Asymmetric Synthesis of the C1–C16 Segment of Lasonolide A

Hartmut Beck[a,b] and H. Martin R. Hoffmann*[a]

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The C1–C16-segment of lasonolide A has been prepared stereoselectively in high chemical and optical yield starting from 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (***rac*-1**).

Introduction

Lasonolide A is a novel, highly cytotoxic macrolide isolated and identified by McConnell et al. from a Caribbean marine sponge, *Forcepia Sponge*.[1] It has been found to inhibit the in vitro proliferation of A-549 human lung carcinoma cells (IC_{50} = 40 ng/mL) and P388 murine leukemia cell lines (IC_{50} = 2 ng/mL). It also inhibits cell adhesion in a newly developed whole cell assay that detects signal transduction agents.[1] The most prominent structural feature is a 20-membered macrocyclic lactone which contains two highly substituted tetrahydropyran units bearing a total of eight stereogenic centres of defined configuration (see Figure 1). Five disubstituted and trisubstituted double bonds of defined (*E*) and (*Z*) stereochemistry are part of the macrocyclic backbone and add to the synthetic challenge.

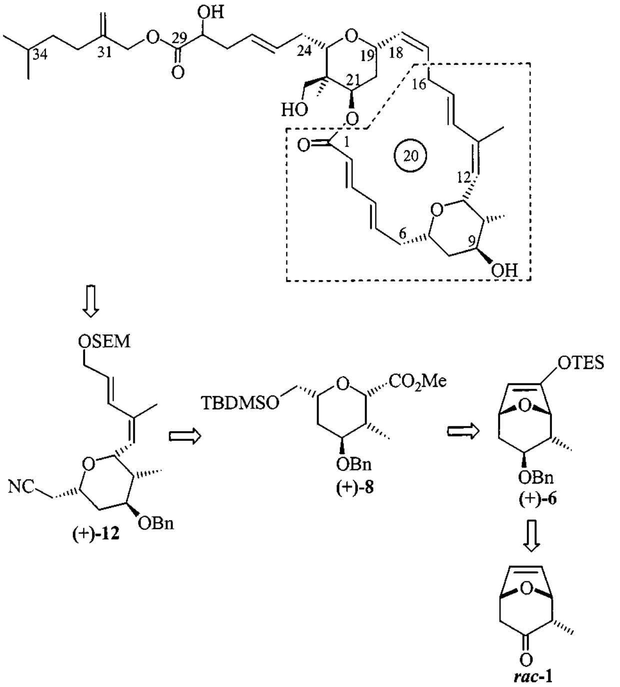
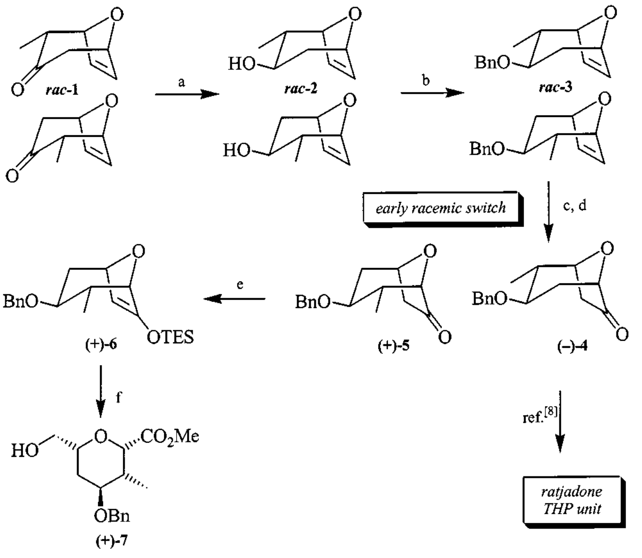


Figure 1. Retrosynthetic plan

Results and Discussion

We have already developed a short route to the northern C18–C24 segment of lasonolide A.[2] Bicyclo[3.2.1] systems were used as viable and convenient precursors for substituted and enantiopure tetrahydropyrans in case of the northern C18–C24 unit and for a continuously growing number of other natural product segments.[3] Extending our methodology we now report an efficient stereoselective route to the southern C1–C16 segment of lasonolide A starting from 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (***rac*-1**).



Scheme 1. *Early racemic switch* to tetrahydropyran **(+)-7** containing 4 stereogenic centres: (a) SmI_2, *i*PrOH, THF, reflux, 2 h (57%); (b) NaH, THF, reflux, 1 h, then BnBr, TBAI (0.25 mol-%) (99%); (c) (−)-Ipc_2BH, THF, −15°C, 1 week (90%, 90% *ee*); (d) PCC, DCM, room temp., 16 h (45%, 45%); (e) LDA, TESCl, NEt_3, THF, −78°C, 1 h (84%); (f) i) O_3, DCM, MeOH, −78°C, ii) DMS, then −10°C, iii) CH_2N_2, iv) $NaBH_4$, −10°C → room temp., 1 h (75%)

Ketone ***rac*-1**[4] was reduced to equatorial alcohol ***rac*-2** using SmI_2[5] and the resulting alcohol was converted into benzyl ether ***rac*-3**. Asymmetric hydroboration[6] with (−)-diisopinocampheylborane [(−)-Ipc_2BH] and subsequent pyridinium chorochromate (PCC) oxidation afforded two regioisomeric ketones **(−)-4** and **(+)-5** in high yield, which were easily separable by flash chromatography. Each regioisomer serves as an *early racemic switch*[7] for a valuable tetrahydropyran precursor of a bioactive natural product:

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[a] Department of Organic Chemistry, University of Hannover
Schneiderberg 1 B, D-30167 Hannover, Germany
Fax: (internat.) + 49-(0)511/762-3011
E-mail: hoffmann@mbox.uni-hannover.de
[b] Current address: Bayer AG, Central Research,
D-51368 Leverkusen

