Total Synthesis of Natural and Non-Natural $\Delta^{5,6}\Delta^{12,13}$ Jatrophane Diterpenes and their Evaluation as MDR-Modulators

• SUPPORTING INFORMATION•

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GENERAL EXPERIMENTAL METHODS

Methods and Materials: Unless otherwise stated, commercially available reagents were used as purchased. Solvents were dried by passage through activated alumina columns of a solvent purification system: tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethylether (Et_2O), acetonitrile, and toluene (PhMe). Diisopropylamine was distilled from CaH_2 and stored over activated 3 Å molecular sieves. Methanol was distilled from magnesium and stored over activated 3 Å molecular sieves. Dimethyl sulfoxide (DMSO, ≥99.5%, stored over molecular sieves) was used as purchased.

2-Iodoxybenzoic acid (IBX) was prepared according to the literature[1] and was stored in the refrigerator. The concentrations of *n*-BuLi and MeLi were determined employing 4-biphenylmethanol as indicator.[2]

All moisture-sensitive reactions were performed in flame-dried septum-sealed glassware under an atmosphere of argon. Reagents were transferred by means of syringe or cannula. Analytical TLC was performed using pre-coated silica gel foils (4 cm). Visualization was achieved using 365 nm ultraviolet irradiation followed by staining with the Kägi-Miescher reagent[3] (*p*-anisaldehyde 2.53 vol%, acetic acid 0.96 vol%, ethanol 93.06 vol%, conc. H_2SO_4 3.45 vol%) or the $KMnO_4$ reagent (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL NaOH (5%), 300 mL H_2O). Flash chromatography[4] was performed using silica gel (particle size 0.040–0.063 mm) and mixtures of cyclohexane and ethyl acetate as eluent. A commercially available ozonizer with oxygen as source was employed with an amperage of 1 A.

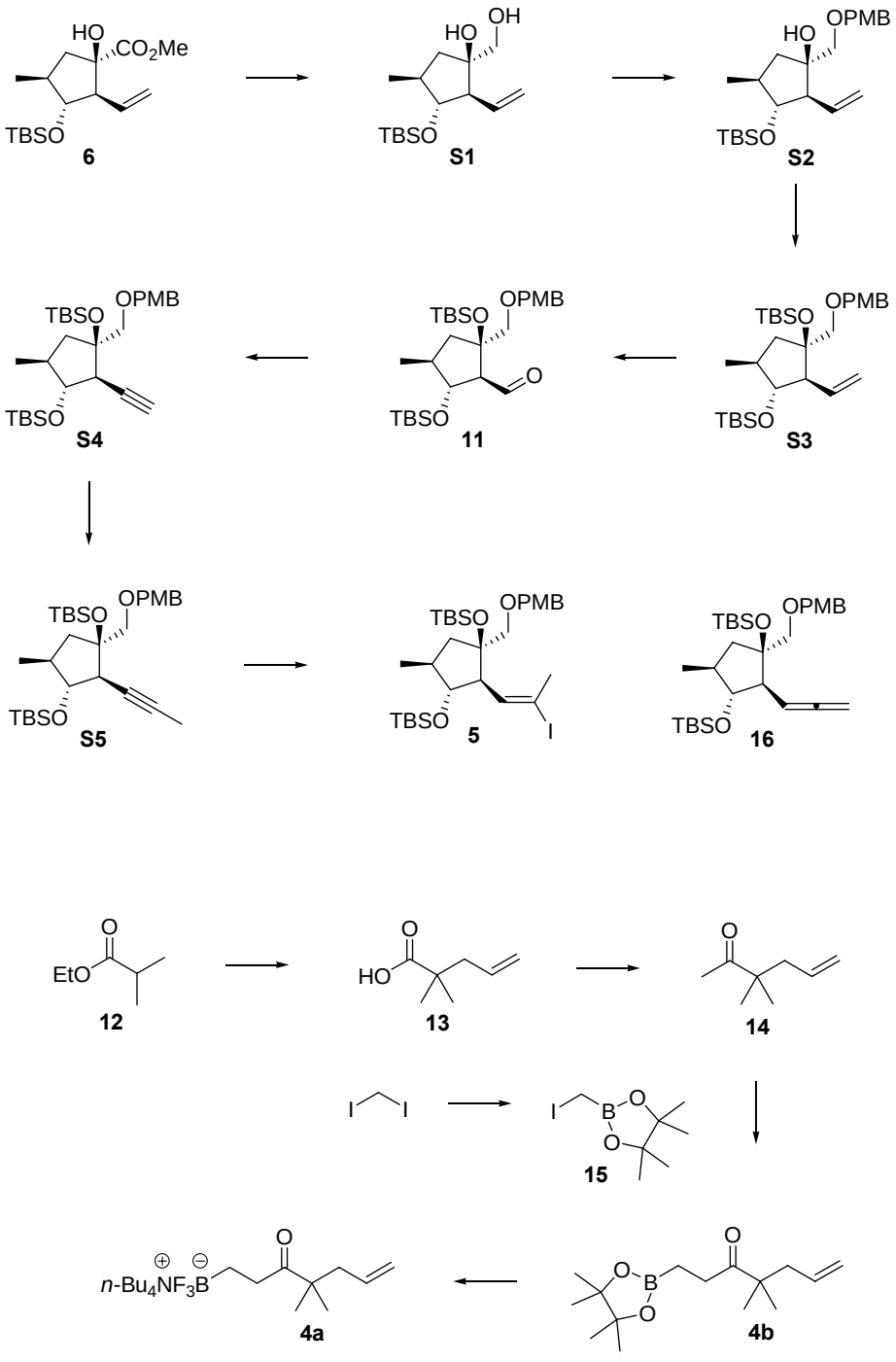
[1] (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. b) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
[2] Juaristi, E.; Martinez-Richa, A.; Garcia-Rivera, A.; Cruz-Sanchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603–2606.
[3] (a) Miescher, K. *Helv. Chim. Acta* **1946**, *29*, 743–752. (b) Stahl, E., Kaltenbach. U. *J. Chromatog.* **1961**, *5*, 351–355.
[4] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

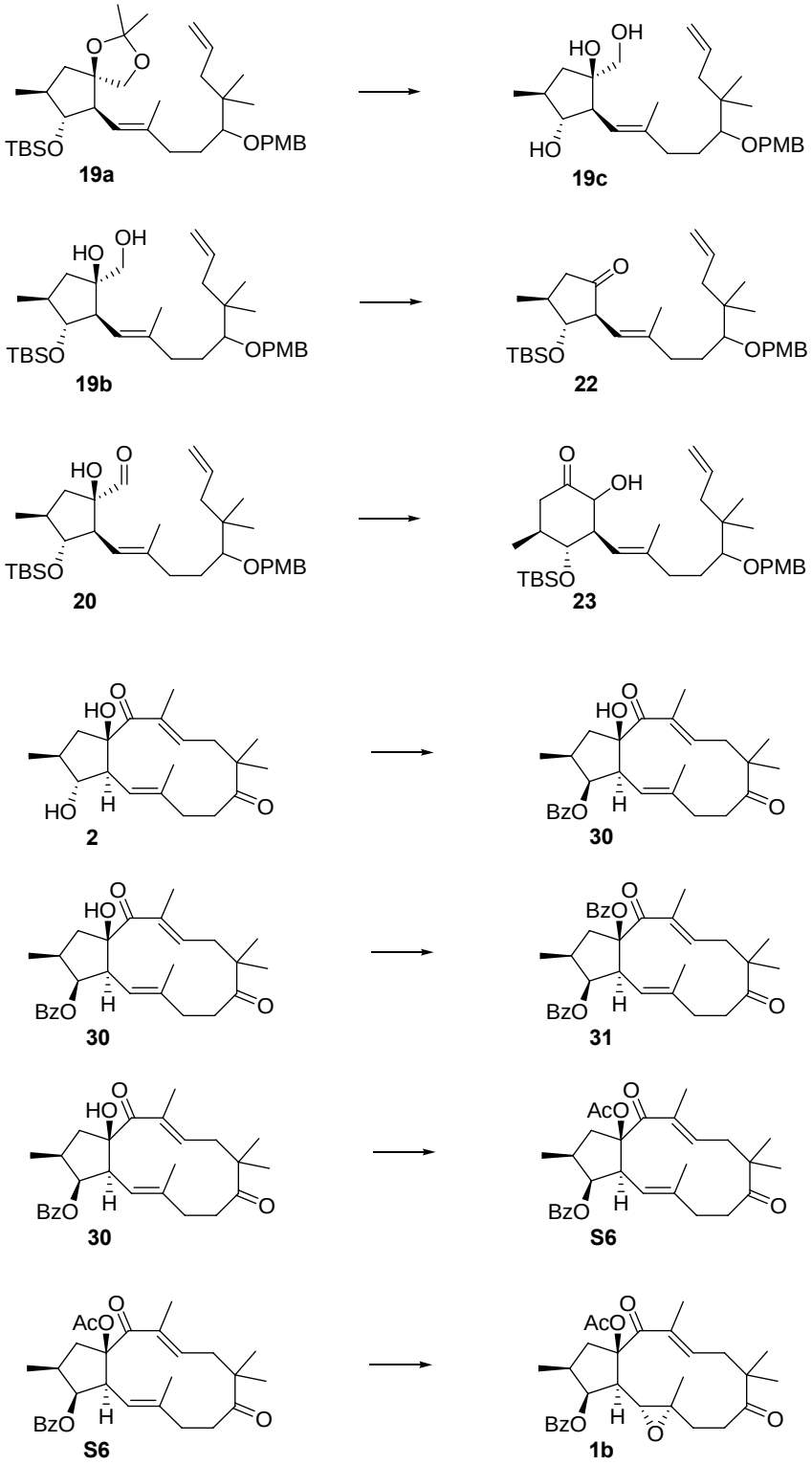
^{1}H NMR spectra were recorded at 400 MHz, 500 MHz, or 600 MHz. Chemical shifts are reported in ppm relative to chloroform (δ 7.26 ppm).[5] Signal splitting patterns are labeled by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non equivalent resonances. ^{13}C NMR spectra were recorded at 101 or 125 MHz. Chemical shifts are reported in ppm relative to $CDCl_3$ (77.1 ppm).[5] The assignment of CH_2 is based on APT (attached proton test). ^{19}F NMR spectra were recorded at 188 MHz. Chemical shifts are reported in ppm relative to C_6F_6 (−164.9 ppm). ^{11}B NMR spectra were recorded at 96 MHz. Chemical shifts are reported in ppm relative to $F_3B{\bullet}OEt_2$ (0.00 ppm).

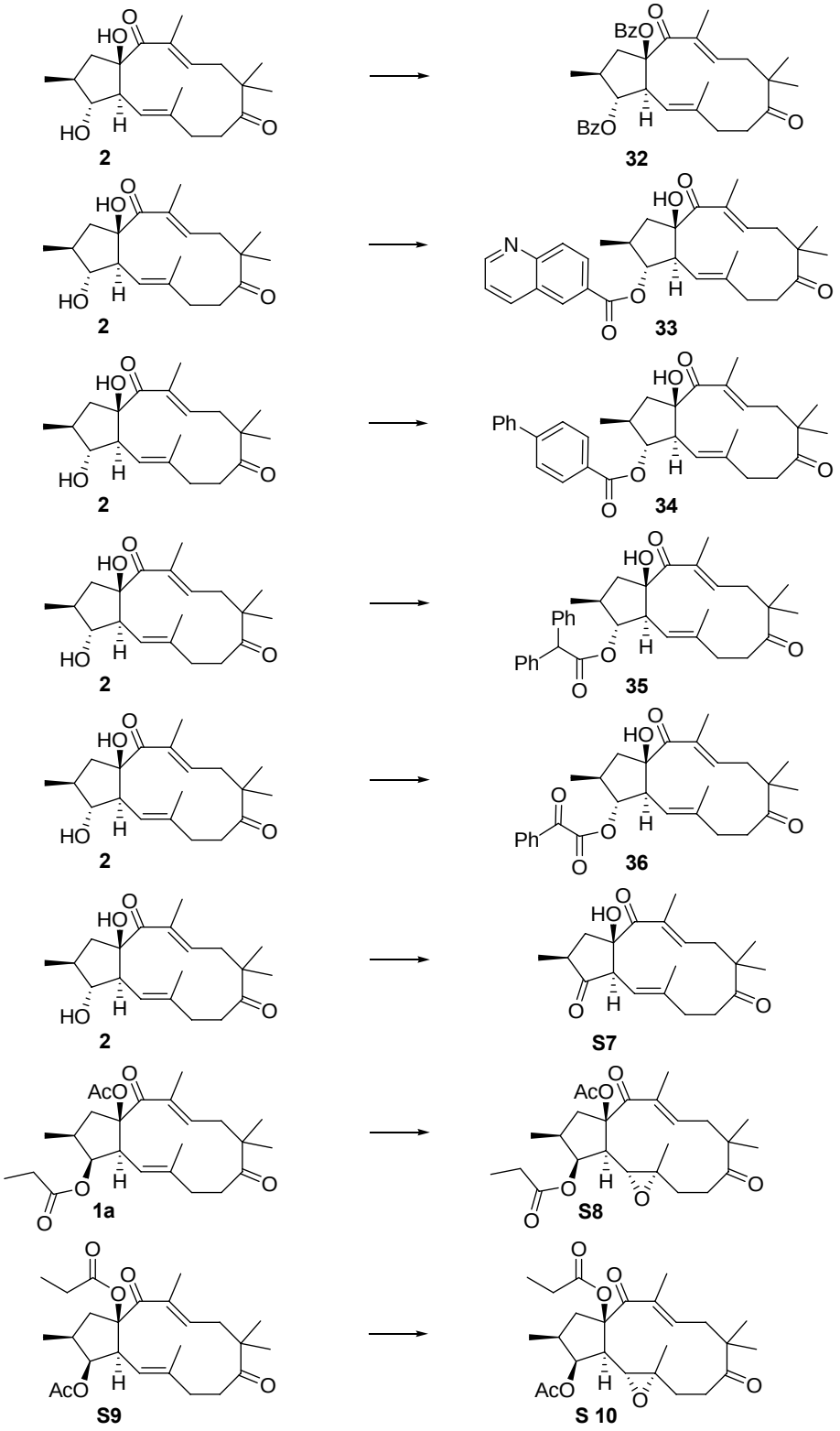
Infrared spectra were recorded as a thin film on a KBr disk ("film on KBr"). Molecular formula assignment was confirmed by combustion elemental analysis. High resolution mass spectra were recorded on a LTQ Orbitrap spectrometer by electrospray ionization (ESI). Melting points were measured with a capillary melting point device. For water determinations of solvents a coulometer according to Karl Fischer was applied.

[5] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

CHART OF ALL SYNTHESIZED COMPOUNDS IN ORDER OF THEIR APPEARANCE




19a
19c
19b
22
20
23
2
30
30
31
30
S6
S6
1b


2
32
2
33
2
34
2
35
2
36
2
S7
1a
S8
S9
S 10

KINETIC EXPERIMENTS

Kinetic experiments were conducted in a sealed glass tube in decane at 180 °C (oil bath temperature). The relative ratio of **8** to **6** and **7** was determined from the ^{1}H NMR spectra of the crude product mixture. The two diastereomers **6** and **7** possess sufficiently separated resonances in the ^{1}H NMR spectrum to enable a determination of the consumption of the substrate and the build-up of the product as a function of time. Initial first order rate constants (k_i) were calculated by considering the conversion data from an initial 16 h reaction period.

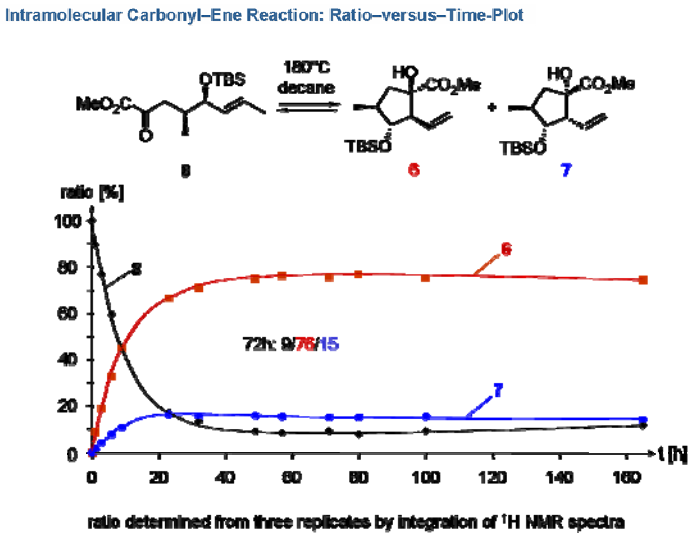


FIGURE SI-1. Ratio–versus–time-plot for the carbonyl–ene reaction of **8** to **6** and **7** at 180 °C in decane. Averaged ratios from three replicates based on the integration of ^{1}H NMR spectra.

