Synthetic Studies towards the Total Synthesis of Providencin

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Abstract: A synthetic approach to assemble the uncommon furylcyclobutane substructure in providencin has been developed starting from a commercially available cyclobutane precursor.

Key words: furans, cyclizations, natural products, stereoselective synthesis, total synthesis

The abundance of variably functionalized furans in biologically active compounds has stimulated considerable synthetic interest.[1] Hence, a variety of methods have been devised to assemble furan intermediates.[2] Furanocembranes (Figure 1) have received particular attention, because they are effective against various cancer types, reveal analgesic or anti-inflammatory activity, or display potent neuro- and cytotoxic properties.[3] Most notable contributions came from the groups of Paquette, Marshall, Wipf, and Pattenden,[4] who developed 'furan first'[5] or 'furan last' strategies, depending on the stage at which the furan moiety was introduced into the carbon skeleton.

Quite recently, the diterpene providencin [(+)-**1**][6] was isolated from the gorgonian octocoral *Pseudopterogorgia kallos*, featuring an uncommon furylcyclobutane ring system. Bray and Pattenden recently reported a photochemical access to the furylcyclobutane segment of **1**.[7] We also envisaged a 'furan first' strategy for the synthesis of **1** starting from a readily available cyclobutane. Thus, the deoxy compound **2** would serve as a late-stage key intermediate, which might be accessible via metathesis and Horner–Wadsworth–Emmons (HWE) olefination from the cyclobutylfuran **4** (Scheme 1). Fragment **4** can be further disconnected to aldehyde **5**, in turn obtainable from the commercially available bicycloheptenone **6** (Scheme 1).

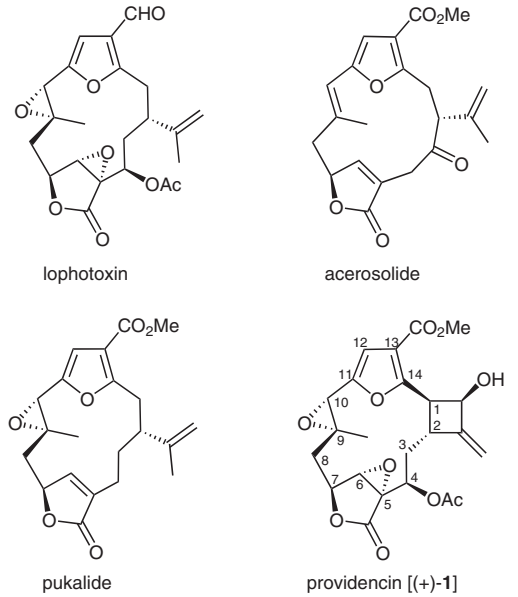
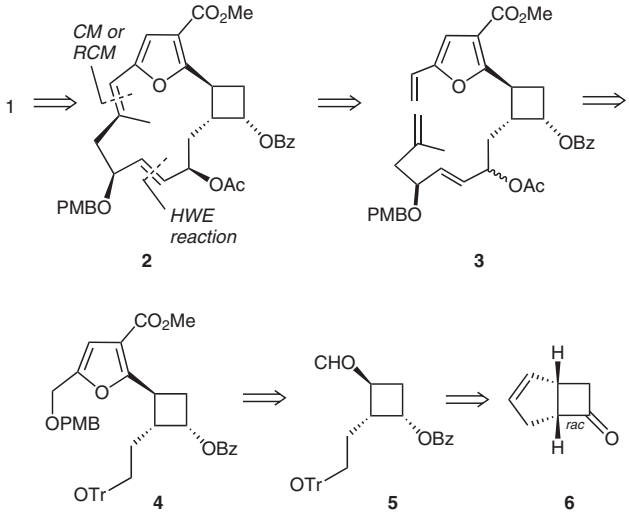


Figure 1 Examples of furanocembranolides isolated from marine invertebrates



Scheme 1 Retrosynthetic considerations for the total synthesis of providencin [(+)-**1**]

First we had to develop methodology for attaching a highly substituted furan ring to the cyclobutane moiety present in **5**. After extensive experimentation, a Paal–Knorr-type reaction turned out to be the method of choice. Therefore, in a preliminary model study, ethyl ester **7**, obtained by a Roskamp reaction[8] from 2-methylbutyraldehyde and commercially available ethyl diazoacetate, was alkylated with chloroacetone, leading to 1,4-diketone **8** (Scheme 2). Microwave-assisted cyclization led to furan **9** in excellent yield (Scheme 2). Further functionalization by selective bromination at the less substituted α-position afforded furans **10**–**12** (Scheme 2) as versatile intermediates for a variety of potential coupling reactions.

For the synthesis of furylcyclobutane **19** (Scheme 3), racemic bicycloheptenone **6** (see Scheme 1) was stereoselectively reduced to the alcohol and converted into the corresponding benzoate **13**. Ozonolysis of the double bond by reductive workup with sodium borohydride fol-

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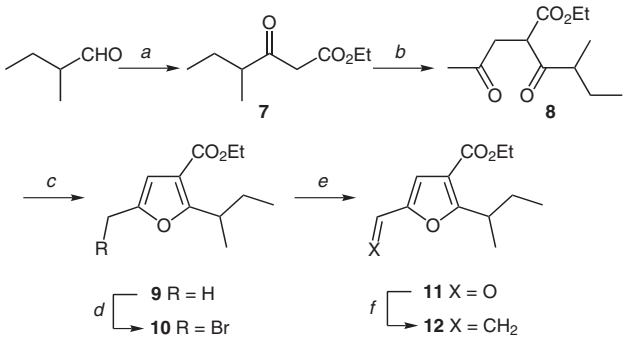
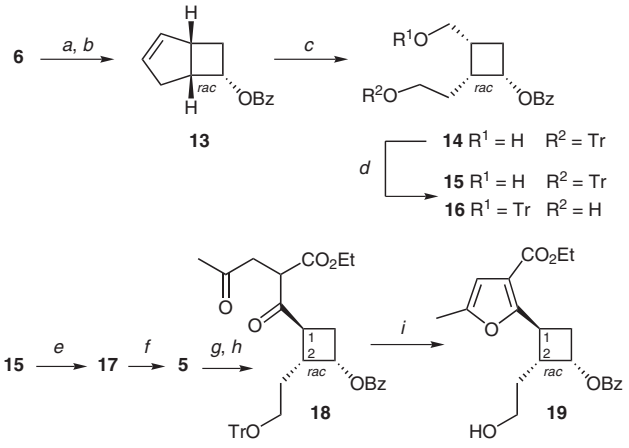


Scheme 2 Synthesis of furans **9**–**12**. *Reagents and conditions*: (a) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 25 °C, 4 h (97%); (b) chloroacetone, NaH, THF, 25 °C, 36 h (63%); (c) concd HCl, EtOH, MW, 100 °C, 8 min (98%); (d) NBS, AIBN, CCl_4, 76 °C, 1 h (79%); (e) DMSO, 190 °C, 10 min (45%); (f) $Ph_3PMe^+Br^-$, *n*-BuLi, THF, 0–25 °C, 12 h (55%).

