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Total Synthesis of (–)-Invictolide

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Abstract: A convergent approach to the total synthesis of (–)-invictolide, a component of the queen recognition pheromone of *Solenopsis invicta*, is described. Key steps involve the desymmetrization of a bicyclic olefin with Brown's chiral hydroboration, C–C bond formation, 1,3-*syn* reduction, and oxidative lactonization of a 1,3,5-triol with TEMPO/PhI(OAc)$_2$.

Key words: pheromones, desymmetrization strategy, *syn*-1,3-reduction, oxidative lactonization

Invictolide (**1**) is a component of the queen recognition pheromone of the red fire ant, *Solenopsis invicta*. Invictolide, exhibits pheromone activity in both the laevorotatory and racemic forms in surrogate queen field tests.[1] (–)-Invictolide [(–)-**1**] is isolated from the red fire ant queen, *Solenopsis invicta* Buren (Figure 1).[2a] Its relative stereochemistry was proposed by Rocca et al.[2b] and its absolute stereochemistry was established by Mori's group[3] to have the (3*R*,5*R*,6*S*,1′*R*)-configuration. The significant stereochemistry and the fascinating biosynthetic pathways involving δ-lactone compounds have driven many groups to attempt the synthesis of invictolide and several synthetic approaches have been reported.[4] In fact, ongoing research studies at our group on the synthesis of polyketide natural products exploring a desymmetrization strategy[6] has given impetus to attempt the synthesis of invictolide in a hitherto unreported approach. The present work depicts a radically different, novel strategy for total synthesis of (–)-invictolide [(–)-**1**] and efforts are mainly centered on the construction of a Prelog–Djerassi-type lactone unit as a key intermediate.[5]

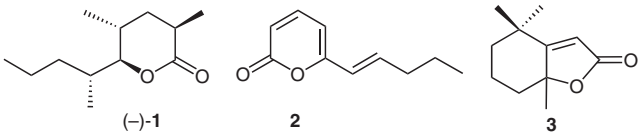
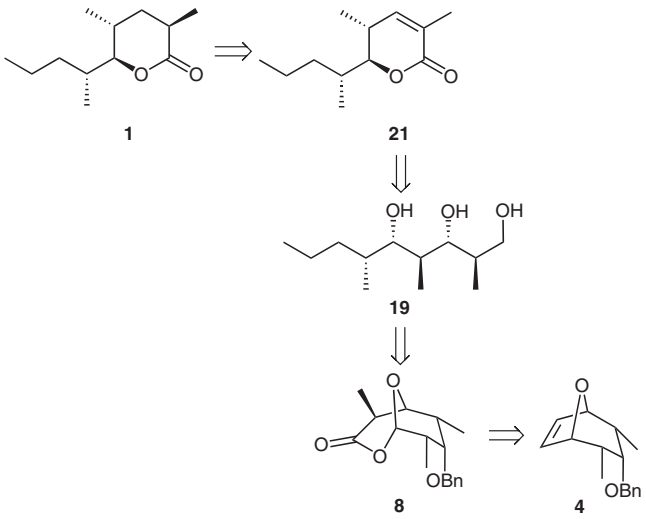


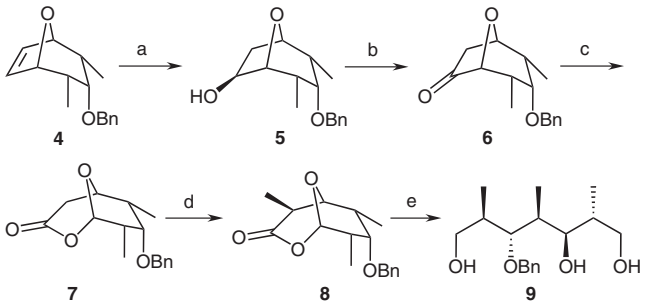
Figure 1 Fire ant queen pheromone components: (–)-invictolide [(–)-**1**]; (*E*)-6-pent-1-enyl-2*H*-pyran-2-one (**2**); dihydroactinidiolide (**3**)

Accordingly, the envisaged retrosynthetic strategy for (–)-invictolide [(–)-**1**] is shown in Scheme 1. (–)-Invictolide [(–)-**1**] can be prepared by short sequential manipulations of triol **19** embedded with all the required stereocenters, which in turn can be generated from bicyclic lactone **8** via



Scheme 1

triol **9**. Bicyclic lactone **8** could be obtained from bicyclic olefin **4**[6f] as shown in Scheme 2.



Scheme 2 *Reagents and conditions:* (a) (–)-Ipc$_2$BH, –23 °C, 24 h, 3 M NaOH, 30% H_2O_2, 0 °C–r.t., 6 h; (b) PCC, CH_2Cl_2, r.t., 3 h; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C–r.t., 10 h, 97%; (d) LDA, MeI, THF, –78 °C, 99%; (e) $LiAlH_4$, THF, 0 °C–r.t., 5 h, 97%.

