Hz, 1H), 3.88-3.81 (m, 2H), 3.79 (s, 3H), 3.55 (dq, *J* 8.0, 6.1 Hz, 1H), 3.16 (br s, 1H), 2.20 (dd, *J* 13.5, 4.9 Hz, 1H), 1.82 (dt, *J* 15.2, 9.1 Hz, 2H), 1.75-1.70 (m, 2H), 1.69 (s, 3H), 1.53 (ddd, *J* 14.5, 6.8, 1.9 Hz, 1H), 1.26 (d, *J* 6.1 Hz, 3H), 0.86 (d, *J* 6.8 Hz, 3H), 0.79 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 144.5, 129.9, 129.5, 113.9, 111.6, 80.3, 73.9, 71.3, 70.3, 55.2, 43.4, 41.5,

36.5, 22.1, 17.3, 13.9, 13.0; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 373.23548, found: 373.23481.

(4*S*,6*S*)-4-((2*R*,3*R*)-3-((4-Methoxybenzyl)oxy)butan-2-yl)-2,2-dimethyl-6-((*S*)-4-methylpent-4-en-2-yl)-1,3-dioxane (**21**)

To a 250 mL flask containing the diol **20** (1 equiv., 2.0 mmol, 0.7010 g) in 2,2-dimethoxypropane (70 mL), CSA (0.1 equiv., 0.2 mmol, 0.0465 g) was added. The reaction mixture was stirred for 12 h at room temperature. Subsequently, the reaction was diluted with Et_2O (50 mL), followed by saturated aqueous solution of $NaHCO_3$ (50 mL) and extraction with Et_2O (3 × 50 mL). The organic phase was dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (9:1) as eluent to provide acetonide **21** (colorless oil) in 0.7108 g, 91% yield (1.8 mmol). Rf: 0.43, UV/PMA (Hex:EtOAc, 9:1); $[\alpha]_D^{20}$ –40.7 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3074, 2982, 2968, 2836, 1613, 1513, 1457, 1376, 1240, 1224, 1108, 1038, 886, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* 8.5 Hz, 2H), 6.86 (d, *J* 8.6 Hz, 2H), 4.76 (s, 1H), 4.68 (s, 1H), 4.45 (d, *J* 11.3 Hz, 1H), 4.40 (d, *J* 11.3 Hz, 1H), 3.63 (td, *J* 9.1, 6.1 Hz, 1H), 3.53 (dt, *J* 9.8, 6.1 Hz, 1H), 3.79 (s, 3H), 3.75 (dq, *J* 6.2, 5.1 Hz, 1H), 2.15 (dd, *J* 13.6, 4.8 Hz, 1H), 2.03-1.95 (m, 1H), 1.74 (dd, *J* 13.2, 9.8 Hz, 1H), 1.70-1.52 (m, 6H), 1.30 (s, 3H), 1.29 (s, 3H), 1.08 (d, *J* 6.3 Hz, 3H), 0.86 (d, *J* 6.5 Hz, 3H), 0.84 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 144.0, 131.4, 129.1, 113.7, 111.8, 100.1, 74.4, 69.9, 69.8, 68.0, 55.2, 41.8, 40.9, 35.4, 34.6, 24.5, 24.4, 22.1, 14.7, 14.3, 8.9; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 413.26592, found: 413.26678.

(2*S*,3*S*)-1-((2*R*,4*S*,5*R*,6*R*)-2-(4-Methoxyphenyl)-5,6-dimethyl-1,3-dioxan-4-yl)-3,5-dimethylhex-5-en-2-ol (**22**)

