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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'**.

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Scheme S10. Coupling of the Bicyclic Building Block *ent*-10a With the ω -Side Chain Building Block **9a** ($R^1 = \text{Si}t\text{-BuPh}_2$)^a

^a Reagents and conditions: (I) *ent*-10a, *n*-BuLi, THF, $-78\text{ }^\circ\text{C} \rightarrow 0\text{ }^\circ\text{C}$. (II) **9a**, $-19\text{ }^\circ\text{C}$. (III) Catecholborane, **37**, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$. (IV) Aqueous HCl, THF, rt. (V) PhCOCl, pyridine, $0\text{ }^\circ\text{C} \rightarrow \text{rt}$. (VI) NBu_4F , THF, rt. (VII) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , $-60\text{ }^\circ\text{C}$. (VIII) NaOH, MeOH, rt.

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Scheme S11. Coupling of the Bicyclic Building Block **10a** (94% ee) with the ω -Side Chain Building Block *ent*-**9a** (>99% ee) (R = *Sit*-BuPh₂)

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Scheme S12. Coupling of the Bicyclic Building Block *ent*-10b With the ω -Side Chain Building Block 9a ($R^1 = \text{Si}t\text{-BuMe}_2$)^a

^a Reagents and conditions: (I) *ent*-10b, *n*-BuLi, THF, -78 °C → rt. (II) 9a, THF, -19 °C. (III) Catecholborane, 37, CH₂Cl₂, -78 °C, HPLC. (IV) Acetone, TsOH, H₂O, rt. (V) *t*-BuMe₂SiCl, imidazole, DMF, rt.

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Scheme S13. Attachment of the α -Side Chain to Ketone **7b'** via Reaction With the Chiral Phosphonate **43** (R = Sit-BuMe₂)^a

^a Reagents and conditions: (I) THF, first 6 d at $-62\text{ }^{\circ}\text{C}$ then 15 h at $-30\text{ }^{\circ}\text{C}$ and finally 30 min at rt. (II) DIBALH, THF, $0\text{ }^{\circ}\text{C}$, HPLC.

(+)-(2*S*,3*aS*,6*aS*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-5-(trimethyl-silanyloxy)-

1,2,3,3*a*,4,6*a*-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 $-78\text{ }^{\circ}\text{C}$. 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 $-105\text{ }^{\circ}\text{C}$ 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 $-105\text{ }^{\circ}\text{C}$. Then Me_3SiCl (1 mL, 7.8 mmol) was added, and the solution was stirred for 30 min at $-105\text{ }^{\circ}\text{C}$. Subsequently the mixture was warmed to $-78\text{ }^{\circ}\text{C}$, and after stirring the mixture for 30 min saturated aqueous NaHCO_3 (3 mL) was added. Then the mixture was warmed to ambient temperature, and the organic phase was dried (MgSO_4) for 30 min and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 10:1; 30 cm $\times$ 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); $[\alpha]_D +6.7$ (c 3.9, THF); ^1H NMR (400 MHz, C_6D_6): 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); ^{13}C NMR (100 MHz, C_6D_6): 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 $\text{C}_{27}\text{H}_{38}\text{O}_2\text{Si}_2$ (450.76): C, 71.94; H, 8.50. Found: C, 71.86; H, 8.64.

(–)-(1*R*,2*R*,3*aR*,5*S*,6*aS*)-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*t*-BuPh₂), 4.40 (dd, *J* = 6.5, *J* = 1.5 Hz, 1 H, CHOH), 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.

(–)-(1*R*,2*R*,3*aR*,5*S*,6*aS*)-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. $[\alpha]_D -18.2$ (*c* 1.9, Et₂O); ¹H NMR (400 MHz, C₆D₆): δ 0.77 (dq, *J* = 7.5, *J* = 2.5 Hz, 6 H, SiCH₂Me), 1.10 (t, *J* = 7.5 Hz, 9 H, SiCH₂Me), 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, CHOSi*t*-BuPh₂), 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 (CI, 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. Calcd for C₃₃H₄₉Cl₃O₅SSi₂ (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. *R*_f 0.62 (hexanes/EtOAc, 3:1); $[\alpha]_D -0.59$ (*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* =

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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_6D_6): δ -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): ν 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 $\text{C}_{20}\text{H}_{35}\text{NO}_3\text{Si}$ (365.58): C, 65.71; H, 9.65; N 3.83, Found: C, 65.41; H, 10.02; N, 4.11.