The synthesis commenced with precursor **4**, the compound synthesized in our group and utilized for the synthesis of several natural products. The desymmetrization approach is explored to create five stereogenic centers at once.[6] The bicyclic olefin **4** was subjected to the key desymmetrization reaction using the enantioselective hydroboration reaction of Brown et al.[7] [(–)-Ipc$_2$BH, THF, 0 °C, NaOH, H_2O_2] to afford the required alcohol **5** with 97% ee in 95% yield. Alcohol **5** was converted into the bicyclic lactone **7** in 97% yield by pyridinium chlorochromate oxidation followed by Baeyer–Villiger oxidation (MCPBA, $NaHCO_3$, CH_2Cl_2). The thus-formed bicyclic

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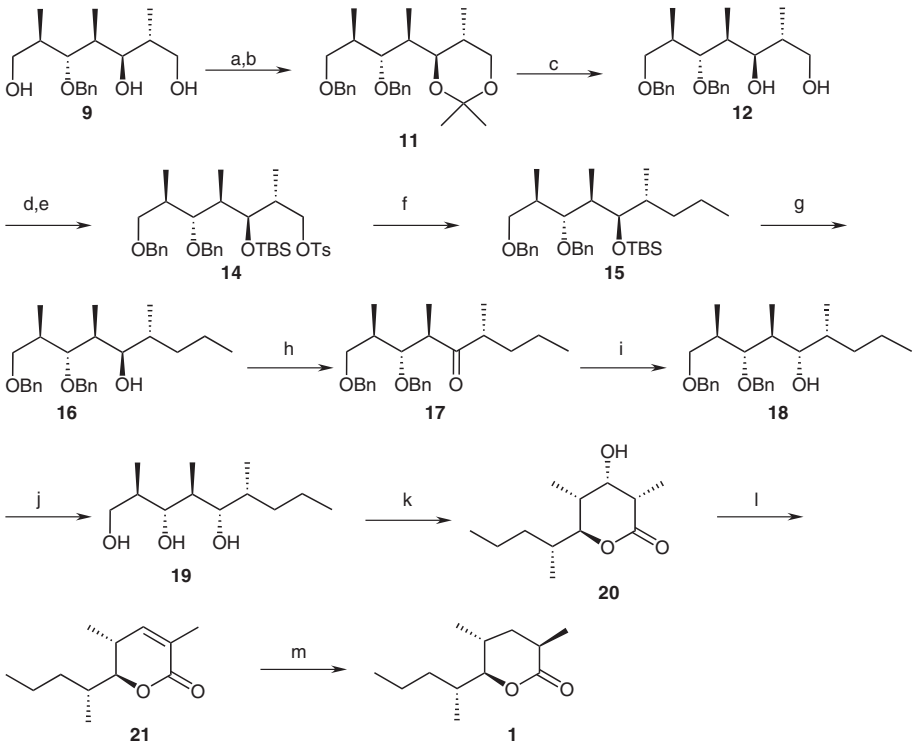

Scheme 3 *Reagents and conditions:* (a) 2,2-dimethoxypropane, CSA, anhyd CH_2Cl_2, 0 °C–r.t., 5 h, 89%; (b) NaH, BnBr, TBAI (cat.), anhyd THF, 0 °C–reflux, 3 h, 93%; (c) CSA, MeOH, r.t., 3 h, 96%; (d) TsCl, Et_3N, Bu_2SnO (cat.), anhyd CH_2Cl_2, 0 °C–r.t., 12 h, 92%; (e) TBSOTf, 2,6-lutidine, anhyd CH_2Cl_2, 0 °C–r.t., 1 h, 94%; (f) EtMgBr, CuBr·Me_2S, anhyd THF, –20 °C to r.t., 5 h, 83%; (g) PTSA, MeOH, 0 °C–r.t., 2 h, 92%; (h) Dess–Martin periodinane, $NaHCO_3$, anhyd CH_2Cl_2, r.t., 1 h, 96%; (i) DIBAL-H, anhyd CH_2Cl_2, –78 °C, 1 h, 94%; (j) Li/naphthalene, anhyd THF, –20 °C, 93%; (k) $PhI(OAc)_2$, TEMPO, anhyd CH_2Cl_2, r.t., 3 h, 83%; (l) (i) MsCl, Et_3N, 0 °C to r.t., 1 h; (ii) DBU, anhyd THF, r.t., 2 h, 88%; (m) H_2, 10% Pd/C, EtOAc, 6 h, 80%.

