Supporting Information Available

Asymmetric Synthesis of the Highly Potent Anti-Metastatic Prostacyclin Analog Cicaprost and its Isomer Isocicaprost

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Schemes S10 and S12 show the structures of the minor diastereomers 8a', 38', 39', 40', 41', 7a', 8b', and 42' which are derived from the coupling of the enantiomeric alkynes ent-10 and ent-10b contained in 10a with 94% ee and in 10b with 92% ee, respectively, with amide 9a. It is assumed that the reductions of ketones 8a' and 8b' with catecholborane in the presence of oxazaborolidine 37 proceed with the same sense of asymmetric induction as in the case of the reduction of 8a and 8b. In Scheme S11 the coupling of 10a and ent-10a in a ratio of 97:3 with the enantiomeric amide ent-9a with 99% ee is depicted, which gave a mixture of ent-8a' and ent-8a in a ratio of 97:3. Finally, Scheme S13 shows the alleged structures of the α,β-unsaturated esters Z-6' and E-6' formed through olefination of the minor diastereomer 7b' which was contained in ketone 7b because of the utilization of alkyne 10b with 92% ee as the starting material for the synthesis of the ketone. We assume that the olefinations of 7b and 7b' with 43 occur with the sense and with a similar degree of asymmetric induction. Thus reaction of ketone 7b' with 43 should give the Z-configured alkene Z-6' as the major and alkene E-6' as the minor product whereas the corresponding reaction of 7b gives the E-configured alkene E-6 as the major and the Z-configured alkene Z-6 as the minor product (cf. Scheme 8 in the text). Reduction of the mixture of Z-6' and E-6' would lead to the allylic alcohols Z-44' and E-44'.
Scheme S10. Coupling of the Bicyclic Building Block ent-10a With the
ω-Side Chain Building Block 9a (R^1 = Si-BuPh₂)\(^a\)

\[\text{ent-10a} \rightarrow 39' \rightarrow 38' \rightarrow 40' \rightarrow 41' \rightarrow 7a'; R^2 = H\]

\(^a\) Reagents and conditions: (I) ent-10a, n-BuLi, THF, -78 °C \(\rightarrow\) 0 °C. (II) 9a, -19
\(^b\)C. (III) Catecholborane, 37, CH₂Cl₂, -78 °C. (IV) Aqueous HCl, THF, rt. (V)
PhCOCl, pyridine, 0 °C \(\rightarrow\) rt. (VI) NBU₄F, THF, rt. (VII) DMSO, (COCl)₂,
Et₃N, CH₂Cl₂, -60 °C. (VIII) NaOH, MeOH, rt.
Scheme S11. Coupling of the Bicyclic Building Block 10a (94% ee) with the ω-Side Chain Building Block ent-9a (>99% ee) (R = SiF-BuPh₂)
Scheme S12. Coupling of the Bicyclic Building Block ent-10b With the ω-Side Chain Building Block 9a (R\(^1\) = Si-BuMe\(_2\))\(^a\)

![Chemical Structure Diagram]

\(^a\) Reagents and conditions: (I) ent-10b, n-BuLi, THF, \(-78\) °C \(\rightarrow\) rt. (II) 9a, THF, \(-19\) °C. (III) Catecholborane, 37, CH\(_2\)Cl\(_2\), \(-78\) °C, HPLC. (IV) Acetone, TsOH, H\(_2\)O, rt. (V) t-BuMe\(_2\)SiCl, imidazole, DMF, rt.
Scheme S13. Attachment of the α-Side Chain to Ketone 7b' via Reaction
With the Chiral Phosphonate 43 (R = Sit-BuMe2)

Reagents and conditions: (I) THF, first 6 d at -62 °C then 15 h at -30 °C and finally 30 min at rt. (II) DIBALH, THF, 0 °C, HPLC.
(+-)(2S,3aS,6aS)-2-(tert-Butyl-diphenyl-silanyloxy)-5-(trimethyl-silanyloxy)-1,2,3,3a,4,6a-hexahydropentalene (14): To a suspension of (R,R)-bis-(phenylethyl)amine hydrochloride (2.0 g, 7.6 mmol) in THF (40 mL) was added n-BuLi (9.5 mL of 1.6 M in hexanes, 15.2 mmol) at -78 °C. Then the mixture was warmed to ambient temperature, whereby a clear yellow solution of the lithium amide 12 was formed. The solution was cooled to -105 °C and a solution of ketone 11a (2.0 g, 5.3 mmol) in THF (10 mL) was added within 15 min. The mixture was stirred for further 25 min at -105 °C. Then Me₂SiCl (1 mL, 7.8 mmol) was added, and the solution was stirred for 30 min at -105 °C. Subsequently the mixture was warmed to -78 °C, and after stirring the mixture for 30 min saturated aqueous NaHCO₃ (3 mL) was added. Then the mixture was warmed to ambient temperature, and the organic phase was dried (MgSO₄) for 30 min and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 10:1; 30 cm × 4 cm, preconditioned with hexanes/EtOAc, 10:1; flow rate: 66 mL/min) gave the silyl enol ether 14 (2.2 g, 92%) as a colorless oil: R_f 0.72 (hexanes/EtOAc, 10:1); [α]_D +6.7 (c 3.9, THF); ¹H NMR (400 MHz, C₆D₆): δ 0.16 (s, 9 H, SiMe), 1.18 (s, 9 H, t-Bu), 1.54–1.64 (m, 2 H) 1.90–2.02 (m, 2 H), 2.06–2.21 (m, 2 H), 2.48–2.57 (m, 1 H), 2.71–2.78 (m, 1 H), 4.11–4.18 (m, 1 H, CHOSi), 4.67 (m, 1 H, C=CH), 7.22–7.26 (m, 6 H, Ph), 7.78–7.84 (m, 4 H, Ph); ¹³C NMR (100 MHz, C₆D₆): δ 0.11 (d), 19.35 (u), 27.14 (d), 35.72 (d), 41.15 (u), 42.41 (u), 43.57 (u), 44.01 (d), 75.29 (d), 106.84 (d), 127.71 (d), 129.64 (d), 134.74 (u), 135.92 (d), 135.98 (d), 152.64 (u); IR (neat): ν 3069 (m), 2997 (w), 2955 (s), 2931 (s), 2894 (s), 2857 (s), 1643 (s), 1472 (m), 1427 (m), 1372 (w), 1343 (m), 1326 (m), 1283 (m), 1252 (s), 1222 (m), 1190 (m), 1110 (s), 1038 (m), 1000 (w) cm⁻¹; MS (EI) m/z (relative intensity, %): 450 (M⁺, 0.3), 395 (12), 394 (36), 393 (100), 199 (16), 193 (10); Anal. Calcd for C₂₇H₃₈O₂Si₂ (450.76): C, 71.94; H, 8.50. Found: C, 71.86; H, 8.64.
(-)-(1R,2R,3aR,5S,6aS)-1-[5-(tert-Butyl-diphenyl-silanyloxy)-2-(triethyl-silanyloxy)-octahydro-pentalen-1-yl]-2,2,2-trichloro-ethanol (17): To a solution of diol 16 (900 mg, 1.7 mmol) in DMF (3 mL) were added imidazole (450 mg, 6.6 mmol) and Et₃SiCl (0.4 mL, 2.4 mmol). After the mixture was stirred at ambient temperature for 25 min, EtOH (1.5 mL) was added and stirring was continued for 30 min. Then the mixture was concentrated to a volume of 1.5 mL in a rotary evaporator. Purification by column chromatography (hexanes/EtOAc, 5:1) provided the silyl ether 17 (866 mg, 79%) as a colorless oil. R_f 0.41 (hexanes/EtOAc, 1:5); [α]D -24.4 (c 1.35, CH₂Cl₂); ¹H NMR (300 MHz, C₆D₆): δ 0.62 (m, 6 H, SiCH₂Me), 1.04 (t, J = 8.0 Hz, 9 H, SiCH₂Me), 1.20 (s, 9 H, t-Bu), 1.52–1.76 (m, 3 H) 1.80–1.90 (m, 1 H), 1.96–2.16 (m, 3 H), 2.35–2.47 (m, 2 H), 2.84 (t, J = 9.0 Hz, 1 H, CHCHOH), 4.00–4.10 (m, 1 H, CHOSiEt₃), 4.28 (m, 1 H, CHOSi-BuPh₂), 4.40 (dd, J = 6.5, J = 1.5 Hz, 1 H, CHOHOH), 7.20–7.26 (m, 6 H, Ph), 7.74–7.81 (m, 4 H, Ph); ¹³C NMR (75 MHz, C₆D₆): δ 5.32 (u), 7.10 (d), 19.25 (u), 27.16 (d), 35.86 (d), 38.66 (d), 41.35 (u), 41.62 (u), 43.43 (u), 55.70 (d), 76.80 (d), 77.36 (d), 82.19 (d), 104.51 (u), 127.67 (d), 129.60 (d), 129.65 (d), 134.31 (u), 134.44 (u), 136.00 (d); IR (neat): ν 3581 (w), 3070 (w), 3049 (w), 2955 (s), 2876 (s), 1462 (m), 1427 (m), 1368 (m), 1240 (m), 1151 (m), 1112 (s), 1023 (s); MS (CI, isobutane) m/z (relative intensity, %): 646 (15), 645 (36), 644 (43), 643 (100), 642 (M⁺, 37), 641 (M+H⁺, 92), 609 (14), 607 (22), 439 (11), 389 (15), 386 (47), 385 (40); Anal. Calcd for C₃₂H₄₇Cl₃O₃Si₂ (642.24): C, 59.84; H, 7.38. Found: C, 59.92; H, 7.37.