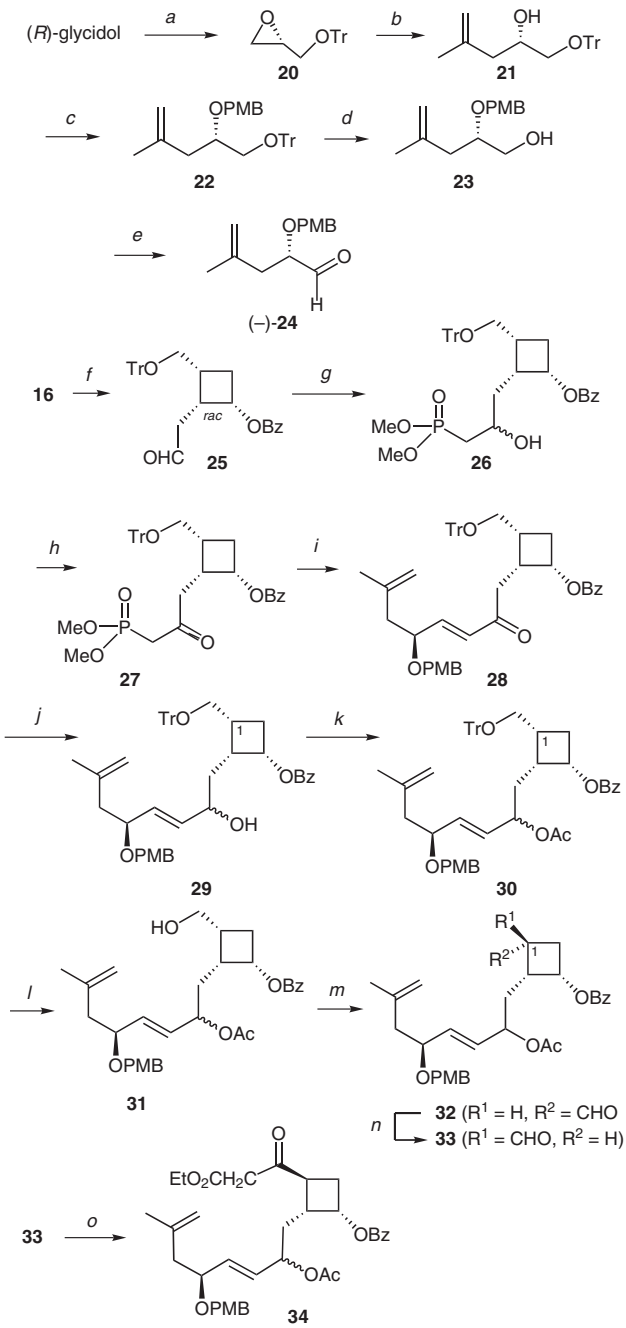
lowed, affording diol **14**, which was tritylated with trityl chloride to give both monoprotected regioisomers **15** and **16**, which are separable by column chromatography, in a 4:1 ratio (Scheme 3). The bis-tritylated diol and unchanged starting material were recovered and recycled. Alcohol **15** was oxidized to aldehyde **17**, which was isomerized at C1 with aqueous potassium carbonate and then converted into the 1,4-diketone **18** (Scheme 3). Microwave irradiation led, finally, to the desired furan **19**, under cleavage of the trityl protecting group (Scheme 3).



Scheme 3 Synthesis of the 1,2-*trans*-substituted furylcyclobutane **19**. *Reagents and conditions*: (a) $NaBH_4$, MeOH, –78 °C, 1 h; (b) BzCl, py, 0–25 °C, 4 h (97%, over 2 steps); (c) 1. O_3, CH_2Cl_2, –78 °C, 20 min; 2. $NaBH_4$, 0 °C, 2 h (85%); (d) TrCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 18 h (**15**: 35%; **16**: 9%); (e) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h (87%); (f) 0.1 M K_2CO_3, MeOH, CH_2Cl_2, 25 °C, 15 min (87%); (g) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 25 °C, 2 h (73%); (h) chloroacetone, NaH, THF, 25 °C, 50 h (46%); (i) concd HCl, MeOH, CH_2Cl_2, MW, 100 °C, 10 min (90%).

For the synthesis of enantiomerically pure compounds, bicycloheptenone **6** was reduced with sodium borohydride and converted into the corresponding acetate. Digestion with the lipase SAM-II afforded the undesired alcohol and the desired enantiomer as unchanged acetate, which was hydrolyzed with lithium hydroxide. The alcohol thus obtained can be benzoylated and further transformed as described for the racemate **13** (Scheme 3).

To validate our approach towards the total synthesis of the providencin macrolide [(+)-**1**], (*R*)-glycidol was tritylated



Scheme 4 Synthesis of fragment **34**. *Reagents and conditions*: (a) TrCl, Et_3N, DMAP, CH_2Cl_2, 0–25 °C, 24 h (100%); (b) H_2C=C(Me)MgBr, CuI, THF, –78 to –40 °C, 2 h (100%); (c) PMBCl, NaH, TBAB, THF, 25 °C, 1 h, then 60 °C, 24 h; (d) TsOH, MeOH, 25 °C, 30 min (71%); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, then 0 °C, 2 h (88%); (f) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h (95%); (g) $MeP(O)(OMe)_2$, *n*-BuLi, THF, –78 °C, 6 h (84%); (h) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 2 h (78%); (i) NaH, (–)-**24**, THF, –10 °C, 10 min, then 25 °C, 2 h (92%); (j) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, –78 °C, 3 h (78%); (k) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 2 h (97%); (l) TsOH, MeOH, 25 °C, 2 h (81%); (m) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 2 h (85%); (n) 0.1 M K_2CO_3, MeOH, 25 °C, 15 min (66%); (o) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 25 °C, 2 h (79%).

to **20** (Scheme 4), and then treated with isopropenylmagnesium bromide in the presence of copper(I) iodide to give alcohol **21**, which was protected as the *p*-methoxybenzyl ether **22**. After detritylation, alcohol **23** formed, and was oxidized to aldehyde **24** (Scheme 4). In a parallel sequence, alcohol **16** was oxidized to aldehyde **25**, which was converted into β-keto phosphonate **27** and coupled with aldehyde **24** to give ketone **28**, which was reduced to alcohol **29** and acetylated (Scheme 4). After detritylation, alcohol **31** was obtained, and was oxidized to aldehyde **32**. Base-catalyzed epimerization delivered aldehyde **33** (Scheme 4), which corresponds to the C14–C9 fragment of (+)-**1**. The Roskamp reaction finally led to keto ester **34** (Scheme 4).

In conclusion, we have described the synthesis of the *trans*-fused furylcyclobutane moiety **34** of providencin [(+)-**1**], starting from the commercially available cyclobutane derivative **6**. Functionalization of the substituents at both the C1 and C2 positions of the cyclobutane ring was possible, thus corroborating our strategy. Moreover, the synthesis of highly functionalized furan derivatives provided versatile intermediates, which might be employed in a variety of coupling reactions.

All ^{1}H NMR (250 MHz or 400 MHz) and ^{13}C NMR (63 MHz or 100 MHz) spectra were recorded on Bruker Avance DPX 250 or DRX 400 spectrometers. The chemical shifts δ are reported relative to the solvent peaks. IR spectra were recorded of samples prepared as films on NaCl plates on a Perkin-Elmer Spectrum 1600 Series FTIR spectrometer. MS spectra were recorded on a Finnigan MAT 8230 apparatus with a resolution of 10000. Products were purified by flash column chromatography (silica gel from Merck, 40–63 μm, 240–400 mesh). THF was distilled from sodium/benzophenone.

Microwave-Assisted Furan Cyclization; General Procedure

The diketone (1.75 mmol) was dissolved in MeOH or EtOH (3 mL), then concd HCl (30 μL) was added, and the mixture was subjected to microwave irradiation (Biotage Initiator) for 4–15 min at 100–120 °C. Sat. aq $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo.

Ethyl 2-*sec*-Butyl-5-methylfuran-3-carboxylate (9)

Keto Ester 7

$SnCl_2$ (38 mg, 0.2 mmol), N_2CHCO_2Et (126 μL, 1.2 mmol), and *s*-BuCHO (107 μL, 1.0 mmol) in CH_2Cl_2 (2 mL) were stirred for 4 h. The mixture was quenched with sat. aq NH_4F and extracted with Et_2O (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography (silica gel, hexane–EtOAc, 3:1); this gave **7**.

Yield: 171 mg (97%); colorless oil.

IR (film): 2961, 2930, 2870, 1740, 1709, 1649, 1626, 1459, 1406, 1368, 1307, 1224, 1171, 1148, 1125, 1095, 1027 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H, H–C1), 1.13 (d, *J* = 7.0 Hz, 3 H, H–C4), 1.30 (t, *J* = 7.2 Hz, 3 H, H–C7), 1.38–1.55 (m, 1 H, H–C2), 1.62–1.84 (m, 1 H, H–C2), 2.53–2.68 (m, 1 H, H–C3), 3.49 (s, 2 H, H–C5), 4.22 (q, *J* = 7.2 Hz, 2 H, H–C6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.8, 14.5, 15.8, 26.0, 48.1, 48.4, 61.6, 167.7, 206.8.

