

Total Synthesis of 15-D_{2t}- and 15-*epi*-15-E_{2t}- Isoprostanes

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Supporting Information

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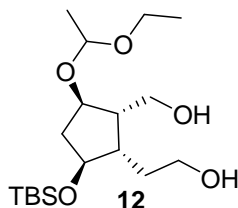
I.1 General

Unless otherwise stated, reactions were performed under nitrogen using oven-dried glassware. Solvents were distilled under nitrogen. CH_2Cl_2 was distilled from CaH_2 , EtOH from sodium metal; THF and diethyl ether were distilled from sodium metal/benzophenone ketyl. All other reagent quality solvents were used without further purification. The Wittig reactions were carried out in degassed THF using commercially available (4-carboxybutyl)triphenylphosphonium bromide that was oven-dried (70 °C) under vacuum for 18 h prior use. All reactions were monitored by thin layer chromatography that was performed on pre-coated sheets of silica gel 60. Visualization was accomplished with UV light (254 nm) and /or acidic *p*-anisaldehyde followed by gentle heating. Organic layers were dried over MgSO_4 . Column chromatography was performed with silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer in CDCl_3 or MeOD. Chemical shifts of ^1H NMR spectra are reported in part per million (ppm) on the δ scale from an internal standard of residual CHCl_3 (fixed at 7.25 ppm) in CDCl_3 or residual CH_3OD (fixed at 3.36 ppm) in CD_3OD . Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet), coupling constant (Hz), integration. Chemical shifts of ^{13}C NMR data are reported in ppm using the central peak of CDCl_3 as internal reference (fixed at 77.0 ppm) or MeOD (49.0 ppm). The assignment of NMR spectra was assisted by homo- (^1H - ^1H) and heteronuclear (^1H - ^{13}C) correlation spectroscopy. Infrared spectra were recorded using a *FT-IR* spectrophotometer. They are reported as wavenumbers (cm^{-1}) of significant peaks. High resolution mass spectra (HRMS) were obtained in the ESI mode. Optical rotations were measured at 20° C. Melting points are uncorrected.

I. 2 Synthesis and characterization of all new compounds

Preparation and ^1H and ^{13}C spectra of compounds 8, 9, 10, 11 and 3 are reported in Oger, C.; Brinkmann, Y.; Bouazzaoui, S.; Durand, T.; Galano, J. M. *Org. Lett.* **2008, *10*, 5087-90.**

12:

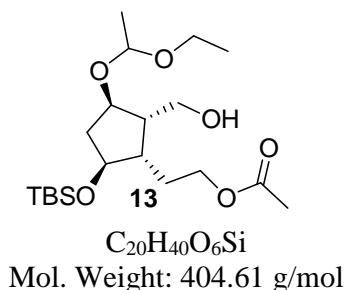


$\text{C}_{18}\text{H}_{38}\text{O}_5\text{Si}$
Mol. Weight: 362.58 g/mol

3 (4.36 g, 13 mmol) was dissolved in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (5/1) (60 mL) and the resulting solution was cooled to $-78\text{ }^\circ\text{C}$. A stream of ozone was bubbled through the solution until a blue color of the later one was obtained indicating an excess of ozone (after 1 hour 30 minutes of reaction time). The reaction medium was then flushed with nitrogen until discoloration. NaBH_4 (5.06 g, 133 mmol, 10 equiv.) was added by little portions and the solution was allowed to warm up to room temperature. After 30 minutes the reaction medium was cooled to $0\text{ }^\circ\text{C}$ before being hydrolyzed by addition of water (30 mL). The layers were separated and the aqueous one was extracted three times with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure affording **12** as colorless oil (4.47 g, 92% (2 steps)). **12** was used without further purification in the next step.

R_f : ~ 0.63 (AcOEt); ^1H -NMR (300 MHz, CDCl_3): δ 4.71 (m, 1H), 3.95 (m, 1H), 3.83 (m, 1H), 3.70 (m, 3H), 3.58 (m, 2H), 3.47 (m, 1H), 2.32 (m, 2H and 1 OH), 2.13 (q, 1H, $J = 7.5\text{ Hz}$), 1.62 (m, 3H and 1 OH), 1.29 (d, 3H, $J = 5.4\text{ Hz}$), 1.19 (t, 3H, $J = 6.5\text{ Hz}$), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 99.0, 77.0, 76.4, 62.2, 60.1, 48.4, 45.6, 42.1, 41.2, 30.7, 25.8, 20.4, 18.0, 15.3,

-4.2, -4.7; IR: ν_{\max} (cm^{-1}): 3387, 2930, 2858, 1472, 1378, 1252, 1084, 1052, 937, 834, 773, 669; HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{38}\text{O}_5\text{Si Na}$ $[\text{M}+\text{Na}]^+$ 385.2386, found: 385.2374.

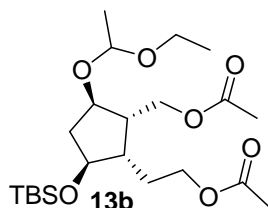
13:

To a solution of diol **12** (4.47 g, 12.3 mmol) in THF (55 mL) under nitrogen were added 33 mL of freshly distilled vinyl acetate and the enzyme *Candida antarctica* (0.7 g). The resulting reaction mixture was stirred at room temperature overnight (15 hours). TLC checking indicated the complete consumption of starting material. The enzymes were separated from the solution by filtration and the solvent was evaporated under reduced pressure. Purification by column chromatography with deactivated silica gel (treated with a 1% solution of NEt_3 prior use) (solvent: petroleum spirit/diethyl ether: 1/1) afforded the desired monoacetylated compound **13** (4.3 g, colorless oil, 88%) and bis-acetylated side product **13b** (0.4 g, colorless oil).

13: R_f : ~ 0.55 (cyclohexane/AcOEt, 1:1); ^1H -NMR (300 MHz, CDCl_3): δ 4.70 (m, 1H), 4.11 (t, 2H, $J = 7.2$ Hz), 3.99 (m, 1H), 3.80 (m, 1H), 3.72 (m, 1H), 3.58 (m, 2H), 3.45 (m, 1H), 2.33 (m, 2H), 2.02 (s, 3H), 1.63 (m, 2H), 1.28 (d, 3H, $J = 5.4$ Hz), 1.17 (t, 3H, $J = 7.2$ Hz), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 170.9, 98.7, 77.0, 76.3, 75.7 (dia), 63.6, 61.7, 61.4 (dia), 60.0, 59.9 (dia), 47.5, 44.8, 44.6 (dia), 42.0, 41.1 (dia), 26.7, 25.6, 20.7, 20.2, 17.7, 15.0, -4.6, -5.0; IR: ν_{\max} (cm^{-1}): 3471, 2930, 2858, 1739, 1472, 1365, 1242, 1085, 1030, 935, 835, 773, 669; HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{41}\text{O}_6\text{Si}$ $[\text{M}+\text{H}]^+$ 405.2672, found: 405.2666.

S-5

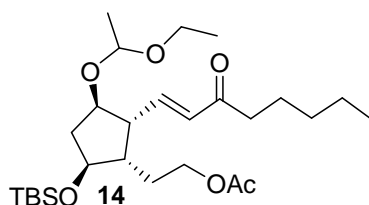
13b:



$C_{22}H_{42}O_7Si$
Mol. Weight: 446.65 g/mol

13b: R_f : ~ 0.87 (cyclohexane/AcOEt, 1:1); 1H -NMR (300 MHz, $CDCl_3$): δ 4.67 (m, 1H), 4.12 (m, 3H), 3.94 (m, 2H), 3.82 (m, 1H), 3.60 (m, 1H), 3.45 (m, 1H), 2.37 (m, 2H), 2.03 (s, 6H), 1.76-1.5 (m, 4H), 1.28 (d, 3H, $J = 5.3$ Hz), 1.18 (t, 3H, $J = 7.3$ Hz), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C -NMR (75 MHz, $CDCl_3$): δ 170.9, 98.9, 98.3 (dia), 75.9, 75.4, 63.5, 63.0, 60.1, 59.7 (dia), 45.0, 44.8 (dia), 44.6, 42.0, 41.2 (dia), 26.7, 25.7, 20.8, 20.4, 20.2, 15.2, 17.9, -4.4, -4.9; IR: ν max (cm^{-1}): 2931, 2858, 1740, 1472, 1365, 1232, 1095, 1032, 935, 835, 774, 669.); HRMS (ESI) calculated for $C_{18}H_{35}O_6Si$ $[(M+H)-C_4H_8O]^+$ 375.2203, found: 375.2215.