(-)-(1R,2R,3aR,5S,6aS)-Methanesulfonic acid 1-[5-(tert-butyl-diphenyl-silanyloxy)-2-(triethyl-silanyloxy)-octahydro-pentalen-1-yl]-2,2,2-trichloro-ethyl ester (18): To a solution of alcohol 17 (1.8 g, 2.8 mmol) and DABCO (1.3 g, 11.6 mmol) in THF (25 mL) was added dropwise MeSO₂Cl (0.54 mL, 7 mmol) at ambient temperature, whereby a colorless precipitate was formed. After the mixture was stirred for 2 h, TLC showed a full conversion of the alcohol. Column chromatography (hexanes/Et₂O, 1:1) of the reaction
mixture provided mesylate 18 (2.0 g, 98%) as a colorless oil. [α]D −18.2 (c 1.9, Et2O); 1H NMR (400 MHz, C6D6): δ 0.77 (dq, J = 7.5, J = 2.5 Hz, 6 H, SiCH3Me), 1.10 (t, J = 7.5 Hz, 9 H, SiCH3Me), 1.18 (s, 9 H, t-Bu), 1.49−1.57 (m, 1 H), 1.64−1.75 (m, 2 H), 1.81−1.89 (m, 1 H), 1.96−2.14 (m, 2 H), 2.16−2.26 (m, 1 H), 2.43 (s, 3 H, SO2Me), 2.52−2.61 (m, 1 H), 3.00 (t, J = 8.9 Hz, 1 H, CH−CHOSO2Me), 4.23−4.31 (m, 2 H, CHOSiEt3, CHOSiBuPh2), 5.62 (s, 1 H), 7.22−7.27 (m, 6 H, Ph), 7.73−7.77 (m, 4 H, Ph); 13C NMR (100 MHz, C6D6): δ 5.39 (u), 7.19 (d), 19.21 (u), 27.14 (d), 37.06 (d), 38.56 (d), 38.69 (d), 41.00 (u), 41.45 (u), 43.25 (u), 55.92 (d), 76.20 (d), 77.35 (d), 88.48 (d), 99.67 (u), 127.69 (d), 127.77 (d), 129.69 (d), 134.24 (u), 134.37 (u), 136.01 (d); IR (CHCl3): ν 3071 (m), 3047 (m), 2954 (s), 2876 (s), 1470 (m), 1427 (m), 1415 (m), 1363 (s), 1333 (m), 1265 (w), 1239 (m), 1219 (w), 1179 (s), 1150 (m), 1112 (s), 1062 (w), 1032 (s) cm−1; MS (Cl, isobutane) m/z (relative intensity, %): 725 (5), 724 (9), 723 (24), 722 (23), 721 (47), 720 (M+ , 23), 719 (49), 593 (13), 592 (22), 591 (51), 590 (34), 589 (73), 533 (10), 531 (13), 257 (15), 212 (14), 211 (100); Anal. Calc'd for C33H46Cl3O8Si2 (720.33): C, 55.02; H, 6.86. Found: C, 55.33; H, 6.91.

(−)-(3a′S,4′S,5′R,6a′R)-5′-(tert-Butyl-dimethyl-silanyloxy)-[4′-cyano-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2′(1'H)-pentalene]] (23): To a solution of alcohol 22 (1.0 g, 3.98 mmol) in DMF (5 mL) were added imidazole (730 mg, 10.7 mmol) and t-BuMe2SiCl (600 mg, 3.98 mmol). After the mixture was stirred for 16 h at ambient temperature, it was diluted with Et2O (50 mL) and washed with aqueous NaHCO3 (50 mL). The aqueous phase was separated and extracted with Et2O (3 × 10 mL). The combined organic phases were dried (MgSO4) and concentrated in vacuo. Purification by column chromatography (Et2O) afforded the silyl ether 23 (1.42 g, 98%) as a colorless oil. Rf 0.62 (hexanes/EtOAc, 3:1); [α]D −0.59 (c 2.7, CDCl3); 1H NMR (400 MHz, C6D6): δ 0.07 (s, 3 H), 0.17 (s, 3 H), 0.64 (s, 3 H), 0.79 (s, 3 H), 0.96 (s, 9 H), 1.38 (m, 1 H), 1.65−1.85 (m, 5 H), 2.07 (m, 1 H), 2.35 (m, 1 H), 2.58 (t, J =
S10

9.0 Hz, 1 H, CHCN), 3.03 (s, 2 H), 3.17 (s, 2 H), 3.98 (m, 1 H, CHOSi), $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ -4.72 (d), -4.56 (d), 18.16 (u), 22.20 (d), 22.45 (d), 25.87 (d), 29.78 (u), 35.58 (d), 36.92 (u), 40.55 (u), 41.43 (u), 42.60 (d), 43.64 (d), 71.21 (u), 72.09 (u), 77.31 (d), 109.29 (u), 121.43 (u); IR (neat): v 2954 (s), 2857 (s), 2238 (m), 1739 (w), 1472 (s), 1434 (m), 1395 (m), 1362 (s), 1352 (m), 1331 (m), 1313 (m), 1285 (m), 1254 (s), 1221 (m), 1209 (m), 1190 (m), 1171 (m), 1143 (s), 1120 (s), 1049 (s), 1021 (m), 1006 (s) cm$^{-1}$; MS (EI, 70 eV) m/z (relative intensity %): 365 (M$^+$, 2), 308 (29), 223 (17), 222 (100), 128 (11); Anal. Calcd for C$_{20}$H$_{35}$NO$_3$Si (365.58): C, 65.71; H, 9.65; N 3.83, Found: C, 65.41; H, 10.02; N, 4.11.