(-)-(3a*S*,4*S*,5*R*,6a*R*)-5-(*tert*-Butyl-dimethyl-silyloxy)-[4-ethynyl-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2'(1'*H*)-pentalene] (10b): *From aldehyde 24:* Preparation of $[\text{Ph}_3\text{PCHBr}_2]\text{Br}$: To a solution of PPh_3 (158 g, 0.6 mol) in dry CH_2Cl_2 (800 mL) was added within 10 min a solution of CBr_4 (100 g, 0.3 mol) in CH_2Cl_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 $[\text{Ph}_3\text{PCHBr}_2]\text{Br}$ (115 g, 70%) still contained some MeOH, which did, however, not affect its subsequent use. ^1H NMR (400 MHz, CDCl_3) δ 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) δ 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): δ 33.92; IR (KBr): ν 3426 (w), 3053 (w), 3018 (w), 2960 (w), 2807 (s), 1584 (w), 1484 (m), 1436 (s), 1338 (w),

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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 $[\text{Ph}_3\text{PCHBr}_2]\text{Br}$ (2.06 g, 4 mmol) in THF (25 mL) was treated with $\text{KO}^t\text{-Bu}$ (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 $\text{KO}^t\text{-Bu}$ (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_2O (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); ^1H NMR (500 MHz, C_6D_6): δ 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, $\text{C}\equiv\text{CH}$), 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, $\text{CHC}\equiv\text{CH}$), 3.09–3.17 (m, 2 H), 3.22 (s, 2 H), 4.02 (m, 1 H, CHOSi); ^{13}C NMR (100 MHz, C_6D_6): δ -4.53 (d), -4.27 (d), 18.30 (u), 22.26 (d), 22.56 (d), 26.04 (d), 29.80 (u), 35.70 (d), 37.58 (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): ν 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

(15), 105 (12). Anal. Calcd for $C_{21}H_{36}O_3Si$ (364.59): C, 69.18; H, 9.95. Found: C, 69.11; H, 9.97.

(-)-4*R*-Benzyl-3-(2*S*-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 $-78\text{ }^\circ\text{C}$. After the mixture was stirred for 60 min at $-78\text{ }^\circ\text{C}$, iodide **32** (32.0 g, 165 mmol) was added within 40 min at $-78\text{ }^\circ\text{C}$. Then the mixture was stirred for 60 min, and acetic acid (10 mL) was added at $-78\text{ }^\circ\text{C}$. 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_2O ($3 \times 100\text{ mL}$). 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 (1H NMR: δ ($CHMe$) 1.258 (**33**); δ ($CHMe$) 1.303 (*epi*-**33**)) as a colorless oil which solidified at $-26\text{ }^\circ\text{C}$ within days. Mp $40\text{ }^\circ\text{C}$; R_f 0.34 (hexanes/ $EtOAc$, 3:1); $[\alpha]_D -52.7$ (c 2.0, $CDCl_3$); 1H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, $J = 7.5\text{ Hz}$, 3 H, CH_2Me), 1.26 (d, $J = 6.5\text{ Hz}$, 3 H, $CHMe$), 2.15 (m, 2 H, CH_2Me), 2.42–2.60 (m, 2 H, $CH_2C\equiv CEt$), 2.80 (dd, $J = 9.5, J = 13.5\text{ Hz}$, 1 H, CH_2Ph), 3.29 (dd, $J = 3.2, J = 13.5\text{ Hz}$, 1 H, CH_2Ph), 3.91 (m, 1 H, $CHMe$), 4.19 (m, 2 H, CH_2O), 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

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(55), 93 (10), 91 (28); Anal. Calcd for $C_{18}H_{21}NO_3$ (299.36): C, 72.22; H, 7.07; N 4.68. Found: C, 71.94; H, 7.41; N 4.60.