14:



$C_{27}H_{50}O_6Si$
Mol. Weight: 498.77 g/mol

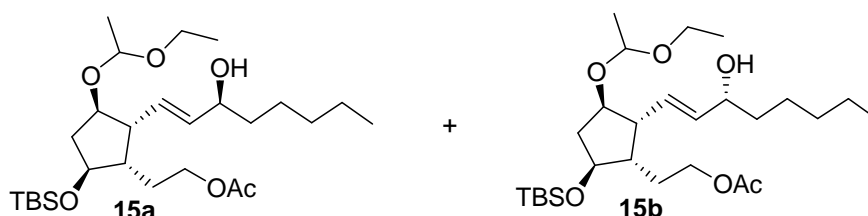
To a solution of **13** (2.1 g, 5.2 mmol, 1 equiv.) in CH_2Cl_2 (70 mL) under nitrogen containing solid $NaHCO_3$ (486 mg, 6.75 mmol, 1.3 equiv.) was added dropwise at 0 °C a 0.3 M solution of solid Dess-Martin periodinane (2.87 g, 6.76 mmol, 1.3 equiv.) in 23 mL of CH_2Cl_2 . The reaction medium was stirred at room temperature for 1 hour and 30 minutes. After disappearance of the starting material (TLC) the reaction mixture was cooled to 0 °C and then quenched by addition of a solution

of Na₂S₂O₃/NaHCO₃ (1/1, 10 % weight). The resulting mixture was stirred at room temperature for 1 hour until layers were well separated. The aqueous layer was extracted three times with CH₂Cl₂ and then the combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The intermediate aldehyde (2.08 g, 96%, R_f : ~ 0.78 (cyclohexane/AcOEt, 1:1)) was directly used in the next reaction step. Dimethyl-(2-oxoheptyl)-phosphonate (3.25 mL, 15.6 mmol, 3 equiv.) was added dropwise at 0 °C to a suspension of NaH (60% in oil, 0.438 g, 13 mmol, 2.5 eq.) in THF (100 mL) under nitrogen. The resulting solution was stirred for 1 hour at room temperature before being cooled again to 0 °C. A solution of intermediate aldehyde (2.08 g, 5.2 mmol, 1 equiv.) in THF (25 mL) was then added dropwise. The reaction medium was allowed to reach room temperature under stirring. Once the reaction finished (after 1 hour approximately) the reaction medium was cooled to 0 °C and then quenched by addition of H₂O/NaCl. The layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. Crude **14** was purified by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt₃ prior use) (solvent: petroleum spirit/diethyl ether: 7/3) giving rise to pure **14** (2.1 g, colorless oil, 82%).

R_f : ~ 0.42 (petroleum spirit/diethyl ether, 7:3); ¹H-NMR (300 MHz, CDCl₃): δ 6.62 (ddd, 1H, *J* = 15.7 Hz, *J* = 10.5 Hz, *J* = 2.9 Hz), 6.18 (dd, 1H, *J* = 15.7 Hz, *J* = 2.8 Hz), 4.64 (m, 1H), 4.03 (m, 2H), 3.92 (m, 1H), 3.87 (m, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 2.89 (m, 1H), 2.49 (m, 2H), 2.40 (m, 1H), 2.16 (m, 1H), 2.01 (s, 3H), 1.58 (m, 6H), 1.28 (m, 3H), 1.25 (d, 3H, *J* = 5.3 Hz), 1.15 (t, 3H, *J* = 6.9 Hz), 0.86 (s, 12H), 0.03 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 200.0, 170.9, 144.0, 131.4, 99.1, 98.6 (dia), 77.5, 77.0 (dia), 75.8, 63.1, 60.4, 60.2 (dia), 50.2, 50.0 (dia), 46.7, 42.1, 41.1, 31.4, 27.6, 25.7, 23.8, 22.4, 20.9, 20.4, 17.9, 15.2, 13.8, -4.4, -4.9; IR: ν_{max} (cm⁻¹): 2930, 2858, 1740,

1697, 1673, 1626, 1462, 1365, 1238, 1090, 1032, 936, 835, 774, 670; HRMS (ESI) calculated for $C_{27}H_{51}O_6Si$ $[M+H]^+$ 499.3455, found: 499.3454.

15a and 15b:



$C_{27}H_{52}O_6Si$
Mol. Weight: 500.78 g/mol

To a solution of enone **14** (3.97 g, 7.96 mmol, 1 equiv.) in MeOH (140 mL) was added at 0 °C a solution of Ce(III)Cl₃ · 7 H₂O (3.73 g, 4.096 mmol, 1 equiv.) in MeOH (50 mL). After stirring the resulting solution for 5 minutes, solid NaBH₄ (301 mg, 7.96 mmol, 1 equiv.) was added. The reaction medium was quenched after 10 minutes of reaction time at the same temperature by addition of water. For a better phase separation a 1M aqueous solution of Na/K tartrate was added and the mixture was stirred at room temperature for 1 hour. Layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO₄, filtered and the solvent was evaporated. A rapid filtration over deactivated silica gel (treated with a 1% solution of NEt₃ prior use) (solvent: petroleum spirit/diethyl ether: 1/1) afforded the mixture of pure epimers **15a** and **15b** (3.72 g, colorless oil, 82%). Then epimers were separated by slow chromatography with deactivated silica gel (solvent: cyclohexane/AcOEt: 4/1).

15a (higher spot): R_f : ~ 0.28 (cyclohexane/AcOEt, 1:1); 1H -NMR (300 MHz, CDCl₃): δ 5.56 (ddd, 1H, J = 15.7 Hz, J = 7.6 Hz, J = 2.7 Hz), 5.40 (ddd, 1H, J = 15.7 Hz, J = 10.5 Hz, J = 5.3 Hz), 4.66

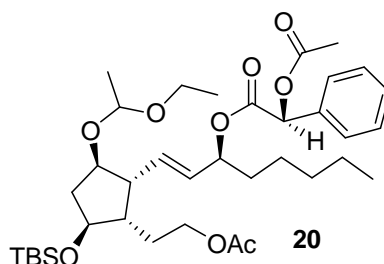
(m, 1H), 4.25 (m, 1H), 4.04 (m, 1H), 3.83 (m, 3H), 3.60 (m, 1H), 3.42 (m, 1H), 2.67 (m, 1H), 2.36 (m, 1H), 2.19 (dd, 1H, $J = 15.2$ Hz, $J = 2.9$ Hz), 2.01 (s, 3H), 1.69 (m, 1H), 1.57 (m, 4H), 1.28 (m, 6H), 1.26 (d, 3H, $J = 5.2$ Hz), 1.16 (t, 3H, $J = 7.2$ Hz), 0.87 (bs, 12H), 0.03 (s, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 171.2, 136.2, 129.1, 99.0, 98.4 (dia), 78.6, 78.0 (dia), 75.9, 72.9, 63.4, 60.5, 60.1 (dia), 49.9, 49.7 (dia), 46.0, 42.0, 41.3 (dia), 37.0, 31.8, 27.6, 25.8, 25.1, 22.6, 21.0, 20.5, 17.9, 15.2, 14.0, -4.4, -4.8; IR: ν_{max} (cm^{-1}): 3360, 2930, 2858, 1741, 1462, 1365, 1251, 1035, 974, 837, 776; HRMS (ESI) calculated for $\text{C}_{33}\text{H}_{68}\text{NO}_6\text{Si}$ $[(\text{M} + \text{NC}_6\text{H}_{16})]^+$ 602.4816, found: 602.4818.

15b (lower spot): R_f : ~ 0.21 (cyclohexane/AcOEt, 4:1); ^1H -NMR (300 MHz, CDCl_3): δ 5.56 (ddd, 1H, $J = 15.7$ Hz, $J = 7.2$ Hz, $J = 2.9$ Hz), 5.40 (dd, 1H, $J = 15.7$ Hz, $J = 9.3$ Hz), 4.66 (m, 1H), 4.03 (m, 3H), 3.85 (m, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 3.42 (m, 1H), 2.67 (m, 1H), 2.35 (m, 1H), 2.05 (m, 1H), 2.00 (s, 3H), 1.79-1.43 (m, 5H), 1.30 (m, 6H), 1.25 (d, 3H, $J = 5.8$ Hz), 1.15 (t, 3H, $J = 7.2$ Hz), 0.86 (bs, 12H), 0.02 (s, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 171.0, 135.9, 128.8, 98.9, 98.5 (dia), 78.6, 78.0 (dia), 76.0, 72.5, 63.3, 60.4, 50.0, 49.7 (dia), 45.9, 41.9, 41.2 (dia), 37.2, 31.7, 27.6, 26.9 (dia), 25.8, 25.1, 22.6, 20.9, 20.6, 15.2, 17.9, 14.0, -4.4, -4.9; IR: ν_{max} (cm^{-1}): 3360, 2930, 2858, 1741, 1462, 1365, 1251, 1035, 974, 837, 776; HRMS (ESI) calculated for $\text{C}_{33}\text{H}_{68}\text{NO}_6\text{Si}$ $[(\text{M} + \text{NC}_6\text{H}_{16})]^+$ 602.4816, found: 602.4825.