$\text{(-)-(3aS,4S,5R,6aR)-5-(tert-Butyl-dimethyl-silyloxy)-[4-ethyl-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2' (1'H)-pentalene]}$ (10b): From aldehyde 24: Preparation of [Ph$_3$PCHBr$_2$]Br: To a solution of PPh$_3$ (158 g, 0.6 mol) in dry CH$_2$Cl$_2$ (800 mL) was added within 10 min a solution of CBr$_4$ (100 g, 0.3 mol) in CH$_2$Cl$_2$ at ambient temperature. The dark brown solution was stirred for 20 min, and water (50 mL) was added very slowly (highly exothermic reaction!). After the mixture was cooled to ambient temperature, the aqueous phase was separated and the bright yellow organic phase was dried (MgSO$_4$) and concentrated in vacuo. The residue was dried in vacuo (10$^{-3}$ mbar) and subsequently dissolved in boiling dry MeOH (800 mL). The mixture was filtered and cooled to 20 °C. Then EtOAc was added until the precipitate, which had been formed, did not dissolve completely upon stirring. The slightly turbid solution was cooled to -26 °C, and the crystals formed were separated and dried in vacuo (10$^{-3}$ mbar). The thus obtained [Ph$_3$PCHBr$_2$]Br (115 g, 70%) still contained some MeOH, which did, however, not affect its subsequent use. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 (m, 6 H); 7.76 (m, 3 H); 8.09 (m, 6 H); 10.17 (d, J = 2.2 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 29.93 (d), 30.40 (d), 116.10 (u), 116.98 (u), 130.44 (d), 130.57 (d), 135.17 (d), 135.27 (d), 135.80 (d), 135.83 (d); $^{31}$P NMR (160 MHz, CDCl$_3$): $\delta$ 33.92; IR (KBr): v 3426 (w), 3053 (w), 3018 (w), 2960 (w), 2807 (s), 1584 (w), 1484 (m), 1436 (s), 1338 (w),
1321 (w), 1268 (m), 1164 (w), 1103 (s) cm\(^{-1}\); MS (EI, 70 eV) m/z (relative intensity, %): 436 (11), 435 (16), 434 (22), 433 (26), 432 (10), 431 (11), 278 (44), 277 (100), 273 (17), 263 (12), 262 (68), 261 (15), 252 (17), 250 (17), 201 (13), 199 (16), 185 (12), 184 (12), 183 (66), 172 (15), 165 (26), 161 (23), 160 (46), 157 (24), 155 (22), 152 (15), 108 (15), 91 (33), 82 (14), 81 (13), 80 (16). A suspension of [Ph\(_3\)PCHBr\(_2\)]Br (2.06 g, 4 mmol) in THF (25 mL) was treated with KOt-Bu (426 mg, 3.8 mmol) whereby a yellow turbid solution was formed, which turned brown within 20 min. Then a solution of aldehyde 24 (498 mg, 1.3 mmol) in THF (5 mL) was added. The mixture was stirred at ambient temperature for 10 min. Subsequently a further portion of KOt-Bu (1.2 g, 10.6 mmol) was added. After the dark brown mixture was stirred for 30 min, saturated aqueous NaCl (50 mL) was added. The aqueous phase was separated and extracted with Et\(_2\)O (100 mL). The combined organic phases were dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography (first hexanes/EtOAc, 10:1, then hexanes/EtOAc, 20:1) afforded alkyne 10b (413 mg, 84%) with 92% ee (GC: Macherey-Nagel Lipodex-C, 25 m, \(t_r\) (ent-10b) = 193.07 min, \(t_r\) (10b) = 195.30 min) as a colorless oil.
\(R_f\) 0.59 (hexanes/EtOAc, 3:1); [\(\alpha\)]\(_D\) \(-1.5\) (c 5.4, CDCl\(_3\)); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 0.12 (s, 3 H), 0.19 (s, 3 H), 0.64 (s, 3 H), 0.82 (s, 3 H), 1.01 (s, 9 H), 1.53 (m, 1 H), 1.80 (dd, \(J = 5.0, J = 13.0\) Hz, 1 H), 1.95 (d, \(J = 2.5\) Hz, 1 H, C=CH), 1.96–2.07 (m, 4 H), 2.28 (m, 1 H), 2.50 (m, 1 H), 2.68 (dt, \(J = 2.5, J = 8.8\) Hz 1 H, CH=C=CH), 3.09–3.17 (m, 2 H), 3.22 (s, 2 H), 4.02 (m, 1 H, CHOSi); \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \(\delta\) −4.53 (d), −4.27 (d), 18.30 (u), 22.26 (d), 22.56 (d), 26.04 (d), 29.88 (u), 35.70 (d), 37.53 (u), 41.30 (u), 41.67 (u), 45.35 (d), 45.51 (d), 69.79 (u), 71.50 (u), 71.92 (u), 79.60 (d), 86.72 (u), 109.74 (u); IR (neat): \(\nu\) 3311 (s), 2955 (s), 2886 (s), 2857 (s), 2738 (s), 2708 (s), 2280 (w), 2115 (w), 1472 (s), 1464 (s), 1435 (m), 1395 (s), 1362 (s), 1352 (s), 1330 (s), 1312 (m), 1284 (m), 1256 (s), 1221 (s), 1210 (m), 1190 (m), 1171 (s), 1118 (s), 1049 (s), 1019 (s), 1007 (s) cm\(^{-1}\); MS (EI, 70 eV) m/z (relative intensity, %): 364 (M\(^+\), 6), 308 (19), 307 (80), 222 (18), 221 (100), 203 (46), 179 (18), 178 (89), 128