Ethyl Furan-3-carboxylate 9

A mixture of a 60% suspension of NaH in mineral oil (650 mg, 16.3 mmol) and keto ester **7** (2.80 g, 16.3 mmol) in THF (20 mL) was stirred at 25 °C for 1 h. Chloroacetone (1.2 mL, 15.5 mmol) was added dropwise, and the mixture was stirred at 25 °C for 50 h. Workup with H_2O and Et_2O followed by chromatography (silica gel, hexane–EtOAc, 20:1) furnished diketone **8** as a colorless oil, which was used in the next step without further purification; yield: 2.24 g (63%).

A mixture of diketone **8** (400 mg, 1.75 mmol), EtOH (3 mL), and concd HCl (30 μL) was subjected to microwave-assisted furan cyclization as described by the general procedure above. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 20:1); this gave **9**.

Yield: 360 mg (98%); pale yellow oil.

IR (film): 2968, 2930, 1709, 1580, 1383, 1277, 1231, 1201, 1064 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3 H), 1.23 (d, *J* = 6.9 Hz, 3 H), 1.33 (t, *J* = 6.9 Hz, 3 H), 1.49–1.79 (m, 2 H), 2.24 (d, *J* = 0.9 Hz, 3 H), 3.45–3.61 (m, 1 H), 4.24 (q, *J* = 6.9 Hz, 2 H), 6.20 (d, *J* = 0.9 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.3, 13.5, 14.7, 18.9, 28.9, 34.2, 60.1, 106.4, 113.7, 150.1, 164.6, 165.2.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}O_3$: 210.1256; found: 210.1258.

Ethyl 5-(Bromomethyl)-2-*sec*-butylfuran-3-carboxylate (10)

Methylfuran **9** (360 mg, 1.71 mmol), NBS (320 mg, 1.80 mmol), and AIBN (32 mg, 0.19 mmol) were dissolved in CCl_4 (10 mL) and the mixture was refluxed for 1 h. The succinimide was removed by filtration and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, hexane–EtOAc, 10:1) afforded **10**.

Yield: 390 mg (79%); pale yellow oil.

IR (film): 2968, 2930, 1709, 1611, 1558, 1216, 1057 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.4 Hz, 3 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.56–1.84 (m, 2 H), 3.49–3.62 (m, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.44 (s, 2 H), 6.63 (s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.4, 14.6, 18.8, 23.6, 28.8, 34.5, 60.5, 110.9, 114.6, 148.3, 167.1, 167.7.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}O_3Br$: 288.0361; found: 288.0332.

Ethyl 2-*sec*-Butyl-5-formylfuran-3-carboxylate (11)

Bromide **10** (40 mg, 0.14 mmol) was dissolved in anhyd DMSO (5 mL) and the soln was heated under reflux at 190 °C for 10 min; then H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, hexane–EtOAc, 5:1) yielded **11**.

Yield: 14 mg (45%); pale yellow oil.

IR (film): 2968, 2930, 1721, 1688, 1586, 1535, 1459, 1216, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.6 Hz, 3 H), 1.31 (d, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.61–1.86 (m, 2 H), 3.62–3.71 (m, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 7.47 (s, 1 H), 9.57 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 14.6, 18.5, 28.7, 34.9, 60.8, 110.6, 116.2, 150.7, 163.0, 172.3, 177.6.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}O_4$: 224.1049; found: 224.1047.

Ethyl 2-*sec*-Butyl-5-vinylfuran-3-carboxylate (12)

$Ph_3PMe^+Br^-$ (96 mg, 0.27 mmol) was dissolved under argon in anhyd THF (2 mL) and the suspension was cooled to 0 °C. A 2.5 M soln of *n*-BuLi in hexane (0.1 mL, 0.25 mmol) was added, and the mixture was warmed to 25 °C and stirred for 1 h before aldehyde **11** (50 mg, 0.22 mmol) in THF (3 mL) was added. Then the mixture was stirred for 12 h at 25 °C, treated with sat. aq $NaHCO_3$ (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, hexane–EtOAc, 20:1) gave **12**.

Yield: 27 mg (55%); pale yellow oil.

IR (film): 2961, 2930, 2877, 1717, 1588, 1535, 1451, 1375, 1209, 1057 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3 H), 1.30 (d, *J* = 7.1 Hz, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.56–1.89 (m, 2 H), 3.52–3.68 (m, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 5.19 (d, *J* = 11.3 Hz, 1 H), 5.66 (d, *J* = 17.5 Hz, 1 H), 6.45 (dd, *J* = 17.5, 11.3 Hz, 1 H), 6.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 14.7, 18.9, 29.0, 34.4, 60.4, 108.7, 113.0, 114.6, 124.9, 151.1, 164.3, 166.3.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1245.

(1*SR*,5*RS*,6*SR*)-Bicyclo[3.2.0]hept-2-en-6-yl Benzoate (13)

A suspension of $NaBH_4$ (870 mg, 23.0 mmol) in MeOH (75 mL) at –78 °C was treated dropwise with racemic bicycloheptenone **6** (4.9 mL, 46.0 mmol) in MeOH (25 mL). The mixture was stirred for 1 h at –78 °C, warmed to 25 °C, and diluted with Et_2O (100 mL) and 2 M HCl (70 mL). The organic layer was dried ($MgSO_4$), concentrated, and diluted with CH_2Cl_2 (50 mL) and py (7.5 mL, 92.0 mmol). BzCl (7.5 mL, 64.4 mmol) was added dropwise and the mixture was stirred at 25 °C for 4 h, quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The organic layer was washed with brine (3 × 10 mL), dried ($MgSO_4$), and concentrated; chromatography of the residue (silica gel, hexane–EtOAc, 10:1) gave benzoate **13**.

Yield: 9.6 g (97% over 2 steps); colorless oil.

IR (film): 3056, 2939, 2850, 1716, 1602, 1585, 1491, 1452, 1347, 1314, 1271, 1176, 1113, 1070, 1046 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.90–2.01 (m, 1 H, H–C2), 2.50 (dd, *J* = 17.1 Hz, 9.8, 1 H, H–C6), 2.60–2.73 (m, 1 H, H–C6), 2.88 (dt, *J* = 8.0, 2.2 Hz, 1 H, H–C2), 3.10–3.23 (m, 1 H, H–C3), 3.36–3.50 (m, 1 H, H–C7), 5.41–5.52 (m, 1 H, H–C1), 5.88 (s, 2 H, H–C4), H–C5), 7.46 (t, *J* = 7.6 Hz, 2 H, Ph), 7.59 (t, *J* = 7.6 Hz, 1 H, Ph), 8.07 (d, *J* = 7.6 Hz, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 33.1, 37.1, 41.3, 41.7, 69.8, 128.7, 130.0, 130.1, 132.6, 133.2, 134.6, 144.4.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{14}H_{14}O_2$: 214.0994; found: 214.0991.

(1*SR*,2*RS*,3*RS*)-2-(2-Hydroxyethyl)-3-(hydroxymethyl)cyclobutyl Benzoate (14)

Olefin **13** (4.60 g, 21.5 mmol) in CH_2Cl_2 (30 mL) was treated at –78 °C with O_3 for 20 min, then warmed to 0 °C and diluted with MeOH (30 mL). Solid $NaBH_4$ (3.25 g, 85.9 mmol) was added in small portions and the mixture was stirred for 2 h at 0 °C, quenched with 2 M HCl (300 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The organic layer was washed with brine (3 × 100 mL), dried ($MgSO_4$), and evaporated; purification of the residue by chromatography (silica gel, EtOAc) gave **14**.

Yield: 4.6 g (85% over 2 steps); colorless oil.