Determination of the absolute configuration of epimeric alcohols 15a and 15b by preparation of mandelic esters of each epimer from *R*-(-)- α -acetoxyphenylacetic acid and *S*-(+)- α -acetoxyphenylacetic acid¹

15a and **15b** (100 mg, 0.2 mmol, 1 equiv.), *R*-(-)- α -acetoxyphenylacetic acid or *S*-(+)- α -acetoxyphenylacetic acid (42.7 mg, 0.22 mmol, 1.1 equiv.), EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and a catalytic amount of DMAP were dissolved in 1 mL of CH₂Cl₂ under nitrogen. The reaction medium was stirred at room temperature for three days before being cooled to 0 °C. 10 mL of ether and 5 mL of H₂O were added. Layers were separated and the organic layer was washed with a solution of HCl (1 %, 2 x 5 mL), followed by washing with brine (2 x 5 mL). The organic layer was dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using deactivated silica gel (treated with a 1% solution of NEt₃ prior use, solvent: petroleum spirit/diethylether: 7/3) affording the corresponding mandelic esters.

20:

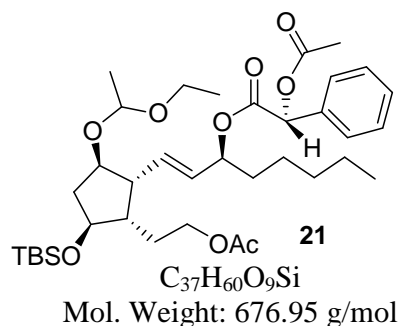


C₃₇H₆₀O₉Si
Mol. Weight: 676.95 g/mol

20 (*R*-mandelic ester obtained from **15a** and *R*-(-)- α -acetoxyphenylacetic acid): ¹H-NMR (300 MHz, CDCl₃): δ 7.44 (m, 2H), 7.36 (m, 3H), 5.88 (s, 1H), 5.30 (dd, 1H, *J* = 15.0 Hz, *J* = 6.0 Hz), 5.15 (m, 1H), 4.56 (m, 1H), 4.17 (m, 1H), 3.91 (m, 2H), 3.60 (m, 3H), 3.37 (m, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 2.17 (m, 4H), 2.00 (s, 3H), 1.58 (m, 5H), 1.25 (m, 6H), 1.19 (d, 3H, *J* = 5.0 Hz), 1.14 (dd, 3H, *J* = 7.0 Hz, *J* = 3.0 Hz), 0.86 (m, 12H), 0.02 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.0,

¹ (a) Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villieras, J. *Tetrahedron Lett.* **1998**, 39, 1759. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512.

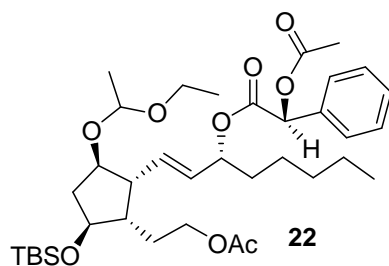
170.2, 168.0, 133.9, 131.6, 130.0, 129.1, 128.7, 127.6, 99.0, 98.4 (dia), 78.4, 77.5, 75.7, 74.5, 63.1, 61.6 (dia), 60.5, 60.2 (dia), 50.0, 49.7 (dia), 45.7, 41.8, 41.3 (dia), 34.3, 31.4, 27.3, 25.7, 24.6, 22.4, 21.0, 20.7, 20.5, 17.9, 15.2, 13.9, -4.4, -4.9; IR: ν_{\max} (cm⁻¹): 2956, 2931, 2858, 1742, 1456, 1372, 1232, 1085, 1055, 971, 837, 776, 697; HRMS (ESI) calculated for C₃₅H₅₅O₈Si [(M+H)-C₂H₆O]⁺ 631.3666, found: 631.3651.

21:

21 (*S*-mandelic ester obtained from **15a** and *S*-(+)- α -acetoxyphenylacetic acid): ¹H-NMR (300 MHz, CDCl₃): δ 7.46 (m, 2H), 7.36 (m, 3H), 5.88 (d, 1H, *J* = 10.5 Hz), 5.47 (m, 1H), 5.15 (m, 1H), 4.63 (m, 1H), 4.17 (m, 1H), 4.02 (t, 2H, *J* = 6.5 Hz), 3.81 (m, 2H), 3.59 (m, 1H), 3.41 (m, 1H), 2.69 (m, 1H), 2.35 (m, 1H), 2.17 (m, 4H), 2.02 (s, 3H), 1.54 (m, 5H), 1.25 (m, 6H), 1.19 (d, 3H, *J* = 6.8 Hz), 1.15 (dd, 3H, *J* = 6.8 Hz, *J* = 1.7 Hz), 0.87 (s, 9H), 0.78 (t, 3H, *J* = 6.8 Hz), 0.03 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.0, 170.0, 168.2, 133.9, 132.2, 130.0, 129.1, 128.6, 127.5, 99.0, 98.4 (dia), 78.6, 77.7, 75.8, 74.6, 63.3, 61.6 (dia), 60.6, 60.2 (dia), 50.0, 49.7 (dia), 45.9, 41.9, 41.3 (dia), 34.1, 31.2, 27.3, 25.8, 24.4, 22.3, 21.0, 20.6, 20.5, 17.9, 15.2, 13.8, -4.4, -4.9; IR: ν_{\max} (cm⁻¹): 2956, 2931, 2858, 1740, 1456, 1371, 1230, 1084, 1053, 970, 836, 775, 696; HRMS (ESI) calculated for C₃₅H₅₅O₈Si [(M+H)-C₂H₆O]⁺ 631.3666, found: 631.3694.

S-11

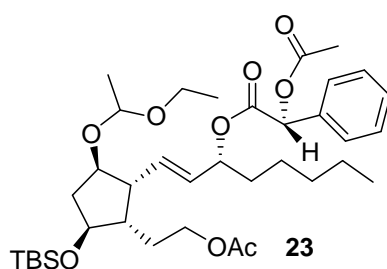
22:



$C_{37}H_{60}O_9Si$
Mol. Weight: 676.95 g/mol

(*R*-mandelic ester obtained from **15b** and *R*-(-)- α -acetoxyphenylacetic acid): 1H -NMR (300 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.36 (m, 3H), 5.87 (d, 1H, $J = 9.9$ Hz), 5.45 (m, 1H), 5.16 (m, 1H), 4.64 (m, 1H), 4.16 (m, 1H), 4.02 (t, 2H, $J = 6.8$ Hz), 3.82 (m, 2H), 3.58 (m, 1H), 3.41 (m, 1H), 2.68 (m, 1H), 2.37 (m, 1H), 2.16 (m, 4H), 2.00 (s, 3H), 1.61 (m, 2H), 1.47 (m, 3H), 1.24 (m, 3H), 1.20 (dd, 3H, $J = 7.2$ Hz, $J = 4.3$ Hz), 1.15 (d, 3H, $J = 7.0$ Hz), 1.12-0.92 (m, 6H), 0.86 (m, 9H), 0.77 (t, 3H, $J = 6.7$ Hz), 0.03 (s, 6H); ^{13}C -NMR (75 MHz, $CDCl_3$): δ 171.0, 170.0, 168.2, 133.9, 131.7, 130.0, 129.1, 128.6, 127.5, 99.2, 98.5 (dia), 78.7, 77.7, 75.7, 74.6, 63.2, 61.6 (dia), 60.7, 60.4 (dia), 49.9, 45.9, 41.8, 41.3 (dia), 34.2, 31.2, 27.4, 25.7, 24.4, 22.3, 21.0, 20.7, 20.6, 17.9, 15.2, 13.8, -4.4, -4.9; IR: ν_{max} (cm^{-1}): 2956, 2931, 2858, 1740, 1456, 1371, 1231, 1084, 1055, 969, 836, 775, 696; HRMS (ESI) calculated for $C_{35}H_{55}O_8Si$ $[(M+H)-C_2H_6O]^+$ 631.3666, found: 631.3682.