The conversion of **8** to **6** and **7** was determined as a function of time; the resulting conversion–versus–time-plot is depicted in Figure SI-1. The consumption of **8** proceeds with an initial first order rate constant (k_{obs}) of 8.8×10^{-5} s^{-1}. The k_{obs} for the formation of **6** (8.3×10^{-5} s^{-1}) and **7** (1.2×10^{-5} s^{-1}) from **8** indicate that the formation of **6** proceeds 7 times faster than the formation of **7**. This approximated value corresponds to a difference in the free energy of activation ($\Delta\Delta G^{\ddagger}$) of 1.7 kcal/mol. The persisting residual amount of the substrate **8** indicates an apparent equilibrium concentration of **8** as a consequence of an only weakly exergonic process.

Next, we set out establishing experimentally that the ene reaction of **8** to **6** and **7** is reversible, and that the formation of **6** is not only preferred kinetically but also thermodynamically. For that purpose, the chromatographically separated diastereomers **6** and **7** were subjected to the reaction conditions of the uncatalyzed carbonyl–ene reaction of **8**. Hence, heating **6** in decane to 180 °C resulted in the formation of a mixture of **6** and **7** via the retro-ene / ene reaction pathway (Figure SI-2); the apparent equilibrium at 180 °C was reached after 90 h, thus providing an estimated equilibrium constant ($K_{6/7}$ = 85/15, $\Delta\Delta G^{r}_{180°C}$ = 1.6 kcal/mol). Subjecting **7** to analogous reaction conditions also resulted in the formation of a **6/7** mixture (Figure SI-2). Again, the estimated equilibrium constant ($K_{6/7}$ = 85/15) can be determined from the conversion-versus-time plot; however, the apparent equilibrium was reached already after 50 h, indicating that the conversion of **6** or **7** to a mixture of **6** and **7** proceeds with different rates. Accordingly, the approximated initial rate constants indicate that **7** is consumed ten times faster than **6**. The equilibrium concentration of **8** was not determined in these experiments.

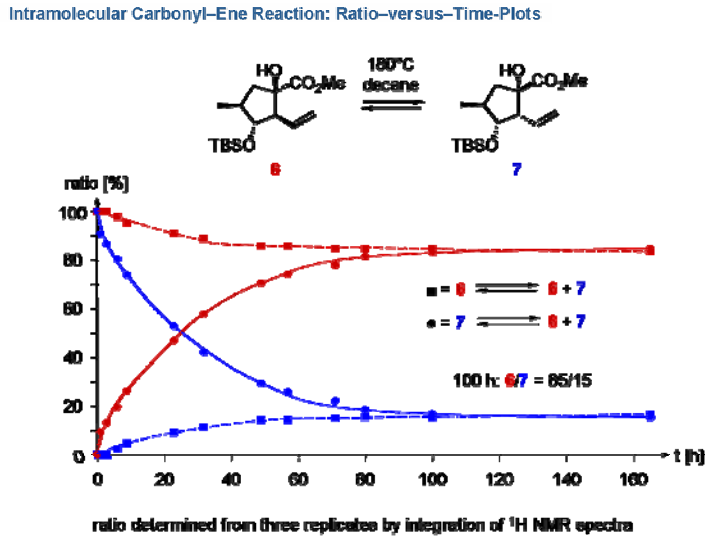
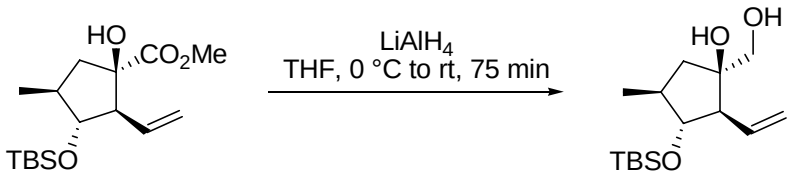


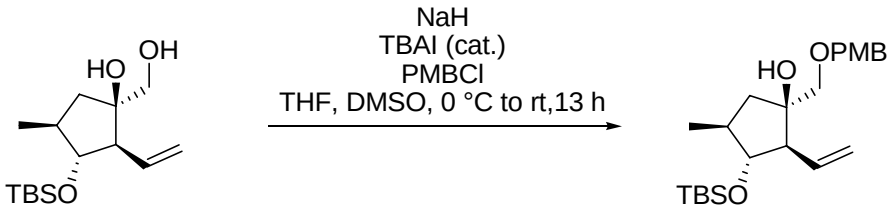
FIGURE SI-2. Conversion–versus–time-plot for the retro-ene / ene reaction equilibrium between **6** and **7** at 180 °C in decane

EXPERIMENTAL PROCEDURES AND ANALYTICAL DATA FOR COMPOUND



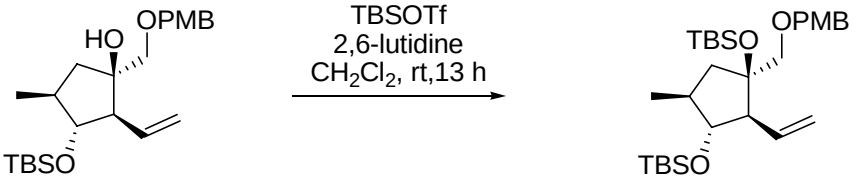
6 **S1** (90%)

Diol S1: To a stirred solution of the ester **6** (2.73 g, 8.69 mmol, 1 equiv) in THF (42 mL, 4.8 mL/mmol **6**) $LiAlH_4$ (989 mg, 26.06 mmol, 3 eq) was carefully added at 0 °C. After being stirred for 75 minutes at ambient temperature, the reaction was carefully diluted at 0 °C by with saturated aqueous NH_4Cl solution. The phases were then separated, the aqueous layer was extracted with CH_2Cl_2 (5×), the combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. After purification by chromatography (cyclohexane/ethyl acetate 10/1 to 2/1), the diol **S1** (2.25 g, 7.82 mmol, 90%) was obtained as a white solid (mp: 57 °C): R_f 0.56 (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.08 (d, ^3J = 7.0 Hz, 3H), 1.29 (dd, ^3J = 9.7 Hz, ^2J = 13.9 Hz, 1H), 1.63 (s, br, 2OH), 1.71–1.83 (m, 1H), 2.13 (dd, ^3J = 9.0 Hz, ^2J = 13.9 Hz, 1H), 2.20 (dd, $^3J_1 = {}^3J_2$ = 9.2 Hz, 1H), 3.43 (d^{AB}, ^2J = 11.0 Hz, 1H), 3.53 (d^{AB}, ^2J = 11.0 Hz, 1H), 3.70 (dd, $^3J_1 = {}^3J_2$ = 8.8 Hz, 1H), 5.17 (dd, ^2J = 1.5 Hz, ^3J = 17.3 Hz, 1H), 5.24 (dd, ^2J = 1.5 Hz, ^3J = 10.3 Hz, 1H), 5.87 (ddd, $^3J_1$ = 9.2 Hz, $^3J_2$ = 10.3 Hz, $^3J_3$ = 17.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.0 (CH_3), –3.4 (CH_3), 18.1 (C), 18.5 (CH_3), 26.0 (3 × CH_3), 39.9 (CH), 41.7 (CH_2), 60.1 (CH), 70.3 (CH_2), 78.9 (C), 83.1 (CH), 119.5 (CH_2), 136.9 (CH); IR (film on KBr) ν 3310, 2955, 2930, 2860, 1125, 1045, 775 cm^{-1}; Anal. Calcd for $C_{15}H_{30}SiO_3$: C, 62.89; H, 10.55. Found: C, 62.8; H, 10.7; $[\alpha]^{25}_D$ +16.6 (c 0.308, $CHCl_3$).



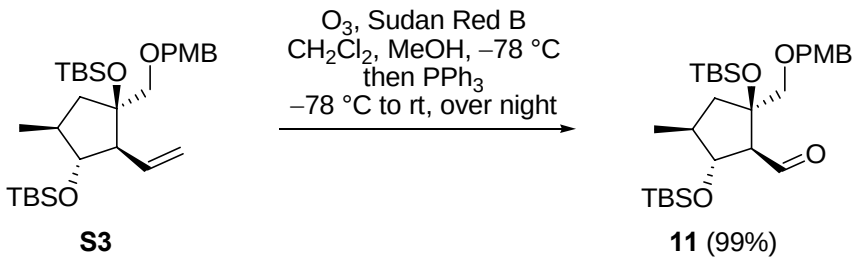
S1 **S2** (98%)

PMB ether S2: To a solution of the diol **S1** (729 mg, 2.562 mmol, 1 equiv) in THF (13 mL, 5 mL/mmol **S1**) and DMSO (6.5 mL, 2.5 mL/mmol **S1**) NaH (257 mg, 60% dispersion in mineral oil, 6.415 mmol, 2.5 equiv), TBAI (48 mg, 0.13 mmol, 0.05 equiv) and PMBCl (0.35 mL, 2.57 mmol, 1 equiv) were added at 0 °C. The reaction mixture was stirred for 13 hours at ambient temperature and subsequently diluted with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. Purification by chromatography (cyclohexane/ethyl acetate 100/1 to 50/1) provided the PMB ether **S2** (1027 mg, 2.526 mmol, 98%) as a light yellow oil: R_f 0.52 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.06 (d, ^3J = 6.5 Hz, 3H), 1.34 (dd, $^3J_1$ = 9.0 Hz, $^3J_2$ = 13.6 Hz, 1H), 1.68–1.80 (m, 1H), 2.13 (dd, $^3J_1$ = 9.0 Hz, $^3J_2$ = 13.6 Hz, 1H), 2.21 (dd, $^3J_1$ = $^3J_2$ = 9.2 Hz, 1H), 2.28 (s, 1H), 3.30 (d^{AB}, ^2J = 9.0 Hz, 2H), 3.70 (dd, $^3J_1$ = $^3J_2$ = 8.8 Hz, 1H), 3.81 (s, 3H), 4.47 (d^{AB}, ^2J = 11.5 Hz, 2H), 5.08 (dd, ^2J = 1.9 Hz, ^3J = 17.3 Hz, 1H), 5.17 (dd, ^2J = 1.9 Hz, ^3J = 10.5 Hz, 1H), 5.83 (ddd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 10.5 Hz, $^3J_3$ = 17.3 Hz, 1H), 6.88 (d, ^3J = 8.5 Hz, 2H), 7.24 (d, ^3J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.0 (CH_3), –3.4 (CH_3), 18.1 (C), 18.6 (CH_3), 26.0 (3 × CH_3), 39.9 (CH), 42.9 (CH_2), 55.3 (CH_3), 59.9 (CH), 73.2 (CH_2), 77.1 (CH_2), 78.2 (C), 83.2 (CH), 113.8 (2 × CH), 118.8 (CH_2), 129.3 (2 × CH), 130.1 (C), 136.6 (CH), 159.3 (C); IR (film on KBr) ν 3480, 2955, 2930, 2855, 1615, 1515, 1465, 1250, 1115, 875, 835, 775 cm^{-1}; Anal. Calcd for $C_{23}H_{38}SiO_4$: C, 67.94; H, 9.42. Found: C, 67.96; H, 9.43; $[\alpha]^{25}_D$ +18.6 (c 1.18, $CHCl_3$).

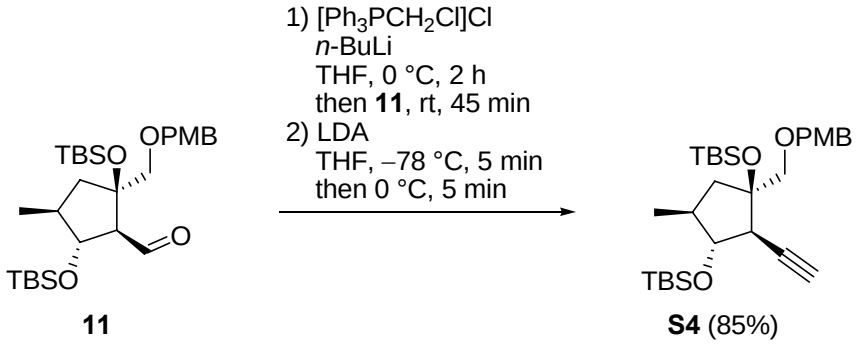


S2 **S3** (88%)

Bis(silyl) ether S3: To a solution of the alcohol **S2** (344 mg, 0.846 mmol, 1 equiv) in CH_2Cl_2 (5 mL, 6 mL/mmol **S2**) 2,6-lutidine (0.42 mL, 3.618 mmol, 4.3 equiv) and TBSOTf (0.42 mL, 1.827 mmol, 2.2 equiv) were added. The reaction mixture was stirred for 13 hours at ambient temperature and then diluted with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. Purification by chromatography (cyclohexane to cyclohexane/ethyl acetate 100/1) afforded the bis(silyl) ether **S3** (388 mg, 0.745 mmol, 88%) as a light yellow oil: R_f 0.71 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.03 (s, 3H), 0.06 (s, 3H), 0.86 (s, 18H), 1.06 (d, ^3J = 6.5 Hz, 3H), 1.29 (dd, $^3J_1$ = 8.5 Hz, $^3J_2$ = 14.1 Hz, 1H), 1.71–1.83 (m, 1H), 2.23–2.34 (m, 2H), 3.22 (d^{AB}, ^2J = 8.8 Hz, 2H), 3.74 (dd, $^3J_1$ = $^3J_2$ = 9.0 Hz, 1H), 3.81 (s, 3H), 4.31 (d^{AB}, ^2J = 11.5 Hz, 2H), 4.97 (dd, ^2J = 2.0 Hz, ^3J = 17.6 Hz, 1H), 5.06 (dd, ^2J = 2.0 Hz, ^3J = 10.0 Hz, 1H), 5.82 (ddd, $^3J_1$ = 7.5 Hz, $^3J_2$ = 10.0 Hz, $^3J_3$ = 17.6 Hz, 1H), 6.88 (d, ^3J = 8.5 Hz, 2H), 7.24 (d, ^3J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.0 (CH_3), –3.3 (CH_3), –2.4 (CH_3), –2.4 (CH_3), 18.2 (C), 18.6 (C), 19.2 (CH_3), 26.1 (6 × CH_3), 39.8 (CH), 42.6 (CH_2), 55.4 (CH_3), 60.5 (CH), 72.9 (CH_2), 75.0 (CH_2), 82.0 (C), 83.2 (CH), 113.7 (2 × CH), 117.8 (CH_2), 129.2 (2 × CH), 130.6 (C), 137.4 (CH), 159.1 (C); IR (film on KBr) ν 2955, 2930, 2895, 2855, 1615, 1515, 1470, 1465, 1250, 1120, 1045, 835, 775 cm^{-1}; Anal. Calcd for $C_{29}H_{52}Si_2O_4$: C, 66.87; H, 10.06; Found: C, 66.89; H, 9.72; $[\alpha]^{25}_D$ +4.2 (c 0.94, $CHCl_3$).



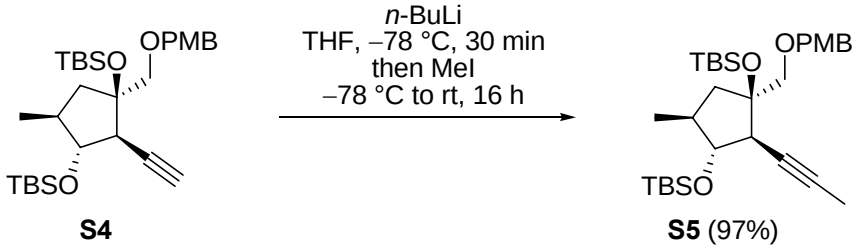
Aldehyde 11: To a solution of the alkene **S3** (354 mg, 0.679 mmol, 1 equiv) in CH_2Cl_2 (4 mL, 6 mL/mmol **S3**) and methanol (2 mL, 3 mL/mmol **S3**) was added a catalytic amount of Sudan Red B. The raspberry red solution was cooled to −78 °C and an ozone/oxygen mixture was passed through the solution until the red color disappeared. The flask was then purged with argon for five minutes and PPh_3 (552 mg, 2.104 mmol, 3.1 equiv) was subsequently added; the solution was then allowed to warm to room temperature over night. Removal of the solvents at reduced pressure deliver the crude product which was purified by vhromatography (cyclohexane to cyclohexane/ethyl acetate 100/1) to afford the aldehyde **11** (355 mg, 0.678 mmol, 99%) as a clear oil: R_f 0.52 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 3H), 0.01 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.81 (s, 9H), 0.84 (s, 9H), 1.05 (d, ^3J = 6.5 Hz, 3H), 1.32 (dd, $^3J_1$ = 10.8 Hz, $^3J_2$ = 13.1 Hz, 1H), 1.69–1.81 (m, 1H), 2.16 (dd, $^3J_1$ = 8.3 Hz, $^3J_2$ = 13.3 Hz, 1H), 2.65 (dd, $^3J_1$ = 2.5 Hz, $^3J_2$ = 8.0 Hz, 1H), 3.43 (d^{AB}, ^2J = 9.5 Hz, 2H), 3.81 (s, 3H), 4.24 (dd, $^3J_1$ = $^3J_2$ = 8.3 Hz, 1H), 4.48 (s, 2H), 6.88 (d, ^3J = 8.5 Hz, 2H), 7.26 (d, ^3J = 8.5 Hz, 2H), 9.72 (d, ^3J = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.4 (CH_3), –4.3 (CH_3), –2.7 (CH_3), –2.5 (CH_3), 17.8 (CH_3), 18.0 (C), 18.3 (C), 25.8 (3 × CH_3), 25.9 (3 × CH_3), 40.3 (CH), 44.0 (CH_2), 55.3 (CH_3), 66.7 (CH), 73.0 (CH_2), 76.7 (CH_2), 77.6 (CH), 83.1 (C), 113.8 (2 × CH), 129.3 (2 × CH), 130.1 (C), 159.2 (C), 202.7 (C); IR (film on KBr) ν 2960, 2860, 1465, 1380, 1255, 1115, 1065, 885, 775 cm^{-1}; Anal. Calcd for $C_{28}H_{50}Si_2O_5$: C, 64.32; H, 9.64; Found: C, 64.56; H, 9.67; $[\alpha]^{25}_D$ +36.6 (c 1.28, $CHCl_3$).