lactone **7** was then subjected to enolization using lithium diisopropylamide in tetrahydrofuran at –78 °C followed by treatment with iodomethane to furnish the methylated lactone **8** as a single diastereomer in 99% yield. Reductive cleavage of bicyclic lactone **8** with lithium aluminum hydride in tetrahydrofuran at room temperature furnished triol **9** in 97% yield, which is the key intermediate in the desymmetrization strategy with five stereogenic centers as shown in Scheme 3.[6]

The 1,3-diol functionality of triol **9** is protected by using 2,2-dimethoxypropane and a catalytic amount of 10-camphorsulfonic acid to give acetonide compound **10** followed by protection of the free hydroxy group as benzyl ether **11** using sodium hydride, benzyl bromide, and a catalytic amount of tetrabutylammonium iodide in 93% yield. Deprotection of the acetonide group using catalytic 10-camphorsulfonic acid in methanol afforded diol **12** in 96% yield. Selective protection of the primary hydroxy group with tosyl chloride, triethylamine, and catalytic dibutyltin oxide gave tosylate **13** in 92% yield. Protection of the secondary hydroxy group as its *tert*-butyldimethylsilyl ether with *tert*-butyldimethylsilyl triflate and 2,6-lutidine in dichloromethane afforded **14** in 94% yield.[8] The C–C bond formation occurred by treating **14** with ethylmagnesium bromide in tetrahydrofuran with copper(I) bromide–dimethyl sulfide complex to provide **15** in 83% yield.[9] Deprotection of the silyl ether with 4-toluenesulfonic acid in methanol provided **16** in 92% yield.

Inversion of the configuration of the secondary hydroxy group in the intermediate **16** was achieved by an oxidation–reduction strategy. Thus, oxidation of **16** with Dess–Martin periodinane in dichloromethane yielded ketone **17** in 96% yield, followed by reduction of **17** with diisobutylaluminum hydride in dichloromethane at –78 °C to afford exclusively alcohol **18** in 94% yield, as a result of 1,3-*syn* reduction.[10] Deprotection of the benzyl ethers of compound **18** was achieved using lithium/naphthalene in anhydrous tetrahydrofuran at –20 °C to yield the triol **19** in 93% yield.[11] The resulting triol is subjected to oxidative lactonization in the presence of (diacetoxyiodo)benzene/2,2,6,6-tetramethylpiperdin-1-oxyl to obtain Prelog–Djerassi-type lactone **20** in 83% yield.[12] Epimerization of lactone **20** at C3 was carried out by mesylation, elimination with DBU, followed by catalytic reduction with 10% palladium on carbon to provide (–)-invictolide [(–)-**1**] and its 3-epimer in the ratio of 3:1. Pure (–)-invictolide [(–)-**1**] was separated from its 3-epimer by crystallization from *n*-hexane at –78 °C. The spectroscopic data (^1H and ^{13}C NMR) and specific rotation of the synthetic (–)-invictolide [(–)-**1**] is in good agreement with those of the reported data.[3]

In conclusion total synthesis of (–)-invictolide is presented with an overall yield of 23%. The stereogenic centers are all obtained through a desymmetrization strategy and 1,3-*syn* reduction.

All reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, EtOAc, and Et_2O. Preparative chromatographic separations were performed on silica gel (35–75 μm); reactions were monitored by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp, anisaldehyde or β-naphthol soln or alkaline $KMnO_4$ soln. All commercially available reagents were purchased and were typically used as supplied.

Optical rotations were measured at r.t. (25 °C) on $CHCl_3$ solns with a polarimeter using a 2-mL capacity cell with a 100-mm path length. Infrared spectra were recorded using a thin film between NaCl plates or as a solid embedded in a KBr disc. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in Fourier transform mode on a Bruker UXNMR FT-300 MHz (Avance). Spectra were obtained on $CDCl_3$ solns in 5-mm diameter tubes, and signals are reported relative to the residual signals of $CHCl_3$ (δ_H = 7.25 or δ_C = 77.0).

7-(Benzyloxy)-6,8-dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-one (7)

To a stirred soln of $NaHCO_3$ (13.56 g, 161 mmol) and ketone **6** (14 g, 53.8 mmol) in CH_2Cl_2 (150 mL) was added anhyd MCPBA (18.57 g, 107 mmol) at 0 °C. The mixture was stirred for 10 h at r.t. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (100 mL) and quenched with sat. $NaHCO_3$ soln (50 mL) at 0 °C. The organic layer was separated and washed with sodium metabisulfite soln (50 mL) followed by brine (50 mL). The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by column chromatography to afford pure **7** as a pale-yellow liquid; yield: 14 g (97%); R_f = 0.5 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –46.5 (*c* 2.0, $CHCl_3$).