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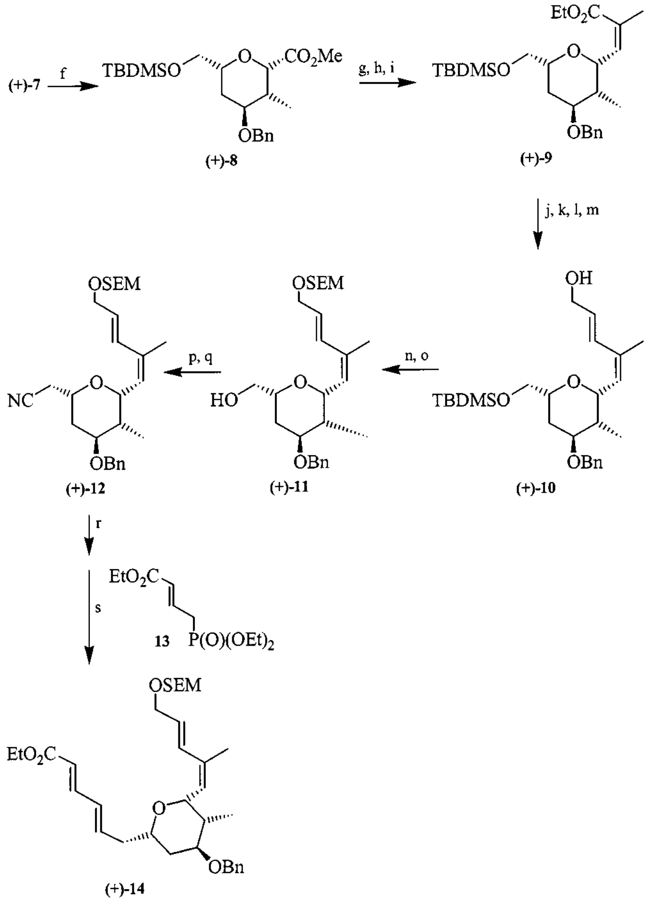
The *anti* regioisomer **(−)-4** has been used[8a] as a precursor of the C15−C24-tetrahydropyran unit of ratjadone, which is an antifungal and cytotoxic polyketide from myxobacteria isolated recently by Höfle, Reichenbach et al.[9] The desired *syn* regioisomer **(+)-5** was transformed into the corresponding triethylsilyl enol ether **(+)-6**. Ozonolysis of the double bond,[8b] followed by in situ esterification with CH_2N_2 and in situ reduction with $NaBH_4$ afforded the ester **(+)-7** in good yield. The correct 2,6-*cis* configuration of the tetrahydropyran unit **(+)-7** resulted from the bicyclic structure of intermediate **(+)-6**. Furthermore, carbon atoms C-6 and C-12 are chemodifferentiated bearing useful functional groups for the following chain elongation.



Scheme 2. Key intermediates en route to target **(+)-14**; reagents: (f) TBDMSCl, imidazole, DCM, room temp., 3 h (98%); (g) LAH, THF, 0°C; (h) Dess−Martin periodinane, DCM, room temp., 2 h [87%, 2 steps from **(+)-8**]; (i) $(F_3CCH_2O)_2P(O)CHMeCO_2Et$ (Still−Gennari reagent), KHMDS, 18-crown-6, THF, −78°C [92%, (*Z*)/(*E*) = 33:1 (GC)], (j) DIBAH, toluene, −78°C; (k) MnO_2, DCM, room temp., 5 h; (l) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene, 0°C → room temp., 1 h, (*E*)/(*Z*) = 25:1 (GC); (m) DIBAH, DCM, −78°C, 2 h [76%, 4 steps from **(+)-9**]; (n) $i\text{Pr}_2\text{EtN}$, TBAI, SEMCl, DCM, room temp., 16 h; (o) TBAF, THF, room temp., 2 h [97%, 2 steps from **(+)-10**]; (p) Tf_2O, pyridine, DCM; (q) KCN, DMSO, 18-crown−6, 50°C, 4 h [90%, 2 steps from **(+)-11**]; (r) i) DIBAH, DCM, −78°C, 1 h, ii) 1 N HCl, MeOH, room temp., 1 h; (s) triethyl phosphonocrotonate **13**, NaH, THF, 0°C → room temp., 2 h [70%, 2 steps from **(+)-12**]

The eastern unsaturated segment C12−C16 was built up after quantitative conversion of the alcohol group into the corresponding TBDMS ether [**(+)-7** → **(+)-8**] (see Scheme 2). Ester **(+)-8** was converted into the corresponding aldehyde by reduction (DIBAH) to the primary alcohol and subsequent oxidation (Dess−Martin periodinane). The Still−Gennari protocol[10] provided the unsaturated ester **(+)-9** in excellent chemical yield (92%) and high (*Z*) selectivity [(*Z*)/(*E*) = 33:1]. The (*Z*) configuration of the trisubstituted olefin **(+)-9** was determined by NOE mesasurements, and is in accordance with the natural product.[1] Pentadienyl alcohol **(+)-10** was prepared in four steps starting from ester **(+)-9**. The conjugated double bond was (*E*)-selectively introduced by Horner−Wadsworth−Emmons (HWE) olefination [(*E*)/(*Z*) = 20:1] of the corresponding aldehyde which was prepared in two steps from ester **(+)-9** by reduction (DIBAH) and subsequent oxidation (MnO_2). Reduction with DIBAH afforded the pentadienyl alcohol **(+)-10** in 76% starting from ester **(+)-9** (four steps). In order to elaborate the western C1−C6 segment we protected the C-16 terminus as its SEM [2-(trimethylsilyl)ethoxymethyl], $Me_3SiCH_2CH_2OCH_2$) ether (Scheme 2), allowing for rather acidic conditions later (see below). Subsequent deprotection at C-6 with TBAF was chemoselective and afforded the alcohol **(+)-11**. Alcohol **(+)-11** was converted into the corresponding triflate and homologated with KCN in DMSO to give the nitrile **(+)-12** in very good yield. Reduction with DIBAH and subsequent hydrolysis (1N HCl in MeOH) provided the aldehyde which was elongated by an HWE olefination. Triethyl phosphonocrotonate served as a C_4 component and afforded the target **(+)-14** in good yield. Thus, the convergent and (*E*,*E*)-selective HWE olefination with a crotyl phosphonate established the required functionality at C-1, C-2, C-3 and C-4 in a single step. The newly formed double bond was obtained in excellent chemical yield and (*E*) selectivity (20:1).