(−)-4R-Benzyl-3-(2S-methyl-hept-4-ynoyl)-oxazolidin-2-one (33): To a solution of NaN(SiMe$_3$)$_2$ (25.6 g, 139 mmol) in THF (250 mL) was added dropwise a solution of oxazolidinone 31 (25.1 g, 0.107 mol) in THF (40 mL) at −78 °C. After the mixture was stirred for 60 min at −78 °C, iodide 32 (32.0 g, 165 mmol) was added within 40 min at −78 °C. Then the mixture was stirred for 60 min, and acetic acid (10 mL) was added at −78 °C. The mixture was warmed to ambient temperature and treated with aqueous NaCl (100 mL). Then water was added until two clear phases were formed. The aqueous phase was separated and extracted with Et$_2$O (3 × 100 mL). The combined organic phases were washed with aqueous NaHCO$_3$ (100 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography (first hexanes, then hexanes/EtOAc, 3:1) afforded oxazolidinone 33 (29.8 g, 93%) with 97% de ($^1$H NMR: δ (CHMe) 1.258 (33); δ (CHMe) 1.303 (epi-33)) as a colorless oil which solidified at −26 °C within days. Mp 40 °C; R$_f$ 0.34 (hexanes/EtOAc, 3:1); [α]$_D$ −52.7 (c 2.0, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.10 (t, J = 7.5 Hz, 3 H, CH$_2$Me), 1.26 (d, J = 6.5 Hz, 3 H, CHMe), 2.15 (m, 2 H, CH$_2$Me), 2.42–2.60 (m, 2 H, CH$_2$C=C Et), 2.80 (dd, J = 9.5, J = 13.5 Hz, 1 H, CH$_2$Ph), 3.29 (dd, J = 3.2, J = 13.5 Hz, 1 H, CH$_2$Ph), 3.91 (m, 1 H, CHMe), 4.19 (m, 2 H, CH$_3$O), 4.71 (m, 1 H, CHN), 7.22–7.36 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 12.40 (u), 14.20 (d), 16.51 (d), 23.07 (u), 37.76 (d), 37.91 (u), 55.21 (d), 66.05 (u), 76.22 (u), 83.55 (u), 127.35 (d), 128.95 (d), 129.46 (d), 135.28 (u), 153.05 (u), 175.56 (u). IR (KBr) ν 3062 (w), 3028 (w), 2976 (m), 2935 (m), 2877 (w), 1780 (s), 1736 (m), 1700 (s), 1604 (w), 1497 (m), 1481 (m), 1454 (m), 1387 (s), 1350 (s), 1325 (m), 1294 (m), 1242 (s), 1209 (s), 1103 (m), 1076 (m), 1054 (m), 1016 (m) cm$^{-1}$; MS (EI, 70 eV) m/z (relative intensity, %): 299 (M$^+$, 39), 284 (22), 182 (11), 181 (21), 123 (100), 117 (51), 95
(+)-(S)-2-Methyl-hept-4-ynoic acid ethyl ester (34): To a solution of oxazolidinone 33 (16.0 g, 53.4 mmol) in dry EtOH (70 mL) was added Ti(OEt)$_4$ (6 mL), and the mixture was heated for 8 h at reflux. Then the solvent was removed in a rotary evaporator at 30 °C/15 mbar. The residue was diluted with EtOAc (250 mL), water (25 mL) was added and the mixture was stirred for 20 min, whereby a white suspension was formed. The solid was filtered off and washed thoroughly with EtOAc. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. Column chromatography (first hexanes/EtOAc, 10:1, then EtOAc) gave ester 34 (7.3 g, 81%) with 97% ee (GC: Macherey-Nagel Lipodex-E, 25 m, $t_R$ (ent-34) = 43.39 min; $t_R$ (34) = 46.87 min) as a colorless oil and (4R)-benzyl-oxazolidin-2-one (7.1 g, 75%) as a colorless solid. 34: $R_f$ 0.55 (hexanes/EtOAc, 3:1); $[\alpha]_D ^+7.42$ (c 1.28, CHCl$_3$); $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 0.98 (t, $J$ = 7.4 Hz, 3 H, C=CCH$_2$Me), 1.02 (t, $J$ = 7.1 Hz, 3 H, OCH$_2$Me), 1.19 (d, $J$ = 7.0 Hz, 3 H, CHMe), 1.97–2.04 (m, 2 H, C=CCH$_2$Me), 2.27–2.36 (m, 1 H, CH$_2$C=CEt), 2.44–2.55 (m, 2 H, CH$_2$C=CEt, CHMe), 3.95–4.03 (m, 2 H, OCH$_2$Me); $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 12.69 (u), 14.27 (d), 14.40 (d), 16.49 (d), 23.46 (u), 39.55 (d ), 60.17 (u), 76.91 (u), 83.27 (u), 174 (u); IR (neat): v 2977 (s), 2938 (s), 2879 (m), 2850 (m), 1735 (s), 1461 (m), 1375 (s), 1349 (m), 1321 (m), 1285 (m), 1229 (m), 1179 (s), 1113 (s), 1050 (s), 1025 (m) cm$^{-1}$; GC-MS (EI, 70 eV) m/z (relative intensity, %): 168 (M$^+$, 4), 153 (100), 140 (13), 139 (12), 126 (14), 125 (87), 123 (28), 111 (18), 97 (29), 95 (37), 94 (10), 93 (12). Anal. Caled for C$_{10}$H$_{16}$O$_2$ (168.23): C, 71.39; H, 9.59. Found: C, 71.23; H, 9.62.

(+)-(2S)-Methyl-hept-4-ynoic acid methoxy-methyl-amide (9a): To a mixture of ester 34 (1.16 g, 6.9 mmol) and [MeO(Me)NH$_2$]Cl (950 mg, 9.7 mmol) in THF (10 mL) was added $i$-PrMgCl (2 N in THF, 9.5 mL, 9.5 mmol) within 25 min at -19 °C by means of a
syringe pump. After the mixture was stirred for 30 min at -19°C, aqueous NH₄Cl (20 mL) was added. The mixture was warmed to ambient temperature and diluted with Et₂O (50 mL). Then water was added until two clear phases were formed. The aqueous phase was extracted with Et₂O (50 mL), and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. Column chromatography (pentanes/Et₂O, 1:4) afforded amide 9a (1.17 g, 92%) with 97% ee (GC: Macherey-Nagel Hydro-Dex-β-Cyclodextrin-6-TBDM, 25 m, tᵣ (ent-9a) = 136.4 min; tᵣ (9a) = 136.59 min) as a colorless liquid. HPLC (Ciracel AD, 250 mm × 50 mm, i-PrOH/hexanes 5:95, UV: 254 nm) afforded amide 9a with ≥99% ee in 90% yield. Rₓ 0.19 (hexanes/EtOAc, 3:1); [α]D +15.5 (c 4.5, CDCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.10 (t, J = 7.4 Hz, 3 H, CH₂Me), 1.19 (d, J = 6.9 Hz, 3 H, CHMe), 2.10–2.19 (m, 2 H, C=CH₂Me), 2.20–2.28 (m, 1 H, CH₂C≡CEt), 2.40–2.52 (m, 1 H, CH₂C≡CEt), 3.00–3.10 (brm, 1 H, CHMe), 3.20 (s, 3 H, NMe), 3.73 (s, 3 H, OMe); ¹³C NMR (100 MHz, CDCl₃): δ 12.40 (u), 14.23 (d), 16.98 (d), 23.02 (u), 32.15 (u), 35.55 (d), 61.48 (d), 77.26 (u), 82.70 (u), 176 (o); IR (neat): ν 2974 (s), 2937 (s), 2878 (m), 1665 (s), 1462 (s), 1426 (m), 1386 (s), 1320 (m), 1277 (w), 1178 (m), 1152 (m), 1120 (m), 1085 (m), 1044 (w) cm⁻¹; GC-MS (EI, 70 eV) m/z (relative intensity, %): 183 (M⁺, 0.6), 168 (21), 152 (35), 138 (49), 123 (31), 95 (60), 93 (30); Anal. Calcd for C₁₀H₁₇NO₂ (183.25): C, 65.54; H, 9.35; N 7.64. Found: C, 65.81; H, 9.48; N 7.46.