IR (neat): 2963, 2882, 1742, 1225, 1064, 970 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 7.5 Hz, 3 H), 1.15 (d, *J* = 7.5 Hz, 3 H), 2.01–2.11 (m, 1 H), 2.20–2.30 (m, 1 H), 2.71–2.73 (m, 2 H), 3.58–3.60 (m, 1 H), 4.06–4.12 (m, 1 H), 4.48–4.52 (m, 1 H), 4.65–4.69 (m, 1 H), 5.43–5.44 (d, *J* = 2.3 Hz, 1 H), 7.23–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 13.7, 31.0, 37.5, 39.6, 70.1, 76.7, 79.3, 99.8, 127.4, 128.2, 137.6, 166.2.

LC-MS: *m*/*z* = 299 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}O_4Na$: 219.1250; found: 299.1253.

(4*S*)-7-(Benzyloxy)-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-one (8)

LDA [prepared by the addition of 1.6 M BuLi in hexane (52 mL, 82 mmol) to a cooled soln of *i*-Pr_2NH (10.5 g, 15 mmol) at –10 °C in THF (100 mL)] was added to a soln of lactone **7** (14.3 g, 52 mmol) in THF (50 mL) at –78 °C. The lithium enolate thus generated was alkylated with MeI (6.5 mL, 103.5 mmol) after 1 h. Stirring was continued for a further 2 h and the reaction was quenched with sat. NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL), the solvent was evaporated, and the residue was purified by column chromatography to afford pure **8** as a pale-yellow liquid; yield: 15 g (99%); R_f = 0.4 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –54.7 (*c* 3.0, $CHCl_3$).

IR (neat): 2970, 2937, 2881, 1742, 1457, 1392, 1210, 1073, 977, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 8.0 Hz, 3 H), 1.16 (d, *J* = 8.0 Hz, 3 H), 1.42 (d, *J* = 5.0 Hz, 3 H), 2.06–2.08 (m, 1 H), 2.24–2.26 (m, 1 H), 2.76–2.81 (m, 1 H), 3.57–3.60 (m, 1 H), 3.69–3.71 (m, 1 H), 4.49–4.70 (m, 2 H), 5.43 (s, 1 H), 7.27–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 13.5, 20.4, 35.8, 37.6, 39.7, 76.6, 77.4, 79.2, 100.0, 127.4, 128.1, 137.7, 170.5.

LC-MS: *m*/*z* = 313 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}O_4Na$: 313.1407; found: 313.1410.

(2*R*,3*R*,4*S*,5*R*,6*R*)-5-(Benzyloxy)-2,4,6-trimethylheptane-1,3,7-triol (9)

To an ice-cooled suspension of $LiAlH_4$ (5.7 g, 150 mmol) in THF (100 mL) was added a soln of lactone **8** (14.5 g, 50 mmol) in THF (50 mL) under a N_2 atmosphere. The mixture was stirred for 5 h at r.t. After completion of the reaction, the mixture was quenched with H_2O (6 mL) and 5 M NaOH (6 mL) and H_2O (18 mL), and the thus-formed precipitate was filtered through a Celite pad using EtOAc. The filtrate was dried (anhyd Na_2SO_4), the solvent was evaporated, and the residue was purified by column chromatography to afford pure **9** as a pale-yellow liquid; yield: 14.5 g (97%); R_f = 0.1 (50% EtOAc–hexane); $[\alpha]_D^{25}$ +0.26 (*c* 1.0, $CHCl_3$).

IR (neat): 3403, 3032, 2967, 1458, 1061 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 1.81–1.86 (m, 2 H), 2.25 (m, 1 H), 3.48–3.50 (dd, *J* = 2.0 Hz, 6.1 Hz, 1 H), 3.55–3.62 (m, 2 H), 3.63–3.66 (dd, *J* = 5.0, 6.1 Hz, 1 H), 3.70–3.72 (m, 1 H), 3.82 (d, *J* = 10.0 Hz, 1 H), 4.61–4.66 (q, *J* = 11.0, 5.1 Hz, 2 H), 7.25–7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 13.2, 14.6, 35.5, 37.2, 37.8, 65.1, 69.0, 76.4, 88.4, 127.8, 128.1, 128.6, 137.4.

LC-MS: *m*/*z* = 319 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{28}O_4Na$: 319.1885; found: 319.1901.