IR (film): 3339, 2944, 2874, 1720, 1699, 1278, 1177, 1115, 1071, 1050, 1025 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.70–2.07 (m, 3 H, H–C2, H–C6), 2.38–2.59 (m, 2 H, H–C2, H–C3), 2.83–2.99 (m, 1 H, H–C7), 3.52–3.67 (m, 2 H, H–C4), 3.73–4.00 (m, 4 H, H–C5, OH), 5.25–5.37 (m, 1 H, H–C1), 7.38–7.48 (m, 2 H, Ph), 7.51–7.60 (m, 1 H, Ph), 7.99–8.06 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.4, 30.9, 34.4, 40.6, 62.8, 62.9, 69.4, 128.8, 129.9, 130.5, 133.5, 166.5.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1103; found: 273.1105.

(1*SR*,2*RS*,3*RS*)-2-(2-Hydroxyethyl)-3-[(trityloxy)methyl]cyclobutyl Benzoate (16) and (1*SR*,2*RS*,3*RS*)-3-(Hydroxymethyl)-2-[2-(trityloxy)ethyl]cyclobutyl Benzoate (15)

TrCl (4.66 g, 16.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with Et_3N (5.1 mL, 36.8 mmol) and DMAP (22 mg, 0.18 mmol). Diol **14** (4.60 g, 18.4 mmol) in CH_2Cl_2 (60 mL) was added dropwise and the mixture was stirred for 18 h at 25 °C. The mixture was quenched with aq NH_4Cl (200 mL) and extracted with Et_2O (3 × 50 mL), and the organic layer was washed with brine (3 × 100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (silica gel, hexane–EtOAc, 5:1, then 1:1) gave **15** and **16** as colorless oils.

Compound 15

Yield: 1.63 g (35%); colorless oil.

IR (film): 1716, 1490, 1449, 1314, 1275, 1176, 1112, 1070, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 5.1 Hz, 1 H, OH), 1.77–2.01 (m, 3 H, H–C2, H–C6), 2.23–2.34 (m, 1 H, H–C3), 2.43–2.52 (m, 1 H, H–C2), 2.78–2.86 (m, 1 H, H–C7), 3.02 (dd, *J* = 15.0, 7.7 Hz, 1 H, H–C5), 3.13 (dd, *J* = 15.0, 7.7 Hz, 1 H, H–C5), 3.52–3.60 (m, 1 H, H–C4), 3.63–3.71 (m, 1 H, H–C4), 5.17 (q, *J* = 7.0 Hz, 1 H, H–C1), 7.07–7.19 (m, 9 H, CPh_3), 7.29–7.35 (m, 8 H, Ph, CPh_3), 7.47 (t, *J* = 8.1, 1 H, Ph), 7.85 (d, *J* = 8.1 Hz, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 31.5, 34.0, 39.2, 63.2, 63.7, 69.1, 87.1, 127.4, 128.1, 128.8, 129.0, 130.0, 130.6, 133.3, 144.6, 166.3.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{32}O_4Na$: 515.2198; found: 515.2196.

Compound 16

Yield: 600 mg (9%); colorless oil.

IR (film): 3456, 3060, 2938, 1717, 1699, 1601, 1490, 1451, 1314, 1276, 1113, 1069, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 5.7 Hz, 1 H, OH), 1.60–1.81 (m, 2 H, H–C6), 1.85–2.00 (m, 1 H, H–C2), 2.57–2.71 (m, 2 H, H–C2, H–C3), 2.91–3.03 (m, 1 H, H–C7), 3.21 (dd, *J* = 9.4, 7.8 Hz, 1 H, H–C4), 3.32 (dd, *J* = 9.4, 5.3, 1 H, H–C4), 4.83–4.64 (m, 2 H, H–C5), 5.29–5.40 (m, 1 H, H–C1), 7.20–7.38 (m, 9 H, CPh_3), 7.39–7.51 (m, 8 H, Ph, CPh_3), 7.53–7.63 (m, 1 H, Ph), 7.90–7.96 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 31.7, 32.3, 39.2, 62.3, 64.3, 69.8, 87.2, 127.4, 128.2, 128.8, 129.0, 129.9, 130.5, 133.4, 144.4, 166.3.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{32}O_4Na$: 515.2198; found: 515.2189.

(1*SR*,2*RS*,3*RS*)-3-Formyl-2-[2-(trityloxy)ethyl]cyclobutyl Benzoate (17)

Alcohol **15** (1.63 g, 3.31 mmol) was treated with $NaHCO_3$ (1.3 g, 14.9 mmol) and DMP (2.1 g, 4.96 mmol) in CH_2Cl_2 (30 mL) for 2 h. The mixture was quenched with aq $Na_2S_2O_4$ (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layer was washed with

brine (3 × 100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (silica gel, hexane–EtOAc, 10:1) gave aldehyde **17**.

Yield: 1.41 g (87%); colorless oil.

IR (film): 3060, 3032, 2937, 2870, 2723, 1716, 1601, 1490, 1449, 1386, 1314, 1274, 1224, 1177, 1153, 1115, 1070, 1026, 1002 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.86–2.08 (m, 2 H, H–C6), 2.43–2.55 (m, 1 H, H–C2), 2.65–2.78 (m, 1 H, H–C2), 3.03–3.16 (m, 3 H, H–C3, H–C5), 3.35–3.53 (m, 1 H, H–C7), 5.29–5.43 (m, 1 H, H–C1), 7.18–7.36 (m, 9 H, CPh_3), 7.38–7.47 (m, 8 H, Ph, CPh_3), 7.55–7.61 (m, 1 H, Ph), 7.95–7.97 (m, 2 H, Ph), 9.71 (d, *J* = 1.9 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 27.9, 42.0, 43.0, 62.5, 68.3, 87.1, 127.4, 128.2, 128.8, 129.0, 130.0, 130.3, 133.5, 144.5, 166.2, 202.0.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{30}O_4Na$: 513.2042; found: 513.2053.

(1*SR*,2*RS*,3*SR*)-3-Formyl-2-[2-(trityloxy)ethyl]cyclobutyl Benzoate (5)

Aldehyde **17** (290 mg, 0.59 mmol) in CH_2Cl_2 (2 mL) was treated with 0.1 M K_2CO_3 in MeOH (10 mL) and CH_2Cl_2 (5 mL) for 15 min at 25 °C. Purification of the residue by column chromatography (silica gel, hexane–EtOAc, 7:1) furnished **5**.

Yield: 252 mg (87%); colorless oil.

IR (film): 3059, 2946, 1709, 1595, 1489, 1451, 1307, 1277, 1178, 1155, 1110, 1072, 1027 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.84–2.19 (m, 2 H), 2.24–2.37 (m, 1 H), 2.63–2.81 (m, 1 H), 2.98–3.16 (m, 3 H), 3.17–3.24 (m, 1 H), 5.27–5.39 (m, 1 H), 7.20–7.33 (m, 9 H), 7.41–7.48 (m, 8 H), 7.50–7.60 (m, 1 H), 8.01–8.09 (m, 2 H), 9.64 (d, *J* = 1.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 27.6, 29.0, 39.3, 47.2, 61.3, 69.3, 86.7, 127.0, 127.8, 128.4, 128.6, 129.6, 129.9, 133.1, 144.0, 165.8, 201.4.

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{30}O_4Na$: 513.2042; found: 513.2053.

(1*SR*,2*RS*,3*SR*)-3-[2-(Ethoxycarbonyl)-4-oxopentanoyl]-2-[2-(trityloxy)ethyl]cyclobutyl Benzoate (18)

As described for the preparation of **7**, reaction of $SnCl_2$ (62 mg), N_2CHCO_2Et (206 μL, 1.96 mmol), and aldehyde **5** (800 mg, 1.64 mmol) in CH_2Cl_2 (6 mL) gave the corresponding β-keto ester; yield: 690 mg (73%). The crude ester was transformed into diketone **18** as described for the preparation of **8** from **7**. Purification of the crude product by chromatography (silica gel, hexane–EtOAc, 10:1, then 5:1) furnished **18**.