Conclusion

In conclusion we have stereoselectively built up the C1−C16 segment of lasonolide A in 20 steps with an overall yield of 6% and 90% *ee.*[11] The synthesis is challenging due to the four chiral centres and the four double bonds in the target compound. The power of [4+3] cycloaddition methodology developed by us is demonstrated. The Still−Gennari and Horner−Wadsworth−Emmons olefination protocols have facilitated (*Z*)- and (*E*)-selective formation of the polyolefinic segments.

Experimental Section

General Remarks: IR: Perkin−Elmer 1710 infrared spectrometer. − ^1H NMR and ^{13}C NMR: Bruker AM 400 spectrometer in deuterated chloroform with tetramethylsilane as internal standard. ^{13}C-NMR signal assignments for each signal were established by DEPT measurements; multiplicities are indicated by s (primary), d (secondary), t (tertiary) and q (quaternary). − MS: Finnigan MAT 312 (70 eV) or VG Autospec spectrometer at room temp. unless otherwise stated. − Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30−60 μm). − Analytical TLC was carried out on aluminium-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). − THF was distilled from sodium and benzophenone before use. CH_2Cl_2 (DCM) was distilled from CaH_2 before use. DMF was dried with BaO and distilled from CaH_2 before use. *tert*-Butyl methyl ether (MTBE), ethyl acetate (EA) and light petroleum ether (PE, b.p. 40−60 °C) were distilled before use. − For spectral data of compounds ***rac*-1**, ***rac*-2**, ***rac*-3**, **(−)-4** and **(+)-5** see ref.[3a]

(1*S*,2*R*,3*S*,5*R*)-3-Benzyloxy-2-methyl-7-triethylsilyloxy-8-oxabicyclo[3.2.1]octane [(+)-6]: To a solution of *syn*-ketone **(+)-5** (1.5 g, 6.1 mmol) in THF (10 mL) was added LDA [prepared at 0 °C from diisopropylamine (1.28 mL, 9.15 mmol) and BuLi (5.7 mL, 9.15 mmol, 1.6 M solution in hexane) in THF (7 mL)] at −78 °C. The mixture was allowed to reach room temp. and then cooled to −78 °C again. TESCl (1.38 g, 9.15 mmol) was added followed by NEt_3 (2.50 mL, 18.3 mmol) and the resulting mixture was stirred for 3 h at −78 °C. Satd. aq. $NaHCO_3$ solution was added and the aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated and purified by column chromatography (silica gel; PE/MTBE, 15:1) to afford **(+)-6**, 1.86 g (84%), colourless oil. − $[\alpha]_D^{20}$ = +76.5 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3004 cm^{-1}, 2960, 2912, 2876, 1636, 1496, 1412, 1352, 1313, 1280, 1244, 1144, 1072, 1044, 1028, 996, 924, 900, 820. − ^{1}H NMR: δ = 7.33−7.26 (m, 5 H, Ph), 4.76 (d, *J* = 2.02 Hz, 1 H, 6-H), 4.73 (m, 1 H, 5-H), 4.61 (d, *J* = 11.58 Hz, 1 H, 10-H), 4.39 (d, *J* = 11.58 Hz, 1 H, 10-H), 4. 06 (d, *J* = 3.5 Hz, 1 H, 1-H), 3.33 (dt, *J* = 15.44 Hz, *J* = 9.38 Hz, 1 H, 3-H), 2.05 (dd, *J* = 6.07 Hz, *J* = 1.84 Hz, 1 H, 4-H_{ax}), 1.92 (m, 1 H, 4-H_{eq}), 1.68 (m, 1 H, 2-H), 1.03 (d, *J* = 6.99 Hz, 3 H, 9-H), 0.94 [m, 9 H, 3 × CH_3 (TESO)], 0.67 [m, 6 H, 3 × CH_2 (TESO)]. − ^{13}C NMR: δ = 156.18 (C-7), 138.78, 128.26, 127.78, 127.47 (Ph), 99.52 (C-6), 81.11 (C-5), 78.33 (C-1), 78.09 (C-3), 70.54 (C-10), 38.65 (C-2), 33.20 (C-4), 13.45 (C-9), 6.49 (3 × TES−CH_3), 4.42 (3 × TES−CH_2). − MS; *m/z*: 360 (8) [M^+], 331 (1), 289 (1), 269 (6), 253 (3), 237 (5), 225 (73), 211 (8), 198 (15), 169 (6), 159 (12), 132 (5), 115 (17), 103 (100), 91 (46), 75 (88). − HR MS: calcd. for $C_{121}H_{32}O_3Si$ [M^+] 360.2121, found 360.2120.