23:



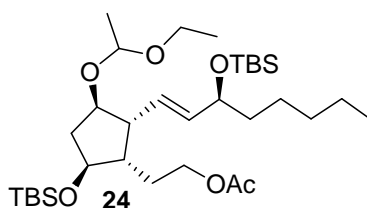
$C_{37}H_{60}O_9Si$
Mol. Weight: 676.95 g/mol

(*S*-mandelic ester obtained from **15b** and *S*-(+)- α -acetoxyphenylacetic acid): 1H -NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.36 (m, 3H), 5.90 (d, 1H, $J = 2.9$ Hz), 5.31 (dd, 1H, $J = 15.3$ Hz, $J = 6.2$

Hz), 5.18 (m, 1H), 4.54 (m, 1H), 4.17 (m, 1H), 3.96 (t, 2H, $J = 7.1$ Hz), 3.66 (m, 2H), 3.45 (m, 2H), 2.55 (m, 1H), 2.28 (m, 1H), 2.17 (m, 4H), 2.00 (s, 3H), 1.72-1.46 (m, 5H), 1.26 (m, 6H), 1.22-1.11 (m, 6H), 1.02 (t, 3H, $J = 7.1$ Hz), 0.86 (m, 9H), 0.02 (m, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 171.0, 170.2, 168.0, 133.9, 131.8, 129.9, 129.1, 128.7, 127.5, 99.1, 98.4 (dia), 78.7, 77.5, 75.8, 74.5, 63.1, 61.7 (dia), 60.6, 60.3 (dia), 50.0, 49.8 (dia), 45.8, 41.8, 41.2 (dia), 34.3, 31.4, 27.4, 25.7, 24.6, 22.5, 21.0, 20.7, 20.5, 17.9, 15.2, 13.9, -4.4, -4.8 ; IR: ν_{max} (cm^{-1}): 2960, 2931, 2858, 1742, 1456, 1371, 1231, 1085, 1054, 969, 837, 775, 696; HRMS (ESI) calculated for $\text{C}_{35}\text{H}_{55}\text{O}_8\text{Si}$ $[(\text{M}+\text{H})-\text{C}_2\text{H}_6\text{O}]^+$ 631.3666, found: 631.3689.

Total synthesis of (-)-(9S,15S)-15-D_{2t}-IsoP

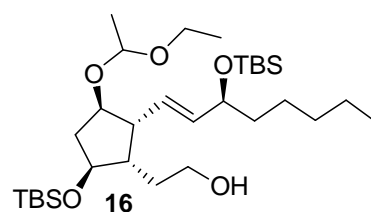
24:



$\text{C}_{33}\text{H}_{66}\text{O}_6\text{Si}_2$
Mol. Weight: 615.04 g/mol

TBSCl (1.2 g, 7.6 mmol, 1.5 equiv.) was dissolved in 10 mL of CH_2Cl_2 and was then added dropwise at 0 °C to a solution of CH_2Cl_2 (25 mL) containing **15a** (2.54 g, 5.08 mmol, 1 equiv.), imidazole (1.4 g, 20.32 mmol, 4 equiv.) and a catalytic amount of DMAP, the resulting reaction medium was stirred overnight at room temperature. The following day after cooling to 0 °C water was added and layers were separated. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with a saturated solution of NaCl, dried over MgSO_4 , filtered and the solvent was eliminated under reduced pressure. After 12 hours of drying under vacuum, **24** was obtained in quantitative yield (3.1 g, colorless oil) and was used without

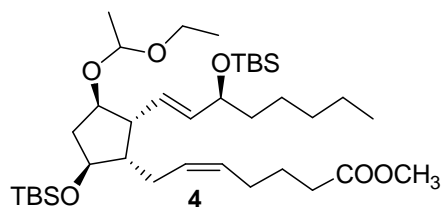
further purification in the next step. R_f : ~0.89 (cyclohexane/AcOEt, 1:1), ~0.73 (cyclohexane/AcOEt, 4:1); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.49 (dd, 1H, $J = 15.2$ Hz, $J = 5.9$ Hz), 5.32 (ddd, 1H, $J = 15.2$ Hz, $J = 9.2$ Hz, $J = 3.9$ Hz), 4.66 (m, 1H), 4.05 (m, 3H), 3.82 (m, 2H), 3.60 (m, 1H), 3.43 (m, 1H), 2.68 (m, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 2.01 (s, 3H), 1.76-1.39 (m, 5H), 1.26 (m, 9H), 1.16 (t, 3H, $J = 6.6$ Hz), 0.87 (m, 21H), 0.03 (s, 12H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 170.9, 136.3, 127.1, 99.0, 98.3 (dia), 78.9, 78.0 (dia), 76.2, 73.1, 63.4, 60.4, 60.2 (dia), 49.8, 49.4 (dia), 45.9, 41.9, 41.3 (dia), 38.4, 31.8, 27.5, 25.8, 24.8, 22.6, 20.9, 20.5, 18.2, 17.9, 15.2, 14.0, -4.4, -4.8; IR: ν_{max} (cm^{-1}): 2930, 2857, 1742, 1472, 1363, 1249, 1061, 972, 834, 774, 665. HRMS (ESI) calculated for $\text{C}_{39}\text{H}_{82}\text{NO}_6\text{Si}_2$ $[(\text{M} + \text{NC}_6\text{H}_{16})^+]$ 716.5681, found: 716.5679.

16:

Mol. Weight: 573.00786 g/mol

Solid K_2CO_3 (15.3 mmol, 2.1 g, 3 equiv.) was added to a solution of **24** (3.14 g, 5.1 mmol, 1 equiv.) in MeOH (100 mL) under nitrogen at room temperature. The reaction medium was stirred 3 hours at the same temperature before being poured into a cooled solution (0 °C) of $\text{Et}_2\text{O}/\text{H}_2\text{O}$ (1/1) (100 mL). Layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO_4 , filtered and the solvent was eliminated under reduced pressure. Purification by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt_3 prior use) (solvent: petroleum spirit/diethyl ether 1/1) afforded pure **16** (2.25 g, colorless oil, 78%). R_f : ~ 0.56 (cyclohexane/AcOEt, 4:1); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.48 (dd, 1H, $J = 15.7$ Hz, $J = 5.9$ Hz),

5.33 (ddd, 1H, $J = 15.7$ Hz, $J = 8.9$ Hz, $J = 4.4$ Hz), 4.68 (m, 1H), 4.04 (m, 1H), 3.85 (m, 2H), 3.63 (m, 3H), 3.43 (m, 1H), 2.66 (m, 1H), 2.44 (m, 1H), 2.17 (m, 1H), 1.95 (d, OH, $J = 4.5$ Hz), 1.69-1.56 (m, 5H), 1.45-1.26 (m, 9H), 1.17 (t, 3H, $J = 6.9$ Hz), 0.89 (m, 21H), 0.06-0.01 (m, 12H); ^{13}C -NMR (75 MHz, CDCl_3): δ 136.1, 127.4, 98.9, 98.3 (dia), 78.9, 78.1 (dia), 76.6, 73.1, 61.7, 60.1, 50.6, 50.1 (dia), 46.1, 42.0, 41.4 (dia), 38.4, 32.1, 31.7, 25.8, 24.9, 22.6, 20.6, 20.4, 18.1, 17.9, 15.2, 13.9, -4.3, -4.5, -4.8; IR: ν_{max} (cm^{-1}): 3470, 2929, 2857, 1472, 1388, 1361, 1252, 1085, 1005, 971, 937, 834, 774, 670; HRMS (ESI) calculated for $\text{C}_{31}\text{H}_{65}\text{O}_5\text{Si}_2$ $[\text{M}+\text{H}]^+$ 573.4371, found: 573.4352.