Alkyne S4: *n*-BuLi (0.79 mL, 2.2 M in *n*-hexane, 1.738 mmol, 3.1 equiv) was added to a solution of $[Ph_3PCH_2Cl]Cl$ (775 mg, 2.231 mmol, 4 equiv) in THF (8 mL, 14.4 mL/mmol **11**) at 0 °C and subsequently stirred for 2 h at 0 °C. A solution of the aldehyde **11** (290 mg, 0.555 mmol, 1 equiv) in THF (4 mL, 7.2 mL/mmol **11**) was then added at 0 °C, stirred for 45 minutes at room temperature and then diluted with saturated aqueous NH_4Cl solution and CH_2Cl_2. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×).The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining solid was dissolved in CH_2Cl_2 (~1 mL) and cyclohexane (~50 mL), filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. This procedure was repeated two times. Chromatographic purification (cyclohexane to cyclohexane/ethyl acetate 100/1) afforded the vinyl chloride as light yellow oil: R_f 0.65 (cyclohexane/ethyl acetate 10/1).

A freshly prepared LDA solution [*i*-Pr_2NH (0.74 mL, 5.265 mmol, 9.5 equiv) and *n*-BuLi (2.3 mL, 2.2 M in *n*-hexane, 5.06 mmol, 9.1 equiv) in THF for 20 minutes at 0 °C] was added at −78 °C to a solution of the vinyl chloride in THF (3 mL, 5.4 mL/mmol **11**). After stirring for five minutes at −78 °C and for five minutes at 0 °C, the reaction mixture was diluted by the addition of saturated aqueous NH_4Cl solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane to cyclohexane/ethyl acetate 100/1) delivered the alkyne **S4** (246 mg, 0.474 mmol, 85%) as a light yellow oil: R_f 0.63 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR

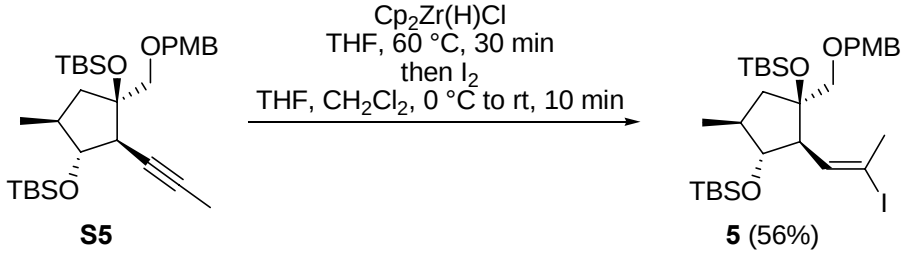
(400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 1.05 (d, ^3J = 6.5 Hz, 3H), 1.28 (dd, $^3J_1$ = 8.0 Hz, $^3J_2$ = 13.6 Hz, 1H), 1.70–1.81 (m, 1H), 2.01 (d, ^4J = 2.0 Hz, 1H), 2.29 (dd, $^3J_1$ = 10.5 Hz, $^3J_2$ = 13.6 Hz, 1H), 2.63 (dd, ^4J = 2.0 Hz, ^3J = 9.3 Hz, 1H), 3.36 (d^{AB}, ^2J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.90 (dd, $^3J_1$ = $^3J_2$ = 8.8 Hz, 1H), 4.45 (d^{AB}, ^2J = 11.5 Hz, 2H), 6.88 (d, ^3J = 8.5 Hz, 2H), 7.25 (d, ^3J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.3 (CH_3), –3.5 (CH_3), –2.4 (CH_3), –2.2 (CH_3), 18.1 (C), 18.6 (C), 19.2 (CH_3), 26.0 (3 × CH_3), 26.1 (3 × CH_3), 39.7 (CH), 42.2 (CH_2), 48.1 (CH), 55.3 (CH_3), 71.5 (CH_2), 73.0 (CH_2), 74.3 (C), 81.3 (C), 83.8 (CH), 83.9 (CH), 113.8 (2 × CH), 129.2 (2 × CH), 130.4 (C), 159.2 (C); IR (film on KBr) ν 3310, 2955, 2930, 2855, 1615, 1515, 1250, 1140, 1115, 835, 775 cm^{-1}; Anal. Calcd for $C_{29}H_{50}Si_2O_4$, 67.13; H, 9.71; Found: C, 67.2; H, 10.0; $[\alpha]^{25}_D$ +10.7 (c 0.608, $CHCl_3$).



S4 **S5** (97%)

Alkyne S5: *n*-BuLi (0.94 mL, 1.9 M in *n*-hexane, 1.786 mmol, 2.8 equiv) was added at –78 °C to a solution of the alkyne **S4** (326 mg, 0.629 mmol, 1 equiv) in THF (7 mL, 11 mL/mmol **S4**). The reaction mixture was stirred for 30 minutes at –78 °C, and MeI (0.56 mL, 8.993 mmol, 14.3 equiv) was subsequently added at –78 °C. While warming to room temperature, the solution was stirred for 16 hours. After dilution with saturated aqueous NH_4Cl solution, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (cyclohexane to cyclohexane/ethyl acetate 100/1) provided the alkyne **S5** (326 mg, 0.612 mmol, 97%) as a light yellow oil: R_f 0.48 (cyclohexane/ethyl acetate 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.10 (s, 3H), 0.14 (s, 3H),

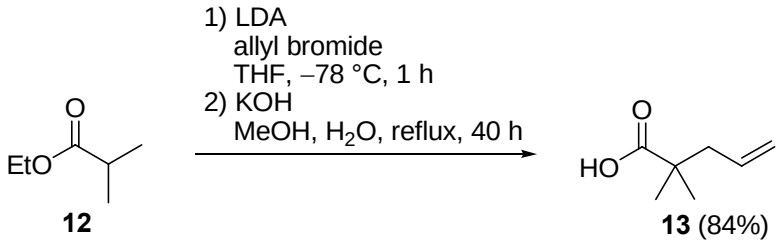
0.88 (s, 9H), 0.90 (s, 9H), 1.04 (d, ^3J = 7.0 Hz, 3H), 1.25 (dd, $^3J_1$ = 8.0 Hz, $^3J_2$ = 13.6 Hz, 1H), 1.67–1.79 (m, 1H), 1.76 (d, ^5J = 2.0 Hz, 3H), 2.27 (dd, $^3J_1$ = 10.5 Hz, $^3J_2$ = 13.6 Hz, 1H), 2.63 (dd, ^5J = 2.0 Hz, ^3J = 9.5 Hz, 1H), 3.34 (d^{AB}, ^2J = 9.0 Hz, 2H), 3.81 (s, 3H), 3.83 (dd, $^3J_1$ = $^3J_2$ = 9.0 Hz, 1H), 4.45 (d^{AB}, ^2J = 11.5 Hz, 2H), 6.87 (d, ^3J = 8.5 Hz, 2H), 7.25 (d, ^3J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.4 (CH_3), –3.8 (CH_3), –2.4 (CH_3), –2.3 (CH_3), 3.8 (CH_3), 18.2 (C), 18.5 (C), 19.2 (CH_3), 25.9 (3 × CH_3), 26.0 (3 × CH_3), 39.4 (CH), 42.3 (CH_2), 48.3 (CH), 55.3 (CH_3), 73.0 (CH_2), 74.5 (CH_2), 78.6 (C), 78.7 (C), 81.4 (C), 84.2 (CH), 113.7 (2 × CH), 129.2 (2 × CH), 130.6 (C), 159.1 (C); IR (film on KBr) ν 2955, 2930, 2855, 1615, 1515, 1385, 1250, 1135, 1110, 835, 775 cm^{-1}; Anal. Calcd for $C_{30}H_{52}Si_2O_4$, 67.61; H, 9.84; Found: C, 67.7; H, 9.7; $[\alpha]^{25}_D$ +16.6 (c 1.32, $CHCl_3$).



Vinyl iodide 5: $Cp_2Zr(H)Cl$ (301 mg, 1.11 mmol, 4.5 equiv) was added at room temperature to a solution of the alkyne **S5** (131 mg, 0.246 mmol, 1 equiv) in THF (5.5 mL, 22.4 mL/mmol **S5**). After the gas evolution had ceased, the solution was stirred for 30 minutes at 60 °C and a solution of iodine (saturated) in CH_2Cl_2 (5 mL, 20 mL/mmol **S5**) was subsequently added to the brownish-yellow reaction mixture at 0 °C. A change of color from brown to yellow to dark purple was observed. After stirring for ten minutes at 0 °C at room temperature, the reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ solution and with water. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (cyclohexane to cyclohexane/ethyl acetate 100/1) afforded the vinyl iodide **5** (91 mg, 0.138 mmol, 56%) as a light yellow oil: R_f 0.56 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H),

1.04 (d, ^{3}J = 7.0 Hz, 3H), 1.27 (dd, ^{2}J = 13.5 Hz, ^{3}J = 8.5 Hz, 1H), 1.74–1.84 (m, 1H), 2.32 (dd, $^{2}J = {}^{3}J$ = 12.0 Hz, 1H), 2.33 (d, ^{4}J = 1.0 Hz, 3H), 2.64 (dd, $^{3}J_1 = {}^{3}J_2$ = 10.0 Hz, 1H), 3.20 (d^{AB}, ^{2}J = 9.0 Hz, 2H), 3.70 (dd, $^{3}J_1 = {}^{3}J_2$ = 9.0 Hz, 1H), 3.82 (s, 3H), 4.41 (d^{AB}, ^{2}J = 11.5 Hz, 2H), 6.21 (dd, ^{3}J = 10.5 Hz, ^{4}J = 1.0 Hz, 1H), 6.88 (d, ^{3}J = 8.5 Hz, 2H), 7.23 (d, ^{3}J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.2 (CH_3), –3.8 (CH_3), –2.2 (CH_3), –2.2 (CH_3), 18.0 (C), 18.5 (C), 19.1 (CH_3), 25.9 (3 × CH_3), 26.0 (3 × CH_3), 28.2 (CH_3), 39.8 (CH), 42.6 (CH_2), 55.3 (CH_3), 56.2 (CH), 73.0 (CH_2), 74.5 (CH_2), 81.9 (C), 83.2 (CH), 96.3 (C), 113.8 (2 × CH), 129.3 (2 × CH), 130.3 (C), 140.9 (CH), 159.2 (C); IR (film on KBr) ν 2955, 2930, 2895, 2855, 1615, 1515, 1470, 1385, 1250, 1115, 1055, 835, 775 cm^{-1}; Anal. Calcd for $C_{30}H_{53}Si_2O_4I$ ($[M]^+$): 660.2522; Found: 660.2498.

Allene 16. Characteristics of the allene moiety are highlighted in blue. ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.02–0.07 (4 × s, 4 × C*H*$_3$-TBS), 0.86 (s, 3 × C*H*$_3$-TBS), 0.88 (s, 3 × C*H*$_3$-TBS), 1.05 (d, ^{3}J = 6.7 Hz, 16-C*H*$_3$), 1.27–1.30 (m, 1-C*H*$_2$, 1H^{Re}), 1.74–1.82 (m, 2-C*H*), 2.29–2.36 (m, 1-C*H*$_2$, 1H^{Re} + 4-C*H*), 3.27 (d, ^{2}J = 9.0 Hz, 14-C*H*$_2$ or OC*H*$_2$Ar, 1H), 3.30 (d, ^{2}J = 9.0 Hz, 14-C*H*$_2$ or OC*H*$_2$Ar, 1H), 3.66–3.70 (m, 3-C*H*), 3.81 (s, OC*H*$_3$), 4.38 (d, ^{2}J = 11.7 Hz, 14-C*H*$_2$ or OC*H*$_2$Ar, 1H), 4.47 (d, ^{2}J = 11.7 Hz, 14-C*H*$_2$ or OC*H*$_2$Ar, 1H), **4.56–4.64 (m, 17-C*H*$_2$)**, 5.12–5.16 (m, 5-C*H*), 6.87 (d, ^{3}J = 8.3 Hz, 2 × C*H*-PMB), 7.24 (d, ^{3}J = 8.3 Hz, 2 × C*H*-PMB); ^{13}C-NMR (101 MHz, $CDCl_3$, δ): –4.0 (CH_3), –3.9 (CH_3), –2.4 (2 × CH_3), 18.1 (C), 18.6 (C), 19.2 (CH_3), 26.0 (3 × CH_3), 26.1 (3 × CH_3), 39.6 (CH), 42.3 (CH_2), 55.3 (CH or CH_3), 55.9 (CH or CH_3), 73.0, 73.6, 75.1, 81.8, 83.4, 88.6, 113.7 (2 × CH), 129.2 (2 × CH), 130.6 (C), 159.1 (C), **210.1 (C)**; IR (KBr-Film, δ): 2955, 2929, 2895, 2856, **1956**, 1614, 1514, 1385, 1250, 1118, 1041, 835, 775.

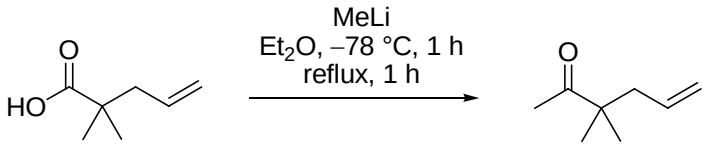


Carboxylic acid 13:[6] *n*-BuLi (25 mL, 2 M in *n*-hexane, 50 mmol, 1.1 equiv) was added at −78 °C to a solution of *i*-Pr_2NH (7 mL, 50 mmol, 1.1 equiv) in THF (16 mL, 0.35 mL/mmol **12**). After stirring for 15 min at −78 °C, ester **12** (6 mL, 45 mmol, 1 equiv) in THF (16 mL, 0.35 mL/mmol **12**) was added within 15 minutes and stirring was continued for 1 h. A solution of allyl bromide (4.4 mL, 51 mmol, 1.1 equiv) in THF (16 mL, 0.35 mL/mmol **12**) was then added within 15 minutes. After stirring for 1 h at −78 °C, the reaction mixture was carefully diluted with saturated aqueous NH_4Cl solution. The layers were subsequently separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was used without further purification: R_f 0.7 (cyclohexane/ethyl acetate 10/1, staining with $KMnO_4$ reagent)

KOH (15 g, 227 mmol, 5 equiv) was added to a solution of the crude product in methanol (180 mL, 4 mL/mmol **12**) and water (90 mL, 2 mL/mmol **12**). After stirring for 40 h under reflux, the methanol was removed under reduced pressure. The residue was acidified with aqueous HCl (1 M) to pH = 1 and diluted with CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (6×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography (cyclohexane/ethyl acetate 10/1) provided the carboxylic acid **13** (4.84 g, 37.76 mmol, 84%) as a light yellow oil: R_f 0.77 (cyclohexane/ethyl acetate 2/1, staining with $KMnO_4$ reagent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.30 (d, ^3J = 7.5 Hz, 2H), 5.06–5.09 (m,

[6] a) Pirkle, W. H.; Murray, P. G. *J. Chromatogr.* **1993**, *641*, 11–19. b) Rudler, H.; Harris, P.; Parlier, A.; Cantagrel, F.; Denise, B.; Bellassoued, M.; Vaissermann, J. *J. Organometal. Chem.* **2001**, *624*, 186–202.