(+)-(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 (4*R*)-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, $CHCl_3$); 1H NMR (400 MHz, C_6D_6): δ 0.98 (t, J = 7.4 Hz, 3 H, $C\equiv CCH_2Me$), 1.02 (t, J = 7.1 Hz, 3 H, OCH_2Me), 1.19 (d, J = 7.0 Hz, 3 H, $CHMe$), 1.97–2.04 (m, 2 H, $C\equiv CCH_2Me$), 2.27–2.36 (m, 1 H, $CH_2C\equiv CEt$), 2.44–2.55 (m, 2 H, $CH_2C\equiv CEt$, $CHMe$), 3.95–4.03 (m, 2 H, OCH_2Me); ^{13}C NMR (100 MHz, C_6D_6): δ 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): ν 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. Calcd 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

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syringe pump. After the mixture was stirred for 30 min at -19°C , aqueous NH_4Cl (20 mL) was added. The mixture was warmed to ambient temperature and diluted with Et_2O (50 mL). Then water was added until two clear phases were formed. The aqueous phase was extracted with Et_2O (50 mL), and the combined organic phases were dried (MgSO_4) and concentrated in vacuo. Column chromatography (pentanes/ Et_2O , 1:4) afforded amide **9a** (1.17 g, 92%) with 97% ee (GC: Macherey-Nagel Hydro-Dex- β -Cyclodextrin-6-TBDM, 25 m, t_{R} (*ent*-**9a**) = 136.4 min; t_{R} (**9a**) = 136.59 min) as a colorless liquid. HPLC (Ciralcel AD, 250 mm $\times$ 50 mm, *i*-PrOH/hexanes 5:95, UV: 254 nm) afforded amide **9a** with $\geq 99\%$ ee in 90% yield. R_f 0.19 (hexanes/ EtOAc , 3:1); $[\alpha]_{\text{D}} +15.5$ (c 4.5, CDCl_3); ^1H NMR (400 MHz, CDCl_3): δ 1.10 (t, J = 7.4 Hz, 3 H, $\text{C}\equiv\text{CCH}_2\text{Me}$), 1.19 (d, J = 6.9 Hz, 3 H, CHMe), 2.10–2.19 (m, 2 H, $\text{C}\equiv\text{CCH}_2\text{Me}$), 2.20–2.28 (m, 1 H, $\text{CH}_2\text{C}\equiv\text{CEt}$), 2.40–2.52 (m, 1 H, $\text{CH}_2\text{C}\equiv\text{CEt}$), 3.00–3.10 (brm, 1 H, CHMe), 3.20 (s, 3 H, NMe), 3.73 (s, 3 H, OMe); ^{13}C NMR (100 MHz, CDCl_3): 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 $\text{C}_{10}\text{H}_{17}\text{NO}_2$ (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 $\text{HN}(i\text{-Pr})_2$ (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. *R*_f 0.43 (hexanes/EtOAc, 3:1); ¹H NMR (400 MHz, CDCl₃): δ 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): δ 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 calcd 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.

(±)-(2*S*)-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).

(-)-(1*S*,2*R*,3*aR*,5*S*,6*aS*)-1-[5-(*tert*-Butyl-diphenyl-silanyloxy)-2-(triethyl-silanyl-oxy)-octahydro-pentalen-1-yl]-4(*S*)-methyl-nona-1,6-diyn-3(*S*)-ol (**38**): To a solution of ketone **8a** (150 mg, 0.23 mmol) in CH₂Cl₂ (2 mL) was added oxazaborolidine **37** (0.86 M solution in C₆D₆, 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 CH₂Cl₂) 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/Et₂O, 1:1) of the mixture afforded alcohol **38** (132 mg, 88%) with 94% de as a colorless oil. *R*_f 0.68 (hexanes/Et₂O, 1:1); [α]_D -6.1 (*c* 2.7, THF); ¹H NMR (300 MHz, C₆D₆): δ 0.65–0.76 (m, 6 H, SiCH₂Me), 0.98 (t, *J* = 7.4 Hz, 3 H, C≡CCH₂Me), 1.10 (t, *J* = 7.9 Hz, 9 H, SiCH₂Me), 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, CHOSiEt₃-CHC≡C), 4.03–4.12 (m, 1 H, CHOSiEt₃), 4.21–4.29 (m, 1 H, CHOSi*t*-BuPh₂), 4.39–4.45 (m, 1 H, C≡CCHOH), 7.22–7.28 (m, 6 H), 7.74–7.80 (m, 4 H); ¹³C NMR (75 MHz, C₆D₆): 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), 1020 (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 C₄₀H₅₈O₃Si₂ (643.06): C, 74.71; H, 9.09. Found: C, 74.66; H, 9.06.