Yield: 138 mg (46%); colorless oil.

IR (film): 3059, 2984, 2946, 2870, 1740, 1717, 1599 (w), 1489, 1448, 1398, 1364, 1311, 1269, 1228, 1178, 1155, 1114, 1068, 1023 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.18–1.33 (m, 3 H, CH_2CH_3), 1.84–2.10 (m, 1 H, H–C6), 2.10–2.54 (m, 2 H, H–C2, H–C6), 2.18 (s, 3 H, H–C11), 2.66–2.80 (m, 1 H, H–C2), 2.85–3.29 (m, 5 H, H–C3, H–C5, H–C7, H–C9), 3.38–3.57 (m, 1 H, H–C9), 3.88–4.03 (m, 1 H, H–C8), 4.05–4.42 (m, 2 H, CH_2CH_3), 5.27–5.38 (m, 1 H, H–C1), 7.14–7.32 (m, 9 H, CPh_3), 7.36–7.52 (m, 8 H, Ph, CPh_3), 7.56–7.66 (m, 1 H, Ph), 7.99–8.09 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.4, 29.8, 30.0, 31.0, 31.6, 40.8, 42.0, 47.6, 52.7, 62.1, 69.5, 87.1, 127.3, 128.1, 128.8, 129.0, 130.0, 130.6, 133.4, 144.6, 166.2, 168.9, 205.0, 205.5.

Ethyl 2-[(1*SR*,2*RS*,3*SR*)-3-(Benzoyloxy)-2-(2-hydroxyethyl)cyclobutyl]-5-methylfuran-3-carboxylate (19)

A mixture of diketone **18** (63 mg, 0.1 mmol), MeOH (1 mL), CH_2Cl_2 (0.5 mL), and concd HCl (30 μL) was subjected to microwave-assisted furan cyclization as described by the general procedure above. Purification of the residue by column chromatography (silica gel, hexane–EtOAc, 3:1) afforded **19**.

Yield: 27 mg (90%); pale yellow oil.

IR (film): 3515, 2946, 1717, 1580, 1451, 1375, 1315, 1277, 1209, 1110, 1057 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 1.83 (br s, 1 H), 1.88–2.02 (m, 2 H), 2.29 (s, 3 H), 2.51–2.62 (m, 1 H), 2.74–2.85 (m, 1 H), 3.02–3.12 (m, 1 H), 3.66 (t, *J* = 6.4 Hz, 2 H), 4.16–4.23 (m, 1 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 5.55–5.61 (m, 1 H), 6.23 (s, 1 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.58 (t, *J* = 7.7 Hz, 1 H), 8.08 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 14.7, 32.3, 32.6, 34.8, 43.8, 60.6, 61.1, 70.8, 106.9, 122.8, 128.8, 130.0, 130.6, 133.5, 150.9, 161.4, 164.7, 166.7.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{24}O_6$: 372.1573; found: 372.1584.

(*S*)-2-[(Trityloxy)methyl]oxirane [(–)-20][9]

A soln of TrCl (2.46 g, 8.8 mmol) in CH_2Cl_2 (8 mL) was treated under argon at 0 °C with Et_3N (2.2 mL, 16.0 mmol) and (*R*)-glycidol (540 μL, 8.0 mmol) in CH_2Cl_2 (4 mL). DMAP (10 mg, 0.08 mmol) was added and the mixture was stirred for 24 h at 25 °C. The mixture was quenched with NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$), and concentrated; this gave white crystals which were recrystallized from MeOH.

Yield: 2.5 g (100%); mp 94–96 °C (MeOH) (Lit.[9] 100 °C); $[\alpha]_D^{25}$ –9.7 (*c* 1.0, $CHCl_3$) {Lit.[9] $[\alpha]_D^{25}$ –10.5 (*c* 1, $CHCl_3$)}.

IR (film): 3023, 2925, 2874, 1595, 1490, 1448, 1158, 1071, 1032, 1002 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.68 (dd, *J* = 4.9, 2.2 Hz, 1 H, H–C3), 2.82 (dd, *J* = 4.9, 3.9 Hz, 1 H, H–C3), 3.17–3.28 (m, 2 H, H–C1), 3.38–3.48 (m, 1 H, H–C2), 7.26–7.45 (m, 9 H, CPh_3), 7.51–7.62 (m, 6 H, CPh_3).

(*S*)-4-Methyl-1-(trityloxy)pent-4-en-2-ol [(–)-21][9]

CuI (121 mg, 0.63 mmol) under argon in THF (2 mL) was treated dropwise at –78 °C with 0.5 M $H_2C{=}C(Me)MgBr$ in THF (13.3 mL, 6.64 mmol). After 30 min, (–)-**20** (1.0 g, 3.16 mmol) in THF (1 mL) was added and the mixture was stirred for 2 h at –40 °C, quenched with NH_4Cl, and stirred for 30 min at 25 °C. Workup with H_2O and Et_2O followed by chromatography (silica gel, hexane–EtOAc, 5:1) furnished (–)-**21**.

Yield: 1.14 g (100%); colorless oil; $[\alpha]_D^{25}$ –3.8 (*c* 0.6, $CHCl_3$) {Lit.[9] $[\alpha]_D^{25}$ –3.0 (*c* 1.15, $CHCl_3$)}.

IR (film): 3058, 3020, 2926, 2875, 1595, 1489, 1449, 1220, 1103, 1071 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.74 (s, 3 H, H–C5), 2.19 (d, *J* = 6.7 Hz, 2 H, H–C3), 2.25 (d, *J* = 3.3 Hz, 1 H, OH), 3.11–3.24 (m, 2 H, H–C1), 3.87–4.00 (m, 1 H, H–C2), 4.75 (s, 1 H, H–C6), 4.82 (s, 1 H, H–C6), 7.23–7.38 (m, 9 H, CPh_3), 7.44–7.50 (m, 6 H, CPh_3).

(*S*)-2-[(4-Methoxybenzyl)oxy]-4-methylpent-4-en-1-ol [(+)-23]

A 60% suspension of NaH in mineral oil (633 mg, 15.8 mmol) in THF (15 mL) was treated dropwise at 0 °C with (–)-**21** (3.78 g, 10.6 mmol) in THF (5 mL). The mixture was stirred at 25 °C for 1 h, then PMBCl (2.14 mL, 15.8 mmol) and TBAB (68 mg, 0.21 mmol) were added and the mixture was stirred for 24 h at 60 °C. Usual workup

with NH_4Cl, H_2O, and Et_2O furnished **22** after chromatography (silica gel, hexane–EtOAc, 20:1). Compound **22** was detritylated in MeOH (20 mL) with $TsOH·H_2O$ (200 mg, 1.1 mmol) for 30 min at 25 °C. Usual workup and chromatography (silica gel, hexane–EtOAc, 5:1, then 0:1) gave **23**.

Yield: 1.77 g (71%, 2 steps); colorless oil; $[\alpha]_D^{25}$ +14.7 (*c* 0.3, $CHCl_3$).

IR (film): 3401, 2929, 1738, 1713, 1613, 1514, 1455, 1301, 1249, 1173, 1103, 1035 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, H–C5), 1.94 (dd, *J* = 6.9, 5.6 Hz, 1 H, OH), 2.22 (dd, *J* = 14.1, 7.2 Hz, 1 H, H–C3), 2.42 (dd, *J* = 14.1, 5.6 Hz, 1 H, H–C3), 3.47–3.59 (m, 1 H, H–C2), 3.64–3.76 (m, 2 H, H–C1), 3.84 (s, 3 H, OCH_3), 4.50, 4.64 (AB, *J* = 11.2 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.81 (s, 1 H, H–C6), 4.85 (s, 1 H, H–C6), 6.91, 7.30 (AA′BB′, *J* = 8.5 Hz, 4 H, $C_6H_4CH_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.2, 39.9, 55.7, 64.7, 71.6, 78.1, 113.6, 114.3, 129.8.

EI-HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{20}O_3$: 236.1412; found: 236.1417.