2-Methyl-2-pent-2-ynyl-malonic acid diethyl ester (36): To a solution of HN(i-Pr)₂ (2.1 g, 21.1 mmol) in THF (15 mL) was added n-BuLi (1.6 M in hexanes, 12.6 mL, 20.2 mmol) at -78 °C. Then the mixture was warmed to ambient temperature for 15 min, cooled to -78 °C and treated dropwise with malonate 35 (3.4 g, 19.3 mmol). After the mixture was stirred for 60 min, iodide 33 (5.3 g, 27.3 mmol) was added dropwise at -78°C, and stirring of the mixture was continued for 60 min. Then the mixture was warmed to ambient temperature
and aqueous NaCl was added (10 mL). The aqueous phase was separated and extracted with Et₂O (3 × 30 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 20:1) provided malonate 36 (4.2 g, 91%) as a colorless liquid. R₇ 0.43 (hexanes/EtOAc, 3:1); ¹H NMR (400 MHz, CDCl₃): 8 1.09 (t, J = 7.4 Hz, 3 H, C≡CCH₂Me), 1.25 (t, J = 6.9 Hz, 6 H, OCH₂Me), 1.51 (s, 3 H, CHMe), 2.10–2.17 (m, 2 H, C≡CCH₂), 2.73 (t, J = 2.4 Hz, 2 H, CH₂C≡CEt), 4.15–4.24 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃): 8 12.35 (u), 14.04 (d), 14.13 (d), 19.77 (d), 26.12 (u), 53.43 (u), 61.33 (u), 74.01 (u), 84.59 (u), 170.95 (u); IR (neat): ν 2980 (s), 2938 (m), 2878 (w), 1736 (s), 1458 (m), 1377 (m), 1321 (m), 1294 (s), 1246 (s), 1196 (s), 1108 (s), 1023 (m) cm⁻¹; MS (EI, 70 eV) m/z (relative intensity, %): 240 (M⁺, 30), 195 (16), 181 (12), 167 (100), 166 (16), 165 (24), 151 (12), 139 (53), 138 (54), 137 (38), 120 (16), 111 (17), 109 (13), 95 (19), 93 (15), 91 (11), 81 (12). HRMS calc'd for C₁₃H₂₀O₄⁺ (M⁺) 240.13615 found 240.13609.

(±)-2-Methyl-hept-4-ynoic acid ethyl ester (rac-34): To a solution of malonate 36 (4.0 g, 16.6 mmol) in DMSO (12 mL) was added LiCl (0.86 g, 20 mmol) and water (0.4 mL, 0.22 mmol), and the mixture was heated for 5 h at reflux. Then the mixture was cooled to ambient temperature and extracted with Et₂O (100 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 10:1) afforded ester rac-34 (2.14 g, 75%) as a colorless oil.

