SUPPORTING INFORMATION

Total Synthesis of Amphidinolide X

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General. All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine, DMF (CaH_2), MeOH (Mg), hexane, cyclohexane, toluene, benzene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: Spectra were recorded on a DPX 300, AV 400 or DMX 600 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in ppm relative to residual solvent peaks, coupling constants (*J*) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95, Bruker APEX III FT-ICR-MS (7 T magnet). Melting points: Büchi melting point apparatus (uncorrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Fluka, Aldrich) were used as received unless stated otherwise.

[(2*S*,3*S*)-3-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)oxiran-2-yl]methanol (3). L(+)-Diethyl tartrate (L(+)-DET, 312 mg, 1.5 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (359 mg, 1.3 mmol) were added to a suspension of powdered 4Å molecular sieves (100 mg/mmol) in CH_2Cl_2 (32 mL) at –20 °C. the mixture was stirred for 30 min at that temperature before a solution of anhydrous *t*-BuOOH in decane (5 M, 5.0 mL, 25.0 mmol) was added dropwise. After stirring for another 30 min at –20 °C, a solution of allylic alcohol **2** (4.3 g, 12.5 mmol) in CH_2Cl_2 (24 mL) was added slowly via syringe and the resulting mixture was stirred for 18 h at -20 °C. For work-up, the reaction was quenched with a solution of citric acid (2.0 g) and $FeSO_4$ (6.6 g) in water (20 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted three times with methyl *tert*-butylether. The combined organic layers were treated with 30% NaOH saturated with NaCl (50 mL) and stirred vigorously for 30 min at 0 °C. The organic layer was

separated and the aqueous layer was again repeatedly extracted with methyl *tert*-butylether. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography of the residue (hexanes/ethyl acetate, 5/1) provided epoxide **3** as a colorless oil (4.4 g, 97%). The enantiomeric excess (ee = 83%) was determined by HPLC by comparison with the racemate (250 mm Chiralcel OD-H, Ø 4.6 mm, n-heptane/2-propanol = 90/10, 0.5 mL/min, 3.2 MPa, 298 K, UV, 220 nm). $[\alpha]_D^{20}$ = –16.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (4H, m), 7.46-7.37 (6H, m), 3.91 (1H, ddd, *J* = 12.5, 5.1, 2.5 Hz), 3.83 (1H, t, *J* = 6.4 Hz), 3.81 (1H, t, *J* = 5.7 Hz), 3.62 (1H, ddd, *J* = 12.5, 6.9, 4.5 Hz), 3.13 (1H, dt, *J* = 5.7, 2.3 Hz), 2.98 (1H, dt, *J* = 4.5, 2.5 Hz), 1.82 (2H, q, *J* = 6.0 Hz), 1.74 (1H, t, *J* = 6.3 Hz), 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.7, 129.8, 127.8, 61.8, 60.9, 58.7, 53.9, 35.0, 27.0, 19.3. IR: 3433, 3071, 2957, 2930, 2857, 1472, 1428, 1111, 823, 739, 703 cm^{-1}. MS (EI) *m/z* (rel. intensity): 299 ([M-^{t}Bu]$^+$, <0.2), 269 (32), 225 (9), 199 (100). HRMS (ESI): *calcd.* for ($C_{21}H_{28}O_3Si$+Na): 379.1705, *found* 379.1701 (M+Na). Anal. *calcd.* for $C_{21}H_{28}O_3Si$: C 70.74, H 7.92, *found* C 70.67, H 8.04.

***tert*-Butyl{2-[(2*S*,3*S*)-3-ethynyloxiran-2-yl]ethoxy}diphenylsilane (4).** Oxalyl chloride (2.3 mL, 25.9 mmol) was added dropwise to a solution of DMSO (2.8 mL, 38.9 mmol) in CH_2Cl_2 (30 mL) at –78 °C. A solution of the epoxy alcohol **3** (4.6 g, 13.0 mmol) in CH_2Cl_2 (30 mL) was then introduced and the mixture was stirred for 1 h at –78 °C before it was treated with Et_3N (7.2 mL, 51.9 mmol) and allowed to warm to ambient temperature. After stirring for an additional hour, the reaction was quenched with brine (60 mL) and the organic layer was successively washed with sat. $NaHCO_3$ (aq.), water, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude aldehyde (4.6 g), which was used without further purification.

Dry K_2CO_3 (3.6 g, 26.0 mmol) was added to a solution of the aldehyde in MeOH (200 mL), followed by the slow addition of dimethyl-1-diazo-2-oxopropyl phosphonate (3.0 g, 15.6 mmol) at 0 °C. The mixture was stirred for 6 h at that temperature before it was brought to ambient temperature and stirred for additional 2 h. For work up, the mixture was diluted with methyl *tert*-butylether (100 mL) and quenched with aq. sat. $NaHCO_3$ (150 mL). The aqueous layer was repeatedly extracted with methyl *tert*-butylether and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate, 20/1) of the residue gave acetylene **4** as a colorless oil (3.0 g, 67% over both steps). $[\alpha]_D^{20}$ = +1.1 (c = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (4H, m), 7.46-7.37 (6H, m), 3.82-3.78 (2H, m), 3.30 (1H, dt, *J* = 5.7, 2.1 Hz), 3.19 (1H, t, *J* = 1.8 Hz), 2.33 (1H, d, *J* = 2.6 Hz), 1.83-1.76 (2H, m), 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.6, 129.9, 127.9, 80.7, 72.0, 60.5, 58.4, 45.3, 35.0, 27.0, 19.3. IR: 3288, 3071, 2957, 2931, 2858, 2126, 1472, 1428, 1112, 823, 703 cm^{-1}. MS (EI) *m/z* (rel. intensity): 293 ([M-^{t}Bu]$^+$, 53), 263 (68), 249 (22), 237 (10), 225 (30), 221 (100). HRMS (CI): *calcd.* for ($C_{22}H_{26}O_2Si$+H): 351.1780, *found* 351.1779 (MH^+). Anal. *calcd.* for $C_{22}H_{26}O_2Si$: C 75.38, H 7.48, *found* C 75.48, H 7.39.

***tert*-Butyl(diphenyl){2-[(2*S*,3*S*)-3-prop-1-ynyloxiran-2-yl]ethoxy}silane (5).** Solid LiHMDS (1.8 g, 10.8 mmol) was added in portions over 5 min to a solution of compound **4** (3.15 g, 9.0 mmol) in THF (230 mL) at –78 °C. The resulting mixture was stirred for 1 h at –78 °C before it was treated with MeOTf (1.2 mL, 10.8 mmol) and allowed to reach –20 °C over 1 h. The reaction was quenched at that temperature with sat. $NaHCO_3$ (aq.) and poured into a mixture of methyl *tert*-butylether and aq. sat. $NaHCO_3$. The aqueous layer was repeatedly extracted with methyl *tert*-butylether, the combined organic layers were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 20/1) to give product **5** as a colorless oil (3.1 g, 95%). $[\alpha]_D^{20}$ = –2.0 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (4H, m), 7.46-7.37 (6H, m), 3.81-3.78 (2H, m), 3.23 (1H, dt, *J* = 5.7, 2.2 Hz), 3.15-3.14 (1H, m), 1.86 (3H, d, *J* = 1.7 Hz), 1.79-1.75 (2H, m), 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.7, 129.8, 127.8, 80.5, 76.2, 60.6, 58.5, 45.2, 35.1, 27.0, 19.3, 3.8. IR: 3071, 2957, 2930, 2857, 2244, 1472, 1428, 1112, 823, 702 cm^{-1}. MS (EI) *m/z* (rel. intensity): 307 ([M-^{t}Bu]$^+$, 100). HRMS (CI): *calcd.* for ($C_{23}H_{28}O_2Si$+H): 365.1937, *found* 365.1938 (MH^+). Anal. *calcd.* for $C_{23}H_{28}O_2Si$: C 75.78, H 7.74, *found* C 75.69, H 7.62.

(3*S*,4*R*)-1-{[*tert*-Butyl(diphenyl)silyl]oxy}-6-methylnona-4,5-dien-3-ol (6). A solution of $Fe(acac)_3$ (120 mg, 0.34 mmol) in toluene (30 mL) was added to a solution of propargyl epoxide **5** (2.5 g, 6.9 mmol) in toluene (280 mL) at –5 °C. The resulting mixture was stirred for 5 min at –5 °C before a solution of propylmagnesium chloride in Et_2O (2 M, 4.5 mL, 8.9 mmol) was added via syringe over a period of 10 min, causing a color change from bright red to black during the addition. After stirring for 5 min at –5 °C, the reaction was quenched with aq. sat. NH_4Cl (150 mL) and diluted with methyl *tert*-butylether. The aqueous layer was repeatedly extracted with methyl *tert*-butylether, the combined organic layers were dried over Na_2SO_4, filtered and concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 25/1) to give an inseparable *syn/anti*= 8:1 mixture of allenol **6** as a pale yellow oil (1.7 g, 62%). $[\alpha]_D^{20}$ = –10.8 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m), 7.46-7.37 (6H, m), 5.19 (1H, o, *J* = 2.8 Hz), 4.43-4.40 (1H, m), 3.91 (1H, dt, *J* = 10.4, 5.7 Hz), 3.84 (1H, dt, *J* = 10.4, 6.0 Hz), 2.70 (1H, bs), 1.96-1.91 (2H, m), 1.81 (2H, q, *J* = 5.9 Hz), 1.67 (3H, d, *J* = 2.8 Hz), 1.44 (2H, h, *J* = 7.4 Hz), 1.06 (9H, s), 0.91 (3H, t, *J* = 7.3 Hz). (Minor isomer: 0.90 (t, *J* = 7.3 Hz)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 135.7, 133.5, 129.9, 127.9, 102.8, 94.9, 69.3, 62.4, 39.4, 36.3, 27.0, 20.9, 19.3, 19.2, 13.9. IR: 3435, 3071, 2958, 2931, 2858, 1964, 1472, 1428, 1112, 823, 702 cm^{-1}. MS (EI) *m/z* (rel. intensity): 351 ([M-^{t}Bu]$^+$, 5), 333 (10), 229 (12), 211 (9), 199 (100). HRMS (ESI): *calcd.* for ($C_{26}H_{36}O_2Si$+Na): 431.2382, *found* 431.2385 (M+Na). Anal. *calcd.* for $C_{26}H_{36}O_2Si$: C 76.42, H 8.88, *found* C 76.26, H 8.98.