(2*R*,3*R*,4*R*)-3-(Benzyloxy)-2-methyl-4-[(4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-1-ol (10)

To a stirred soln of triol **9** (11 g, 37 mmol) in anhyd CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (9.12 mL, 74.3 mmol) and CSA (1.5 g); the mixture was stirred at r.t. for 5 h. The mixture was quenched with solid $NaHCO_3$ (2 g) and it was filtered through a small Celite pad. Solvent was evaporated in vacuo and the residue was purified by column chromatography to afford pure **10** as a colorless solid; yield: 11.2 g (89%); R_f = 0.3 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –40.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3480, 2964, 2929, 2879, 1458, 1382, 1198, 1060, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.83–2.06 (m, 3 H), 2.92 (br s, OH), 3.46–3.54 (m, 3 H), 3.66–3.72 (m, 1 H), 3.88–3.92 (m, 2 H), 4.6–4.71 (q, *J* = 10.5, 11.3 Hz, 2 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 12.4, 16.3, 19.4, 29.8, 30.2, 36.0, 37.4, 64.2, 66.1, 73.3, 75.4, 85.5, 97.9, 126.9, 127.5, 128.4, 138.3.

LC-MS: *m*/*z* = 359 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{32}O_4Na$: 359.2198; found: 359.2210.

(4*R*,5*R*)-4-[(2*R*,3*R*,4*R*)-3,5-Bis(benzyloxy)-4-methylpentan-2-yl]-2,2,5-trimethyl-1,3-dioxane (11)

To an ice-cooled suspension of NaH (2 g, 83.3 mmol, 60% in mineral oil) in anhyd THF (100 mL) was added a soln of alcohol **10** (11.1 g, 33 mmol) in THF (50 mL) under a N_2 atmosphere. After stirring for 10 min, BnBr (5.89 mL, 49.5 mmol) in THF (10 mL) was added slowly; TBAI (cat.) was then added at the same temperature. The resulting mixture was heated to reflux for 3 h. After completion of the reaction, it was cooled to 0 °C and the excess hydride was quenched with sat. NH_4Cl soln (25 mL). The mixture was extracted with EtOAc (3 × 60 mL), and the combined extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and evaporated. The residue was purified by column chromatography to afford pure

11 as a pale-yellow liquid; yield: 13.1 g (93%); R_f = 0.8 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –35.6 (*c* 1.0, $CHCl_3$).

IR (neat): 3060, 3031, 2965, 1602, 1457, 1382, 1198, 1101, 735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.64 (d, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 7.5 Hz, 3 H), 1.35 (s, 3 H), 1.37 (s, 3 H), 1.78–1.96 (m, 2 H), 2.14–2.21 (m, 1 H), 3.34–3.51 (m, 3 H), 3.62–3.70 (m, 2 H), 3.84–3.88 (m, 1 H), 4.43–4.51 (m, 2 H), 4.56–4.65 (q, *J* = 11.3, 5.2 Hz, 2 H), 7.22–7.31 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 13.3, 14.9, 26.5, 34.7, 36.7, 37.2, 69.1, 72.1, 73.1, 76.0, 76.8, 87.2, 127.3, 127.5, 127.6, 127.9, 128.3, 128.5, 137.7, 138.3.

LC-MS: *m*/*z* = 449 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{38}O_4Na$: 449.2667; found: 449.2667.

(2*R*,3*R*,4*S*,5*R*,6*R*)-5,7-Bis(benzyloxy)-2,4,6-trimethylheptane-1,3-diol (12)

Compound **11** (13 g, 30.5 mmol) was dissolved in MeOH (100 mL), CSA (cat.) was added and the mixture was stirred at r.t. for 3 h. After completion of the reaction, it was quenched with solid $NaHCO_3$ (2 g). The solvent was evaporated, and the residue was purified by column chromatography to afford pure **12** as a pale-yellow liquid; yield: 11.3 g (96%); R_f = 0.2 (30% EtOAc–hexane); $[\alpha]_D^{25}$ +22.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3441, 3060, 3032, 2968, 1457, 1091, 738, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.9 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.86–1.93 (m, 2 H), 2.13–2.20 (m, 1 H), 3.52–3.74 (m, 4 H), 3.88 (d, *J* = 9.6 Hz, 1 H), 4.14 (s, 1 H), 4.54–4.66 (m, 4 H), 7.26–7.37 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7, 13.3, 14.9, 34.7, 36.8, 37.3, 69.1, 72.2, 73.2, 76.1, 76.8, 87.3, 127.6, 127.6, 127.7, 127.9, 128.3, 128.5, 137.8, 138.4.

LC-MS: *m*/*z* = 409 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{34}O_4Na$: 409.2354; found: 409.2366.