(*S*)-2-[(4-Methoxybenzyl)oxy]-4-methylpent-4-enal [(–)-24]

Oxalyl chloride (100 μL, 1.18 mmol) under argon in CH_2Cl_2 (3 mL) was treated at –78 °C with DMSO (167 μL, 2.36 mmol). After 15 min, (+)-**23** (254 mg, 1.07 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was stirred for 1 h at –78 °C. Et_3N (748 μL, 5.37 mmol) was added and the mixture was warmed to 0 °C and stirred for 2 h. Usual workup with H_2O and Et_2O followed by chromatography (silica gel, hexane–EtOAc, 5:1) furnished aldehyde (–)-**24**.

Yield: 220 mg (88%); colorless oil; $[\alpha]_D^{25}$ –44.9 (*c* 2.0, $CHCl_3$).

IR (film): 3078, 2936, 2839, 1733, 1700, 1652, 1613, 1514, 1464, 1456, 1375, 1303, 1250, 1174, 1103, 1035 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, H–C5), 2.43 (d, *J* = 6.6 Hz, 2 H, H–C3), 3.84 (s, 3 H, OCH_3), 3.92 (dt, *J* = 6.6, 2.2 Hz, 1 H, H–C2), 4.55, 4.63 (AB, *J* = 11.3 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.83 (s, 1 H, H–C6), 4.89 (s, 1 H, H–C6), 6.91, 7.30 (AA′BB′, *J* = 8.5 Hz, 4 H, $C_6H_4CH_3$), 9.65 (d, *J* = 2.2 Hz, 1 H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.1, 38.8, 55.6, 72.6, 82.0, 114.2, 114.3, 129.7, 129.9, 140.8, 160.0, 203.6.

EI-HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{18}O_3$: 234.1261; found: 234.1261.

(1*SR*,2*RS*,3*RS*)-2-(2-Oxoethyl)-3-[(trityloxy)methyl]cyclobutyl Benzoate (25)

A mixture of alcohol **16** (600 mg, 1.22 mmol), $NaHCO_3$ (460 g, 5.48 mmol), and DMP (776 mg, 1.83 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 3 h. Usual workup and chromatography (silica gel, hexane–EtOAc, 10:1) furnished aldehyde **25**.

Yield: 570 mg (95%); colorless oil.

IR (film): 3060, 2935, 1721, 1601, 1490, 1450, 1314, 1275, 1154, 1112, 1069, 1026 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.88–2.05 (m, 1 H, H–C2), 2.59 (d, *J* = 9.1 Hz, 2 H, H–C6), 2.64–2.78 (m, 2 H, H–C2, H–C3), 3.02–3.17 (m, 1 H, H–C4), 3.22–3.33 (m, 1 H, H–C4), 3.37–3.57 (m, 1 H, H–C7), 5.33–5.46 (m, 1 H, H–C1), 7.21–7.37 (m, 9 H, CPh_3), 7.40–7.49 (m, 8 H, Ph, CPh_3), 7.54–7.63 (m, 1 H, Ph), 7.86–7.93 (m, 2 H, Ph), 9.69 (t, *J* = 1.4 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 31.6, 36.7, 39.2, 64.0, 68.6, 87.2, 127.5, 128.2, 128.8, 129.0, 129.9, 130.5, 133.5, 144.3, 166.1, 201.8.

ESI-HRMS: *m*/*z* [M^+] calcd for $C_{33}H_{30}O_4Na$: 513.2042; found: 513.2028.

(1*SR*,2*RS*,3*RS*)-2-[3-(Dimethoxyphosphoryl)-2-hydroxypropyl]-3-[(trityloxy)methyl]cyclobutyl Benzoate (26)

$MeP(O)(OMe)_2$ (138 μL, 1.16 mmol) in THF (7 mL) was treated dropwise at –78 °C under argon with 2.5 M *n*-BuLi in hexane (464 μL, 1.16 mmol). After 30 min, aldehyde **25** (570 mg, 1.16 mmol) in THF (3 mL) was added and the mixture was stirred for 6 h at –78 °C. Workup with $NaHCO_3$, H_2O, and Et_2O followed by chromatography (silica gel, hexane–EtOAc, 5:1, 0:1) furnished **26** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.21 (hexane–EtOAc, 5:1)].

Yield: 380 mg (84%, based on recovered starting material).

IR (film): 3392, 3058, 3033, 2953, 2874, 1716, 1601, 1490, 1450, 1449, 1360, 1314, 1275, 1223, 1178, 1154, 1113 (s), 1064, 1032 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.57–1.97 (m, 3 H, H–C2, H–C6), 2.59–2.75 (m, 2 H, H–C2, H–C3), 3.02–3.42 (m, 4 H, H–C4, H–C5, H–C7), 3.57–3.85 (m, 8 H, H–C8, 2 × OCH_3), 3.86–4.09 (br s, 1 H, OH), 5.30–5.42 (m, 1 H, H–C1), 7.20–7.36 (m, 9 H, CPh_3), 7.39–7.49 (m, 8 H, Ph, CPh_3), 7.50–7.65 (m, 1 H, Ph), 7.86–8.06 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.8, 32.7, 34.2, 38.5, 39.0, 52.6, 52.7, 64.4, 65.5, 70.2, 87.1, 127.4, 128.2, 128.8, 129.1, 129.9, 130.6, 133.3, 144.4, 166.2.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{39}O_7PNa$: 637.2331; found: 637.2344.

(1*SR*,2*RS*,3*RS*)-2-[3-(Dimethoxyphosphoryl)-2-oxopropyl]-3-[(trityloxy)methyl]cyclobutyl Benzoate (27)

A mixture of alcohol **26** (472 mg, 0.77 mmol), $NaHCO_3$ (291 mg, 3.47 mmol), and DMP (489 mg, 1.15 mmol) in CH_2Cl_2 (20 mL) was stirred for 2 h at 25 °C. Workup as before including chromatography (silica gel, EtOAc) furnished keto phosphonate **27**.

Yield: 370 mg (78%); colorless oil.

IR (film): 3058, 2953, 1716, 1600, 1490, 1449, 1399, 1314, 1274, 1179, 1112, 1028 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.83–1.96 (m, 1 H, H–C2), 2.59–2.77 (m, 2 H, H–C2, H–C3), 2.87 (s, 1 H, H–C8), 2.96 (s, 1 H, H–C8), 3.13 (dd, *J* = 9.6, 8.4 Hz, 1 H, H–C4), 3.26 (dd, *J* = 9.6, 5.4 Hz, 1 H, H–C4), 3.34–3.46 (m, 1 H, H–C7), 5.32–5.42 (m, 1 H, H–C1), 7.21–7.37 (m, 9 H, CPh_3), 7.39–7.48 (m, 8 H, Ph, CPh_3), 7.53–7.62 (m, 1 H, Ph), 7.83–7.89 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.3, 31.9, 37.2, 39.7, 42.5, 64.3, 69.4, 88.0, 127.4, 128.2, 128.8, 129.0, 129.9, 130.5, 133.4, 144.4, 166.1, 201.9.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{37}O_7PNa$: 635.2175; found: 635.2182.

(1*SR*,2*RS*,3*RS*)-2-{(*E*,5*S*)-5-[(4-Methoxybenzyl)oxy]-7-methyl-2-oxoocta-3,7-dienyl}-3-[(trityloxy)methyl]cyclobutyl Benzoate (28)

A 60% suspension of NaH in mineral oil (26 mg, 0.66 mmol) in THF (6 mL) was treated dropwise at –10 °C with **27** (370 mg, 0.60 mmol) in THF (2 mL). After 10 min, aldehyde (–)-**24** (155 mg, 0.66 mmol) in THF (2 mL) was added and the mixture was stirred for 2 h at 25 °C. Usual workup with H_2O and Et_2O including chromatography (silica gel, hexane–EtOAc, 5:1) furnished **28** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.38 (hexane–EtOAc, 5:1)].

Yield: 400 mg (92%); colorless oil.