Methyl (2*S*,3*R*,4*S*,6*R*)-4-Benzyloxy-6-hydroxymethyl-3-methyltetrahydropyran-2-carboxylate [(+)-7]: A solution of olefin **(+)-6** (652 mg, 1.81 mmol) in DCM/MeOH (1:1.5; 25 mL) was cooled to −78 °C. Ozone was bubbled through the solution until saturation with ozone occurred (light-blue colour). DMS (146 µL, 1.99 mmol) was added, the mixture was allowed to reach 0 °C and then treated with diazomethane in THF until the yellow colour of the added solution presisted. Then $NaBH_4$ (68.5 mg, 1.81 mmol) was added and the mixture was stirred for 30 min at room temp. Satd. aq. NH_4Cl solution and MTBE were added, the aqueous layer was extracted with MTBE (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$). The crude product was purified by column chromatography (silica gel; PE/MTBE, 1:1) to afford **(+)-7**, 400 mg (75%), colourless solid. − $[\alpha]_D^{20}$ = +12.9 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3672 cm^{-1}, 3596, 3476, 3088, 3064, 3000, 2956, 2880, 1748, 1452, 1440, 1392, 1348, 1300, 1228, 1152, 1112, 1080, 1040, 992, 908. − ^{1}H NMR: δ = 7.40−7.24 (m, 5 H, Ph), 4.66−4.52 (m, 3 H, 2-H, Bn-CH_2), 3.94 (m, 1 H, 6-H), 3.75 (s, 1 H, 9-H), 3.70−3.54 (m, 2 H, 4-H, 7-H), 2.33 (m, 1 H, 5-H_{ax}), 1.72 (m, 1 H, 5-H_{eq}), 1.60 (m, 1 H, 3-H), 0.91 (d, *J* = 7.2 Hz, 3 H, 10-H). − ^{13}C NMR: δ = 172.12 (q, C-8), 138.47 (q, Ph), 128.43, 127.61, 127.33 (t, Ph), 76.14, 74.21, 73.84 (t, C-2, C-4, C-6), 70.33 (d, Bn-CH_2), 65.55 (d, C-7), 51.91 (s, C-9) 34.48 (t, C-3), 26.46 (d, C-5), 11.62 (s, C-10). − MS; *m/z*: 294 (8.1) [M^+], 263 (3.5), 235 (2.2), 220 (3.1), 205 (11.1), 185 (3.8), 167 (1.6), 155 (17.9), 127 (6.3), 118 (20.0), 101 (7.3), 91 (100), 81 (3.1), 69 (9.6). − HR MS: calcd. for $C_{16}H_{22}O_5$ [M^+] 294.1467, found 294.1470.

Methyl (2*S*,3*R*,4*S*,6*R*)-4-Benzyloxy-6-*tert*-butyldimethylsilyloxymethyl-3-methyltetrahydropyran-2-carboxylate [(+)-8]: To a solution of ester **(+)-7** (260 mg, 0.884 mmol) and imidazole (180 mg, 2.65 mmol) in DCM (3 mL) was added TBDMSCl (159 mg, 1.06 mmol) in DCM (1.5 mL). The mixture was stirred for 3 h at room temp. and a white solid precipitated. The suspension was treated with satd. aq. $NaHCO_3$ solution, the aqueous layer was extracted with DCM (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$). The crude product was purified by column chromatography (silica gel; PE/MTBE, 20:1) to give **(+)-8**, 354 mg (98%), colourless oil. − $[\alpha]_D^{20}$ = +14.d (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3672 cm^{-1}, 3000, 2956, 2928, 2880, 2856, 1752, 1460, 1256, 1140, 1108, 1084, 836. − ^{1}H NMR: δ = 7.40−7.25 (m, 5 H, Ph), 4.66−4.55 (m, 3 H, 2-H, Bn-CH_2), 3.86 (m, 1 H, 6-H), 3.78 (m, 1 H, 4-H), 3.76 (s, 3 H, 9-H), 3.62 (m, 2 H, 7-H), 2.31 (m, 1 H, 5-H_{ax}), 1.80 (m, 1 H, 5-H_{eq}), 1.60 (m, 1 H, 3-H), 0.90 (d, *J* = 8.0 Hz, 3 H, 8-H). − ^{13}C NMR: δ = 171.97 (q, C-8), 138.65 (q, Ph), 128.41, 127.56, 127.38 (t, Ph), 76.31, 74.49, 73.58 (t, C-2, C-4, C-6), 70.26 (d, Bn-CH_2), 66.13 (d, C-7), 51.79 (s, C-9) 34.82 (t, C-3), 27.45 (d, C-5), 25.93 [s, $SiC(CH_3)_3$], 18.36 [q, $SiC(CH_3)_3$], 11.62 (s, C-10), −5.27, −5.30 [$Si(CH_3)_2$]. − MS; *m/z*: 408 (0) [M^+], 351 (48.8), 292 (2.5), 243 (1.3), 203 (4.0), 185 (6.0), 175 (10.1), 143 (9.3), 117 (7.3), 105 (5.0), 91 (100), 75 (9.8). − FAB MS; *m/z*: 445 (10) [M^+ + Na], 431 (100), 409 (11), 351 (52), 281 (10), 207 (13), 147 (26).