***tert*-Butyl {2-[(2*S*,5*R*)-5-methyl-5-propyl-2,5-dihydrofuran-2-yl]ethoxy}diphenyl silane (7).** $AgNO_3$ (750 mg, 4.4 mmol) and $CaCO_3$ (800 mg, 8.0 mmol) were added to a solution of allenol **6** (1.6 g, 4.0 mmol) in acetone/water (4/1, 110 mL). The reaction mixture was stirred

for 15 h in the dark before it was diluted with water (30 mL). The acetone was removed under reduced pressure, the remaining aqueous phase was repeatedly extracted with methyl *tert*-butylether, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography of the residue (hexanes/ethyl acetate, 30/1) provided dihydrofuran **7** as a colorless oil (1.5 g, 90%). The diastereomeric ratio (d.r. = 8/1) was determined by integration of the corresponding signals in ^{1}H NMR. $[\alpha]_D^{20}$ = +30.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 7.82-7.78 (4H, m), 7.24-7.22 (6H, m), 5.52 (1H, dd, *J* = 6.0, 1.3 Hz), 5.40 (1H, dd, *J* = 6.0, 2.4 Hz), 5.03-4.99 (1H, m), 3.97-3.85 (2H, m), 1.92-1.77 (2H, m), 1.57-1.22 (5H, m), 1.23 (3H, s), 1.18 (9H, s), 0.87 (3H, t, *J* = 7.2 Hz). (minor diastereomer: 5.37 (dd, *J* = 6.0, 2.3 Hz)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.0, 134.50, 134.0, 129.9, 129.5, 83.1, 82.0, 61.7, 44.2, 40.1, 27.2, 26.6, 19.5, 18.4, 14.9. IR: 3071, 2959, 2931, 2858, 1472, 1428, 1112, 823, 702 cm^{-1}. MS (EI) *m/z* (rel. intensity): 408 ([M$^+$], 0.7), 351 (31), 199 (82), 183 (19), 154 (22) 135 (100). HRMS (ESI): *calcd.* for ($C_{26}H_{36}O_2Si$+Na): 431.2382, *found* 431.2380 (M+Na). Anal. *calcd.* for $C_{26}H_{36}O_2Si$: C 76.42, H 8.88, *found* C 76.28, H 8.94.

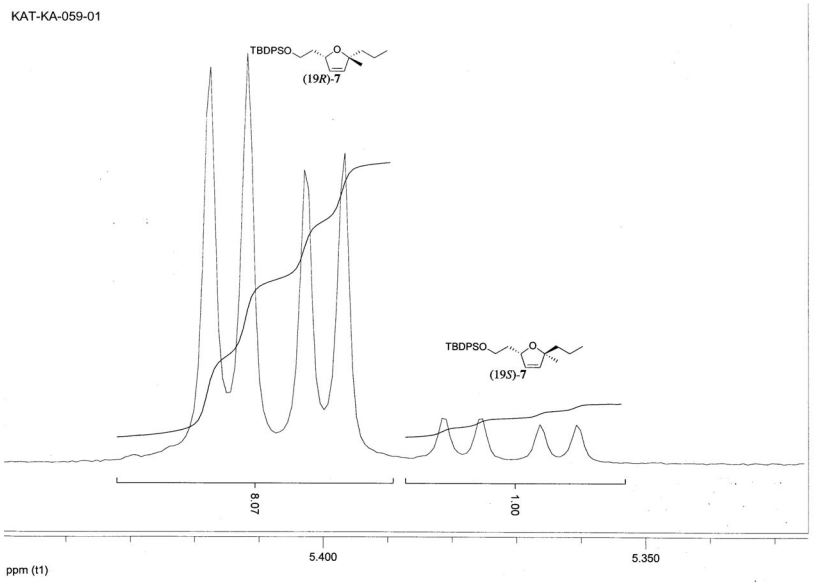
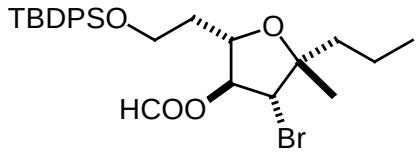


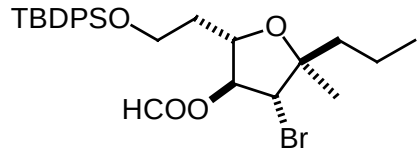
Figure S-1. Relevant part of the ^{1}H NMR spectrum (400 MHz, C_6D_6) of compound **7** showing the C19-isomer ratio.

(2*S*,3*S*,4*R*,5*R*)-4-Bromo-2-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-5-propyl-tetrahydrofuran-3-yl formate (8). NBS (1.9 g, 10.4 mmol) was added in portions to a solution of dihydrofuran **7** (1.45 g, 3.7 mmol) in DMF/water (15/1, 38 mL) at –5 °C. After stirring for 6 h in the dark at –5 °C, the reaction was diluted with water (100 mL), the aqueous phase was repeatedly extracted with pentane, the combined organic layers were dried over Na_2SO_4, filtered and concentrated, and the residue was purified by flash chromatography

(hexanes/ethyl acetate, 50/1). The diastereoisomers generated in the iron catalyzed allenol formation were separated at this stage yielding the (19*R*)-configured[§] bromoformate **8** (1.1 g, 58%) and the diastereomeric (19*S*)-bromoformate[§] (140 mg, 7%) as pale yellow oils. Analytical and spectroscopic data of (19*R*)-**8**: $[\alpha]_D^{20}$ = –1.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, s), 7.69-7.65 (4H, m), 7.44-7.35 (6H, m), 5.44 (1H, dt, *J* = 4.5, 0.8 Hz), 4.14 (1H, dt, *J* = 9.4, 4.8 Hz), 4.09 (1H, d, *J* = 4.5 Hz), 3.85-3.75 (2H, m), 2.09-2.01 (1H, m), 1.90 (1H, ddt, *J* = 14.0, 9.0, 5.2 Hz), 1.73-1.32 (5H, m), 1.36 (3H, s), 1.05 (9H, s), 0.94 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 135.7, 133.9, 129.7, 127.8, 84.3, 83.8, 77.3, 60.6, 59.1, 42.4, 37.7, 27.0, 23.2, 19.4, 17.6, 14.6. IR: 3071, 2959, 2931, 2858, 1733, 1472, 1428, 1159, 1112, 823, 702 cm^{-1}. MS (EI) *m/z* (rel. intensity): 477 and 475 ($[M-^tBu]^+$, 7), 431 (45) and 429 (43), 349 (68), 255 (98), 227 (37), 199 (96), 183 (31), 151 (100). HRMS (ESI): *calcd.* for ($C_{27}H_{37}BrO_4Si$+Na): 555.1542, *found* 555.1545 (M+Na). Anal. *calcd.* for $C_{27}H_{37}BrO_4Si$: C 60.78, H 6.99, Br 14.98, Si 5.26, *found* C 60.83, H 6.85, Br 14.87, Si 5.30.



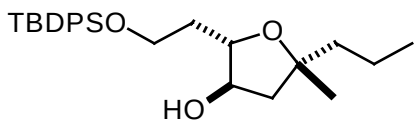
(19*R*)-**8**



(19*S*)-**8**

Analytical and spectroscopic data of the minor isomer (19*S*)-**8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, s), 7.68-7.65 (4H, m), 7.44-7.35 (6H, m), 5.45 (1H, dt, *J* = 6.4, 0.8 Hz), 4.13 (1H, d, *J* = 6.3 Hz), 4.04 (1H, ddd, *J* = 9.0, 6.5, 4.0 Hz), 3.84-3.73 (2H, m), 2.05-1.96 (1H, m), 1.84 (1H, ddt, *J* = 13.9, 9.1, 5.1 Hz), 1.70-1.35 (5H, m), 1.34 (3H, s), 1.04 (9H, s), 0.95 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 135.7, 133.9, 129.7, 127.7, 83.5, 83.3, 76.4, 60.4, 56.9, 41.5, 37.6, 27.0, 25.7, 19.4, 17.3, 14.6.

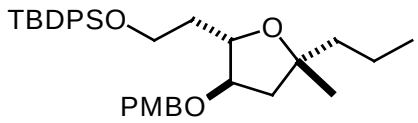
(2*S*,3*R*,5*R*)-2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-5-propyltetrahydrofuran-3-ol. $(TMS)_3SiH$ (850 µL, 2.76 mmol) and AIBN (30 mg, 0.18 mmol) were added to a solution of bromoformate (19*R*)-**8** (980 mg, 1.84 mmol) in toluene (90 mL) and the resulting mixture was stirred at 80 °C for 4 h. The solution was allowed to reach ambient temperature before the solvent was evaporated. The residue was dissolved in MeOH (100 mL). Aq. sat. $NaHCO_3$ (ca. 12 mL) was added dropwise and the reaction mixture was stirred for 2 h before it was diluted with water (25 mL). A standard extractive work up with methyl *tert*-butylether followed by flash chromatography (hexanes/ethyl acetate, 8/1) of the crude product provided the title compound as a colorless oil (705 mg, 90%). $[\alpha]_D^{20}$ = –18.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m), 7.47-7.38 (6H, m), 4.05 (1H, q, *J* = 7.5 Hz), 3.84 (2H, dd, *J* = 7.1, 4.1



[§] Amphidinolide X numbering

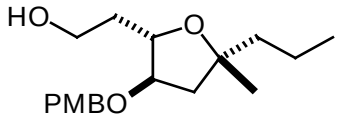
Hz), 3.79 (1H, ddd, *J* = 8.2, 7.1, 4.7 Hz), 3.52 (1H, bs), 2.24 (1H, dd, *J* = 12.4, 8.1 Hz), 1.90-1.73 (3H, m), 1.48-1.33 (4H, m), 1.31 (3H, s), 1.07 (9H, s), 0.92 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.1, 130.0, 128.0, 82.8, 81.8, 76.6, 62.3, 45.4, 44.9, 36.8, 27.6, 27.0, 19.2, 17.9, 14.8. IR: 3438, 3071, 2959, 2932, 1613, 1513, 1428, 1249, 1111, 1087, 1038, 822, 703 cm^{-1}. MS (EI) *m/z* (rel. intensity): 369 ([M-^{t}Bu]$^+$, 9), 351 (100). HRMS (ESI): *calcd.* for ($C_{26}H_{38}O_3Si$+Na): 449.2488, *found* 449.2493 (M+Na). Anal. *calcd.* for $C_{26}H_{38}O_3Si$: C 73.19, H 8.98, *found* C 72.98, H 9.06.