IR (film): 2934, 1718, 1684, 1654, 1560, 1512, 1448, 1274, 1148, 1068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 3 H, H–C13), 1.84–1.93 (m, 1 H, H–C2), 2.05–2.13 (m, 1 H, H–C11), 2.25–2.34 (m, 1 H, H–C11), 2.60–2.76 (m, 3 H, H–C2, H–C3, H–C6), 2.77–2.87 (m, 1 H, H–C6), 3.09 (t, *J* = 8.9 Hz, 1 H, H–C4), 3.26 (dd, *J* = 9.4, 5.0 Hz, 1 H, H–C4), 3.42–3.52 (m, 1 H, H–C7), 3.80 (s, 3 H, OCH_3), 3.95–4.01 (m, 1 H, H–C10), 4.20, 4.39 (AB, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.65 (s, 1 H, H–C14), 4.75 (s, 1 H, H–C14), 5.34–5.40 (m, 1 H, H–C1), 6.13 (ddd, *J* = 16.0, 4.5, 1.1 Hz, 1 H, H–C8), 6.51 (dt, *J* = 16.0, 6.0 Hz, 1 H, H–C9), 6.81–6.86 (m, 2 H, $C_6H_4CH_3$), 7.13–7.18 (m, 2 H, $C_6H_4CH_3$), 7.19–7.25 (m, 9 H, CPh_3), 7.33–7.39 (m, 2 H, Ph), 7.41–7.45 (m, 6 H, CPh_3), 7.48–7.53 (m, 1 H, Ph), 7.78–7.83 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 31.5, 31.6, 35.8, 37.2, 43.8, 55.7, 64.2, 69.3, 71.1, 76.9, 86.9, 113.8, 114.2, 127.4, 128.2, 128.7, 129.0, 129.7, 129.9, 130.3, 130.4, 130.6, 133.2, 141.6, 144.4, 145.8, 159.6, 166.1, 198.8.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{48}O_6Na$: 743.3349; found: 743.3343.

(1*SR*,2*RS*,3*RS*)-2-{(*E*,5*S*)-2-Hydroxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-[(trityloxy)methyl]cyclobutyl Benzoate (29)

Ketone **28** (91 mg, 0.13 mmol) and $CeCl_3·H_2O$ (48 mg, 0.13 mmol) were stirred for 30 min in MeOH (4 mL) at –78 °C. $NaBH_4$ (6 mg, 0.14 mmol) was added and the mixture was stirred for 3 h at –78 °C. Usual workup with NH_4Cl, H_2O, and Et_2O followed by chromatography (silica gel, hexane–EtOAc, 1:1) gave **29** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.38 (hexane–EtOAc, 1:1)].

Yield: 73 mg (78%); colorless oil.

IR (film): 3468, 3061, 2934, 2862, 1717, 1612, 1514, 1490, 1450, 1368, 1314, 1276, 1249, 1174, 1111, 1069, 1033 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.58–1.76 (m, 2 H, H–C6, OH), 1.70 (s, 3 H, H–C13), 1.76–1.96 (m, 2 H, H–C2, H–C6), 2.11–2.24 (m, 1 H, H–C11), 2.29–2.45 (m, 1 H, H–C11), 2.59–2.78 (m, 2 H, H–C2, H–C3), 2.98–3.14 (m, 1 H, H–C4), 3.17–3.30 (m, 1 H, H–C4), 3.31–3.41 (m, 1 H, H–C7), 3.82 (s, 3 H, OCH_3), 3.84–3.95 (m, 1 H, H–C10), 4.06–4.21 (m, 1 H, H–C5), 4.31, 4.50 (AB, *J* = 11.4 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.73 (s, 1 H, H–C14), 4.78 (s, 1 H, H–C14), 5.29–5.65 (m, 3 H, H–C1, H–C8, H–C9), 6.83–6.93 (m, 2 H, $C_6H_4CH_3$), 7.17–7.38 (m, 11 H, $C_6H_4CH_3$, CPh_3), 7.39–7.53 (m, 8 H, Ph, CPh_3), 7.54–7.64 (m, 1 H, Ph), 7.87–7.97 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.3, 31.8, 32.0, 32.8, 38.5, 44.6, 55.7, 64.6, 70.2, 70.4, 71.3, 78.0, 87.2, 113.1, 114.1, 127.4, 128.2, 128.8, 129.0, 129.7, 129.9, 130.6, 131.2, 131.8, 133.4, 136.1, 142.5, 144.4, 159.5, 166.3.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{50}O_6Na$: 745.3505; found: 745.3489.

(1*SR*,2*RS*,3*RS*)-2-{(*E*,5*S*)-2-Acetoxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-[(trityloxy)methyl]cyclobutyl Benzoate (30)

Alcohol **29** (82 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) was treated with Ac_2O (32 μL, 0.34 mmol), Et_3N (63 μL, 0.45 mmol), and DMAP (3 mg, 0.02 mmol) for 2 h at 25 °C. Usual workup and chromatography (silica gel, hexane–EtOAc, 5:1) gave **30** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.32 (hexane–EtOAc, 5:1)].

Yield: 84 mg (97%); colorless oil.

IR (film): 3061, 2934, 1737, 1717, 1612, 1514, 1490, 1450, 1370, 1314, 1274, 1247, 1174, 1155, 1111, 1069, 1027 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.66–1.96 (m, 3 H, H–C2, H–C6), 1.69 (s, 3 H, H–C13), 2.02 (s, 3 H, CH_3CO), 2.07–2.21 (m, 1 H, H–C11), 2.28–2.43 (m, 1 H, H–C11), 2.57–2.77 (m, 2 H, H–C2, H–C3), 2.84–3.00 (m, 1 H, H–C4), 3.17–3.39 (m, 2 H, H–C4, H–C7), 3.78–3.92 (m, 1 H, H–C10), 3.83 (s, 3 H, OCH_3), 4.24, 4.46 (AB, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.71 (s, 1 H, H–C14), 4.77 (s, 1 H, H–C14), 5.25–5.58 (m, 4 H, H–C1, H–C5, H–C8, H–C9), 6.83–6.91 (m, 2 H, $C_6H_4CH_3$), 7.18–7.38 (m, 11 H, $C_6H_4CH_3$, CPh_3), 7.40–7.54 (m, 8 H, Ph, CPh_3), 7.55–7.64 (m, 1 H, Ph), 7.90–7.99 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 29.5, 31.7, 32.9, 38.4, 44.4, 55.7, 64.5, 70.2, 70.3, 73.4, 77.7, 87.1, 113.2, 114.1, 127.4, 128.2, 128.8, 129.1, 129.7, 130.0, 130.6, 131.0, 131.5, 133.3, 134.0, 142.4, 144.5, 159.5, 166.3, 170.6.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{52}O_7Na$: 787.3611; found: 787.3626.

(1*SR*,2*RS*,3*RS*)-2-{(*E*,5*S*)-2-Acetoxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-(hydroxymethyl)cyclobutyl Benzoate (31)

Trityl ether **30** (72 mg, 0.094 mmol) in MeOH (2 mL) was detritylated with TsOH (4 mg, 0.019 mmol) for 2 h at 25 °C. Workup as described for **22** followed by chromatography (silica gel, hexane–EtOAc, 1:2) gave **31** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.45 (hexane–EtOAc, 1:2)].

Yield: 40 mg (81%); colorless oil.