(±)-(2S,5S)-Methyl-hept-4-ynoic acid methoxy-methyl-amide (rac-9a): Following the procedure for the synthesis of 9a, rac-9a (4.2 g, 90%) was obtained by addition of i-PrMgCl (2 N in THF, 35 mL, 70.0 mmol) at −19 °C to a mixture of [MeO(Me)NH₂]Cl (3.5 g, 35.7 mmol) and ester rac-34 (4.3 g, 25 mmol) in THF (40 mL).
(−)-(1S,2R,3aR,S,6aS)-1-[5-(tert-Butyl-diphenyl-silyloxy)-octahydro-pentalen-1-yl]-4(5S)-methyl-nona-1,6-diyn-3(S)-ol (38): To a solution of ketone 8a (150 mg, 0.23 mmol) in CH$_2$Cl$_2$ (2 mL) was added oxazaborolidine 37 (0.86 M solution in C$_6$D$_6$, 0.1 mL, 0.086 mmol). The mixture was cooled to −78 °C and catecholborane (0.15 mL, 1.4 mmol, diluted with 0.2 mL CH$_2$Cl$_2$) was added within 5 min. After the mixture was stirred for 12 h at −78 °C, it was warmed to ambient temperature. Column chromatography (hexanes/Et$_2$O, 1:1) of the mixture afforded alcohol 38 (132 mg, 88%) with 94% de as a colorless oil. R$_f$ 0.68 (hexanes/Et$_2$O, 1:1); [α]$_D$ −6.1 (c 2.7, THF); $^1$H NMR (300 MHz, C$_6$D$_6$): δ 0.65–0.76 (m, 6 H, SiCH$_2$Me), 0.98 (t, J = 7.4 Hz, 3 H, C=CC$\equiv$Me), 1.10 (t, J = 7.9 Hz, 9 H, SiCH$_2$Me), 1.18 (s, 9 H, t-Bu), 1.23 (d, J = 6.7 Hz, 3 H, CHMe), 1.54–2.14 (m, 11 H), 2.22–2.48 (m, 3 H), 3.09 (dt, J = 8.6, J = 1.5 Hz, 1 H, CHOSiEt$_3$-CHC≡C), 4.03–4.12 (m, 1 H, CHOSiEt$_3$), 4.21–4.29 (m, 1 H, CHOSi-t-BuPh$_2$), 4.39–4.45 (m, 1 H, C≡CCHOH), 7.22–7.28 (m, 6 H), 7.74–7.80 (m, 4 H); $^{13}$C NMR (75 MHz, C$_6$D$_6$): δ 5.14 (u), 7.21 (d), 12.78 (u), 14.52 (d), 15.42 (d), 19.33 (u), 22.59 (u), 27.19 (d), 37.51 (d), 40.07 (d), 41.00 (u), 42.51 (u), 42.71 (u), 46.59 (d), 47.26 (d), 66.33 (d), 77.32 (d), 77.93 (u), 79.98 (d), 81.39 (u), 83.22 (u), 88.96 (u), 128.00 (d), 129.90 (d), 129.94 (d), 134.55 (u), 134.66 (u), 136.25 (d); IR (neat): ν 3423 (m), 3135 (s), 3071 (m), 3049 (m), 2956 (s), 2876 (s), 2733 (s), 2232 (w), 1461 (m), 1428 (m), 1375 (m), 1321 (w), 1263 (w), 1240 (m), 1112 (s), 1040 (s) cm$^{-1}$; MS (EI, 70 eV) m/z (relative intensity, %): 642 (M$^+$, 3), 614 (10), 613 (18), 586 (23), 585 (44), 453 (30), 453 (13), 357 (26), 314 (14), 313 (48), 301 (18), 285 (13), 255 (26), 253 (19), 238 (19), 237 (100), 209 (19), 208 (12), 207 (11), 200 (11), 199 (65), 197 (30), 196 (13), 195 (32), 193 (11), 183 (25), 181 (31), 179 (10), 171 (21), 169 (15), 167 (21), 157 (16), 155 (13), 145 (11), 143 (27), 141 (11), 135 (31), 131 (19), 129 (21), 128 (12), 119 (10), 117 (13), 115 (23), 105 (23), 103 (14), 93 (10), 91 (19), 87 (41); Anal. Calcd for C$_{49}$H$_{58}$O$_3$Si$_2$: C, 74.71; H, 9.09. Found: C, 74.66; H, 9.06.
(-)-(15,2R,3aS,5S,6aS)-Benzoic acid 5-hydroxy-1-(3(S)-benzoyloxy-4(S)-methyl-nona-1,6-diynyl)-octahydro-pentalen-2-yl-ester (40): To a solution of diol 39 (320 mg, 0.6 mmol) in C₅H₅N (4 mL) was added PhCOCl (0.55 mL, 4.75 mmol) at 0 °C. After the mixture was stirred for 1.5 h, TLC showed a complete conversion of the diol, and the excess of PhCOCl was destroyed by addition of EtOH (2 mL). Then the mixture was warmed to ambient temperature and stirring was continued for further 12 h. Column chromatography (Et₂O) of the reaction mixture afforded the dibenzoate of 39 admixed with ethyl benzoate. This mixture was treated with Bu₄NF in THF (1 M, 3 mL, 3 mmol) for 12 h at ambient temperature. Then the mixture was concentrated in vacuo, and the residue was purified by column chromatography (Et₂O). A further purification by HPLC (Kromasil Si 100, 250 mm × 20 mm, Et₂O, UV detector 225 nm, RI, flow: 8 mL/min, 30 mg per injection) afforded alcohol 40 (260 mg, 86%) with 94% de (¹H NMR: δ (C=CC/OCPPh) 6.02 (40); δ (C=CC/OCPPh) 5.95 (40°)) as a colorless oil. Rf 0.42 (Et₂O); [α]D -65.14 (c 0.35, CH₂Cl₂); ¹H NMR (400 MHz, C₅D₅): δ 0.97 (t, J = 7.6 Hz, 3 H, C=CCH₂Me), 1.21 (d, J = 6.6 Hz, 3 H, CHMe), 1.35–1.43 (m, 1 H), 1.46–1.80 (m, 5 H), 1.92–2.00 (m, 2 H), 2.07–2.46 (m, 6 H) 3.11 (dt, J = 8.8, J = 1.9 Hz, 1 H, CHMe), 3.97 (m, 1 H, CHO), 5.44 (m, 1 H, CH/OCPPh), 6.00 (dd, J = 5.5, J = 1.9 Hz, 1 H, C=C/C(OCPPh), 7.00–7.20 (m, 6 H), 8.04–8.16 (m, 4 H); ¹³C NMR (100 MHz, C₅D₅): δ 12.68 (u), 14.39 (d), 15.25 (d), 22.82 (u), 37.92 (d), 37.98 (d), 38.55 (u), 40.35 (u), 41.96 (u), 43.15 (d), 46.69 (d), 68.23 (d), 75.38 (d), 76.91 (u), 77.97 (u), 80.30 (d), 83.47 (u), 88.16 (u), 128.29 (d), 128.31 (d), 129.80 (d), 129.82 (d), 130.46 (u), 130.64 (u), 132.62 (d), 132.71 (d), 165.04 (u), 165.79 (u); MS (Cl, methane) m/z (relative intensity, %): 499 (M⁺ + H, 1), 378 (29), 377 (100), 256 (12), 255 (62), 238 (10), 237 (58), 105 (23); HRMS (ESI, TOF) calcd for C₃₃H₃₅O₅⁺ (M⁺ + H) 499.2484, found 499.2455.
(−)-(1S,2R,3aR,6aS)-Benzoic acid 1-(3(S)-benzoyloxy-4(S)-methyl-nona-1,6-diylnyl)-5-oxo-octahydropentalen-2-yl ester (41): To a solution of (COCl)₂ (0.1 mL, 1.14 mmol) in CH₂Cl₂ (1 mL) was added a solution of DMSO (0.3 mL, 4.22 mmol) in CH₂Cl₂ (0.5 mL) at −60 °C. The mixture was stirred for 10 min at −60 °C and a solution of alcohol 40 (200 mg, 0.4 mmol) in CH₂Cl₂ (1.5 mL) was added within 5 min. After the mixture was stirred for 35 min at −60 °C, NEt₃ (2 mL, 14.4 mmol) was added dropwise. Then the mixture was allowed to warm to ambient temperature and water (2 mL) was added. The aqueous phase was separated and extracted with Et₂O (3 × 10 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (hexanes/Et₂O, 1:2) afforded ketone 41 (178 mg, 89%) with 94% de (¹H NMR: δ (C≡CCHOCOPh) 5.99 (41); δ (C≡CCHOCOPh) 5.92 (41')) as a colorless oil. Rf 0.35 (hexanes/Et₂O, 1:2); [α]D −67.5 (c 0.35, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆): δ 0.97 (t, J = 7.7 Hz, 3 H, C≡CCH₂Me), 1.18–1.25 (m, 1 H), 1.22 (d, J = 6.6 Hz, 3 H, CHMe), 1.70 (dd, J = 18.6, J = 5.4 Hz, 1 H), 1.95–2.05 (m, 5 H), 2.14–2.45 (m, 6 H), 2.54 (dt, J = 7.1, J = 1.6 Hz, 1 H, CHMe), 5.39 (q, J = 6.0 Hz, 1 H, CHO-COCOPh-CHC≡C), 5.99 (dd, J = 5.8, J = 1.9 Hz, 1 H, C≡CCHOCOPh), 7.02–7.20 (m, 6 H), 8.06–8.14 (m, 4 H); ¹³C NMR (100 MHz, C₆D₆): δ 12.68 (u), 14.39 (d), 15.33 (d), 22.85 (u), 36.37 (d), 37.87 (d), 38.67 (u), 43.01 (u), 43.56 (d), 44.89 (u), 44.98 (d), 67.98 (d), 76.75 (u), 79.11 (u), 81.03 (d), 83.69 (u), 86.74 (u), 128.39 (d), 128.43 (d), 129.73 (d), 129.77 (d), 130.20 (u), 130.36 (u), 132.88 (d), 132.94 (d), 164.93 (u), 165.30 (u), 215.74 (u); MS (Cl, isobutane) m/z (relative intensity, %): 497 (M⁺ + H, 2), 377 (11), 376 (27), 375 (100), 255 (9), 254 (3), 253 (10). HRMS (ESI, TOF) calcd for C₃₃H₃₃O₅ (M⁺ + H) 497.2328, found 497.2354.