(2*R*,3*R*,4*S*,5*R*,6*R*)-5,7-Bis(benzyloxy)-3-hydroxy-2,4,6-trimethylheptyl 4-Methylbenzenesulfonate (13)

To a stirred soln of **12** (11 g, 28.5 mmol) in anhyd CH_2Cl_2 (100 mL) was added Et_3N (8.72 mL, 62 mmol) and Bu_2SnO (cat.), the mixture was stirred for 15 min, and then cooled to 0 °C; TsCl (8.86 g, 47 mmol) was added and the mixture was stirred overnight. After completion of the reaction, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were dried (Na_2SO_4), the solvent was evaporated in vacuo, and the residue was purified by column chromatography to afford pure **13** as a pale-yellow liquid; yield: 14.3 g (92%); R_f = 0.5 (20% EtOAc–hexane); $[\alpha]_D^{25}$ +18.43 (*c* 1.0, $CHCl_3$).

IR (neat): 3482, 3032, 2970, 1599, 1457, 1358, 1176, 1081, 963 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 7.9 Hz, 3 H), 1.83–1.85 (m, 2 H), 2.01–2.05 (m, 1 H), 2.37 (s, 3 H), 3.45–3.48 (dd, *J* = 3.0, 5.9 Hz, 1 H), 3.50–3.53 (dd, *J* = 2.0, 8.8 Hz, 1 H), 3.56–3.59 (m, 2 H), 3.97–4.01 (m, 1 H), 4.07–4.10 (dd, *J* = 2.9, 5.9 Hz, 1 H), 4.45–4.55 (m, 4 H), 7.17 (d, *J* = 7.9 Hz, 2 H), 7.24–7.31 (m, 10 H), 7.74 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 13.4, 15.3, 21.9, 34.2, 36.5, 37.0, 70.8, 72.4, 73.5, 73.6, 76.4, 87.3, 127.9, 128.0, 128.1, 128.2, 128.3, 128.7, 128.8, 130.0, 133.4, 138.1.

LC-MS: *m*/*z* = 563 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{40}O_6NaS$: 563.2432; found: 563.2437.

(2*R*,3*R*,4*S*,5*R*,6*R*)-5,7-Bis(benzyloxy)-3-(*tert*-butyldimethylsilyoxy)-2,4,6-trimethylheptyl 4-Methylbenzenesulfonate (14)

To a stirred soln of **13** (13.2 g, 24.4 mmol) in anhyd CH_2Cl_2 (130 mL) was added 2,6-lutidine (5.6 mL, 48.8 mmol), the mixture was cooled to 0 °C and TBSOTf (8.4 mL, 36.6 mmol) was added. The mixture was stirred at r.t. for 1 h. After completion of the reaction, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was purified by column chromatography to afford pure **14** as a pale-yellow liquid; yield: 15.1 g (94%); R_f = 0.6 (10% EtOAc–hexane); $[\alpha]_D^{25}$ +16.1 (*c* 0.5, $CHCl_3$).

IR (neat): 3060, 3032, 2958, 1600, 1458, 1364, 1178, 1095, 967, 836 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 3 H), 0.19 (s, 3 H), 0.98 (d, *J* = 4.5 Hz, 3 H), 1.0 (s, 9 H), 1.02–1.05 (d, *J* = 6.8 Hz, 3 H), 1.28 (d, *J* = 6.8 Hz, 3 H), 1.98–2.16 (m, 2 H), 2.29–2.34 (m, 1 H), 2.6 (s, 3 H), 3.46–3.50 (dd, *J* = 3.7, 5.3 Hz, 1 H), 3.55–3.6 (t, *J* = 9.1, 7.5 Hz, 1 H), 3.75–3.79 (m, 1 H), 3.95–4.01 (m, 2 H), 4.28–4.32 (m, 1 H), 4.61–4.83 (m, 4 H), 7.45–7.52 (m, 12 H), 7.90–7.92 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.2, –3.2, 12.1, 14.4, 16.0, 18.6, 25.7, 26.1, 35.7, 39.0, 39.4, 72.2, 72.9, 73.1, 73.7, 74.0, 84.5, 127.2, 127.4, 127.5, 127.7, 127.7, 127.9, 128.3, 128.5, 129.7, 138.7, 138.9, 144.5.

LC-MS: *m*/*z* = 677 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{37}H_{54}O_6SSiNa$: 677.1724; found: 677.1723.

[(2*R*,3*R*,4*R*,5*R*,6*R*)-1,3-Bis(benzyloxy)-2,4,6-trimethylnonan-5-yloxy]-*tert*-butyldimethylsilane (15)

To a stirred soln of $CuBr·Me_2S$ (12.6 g, 87 mmol) in anhyd THF (130 mL) was added 1 M EtMgBr in THF (150 mL), the mixture was stirred for 1 h; it was then cooled to –20 °C and **14** (15 g, 29.2 mmol) dissolved in anhyd THF (50 mL) was added and the mixture was for 5 h at r.t. After completion of the reaction, it was quenched with sat. NH_4Cl soln (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography to afford pure **15** as a pale-yellow liquid; yield: 9.8 g (83%); R_f = 0.5 (10% EtOAc–hexane); $[\alpha]_D^{25}$ +3.83 (*c* 0.5, $CHCl_3$).