To a flask containing diol **20** (1 equiv., 57.1 μmol, 20 mg) in CH_2Cl_2 (2 mL, 0.03 M) under argon atmosphere was added activated 4 Å molecular sieves (36 mg). After 15 min, the mixture was cooled to −10 °C followed by addition of DDQ (1.25 equiv., 32.0 μmol, 32 mg). The mixture was stirred for 5 min at −10 °C and 2 h at 0 °C. Then the reaction was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (9:1) as the eluent, affording acetal **22** (yellowish oil) in 15.7 mg, 79% yield (45.1 μmol). Rf: 0.12, PMA (Hex:EtOAc, 9:1); $[\alpha]_D^{20}$ –4.9 (*c* 0.5, $CHCl_3$); IR (ATR) ν / cm^{-1} 3497, 3073, 2968, 2933, 2892, 2840, 1615, 1518, 1455, 1401, 1250, 1075, 1035, 826; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* 8.7 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 5.51 (s, 1H), 4.77 (s, 1H), 4.70 (s, 1H), 3.91 (ddd, *J* 9.9, 3.8, 1.7 Hz, 1H), 3.79 (s, 3H), 3.75 (ddd, *J* 10.2, 7.7, 2.8 Hz, 1H), 3.58 (dq, *J* 9.8, 6.1 Hz, 1H), 2.40 (br s, 1H), 2.20 (dd, *J* 13.5, 5.0 Hz, 1H), 1.92-1.84 (m, 2H), 1.77-1.62 (m, 5H), 1.62-1.53 (m, 1H), 1.33 (d, *J* 6.1 Hz, 3H), 0.87 (d, *J* 6.8 Hz, 3H), 0.85 (d, *J* 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 144.4, 131.2, 113.6, 111.7, 100.5, 80.0, 78.5, 70.6, 55.3, 41.7, 39.7, 36.4, 36.2, 22.1, 19.4, 13.7, 12.3; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 371.21918, found: 371.21983.

(2*R*,4*R*,5*R*,6*S*)-2-(4-Methoxyphenyl)-4,5-dimethyl-6-(((2*S*,3*S*)-3,5,5-trimethyltetrahydrofuran-2-yl)methyl)-1,3-dioxane (**23**)

To a solution containing the acetal **24** (1 equiv., 9.4 μmol, 3.3 mg) in MeCN (1 mL, 0.01 M), it was added $HCl_{(aq)}$ (37%) (0.5 equiv., 4.7 μmol, 0.4 μL). The reaction mixture was stirred for 24 h. Subsequently, the reaction was washed with saturated aqueous solution $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 15 mL). The organic phase was dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (9:1) as the eluent to give the hydrofuran **23** in 2.6 mg, 79% yield (7.4 μmol). Rf: 0.16, PMA (Hex:EtOAc, 9:1); $[\alpha]_D^{20}$ –54.7 (*c* 0.35, $CHCl_3$); IR (ATR) ν / cm^{-1} 2967, 2931, 2889, 2838, 1615, 1518, 1457, 1379, 1248, 1036, 826; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H, Ar*H*), 6.89-6.85 (m, 2H, Ar*H*), 5.56 (s, 1H, OC(*H*)O), 4.27 (ddd, *J* 9.8, 6.6, 2.9 Hz, 1H, H-11), 3.79 (s, 3H, OCH_3), 3.68 (td, *J* 10.1, 1.4 Hz, 1H, H-13), 3.57 (dq, *J* 9.7, 6.1 Hz, 1H, H-15), 2.43 (apparent septet, *J* 7.2 Hz, 1H, H-10), 1.92 (dd, *J* 12.3, 7.4 Hz, 1H, H-9), 1.75 (ddd, *J* 13.9, 10.2, 1.5 Hz, 1H, H-12), 1.50-1.44 (m, 2H, H-9 and H-12), 1.39 (tq, *J* 9.8, 6.7 Hz, 1H, H-14), 1.31 (d, *J* 6.1 Hz, 3H, H-16), 1.31 (s, 3H, H-7), 1.21 (s, 3H, H-22), 0.95 (d, *J* 7.0 Hz, 3H, H-23), 0.85 (d, *J* 6.6 Hz, 3H, H-24); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 131.8, 127.3, 113.4, 99.9, 79.3, 78.9, 78.4, 76.8, 55.3, 46.6, 41.2, 36.5, 34.5, 30.8, 29.2, 19.5, 14.8, 12.5; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 371.21909, found: 371.21983.

Synthesis and characterization, spectra data of enolsilane **6** (C(7)-C(16) fragment)

(2*R*,3*R*,4*S*,6*S*,7*S*)-4,6-Bis(methoxymethoxy)-3,7,9-trimethyldec-9-en-2-ol (**25**)

To a flask containing the diol **21** (1 equiv., 2.0 mmol, 0.702 g) in CH_2Cl_2 (20 mL, 0.1 M) at 0 °C, it was added DIPEA (9 equiv., 36.0 mmol, 4.6520 g, 6.2 mL) and MOMCl (6 equiv., 24.0 mmol, 2.8980 g, 2.73 mL). The