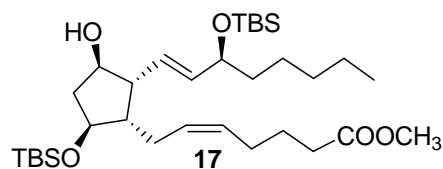
4:

$\text{C}_{37}\text{H}_{72}\text{O}_6\text{Si}_2$
Mol. Weight: 669.13 g/mol

A 0.3 M solution of solid Dess-Martin periodinane (1.18 g, 2.77 mmol, 1.3 equiv.) in 23 mL of CH_2Cl_2 was added dropwise at 0 °C to a solution of **16** (1.06 g, 1.85 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) under nitrogen containing solid NaHCO_3 (265 mg, 3.7 mmol, 2 equiv.). The reaction medium was stirred at room temperature for 1 hour and 30 minutes. After disappearance of the starting material (TLC) the reaction mixture was cooled to 0 °C and then quenched by addition of a 1 M solution of $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (1/1). The resulting mixture was stirred at room temperature for 1 hour until layers were well separated. The aqueous layer was extracted three times with CH_2Cl_2 and then the combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was evaporated under reduced pressure. The intermediate aldehyde was used in the next reaction step without further purification. A solution of NaHMDS (2M, THF, 10.5 mL, 21 mmol, 12 equiv.) was added dropwise at 0 °C to a suspension of (4-carboxybutyl)triphenylphosphonium

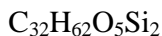
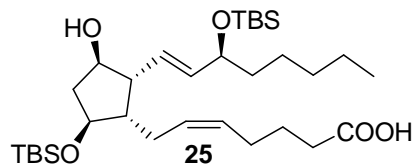
bromide (4.66 g, 10.5 mmol, 6 equiv.) in degassed THF (90 mL) under nitrogen. The reaction medium was stirred for one hour at room temperature. The intermediate aldehyde (1 g, 1.75 mmol, 1 equiv.) was dissolved in 35 mL of degassed THF under nitrogen and the solution was cooled to -78 °C. Then, the ylide was added dropwise to the solution containing the aldehyde. The resulting reaction medium was allowed to react at -78 °C until completion (1-2 hours reaction time). Afterwards the reaction was quenched by addition of a saturated solution of NH₄Cl. Layers were separated and the aqueous one was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The crude product (2.46 g) was then dissolved under nitrogen in distilled diethyl ether (10 mL) and anhydrous CH₃OH (3 mL) before being cooled to 0 °C. TMSCHN₂ (2 M in ether, 2 x 1.8 mL, 2 equiv.) was added dropwise. The reaction was allowed to warm up to room temperature. After 3 hours, the reaction medium was cooled to 0 °C before being quenched by addition of AcOH. Then the pH was brought to 7 by addition of a saturated solution of NaHCO₃. Layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO₄, filtered and the solvent was eliminated under reduced pressure affording crude **4**. Purification by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt₃ prior use) (solvent: petroleum spirit/diethyl ether: 9:1) gave rise to pure ester **4** (0.868 g, colorless oil, 67 %, 3 steps). *R*_f : ~ 0.34 (petroleum spirit/diethyl ether, 9:1); ¹H-NMR (300 MHz, CDCl₃): δ 5.40 (m, 4H), 4.66 (m, 1H), 4.03 (m, 1H), 3.85 (m, 2H), 3.65 (s, 3H), 3.59 (m, 1H), 3.42 (m, 1H), 2.74 (m, 1H), 2.39 (m, 1H), 2.29 (t, 2H, *J* = 7.6 Hz), 2.00 (m, 4H), 1.67 (m, 2H), 1.43 (m, 2H), 1.25 (m, 9H), 1.15 (td, 3H, *J* = 6.0 Hz, *J* = 2.1 Hz), 0.87 (m, 21H), 0.01 (s, 12 H); ¹³C-NMR (75 MHz, CDCl₃): δ 173.8, 135.9, 129.4, 129.0, 127.8, 99.1, 98.2 (dia), 79.1, 77.9 (dia), 75.6, 73.3, 60.1, 59.8 (dia), 51.2, 50.4, 49.4, 49.2 (dia), 41.9, 41.2, 38.4, 33.4, 31.8, 26.6, 25.8, 24.9, 22.5, 20.5, 18.1, 17.9, 15.2, 13.9, -4.4, -4.8;

IR: ν_{max} (cm^{-1}): 2929, 2857, 1742, 1462, 1361, 1250, 1085, 970, 834, 773, 670; HRMS (ESI) calculated for $\text{C}_{43}\text{H}_{88}\text{NO}_6\text{Si}_2$ $[(\text{M} + \text{NC}_6\text{H}_{16})]^+$ 770.6150, found: 770.6176.

17:

$\text{C}_{33}\text{H}_{64}\text{O}_5\text{Si}_2$
Mol. Weight: 597.03 g/mol

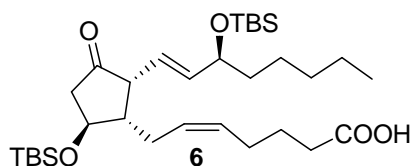
4 (0.485 g, 0.72 mmol, 1 equiv.) was dissolved in freshly distilled EtOH/ CH_2Cl_2 (6/1) (49 mL) under nitrogen and a catalytic amount of PPTS was added. The resulting reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the crude was purified by flash chromatography (solvent: cyclohexane/AcOEt: 9/1) affording pure **17** (325 mg, colorless oil, 75%). R_f : ~ 0.43 (petroleum spirit/diethyl ether, 7:3); $[\alpha]_{\text{D}}^{20} = +10.8$ (c 1.2 10^{-2} , CH_2Cl_2); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.53 (dd, 1H, $J = 15.1$ Hz, $J = 6.2$ Hz), 5.38 (m, 3H), 4.04 (m, 1H), 3.93 (m, 2H), 3.65 (s, 3H), 2.76 (m, 1H), 2.28 (m, 3H), 2.13 (m, 2H), 2.03 (m, 2H), 1.93 (m, 2H), 1.66 (m, 2H), 1.43 (m, 2H), 1.25 (m, 6H), 0.87 (m, 21H), 0.00-0.03 (m, 12H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 173.8, 136.3, 129.4, 127.6, 77.3, 76.9, 73.3, 53.1, 51.4, 51.1, 42.7, 38.4, 33.5, 31.8, 26.7, 25.9, 25.0, 24.8, 22.6, 18.2, 17.9, 14.0, -4.3, -4.8; IR: ν_{max} (cm^{-1}): 3470, 2929, 2857, 1742, 1462, 1436, 1361, 1250, 1076, 970, 833, 773, 670; HRMS (ESI) calculated for $\text{C}_{33}\text{H}_{65}\text{O}_5\text{Si}_2$ $[\text{M} + \text{H}]^+$ 597.4371, found: 597.4350.

25:

Mol. Weight: 583.00 g/mol

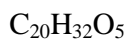
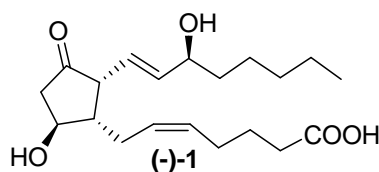
17 (325 mg, 0.544 mmol, 1 equiv.) was dissolved in THF (6 mL) under nitrogen. The resulting solution was cooled to 0 °C and a suspension of LiOH (150 mg, 6.25 mmol, 11 equiv.) in H₂O (3 mL), and MeOH (1.5 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 5 hours until completion. The reaction medium was cooled to 0 °C before being quenched by addition of HCl 1M until a pH value of 4 was reached. Layers were separated and the aqueous one was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was eliminated under reduced pressure. The crude was purified by flash chromatography using demetallated² silica gel (solvent: cyclohexane/AcOEt: 7/3) affording pure **25** (274 mg, colorless oil, 86%). R_f: ~ 0.35 (cyclohexane/AcOEt, 7:3); [α]_D²⁰ = + 12.8 (*c* 1.2 · 10⁻², CH₂Cl₂); ¹H-NMR (300 MHz, CDCl₃): δ 5.53 (dd, 1H, *J* = 15.4 Hz, *J* = 5.6 Hz), 5.38 (m, 3H), 4.05 (m, 1H), 3.94 (m, 2H), 2.77 (m, 1H), 2.33 (t, 2H, *J* = 7.3 Hz), 2.27 (m, 1H), 2.14 (m, 1H), 2.04 (m, 2H), 1.46 (m, 1H), 1.68 (m, 2H), 1.41 (m, 4H and H₂O), 1.26 (m, 6H), 0.87 (m, 21H), 0.02 (m, 12H); ¹³C-NMR (75 MHz, CDCl₃): δ 179.0, 136.3, 129.7, 129.3, 127.6, 77.5, 77.0, 73.4, 53.1, 51.2, 42.7, 38.5, 33.4, 31.9, 27.0, 26.7, 25.9, 25.1, 24.6, 22.7, 18.3, 18.0, 14.1, -4.3, -4.7; IR: ν max (cm⁻¹): 2928, 2857, 1710, 1462, 1361, 1251, 1079, 970, 834, 773, 670; HRMS (ESI) calculated for C₃₂H₆₃O₅Si₂ [M+H]⁺ 583.4214, found: 583.4205.

² Hubbard, J. S. ; Harris, T. M. *J. Org. Chem.* **1981**, 46, 2566.