***tert*-Butyl(2-{(2*S*,3*R*,5*R*)-3-[(4-methoxybenzyl)oxy]-5-methyl-5-propyltetrahydro-furan-2-yl}ethoxy)diphenylsilane.** *p*-Methoxybenzyl trichloroacetimidate (800 mg, 2.81 mmol) and



PPTS (29 mg, 0.12 mmol) were added over 5 min to a solution of (2*S*,3*R*,5*R*)-2-(2-{[*tert*-butyl (diphenyl)silyl] oxy}ethyl)-5-methyl-5-propyltetrahydrofuran-3-ol (200 mg, 0.47 mmol) in CH_2Cl_2/cyclohexane (1/2, 6.0 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 48 h before it was filtered through a pad of Celite. The filtrate was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 40/1) to give the title compound as a colorless oil (196 mg, 76%). $[\alpha]_D^{20}$ = –19.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m), 7.43-7.34 (6H, m), 7.21 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 4.41 (1H, d, *J* = 11.4 Hz), 4.37 (1H, d, *J* = 11.4 Hz), 4.11 (1H, dt, *J* = 7.2, 5.0 Hz), 3.80 (3H, s), 3.81-3.76 (3H, m), 1.94 (1H, dd, *J* = 13.1, 7.3 Hz), 1.88-1.74 (3H, m), 1.46-1.27 (4H, m), 1.28 (3H, s), 1.05 (9H, s), 0.90 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 135.8, 134.2, 130.7, 129.6, 129.2, 127.7, 114.0, 84.2, 82.8, 79.6, 71.3, 61.3, 55.4, 45.5, 42.7, 37.9, 27.0, 26.4, 19.3, 18.0, 14.8. IR: 3070, 2958, 2931, 1613, 1428, 1112, 1086, 1038, 702 cm^{-1}. MS (EI) *m/z* (rel. intensity): 489 ([M-^{t}Bu]$^+$, 0.3), 351 (6), 199 (4), 121 (100). HRMS (ESI): *calcd.* for ($C_{34}H_{46}O_4Si$+Na): 569.3063, *found* 569.3064 (M+Na). Anal. *calcd.* for $C_{34}H_{46}O_4Si$: C 74.68, H 8.48, *found* C 74.53, H 8.42.

2-{(2*S*,3*R*,5*R*)-3-[(4-Methoxybenzyl)oxy]-5-methyl-5-propyltetrahydrofuran-2-yl}-ethanol. A solution of TBAF in THF (1 M, 990 µL, 0.99 mmol) was added dropwise to a



solution of *tert*-butyl(2-{(2*S*,3*R*,5*R*)-3-[(4-methoxybenzyl)oxy]-5-methyl-5-propyltetrahydro-furan-2-yl}ethoxy)diphenylsilane (180 mg, 0.33 mmol) in THF (9.5 mL). After stirring for 3 h, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and diluted with methyl *tert*-butylether and water. The aqueous layer was extracted with methyl *tert*-butylether and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. Flash chromatography (hexanes/ethyl acetate, 2/1) of the residue provided the title alcohol as a colorless oil (98 mg, 97%). $[\alpha]_D^{20}$ = –37.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 4.47 (1H, d, *J* = 11.3 Hz), 4.38 (1H, d, *J* = 11.3 Hz), 4.06 (1H, ddd, *J* = 8.0, 5.7, 4.7 Hz), 3.80 (3H, s), 3.80-3.74 (3H, m), 2.49 (1H, bs), 2.04 (1H, dd, *J* = 12.9, 7.6 Hz), 1.90-1.71 (2H, m), 1.77 (1H, dd, *J* = 12.9,

5.1 Hz), 1.50-1.28 (3H, m), 1.30 (3H, s), 0.91 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 130.2, 129.4, 114.1, 83.7, 83.5, 82.3, 71.7, 61.6, 55.4, 45.3, 42.6, 36.3, 26.5, 18.0, 14.7. IR: 3444, 2959, 2933, 1613, 1514, 1249, 1173, 1084, 1036, 821 cm^{-1}. MS (EI) *m/z* (rel. intensity): 308 ([M$^+$], 6), 137 (7), 121 (100). HRMS (ESI): *calcd*. for ($C_{18}H_{28}O_4$+Na): 331.1885, *found* 331.1884 (M+Na).

(2*R*,4*R*,5*S*)-5-(2-Iodoethyl)-4-[(4-methoxybenzyl)oxy]-2-methyl-2-propyltetrahydrofuran (10). PPh_3 (98 mg, 0.38 mmol) and imidazole (31 mg, 0.50 mmol) were added to a solution of 2-{(2*S*,3*R*,5*R*)-3-[(4-methoxybenzyl)oxy]-5-methyl-5-propyltetrahydrofuran-2-yl}ethanol (77 mg, 0.25 mmol) in Et_2O/MeCN (3/1, 2.6 mL). After stirring for 5 min, a solution of iodine (95 mg, 0.38 mmol) in Et_2O/MeCN (3/1, 0.65 mL) was added dropwise and the resulting mixture was stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with methyl *tert*-butylether and water, the aqueous layer was repeatedly extracted with methyl *tert*-butylether, the combined organic layers were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 25/1) to give iodide **10** as a colorless oil (96 mg, 92%). $[\alpha]_D^{20}$ = –34.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 4.46 (1H, d, *J* = 11.4 Hz), 4.39 (1H, d, *J* = 11.4 Hz), 3.95 (1H, dt, *J* = 8.3, 4.6 Hz), 3.81 (3H, s), 3.73 (1H, dt, *J* = 7.5, 4.6 Hz), 3.26-3.15 (2H, m), 2.16-1.94 (3H, m), 1.79 (1H, dd, *J* = 13.1, 4.2 Hz), 1.47-1.26 (4H, m), 1.29 (3H, s), 0.91 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 130.4, 129.3, 114.1, 83.3, 83.2, 82.2, 71.5, 55.5, 45.4, 42.7, 39.4, 26.5, 18.0, 14.8, 1.9. IR: 2958, 2932, 2870, 1613, 1513, 1249, 1173, 1037, 821 cm^{-1}. MS (EI) *m/z* (rel. intensity): 418 ([M$^+$], 7), 375 (5), 233 (4), 137 (4), 121 (100). HRMS (ESI): *calcd.* for ($C_{18}H_{27}IO_3$+Na): 441.0903, *found* 441.0899 (M+Na). Anal. *calcd.* for $C_{18}H_{27}IO_3$: C 51.68, H 6.51, *found* C 51.64, H 6.43.

(2*S*,3*R*)-3-Methyl-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-yn-2-ol (13). PPh_3 (50 mg, 0.20 mmol) was added to a solution of $Pd(OAc)_2$ (45 mg, 0.20 mmol) in THF (40 mL) at –78°C and the mixture was stirred until a clear solution had formed. Mesylate **12** (855 mg, 5.77 mmol) was then added followed by aldehyde **11** (500 mg, 3.84 mmol).[1] A solution of Et_2Zn in hexane (1 M, 11.5 mL, 11.5 mmol) was added dropwise over 10 min at –78°C. After stirring at that temperature for 10 min, the solution was stirred for 16 h at –20°C. For work up, an aq. sat. solution of $NaHCO_3$ was slowly added (gas evolution!) and the product was extracted with methyl *tert*-butylether. The combined organic phases were washed with water, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1 + 2% Et_3N) to afford a 4.5:1 mixture of the *anti*-configured alcohol **13** and its *syn*-configured isomer (460 mg, 65 %). These isomers can be separated by flash chromatography (hexanes/EtOAc, 10:1 + 2% Et_3N → hexanes/EtOAc, 4:1 + 2% Et_3N). The

[1] Langer, P.; Freifeld, I. *Synlett* **2001**, 523-525.

enantiomeric excess of *anti*-**13** (ee = 94%) was determined by HPLC by comparison with of both enantiomers (250 mm Chiralpak AD, *n*-heptane/2-propanol = 99/1, 0.5 mL/min, 0.7 mPa, RI, E = 32). Analytical and spectroscopic data of *anti*-**13**: $[\alpha]_D^{20}$ = +2.1° (c = 1.1, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 4.00-3.95 (1H, m), 3.40-3.26 (5H, m), 2.59-2.53 (1H, m), 2.02 (1H, dd, *J* = 9.6, 14.5 Hz), 1.95 (1H, dd, *J* = 2.3, 14.5 Hz), 1.86 (1H, d, *J* = 2.5 Hz), 1.31 (3H, d, *J* = 7.0 Hz), 1.21 (3H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 110.4, 86.0, 70.5, 70.1, 64.6, 64.2, 42.3, 32.8, 24.2, 16.1. IR: 3515, 3290, 2983, 2887, 2112, 1379, 1257, 1220, 1156, 1109, 1042, 983, 949, 822 cm^{-1}. MS (EI) *m/z* (rel. intensity): 169 ([M-CH$_3$]$^+$, 4), 87 (100), 43 (46). HRMS (ESI): *calcd.* for ($C_{10}H_{16}O_3$+Na): 207.0997, *found* 207.0997 (M+Na). Anal. *calcd.* for $C_{10}H_{16}O_3$: C 65.19, H 8.75, *found* C 65.08, H 8.71.

2-{(2*S*,3*R*)-2-[(4-Methoxybenzyl)oxy]-3-methylpent-4-ynyl}-2-methyl-1,3-dioxolane (14). NaH (391 mg, 16.3 mmol) was added to a solution of alcohol **13** (1.00 g, 5.43 mmol) in DMF (54 mL) at 0°C. The mixture was stirred for 1 h at that temperature before *p*-methoxy-benzylchloride (1.58 mL, 10.9 mmol) was added followed by tetra-*n*-butylammonium iodide (199 mg, 0.543 mmol). The mixture was stirred for 1 h at 0°C and for 16 h at room temperature. For work up, the reaction was carefully quenched with brine (H_2 evolution!) and the mixture was repeatedly extracted with methyl *tert*-butylether. The combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1 + 2 % Et_3N → hexanes/EtOAc, 4:1 + 2 % Et_3N) to afford protected alcohol **14** as a colorless syrup (1.55 g, 94 %). $[\alpha]_D^{20}$ = –5.4° (c = 0.85, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 7.23 (2H, d, *J* = 8.7 Hz), 6.78 (2H, d, *J* = 8.7 Hz), 4.37 (1H, d, *J* = 11.2 Hz), 4.29 (1H, d, *J* = 11.2 Hz), 3.78-3.74 (1H, m), 3.63-3.53 (4H, m), 2.90-2.86 (1H, m), 2.29 (1H, dd, *J* = 3.5, 14.6 Hz), 2.07 (1H, dd, *J* = 7.2, 14.6 Hz), 1.89 (3H, d, *J* = 2.5 Hz), 1.46 (3H, s). ^{13}C NMR (100 MHz, C_6D_6) δ 159.7, 131.1, 129.5, 114.0, 109.6, 86.5, 78.0, 71.2, 70.2, 64.5, 64.4, 54.8, 40.2, 29.9, 25.0, 15.3. IR: 3289, 2982, 2882, 2111, 1613, 1514, 1249, 1052, 821 cm^{-1}. MS (EI) *m/z* (rel. intensity): 304 ([M$^+$], 1), 121 (100), 115 (19), 87 (23), 43 (13). HRMS (ESI): *calcd.* for ($C_{18}H_{24}O_4$+Na): 327.1572, *found* 327.1578 (M+Na). Anal. *calcd.* for $C_{18}H_{24}O_4$: C 71.03, H 7.95, *found* C 70.89, H 7.86.