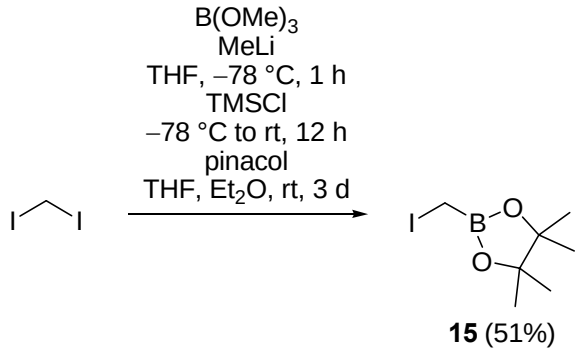
2H), 5.77 (ddd, $^3J_1$ = 7.5 Hz, $^3J_2$ = 9.5 Hz, $^3J_3$ = 17.1 Hz, 1H), 11.72 (s, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7 (2 × CH_3), 42.3 (C), 44.5 (CH_2), 118.3 (CH_2), 134.0 (CH), 184.6 (C); IR (film on KBr) ν 3200, 3080, 2980, 2930, 1700, 1640, 1475, 1235, 1180, 920 cm^{-1}.



13 **14** (69%)

Ketone 14:[7] Methyllithium (15.4 mL, 1.6 M in Et_2O, 24.64 mmol, 2.2 equiv) was added to a cooled (–78 °C) solution of the carboxylic acid **13** (1.43 g, 11.14 mmol, 1 equiv) in Et_2O (50 mL, 4.5 mL/mmol **13**). After stirring the reaction mixture for 1 h at –78 °C and, subsequently, at reflux for 1h, water was added at 0 °C. The phases were separated, and the aqueous layer was extracted with Et_2O (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure (40 °C, 850 mbar). The residue was purified by Kugelrohr distillation (80 °C, 35 mbar)) to deliver the ketone **14** (963 mg, 7.63 mmol, 69%) as a colorless liquid: R_f 0.72 (cyclohexane/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 6H), 2.12 (s, 3H), 2.25 (d, ^3J = 7.5 Hz, 2H), 5.02–5.06 (m, 2H), 5.67 (ddd, $^3J_1$ = 7.5 Hz, $^3J_2$ = 10.4 Hz, $^3J_3$ = 17.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.1 (2 × CH_3), 25.4 (CH_3), 44.0 (CH_2), 47.8 (C), 118.0 (CH_2), 134.0 (CH), 213.5 (C); IR (film on KBr) ν 2975, 2935, 1705, 1640, 1470, 1385, 1355, 1135, 915, 735 cm^{-1}.

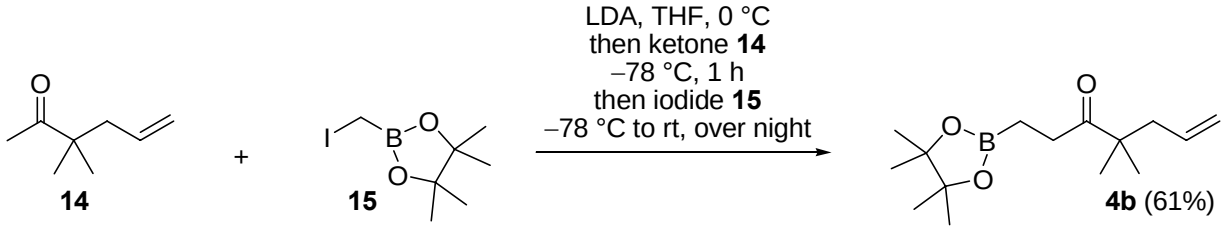
[7] House, H. O.; Chu, C.-Y., Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1977**, *42*, 1709–1717.



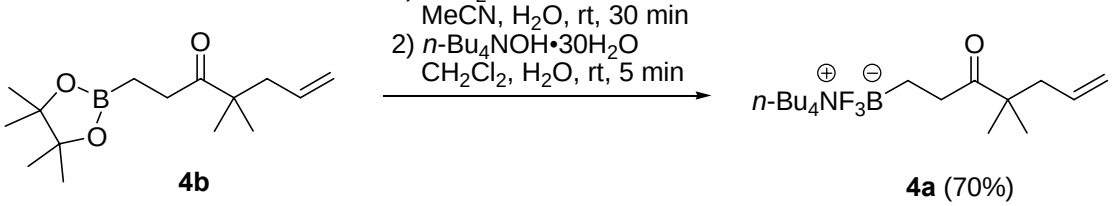
15 (51%)

Iodide 15:[8] MeLi (16.6 mL, 1.5 M in Et_2O, 24.9 mmol, 1 equiv) was added at −78 °C very carefully within 20 minutes to a solution of diiodomethane (2 mL, 24.8 mmol, 1 equiv) and $B(OMe)_3$ (2.8 mL, 25.1 mmol, 1 equiv) in THF (30 mL, 1.2 mL/mmol CH_2I_2). After being stirred for 1 h at −78 °C, TMSCl (3.2 mL, 25.2 mmol, 1 equiv) was added. The solution was stirred for 12 h while warming to room temperature. A white solid formed which was dissolved by the addition of pinacol (2.97 g, 25.1 mmol, 1 equiv) in Et_2O (5 mL, 0.2 mL/mmol pinacol). The resulting red solution was stirred for 3 d at ambient temperature followed by the addition of water. The phases were separated, the aqueous layer was extracted with Et_2O (3×), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure (40 °C, 850 mbar to 90 °C, 20 mbar). Chromatographic purification of the residue (cyclohexane/ethyl acetate 100/1 to 50/1 to 20/1) followed by Kugelrohr distillation (70 °C, 1 mbar) afforded the iodide **15** (3.41 g, 12.73 mmol, 51%) as a light orange, oily liquid: R_f 0.51 (cyclohexane/ethyl acetate 10/1, staining with $KMnO_4$ reagent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 12H), 2.12 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ −23.0 (br, CH_2), 24.4 (4 × CH_3), 84.1 (2 × C); ^{11}B-NMR (96 MHz, $CDCl_3$): δ 31.47 (s); IR (film on KBr) ν 2980, 2930, 1470, 1410, 1325, 1145, 970, 845, 675 cm^{-1}.

[8] a) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137–141. b) Mears, R. J.; Whiting, A. *Tetrahedron* **1993**, *49*, 177–186. c) Phillion, D. P.; Neubauer, R.; Andrew, S. S. *J. Org. Chem.* **1986**, *51*, 1610–1612.



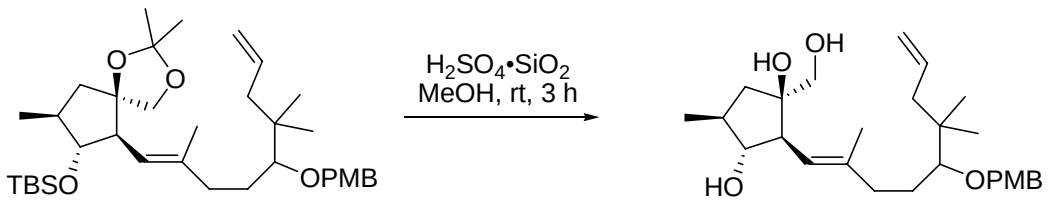
Boronic acid ester 4b: *n*-BuLi (4.75 mL, 2 M in *n*-hexane, 9.5 mmol, 1.4 equiv) was added to a solution of *i*-Pr_2NH (1.43 mL, 10.175 mmol, 1.5 equiv) in THF (15 mL, 2.2 mL/mmol **14**) at 0 °C. After stirring for 15 minutes at 0 °C and cooling to –78 °C, a solution of the ketone **14** (863 mg, 6.84 mmol, 1 equiv) in THF (2 mL, 0.3 mL/mmol **14**) was added. The iodide **15** (2.02 g, 7.9 mmol, 1.1 equiv) in THF (1.5 mL, 0.2 mL/mmol **14**) was then added and he light yellow solution was stirred over night while warming to ambient temperature. Saturated aqueous NH_4Cl solution was subsequently added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (cyclohexane to cyclohexane/ethyl acetate 100/1 to 50/1 to 20/1) provided the boronic acid ester **4b** (1.11 g, 4.17 mmol, 61%) as a pale yellow oil. R_f 0.44 (cyclohexane/ethyl acetate 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, ^3J = 6.8 Hz, 2H), 1.09 (s, 6H), 1.20 (s, 12H), 2.22 (d, ^3J = 7.0 Hz, 2H), 2.60 (t, ^3J = 6.8 Hz, 2H), 4.97–5.00 (m, 2H), 5.65 (ddd, $^3J_1$ = 7.0 Hz, $^3J_2$ = 9.5 Hz, $^3J_3$ = 17.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 5.2 (br, CH_2), 24.4 (2 × CH_3), 24.8 (4 × CH_3), 32.6 (CH_2), 44.3 (CH_2), 46.9 (C), 83.0 (2 × C), 117.7 (CH_2), 134.4 (CH), 215.8 (C); ^{11}B-NMR (96 MHz, $CDCl_3$): δ 33.96 (s); IR (film on KBr) ν 2975, 2930, 1705, 1640, 1470, 1385, 1315, 1245, 1145, 970, 915 cm^{-1}; Anal. Calcd for $C_{15}H_{27}BO_3$: C, 67.68; H, 10.22; Found: C, 67.8; H, 10.5.



Trifluoroborate 4a: KHF_2 (317 mg, 4.056 mmol, 2.92 equiv) was added to a solution of the boronic acid ester **4b** (368 mg, 1.382 mmol, 1 equiv) in MeCN (8 mL, 6 mL/mmol **4b**) and water (1.4 mL, 1 mL/mmol **4b**). The reaction mixture was stirred for 30 min at room temperature and decanted (acetone) to separate insoluble salts. The solvents were removed under reduced pressure. The residue was dissolved in acetone (~2 mL) and subsequently diluted with cyclohexane (~50 mL). After filtration the crude product was recrystallized from cyclohexane to afford the potassium trifluoroborate (276 mg, 1.122 mmol, 81%) as white foam: R_f 0.59 (cyclohexane/ethyl acetate 1/2).

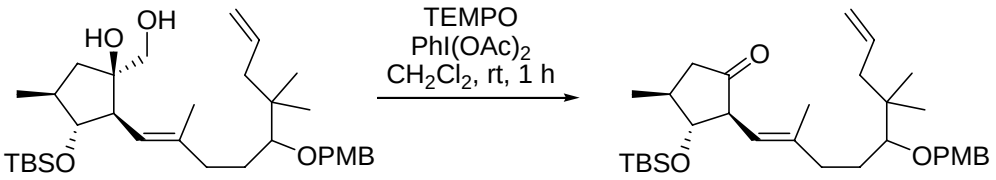
The potassium trifluoroborate (276 mg, 1.122 mmol, 1 equiv) was dissolved in a separation funnel in CH_2Cl_2 (3 mL, 2.7 mL/mmol **4b**). After adding *n*-$Bu_4NOH•30H_2O$ (902 mg, 1.128 mmol, 1 equiv) and water (3 mL, 2.7 mL/mmol **4b**), the separation funnel was shaken for 5 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. After drying (50 °C, 5×10^{-2} mbar, 2 h) the trifluoroborate **4a** (434 mg, 0.966 mmol, 86%) was obtained as a light yellow oil: R_f 0.51 (cyclohexane/ethyl acetate 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (qt, ^3J (^{1}H-^{1}H) = ^3J (^{1}H-^{19}F) = 7.0 Hz, 2H), 0.93 (t, ^3J = 7.5 Hz, 12H), 1.02 (s, 6H), 1.36 (tq, $^3J_1$ = $^3J_2$ = 7.5 Hz, 8H), 1.57 (tt, $^3J_1$ = $^3J_2$ = 7.5 Hz, 8H), 2.18 (d, ^3J = 7.0 Hz, 2H), 2.43 (t, ^3J = 7.0 Hz, 2H), 3.18 (t, ^3J = 7.5 Hz, 8H), 4.81–4.86 (m, 2H), 5.59 (ddd, $^3J_1$ = 7.0 Hz, $^3J_2$ = 9.5 Hz, $^3J_3$ = 17.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.7 (4 × CH_3), 19.7 (4 × CH_2), 23.9 (4 × CH_2), 24.3 (2 × CH_3), 34.2 (CH_2), 44.2 (CH_2), 47.3 (C), 58.6 (4 × CH_2), 117.1 (CH_2), 135.0 (CH), 219.5 (C);[9] ^{19}F-NMR (188 MHz, $CDCl_3$): δ −144.6 (s); IR (film on KBr) ν 3485, 2965, 2935, 2875, 1695, 1640, 1470, 1385, 1315, 1220, 1050, 1020, 915, 885 cm^{-1}; Anal. Calcd for $C_{25}H_{51}BONF_3$: C, 66.80; H, 11.44; N, 3.12; Found: C, 66.5; H, 11.3; N, 2.8.

[9] No resonance for the carbon atom which is connected to the boron atom could be detected.



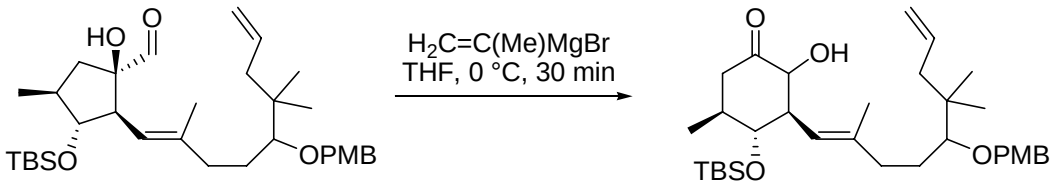
19a **19c** (65%)

Triol 19c: H_2SO_4•SiO_2 (27 mg) was added at ambient temperature to a solution of the diene **19a** (153 mg, 0.255 mmol, 1 equiv) in methanol (1.3 mL, 5 mL/mmol **19a**). The reaction mixture was stirred for 3 h at ambient temperature. Saturated aqueous $NaHCO_3$ solution was then added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (5×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane/ethyl acetate 5/1 to 1/1) of the residue afforded the triol **19c** (74 mg, 0.166 mmol, 65%) as a light yellow oil. Triol **19c** was obtained as a 1:1 mixture of C9 epimers: R_f 0.27 (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3 + 3H), 0.94 (s, 3 + 3H), 1.12 (d, ^3J = 6.3 Hz, 3 + 3H), 1.31 (dd, ^3J = 9.5 Hz, ^2J = 13.8 Hz, 1 + 1H), 1.52–1.62 (m, 1 + 1H), 1.64–17.3 (m, 1 + 1H), 1.69 (s, 3 + 3H), 1.74–1.83 (m, 1 + 1H), 1.88–2.14 (m, 6 + 6H), 2.19 (dd, ^3J = 9.3 Hz, ^2J = 13.3 Hz, 1 + 1H), 2.31–2.39 (m, 1 + 1H), 2.44 (dd, $^3J_1 = {}^3J_2$ = 9.6 Hz, 1 + 1H), 3.06 (d, ^3J = 9.0 Hz, 1 + 1H), 3.39 (d^{AB}, ^2J = 10.9 Hz, 1 + 1H), 3.46 (d^{AB}, ^2J = 10.9 Hz, 1 + 1H), 3.60 (dd, $^3J_1 = {}^3J_2$ = 9.0 Hz, 1 + 1H), 3.80 (s, 3 + 3H), 4.50–4.56 (m, 2 + 2H), 5.00–5.05 (m, 2 + 2H), 5.23 (d, ^3J = 10.0 Hz, 1 + 1H), 5.79–5.89 (m, 1 + 1H), 6.88 (d, ^3J = 8.5 Hz, 2 + 2H), 7.28 (d, ^3J = 8.5 Hz, 2 + 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.2 (1 + 1CH_3), 18.3 (1 + 1CH_3), 23.6 (2 + 2CH_3), 29.6 (1 + 1CH_2), 38.0 (1 + 1CH_2), 39.0 (1 + 1CH), 39.1 (1 + 1C), 42.0 (1 + 1CH_2), 43.8 (1 + 1CH_2), 53.4 (1 + 1CH), 55.4 (1 + 1CH_3), 70.1 (1 + 1CH_2), 74.8 (1 + 1CH_2), 79.5 (1 + 1C), 83.5 (1 + 1CH), 86.7 (1 + 1CH), 113.8 (2 + 2CH), 117.2 (1 + 1CH_2), 121.1 (1 + 1CH), 129.0 (2 + 2CH), 131.3 (1 + 1C), 135.5 (1 + 1CH), 142.1 (1 + 1C), 159.1 (1 + 1C); IR (film on KBr) ν 3425, 2955, 2930, 2870, 1615, 1515, 1465, 1250, 1065, 1035 cm^{-1}; Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48; Found: C, 72.3; H, 9.4.