Ethyl (*Z*)-3-[(2*S*,3*R*,4*S*,6*R*)-4-Benzyloxy-6-*tert*-butyldimethylsilyloxymethyl-3-methyltetrahydropyran-2-yl]-2-methylacrylate [(+)-9]: To a suspension of $LiAlH_4$ (128 mg, 3.67 mmol) in THF (30 mL) was added ester **(+)-8** (3.00 g, 7.34 mmol) in THF (20 mL). The mixture was stirred for 2 h at room temp. and then cooled to 0 °C. EA (631 µL) was added, followed by H_2O (279 µL), 2 N NaOH (279 µL) and H_2O (837 µL). The resulting mixture was filtered through silica gel and the solvent was evaporated. The crude alcohol was dissolved in DCM (15 mL) and Dess−Martin reagent (3.68 g, 8.81 mmol) was added. After 5 h at room temp., MTBE (60 mL) and satd. aq. $NaHCO_3/Na_2S_2O_3$ (30 mL) were added. The aqueous layer was extracted with MTBE, dried ($MgSO_4$) and the solvent was removed. The crude product was filtered through silica gel to yield the pure aldehyde (GC), 2.418 g (87%). To a solution of 18-crown-6 (77 mg, 0.29 mmol) in THF (1 mL) was added Still−Gennari reagent[10] (58 mg, 0.17 mmol) in THF (0.5 mL) at −40 °C. The mixture was cooled to −78 °C and KHMDS [potassium *bis*(trimethylsilyl)amide] (252 µL, 0.17 mmol, 0.67 M solution in toluene) was added followed by the aldehyde (58 mg, 0.15 mmol) in THF (0.5 mL). The reaction was complete after 10 min and satd. aq. NH_4Cl solution (10 mL) and MTBE (15 mL) were added. The aqueous layer was extracted with MTBE (3 × 5 mL), the combined organic phases dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography (silica gel; PE/MTBE, 16:1) to give **(+)-9**, 65 mg (92%), colourless oil. − $[\alpha]_D^{20}$ = +12.9 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3000 cm^{-1}, 2956, 2928, 2856, 1704, 1452, 1228, 1172, 1136, 1112, 1064, 1028, 1004, 836. − ^{1}H NMR: δ = 7.43−7.23 (m, 5 H, Ph), 5.94 (dq, *J* = 7.52 Hz, *J* = 1.3 Hz, 1 H, 3-H), 5.18 (dd, *J* = 7.52 Hz, *J* = 2.24 Hz, 1 H, 4-H), 4.70 (d, *J* = 11.8 Hz, 1 H, Bn-CH_2), 4.52 (d, *J* = 11.8 Hz, 1 H, Bn-CH_2), 4.14 (q, *J* = 7.15 Hz, 2 H, Et-CH_2), 3.86 (m, 1 H, 8-H), 3.65 (dd, *J* = 10.5 Hz, *J* = 4.7 Hz, 1 H, 9-H_a), 3.58 (m, 1 H, 6-H), 3.57 (dd, *J* = 10.5 Hz, *J* = 5.4 Hz, 1 H, 9-H_b), 2.24 (m, 1 H, 7-H_{ax}), 1.93 (m, 3 H, 11-H), 1.74−1.60 (m, 2 H, 5-H, 7-H_{eq}), 1.21 (t, *J* = 7.15 Hz, 3 H, Et-CH_3), 0.92 (d, *J* = 7.16, 3 H, 10-H), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.65 (s, 3 H, $SiCH_3$), 0.45 (s, 3 H, $SiCH_3$). − ^{13}C NMR: δ = 167.32 (q, C-1), 142.09 (t, C-3), 139.15 (q, Ph), 128.23, 127.57, 127.30 (t, Ph), 127.05 (q, C-2), 77.19, 72.84, 72.83 (t, C-4, C-6, C-8), 69.94 (d, Bn-CH_2), 66.52 (d, C-9), 60.41 (d, Et-CH_2), 35.18 (t, C-5), 27.34 (d, C-7), 25.96 [s, SiC(CH_3)$_3$], 20.49 (s, C-11), 18.39 [q, SiC(CH_3)$_3$], 14.19 (Et-CH_3), 11.51 (s, C-10), −5.20 [s, Si(CH_3)$_2$]. − MS; *m/z*: 462 (4.3) [M^+], 405 (12.7), 325 (1.5), 298 (8.6), 279 (1.6), 251 (4.6), 239 (4.1), 201 (18.3), 171 (3.6), 150 (7.4), 117 (26.3), 105 (1.6), 91 (100). − HR MS calcd. for $C_{26}H_{42}O_5Si$ [M^+] 462.2802, found 462.2809.

(2*E*,4*Z*)-5-[(2*S*,3*R*,4*S*,6*R*)-4-Benzyloxy-6-*tert*butyldimethylsilyloxymethyl-3-methyltetrahydropyran-2-yl]-4-methyl-2,4-pentadien-1-ol [(+)-10]: To a solution of ester **(+)-9** (55 mg, 0.12 mmol) in DCM (4 mL) was added DIBAH (250 μL, 0.30 mmol, 1.2 M solution in toluene) at −78 °C. The mixture was stirred for 2 h at the same temperature, then 1 N HCl (2 mL) was added. The aqueous layer was extracted with DCM (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and the solvent was removed. The crude alcohol obtained was added to a suspension of MnO_2 (233 mg, 2.68 mmol) in DCM (3 mL). The mixture was stirred for 3 h at room temp. and then filtered through silica gel. The solvent was evaporated and the aldehyde dissolved in toluene (3 mL). To a suspension of NaH (10 mg, 0.25 mmol, 60% in mineral oil) in toluene (5 mL) was added triethyl phosphonoacetate (56 mg, 0.25 mmol). The mixture was stirred for 1 h, then the solution of the aldehyde was added and stirring was continued for 2 h. Work up afforded crude ester, which was dissolved in toluene (2 mL). To this solution was added DIBAH (333 μL, 0.400 mmol) at −78 °C. After 2 h, 1 N HCl (3 mL) and MTBE (10 mL) were added. The aqueous layer was extracted with MTBE (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$). After removal of the solvent, the crude product was purified by chromatography (silica gel; PE/MTBE, 3:1) to yield **(+)-10**, 25 mg (47%), colourless oil. − $[\alpha]_D^{20}$ = +38.8 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3608 cm^{-1}, 3000, 2956, 2928, 2856, 1452, 1380, 1256, 1088, 1072, 1004, 964, 836. − ^1H NMR: δ = 7.40−7.26 (m, 5 H, Ph), 6.60 (dq, *J* = 15.68 Hz, *J* = 0.75 Hz, 1 H, 3-H), 5.85 (dtd, *J* = 15.56 Hz, *J* = 5.90 Hz, *J* = 0.5 Hz, 1 H, 2-H), 4.43 (d, *J* = 7.9 Hz, 1 H, 5-H), 4.92 (dd, *J* = 8.0 Hz, *J* = 2.3 Hz, 1 H, 6-H), 4.59 (s, 2 H, Bn-CH_2), 4.19 (d, *J* = 5.64 Hz, 2 H, 1-H), 3.88 (m, 1 H, 10-H), 3.68 (dd, *J* = 10.42 Hz, *J* = 4.65 Hz, 1 H, 11-H_a), 3.61 (q, *J* = 2.8 Hz, 1 H, 8-H), 3.55 (dd, *J* = 10.4 Hz, *J* = 5.8 Hz, 1 H, 11-H_b), 1.89 (m, 1 H, 7-H), 1.85 (d, *J* = 0.63 Hz, 3 H, 13-H), 1.76 (m, 1 H, 9-H_a), 1.63 (ddd, *J* = 14.4 Hz, *J* = 11.7 Hz, *J* = 2.8 Hz, 1 H, 9-H_b), 1.48 (br. s, 1 H, OH), 0.95 (*J* = 7.15 Hz, 3 H, 12-H), 0.89 [s, 9 H, SiC(CH_3)$_3$], 0.06 [s, 3 H, SiCH_3], 0.05 (s, 3 H, SiCH_3). − ^{13}C NMR: δ = 139.04 (q, Ph), 132.35 (q, C-4), 130.07 (t, C-2), 129.51 (t, C-3), 128.38 (t, Ph), 128.31 (t, C-5), 127.44, 127.22 (t, Ph), 77.46, 73.27, 71.09 (t, C-6, C-8, C-10), 70.14 (d, Bn-CH_2), 66.48 (d, C-11), 63.91 (d, C-1), 36.77 (t, C-7), 27.41 (d, C-9), 25.96 [s, Si(CH_3)$_3$], 20.44 (s, C-13), 18.39 [q, SiC(CH_3)$_3$], 11.17 (s, C-12), −5.22 (s, SiCH_3), −5.23 (s, SiCH_3). − MS (90 °C); *m/z*: 446 (2.6) [M^+], 428 (2.4), 363 (1.4), 347 (1.7), 292 (1.8), 282 (2.7), 251 (3.4), 211 (2.6), 201 (5.7), 171 (4.1), 159 (5.4), 121 (11.1), 105 (5.6), 91 (100), 73 (16.8). − HR MS calcd. for $C_{26}H_{42}O_4Si$ [M^+] 446.2852, found 446.2861. − (*Z*) configuration was corroborated by NOE and comparison with ROESY data of the natural product: 13-H irradiated, 5-H (5%).