2-{(2*S*,3*R*)-2-[(4-Methoxybenzyl)oxy]-3-methylhex-4-ynyl}-2-methyl-1,3-dioxolane (15). LiHMDS (2.00 g, 11.9 mmol) was added to a solution of alkyne **14** (1.21 g, 3.98 mmol) in THF (40 mL) at –78°C. The reaction was stirred for 1 h at that temperature and for 30 min at –20°C. The mixture was cooled to –78°C, before MeI (1.24 mL, 19.9 mmol) was introduced, and stirring was continued for 16 h at –20°C → 5°C. An aq. sat. solution of NH_4Cl was added, the aqueous layer was extracted with methyl *tert*-butylether, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 15:1 + 2 % Et_3N) to afford alkyne **15** as a colorless syrup (1.20 g, 95 %). $[\alpha]_D^{20}$ = –12.1° (c = 1.0, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 7.25 (2H, d, *J* = 8.6 Hz), 6.78 (2H, d, *J* = 8.6 Hz), 4.41 (1H, d, *J* = 11.1 Hz), 4.36 (1H, d, *J* = 11.1 Hz), 3.82-3.78 (1H, m), 3.64-3.54 (4H, m), 3.31 (3H, s), 2.96-2.93 (1H, m), 2.36 (1H, dd, *J* = 3.0, 14.5

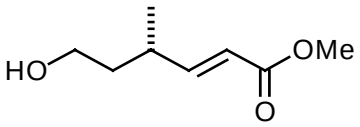
Hz), 2.11 (1H, dd, *J* = 7.3, 14.5 Hz), 1.55 (3H, d, *J* = 2.4 Hz), 1.50 (3H, s), 1.24 (3H, d, J= 7.0 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 159.6, 131.5, 129.5, 113.9, 109.8, 81.6, 78.5, 77.1, 71.1, 64.4, 64.3, 54.7, 40.2, 30.1, 25.0, 15.6, 3.4. IR: 3306, 2980, 2881, 1613, 1514, 1249, 1052, 822 cm^{-1}. MS (EI) *m/z* (rel. intensity): 318 ([M$^+$], 0.4), 121 (100), 87 (15). HRMS (ESI): *calcd.* for ($C_{19}H_{26}O_4$+Na): 341.1729, *found* 341.1726 (M+Na). Anal. *calcd.* for $C_{19}H_{26}O_4$: C 71.67, H 8.23, *found* C 71.48, H 8.20.

2-{(2*S*,3*R*,4*E*)-5-Iodo-2-[(4-methoxybenzyl)oxy]-3-methylhex-4-enyl}-2-methyl-1,3-dioxolane (16). A solution of alkyne **15** (294 mg, 0.923 mmol) in benzene (18 mL) was added to Cp_2ZrHCl (595 mg, 2.31 mmol) under Ar. The mixture was stirred for 4 h at 50°C and then cooled to ambient temperature. The mixture was diluted with CH_2Cl_2 (10 mL), cooled to –15°C and treated with a saturated solution of I_2 in CH_2Cl_2 until the purple color persisted. At that point, a sat. aq. solution of $Na_2S_2O_3$ was immediately added. A standard extractive work up followed by flash chromatography of the crude product (hexanes/EtOAc, 20:1 + 2 % Et_3N → hexanes/EtOAc, 6:1 + 2 % Et_3N) afforded vinylic iodide **16** as a colorless syrup (251 mg, 61 %). $[\alpha]_D^{20}$ = +19.0° (c = 1.0, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 7.27 (2H, d, *J* = 8.6 Hz), 6.80 (2H, d, *J* = 8.6 Hz), 6.43 (1H, dd, *J* = 1.4, 9.9 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 4.32 (1H, d, *J* = 11.2 Hz), 3.52-3.33 (4H, m), 3.32 (3H, s), 2.72-2.67 (1H, m), 2.24 (3H, d, *J* = 1.4 Hz), 1.97 (1H, dd, *J* = 4.9, 14.8 Hz), 1.86 (1H, dd, *J* = 5.6, 14.8 Hz), 1.30 (3H, s), 0.95 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 159.7, 143.7, 131.5, 129.7, 114.1, 109.4, 94.6, 78.4, 71.3, 64.6, 64.4, 54.8, 41.1, 40.2, 28.3, 24.9, 16.7. IR: 2958, 2877, 1612, 1514, 1248, 1038, 821 cm^{-1}. MS (EI) *m/z* (rel. intensity): 431 ([M-CH_3]$^+$, 0.2), 121 (100), 87 (18). HRMS (ESI): *calcd.* for ($C_{19}H_{27}O_4I$+Na): 469.0852, *found* 469.0849 (M+Na).

(2*S*,3*R*,4*E*)-5-Iodo-3-methyl-1-(2-methyl-1,3-dioxolan-2-yl)hex-4-en-2-ol (17). An aq. phosphate buffer solution (pH 7, 3 mL) was added to a solution of alcohol **16** (287 mg, 0.643 mmol) in CH_2Cl_2 (10 mL). DDQ (584 mg, 2.57 mmol) was then introduced at 0°C and the mixture was stirred for 2 h at ambient temperature. H_2O was added, the mixture was extracted with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 15:1 + 1 % Et_3N → hexanes/EtOAc, 4:1 + 1 % Et_3N) to afford alcohol **17** as a colorless syrup (187 mg, 89 %). $[\alpha]_D^{20}$ = +32.0° (c = 1.0, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 6.50 (1H, qd, *J* = 1.5, 9.9 Hz), 3.77 (1H, dd, *J* = 3.7, 10.3 Hz), 3.45 (1H, s), 3.39-3.32 (4H, m), 2.24-2.18 (1H, m), 2.16 (3H, d, *J* = 1.5 Hz), 1.75 (1H, dd, *J* = 10.3, 14.5 Hz), 1.58 (1H, dd, *J* = 1.6, 14.5 Hz), 1.14 (3H, s), 1.01 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 143.4, 110.4, 94.0, 70.9, 64.6, 64.1, 43.3, 41.8, 27.9, 24.2, 16.9. IR: 3520, 2979, 2882, 1634 ,1378, 1040 cm^{-1}. MS (EI) *m/z* (rel. intensity): 311 ([M-CH_3]$^+$, 2), 131 (16), 87 (100), 43 (35). HRMS (ESI): *calcd.* for ($C_{11}H_{19}O_3I$+Na): 349.0277, *found* 349.0274 (M+Na). Anal. *calcd.* for $C_{11}H_{19}O_3I$: C 40.51, H 5.87, *found* C 40.63, H 5.95.

Methyl (2*E*,4*S*)-4-methyl-6-[(triisopropylsilyl)oxy]hex-2-enoate (19). DBU (573 μL, 3.83 mmol) and methyl diethylphosphonoacetate (804 μL, 4.38 mmol) were added to a suspension of flame dried LiCl (186 mg, 4.38 mmol) in CH_3CN (36 mL). Aldehyde **18** (943 mg, 3.65 mmol) in CH_3CN (36 mL) was added and the mixture was stirred for 16 h at ambient temperature. A standard extractive work up followed by flash chromatography of the crude product (hexanes/EtOAc, 15:1) furnished ester **19** as a colorless syrup (1.08 g, 94 %). $[\alpha]_D^{20}$ = +39.5° (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, dd, *J* = 7.8, 15.7 Hz), 5.79 (1H, dd, *J* = 1.1, 15.7 Hz), 3.72 (3H, s), 3.68 (1H, td, *J* = 1.8, 6.3 Hz), 2.60-2.51 (1H, m), 1.64-1.53 (2H, m), 1.09-1.00 (24 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 154.8, 119.4, 61.1, 51.5, 39.1, 33.2, 19.4, 18.1, 12.1. IR: 2944, 2867, 1729, 1657, 1463, 1107, 883, 681 cm^{-1}. MS (EI) *m/z* (rel. intensity): 299 ($[M\text{-}CH_3]^+$, < 0.07), 271 ($[M\text{-}^i Pr]^+$, 100), 145 (25), 133 (13), 117 (14), 109 (17), 89 (10), 81 (29), 75 (17). HRMS (ESI): *calcd.* for ($C_{17}H_{34}O_3Si$+Na): 337.2175, *found* 337.2177 (M+Na). Anal. *calcd.* for $C_{17}H_{34}O_3Si$: C 64.92, H 10.90, *found* C 64.99, H 10.93.

Methyl (2*E*,4*S*)-6-hydroxy-4-methylhex-2-enoate. A solution of alcohol **19** (400 mg, 1.27 mmol) in CH_3CN (13 mL) was placed in a plastic bottle. Excess HF·pyridine (1.00 mL) was added and the mixture was stirred for 90 min at ambient temperature. For work up, aq. sat. $NaHCO_3$ was introduced and the mixture was extracted with methyl *tert*-butylether. The combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (pentanes/ methyl *tert*-butylether, 1:1) to afford the title alcohol as a colorless syrup (202 mg, 100 %).



$[\alpha]_D^{20}$ = +45.0° (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, dd, *J* = 8.0, 15.7 Hz), 5.77 (1H, dd, *J* = 1.2, 15.7 Hz), 3.68 (3H, s), 3.62-3.56 (2H, m), 2.51-2.44 (1H, m), 2.17 (1H, s), 1.59 (2H, q, *J* = 6.7 Hz), 1.04 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 154.3, 119.6, 60.4, 51.5, 38.6, 33.2, 19.4. IR: 3430, 2955, 1725, 1656, 1436, 1275. MS (EI) *m/z* (rel. intensity): 158 ($[M^+]$, 10), 127 (71), 81 (100), 55 (64), 41 (75). HRMS (ESI): *calcd.* for ($C_8H_{14}O_3$): 158.0943, *found* 158.0944 (M). Anal. *calcd.* for $C_8H_{14}O_3$: C 60.74, H 8.92, *found* C 60.83, H 9.06.