(–)-(1*S*,2*R*,3*aS*,5*S*,6*aS*)-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≡CCHOCOPh) 6.02 (**40**); δ (C≡CCHOCOPh) 5.95 (**40'**)) as a colorless oil. *R*_f 0.42 (Et₂O); [α]_D –65.14 (*c* 0.35, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆): 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) 3.31 (dt, *J* = 8.8, *J* = 1.9 Hz, 1 H, CHMe), 3.97 (m, 1 H, CHOH), 5.44 (m, 1 H, CHOCOPh), 6.00 (dd, *J* = 5.5, *J* = 1.9 Hz, 1 H, C≡CCHOCOPh), 7.00–7.20 (m, 6 H), 8.04–8.16 (m, 4 H); ¹³C NMR (100 MHz, C₆D₆): 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 (CI, 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.

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(-)-(1*S*,2*R*,3*aR*,6*aS*)-Benzoic acid 1-(3(*S*)-benzoyloxy-4(*S*)-methyl-nona-1,6-diynyl)-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. *R*_f 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 (CI, 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.

(-)-(3*aS*,4*S*,5*R*,6*aR*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-[4-((3*S*,4*S*)-3-*tert*-butyl dimethyl--silanyloxy-4-methyl-nona-1,6-diynyl)-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 bissilyl ether **7b** (910 mg, 1.76 mmol, 95%) with ≥99% de (¹H NMR) as a colorless oil. R_f 0.54 (hexanes/EtOAc, 3:1), [α]_D -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≡CCH₂Me), 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-CHC≡C), 4.48 (dd, *J* = 6.3, *J* = 1.4 Hz, 1 H, C≡CCHOSi); 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 (CI, 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 C₃₀H₅₂O₃Si₂ (516.90): C, 69.71; H, 10.14. Found: C, 69.44; H, 10.24.

(-)-(3a*S*,4*S*,5*R*,6a*S*)-{5-(*tert*-Butyl-dimethyl-silanyloxy)-4-[(3*S*)-*tert*-butyl-dimethyl-silanyloxy)-(4*S*)-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

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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); [α]_D +23.5 (*c* 1.0, CDCl₃); ¹H NMR (400 MHz, C₆D₆): δ 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); ¹³C NMR (100 MHz, C₆D₆): δ -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 (CI, 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,3a*S*,4*S*,5*R*,6a*S*)-{[5-Hydroxy-4-((3*S*,4*S*)-3-hydroxy-4-methyl-nona-1,6-diynyl)-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), BrCH₂CO₂*t*-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 BrCH₂COO*t*-Bu (500 mg, 2.56 mmol) was added. After the mixture was stirred for 1.5 h, ice (30 g) was added and the