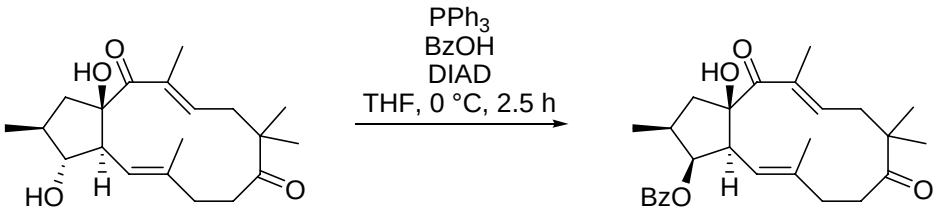
19b **22** (52%)

Ketone 22: TEMPO (1 mg, 0.006 mmol, 0.6 equiv) and $PhI(OAc)_2$ (19 mg, 0.059, 5.5 equiv) were added at ambient temperature to a solution of the diol **19b** (6 mg, 0.011 mmol, 1 equiv) in CH_2Cl_2 (0.6 mL, 55 mL/mmol **19b**). After stirring for 1 h at room temperature, the reaction mixture was diluted with cyclohexane. After concentration under reduced pressure and chromatographic purification (cyclohexane/ethyl acetate 10/1) of the crude product, the ketone **22** (3 mg, 0.006 mmol, 52%) was obtained as a light yellow oil. Ketone **22** was obtained as a 1:1 mixture of C9 epimers: R_f 0.79 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 3 + 3H), 0.08 (s, 3 + 3H), 0.88 (s, 9 + 9H + 3 + 3H), 0.93 (s, 3 + 3H), 1.15 (d, ^3J = 6.3 Hz, 3 + 3H), 1.55–1.72 (m, 2 + 2H), 1.65 (s, 3 + 3H), 1.82 (dd, ^3J = 12.0 Hz, ^2J = 18.6 Hz, 1 + 1H), 2.01–2.19 (m, 4 + 4H), 2.30–2.37 (m, 1 + 1H), 2.59 (dd, ^3J = 8.1 Hz, ^2J = 18.6 Hz, 1 + 1H), 3.04–3.12 (m, 2 + 2H), 3.60 (dd, $^3J_1$ = 8.9 Hz, $^3J_2$ = 17.4 Hz, 1 + 1H), 3.80 (s, 3 + 3H), 4.51–4.56 (m, 2 + 2H), 4.93 (d, ^3J = 8.2 Hz, 1 + 1H), 4.99–5.04 (m, 2 + 2H), 5.79–5.90 (m, 1 + 1H), 6.87 (d, ^3J = 8.5 Hz, 2 + 2H), 7.28 (d, ^3J = 8.5 Hz, 2 + 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.3 (1 + 1CH_3), –3.9 (1 + 1CH_3), 17.2 (1 + 1CH_3), 17.6 (1 + 1CH_3), 18.0 (1 + 1C), 23.6 (2 + 2CH_3), 25.9 (3 + 3CH_3), 29.5 (1 + 1CH_2), 37.7 (1 + 1C), 38.4 (1 + 1CH), 39.1 (1 + 1CH_2), 43.8 (1 + 1CH_2), 45.1 (1 + 1CH_2), 55.3 (1 + 1CH_3), 59.5 (1 + 1CH), 74.6 (1 + 1CH_2), 82.6 (1 + 1CH), 86.8 (1 + 1CH), 113.7 (2 + 2CH), 117.0 (1 + 1CH_2), 119.6 (1 + 1CH), 129.1 (2 + 2CH), 131.4 (1 + 1C), 135.6 (1 + 1CH), 141.8 (1 + 1C), 159.0 (1 + 1C), 215.0 (1 + 1C); IR (film on KBr) ν 2955, 2930, 2855, 1745, 1615, 1515, 1465, 1385, 1360, 1250, 1120, 1100, 1040, 865, 835, 775 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{53}O_4Si$ ([M+H]$^+$): 529.3708; Found: 529.3704.



20 **23** (68%)

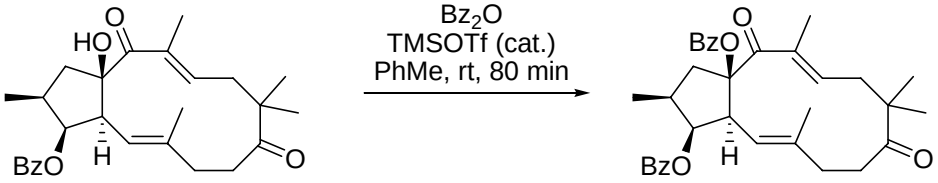
α-Hydroxyketone 23: H_2C=C(Me)MgBr (0.78 mL, 0.5 M in THF, 0.39 mmol, 2.5 equiv) was added to a cooled (0 °C) solution of the aldehyde **20** (87 mg, 0.156 mmol, 1 equiv) in THF (1 mL, 6.4 mL/mmol **20**). The solution was stirred for 30 min at 0 °C. Saturated aqueous NH_4Cl solution was added followed by the separation of the phases and the extraction of the aqueous phase with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography (cyclohexane/ethyl acetate 20/1) afforded the α-hydroxyketone **23** (59 mg, 0.106 mmol, 68%) as a light yellow oil. α-Hydroxyketone **23** was obtained as a mixture of C9/C14 epimers: R_f 0.63 (cyclohexane/ethyl acetate 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 0.93 (s, 9H), 0.95 (d, ^3J = 8.0 Hz, 3H), 1.42 (s, 1H), 1.45–1.63 (m, 2H), 1.66 (s, 3H), 1.92–2.02 (m, 2H), 2.09–2.14 (m, 1H), 2.19–2.27 (m, 2H), 2.32–2.43 (m, 1H), 2.95–3.02 (m, 2H), 3.21–3.33 (m, 1H), 3.41–3.49 (m, 1H), 3.77–3.81 (m, 3H), 4.48–4.51 (m, 2H), 4.77–4.81 (m, 2H), 4.98–5.04 (m, 2H), 5.77–5.88 (m, 1H), 6.86–6.89 (m, 2H), 7.25–7.28 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.8 (CH_3), –4.5 (CH_3), 16.5 (CH_3), 18.0 (C), 19.0 (CH_3), 23.6 (2 × CH_3), 25.8 (3 × CH_3), 29.4 (CH_2), 37.9 (CH_2), 39.1 (C), 40.3 (CH), 41.5 (CH_2), 43.8 (CH_2), 51.1 (CH), 55.4 (CH_3), 73.5 (CH), 74.5 (CH_2), 76.1 (CH), 86.6 (CH), 113.8 (2 × CH), 117.0 (CH_2), 119.7 (CH), 128.9 (2 × CH), 131.4 (C), 135.5 (CH), 139.5 (C), 159.1 (C), 212.1 (C); IR (film on KBr) ν 2955, 2930, 2855, 1715, 1515, 1470, 1465, 1250, 1075, 1040, 835, 775 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{55}O_5Si$ ($[M+H]^+$): 559.3813; Found: 559.3810.



2 **30** (87%)

3-*O*-Benzoylcharaciol (**30**): PPh_3 (55 mg, 0.21 mmol, 2 equiv), benzoic acid (25 mg, 0.205 mmol, 2 equiv) and DIAD (0.045 mL, 0.213 mmol, 2 equiv) were added at 0 °C to a solution of 3-*epi*-characiol (**2**) (34 mg, 0.102 mmol, 1 equiv) in THF (2 mL, 20 mL/mmol **2**). After being stirred for 2.5 h at 0 °C, the reaction mixture was diluted with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by chromatography (cyclohexane/ethyl acetate 20/1 to 10/1) to deliver 3-*O*-benzoylcharaciol (**30**) (39 mg, 0.089 mmol, 87%) as a white solid (mp: 78 °C): R_f 0.54 (cyclohexane/ethyl acetate 2/1); the ^{1}H NMR peak assignments were deduced from ^{1}H-^{1}H COSY spectra and are listed on the basis of the jatrophane numbering; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, ^3J = 6.8 Hz, 16-CH_3), 1.11 (s, 18- or 19-CH_3), 1.19 (s, 18- or 19-CH_3), 1.40 (s, 17-CH_3), 1.58 (dd, ^3J = 12.1 Hz, ^2J = 13.6 Hz, 1-CH_2, 1H^{Re}), 1.74 (s, 20-CH_3), 1.96–2.08 (m, 8-CH_2), 2.22–2.30 (m, 2-CH), 2.31 (s, 1OH), 2.39–2.51 (m, 11-CH_2), 2.61 (dd, $^3J_1$ = 3.8 Hz, $^3J_2$ = 10.3 Hz, 4-CH), 2.76–2.82 (m, 7-CH_2, 1H), 2.88–2.95 (m, 7-CH_2, 1H), 3.27 (dd, ^3J = 8.3 Hz, ^2J = 13.6 Hz, 1-CH_2, 1H^{Si}), 5.36 (d, ^3J = 10.3 Hz, 5-CH), 5.53 (dd, $^3J_1$ = $^3J_2$ = 3.8 Hz, 3-CH), 7.05 (dd, $^3J_1$ = $^3J_2$ = 5.9 Hz, 12-CH), 7.51 (dd, $^3J_1$ = $^3J_2$ = 7.7 Hz, 2 × CH_{ar}), 7.62 (dd, $^3J_1$ = $^3J_2$ = 7.7 Hz, CH_{ar}), 8.03 (d, $^3J_1$ = 7.7 Hz, 2 × CH_{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.6 (CH_3), 14.4 (CH_3), 16.4 (CH_3), 24.1 (CH_3), 25.1 (CH_3), 33.9 (CH_2), 35.1 (CH_2), 38.8 (CH), 40.4 (CH_2), 48.1 (C or CH_2), 48.4 (C or CH_2), 52.8 (CH), 82.9 (CH), 90.6 (C), 120.4 (CH), 128.7 (2 × CH), 129.6 (2 × CH), 130.0 (C), 133.3 (CH), 135.8 (C), 138.9 (C), 144.5 (CH), 166.1 (C), 201.0 (C), 215.2 (C); IR (film on

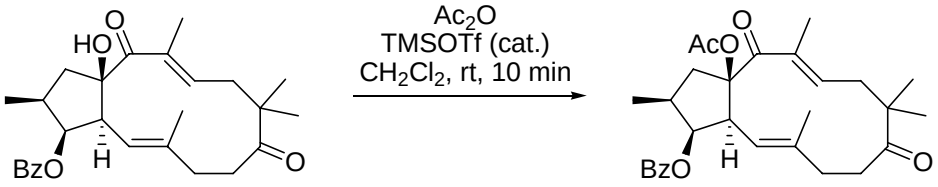
KBr) *v* 3485, 2970, 2930, 1705, 1650, 1450, 1385, 1275, 1115, 1010, 715 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{35}O_5$ ($[M+H]^+$): 439.2479; Found: 439.2476; $[\alpha]^{25}_D$ +162.4 (c 1.55, $CHCl_3$).



30 **31** (62%)

3-*O*-15-*O*-Dibenzoylcharaciol (**31**): Benzoic anhydride (14 mg, 0.062 mmol, 2.9 eq) and TMSOTf (one drop) were added at ambient temperature to a solution of 3-*O*-benzoylcharaciol (**30**) (9 mg, 0.021 mmol, 1 equiv) in toluene (1.4 mL, 67 mL/mmol **30**); the initially colorless solution changed color to pink. After being stirred for 80 min at ambient temperature, the reaction mixture was diluted with methanol and saturated aqueous NH_4Cl solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane/ethyl acetate 20/1 to 10/1) of the residue provided 3-*O*-15-*O*-dibenzoylcharaciol (**31**) (7 mg, 0.013 mmol, 62%) as a clear oil: R_f 0.57 (cyclohexane/ethyl acetate 2/1). The ^1H NMR peak assignments were deduced from ^1H–^1H COSY spectra and are listed on the basis of the jatrophane numbering: ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 18- or 19-CH_3), 0.97 (d, ^3J = 6.5 Hz, 16-CH_3), 1.06 (s, 18- or 19-CH_3), 1.43 (s, 17-CH_3), 1.74 (s, 20-CH_3), 1.77 (dd, ^3J = 12.3 Hz, ^2J = 13.8 Hz, 1-CH_2, 1H^{Re}), 1.98–2.04 (m, 8-CH_2), 2.21 (dd, ^3J = 6.8 Hz, ^2J = 18.8 Hz, 11-CH_2, 1H), 2.30–2.44 (m, 2-CH + 11-CH_2, 1H), 2.81 (dd, $^3J_1$ = 3.9 Hz, $^3J_2$ = 10.4 Hz, 4-CH), 2.88–2.91 (m, 7-CH_2), 3.57 (dd, ^3J = 8.3 Hz, ^2J = 13.8 Hz, 1-CH_2, 1H^{Si}), 5.56 (dd, $^3J_1$ = $^3J_2$ = 3.4 Hz, 3-CH), 5.67 (d, ^3J = 10.4 Hz, 5-CH), 6.51 (dd, $^3J_1$ = $^3J_2$ = 5.1 Hz, 12-CH), 7.28 (dd, $^3J_1$ = $^3J_2$ = 7.8 Hz, 2 × CH_{ar}), 7.52–7.56 (m, 3 × CH_{ar}), 7.63–7.67 (m, 1 × CH_{ar}), 8.03 (d, ^3J = 7.5 Hz, 2 × CH_{ar}), 8.18 (d, ^3J = 7.5 Hz, 2 × CH_{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.2 (CH_3), 14.0 (CH_3), 16.4 (CH_3), 23.0 (CH_3), 25.1 (CH_3), 27.0 (CH_2), 35.2 (CH_2), 39.2 (CH), 40.0 (CH_2), 46.8 (CH_2),

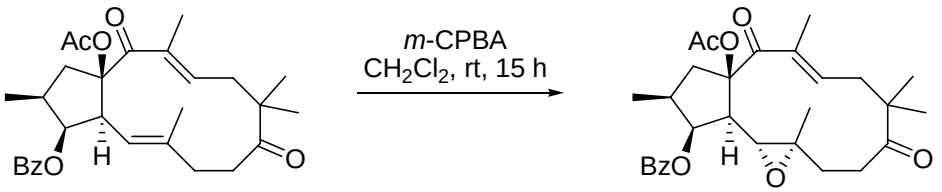
47.6 (C), 52.4 (CH), 81.9 (CH), 94.1 (C), 120.6 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 129.6 (C), 129.9 (2 × CH), 130.0 (C), 130.5 (2 × CH), 133.1 (CH), 133.7 (CH), 135.9 (C), 139.7 (C), 140.2 (CH), 165.8 (C), 165.9 (C), 198.1 (C), 214.6 (C); HRMS (ESI) Calcd for $C_{34}H_{39}O_6$ ($[M+H]^+$): 543.2741; Found: 543.2737.



30 **S6** (80%)

15-*O*-Acetyl-3-*O*-benzoylcharaciol (**S6**): Acetic anhydride (0.06 mL, 0.635 mmol, 35 eq) and TMSOTf (one drop) were added at ambient temperature to a solution of 3-*O*-benzoylcharaciol (**30**) (8 mg, 0.018 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 111 mL/mmol **30**); the initially colorless solution changed color to pink. After being stirred for 10 min at ambient temperature, the reaction mixture was diluted with methanol and saturated aqueous NH_4Cl solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane/ethyl acetate 5/1) of the residue provided 15-*O*-acetyl-3-*O*-benzoylcharaciol (**S6**) (7 mg, 0.015 mmol, 80%) as a white solid (mp: 155 °C): R_f 0.59 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, ^3J = 7.0 Hz, 16-CH_3), 1.03 (s, 18- or 19-CH_3), 1.18 (s, 18- or 19-CH_3), 1.43 (s, 17-CH_3), 1.62 (dd, $^3J = {}^2J$ = 13.4 Hz, 1-CH_2, 1H^{Re}), 1.72 (s, 20-CH_3), 2.00–2.07 (m, 8-CH_2), 2.18 (s, acetate-CH_3), 2.24–2.34 (m, 2-CH), 2.35 (dd, ^2J = 18.3 Hz, ^3J = 5.0 Hz, 11-CH_2, 1H), 2.43 (dd, ^2J = 18.3 Hz, ^3J = 7.0 Hz, 11-CH_2, 1H), 2.68 (dd, $^3J_1$ = 4.0 Hz, $^3J_2$ = 10.5 Hz, 4-CH), 2.77–2.84 (m, 7-CH_2, 1H), 2.91–2.99 (m, 7-CH_2, 1H), 3.40 (dd, ^3J = 8.0 Hz, ^2J = 13.4 Hz, 1-CH_2, 1H^{Si}), 5.47–5.51 (m, 3-CH + 5-CH), 6.40 (dd, $^3J_1 = {}^3J_2$ = 5.6 Hz, 12-CH), 7.49 (dd, $^3J_1 = {}^3J_2$ = 7.5 Hz, 2 × CH_{ar}), 7.62 (dd,

$^3J_1 = {}^3J_2 = 7.5$ Hz, CH_{ar}), 8.07 (d, $^3J_1 = 7.5$ Hz, 2 × CH_{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.1 (CH_3), 13.9 (CH_3), 16.2 (CH_3), 21.5 (CH_3), 24.2 (CH_3), 25.0 (CH_3), 33.7 (CH_2), 35.3 (CH_2), 39.1 (CH), 40.1 (CH_2), 46.5 (CH_2), 47.8 (C), 51.9 (CH), 81.7 (CH), 93.2 (C), 120.8 (CH), 128.6 (2 × CH), 129.7 (2 × CH), 130.2 (C), 133.2 (CH), 135.8 (C), 139.0 (C), 139.3 (CH), 166.0 (C), 170.4 (C), 198.5 (C), 215.0 (C); IR (film on KBr) ν 2970, 2930, 1780, 1705, 1660, 1385, 1275, 1245, 1115, 715 cm^{-1}; Anal. Calcd for $C_{29}H_{36}O_6$: C, 72.48; H, 7.55; Found: C, 72.6; H, 7.7; $[\alpha]^{25}_D$ +51.0 (c 0.95, $CHCl_3$).