(3*S*,4*E*)-6-Methoxy-3-methyl-6-oxohex-4-enoic acid (20). Oxalyl chloride (150 μL, 1.72 mmol) was added to a solution of DMSO (184 μL, 2.58 mmol) in CH_2Cl_2 (7 mL) at –78°C. A solution of methyl (2*E*,4*S*)-6-hydroxy-4-methylhex-2-enoate (136 mg, 0.86 mmol) in CH_2Cl_2 (7 mL) was added and the mixture was stirred for 1 h at –78°C. Et_3N (483 μL, 3.44 mmol) was then introduced and the mixture was stirred for 1 h at ambient temperature. The reaction was quenched with brine, the aqueous layer was extracted with methyl *tert*-butylether, the combined organic phases were evaporated, and the residue was re-dissolved in methyl *tert*-butylether. The organic solution was washed with H_2O, dried over Na_2SO_4, filtered and evaporated to give the crude aldehyde which was used without any further purification.

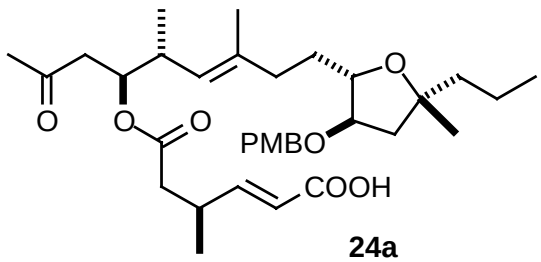
2-Methylbut-2-ene (2.00 mL) and NaH_2PO_4 (306 mg, 2.58 mmol) in H_2O (3.4 mL) were added to a solution of this aldehyde (134 mg, 0.86 mmol) in *t*-BuOH (15 mL) at ambient temperature. $NaClO_2$ (231 mg, 2.58 mmol) was introduced and the mixture was stirred for 2 h. The solvent was evaporated and the residue was dissolved in EtOAc. H_2O was added, the mixture was acidified with 2 M HCl until pH 5 was reached, and the resulting mixture was repeatedly extracted EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 1:1 → EtOAc) to afford carboxylic acid **20** as a colorless syrup (136 mg, 92 % over 2 steps). $[\alpha]_D^{20}$ = +24.8° (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, dd, *J* = 7.2, 15.8 Hz), 5.85 (1H, dd, *J* = 1.4, 15.8 Hz), 3.73 (3H, s), 2.90-2.83 (1H, m), 2.48 (1H, dd, *J* = 7.0, 15.8 Hz), 2.39 (1H, dd, *J* = 7.3, 15.8 Hz), 1.15 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 167.1, 151.8, 120.4, 51.7, 40.0, 32.8, 19.2. IR: 3100, 2967, 2674, 1723, 1657, 1278. MS (EI) *m/z* (rel. intensity): 172 ([M^+], 2), 154 (44), 140 (50), 122 (100), 95 (59), 94 (56), 71 (58), 67 (58), 41 (58). HRMS (ESI): *calcd.* for ($C_8H_{12}O_4$+Na): 195.0633, *found* 195.0634 (M+Na). Anal. *calcd.* for $C_8H_{12}O_4$: C 55.81, H 7.02, *found* C 55.74, 7.12.

Ester 21. Et_3N (180 μL, 1.29 mmol) was added to a solution of carboxylic acid **20** (74 mg, 0.432 mmol) in toluene (4 mL). 2,4,6-Trichlorobenzoyl chloride (68 μL, 0.432 mmol) was introduced and the resulting mixture was stirred for 1h at ambient temperature. A solution of alcohol **17** (128 mg, 0.392 mmol) and DMAP (48 mg, 0.392 mmol) in toluene (4 mL) was added and the reaction mixture was allowed to stir for 1h. Evaporation of the solvent followed by flash chromatography of the residue (hexanes/EtOAc, 4:1 + 1 % Et_3N) provided ester **21** as a colorless syrup (200 mg, 96 %). $[\alpha]_D^{20}$ = +17.4° (c = 1.0, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 6.96 (1H, dd, *J* = 7.1, 15.7 Hz), 6.21 (1H, dd, *J* = 1.5, 9.9 Hz), 5.83 (1H, dd, *J* = 1.4, 15.7 Hz), 5.26-5.22 (1H, m), 3.59-3.45 (4H, m), 3.43 (3H, s), 2.69-2.62 (1H, m), 2.50-2.44 (1H, m), 2.18 (3H, d, 1.5 Hz), 2.09 (1H, dd, *J* = 7.0, 15.5 Hz), 2.00 (1H, dd, *J* = 7.2, 15.5 Hz), 1.93 (1H, dd, *J* = 7.9, 14.8 Hz), 1.72 (1H, dd, *J* = 3.2, 14.8 Hz), 1.24 (3H, s), 0.83 (3H, d, *J* = 6.8 Hz), 0.79 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 170.9, 166.6, 152.3, 142.1, 120.5, 109.0, 95.7, 72.5, 64.6, 64.5, 51.0, 41.3, 40.5, 40.1, 33.1, 28.0, 24.4, 19.0, 16.3. IR: 2968, 1727, 1657, 1273, 1173, 1041, 987. MS (EI) *m/z* (rel. intensity): 480 ([M^+], 0.03), 87 (100), 43 (15). HRMS (ESI): *calcd.* for ($C_{19}H_{29}O_6I$+Na): 503.0907, *found* 503.0907 (M+Na).

Compound 23. A solution of *t*-BuLi in pentane (1.7 M, 438 μL, 0.744 mmol) was added to a mixture of Et_2O (577 μL) and THF (577 μL) at –78°C before a solution of alkyl iodide **10** (52 mg, 0.124 mmol) in THF (3.47 mL) was added dropwise (additional 577 μL of THF were used to rinse the flask). The mixture was stirred for 5 min at –78°C before 9-MeO-9-BBN (126 μL, 0.744 mmol) was introduced causing an immediate color change from yellow to colorless. The mixture was stirred for 15 min at –78°C and for 1 h at ambient temperature. An aq. solution of K_3PO_4 (3 M, 248 μL, 0.744 mmol) was added followed by a solution of the vinyl iodide **21** (60 mg, 0.124 mmol) in DMF (3.47 mL) (additional 577 μL of DMF were used to rinse the flask). A solution of (dppf)$PdCl_2$ (4.5 mg, 0.0062 mmol) and $AsPh_3$ (3.8 mg,

0.012 mmol) in DMF (500 μL) was then added and the mixture was stirred for 2 h at ambient temperature. The mixture was diluted with hexanes/EtOAc (4:1 + 1 % Et_3N) before it was filtered through a pad of silica (hexanes/EtOAc, 4:1 + 1 % Et_3N was used to rinse the silica pad). The combined filtrates were successively washed with sat. aq. $NaHCO_3$, sat. aq. NH_4Cl and brine, the organic phase was dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 15:1 + 1 % Et_3N → hexanes/EtOAc, 6:1 + 1 % Et_3N) to afford compound **23** as a colorless syrup (59 mg, 74 %). $[\alpha]_D^{20}$ = –13.5° (c = 1.0, MeOH). ^{1}H NMR (400 MHz, C_6D_6) δ 7.25 (2H, d, *J* = 8.7 Hz), 7.02 (1H, dd, *J* = 7.1, 15.8 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 5.86 (1H, dd, *J* = 1.4, 15.8 Hz), 5.45-5.41 (1H, m), 5.27 (1H, d, *J* = 9.4 Hz), 4.36 (1H, d, *J* = 11.5 Hz), 4.29 (1H, d, *J* = 11.5 Hz), 4.14 (1H, td, *J* = 5.0, 7.4 Hz), 3.70-3.49 (5H, m), 3.42 (3H, s), 3.34 (3H, s), 2.75-2.67 (2H, m), 2.33-2.23 (1H, m), 2.23-2.16 (2H, m), 2.12-2.03 (2H, m), 1.90 (1H, dd, *J* = 2.4, 14.9 Hz), 1.82-1.70 (4H, m), 1.65 (3H, d, *J* = 1.1 Hz), 1.51-1.33 (4H, m), 1.38 (3H, s), 1.34 (3H, s), 1.00 (3H, d, *J* = 6.8 Hz), 0.90 (3H, t, *J* = 7.2 Hz), 0.86 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 171.0, 166.6, 159.8, 152.5, 137.0, 131.2, 129.4, 126.0, 120.4, 114.2, 109.3, 84.5, 82.4, 82.2, 73.5, 71.5, 64.61, 64.58, 54.9, 51.0, 45.7, 43.2, 41.0, 40.8, 37.4, 36.5, 33.9, 33.2, 26.4, 24.6, 19.0, 18.2, 16.9, 16.6, 14.9. IR: 2960, 2870, 1727, 1514, 1249, 1172, 1036. MS (EI) *m/z* (rel. intensity): 644 ([M^+], 0.4), 140 (39), 122 (11), 121 (100), 87 (68). HRMS (ESI): *calcd.* for ($C_{37}H_{56}O_9$+Na): 667.3822, *found* 667.3819 (M+Na).

Compound 24a. Dry LiI was added to a solution of ester **23** (33 mg, 0.051 mmol) in pyridine (2 mL) and the resulting mixture was stirred for 30 h at 125°C. The mixture was cooled to 0°C before it was diluted with CH_2Cl_2 (10 mL) and washed with HCl (2 M, 12 mL). The aqueous phase was repeatedly extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, filtered and evaporated, and the residue was rapidly passed through silica (hexanes/EtOAc, 1:1 + 1 % HOAc). The crude acid **24** thus formed was used in the next step without further purification.