6:

$C_{32}H_{62}O_5Si_2$
Mol. Weight: 580.99 g/mol

To **25** (274 mg, 0.47 mmol, 1 equiv.) and $NaHCO_3$ (102 mg, 1.41 mmol, 3 equiv.) under nitrogen was added CH_2Cl_2 (15 mL). The resulting reaction medium was cooled to 0 °C before slow addition of a 0.3 M solution of solid Dess-Martin periodinane (503 mg, 1.186 mmol, 2.5 equiv.) in 5 mL of CH_2Cl_2 . The reaction medium was stirred at room temperature for 4 hours before being cooled again to 0 °C. Then a 1 M solution of $Na_2S_2O_3/NaHCO_3$ (1/1) was added and the resulting mixture was stirred at room temperature for one hour until layers were well separated. The aqueous layer was acidified up to pH = 4 by HCl 1M before being extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using demetallated² silica gel (solvent: petroleum spirit/ diethyl ether: 9/1) giving pure **6** (203 mg, colorless oil, 75%). R_f : ~ 0.52 (cyclohexane/AcOEt, 7:3); $[\alpha]_D^{20} = + 1.6$ (c 1 10^{-2} , CH_2Cl_2); 1H -NMR (300 MHz, $CDCl_3$): δ 5.62 (dd, 1H, $J = 15.3$ Hz, $J = 6.1$ Hz), 5.43 (m, 3H), 4.23 (m, 1H), 4.09 (q, 1H, $J = 6.1$ Hz), 3.34 (t, 1H, $J = 7.6$ Hz), 2.46 (dd, 1H, $J = 18.8$ Hz, $J = 6.1$ Hz), 2.33 (t, 2H, $J = 7.1$ Hz), 2.08 (m, 3H), 1.84 (m, 1H), 1.67 (quint, 2H, $J = 7.1$ Hz), 1.92 (m, 2H), 1.27 (m, 6H), 0.87 (m, 21H), 0.04 (m, 12H); ^{13}C -NMR (75 MHz, $CDCl_3$): δ 216.0, 178.9, 139.3, 130.4, 128.1, 121.9, 73.3, 71.1, 53.2, 50.3, 45.2, 38.3, 33.3, 31.8, 26.6, 25.7, 24.9, 24.5, 22.6, 18.2, 18.0, 14.0, -4.4, -4.8; IR: ν_{max} (cm^{-1}): 2929, 2857, 1710, 1462, 1361, 1251, 1067, 833, 774, 670; HRMS (ESI) calculated for $C_{32}H_{61}O_5Si_2$ $[M+H]^+$ 581.4058, found: 581.4035.

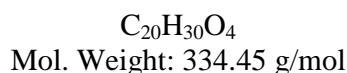
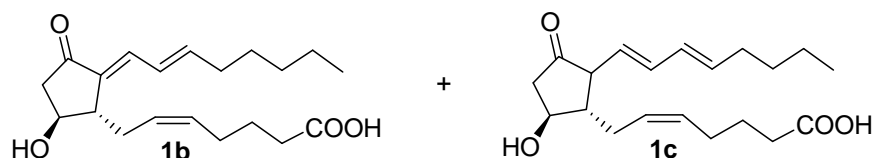
(-)-(9S,15S)-15-D₂-IsoP 1:

Mol. Weight: 352.47 g/mol

6 (90 mg, 0.155 mmol, 1 equiv.) was dissolved under nitrogen in 5 mL of CH₃CN. The solution was cooled to 0 °C and BiBr₃ (400 mg, 0.89 mmol, 5.7 equiv.) was added in one portion under stirring. Then H₂O (40 μL) was added in one portion. After 20 minutes of reaction time at the same temperature another portion of BiBr₃ (226 mg, 0.503 mmol, 3.3 equiv.) and H₂O (30 μL) was added. After 30 minutes of reaction time TLC analysis indicated the complete disappearance of the starting material. The reaction was quenched at 0 °C by dropwise addition of a saturated solution of NaHCO₃ until pH = 4 was reached. Layers were separated and the aqueous one was extracted three times with an excess of AcOEt. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure using a cold water bath. The crude was purified using demetallated² silica gel (solvent: petroleum spirit/AcOEt: 3/7-AcOEt-AcOEt/MeOH: 9/1) affording desired **1** (26 mg, colorless oil, 48%) and elimination side products **1b** and **1c** (14 mg, light yellow-orange oil). *R_f*: ~ 0.64 (AcOEt/MeOH, 9:1); $[\alpha]_{\text{D}}^{20} = -17.5$ (*c* 0.4 10⁻², CDCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 5.66 (dd, 1H, *J* = 15.6 Hz, *J* = 6.5 Hz), 5.52 (m, 3H), 4.41 (m, 1H), 4.17 (m, 1H), 3.39 (t, 1H and 2 OHs, *J* = 7.8 Hz), 2.59 (dd, 1H, *J* = 19.1 Hz, *J* = 6.5 Hz), 2.30 (m, 5H), 2.11 (m, 2H), 1.80 (m, 1H), 1.67 (m, 2H), 1.52 (m, 2H), 1.29 (m, 6H and H₂O), 0.88 (m, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ 215.6, 176.7, 138.3, 131.0, 128.1, 123.7, 73.0, 71.0, 54.0, 50.0, 44.6, 37.0, 32.5, 31.7, 26.2, 25.9, 25.0, 24.3, 22.6, 14.0; IR: ν_{max} (cm⁻¹): 3390, 2930, 2860, 1710, 1404, 1189, 1013, 972; HRMS (ESI) calculated for C₂₀H₃₁O₅ [M-H]⁻ 351.2171, found: 351.2162.

1b and 1c:

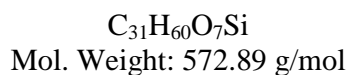
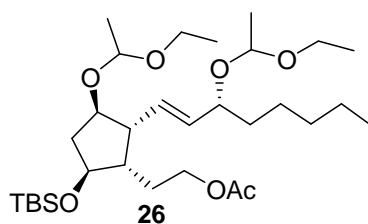
Proposed structures of side products



R_f : ~ 0.79 (AcOEt/MeOH, 9:1), visible at UV light; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.05 (d, 1H, J = 9.1 Hz), 6.22 (m, 2H), 5.47 (m, 4H), 4.30 (m, 2H), 3.03 (t, 1H, J = 7.2 Hz), 2.66 (dd, 1H, J = 18.8 Hz, J = 5.3 Hz), 2.34 (m, 3H), 2.23-2.04 (m, 3H), 1.68 (m, 4H), 1.43 (m, 2H), 1.29 (m, 6H), 0.88 (m, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 205.7, 178.2, 147.9, 136.2, 135.1, 131.2, 127.4, 126.3, 71.2, 60.4, 49.1, 46.0, 33.5, 33.1, 31.4, 30.8, 28.4, 26.5, 24.4, 22.5, 14.0; IR: ν max (cm^{-1}): 3378, 2929, 1708, 1626, 1405, 1189, 976, 860, 726; HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{29}\text{O}_4$ $[\text{M-H}]^-$ 333.2066, found: 333.2069.

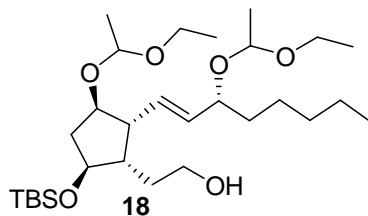
Total synthesis of (+)-(11*R*, 15*R*)-15-*epi*-15-E₂-IsoP

26:



15b (1.48 g, 2.95 mmol) was dissolved under nitrogen in 30 mL of CH₂Cl₂ and cooled to 0 °C. Then 30 mL of ethylvinylether and a catalytic amount of PPTS were added. The resulting reaction mixture was allowed to reach room temperature and was stirred overnight. The solution was cooled down to 0 °C and was quenched by addition of a saturated solution of NaHCO₃. Layers were

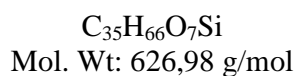
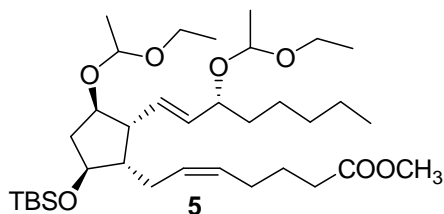
separated and the aqueous one was extracted three times with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was eliminated under reduced pressure. Purification by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt_3 prior use) (solvent: cyclohexane/AcOEt 9.5/0.5) afforded **26** (colorless oil). R_f : ~ 0.27 (cyclohexane/AcOEt, 9:1), ~ 0.67 (cyclohexane/AcOEt, 7:3); ^1H -NMR (300 MHz, CDCl_3): δ 5.48 (dd, 1H, $J = 15.7$ Hz, $J = 6.6$ Hz), 5.36 (m, 1H), 4.67 (m, 2H), 4.07-3.32 (m, 9H), 2.71 (m, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 2.01 (s, 3H), 1.74-1.43 (m, 5H), 1.26 (m, 12H), 1.16 (t, 6H, $J = 6.6$ Hz), 0.86 (m, 12H), 0.02 (s, 6H); ^{13}C -NMR (75 MHz, CDCl_3): δ 171.0, 134.4, 133.6 (dia), 131.1, 129.5 (dia), 99.0, 98.6 (dia), 96.7 (dia), 78.9, 77.9, 76.6, 63.3, 61.2, 60.4 (dia), 58.8, 50.2, 49.7 (dia), 45.9, 42.0, 35.9, 31.8, 27.7, 25.8, 25.7, 24.9 (dia), 22.6, 21.0, 20.6, 20.3, 18.0, 15.5, 15.3, 14.0, -4.4, -4.8; IR: ν_{max} (cm^{-1}): 2931, 1742, 1471, 1377, 1239, 1087, 1056, 1030, 973, 836, 775, 671; HRMS (ESI) calculated for $\text{C}_{37}\text{H}_{76}\text{NO}_7\text{Si}$ $[(\text{M} + \text{NC}_6\text{H}_{16})]^+$ 674.5391, found: 674.5385.