[(2*R*,4*S*,5*R*,6*S*)-4-Benzyloxy-5-methyl-6-{(1*Z*,3*E*)-2-methyl-5-[2-(trimethylsilylethoxy)methoxy]penta-1,3-dienyl}tetrahydropyran-2-yl]methanol[(+)-11]: To a solution of **(+)-10** (236 mg, 0.529 mmol), diisopropyl(ethyl)amine (191 mg, 1.48 mmol) and TBAI (195 mg, 0.529 mmol) in DCM (4 mL) was added SEMCl [2-(trimethylsilyl)ethoxymethyl chloride] (115 mg, 0.688 mmol) at room temp. and the mixture was stirred for 16 h. Satd. aq. NH_4Cl solution and MTBE (20 mL) were added and the aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (silica gel; PE/MTBE, 25:1) afforded the SEM ether (296 mg). To a solution of TBAF (216 mg, 0.616 mmol) in THF (5 mL) was added the SEM ether at 0 °C. The mixture was stirred for 2 h, then H_2O (15 mL) and MTBE (20 mL) were added. The aqueous layer was extracted with MTBE (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and the solvent was removed. The crude product was purified by column chromatography (silica gel; PE/MTBE) to afford **(+)-11**, 213 mg (90%), colourless oil. − $[\alpha]_D^{20}$ = +31.0 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3444 cm^{-1}, 3008, 2956, 2924, 2876, 1652, 1604, 1248, 1100, 1056, 1032, 1028, 860, 836. − ^1H NMR: δ = 7.39−7.24 (m, 5 H, Ph), 6.63 (dq, *J* = 15.6 Hz, *J* = 0.7 Hz, 1 H, 9-H), 5.81 (dt, *J* = 15.6 Hz, *J* = 6.0 Hz, 1 H, 10-H), 5.41 (d, *J* = 7.78 Hz, 1 H, 7-H), 4.95 (dd, *J* = 7.78 Hz, *J* = 2.3 Hz, 1 H, 6-H), 4.66 (s, 2 H, 14-H), 4.62, 4.54 (d, *J* = 12 Hz, 2 H, Bn-CH_2), 4.13 (m, 2 H, 11-H), 3.89 (m, 1 H, 2-H), 3.65−3.56 (m, 4 H, 1-H_a, 4-H, 14-H), 3.49 (dd, *J* = 11.6 Hz, *J* = 6.5 Hz, 1 H, 1-H_b), 1.93 (m, 1 H, 7-H), 1.87 (s, 3 H, 13-H), 1.69 (ddd, *J* = 14.2 Hz, *J* = 12.2 Hz, *J* = 3.0 Hz, 1 H, 3-H_a), 1.55 (m, 1 H, 3-H_b), 0.94 (d, *J* = 7.15 Hz, 3 H, 12-H), 0.90 (m, 2 H, 16-H), 0.00 (s, 9 H, 17-H). − ^{13}C NMR: δ = 138.84 (q, Ph), 132.95 (q, C-8), 129.43 (t, C-10), 129.20 (t, C-9), 128.41 (t, Ph), 127.50 (t, C-7), 127.22, 127.08 (t, Ph), 94.22 (d, C-14), 77.21, 73.26, 71.10 (t, C-2, C-4, C-6), 70.23 (d, Bn-CH_2), 68.17 (d, C-15), 66.12 (d, C-1), 65.16 (d, C-11), 36.30 (t, C-5), 26.70 (d, C-3), 20.40 (s, C-13), 18.09 (d, C-16), 11.10 (s, C-12), −1.408 (s, C-17). − MS (110 °C); *m/z*: 462 (0) [M^+], 315 (7.1) [M^+ − OSEM], 314 (10.0), 300 (3.4), 223 (11.6), 206 (6.2), 193 (3.3), 156 (3.3), 137 (4.5), 121 (5.8), 108 (10.5), 91 (100.0), 81 (10.3), 73 (42.3). − HR MS calcd. for $C_{20}H_{27}O_3$ [M^+ − OSEM] 315.1960, found 315.1960.