reaction mixture was stirred for 12 h at room temperature. Subsequently, saturated aqueous solution of NH_4Cl (10 mL) was added, followed by extraction with CH_2Cl_2 (3 × 10 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. To a mixture of PMB ether **24**, it was added a mixture of CH_2Cl_2:phosphate buffer pH 7 (9:1) (35 mL, 0.5 M) at 0 °C, followed by the addition of DDQ (1.5 equiv., 3.0 mmol, 0.7175 g). The reaction was stirred at 0 °C for 90 min, then the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL). The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (6 × 70 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/ethyl acetate (7:3) as eluent to provide the alcohol **25** (colorless oil) in 0.5031 g, 79% yield for two steps (1.6 mmol). Rf: 0.16, vanillin (Hex/EtOAc, 7:3); $[\alpha]_D^{20}$ –37.1 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3437, 3074, 2996, 2934, 2889, 1649, 1455, 1377, 1147, 1093, 1039, 918; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78-4.63 (m, 6H), 4.01 (ddd, *J* 8.5, 4.0, 1.4 Hz, 1H), 3.68 (dt, *J* 7.4, 2.4 Hz, 1H), 3.57 (dq, *J* 8.5, 6.2 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.27 (dd, *J* 13.5, 3.7 Hz, 1H), 2.03-1.93 (m, 1H), 1.79-1.68 (m, 6H), 1.58 (ddd, *J* 14.7, 9.5, 1.3 Hz, 1H), 1.48 (ddd, *J* 15.0, 8.8, 1.8 Hz, 1H), 1.22 (d, *J* 6.2 Hz, 3H), 0.85 (d, *J* 6.9 Hz, 3H), 0.84 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 111.6, 96.9, 96.1, 80.7, 76.9, 69.8, 55.9, 55.7, 44.5, 39.8, 34.6, 32.1, 22.2, 21.4, 14.9, 10.8; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 341.22985, found: 341.22976.

(3*S*,4*S*,6*S*,7*S*)-4,6-Bis(methoxymethoxy)-3,7,9-trimethyldec-9-en-2-one (**26**)

To a solution containing the alcohol **25** (1 equiv., 0.9 mmol, 0.3180 g) in CH_2Cl_2 (3 mL), it was added $NaHCO_3$ (2.4 equiv., 0.21 mmol, 0.1764 g) and DMP (1.2 equiv., 1.08 mmol, 0.4578 g). The reaction mixture was stirred at room temperature for 90 min. The reaction was washed with saturated aqueous solution of $NaHCO_3$ (30 mL) and Na_2SO_3 (30 mL) and stirred at room temperature for 10 min. This mixture was extracted with dichloromethane (4 × 30 mL). The organic layer was washed with saturated aqueous solution of NaCl (20 mL) and dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (4:1) as eluent to afford methyl ketone **26** (colorless oil) in 0.2761 g, 97% yield (0.9 mmol). Rf: 0.17, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –5.1 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3074, 2962, 2934, 2890, 2824, 1712, 1455, 1366, 1148, 1092, 917; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.72-4.67 (m, 5H), 4.07 (ddd, *J* 9.4, 5.5, 1.5 Hz, 1H), 3.65 (dt, *J* 7.6, 2.4 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.98-2.91 (apparent pentet, *J* 6.5 Hz, 1H), 2.27-2.18 (m, 1H), 2.20 (s, 3H), 2.00-1.92 (m, 1H), 1.76-1.68 (m, 1H), 1.69 (s, 3H), 1.50 (ddd, *J* 14.6, 9.7, 1.8 Hz, 1H), 1.36 (ddd, *J* 14.7, 9.8, 1.6 Hz, 1H), 1.08 (d, *J* 7.0 Hz, 3H), 0.82 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 144.3, 111.6, 97.1, 97.0, 79.5, 76.7, 55.9, 55.8, 51.7, 39.7, 34.7, 33.2, 29.6, 22.2, 14.9, 10.5; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 339.21420, found: 339.21421.

(5*S*,6*S*,8*S*)-6-(Methoxymethoxy)-2,2,5-trimethyl-4-methylene-8-((*S*)-4-methylpent-4-en-2-yl)-3,9,11-trioxa-2-siladodecane (**6**)