18:

Mol. Weight: 530.85 g/mol

26 (2.5 g, 4.37 mmol) was dissolved in 80 mL of MeOH and K_2CO_3 (1.8 g, 13 mmol, 3 equiv.) was added. The resulting reaction mixture was stirred at room temperature for 2 hours. Then the reaction medium was poured into a cooled solution (0 °C) of $\text{Et}_2\text{O}/\text{H}_2\text{O}$ (1/1) (80 mL). Layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO_4 , filtered and the solvent was eliminated under reduced pressure. Purification by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt_3 prior use) (solvent: cyclohexane/AcOEt 9/1 \rightarrow 4/1)

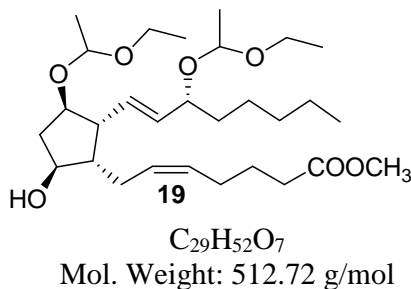
afforded pure **18** (1.1 g, colorless oil, 71%, 2 steps). R_f : ~ 0.51 (cyclohexane/AcOEt, 7:3); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.45 (dd, 1H, $J = 15.3$ Hz, $J = 6.3$ Hz), 5.32 (m, 1H), 4.67 (m, 2H), 3.98-3.35 (m, 9H), 2.67 (m, 1H), 2.40 (m, 1H), 2.15 (m, 1H), 2.05 (bs, OH), 1.69-1.53 (m, 5H), 1.25 (m, 12H), 1.15 (t, 6H, $J = 6.6$ Hz), 0.87 (m, 12 H), 0.05 (s, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 134.2, 133.4, 131.5, 129.8, 99.0, 98.6 (dia), 96.6, 78.8, 77.9, 76.6, 61.7, 61.1 (dia), 60.2, 58.7, 51.1, 50.5 (dia), 46.2, 42.1, 41.3 (dia), 35.9, 32.3, 31.7, 25.8, 25.2, 22.6, 20.6, 20.3, 18.0, 15.4, 15.3, 14.0, -4.1, -4.8; IR: ν_{max} (cm^{-1}): 3480, 2930, 1462, 1378, 1253, 1084, 1030, 972, 835, 774, 670; HRMS (ESI) calculated for $\text{C}_{29}\text{H}_{57}\text{O}_6\text{Si}$ $[\text{M-H}]^-$ 529.3924, found: 529.3941.

5:

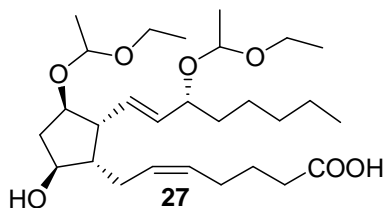
A 0.3 M solution of solid Dess-Martin periodinane (1.08 g, 2.56 mmol, 1.3 equiv.) in 8.5 mL of CH_2Cl_2 was added dropwise at 0 °C to a solution of **18** (1.05 g, 1.97 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) under nitrogen. The reaction medium was stirred at room temperature for 2 hours and 30 minutes. After disappearance of the starting material (TLC) the reaction mixture was cooled to 0 °C and then quenched by addition of a 1 M solution of $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (1/1). The resulting mixture was stirred at room temperature for 1 hour until layers were well separated. The aqueous layer was extracted three times with CH_2Cl_2 and then the combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was evaporated under reduced pressure. The intermediate aldehyde was used in the next reaction step without further purification. A solution of NaHMDS (2 M, THF, 11.35 mL, 22.7 mmol, 12 equiv.) was added dropwise at 0 °C to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (5.04 g, 11.4 mmol, 6 equiv.) in

degassed THF (90 mL) under nitrogen. The reaction medium was stirred for one hour at room temperature. The intermediate aldehyde (1 g, 1.89 mmol, 1 equiv.) was dissolved in 35 mL of degassed THF under nitrogen and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. Then, the ylide was added dropwise to the solution containing the aldehyde. The resulting reaction medium was allowed to react at $-78\text{ }^{\circ}\text{C}$ until completion (1 hour and 30 minutes reaction time). Afterwards the reaction was quenched by addition of a saturated solution of NH_4Cl . Layers were separated and the aqueous one was extracted three times with AcOEt . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was evaporated under reduced pressure. The crude (2.5 g) was dissolved under nitrogen in distilled diethyl ether (7 mL) and anhydrous CH_3OH (3 mL) before being cooled to $0\text{ }^{\circ}\text{C}$. TMSCHN_2 (2 M in ether, 2 x 2.5 mL, 2 equiv.) was added dropwise. The reaction was allowed to warm up to room temperature. After 5 hours the reaction medium was cooled to $0\text{ }^{\circ}\text{C}$ before being quenched by addition of AcOH . Then the pH was brought to 7 by addition of a saturated solution of NaHCO_3 . Layers were separated and the aqueous one was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of NaCl , dried over MgSO_4 , filtered and the solvent was eliminated under reduced pressure affording crude **5**. Purification by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt_3 prior use) (solvent: petroleum spirit/ diethyl ether: 9:1) gave rise to pure ester **5** (0.748 g, colorless oil, 63%, 3 steps). R_f : ~ 0.35 (cyclohexane/ AcOEt , 9:1); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.39 (m, 4H), 4.66 (m, 2H), 3.87 (m, 3H), 3.70-3.34 (m, 4H), 3.64 (s, 3H), 2.77 (m, 1H), 2.39 (m, 1H), 2.28 (t, 2H, $J = 7.6\text{ Hz}$), 2.03 (m, 4H), 1.85-1.52 (m, 4H), 1.41 (m, 2H), 1.25 (m, 12H), 1.15 (t, 6H, $J = 6.5\text{ Hz}$), 0.86 (m, 12H), 0.01 (s, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 173.9, 133.9, 133.2, 131.7 (dia), 130.0, 129.2, 99.1, 98.5 (dia), 96.7, 79.0, 77.7 (dia), 76.8, 75.6, 61.2, 60.0, 58.8, 51.4, 50.5, 49.5, 42.0, 41.3, 35.9, 33.5, 31.8, 26.7, 25.8, 24.8, 22.6, 20.6, 20.4, 18.0,

15.5, 15.3, 14.0, -4.5, -4.8; IR: ν_{max} (cm⁻¹): 2930, 1741, 1438, 1376, 1251, 1086, 969, 835, 774 ;
 HRMS (ESI) calculated for C₄₁H₈₂NO₇Si [(M+ NC₆H₁₆)⁺ 728.5861, found: 728.5864.