IR (neat): 3065, 3031, 2957, 1459, 1252, 1068, 835 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.04 (s, 3 H), 0.80–0.85 (m, 6 H), 0.87 (d, *J* = 2.3 Hz, 3 H), 0.91 (s, 9 H), 1.12 (d, *J* = 7.6 Hz, 3 H), 1.25–1.40 (m, 4 H), 1.47–1.61 (m, 1 H), 1.83–1.95 (m, 1 H), 2.07–2.22 (m, 1 H), 3.22–3.28 (dd, *J* = 3.0, 5.3 Hz, 1 H), 3.34–3.42 (m, 1 H), 3.58–3.64 (m, 1 H), 3.79–3.82 (m, 1 H), 4.46 (s, 2 H), 4.53–4.66 (m, 2 H), 7.20–7.32 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.7, 12.3, 14.3, 15.7, 16.5, 20.7, 26.1, 35.0, 35.7, 38.0, 39.6, 72.3, 73.0, 74.3, 75.3, 85.2, 127.2, 127.3, 127.4, 128.1, 128.2, 138.8, 139.1.

LC-MS: *m*/*z* = 535 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{52}O_3NaSi$: 535.35855; found: 535.35779.

(2*R*,3*R*,4*S*,5*R*,6*R*)-1,3-Bis(benzyloxy)-2,4,6-trimethylnonan-5-ol (16)

To a stirred soln of **15** (9.7 g, 18.9 mmol) in MeOH (100 mL) was added PTSA at 0 °C; the mixture was stirred at r.t. for 2 h. After completion of the reaction, it was quenched with solid $NaHCO_3$ (3 g), the solvent was evaporated, and the residue was purified by column chromatography to afford pure **16** as a pale-yellow liquid; yield: 6.9 g (92%); R_f = 0.4 (10% EtOAc–hexane); $[\alpha]_D^{25}$ +40.1 (*c* 0.5, $CHCl_3$).

IR (neat): 3501, 3064, 3031, 2961, 1456, 1074, 736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.0 Hz, 3 H), 0.79 (t, *J* = 7.0 Hz, 3 H), 0.92 (d, *J* = 6.0 Hz, 3 H), 0.98–0.99 (d, *J* = 7.0 Hz, 3 H), 1.09–1.17 (m, 2 H), 1.31–1.38 (m, 2 H), 1.42–1.47 (m, 1 H), 1.62–1.68 (m, 1 H), 1.83–1.87 (m, 1 H), 2.02–2.07 (br s, OH), 3.41–3.48 (m, 3 H), 3.56–3.59 (m, 1 H), 4.40–4.43 (m, 4 H), 7.14–7.25 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 14.4, 14.9, 15.0, 19.8, 34.3, 35.1, 35.7, 36.7, 72.2, 73.0, 74.2, 76.0, 87.2, 127.5, 127.6, 127.7, 128.2, 128.3, 137.8, 138.4.

LC-MS: *m*/*z* = 421 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{38}O_3Na$: 421.2709; found: 421.2712.

(2*R*,3*R*,4*R*,6*R*)-1,3-Bis(benzyloxy)-2,4,6-trimethylnonan-5-one (17)

To a soln of **16** (3 g, 7.53 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added $NaHCO_3$ (1.89 g, 22.5 mmol) and then Dess–Martin periodinane (4.79 g, 11.3 mmol) and the mixture was stirred at r.t. for 1 h. After completion of the reaction, hexane (50 mL) was added. A white precipitate separated, it was filtered, and the filtrate was concentrated under reduced pressure to a viscous oil, which was purified by column chromatography to afford pure **17** as a colorless oil; yield: 2.87 g (96%); R_f = 0.8 (10% EtOAc–hexane); $[\alpha]_D^{25}$ –28.63 (*c* 0.5, $CHCl_3$).

IR (neat): 3065, 3032, 2963, 1713, 1455, 1090, 735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78–0.83 (t, *J* = 7.5, 6.7 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 1.14–1.22 (m, 2 H), 1.53–1.60 (m, 2 H), 2.05–2.12 (m, 1 H), 2.49–2.56 (m, 1 H), 3.03–3.13 (m, 1 H), 3.30–3.35 (m, 1 H), 3.60–3.66 (m, 2 H), 4.33–4.44 (m, 4 H), 7.14–7.29 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1, 15.1, 16.0, 20.4, 34.3, 35.6, 46.9, 47.4, 71.7, 73.0, 74.8, 84.4, 127.2, 127.3, 127.4, 128.0, 128.2, 138.5, 138.7, 217.3.