(−)-(3aS,4S,5R,6aR)-5-(tert-Butyl-dimethyl-silyloxy)-[4-((3S,4S)-3-tert-butyl-dimethyl-silyloxy-4-methyl-nona-1,6-diylnyl)-hexahydropentalen-2-one] (7b): To a solution of acetal 42 (900 mg, 1.84 mmol) (≥99% de) in acetone (10 mL) were added TsOH (50 mg) and water (4 mL) at ambient temperature. After the mixture was stirred for 72 h,
aqueous Na₂CO₃ (10 mL) was added, and the solution was extracted with Et₂O (3 × 30 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The thus obtained ketone 7a was dissolved in DMF (7 mL), and imidazole (1.5 g, 22 mmol) and t-t-BuMe₂SiCl (1.4 g, 9.3 mmol) were added, and the mixture was stirred for 14 h at ambient temperature. Column chromatography (hexanes/EtOAc, 4:1) afforded a colorless oil, which was further purified by column chromatography (hexanes/Et₂O, 5:1) to give the bis-silyl ether 7b (910 mg, 1.76 mmol, 95%) with ≥99% de (¹H NMR) as a colorless oil. Rf 0.54 (hexanes/EtOAc, 3:1), [α]D₂ -22.4 (c 1.26, CDCl₃); ¹H NMR (400 MHz, C₆D₆): δ 0.04 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe), 0.18 (s, 3 H, SiMe), 0.24 (s, 3 H, SiMe), 0.94 (s, 9 H, SiMe), 1.00 (t, J = 7.7 Hz, 3 H, C=CH₂Me), 1.01 (s, 9 H, t-Bu), 1.17–1.24 (m, 1 H), 1.22 (d, J = 6.9 Hz, 3 H, CHMe), 1.83 (dd, J = 18.4, J = 5.5 Hz, 1 H), 1.98–2.14 (m, 7 H), 2.16–2.29 (m, 1 H), 2.34–2.55 (m, 4 H) 4.07 (m, 1 H, CHOSi-CH₂=), 4.48 (dd, J = 6.3, J = 1.4 Hz, 1 H, C=CH₂Si); ¹³C NMR (100 MHz, C₆D₆): δ -4.93 (d), -4.75 (d), -4.68 (d), -4.16 (d), 12.72 (u), 14.53 (d), 15.46 (d), 18.13 (u), 18.38 (u), 22.39 (u), 25.89 (d), 25.98 (d), 36.11 (d), 40.65 (d), 42.36 (u), 43.49 (u), 45.13 (d), 45.22 (u), 46.90 (d), 66.65 (d), 77.54 (u), 79.94 (d), 82.77 (u), 83.14 (u), 86.55 (u), 215.63 (u); IR (neat): ν 2955 (s), 2931 (s), 2857 (s), 1744 (s), 1471 (m), 1405 (w), 1378 (w), 1360 (w), 1322 (w), 1254 (s), 1130 (s), 1076 (s), 1004 (m) cm⁻¹; MS (Cl, isobutane) m/z (relative intensity, %): 518 (M, 11), 517 (M⁺ + H, 25), 459 (12), 387 (10), 386 (34), 385 (100), 254 (11), 253 (56); Anal. Calcd for C₃₀H₅₂O₁₃Si₂ (516.90): C, 69.71; H, 10.14. Found: C, 69.44; H, 10.24.

(--)-(3aS,4S,5R,6aS)-5-(tert-Butyl-dimethyl-silyloxy)-4-[(3S)-tert-butyl-dimethyl-silyloxy)-(4S)-methyl-nona-1,6-diynyl]-hexahydropentalen-2-ylidene)ethanol (E-44): To a solution of ester E-6 (1.3 g, 1.71 mmol, 90% de) in THF (18 mL) was added a solution of DIBALH in hexanes (1 M, 5.1 mL, 5.1 mmol) at 0 °C. Then the mixture was allowed to warm to ambient temperature and stirred for 2 h. The mixture was diluted with
Et₂O (100 mL) and aqueous NH₄Cl was added (30 mL), whereby a gel was formed. After the addition of pentane (30 mL) the aqueous phase was separated and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. HPLC (Merck Lichrospher, 250 mm × 20 mm, hexanes/EtOAc, 3:1; UV and RI detector) afforded the allylic alcohol \( E-44 \) (790 mg, 84%) with ≥99% de as a colorless oil. \( R_f \) 0.17 (hexanes/Et₂O, 6:4); \( [\alpha]_D \) +23.5 (c 1.0, CDCI₃); \(^1\)H NMR (400 MHz, C₆D₆): \( \delta \) 0.12 (s, 3 H, SiMe), 0.19 (s, 3 H; SiMe), 0.20 (3 H, SiMe), 0.27 (s, 3 H, SiMe), 0.98 (s, 9 H, t-Bu), 1.01 (t, 3 H, C≡CCH₂Me), 1.02 (s, 9 H, t-Bu), 1.08 (brs, 1 H, C=CHCH₂OH), 1.15–1.25 (m, 1 H), 1.27 (d, \( J = 6.6 \) Hz, 3 H, CHMe), 1.90–2.51 (m, 13 H), 3.93 (d, \( J = 6.6 \) Hz, 2 H, C≡CCH₂OH), 3.96–4.03 (m, 1 H, CHOSi-CHC≡C), 4.53 (dd, \( J = 6.3, J = 1.0 \) Hz, 1 H, C≡CCHOSi), 5.42 (m, 1 H, C≡CH); \(^{13}\)C NMR (100 MHz, C₆D₆): \( \delta \) –4.90 (d), –4.43 (d), –4.32 (d), –4.01 (d), 12.75 (u), 14.55 (d), 15.57 (d), 18.24 (u), 18.41 (u), 22.44 (u), 26.02 (d), 26.04 (d), 35.51 (u), 38.39 (d), 39.04 (u), 40.71 (d), 42.39 (u), 45.47 (d), 46.93 (d), 60.34 (u), 66.83 (d), 77.72 (u), 78.94 (d), 81.87 (u), 83.03 (u), 87.49 (u), 122.39 (d), 143.72 (u); IR (neat): ν 3337 (m), 2955 (s), 2929 (s), 2885 (s), 2856 (s), 1472 (m), 1463 (m), 1378 (w), 1360 (m), 1322 (w), 1255 (s), 1135 (s), 1112 (s), 1073 (s), 1025 (m), 1006 (m), 939 (w), 905 (m), 837 (s), 815 (m) cm⁻¹; MS (Cl, isobutane) m/z (relative intensity, %): 545 (M⁺ + H, 6), 527 (11), 413 (28), 397 (14), 396 (36), 395 (100), 281 (13), 264 (10), 263 (44), 133 (10).