[(2*S*,4*S*,5*R*,6*S*)-4-Benzyloxy-5-methyl-6-{(1*Z*,3*E*)-2-methyl-5-[2-(trimethylsilylethoxy)methoxy]-1,3-pentadienyl}tetrahydropyran-2-yl]acetonitrile[(+)-12]: To a solution of **(+)-11** (50 mg, 0.11 mmol) and pyridine (26 mg, 0.33 mmol) in DCM (1.5 mL) was added Tf_2O (46 mg, 0.16 mmol) at −78 °C. After 30 min, the mixture was poured into 1 N HCl (4 mL) and the aqueous layer was extracted with DCM (4 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed carefully. To a solution of KCN (21 mg, 0.33 mmol) and 18-crown-6 (86 mg, 0.33 mmol) in DMSO (3 mL) was added the triflate in DMSO (1 mL). The mixture was stirred for 1 h at room temp., then H_2O (15 mL) and MTBE (10 mL) were added. The aqueous layer was extracted with MTBE (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated and the crude product purified by column chromatography (silica gel; PE/MTBE, 3:1) to give **(+)-12**, 40 mg (79%), colourless oil. − $[\alpha]_D^{20}$ = +32.0 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3444 cm^{-1}, 3088, 2956, 2924, 2856, 2252, 1600, 1452, 1376, 1264, 1248, 1092, 1056, 1028, 976, 860, 836. − ^1H NMR: δ = 7.38−7.24 (m, 5 H, Ph), 6.63 (d, *J* = 5.7 Hz, 1 H, 10-H), 5.83 (dt, *J* = 15.45 Hz, *J* = 6.02 Hz, 1 H, 11-H), 5.41 (d, *J* = 7.78 Hz, 1 H, 8-H), 4.96 (dd, *J* = 7.78 Hz, *J* = 2.0 Hz, 1 H, 7-H), 4.67 (s, 2 H, 15-H), 4.63, 4.54 (d, d, *J* = 11.92 Hz, 2 H, Bn-CH_2), 4.15 (d, *J* = 6.02 Hz, 2 H, 12-H), 4.01 (m, 1 H, 3-H), 3.64 (m, 1 H, 5-H), 3.60 (m, 2 H, 16-H), 2.57 (dd, *J* = 16.69 Hz, *J* = 5.77 Hz, 1 H, 1-H_a), 2.50 (dd, *J* = 16.69 Hz, *J* = 5.27 Hz, 1 H, 2-H_b), 1.95 (m, 1 H, 8-H), 1.87 (s, 3 H, 14-H), 1.77 (m, 1 H, 4-H_a), 1.60 (m, 1 H, 4-H_b), 0.97 (d, *J* = 7.16 Hz, 3 H, 13-H), 0.85 (m, 2 H, 17-H), 0.01 (s, 9 H, 18-H). − ^{13}C NMR: δ = 138.55 (q, Ph), 133.08 (q, C-9), 128.93 (t, C-11), 128.76 (t, C-10), 128.48 (t, Ph), 127.66 (t, C-8), 127.46, 127.32 (t, Ph), 117.09 (q, C-1), 94.26 (d, C-15), 76.97, 71.65 (C-5, C-7), 70.47 (d, Bn-CH_2), 68.19 (d, C-16), 68.17 (t, C-3), 65.18 (d, C-12), 35.81 (t, C-6), 30.29 (t, C-3), 24.72 (d, C-4), 20.41 (s, C-14), 18.13 (d, C-17), 11.05 (s, C-13), −1.40 (s, C-18). − MS (150°C); *m/z*: 471 (0) [M$^+$], 413 (2.3), 398 (1.3), 384 (1.1), 324 (6.8), 308 (2.9), 244 (2.4), 232 (20.6), 209 (11.1), 182 (2.5), 169 (3.9), 156 (2.6), 131 (10.2), 108 (8.0), 91 (100.0), 81 (7.5), 73 (46.1). − HR MS calcd. for $C_{21}H_{26}NO_2$ [M$^+$ − OSEM] 324.1964, found 324.1968.