IR (film): 3467, 2935, 2870, 1718, 1612, 1513, 1452, 1371 (m), 1275, 1248, 1175, 1111, 1071, 1027 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70 (s, 3 H, H–C13), 1.86–2.03 (m, 3 H, H–C2, H–C6), 2.02 (s, 3 H, CH_3CO), 2.11–2.27 (m, 1 H, H–C11), 2.33–2.68 (m, 3 H, H–C2, H–C3, H–C11), 2.81–2.96 (m, 1 H, H–C7), 3.70–3.99 (m, 3 H, H–C4, H–C10), 3.82 (s, 3 H, OCH_3), 4.31, 4.49 (AB, *J* = 11.4 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.72 (s, 1 H, H–C14), 4.78 (s, 1 H, H–C14), 5.28–5.40 (m, 1 H, H–C1), 5.41–5.53 (m, 1 H, H–C5), 5.59–5.68 (m, 2 H, H–C8, H–C9), 6.83–6.92 (m, 2 H, $C_6H_4CH_3$), 7.20–7.31 (m, 2 H, $C_6H_4CH_3$), 7.42–7.52 (m, 2 H, Ph), 7.55–7.65 (m, 1 H, Ph), 8.02–8.13 (m, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 29.7, 31.3, 34.3, 38.4, 44.4, 55.7, 63.5, 69.0, 70.4, 73.2, 77.7, 113.3, 114.2, 126.9, 128.8, 129.7, 130.0, 130.5, 131.2, 133.5, 134.0, 142.4, 159.5, 170.9.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{38}O_7Na$: 545.2515; found: 545.2498.

(1*SR*,2*RS*,3*RS*)-2-{(*E*,5*S*)-2-Acetoxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-formylcyclobutyl Benzoate (32)

Alcohol **31** (14 mg, 0.027 mmol) was oxidized with $NaHCO_3$ (10 mg, 0.122 mmol) and DMP (17 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) as described above for the synthesis of **17** from **15**. Purification by chromatography (silica gel, hexane–EtOAc, 2:1) gave aldehyde **32**.

Yield: 12 mg (85%); colorless oil.

IR (film): 2930, 2855, 1717, 1649, 1611, 1512, 1451, 1375, 1315, 1277, 1246, 1178, 1118, 1072, 1027 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.66 (s, 3 H, H–C13), 1.88–1.99 (m, 2 H, H–C6), 2.04 (s, 3 H, CH_3CO), 2.15 (dd, *J* = 13.9, 6.4 Hz, 1 H, H–C11), 2.36 (dd, *J* = 13.9, 7.3 Hz, 1 H, H–C11), 2.46–2.68 (m, 2 H, H–C2), 3.05–3.31 (m, 2 H, H–C3, H–C7), 3.79 (s, 3 H, OCH_3), 3.82–3.93 (m, 1 H, H–C10), 4.27, 4.45 (AB, *J* = 11.5 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.69 (s, 1 H, H–C14), 4.75 (s, 1 H, H–C14), 5.21–5.32 (m, 1 H, H–C1), 5.33–5.44 (m, 1 H, H–C5), 5.53–5.59 (m, 2 H, H–C8, H–C9), 6.84, 7.20 (AA′BB′, *J* = 8.5 Hz, 4 H, $C_6H_4CH_3$), 7.40–7.50 (m, 2 H, Ph), 7.53–7.63 (m, 1 H, Ph), 8.00–8.09 (m, 2 H, Ph), 9.99 (s, 1 H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 28.1, 30.1, 41.1, 43.3, 44.4, 55.7, 68.5, 70.4, 72.6, 77.7, 113.3, 114.2, 128.9, 129.7, 130.0, 130.5, 130.9, 133.7, 134.1, 142.3, 202.1.

ESI-MS: *m/z* [M + Na]$^+$ calcd for $C_{31}H_{36}O_7Na$: 543.2359; found: 543.2361.

(1*SR*,2*RS*,3*SR*)-2-{(*E*,5*S*)-2-Acetoxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-formylcyclobutyl Benzoate (33)

Aldehyde **32** (160 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was stirred with 0.1 M K_2CO_3 in MeOH–H_2O (10:1, 5 mL) for 15 min at 25 °C. Usual workup followed by chromatography (silica gel, hexane–EtOAc, 5:1) gave aldehyde **33** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.33 (hexane–EtOAc, 5:1)].

Yield: 106 mg (66%); colorless oil.

IR (film): 2995, 2976, 2938, 1769, 1757, 1720, 1612, 1513, 1452, 1375, 1247, 1112, 1057 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67 (s, 3 H, H–C13), 1.91–2.08 (m, 2 H, H–C6), 2.04 (s, 3 H, CH_3CO), 2.09–2.22 (m, 1 H, H–C11), 2.30–2.42 (m, 2 H, H–C2, H–C11), 2.65–2.81 (m, 1 H, H–C2), 2.97–3.26 (m, 2 H, H–C3, H–C7), 3.79 (s, 3 H, OCH_3), 3.83–3.96 (m, 1 H, H–C10), 4.28, 4.47 (AB, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.69 (s, 1 H, H–C14), 4.75 (s, 1 H, H–C14), 5.24–5.44 (m, 2 H, H–C1, H–C5), 5.57–5.62 (m, 2 H, H–C8, H–C9), 6.85, 7.21 (AA′BB′, *J* = 8.5 Hz, 4 H, $C_6H_4CH_3$), 7.42–7.51 (m, 2 H, Ph), 7.54–7.64 (m, 1 H, Ph), 8.01–8.09 (m, 2 H, Ph), 9.79 (d, *J* = 1.7 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.3, 28.4, 33.7, 37.8, 44.4, 47.7, 55.7, 69.6, 70.5, 71.9, 77.7, 113.4, 114.1, 128.9, 129.7, 130.0, 130.5, 130.6, 130.9, 133.8, 134.1, 142.3, 159.5, 166.3, 170.5, 203.0.

ESI-MS: *m/z* [M + Na]$^+$ calcd for $C_{31}H_{36}O_7Na$: 543.2359; found: 543.2358.

(1*SR*,2*RS*,3*SR*)-2-{(*E*,5*S*)-2-Acetoxy-5-[(4-methoxybenzyl)oxy]-7-methylocta-3,7-dienyl}-3-(3-ethoxy-3-oxopropanoyl)cyclobutyl Benzoate (34)

A mixture of $SnCl_2$ (8 mg, 0.04 mmol), N_2CHCO_2Et (25 μL, 0.24 mmol), and aldehyde **33** (106 mg, 0.20 mmol) in CH_2Cl_2 (8 mL) was treated as described for **5** (in the preparation of **18**). Chromatography (silica gel, hexane–EtOAc, 2:1) gave **34** as an inseparable diastereomeric mixture. The NMR data provided below are for the major diastereomer [R_f = 0.29 (hexane–EtOAc, 2:1)].

Yield: 96 mg (79%); colorless oil.

IR (film): 2976, 2938, 2862, 2839, 1740, 1717, 1650, 1611, 1512, 1451, 1368, 1315, 1277, 1239, 1178, 1110, 1072, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.67 (s, 3 H, H–C13), 1.80–1.96 (m, 1 H, H–C6), 2.04 (s, 3 H, CH_3CO), 2.06–2.20 (m, 2 H, H–C6, H–C11), 2.31–2.46 (m, 2 H, H–C2, H–C11), 2.58–2.69 (m, 1 H, H–C2), 2.91–3.14 (m, 1 H, H–C7), 3.30–3.42 (m, 1 H, H–C3), 3.43, 3.48 (AB, *J* = 15.4 Hz, 2 H, H–C15), 3.79 (s, 3 H, OCH_3), 3.85–3.92 (m, 1 H, H–C10), 4.20 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.27, 4.47 (AB, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4CH_3$), 4.69 (s, 1 H, H–C14), 4.75 (s, 1 H, H–C14), 5.25–5.41 (m, 2 H, H–C1, H–C5), 5.56–5.63 (m, 2 H, H–C8, H–C9), 6.84, 7.21 (AA′BB′, *J* = 8.0 Hz, 4 H, $C_6H_4CH_3$), 7.42–7.49 (m, 2 H, Ph), 7.55–7.62 (m, 1 H, Ph), 8.01–8.10 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.2, 31.3, 33.7, 38.8, 44.3, 47.4, 48.4, 55.7, 61.9, 69.4, 70.4, 71.9, 77.7, 113.3, 114.1, 128.9, 129.7, 130.0, 130.3, 130.6, 130.9, 133.6, 134.5, 142.3, 159.5, 166.3, 167.4, 170.5, 203.0.

ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{35}H_{42}O_9Na$: 629.2727; found: 629.2723.

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