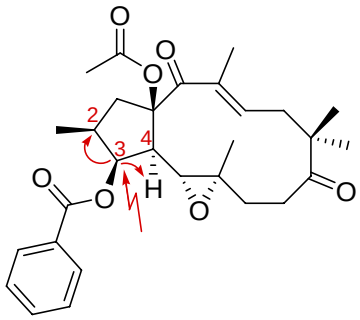


S6 **1b** (69%)

15-*O*-Acetyl-3-*O*-benzoylcharaciol-(5*R*,6*R*)-oxide (**1b**): *m*-CPBA (5 mg, 0.029 mmol, 2 equiv) was added at ambient temperature to a solution of 15-*O*-acetyl-3-*O*-benzoylcharaciol (**S6**) (7 mg, 0.015 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 48 mL/mmol **S6**). The reaction mixture was stirred for 15 h at ambient temperature and then diluted with saturated aqueous $Na_2S_2O_3$ solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 5/1 to 2/1) provided 15-*O*-acetyl-3-*O*-benzoylcharaciol-(5*R*,6*R*)-oxide (**1b**) (5 mg, 0.01 mmol, 69%) as a white solid (mp: 187 °C): R_f 0.33 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, $^3J = 6.5$ Hz, 16-CH_3), 1.04 (s, 18-CH_3), 1.08 (s, 19-CH_3), 1.28 (s, 17-CH_3), 1.72 (dd, $^3J = {}^2J = 13.6$ Hz, 1-CH_2, 1H^{Re}), 1.77 (s, 20-CH_3), 1.87 (dd, $^3J_1 = 3.8$ Hz, $^3J_2 = 8.9$ Hz, 4-CH), 1.92–2.04 (m, 8-CH_2), 2.15–2.29 (m, 2-CH + 7-CH_2, 1H^{Si}), 2.27 (s, acetate-CH_3), 2.42–2.55 (m, 11-CH_2), 2.84–2.91 (m, 7-CH_2, 1H^{Re}), 3.33 (dd, $^3J = 7.3$ Hz, $^2J = 13.6$ Hz, 1-CH_2, 1H^{Si}), 3.39 (d, $^3J = 8.9$ Hz, 5-CH), 5.67 (dd, $^3J_1 = {}^3J_2 = 3.8$ Hz, 3-CH), 6.04–6.07

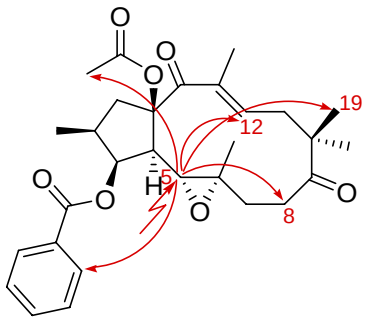
(m, 12-C*H*), 7.49 (dd, $^3J_1 = {}^3J_2 = 7.5$ Hz, 2 × CH_{ar}), 7.61 (dd, $^3J_1 = {}^3J_2 = 7.5$ Hz, CH_{ar}), 8.09 (d, $^3J_1 = 7.5$ Hz, 2 × CH_{ar}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.2 (CH_3), 13.6 (CH_3), 16.8 (CH_3), 21.5 (CH_3), 23.3 (CH_3), 25.1 (CH_3), 32.1 (CH_2), 32.9 (CH_2), 38.6 (CH), 39.4 (CH_2), 47.9 (CH_2), 48.0 (C), 51.5 (CH), 59.4 (CH), 61.4 (C), 80.7 (CH), 90.1 (C), 128.5 (2 × CH), 129.8 (2 × CH), 130.3 (C), 133.1 (CH), 135.6 (CH), 136.9 (C), 165.5 (C), 170.3 (C), 199.9 (C), 213.6 (C); IR (film on KBr) *v* 2970, 2930, 1720, 1670, 1385, 1270, 1245, 1110, 710 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{37}O_7$ ($[M+H]^+$): 497.2534; Found: 497.2529; $[\alpha]^{25}_D$ −20.6 (c 0.34, $CHCl_3$).

Table SI-1. 1D-NOE experiment, irradiation at 5.67 ppm (3-C*H*).



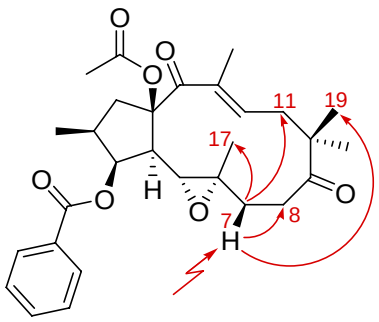
entry	observable NOE	conclusion
1	2.15–2.29 ppm 2-C*H* (strong)	2-C*H* and 3-C*H* are *cis*
2	1.87 ppm 4-C*H* (strong)	4-C*H* and 3-C*H* are *cis*

Table SI-2. 1D-NOE experiment, irradiation at 3.39 ppm (5-C*H*).



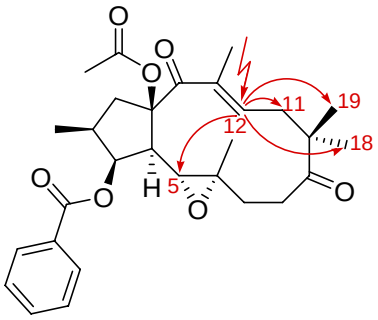
entry	observable NOE	conclusion
1	1.92–2.04 ppm 8-CH_2 (strong)	/
2	6.04–6.07 ppm 12-C*H* (strong)	/
3	1.08 ppm 19-CH_3 (weak)	/
4	2.27 ppm acetate-CH_3 (weak)	/
5	8.09 ppm 2 × aryl-C*H* (weak)	/

Table SI-3. 1D-NOE experiment, irradiation at 2.84–2.91 ppm (7Re-C*H*).



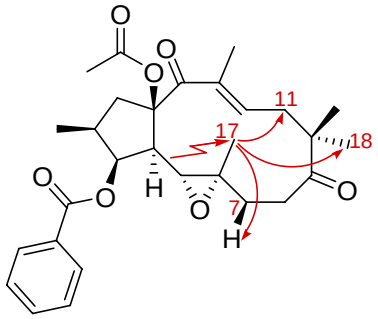
entry	observable NOE	conclusion
1	1.92–2.04 ppm 8-CH_2 (strong)	/
2	2.42–2.55 ppm 11-CH_2 (weak)	/
3	1.28 ppm 17-CH_3 (strong)	/
4	1.08 ppm 19-CH_3 (strong)	/

Table SI-4. 1D-NOE experiment, irradiation at 6.04–6.07 ppm (12-C*H*).



entry	observable NOE	conclusion
1	3.39 ppm 5-C*H* (strong)	/
2	2.42–2.55 ppm 11-CH_2 (strong)	/
3	1.04 ppm 18-CH_3 (strong)	/
4	1.08 ppm 19-CH_3 (strong)	/

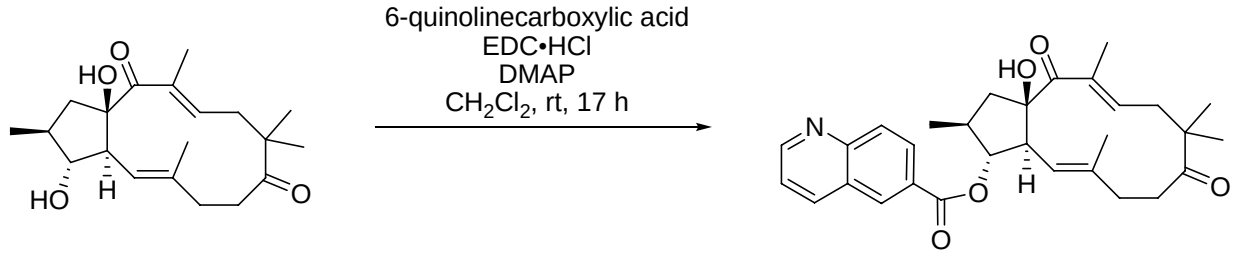
Table SI-5. 1D-NOE experiment, irradiation at 1.28 ppm (17-CH_3).



entry	observable NOE	conclusion
1	3.39 ppm 7^{Re}-C*H* (strong)	/
2	2.42–2.55 ppm 11-CH_2 (strong)	/
3	1.04 ppm 18-CH_3 (strong)	/

2 **32** (61%)

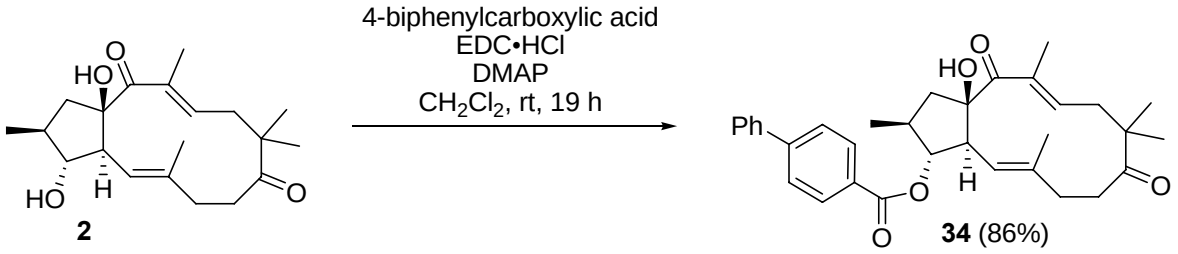
3-*epi*-3-*O*-15-*O*-Dibenzoylcharaciol (**32**): Benzoic anhydride (34 mg, 0.15 mmol, 10 eq) and TMSOTf (one drop) were added at ambient temperature to a solution of 3-*epi*-characiol (**2**) (5 mg, 0.015 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 133 mL/mmol **2**); the initially colorless solution changed color to pink. After being stirred for 1 h at ambient temperature, the reaction mixture was diluted with methanol and saturated aqueous NH_4Cl solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane/ethyl acetate 20/1 to 10/1) of the residue provided 3-*epi*-3-*O*-15-*O*-dibenzoylcharaciol (**32**) (5 mg, 0.009 mmol, 61%) as a clear oil: R_f 0.62 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 18- or 19-CH_3), 1.06 (d, ^3J = 6.8 Hz, 16-CH_3), 1.06 (s, 18- or 19-CH_3), 1.38 (s, 17-CH_3), 1.52 (dd, ^3J = 11.2 Hz, ^2J = 14.3 Hz, 1-CH_2, 1H^{Re}), 1.74 (s, 20-CH_3), 1.91−1.96 (m, 8-CH_2, 1H), 2.00–2.04 (m, 8-CH_2, 1H), 2.19–2.35 (m, 2-CH + 11-CH_2), 2.82–2.89 (m, 4-CH + 7-CH_2, 1H), 2.95–3.01 (m, 7-CH_2, 1H), 3.62 (dd, ^3J = 8.5 Hz, ^2J = 14.3 Hz, 1-CH_2, 1H^{Si}), 5.34 (dd, $^3J_1 = {}^3J_2$ = 9.8 Hz, 3-CH), 5.72 (d, ^3J = 10.5 Hz, 5-CH), 6.52 (dd, $^3J_1 = {}^3J_2$ = 5.2 Hz, 12-CH), 7.44 (dd, $^3J_1 = {}^3J_2$ = 7.6 Hz, 2 × CH_{ar}), 7.54–7.58 (m, 3 × CH_{ar}), 7.61–7.65 (m, 1 × CH_{ar}), 8.00 (d, ^3J = 7.5 Hz, 2 × CH_{ar}), 8.15 (d, ^3J = 7.0 Hz, 2 × CH_{ar}); HRMS (ESI) Calcd for $C_{34}H_{39}O_6$ ([M+H]$^+$): 543.2741; Found: 543.2737.



2 **33** (99%)

3-*epi*-3-*O*-6-Quinolinecarboxylcharaciol (**33**): 6-Quinolinecarboxylic acid (32 mg, 0.185 mmol, 8.8 equiv) was added at 0 °C to a solution of EDC•HCl (38 mg, 0.198 mmol, 9.4 equiv) and DMAP (3 mg, 0.025 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL, 48 mL/mmol **2**). After stirring the reaction mixture for 5 min at 0 °C, a solution of 3-*epi*-characiol (**2**) (7 mg, 0.021 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 95 mL/mmol **2**) was added. The reaction mixture was allowed to warm to ambient temperature and then stirred for 17 h. Saturated aqueous NH_4Cl solution was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 10/1 to 5/1 to 2/1) to furnish 3-*epi*-3-*O*-6-quinolinecarboxylcharaciol (**33**) (10 mg, 0.021 mmol, 99%) as a colorless oil: R_f 0.17 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 18- or 19-CH_3), 1.16 (d, ^3J = 6.5 Hz, 16-CH_3), 1.20 (s, 18- or 19-CH_3), 1.31–1.37 (m, 1-CH_2, 1H^{Re}), 1.39 (s, 17-CH_3), 1.76 (s, 20-CH_3), 1.90–1.95 (m, 8-CH_2, 1H), 2.09–2.13 (m, 8-CH_2, 1H), 2.21–2.28 (m, 2-CH), 2.40–2.51 (m, OH + 11-CH_2), 2.73–2.77 (m, 4-CH), 2.84–2.91 (m, 7-CH_2), 3.33–3.38 (m, 1-CH_2, 1H^{Si}), 5.33–5.37 (m, 3-CH), 5.53 (d, ^3J = 10.3 Hz, 5-CH), 7.00–7.05 (m, 12-CH), 7.47–7.53 (m, 1H$_{ar}$), 8.15–8.20 (m, 1H$_{ar}$), 8.24–8.29 (m, 2H$_{ar}$), 8.52–8.57 (m, 1H$_{ar}$), 8.99–9.04 (m, 1H$_{ar}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.7 (CH_3), 16.3 (CH_3), 18.1 (CH_3), 24.2 (CH_3), 25.2 (CH_3), 34.2, 34.8, 38.4, 40.4, 45.7, 48.1, 53.8, 84.7, 87.1, 121.9, 123.5, 127.5, 128.5, 129.3, 129.5,

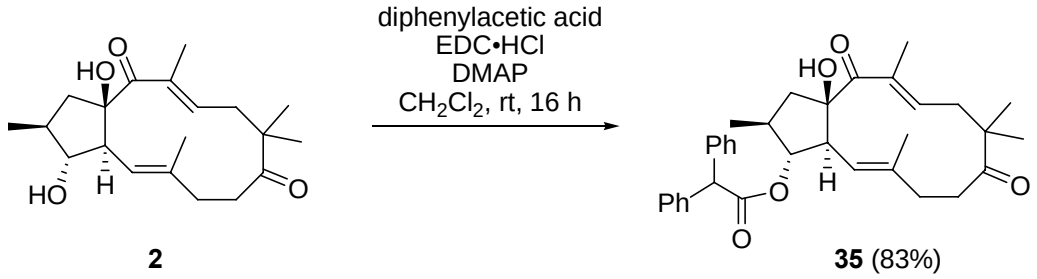
131.1, 135.7, 139.2, 143.7, 152.3, 165.6 (C), 201.5 (C), 216.4 (C);[10] IR (film on KBr) *v* 3475, 2965, 2925, 1715, 1650, 1385, 1275, 1190, 1100, 1020, 730 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{36}O_5N$ ($[M+H]^+$): 490.2588; Found: 490.2575.