Ethyl (2*E*,4*E*)-6-[(2*S*,4*S*,5*R*,6*S*)-4-Benzyloxy-5-methyl-6-{(1*Z*,3*E*)-2-methyl-5-[2-(trimethylsilylethoxy)methoxy]-1,3-pentadienyl}tetrahydropyran-2-yl]-2,4-hexadienoate [(+)-14]: To a solution of nitrile **(+)-12** (20 mg, 0.042 mmol) in DCM (1 mL) was added DIBAH (51 μL, 0.051 mmol, 1.2 M solution in hexane) at −78°C. After 30 min, 1 N HCl (2 mL) was added and the mixture was stirred for 30 min at room temp., then H_2O (10 mL) and DCM (20 mL) were added. The aqueous layer was extracted with PE (3 × 20 mL), the combined organic phases were washed with brine (4 mL) and dried ($MgSO_4$). The solvent was removed and the crude product filtered through silica gel (MTBE) to afford the aldehyde. To a suspension of NaH (3.4 mg, 0.085 mmol, 60% in mineral oil) in THF (1.5 mL) was added triethyl *trans*-phosphonocrotonate (21 mg, 0.085 mmol) at −10°C. The mixture was stirred for 2 h, then a solution of the aldehyde in THF (1 mL) was added and stirring was continued for 1 h. H_2O (15 mL) and MTBE (20 mL) were added. The aqueous layer was neutralized with 1 N HCl and extracted with MTBE (3 × 10 mL). The combined organic phases were washed with brine (4 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (silica gel; PE/MTBE, 2:1) to yield **(+)-14**, 17 mg, (70%), colourless oil. − $[\alpha]_D^{20}$ = +32.0 (*c* = 1 in $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1}, 2924, 2856, 1704, 1644, 1616, 1464, 1368, 1300, 1248, 1140, 1096, 1056, 968, 940, 860, 836. − ^{1}H NMR: δ = 7.38−7.26 (m, 5 H, Ph), 1.25 (dd, *J* = 15.3 Hz, *J* = 10.2 Hz, 1 H, 3-H), 6.65 (d, *J* = 15.56 Hz, 1 H, 14-H), 6.21 (dd, *J* = 15.4, *J* = 10.2, 1 H, 4-H), 6.13 (dt, *J* = 15.4 Hz, *J* = 6.8 Hz, 1 H, 5-H), 5.81 (dt, *J* = 15.56, *J* = 6.15, 1 H, 15-H), 5.78 (d, *J* = 15.3 Hz, 1 H, 2-H), 5.42 (d, *J* = 7.9 Hz, 1 H, 12-H), 4.91 (dd, *J* = 7.9 Hz, *J* = 2.0 Hz, 1 H, 11-H), 4.66 (s, 2 H, 19-H), 4.62, 4.51 (d, d, *J* = 12.05 Hz, 2 H, Bn-CH_2), 4.19 (q, *J* = 7.15 Hz, 2 H, Et-CH_2), 4.13 (m, 2 H, 16-H), 3.92 (m, 1 H, 7-H), 3.60 (m, 3 H, 20-H), 3.57 (m, 1 H, 9-H), 2.40 (m, 2 H, 6-H), 1.92 (m, 1 H, 10-H), 1.87 (s, 3 H, 18-H), 1.75 (m, 1 H, 8-H_a), 1.60 (m, 1 H, 8-H_b), 1.25 (t, *J* = 7.15 Hz, Et-CH_3), 0.96 (d, *J* = 7.1 Hz, 3 H, 17-H), 0.85 (m, 2 H, 21-H), 0.01 (s, 9 H, 22-H). − ^{13}C NMR δ = 167.18 (q, C-1), 144.72 (t, C-3), 140.04 (t, C-5), 138.93 (q, Ph), 132.61 (q, C-13), 130.37 (t, C-15), 129.78 (t, C-14), 129.31 (t, C-4), 128.40 (t, Ph), 127.49 (t, C-12), 127.26, 127.00 (t, Ph), 119.77 (t, C-2), 94.26 (d, C-19), 77.60, 71.96 (t, C-9, C-11), 71.39 (t, C-7), 70.32 (d, Bn-CH_2), 68.29 (d, C-20), 65.16 (d, C-16), 60.18 (d, Et-CH_2), 39.65 (d, C-6), 36.16 (t, C-10), 30.85 (d, C-8), 20.39 (s, C-18), 18.13 (d, C-21), 14.32 (s, Et-CH_3), 11.21 (s, C-17), 1.40 (s, $SiCH_3$). − MS (200°C); *m/z*: 570 (0) [M$^+$], 439 (2.8), 423 (5.7), 422 (8.1), 407 (2.5), 331 (5.8), 314 (2.7), 235 (2.5), 209 (3.9), 195 (4.0), 175 (6.9), 155 (6.8), 121 (9.5), 91 (100.0), 73 (35.9). − HR MS calcd. for $C_{27}H_{35}O_4$ [M$^+$ − OSEM] 423.2535, found 423.2533.

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[1] P. A. Horton, F. E. Koehn, R. E. Longley, O. J. McConnell, *J. Am. Chem. Soc.* **1994**, *116*, 6015−6016.

[2] M. Nowakowski, H. M. R. Hoffmann, *Tetrahedron Lett.* **1997**, *38*, 1001. See also: M. K. Gurjar, A. Chakrabarti, B. V. Rao, P. Kumar, *Tetrahedron Lett.* **1997**, *38*, 6885; M. K. Gurjar, P. Kumar, B. V. Rao, *Tetrahedron Lett.* **1996**, *37*, 8617.

[3] [3a] Spongistatin C29−C37 segment: R. Dunkel, J. Treu, H. M. R. Hoffmann, *Tetrahedron: Asymmetry* **1999**, *10*, 1539. − [3b] Discodermolide C1−C7 segment and Phorboxazole C20−C26 segment: A. Misske, H. M. R. Hoffmann, *Tetrahedron* **1999**, *55*, 4315. − [3c] Phorboxazole C3−C13 segment: P. Wolbers, H. M. R. Hoffmann, *Tetrahedron* **1999**, *55*, 1905. − [3d] Phorboxazole C28−C41 segment: P. Wolbers, H. M. R. Hoffmann, *Synthesis* **1999**, 797. − [3e] Mevinic Acids tetrahydropyran unit: R. Dunkel, M. Mentzel, H. M. R. Hoffmann, *Tetrahedron* **1997**, *53*, 14929. − [3f] Bryostatin C1−C9 segment: J. Weiss, H. M. R. Hoffmann, *Tetrahedron: Asymmetry* **1997**, *8*, 3913. − [3g] Lasonolide A C18−C24 segment, see ref.[2] − [3h] Bryostatin: T. F. J. Lampe, H. M. R. Hoffmann, *J. Chem. Soc., Chem. Commun.* **1996**, 1931.

[4] [4a] 2α-Methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (***rac*-1**) has been prepared in substantial quantities by [4+3] cycloaddition of 1,1,3,3-tetrabromo-2-butanone to furan, see ref.[3a] − [4b] For the generation of oxabicyclic ketone ***rac*-1** by SmI_2 reduction starting from an oxygenated oxabicyclic precursor, see ref.[3b]

[5] J. Treu, H. M. R. Hoffmann, *J. Org. Chem.* **1997**, *62*, 4650.

[6] H. C. Brown, N. N. Joshi, *J. Org. Chem.* **1988**, *53*, 4059

[7] A "racemic switch" has been defined as "*the redevelopment in single-enantiomer form of a drug that was first approved as a racemate*"; see: S. C. Stinson, *Chem. Eng. News* **1998**, *September 21*, 83−104. In our case the early racemic switch provides two key single-isomer precursors of structurally different bioactive natural products.

[8] [8a] P. Schäfer, unpublished work. − [8b] The ozonolysis was performed following a lead by: P. Schäfer, PhD thesis, in preparation.

[9] [9a] K. Gerth, D. Schummer, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiotics* **1995**, *48*, 973. − [9b] D. Schummer, K. Gerth, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1995**, 685.

[10] [10a] The olefination procedure is described in: W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405. − [10b] Methylated fluorophosphonate reagent $(F_3CCH_2O)_2P(O)CHMeCO_2Et$ was prepared according to the procedure recorded in: C. Patois, P. Savignac, *Synth. Commun.* **1991**, *21*, 2391.

[11] The yield is 12% with respect to the *early racemic switch* **rac-1**.

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