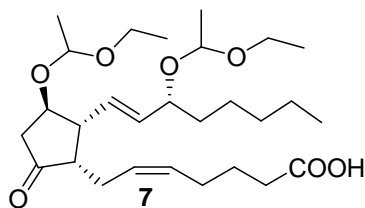
19:

5 (661 mg, 1.054 mmol) was dissolved in THF (35 mL) under nitrogen. The resulting solution was cooled to 0 °C and TBAF (1 M in THF, 1.4 mL, 1.4 mmol, 1.3 equiv) was added. The resulting reaction mixture was allowed to reach room temperature and was stirred for 3 hours and 30 minutes until complete disappearance of the starting material. Then the solution was cooled to 0 °C and quenched by addition of a saturated solution of NH₄Cl. Layers were separated and the aqueous one was extracted three times with AcOEt. The combined organic layers were washed with a saturated solution of NaCl, dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography with deactivated silica gel (treated with a 1% solution of NEt₃ prior use) (solvent: cyclohexane/AcOEt : 7/3) giving rise to **19** (398 mg, colorless oil, 72%). R_f: ~ 0.28 (cyclohexane/AcOEt, 7:3); ¹H-NMR (300 MHz, CDCl₃): δ 5.38 (m, 4H), 4.67 (m, 2H), 3.87 (m, 3H), 3.70-3.31 (m, 4H), 3.63 (s, 3H), 2.82 (m, 1H), 2.39 (m, 1H), 2.28 (t, 2H, *J* = 7.5 Hz), 1.99 (m, 6H), 1.65 (m, 4H), 1.25 (m, 12H), 1.15 (m, 6H), 0.84 (t, 3H, *J* = 6.2 Hz); ¹³C-NMR (75 MHz, CDCl₃): δ 174.0, 134.4, 133.6, 131.1 (dia), 129.7, 129.1, 99.1, 98.4 (dia), 96.7, 79.8, 78.8, 76.6, 61.1, 60.2, 58.8, 51.4, 50.7, 41.2, 40.4, (dia), 35.8, 33.4, 31.7, 27.0, 26.7, 25.1, 24.7, 22.5, 20.6, 20.5, 15.4, 15.2, 14.0; IR: ν_{max} (cm⁻¹): 3463, 2931, 1739, 1438, 1376, 1083, 970; HRMS (ESI) calculated for C₂₉ H₅₁O₇ [M-H]⁻ 511.3635, found: 511.3645.

27:

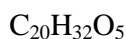
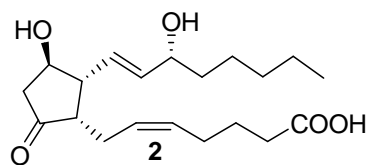
$C_{28}H_{50}O_7$
Mol. Wt: 498.69 g/mol

19 (398 mg, 0.78 mmol, 1 equiv.) was dissolved in THF (10 mL) under nitrogen, the resulting solution was cooled to 0 °C and a suspension of LiOH (205 mg, 8.55 mmol, 11 equiv.) in H₂O (4 mL), and MeOH (2 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 3 hours until completion. The reaction medium was cooled to 0 °C before being quenched by addition of HCl 1 M until a pH value of 5 was reached. Layers were separated and the aqueous one was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was eliminated under reduced pressure affording **27** (337 mg, colorless oil, 87%) which was used without further purification in the next step. R_f : ~ 0.23 (cyclohexane/AcOEt, 1:4); ¹H-NMR (300 MHz, CDCl₃): δ 5.43 (m, 4H), 4.70 (m, 2H), 3.94 (m, 3H), 3.62 (m, 2H), 3.42 (m, 2H), 2.85 (m, 1H), 2.42 (m, 1H), 2.32 (t, 2H, J = 7.1 Hz), 2.06 (m, 4H), 1.74-1.37 (m, 4H), 1.27 (m, 12H), 1.17 (t, 6H, J = 6.9 Hz), 0.86 (m, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ 177.7, 134.3, 133.4, 131.1 (dia), 129.6, 129.1, 99.1, 98.5 (dia), 96.5, 80.0, 78.6, 76.6, 61.1, 60.3, 58.5, 50.4, 41.1, 40.3 (dia), 35.8, 33.2, 31.7, 26.8, 26.5, 25.1, 24.5, 22.5, 20.9, 20.5, 20.2, 15.2, 13.9; IR: ν max (cm⁻¹): 3426, 2931, 2872, 1709, 1378, 1083, 883; HRMS (ESI) calculated for C₂₈ H₄₉O₇ [M-H]⁻ 497.3478, found: 497.3475.

7:

$C_{28}H_{48}O_7$
Mol. Weight: 496.68 g/mol

To **27** (64.5 mg, 0.129 mmol, 1 equiv.) and $NaHCO_3$ (28 mg, 0.387 mmol, 3 equiv.) under nitrogen was added CH_2Cl_2 (5 mL). The resulting reaction medium was cooled to 0 °C before slow addition of a 0.3 M solution of solid Dess-Martin periodinane (137 mg, 0.322 mmol, 2.5 equiv.) in 1 mL of CH_2Cl_2 . The reaction medium was stirred at room temperature for 4 hours before being cooled again to 0 °C. Then a 1 M solution of $Na_2S_2O_3/NaHCO_3$ (1/1) was added and the resulting mixture was stirred at room temperature for one hour until layers were well separated. The aqueous layer was acidified up to pH = 4 by HCl 1 M before being extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using demetallated² silica gel (solvent: cyclohexane/ AcOEt: 7/3) giving pure **7** (48.2 mg, colorless oil, 75%). R_f : ~ 0.69 (cyclohexane/AcOEt, 1:4); 1H -NMR (300 MHz, $CDCl_3$): δ 5.64-5.18 (m, 4H), 4.80 (m, 1H), 4.69 (m, 1H), 4.20 (m, 1H), 3.97, 3.87 (m, 1H), 3.53 (m, 4H), 3.11 (m, 1H), 2.65 (m, 1H), 2.45 (m, 2H), 2.33 (t, 2H, J = 7.5 Hz), 2.03 (m, 2H), 1.89 (m, 1H), 1.68 (quint., 2H, J = 7.5 Hz), 1.55 (m, 1H), 1.28 (m, 12 H), 1.17 (m, 6H), 0.86 (m, 3H); ^{13}C -NMR (75 MHz, $CDCl_3$): δ 216.8, 177.8, 136.0, 135.1, 129.9, 127.7, 127.1 (dia), 99.0, 96.6, 77.2, 76.1 (dia), 75.1, 60.9, 60.5 (dia), 58.4, 50.7, 48.7, 43.6, 42.7 (dia), 35.9, 33.1, 31.7, 26.5, 24.8, 24.5, 23.1, 22.6, 20.5, 20.4, 20.1, 15.3, 14.0. IR: ν max (cm^{-1}): 2932, 1741, 1709, 1381, 1083, 964; HRMS (ESI) calculated for $C_{28}H_{47}O_7$ $[M-H]^-$ 495.3322, found: 495.3309.

(+)-(11*R*,15*R*)-15-*epi*-15-E₂t-IsoP 2

Mol. Weight: 352.46 g/mol

7 (61.8 mg, 0.125 mmol) was dissolved in EtOH (4.5 mL) and CH₂Cl₂ (0.9 mL) under nitrogen and a catalytic amount of PPTS (10 mol%) was added in one portion. The resulting reaction mixture was stirred at room temperature for 1 hour and 30 minutes until complete disappearance of the starting material. Solid NaHCO₃ was added and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using demetallated² silica gel (solvent: AcOEt/cyclohexane 8/2→AcOEt) giving pure **2** (31.6 mg, white solid, 72%). R_f: ~ 0.5 (AcOEt/MeOH, 9:1); [α]_D²⁰ = + 68 (*c* 1 10⁻², MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 5.67 (dd, 1H, *J* = 15.7 Hz, *J* = 5.9 Hz), 5.35 (m, 3H), 4.35 (m, 1H), 4.09 (m, 1H and OH), 2.95 (t, 1H, *J* = 8.1 Hz), 2.71 (dd, 1H, *J* = 14.6 Hz, *J* = 7.1 Hz), 2.57 (dd, 1H, *J* = 18.9 Hz, *J* = 5.9 Hz), 2.34 (m, 4H), 2.04 (m, 3H), 1.68 (m, 2H), 1.50 (m, 2H), 1.28 (m, 6H), 0.87 (m, 3H); ¹H-NMR (300 MHz, MeOD): δ 5.70 (dd, 1H, *J* = 15.5 Hz, *J* = 6.7 Hz), 5.42 (m, 3H), 4.31 (m, 1H), 4.06 (m, 1H), 3.06 (t, 1H, *J* = 8.8 Hz), 2.74 (m, 1H), 2.61 (dd, 1H, *J* = 18.9 Hz, *J* = 6.1 Hz), 2.48 (m, 1H), 2.34 (t, 2H, *J* = 7.1 Hz), 2.25-1.96 (m, 4H), 1.72 (m, 2H), 1.54 (m, 2H), 1.36 (m, 6H), 0.95 (m, 3H); ¹³C-NMR (75 MHz, MeOD): δ 219.5, 177.4, 138.5, 131.0, 129.0, 128.1, 73.3, 72.8, 52.4, 51.7, 45.5, 38.4, 34.4, 32.9, 27.8, 26.2, 26.0, 24.2, 23.7, 14.4.; mp: 101.2 °C; IR: ν max (cm⁻¹): 3394, 2929, 2859, 1728, 1710, 1238, 971; HRMS (ESI) calculated for C₂₀H₃₁O₅ [M-H]⁻ 351.2171, found: 351.2169.