3-*epi*-3-*O*-4-Biphenylcarboxylcharaciol (**34**): 4-Biphenylcarboxylic acid (37 mg, 0.187 mmol, 8.9 equiv) was added at 0 °C to a solution of EDC•HCl (38 mg, 0.198 mmol, 9.4 equiv) and DMAP (6 mg, 0.049 mmol, 2.3 equiv) in CH_2Cl_2 (1 mL, 48 mL/mmol **2**). After stirring the reaction mixture for 5 min at 0 °C, a solution of 3-*epi*-characiol (**2**) (7 mg, 0.021 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 95 mL/mmol **2**) was added. The reaction mixture was allowed to warm to ambient temperature and then stirred for 19 h. Saturated aqueous NH_4Cl solution was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 20/1 to 10/1) to furnish 3-*epi*-3-*O*-4-biphenylcarboxylcharaciol (**34**) (9 mg, 0.018 mmol, 86%) as a colorless oil: R_f 0.61 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 18- or 19-CH_3), 1.14 (d, 16-CH_3), 1.20 (s, 18- or 19-CH_3), 1.30 (dd, ^3J = 9.9 Hz, ^2J = 13.8 Hz, 1-CH_2, 1H^{Re}), 1.40 (s, 17-CH_3), 1.76 (s, 20-CH_3), 1.92–1.98 (m, 8-CH_2, 1H), 2.09–2.14 (m, 8-CH_2, 1H), 2.16–2.23 (m, 2-C*H*), 2.30 (s, br, O*H*), 2.42 (dd, ^3J = 6.3 Hz, ^2J = 17.8 Hz, 11-CH_2,

[10] Due to lack of material two signals from the aromatic or olefinic area could not be detected.

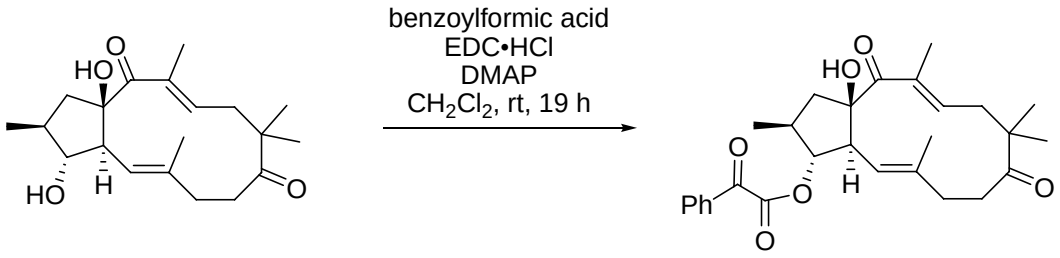
1H), 2.48 (dd, ^3J = 5.7 Hz, ^2J = 17.8 Hz, 11-CH_2, 1H), 2.71 (dd, $^3J_1 = {}^3J_2$ = 10.1 Hz, 4-C*H*), 2.84–2.92 (m, 7-CH_2), 3.32 (dd, ^3J = 9.2 Hz, ^2J = 13.8 Hz, 1-CH_2, 1H^{Si}), 5.30 (dd, $^3J_1 = {}^3J_2$ = 10.1 Hz, 3-C*H*), 5.51 (d, ^3J = 10.1 Hz, 5-C*H*), 7.00 (dd, $^3J_1 = {}^3J_2$ = 5.7 Hz, 12-C*H*), 7.39 (dd, ^3J = 7.3 Hz, 1H$_{ar}$), 7.46 (dd, $^3J_1 = {}^3J_2$ = 7.8 Hz, 2H$_{ar}$), 7.60 (d, ^3J = 7.3 Hz, 2H$_{ar}$), 7.64 (d, ^3J = 8.4 Hz, 2H$_{ar}$), 8.05 (d, ^3J = 7.6 Hz, 2H$_{ar}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.7 (CH_3), 16.3 (CH_3), 18.0 (CH_3), 24.2 (CH_3), 25.2 (CH_3), 27.0, 34.8, 38.4, 40.4, 45.7, 48.1, 53.7, 84.1, 87.1, 123.5, 127.1 (2 × CH), 127.3 (2 × CH), 128.2, 129.0 (2 × CH), 129.2, 130.2 (2 × CH), 135.7, 139.2, 140.2, 143.6, 145.7, 166.0 (C), 201.5 (C), 215.3 (C); IR (film on KBr) ν 3475, 2960, 2925, 1715, 1650, 1385, 1275, 1115, 1020, 785 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{39}O_5$ ([M+H]$^+$): 515.2792; Found: 515.2797.



2 **35** (83%)

3-*epi*-3-*O*-Diphenylacetylcharaciol (**35**): Diphenylacetic acid (35 mg, 0.165 mmol, 7.9 equiv) was added at 0 °C to a solution of EDC•HCl (35 mg, 0.183 mmol, 8.7 equiv) and DMAP (4 mg, 0.033 mmol, 1.6 equiv) in CH_2Cl_2 (1 mL, 48 mL/mmol **2**). After stirring the reaction mixture for 5 min at 0 °C, a solution of 3-*epi*-characiol (**2**) (7 mg, 0.021 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 95 mL/mmol **2**) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 16 h. Saturated aqueous NH_4Cl solution was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 20/1 to 10/1) to furnish 3-*epi*-3-*O*-diphenylacetylcharaciol (**35**) (9 mg, 0.017 mmol, 83%) as a colorless oil: R_f 0.78 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (501 MHz, $CDCl_3$) δ 0.99 (d,

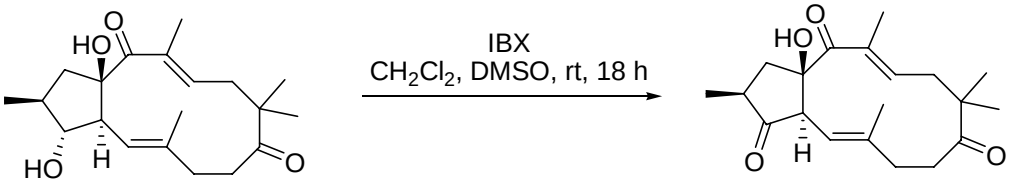
^3J = 6.7 Hz, 16-CH_3), 1.09 (s, 18- or 19-CH_3), 1.11 (s, 18- or 19-CH_3), 1.16 (dd, ^3J = 9.7 Hz, ^2J = 14.0 Hz, 1-CH_2, 1H^{Re}), 1.18 (s, 17-CH_3), 1.69 (s, 20-CH_3), 1.82–1.90 (m, 8-CH_2, 1H), 1.97–2.04 (m, 2-C*H*), 2.06–2.14 (m, 8-CH_2, 1H), 2.37 (dd, ^3J = 5.9 Hz, ^2J = 17.8 Hz, 11-CH_2, 1H), 2.42–2.46 (m, 4-C*H* + 11-CH_2, 1H), 2.81–2.88 (m, 7-CH_2), 3.23 (dd, ^3J = 9.1 Hz, ^2J = 14.0 Hz, 1-CH_2, 1H^{Si}), 4.95 (s, br, O*H*), 5.06 (s, C*H*Ph$_2$), 5.10 (dd, $^3J_1$ = $^3J_2$ = 9.7 Hz, 3-C*H*), 5.38 (d, ^3J = 10.5 Hz, 5-C*H*), 6.91 (dd, $^3J_1$ = $^3J_2$ = 5.9 Hz, 12-C*H*), 7.21–7.30 (m, 10H$_{ar}$); IR (film on KBr) ν 3470, 3030, 2965, 2925, 1740, 1710, 1650, 1385, 1195, 1150, 1075, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{34}H_{41}O_5$ ([M+H]$^+$): 529.2949; Found: 529.2942.



2 **36** (91%)

3-*epi*-3-*O*-Benzoylformylcharaciol (**36**): Benzoylformyl acid (22 mg, 0.146 mmol, 7 equiv) was added at 0 °C to a solution of EDC•HCl (30 mg, 0.156 mmol, 7.5 equiv) and DMAP (3 mg, 0.025 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL, 48 mL/mmol **2**). After stirring the reaction mixture for 5 min at 0 °C, a solution of 3-*epi*-characiol (**2**) (7 mg, 0.021 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 95 mL/mmol **2**) was added. The reaction mixture was allowed to warm to ambient temperature and then stirred for 19 h. Saturated aqueous NH_4Cl solution was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 20/1 to 10/1) to furnish 3-*epi*-3-*O*-benzoylformylcharaciol (**36**) (9 mg, 0.019 mmol, 91%) as a colorless oil: R_f 0.49 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (501 MHz, $CDCl_3$) δ 1.14 (s, 18- or

19-CH_3), 1.17 (d, ^3J = 6.6 Hz, 16-CH_3), 1.21 (s, 18- or 19-CH_3), 1.26 (dd, ^3J = 9.5 Hz, ^2J = 14.0 Hz, 1-CH_2, 1H^{Re}), 1.34 (s, 17-CH_3), 1.72 (s, 20-CH_3), 1.99–2.04 (m, 8-CH_2, 1H), 2.09 (s, O*H*), 2.14–2.24 (m, 2-C*H* + 8-CH_2, 1H), 2.41 (dd, ^3J = 5.8 Hz, ^2J = 17.7 Hz, 11-CH_2, 1H), 2.48 (dd, ^3J = 5.8 Hz, ^2J = 17.7 Hz, 11-CH_2, 1H), 2.64 (dd, $^3J_1$ = $^3J_2$ = 10.4 Hz, 4-C*H*), 2.91 (dd, ^2J = ^3J = 12.9 Hz, 7-CH_2, 1H), 3.01 (dd, ^2J = ^3J = 12.9 Hz, 7-CH_2, 1H), 3.34 (dd, ^3J = 9.5 Hz, ^2J = 14.0 Hz, 1-CH_2, 1H^{Si}), 5.33 (dd, $^3J_1$ = $^3J_2$ = 10.4 Hz, 3-C*H*), 5.55 (d, ^3J = 10.4 Hz, 5-C*H*), 6.97 (dd, $^3J_1$ = $^3J_2$ = 5.8 Hz, 12-C*H*), 7.47 (dd, $^3J_1$ = $^3J_2$ = 7.5 Hz, 2 × CH_m), 7.63 (t, ^3J = 7.5 Hz, CH_p), 7.91 (d, ^3J = 7.5 Hz, 2 × CH_o); IR (film on KBr) ν 3475, 2960, 2925, 1740, 1715, 1695, 1650, 1385, 1200, 1175, 1115, 1000 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{35}O_6$ ([M+H]$^+$): 467.2428; Found: 467.2424.

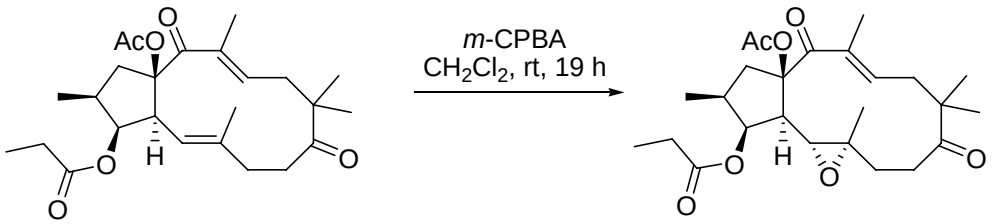


2 **S7** (59%)

3-Oxocharaciol (**S7**): IBX (28 mg, 0.1 mmol, 2 equiv) was added at ambient temperature to a solution of 3-*epi*-characiol **2** (17 mg, 0.051 mmol, 1 equiv) in CH_2Cl_2 (1 mL, 20 mL/mmol **2**) and DMSO[11] (1 mL, 20 mL/mmol **2**). After stirring for 18 h at ambient temperature, the reaction mixture was diluted with water. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (cyclohexane/ethyl acetate 20/1 to 10/1 to 5/1) provided 3-oxocharaciol (**S7**) (10 mg, 0.03 mmol, 59%) as a clear oil.: R_f 0.41 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the

[11] CH_2Cl_2 (water content 55 ppm) and DMSO (water content 246 ppm) were used as purchased (HPLC grade).

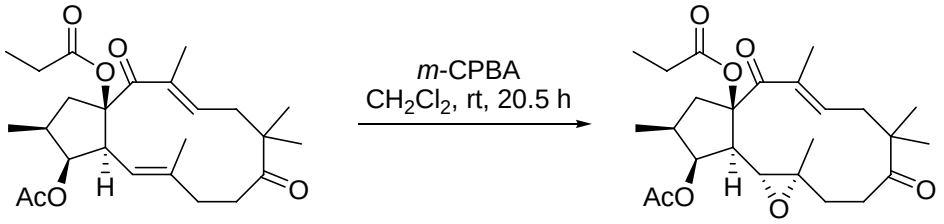
jatrophane numbering: ^{1}H NMR (501 MHz, $CDCl_3$) δ 1.14 (s, 18- or 19-CH_3), 1.20 (s, 18- or 19-CH_3), 1.26 (d, ^3J = 7.3 Hz, 16-CH_3), 1.31 (s, 17-CH_3), 1.59 (dd, ^3J = 2.3 Hz, ^2J = 14.3 Hz, 1-CH_2, 1H^{Re}), 1.75 (s, 20-CH_3), 1.99–2.02 (m, 8-CH_2, 1H), 2.11 (s, br, O*H*), 2.13–2.18 (m, 8-CH_2, 1H), 2.39 (dd, ^3J = 4.9 Hz, ^2J = 18.2 Hz, 11-CH_2, 1H), 2.50–2.59 (m, 2-C*H* + 11-CH_2, 1H), 2.83 (dd, ^2J = ^3J = 13.2 Hz, 7-CH_2, 1H), 3.00 (dd, ^2J = ^3J = 13.2 Hz, 7-CH_2, 1H), 3.06 (d, ^3J = 9.2 Hz, 4-C*H*), 3.39 (dd, ^3J = 11.1 Hz, ^2J = 14.3 Hz, 1-CH_2, 1H^{Si}), 5.32 (d, ^3J = 9.24 Hz, 5-C*H*), 7.02 (dd, $^3J_1$ = $^3J_2$ = 4.9 Hz, 12-C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8 (CH_3), 16.5 (CH_3), 18.3 (CH_3), 24.3 (CH_3), 25.5 (CH_3), 34.2 (CH_2), 34.3 (CH_2), 39.1 (CH), 40.7 (CH_2), 41.0 (CH_2), 48.0 (C), 59.0 (CH), 88.8 (C), 120.2 (CH), 137.0 (C), 141.8 (C), 144.1 (CH), 201.2 (C), 214.9 (C), 218.1 (C); IR (film on KBr) ν 3455, 2960, 2925, 1750, 1700, 1635, 1620, 1385, 1245, 1125, 1075 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{29}O_4$ ([M+H]$^+$): 333.2060; Found: 333.2062.



1a **S8** (72%)

15-*O*-Acetyl-3-*O*-propionylcharaciol-(5*R*,6*R*)-oxide (**S8**): *m*-CPBA (9 mg, 0.052 mmol, 1.9 equiv) was added at ambient temperature to a solution of 15-*O*-acetyl-3-*O*-propionylcharaciol (**1a**) (12 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 71 mL/mmol **1a**). The reaction mixture was stirred for 19 h at room temperature and then diluted with saturated aqueous $Na_2S_2O_3$ solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (cyclohexane/ethyl acetate 5/1 to 2/1) provided 15-*O*-acetyl-3-*O*-propionylcharaciol-(5*R*,6*R*)-oxide (**S8**) (9 mg, 0.02 mmol, 72%) as a white solid (mp: 120 °C): R_f 0.27 (cyclohexane/ethyl acetate 2/1). ^{1}H

NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (501 MHz, $CDCl_3$) δ 0.92 (d, ^{3}J = 6.8 Hz, 16-CH_3), 1.02 (s, 18- or 19-CH_3), 1.05 (s, 18- or 19-CH_3), 1.21 (t, ^{3}J = 7.5 Hz, propionic acid ester CH_3), 1.28 (s, 17-CH_3), 1.56 (dd, $^{3}J = {}^{2}J$ = 13.3 Hz, 1-CH_2, 1H^{Re}), 1.73 (s, 20-CH_3), 1.76 (dd, $^{3}J_1$ = 4.2 Hz, $^{3}J_2$ = 8.6 Hz, 4-C*H*), 1.94–2.06 (m, 8-CH_2), 2.09–2.15 (m, 2-C*H*), 2.16–2.23 (m, 7-CH_2, 1H), 2.19 (s, acetate-CH_3), 2.40–2.53 (m, 11-CH_2 + propionic acid ester CH_2), 2.86–2.93 (m, 7-CH_2, 1H), 3.21 (dd, ^{3}J = 7.5 Hz, ^{2}J = 13.3 Hz, 1-CH_2, 1H^{Si}), 3.34 (d, ^{3}J = 8.6 Hz, 5-C*H*), 5.40 (dd, $^{3}J_1 = {}^{3}J_2$ = 4.2 Hz, 3-C*H*), 5.98–6.00 (m, 12-C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4 (CH_3), 12.1 (CH_3), 13.4 (CH_3), 16.8 (CH_3), 21.5 (CH_3), 23.2 (CH_3), 25.1 (CH_3), 27.9 (CH_2), 32.1 (CH_2), 33.0 (CH_2), 38.1 (CH), 39.4 (CH_2), 47.4 (CH_2), 48.0 (C), 50.9 (CH), 59.4 (CH), 61.3 (C), 79.7 (CH), 89.8 (C), 135.5 (CH), 136.6 (C), 170.4 (C), 173.5 (C), 199.9 (C), 213.7 (C); IR (film on KBr) ν 2970, 2935, 1735, 1705, 1675, 1385, 1370, 1240, 1110, 1085 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{37}O_7$ ([M+H]$^+$): 449.2534; Found: 449.2533; $[\alpha]^{25}_D$ –58.4 (c 0.45, $CHCl_3$).