24a

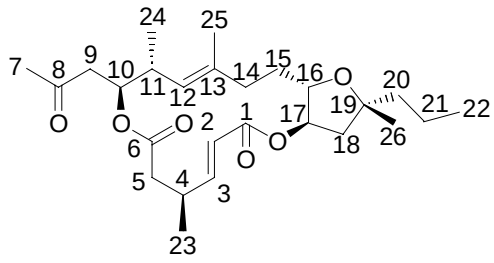
H_2O (1 mL) was added to a solution of crude **24** in HOAc (1 mL) and the resulting mixture was stirred for 15 min at 65°C. After cooling to ambient temperature, the mixture was diluted with EtOAc and H_2O, and the aqueous phase was repeatedly extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1 + 1 % HOAc) to afford carboxylic acid **24a** as a colorless syrup (16 mg, 53 % over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz), 6.99 (1H, dd, *J* = 7.1, 15.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 5.80 (1H, dd, *J* = 1.3, 15.7 Hz), 5.25-5.22 (1H, m), 4.99 (1H, d, *J* = 8.6 Hz), 4.47 (1H, d, *J* = 11.4 Hz), 4.38 (1H, d, *J* = 11.4 Hz), 3.92 (1H, dt, *J* = 6.9, 5.2 Hz), , 3.80 (3H, s), 3.74 (1H, dt, *J* = 7.1, 4.8 Hz), 2.87-2.79 (1H, m), 2.72-2.62 (1H, m), 2.62 (1H, dd, *J* = 7.6, 16.6 Hz), 2.53 (1H, dd, *J* =

5.3, 16.6 Hz), 2.36 (2H, dd, *J* = 1.2, 7.0 Hz), 2.13-1.96 (3H, m), 2.11 (3H, s), 1.78 (1H, dd, *J* = 4.2, 13.0 Hz), 1.63-1.42 (4H, m), 1.59 (3H, d, *J* = 1.1 Hz), 1.38-1.26 (2H, m), 1.31 (3H, s), 1.12 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 5.5 Hz), 0.91 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 171.2, 169.8, 159.4, 154.1, 137.4, 130.5, 129.4, 124.9, 120.1, 114.0, 83.6, 83.2, 81.9, 73.8, 71.4, 55.4, 45.6, 45.2, 42.6, 40.8, 35.9, 35.6, 33.3, 33.0, 30.4, 26.3, 19.0, 18.0, 17.1, 16.5, 14.8. IR: 2961, 1723, 1699, 1514, 1248, 1171, 1036. MS (EI) *m/z* (rel. intensity): 428 (3), 140 (22), 122 (12), 121 (100), 43 (14). HRMS (ESI): *calcd.* for ($C_{34}H_{50}O_8$+Na): 609.3403, *found* 609.3407 (M+Na).

Seco-Acid 25. An aqueous phosphate buffer solution (pH 7, 1 mL) was added to a solution of acid **24a** (15 mg, 0.026 mmol) in CH_2Cl_2 (1 mL). DDQ (23 mg, 0.102 mmol) was introduced at 0°C and the mixture was stirred for 5 h at ambient temperature. H_2O was added and the mixture was repeatedly extracted with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1 + 1 % HOAc → hexanes/EtOAc, 2:1 + 1 % HOAc) to afford carboxylic acid **25** as a colorless syrup (10 mg, 84 %). $[\alpha]_D^{20}$ = –19.5° (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, dd, *J* = 7.5, 15.7 Hz), 5.80 (1H, dd, *J* = 1.2, 15.7 Hz), 5.26-5.20 (1H, m), 5.02 (1H, d, *J* = 9.6 Hz), 4.04 (1H, td, *J* = 5.1, 7.4 Hz), 3.80-3.75 (1H, m), 2.88-2.77 (1H, m), 2.70-2.50 (3H, m), 2.43-2.31 (2H, m), 2.17-2.03 (4H, m), 2.12 (3H, s), 1.75-1.25 (7H, m), 1.59 (3H, d, *J* = 1.2 Hz), 1.33 (3H, s), 1.12 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.2 Hz), 0.91 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 169.4, 154.9, 137.1, 125.2, 120.3, 83.7, 83.0, 73.8, 46.2, 45.8, 45.5, 41.1, 36.0, 35.7, 33.5, 32.3, 30.4, 26.9, 19.3, 18.0, 17.5, 16.4, 14.7. IR: 3427, 2964, 1718, 1656, 1451, 1379, 1264, 1162, 1081, 988. MS (EI) *m/z* (rel. intensity): 466 ([M^+], 1), 308 (14), 156 (67), 107 (26), 95 (33), 84 (31), 71 (40), 55 (25), 43 (100). HRMS (ESI): *calcd.* for ($C_{26}H_{42}O_7$+Na): 489.2828, *found* 489.2827 (M+Na).

Amphidinolide X (1). Et_3N (11 μL, 0.081 mmol) and 2,4,6-trichlorobenzoyl chloride (3.8 μL, 0.024 mmol) were added to a solution of hydroxy acid **25** (7.5 mg, 0.016 mmol) in THF (2 mL). The mixture was stirred for 1h at room temperature before most of the THF was removed under a flow of Ar. The residue was diluted with toluene (5 mL) and the resulting solution was added over 2 h to a solution of DMAP (39 mg, 0.322 mmol) in toluene (20 mL) at ambient temperature. Once the addition was complete, the mixture was stirred for an additional 2h. For work up, the solvent was evaporated and the remaining syrup was purified by flash chromatography (hexanes/EtOAc, 10:1 → 6:1) to afford Amphidinolide X **1** as a colorless syrup (4.5 mg, 62 %). $[\alpha]_D^{17}$ = –25.6° (c = 1.0, $CHCl_3$) [lit.[2]: $[\alpha]_D^{17}$ = –12° (c = 1.0, $CHCl_3$)]. ^{1}H NMR (see Table 1). ^{13}C NMR (see Table 2). IR: 2963, 1721, 1451, 1262, 1185, 1079 cm^{-1}.

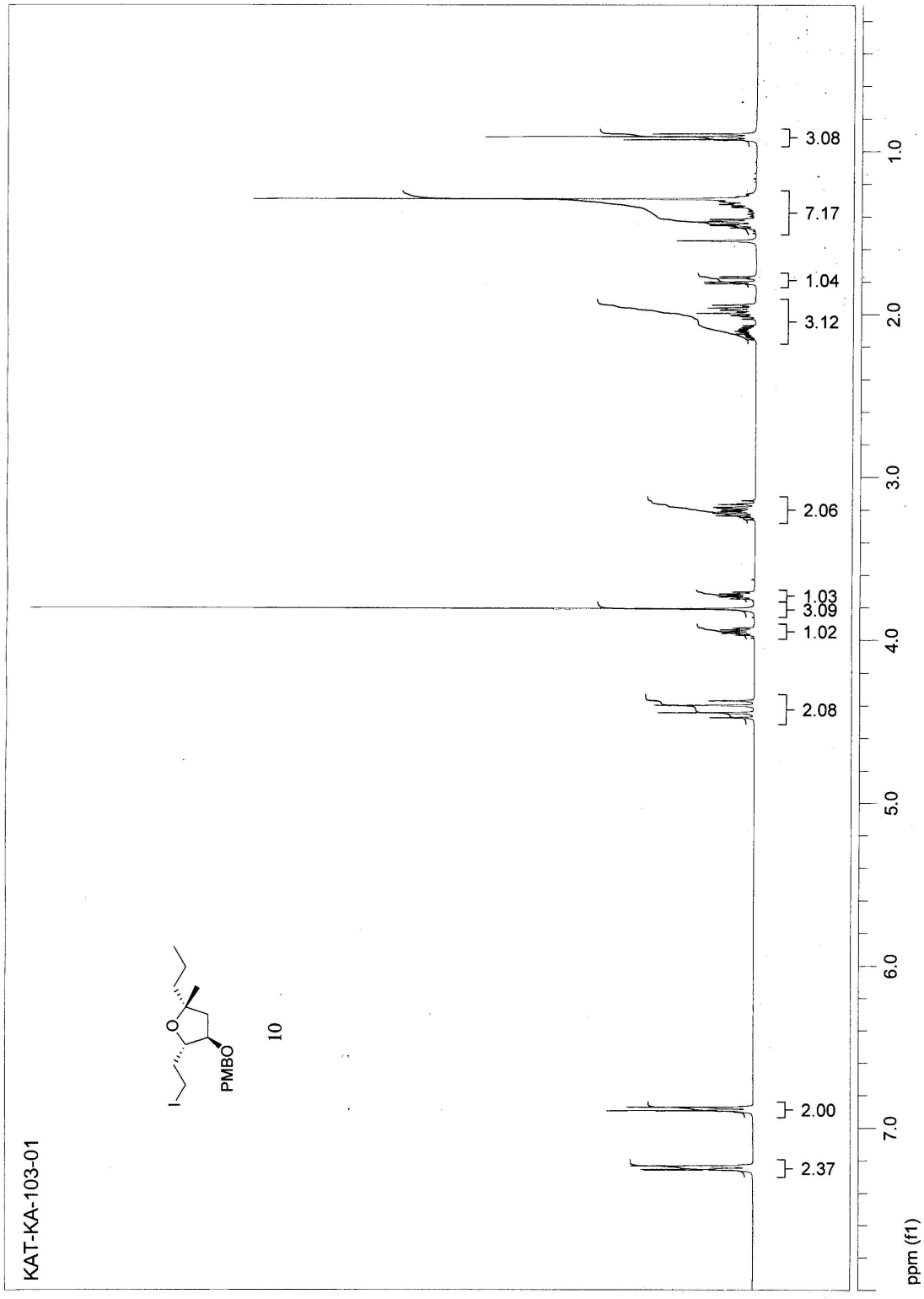
Table 1: Comparison of the ^{1}H NMR spectrum of authentic **1** with that of the synthetic sample (600 MHz, $CDCl_3$). Numbering scheme as shown in the insert.



Position	Natural **1**, δ (multiplicity, *J* in Hz)	Synthetic **1**, δ (multiplicity, *J* in Hz)	Δδ
2	5.79 (d, *15.8*)	5.79 (d, *15.8*)	±0
3	7.12 (dd, *7.2, 15.8*)	7.12 (dd, *7.2, 15.8*)	±0
4	2.79 (m)	2.78 (m)	-0.01
5	2.58 (dd, *3.7, 13.4*)	2.58 (dd, *3.6, 13.4*)	±0
	2.41 (dd, *6.3, 13.4*)	2.41 (dd, *6.4, 13.4*)	±0
7	2.14 (s)	2.14 (s)	±0
9	2.69 (dd, *6.0, 16.5*)	2.69 (dd, *6.0, 16.5*)	±0
	2.57 (dd, *8.2, 16.5*)	2.58 (dd, *7.2, 16.5*)	+0.01
10	5.21 (m)	5.20 (m)	-0.01
11	2.69 (m)	2.69 (m)	±0
12	4.95 (d, *10.3*)	4.96 (d, *10.3*)	+0.01
14	2.18 (m)	2.17 (m)	-0.01
	2.11 (br. t, *9.4*)	2.12 (m)	+0.01
15	1.95 (tt, *2.9, 13.4*)	1.95 (tt, *3.2, 13.5*)	±0
	1.54 (m)	1.54 (m)	±0
16	3.97 (dt, *11.1, 3.6*)	3.97 (dt, *11.3, 3.6*)	±0
17	5.19 (m)	5.21 (m)	+0.02
18	2.16 (m)	2.18 (m)	+0.02
	1.75 (dd, *2.4, 13.8*)	1.75 (dd, *2.5, 13.9*)	±0
20	1.50 (m)	1.51 (m)	+0.01
21	1.34 (m)	1.35 (m)	+0.01
22	0.92 (t, *7.4*)	0.93 (t, *7.3*)	+0.01
23	1.14 (d, *6.8*)	1.15 (d, *6.9*)	+0.01
24	0.92 (d, *6.8*)	0.93 (d, *6.9*)	+0.01
25	1.55 (s)	1.55 (s)	±0
26	1.30 (s)	1.30 (s)	±0

Table 2: Comparison of the ^{13}C NMR spectrum of authentic **1** with that of the synthetic sample (150 MHz, $CDCl_3$). Numbering scheme as shown in the insert to Table 1.