\( (+)-(E,3aS,4S,5R,6aS)\)-[5-Hydroxy-4-((3S,4S)-3-hydroxy-4-methyl-nona-1,6-diyanyl)-hexahydropentalen-2-yliden]-ethoxy]-acetic acid tert-butyl ester (45): To a solution of alcohol \( E-44 \) (550 mg, 1 mmol) in CH₂Cl₂ (6 mL) were added successively NBU₄HSO₄ (300 mg), BrCH₂CO₂t-Bu (500 mg, 2.56 mmol) and aqueous NaOH (50%, 6 mL). The resulting emulsion was stirred for 2.5 h and a further portion of BrCH₂CO₂t-Bu (500 mg, 2.56 mmol) was added. After the mixture was stirred for 1.5 h, ice (30 g) was added and the
aqueous phase was extracted with CH₂Cl₂ (6 × 20 mL). The combined organic phases were
dried (MgSO₄) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 3:1)
afforded a mixture of ester 45 and BrCH₂COO-t-Bu. This mixture was dissolved in THF (15
mL) and NBU₄F (1.5 g, 5.7 mmol) was added. After the mixture was stirred for 16 h at
ambient temperature, it was diluted with Et₂O (50 mL) and washed with aqueous NaCl (50
mL). The aqueous phase was extracted with Et₂O (6 × 20 mL), and the combined organic
phases were dried (MgSO₄) and concentrated in vacuo. Column chromatography
(hexanes/EtOAc, 1:2) afforded ester 45 (395 mg, 90%) with ≥99% de as a colorless oil. Rf
0.36 (hexanes/EtOAc, 1:2); [α]D +81.4 (c 0.76, THF); ¹H NMR (400 MHz, C₆D₆): δ 1.00 (t, J
= 7.4 Hz, 3 H, C=CH₂Me), 1.20–1.30 (m, 1 H), 1.32 (d, J = 6.6 Hz, 3 H, CHMe), 1.37 (s, 9
H, t-Bu), 1.95–2.45 (m, 12 H), 2.50–2.60 (m, 1 H), 3.86 (m, 2 H, OCH₂COO-t-Bu), 3.90–4.09
(m, 5 H), 4.59 (m, 1 H, C=CH₂O), 5.50 (m, 1 H, C=CH), ¹³C NMR (100 MHz, C₆D₆): δ
12.80 (u), 14.53 (d), 15.49 (d), 22.70 (u), 28.05 (d), 35.68 (u), 37.74 (d), 38.94 (u), 40.23 (d),
41.30 (u), 45.33 (d), 46.20 (d), 66.10 (d), 67.49 (u), 68.51 (u), 78.02 (u) 78.33 (d), 80.82 (u),
81.72 (u), 83.04 (u), 87.78 (u), 118.61 (d), 146.82 (u), 169.79 (u). IR (neat): ν 3410 (s), 2973
(s), 2279 (w), 1746 (s), 1456 (m), 1430 (m), 1393 (w), 1369 (s), 1322 (m), 1301 (w), 1227 (s),
1162 (s), 1122 (s), 1022 (m), 940 (m), 845 (m), 813 (w) cm⁻¹; MS (Cl, NH₃) m/z (relative
intensity, %): 450 (29), 449 (27), 448 (M⁺ + NH₃, 100), 446 (10), 318 (15), 316 (32), 298
(11), 150 (82), 148 (41), 147 (27); Anal. Calcd for C₂₆H₃₈O₅ (430.58): C, 72.53; H, 8.90.
Found: C, 72.57; H, 8.83.

(−)-(3aS,S,R,6S,6aS)-5-(tert-Butyl-dimethyl-silanyloxy)-4-[(3S,4S)-tert-butyl-
dimethyl-silanyloxy)-4-methyl-nona-1,6-diynyl]-1,3a,4,5,6,6a-hexahydro-pentalen-2-yl-
ethanol (48): To a solution of ester 47 (450 mg, 0.59 mmol) in THF (10 mL) was added LAH
(30 mg, 0.79 mmol) at −20 °C. After the mixture was stirred for 2 h, it was allowed to warm
to ambient temperature. Then a further portion of LAH (20 mg, 0.52 mmol) was added and
stirring was continued for 4 h. Then EtOAc (1 mL) was added, and after stirring the mixture for 30 min aqueous NH₄Cl (10 mL) was added. The mixture was diluted with Et₂O and the slurry was filtered. The aqueous phase was separated and extracted with Et₂O (30 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. HPLC (Merck Lichrospher, 250 mm × 20 mm, hexanes/EtOAc, 4:1; UV and RI detector) gave alcohol 48 (192 mg, 59%) with ≥99% de (¹H NMR) as a colorless oil. [α]₀D −14.6 (c 1.8, CDCl₃); ¹H NMR (400 MHz, C₆D₆): δ 0.11 (s, 3 H, SiMe), 0.19 (s, 3 H, SiMe), 0.20 (s, 3 H, SiMe), 0.28 (s, 3 H, SiMe), 1.00 (s, 9 H, t-Bu), 1.01 (t, J = 7.7 Hz, 3 H, C≡CCH₂Me), 1.02 (s, 9 H, t-Bu), 1.26 (d, J = 6.8 Hz, 3 H, CHMe), 1.30 (m, 1 H,), 1.39 (s, 1 H, OH), 2.00–2.18 (m, 7 H), 2.36–2.56 (m, 5 H), 2.83 (m, 1 H), 3.46 (t, J = 6.6 Hz, 2 H, C=CHCH₂OH), 3.97 (m, 1 H, CH(OSi)-CH-C=C), 4.52 (dd, J = 6.3, J = 1.3 Hz, 1 H, C≡CCHOSi), 5.18 (m, 1 H, CH=C); ¹³C NMR (100 MHz, C₆D₆): δ −4.90 (d), −4.40 (d), −4.35 (d), −4.01 (d), 12.74 (u), 14.55 (d), 15.55 (d), 18.24 (u), 18.42 (u), 22.42 (u), 26.03 (d), 26.05 (d), 34.47 (u), 40.46 (u), 40.72 (d), 40.76 (u), 45.91 (d), 46.16 (d), 46.48 (d), 60.59 (u), 66.83 (d), 77.75 (u), 78.42 (d), 81.74 (u), 83.00 (u), 87.54 (u), 129.67 (d), 138.35 (u); IR (C₆D₆, measured against C₆D₆): ν 3356 (w), 2955 (s), 2931 (s), 2887 (s), 2857 (s), 1471 (m), 1377 (w), 1360 (w), 1323 (w), 1253 (s), 1118 (s), 1073 (s), 1006 (m) cm⁻¹; MS (Cl, Isobutan) m/z (relative intensity, %): 545 (M⁺ + H, 14), 487 (13), 469 (15), 414 (28), 413 (100), 281 (75), 133 (35).

(1'S,2'R,3a'R,5'S,6a'S)-1-[5'-(tert-Butyl-diphenyl-silanyloxy)-2'-(triethyl-silanyloxy)-octahydro-pentalen-1'-yl]-4(4R)-methyl-nona-1,6-diy-3-one (ent-8a'): To a solution of alkyne 10a (100 mg, 0.19 mmol) in THF (3 mL) at −78 °C was added nBuLi (1.6 M in hexanes, 0.12 mL, 1.9 mmol). The mixture was warmed to room temperature for 10 min, cooled to −78 °C and then transferred to a −19 °C cold stirred solution of amide ent-9a (560 mg, 3.1 mmol) in THF (10 mL) by means of a double-tipped ended needle. After the mixture
was stirred for 3 h at −19 °C, saturated aqueous NH₄Cl (0.2 mL) and water (0.5 mL) were added. Subsequently the mixture was warmed to room temperature, and the aqueous phase was separated and extracted with Et₂O (3 × 3 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography afforded ketone ent-8a′ (105 mg, 85%) with 94% de: ¹H NMR and ¹³C NMR were identical to those of 8a except small differences in the chemical shifts of the signals of the methyl groups (δ (CH₂Me) 0.960, δ (CHMe) 1.266 (ent-8a)); δ (CH₂Me) 0.958, δ (CHMe) 1.275 (ent-8a′)). The signals for each diastereomer were unambiguously assigned by recording a ¹H NMR spectrum of an approximately 1:1 mixture of 8a and ent-8a′. This allowed for the identification of the presence of 3% of ent-8a in ent-8a′ as well as of 3% of 8a′ in 8a. The NMR spectra of ent-8a′ and 8a were resolution enhanced¹¹ (parameter: LB: 0.5 Hz, SB: 2.1 s, SSB: −1.7 s).