S9 **S 10** (95%)

3-*O*-Acetyl-15-*O*-propionylcharaciol-(5*R*,6*R*)-oxide (**S10**): *m*-CPBA (7 mg, 0.041 mmol, 1.9 equiv) was added at ambient temperature to a solution of 3-*O*-acetyl-15-*O*-propionylcharaciol (**S9**) (9 mg, 0.021 mmol, 1 equiv) in CH_2Cl_2 (2 mL, 95 mL/mmol **S9**). The reaction mixture was stirred for 20.5 h at room temperature and then diluted with saturated aqueous $Na_2S_2O_3$ solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography

(cyclohexane/ethyl acetate 5/1 to 2/1) provided 3-*O*-acetyl-15-*O*-propionylcharaciol-(5*R*,6*R*)-oxide (**S8**) (9 mg, 0.02 mmol, 95%) as a white solid (mp: 141 °C): R_f 0.18 (cyclohexane/ethyl acetate 2/1). ^{1}H NMR peak assignments were deduced from ^{1}H–^{1}H COSY spectra and are listed on the basis of the jatrophane numbering: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, ^3J = 6.8 Hz, 16-CH_3), 1.00 (s, 18- or 19-CH_3), 1.05 (s, 18- or 19-CH_3), 1.16 (t, ^3J = 7.5 Hz, propionic acid ester CH_3), 1.27 (s, 17-CH_3), 1.51 (dd, $^3J = {}^2J$ = 13.3 Hz, 1-CH_2, 1H^{Re}), 1.74 (s, 20-CH_3), 1.75 (dd, $^3J_1$ = 4.1 Hz, $^3J_2$ = 8.8 Hz, 4-C*H*), 1.96–2.06 (m, 8-CH_2), 2.08–2.12 (m, 2-C*H*), 2.15 (s, acetate-CH_3), 2.17–2.22 (m, 7-CH_2, 1H), 2.39–2.60 (m, 11-CH_2 + propionic acid ester CH_2), 2.85–2.92 (m, 7-CH_2, 1H), 3.22 (dd, ^3J = 7.5 Hz, ^2J = 13.3 Hz, 1-CH_2, 1H^{Si}), 3.34 (d, ^3J = 8.8 Hz, 5-C*H*), 5.39 (dd, $^3J_1 = {}^3J_2$ = 4.1 Hz, 3-C*H*), 5.98–6.01 (m, 12-C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.7 (CH_3), 12.2 (CH_3), 13.4 (CH_3), 16.9 (CH_3), 21.0 (CH_3), 23.1 (CH_3), 25.1 (CH_3), 27.9 (CH_2), 32.0 (CH_2), 33.0 (CH_2), 38.1 (CH), 39.4 (CH_2), 47.5 (CH_2), 48.0 (C), 51.0 (CH), 59.3 (CH), 61.3 (C), 80.0 (CH), 89.7 (C), 135.6 (CH), 136.7 (C), 170.2 (C), 173.7 (C), 199.9 (C), 213.7 (C); IR (film on KBr) ν 2970, 2935, 1740, 1705, 1675, 1385, 1370, 1240, 1185, 1080 cm^{-1}; Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; Found: C, 67.0; H, 8.1; $[\alpha]^{25}_D$ –52.8 (c 0.45, $CHCl_3$).

EXPERIMENTAL METHODS FOR THE BIOLOGICAL STUDIES OF JATROPHANE DERIVATIVES

Materials

All chemicals, unless otherwise stated, were purchased from Sigma Aldrich (Taufkirchen, Germany). The anthranilamide XR9577 was synthesized using the procedure of Roe et al..[12] Stock solutions (10 mmol/L) of the tested compounds and standards were prepared in DMSO.

Cell Lines

The ABCB1 overexpressing human ovarian cancer cell line A2780 Adr and its parental cell line A2780 were obtained from ECACC (European collection of cell cultures, United Kingdom No. 93112519 and 93112520). The human breast cancer cell line MCF-7 and its ABCG2 overexpressing counterpart MCF-7 MX were kindly provided by Dr. E. Schneider (Wadsworth Center, Albany, NY, USA). The human ovarian cancer cell lines 2008 and 2008 MRP1 were obtained from P. Borst (The Netherlands Cancer Institute, Amsterdam, The Netherlands). All cell lines were cultured in RPMI 1640 Medium (Sigma) supplemented with 10% fetal bovine serum and antibiotics (100 U/mL penicillin G, 100 µg/mL streptomycin) at 37 °C in a humidified atmosphere containing 5% CO_2.

Calcein-AM accumulation assays

Calcein-AM accumulation assays for the determination of ABCB1 (P-gp) and ABCC1 (MRP1) transport activity were performed as described previously.[13] Briefly A2780 Adr (ABCB1) and 2008

[12] Roe, M.; Folkers, A.; Ashworth, P.; Brumwell, J.; Chima, L.; Hunjan, S.; Pretswell, I.; Dangerfield, W.; Ryder, H.; Charlton, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 595–600.

[13] Häcker, H.-G.; Leyers, S.; Wiendlocha, J.; Gütschow, M.; Wiese, M. *J. Med. Chem.* **2009**, *52*, 4586–4595

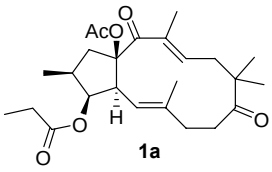
MRP1 (ABCC1) cells and their corresponding wild-type cell lines were harvested by trypsination and seeded into 96-well microplates at a density of 27000 cells per well. After addition of the test compounds and a 30 min pre-incubation (37 °C) calcein-AM (Calbiochem, Schwalbach, Germany) was added to obtain a final concentration of 0.5 µmol/L. The intracellular fluorescence was monitored for 60 min using a BMG Fluostar optima microplate reader (λ_{ex} = 485 nm, λ_{em} = 520 nm). Verapamil and XR9577 were used as standard inhibitors for ABCB1. In the case of ABCC1 cyclosporin A (CsA) was used.

Hoechst 33342 accumulation assay

ABCG2 (BCRP) transport activity was measured using the human MCF-7 MX breast cancer cell line and its corresponding parental cell line MCF-7. The assay was performed as described earlier.[14] Cells were harvested and seeded into black 96-well plates at a density of 27000 per well. Subsequently solutions of the test compounds were added and the plates were stored for 30 min at 37 °C. After addition of Hoechst 33342 (5 µmol/L final concentration) the intracellular fluorescence was measured during 120 min (λ_{ex} = 355 nm, λ_{em} = 460 nm). XR9577 was used as a standard inhibitor of ABCG2.

[14] Pick, A.; Müller, H.; Wiese, M. *Bioorg. Med. Chem.* **2008**, *16*, 8224–8236.

CHART OF TESTED NATURAL AND NON-NATURAL JATROPHANES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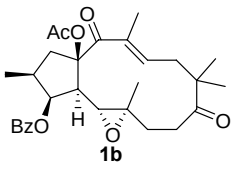
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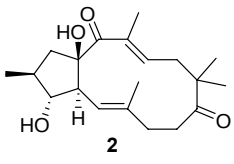
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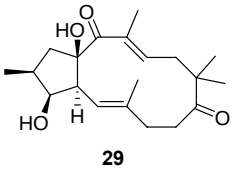
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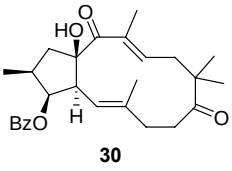
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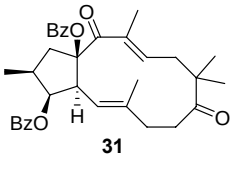
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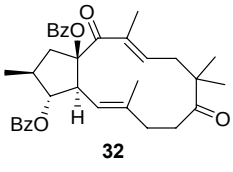
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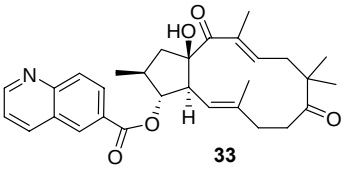
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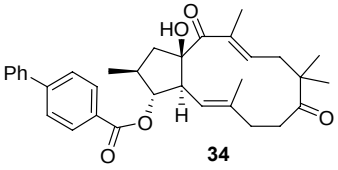
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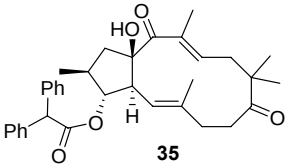
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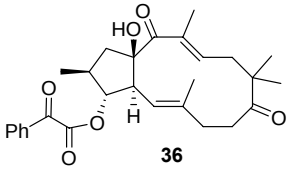
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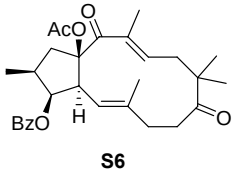
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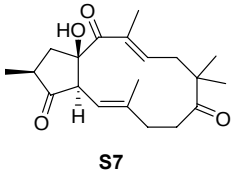
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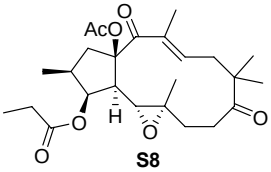
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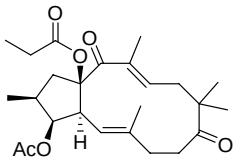
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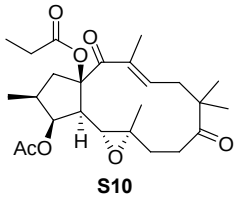
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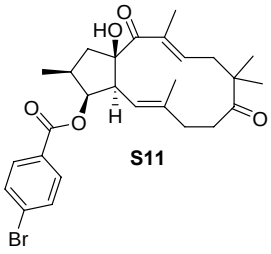
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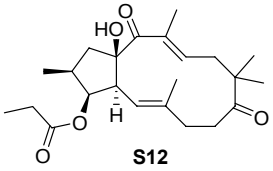
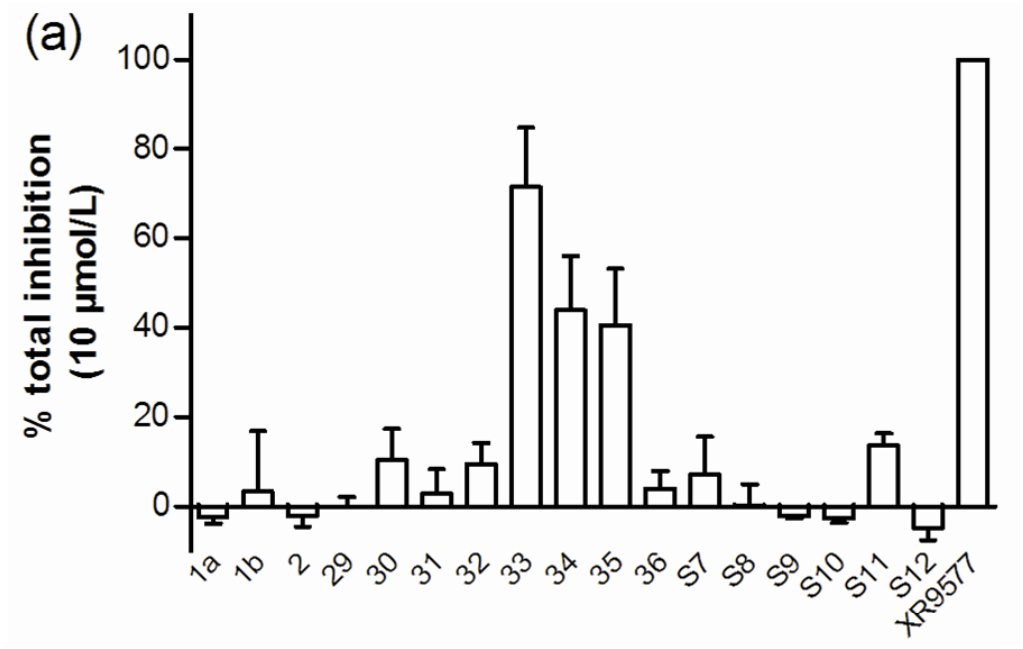
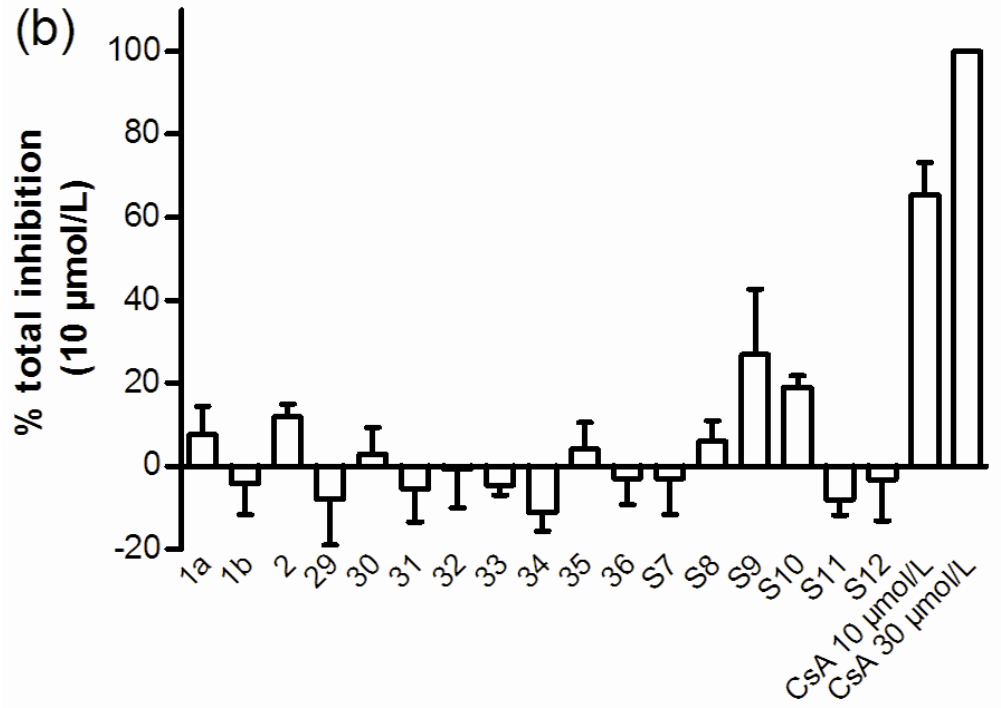

S12

RESULTS OF BIOLOGICAL INVESTIGATIONS

Effects of jatrophane derivatives on the ABCG2 (A) and ABCC1 (B) mediated transport of Hoechst 33342 and calcein-AM, respectively.





Summary of the MDR reversing potency of the natural and non-natural jatrophane diterpenes and their calculated octanol-water partition coefficients.

Compound	% total inhibition ABCB1 ± SD	% total inhibition ABCG2 ± SD	% total inhibition ABCC1 ± SD	logP_{calcd} [a]
XR9577	100	100	---	---
verapamil	57.6 ± 14.3	---	---	---
CsA	---	---	65.4 ± 7.8 [b]	---
1a	7.4 ± 3.6	n.a.	7.7 ± 6.8	4.44
1b	20.9 ± 5.8	n.a.	n.a.	4.89
2	n.a.	n.a.	11.9 ± 3.2	2.29
29	n.a.	n.a.	n.a.	2.29
30	16.6 ± 2.3	10.3 ± 7.0	n.a.	5.11
31	28.9 ± 6.8	2.8 ± 5.4	n.a.	8.07
32	47.2 ± 14.3	9.4 ± 4.9	n.a.	8.07
33	51.3 ± 15.5	71.4 ± 13.4	n.a.	5.03
34	32.0 ± 10.1 [c]	43.9 ± 12.1	n.a.	6.76
35	24.5 ± 10.4 [c]	40.6 ± 12.6	n.a.	6.32
36	7.6 ± 9.2	4.0 ± 4.0	n.a.	4.19
S6	34.6 ± 7.1	---	---	5.99
S7	n.a.	7.0 ± 8.6	n.a.	2.05
S8	n.a.	n.a.	6.0 ± 5.0	3.40
S9	10.0 ± 4.0	n.a.	27.0 ± 15.7	4.44
S10	12.9 ± 6.5	n.a.	19.0 ± 2.8	3.40
S11	31.3 ± 3.0	13.7 ± 2.1	n.a.	5.87
S12	n.a.	n.a.	n.a.	3.32

[a] logP values were calculated using ACD 5.09, Advanced Chemistry Development Inc., Toronto, Canada
[b] ABCC1 function was totally inhibited by 30 µmol/L CsA
[c] Increased fluorescence also in A2780 wildtype cells