To a solution containing LDA (2.0 equiv., 0.6 mmol, 1.2 mL of a 0.5 M solution in THF) in THF (5 mL) at –78 °C, it was added TMSCl (6.0 equiv., 1.8 mmol, 0.2151 g, 0.25 mL) and sequentially the ketone **26** (1 equiv., 0.3 mmol, 0.9481 g) in THF (2 mL) via cannula. The mixture was stirred at –78 °C for 30 min. After this time, the reaction was warmed to room temperature and it was added hexane (30 mL) to the reaction. The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (30 mL) and dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, resulting in enolsilane **6** (colorless oil) in 0.1061 g, 91% yield (0.55 mmol). Rf: 0.57, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –2.5 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3074, 2989, 2958, 2822, 1651, 1619, 1456, 1376, 1252, 1149, 1096, 912, 841; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.77-4.65 (m, 6H), 4.12-4.06 (m, 2H), 3.90 (ddd, *J* 9.8, 4.8, 1.9 Hz, 1H), 3.64 (dt, *J* 7.0, 3.0 Hz, 1H), 3.39 (s, 6H), 2.50 (dq, *J* 6.9, 5.0 Hz, 1H), 2.27 (dd, *J* 13.2, 3.4 Hz, 1H), 1.97 (ddd, *J* 13.8, 6.9, 3.7 Hz, 1H), 1.74 (dd, *J* 13.3, 10.5 Hz, 1H), 1.69 (s, 3H), 1.57-1.49 (m, 1H), 1.47-1.34 (m, 1H), 1.00 (d, *J* 7.0 Hz, 3H), 0.82 (d, *J* 6.8 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 144.6, 111.5, 96.9, 89.9, 79.6, 77.4, 55.8, 55.7, 43.9, 39.9, 34.8, 32.1, 22.2, 14.9, 11.8, 5.4; HRMS (ESI) *m/z*, calcd. for $[M+Na]^+$: 411.25372, found: 411.25373.

Key step and characterization, spectra data of adduct **4** (C(7)-C(20) fragment)

(5*S*,7*S*,8*S*,12*S*,13*R*)-11-Hydroxy-7-(methoxymethoxy)-8,12,13,15,15,16,16-heptamethyl-5-((*S*)-4-methylpent-4-en-2-yl)-2,4,14-trioxa-15-silaheptadecan-9-one (**4**)

To a flask containing the enolsilane **6** (1 equiv., 0.85 mmol, 0.3303 g), and the aldehyde **5** (1.25 equiv., 1.1 mmol, 0.2400 g) in CH_2Cl_2 (10 mL) at –78 °C, it was added $BF_3.Et_2O$ (1.25 equiv., 1.1 mmol, 1.1 mL). The

reaction mixture was stirred at −78 °C for 90 min. The reaction was washed with saturated aqueous solution of $NaHCO_3$ (30 mL), extracted with dichloromethane (3 × 30 mL) and dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using silica gel as the stationary phase and hexane/EtOAc (4:1) as eluent, resulting in aldol adduct **4** (colorless oil) in 0.4031 g, 89% yield (0.76 mmol) and ds > 95:05. Rf: 0.30, PMA (Hex:EtOAc, 4:1); $[\alpha]_D^{20}$ –7.1 (*c* 1.0, $CHCl_3$); IR (ATR) ν / cm^{-1} 3503, 3074, 2957, 2931, 2888, 2857, 1709, 1649, 1462, 1377, 1254, 1148, 1094, 1036, 918, 836, 775; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.66-4.58 (m, 5H), 4.58-4.53 (m, 1H), 4.01 (dd, *J* 7.8, 6.4 Hz, 1H), 3.86 (dq, *J* 6.2, 4.0 Hz, 1H), 3.60 (d, *J* 10.1 Hz, 1H), 3.45 (s, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 2.93 (apparent pentet, *J* 6.7 Hz, 1H), 2.73 (dd, *J* 16.8, 8.0 Hz, 1H), 2.41 (dd, *J* 16.8, 4.6 Hz, 1H), 2.19 (dd, *J* 13.5, 3.4 Hz, 1H), 1.95-1.88 (m, 1H), 1.69-1.62 (m, 1H), 1.64 (s, 3H), 1.44 (ddd, *J* 14.4, 9.5, 1.3 Hz, 1H), 1.41-1.35 (m, 1H), 1.31 (ddd, *J* 14.3, 9.9, 0.9 Hz, 1H), 1.23 (d, *J* 6.3 Hz, 3H), 1.02 (d, *J* 6.9 Hz, 3H), 0.92 (d, *J* 7.1 Hz, 3H), 0.84 (s, 9H), 0.76 (d, *J* 6.9 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 144.1, 111.5, 96.9, 79.4, 76.6, 73.4, 66.2, 55.7, 55.7, 51.4, 47.7, 42.7, 39.5, 34.5, 33.1, 25.7, 22.1, 21.8, 17.8, 14.8, 11.0, 10.4, –4.4, –5.2; HRMS (ESI) *m/z*, calcd. for $[M + Na]^+$: 555.36875, found: 555.36878.

Supplementary Information

Supplementary information (characterization data and copies of ^{1}H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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