Position	Natural **1**	Synthetic **1**	$\Delta\delta$
1	165.7	165.8	+0.1
2	120.2	120.4	+0.2
3	153.2	153.2	±0.0
4	33.1	33.2	+0.1
5	41.4	41.6	+0.2
6	170.7	170.8	+0.1
7	30.4	30.5	+0.1
8	205.5	205.4	-0.1
9	47.1	47.3	+0.2
10	74.2	74.4	+0.2
11	35.5	35.7	+0.2
12	126.0	126.1	+0.1
13	135.5	135.6	+0.1
14	35.3	35.5	+0.2
15	30.4	30.5	+0.1
16	80.5	80.6	+0.1
17	78.4	78.6	+0.2
18	43.5	43.7	+0.2
19	82.9	83.0	+0.1
20	44.2	44.4	+0.2
21	17.8	17.9	+0.1
22	14.6	14.7	+0.1
23	17.5	17.7	+0.2
24	18.1	18.2	+0.1
25	15.4	15.5	+0.1
26	24.5	24.7	+0.2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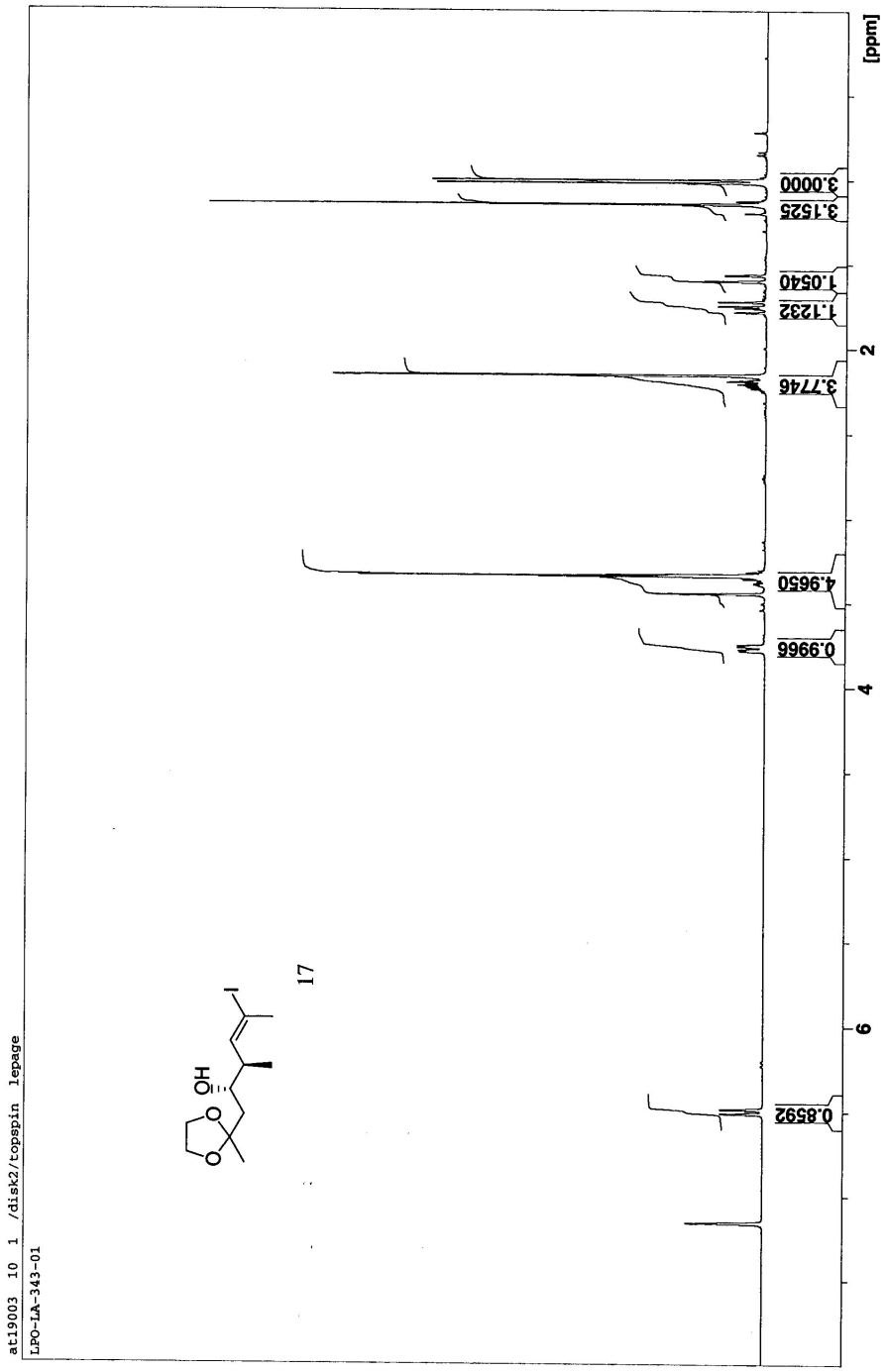
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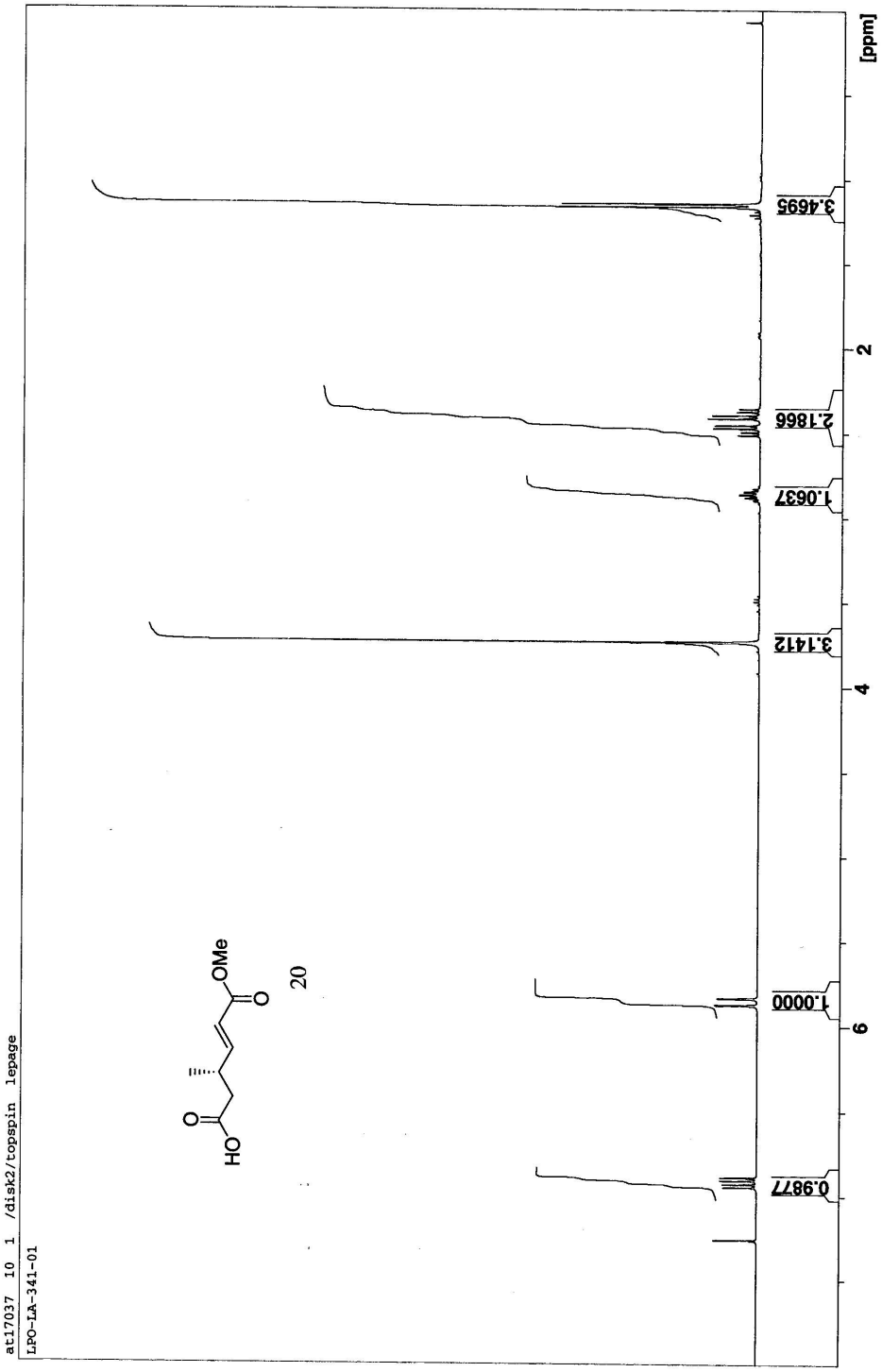
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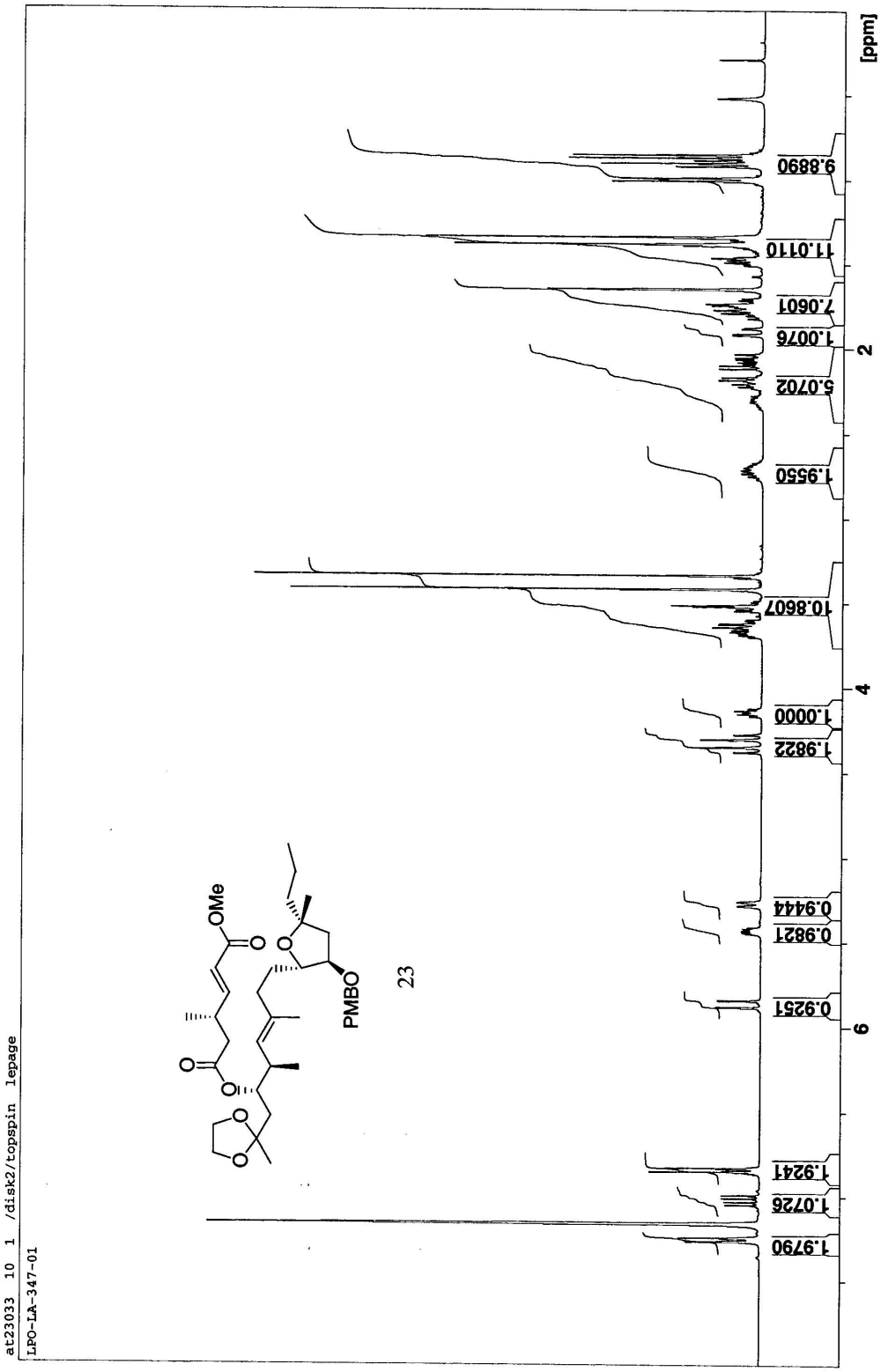
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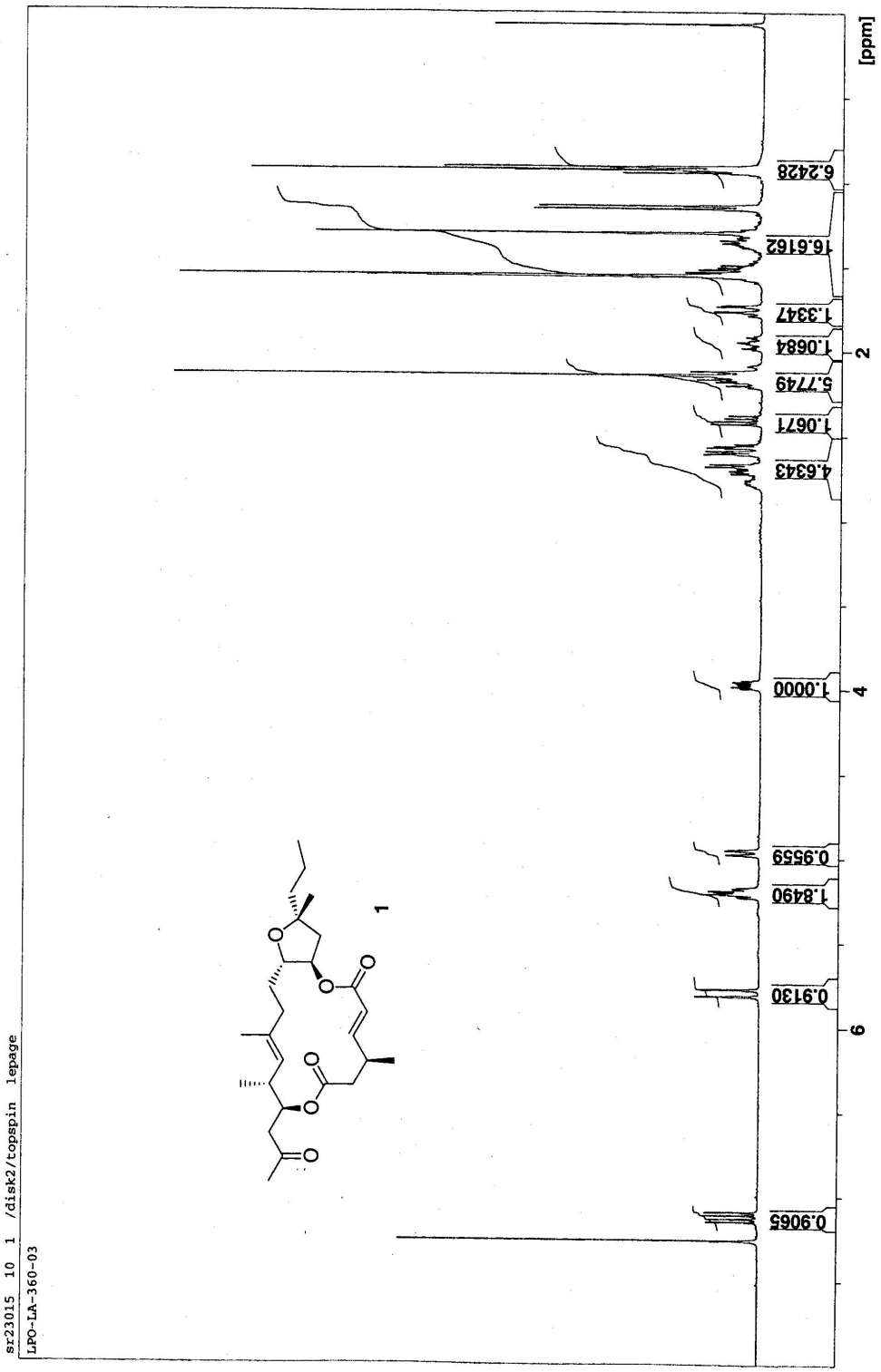
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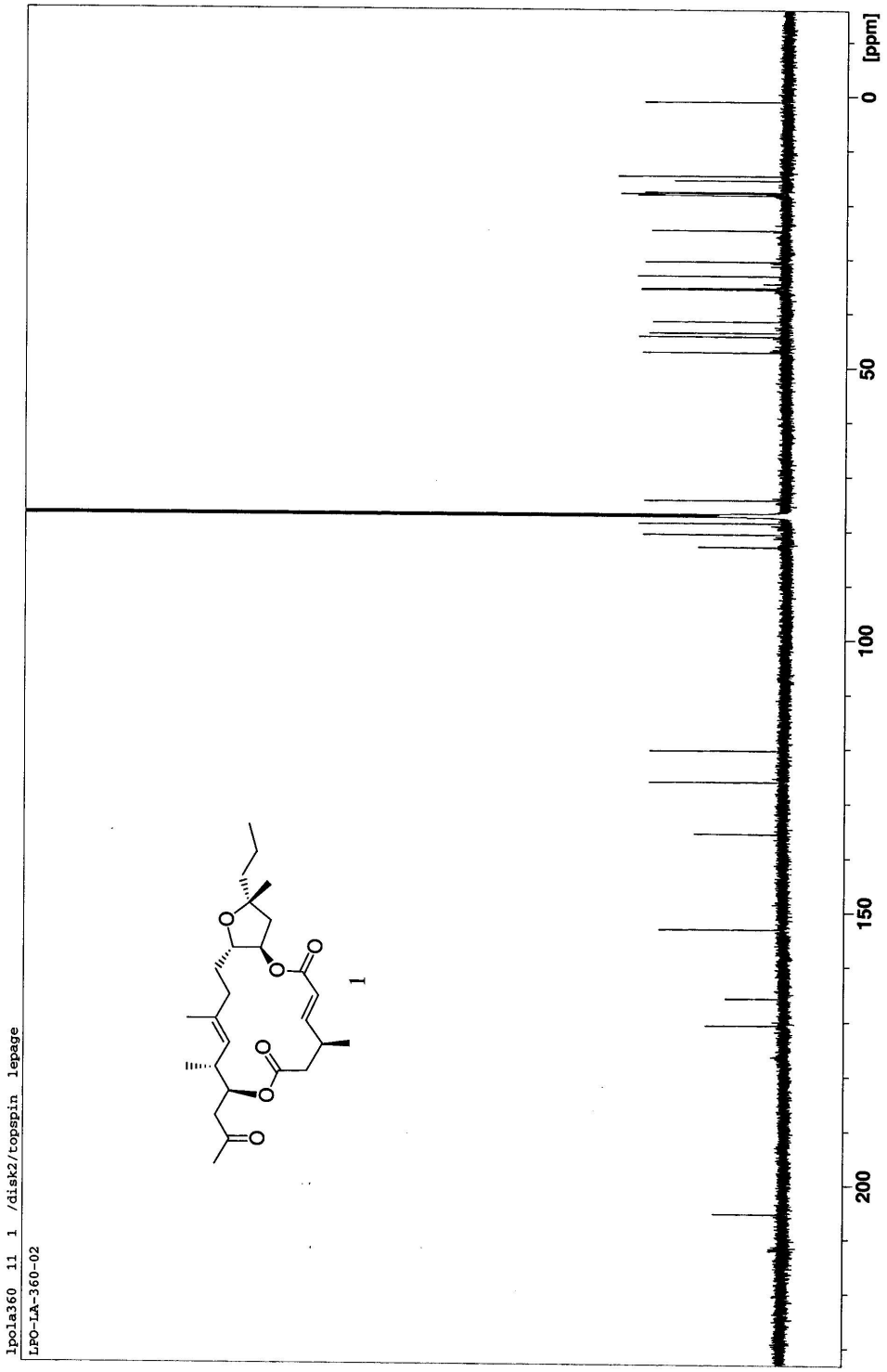
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