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aqueous phase was extracted with CH_2Cl_2 (6×20 mL). The combined organic phases were dried (MgSO_4) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 3:1) afforded a mixture of ester **45** and $\text{BrCH}_2\text{COO}t\text{-Bu}$. This mixture was dissolved in THF (15 mL) and NBu_4F (1.5 g, 5.7 mmol) was added. After the mixture was stirred for 16 h at ambient temperature, it was diluted with Et_2O (50 mL) and washed with aqueous NaCl (50 mL). The aqueous phase was extracted with Et_2O (6×20 mL), and the combined organic phases were dried (MgSO_4) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 1:2) afforded ester **45** (395 mg, 90%) with $\geq 99\%$ de as a colorless oil. R_f 0.36 (hexanes/EtOAc, 1:2); $[\alpha]_D +81.4$ (c 0.76, THF); ^1H NMR (400 MHz, C_6D_6): δ 1.00 (t, $J = 7.4$ Hz, 3 H, $\text{C}\equiv\text{CCH}_2\text{Me}$), 1.20–1.30 (m, 1 H), 1.32 (d, $J = 6.6$ Hz, 3 H, CHMe), 1.37 (s, 9 H, $t\text{-Bu}$), 1.95–2.45 (m, 12 H), 2.50–2.60 (m, 1 H), 3.86 (m, 2 H, $\text{OCH}_2\text{COO}t\text{-Bu}$), 3.90–4.09 (m, 5 H), 4.59 (m, 1 H, $\text{C}\equiv\text{CCHOH}$), 5.50 (m, 1 H, $\text{C}=\text{CH}$); ^{13}C NMR (100 MHz, C_6D_6): 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 (CI, NH_3) m/z (relative intensity, %): 450 (29), 449 (27), 448 ($\text{M}^+ + \text{NH}_4$, 100), 446 (10), 318 (15), 316 (32), 298 (11), 150 (82), 148 (41), 147 (27); Anal. Calcd for $\text{C}_{26}\text{H}_{38}\text{O}_5$ (430.58): C, 72.53; H, 8.90. Found: C, 72.57; H, 8.83.

(–)-(3a*S*,5*R*,6*S*,6a*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-[(3*S*,4*S*)-*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

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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]_D -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 (CI, 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*R*)-methyl-nona-1,6-diyn-3-one (*ent*-8a'**):** To a solution of alkyne **10a** (100 mg, 0.19 mmol) in THF (3 mL) at -78 °C was added *n*BuLi (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 $-19\text{ }^{\circ}\text{C}$, saturated aqueous NH_4Cl (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 Et_2O ($3 \times 3\text{ mL}$). The combined organic phases were dried (MgSO_4) and concentrated in vacuo. Purification by column chromatography afforded ketone *ent-8a'* (105 mg, 85%) with 94% de: ^1H NMR and ^{13}C NMR were identical to those of **8a** except small differences in the chemical shifts of the signals of the methyl groups ($\delta(\text{CH}_2\text{Me})$ 0.960, $\delta(\text{CHMe})$ 1.266 (*ent-8a*); $\delta(\text{CH}_2\text{Me})$ 0.958, $\delta(\text{CHMe})$ 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 enhanced^[1] (parameter: LB: 0.5 Hz, SB: 2.1 s, SSB: -1.7 s).

^[1] Ernst, R. R., Bodenhausen, G., Wokaun, A, *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Claredon Press: Oxford, 1987.

plot at 160 Hz/cm : 0.40 ppm/cm

12.6 12.0 11.4 10.8 ppm

LERM 232D a2021408.g/h inova400/gas Feb 14 2002 (CD2Cl2)

plot at 120 Hz/cm : 0.40 ppm/cm

12.6 12.0 11.4 10.8 ppm

LERM DIOLK a2090931.g/h mercury300/gsw5 Sep 9 2002 (C6D6)

LERM CL2 a2101431.g/h inova400/gas Oct 14 2002 (CDCI3)

12.6 12.0 11.4 10.8 ppm

p101

LERM CL2 a2101431.g/c inova400/gas Oct 14 2002 (CDCl3)

S32

plot at 160 Hz/cm : 0.40 ppm/cm

LERM ML225ALD a2012948.g/h inova400/gas Jan 30 2002 (THF)

12.6 12.0 11.4 10.8 ppm

plot at 806 Hz/cm : 8.01 ppm/cm

LERM ML225ALD a2012948.g/c inova400/gas Jan 30 2002 (THF)

Plot at 805 MHz/cm : 8.00 ppm/cm

LERM 225VS a2010813.g/c inova400/gas Jan 8 2002 (CDCI3)

APT: C, CH2

CH, CH3

DEPT: CH

S38

Plot at 160 Hz/cm : 0.40 ppm/cm

LERM F-LD13 a2060323.g/h inova400/gas Jun 3 2002 (CDCl3)

12.6 12.0 11.4 10.8 ppm

plot at 120 Hz/cm : 0.40 ppm/cm

12.6 12.0 11.4 10.8 ppm

LERM ML-DIOL a2082389.g/h mercury300/gsw5 Aug 28 2002 (C6D6)

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