LC-MS: *m*/*z* = 419 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{36}O_3Na$: 419.2551; found: 419.2556.

(2*R*,3*R*,4*S*,5*S*,6*R*)-1,3-Bis(benzyloxy)-2,4,6-trimethylnonan-5-ol (18)

To a stirred soln of ketone **17** (2.87 g) in anhyd CH_2Cl_2 (7.24 mmol), was added DIBAL-H (15.6 mL, 26 mmol) dropwise at –78 °C. The reaction was stirred at this temperature for 1 h while monitoring the progress of the reaction. After the reaction was complete, the mixture was quenched by the addition of MeOH at –78 °C and the mixture was allowed to reach r.t. The solvent was evaporated under vacuum and the residue was treated with sat. sodium potassium tartrate soln (40 mL). The residue dissolved in the aqueous layer and the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and then dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography to afford pure **18** as a pale-yellow liquid; yield: 2.7 g (94%); R_f = 0.4 (10% EtOAc–hexane); $[\alpha]_D^{25}$ –6.3 (*c* 0.5, $CHCl_3$).

IR (neat): 3499, 3064, 3031, 2925, 1454, 1069, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 3.0 Hz, 3 H), 0.84 (d, *J* = 3.0 Hz, 3 H), 0.89–0.91 (t, *J* = 6.9 Hz, 3 H), 1.11 (d, *J* = 7.9 Hz, 3 H), 1.25–1.41 (m, 4 H), 1.56–1.60 (m, 1 H), 1.93–1.98 (m, 1 H), 2.18–2.23 (m, 1 H), 3.42–3.47 (m, 2 H), 3.51–3.57 (m, 1 H), 3.60–3.63 (m, 1 H), 4.45–4.53 (m, 2 H), 4.60–4.65 (m, 2 H), 7.26–7.34 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 14.3, 15.4, 15.7, 20.6, 34.3, 36.8, 37.6, 38.5, 72.3, 73.0, 74.7, 76.4, 88.0, 127.4, 127.5, 127.7, 128.2, 128.3, 138.0, 138.6.

LC-MS: *m*/*z* = 421 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{38}O_3Na$: 421.2709; found: 421.2713.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2,4,6-Trimethylnonane-1,3,5-triol (19)

To a stirred soln of naphthalene powder (17.36 g, 135.6 mmol) in anhyd THF (30 mL) was added Li metal (0.5 g, 67.7 mmol). The mixture was stirred for 3 h at r.t. then cooled to –20 °C and **18** (2.7 g, 6.78 mmol) in anhyd THF (10 mL) was added. After stirring the mixture for 2 h at –20 °C, it was quenched with sat. aq NH_4Cl soln (20 mL), extracted with Et_2O (3 × 20 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography to afford pure **19** colorless oil; yield: 1.37 g (93%); R_f = 0.1 (40% EtOAc–hexane); $[\alpha]_D^{25}$ –4.37 (*c* 1.0, $CHCl_3$).

IR (neat): 3334, 2961, 1455, 976 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.0 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.87–0.90 (t, *J* = 7.0 Hz, 3 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 1.21–1.35 (m, 4 H), 1.66–1.70 (m, 1 H), 1.82–1.89 (m, 2 H), 3.34 (br s, OH), 3.45 (br s, OH), 3.55–3.61 (m, 3 H), 3.95 (d, *J* = 11.0 Hz, 1 H), 4.98 (br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 13.4, 14.2, 15.3, 20.4, 34.5, 35.4, 36.3, 38.7, 64.6, 80.0, 83.1.

LC-MS: *m*/*z* = 241 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{26}O_3Na$: 241.1781; found: 241.1774.

(3*S*,4*S*,5*R*,6*R*)-4-Hydroxy-3,5-dimethyl-6-[(*R*)-pentan-2-yl]-2*H*-tetrahydropyran-2-one (20)

To a stirred soln of triol **19** (1.37 g, 6.28 mmol) in anhyd CH_2Cl_2 (20 mL) was added $PhI(OAc)_2$ (7 g, 22 mmol) and TEMPO (0.2 g, 1.28 mmol) at r.t. The mixture was stirred at r.t. for 3 h. After completion of the reaction, sat. $Na_2S_2O_3$ soln (20 mL) and Et_2O (20 mL) were added. The organic layer was washed with sat. $NaHCO_3$ (15 mL) and H_2O (15 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography to afford pure **20** as a colorless solid; yield: 1.1 g (83%); R_f = 0.4 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –24.36 (*c* 1.0, $CHCl_3$).

IR (neat): 3445, 2963, 1714, 1461, 1211, 977 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.88 (t, *J* = 7.0, 5.0 Hz, 3 H), 0.89–0.90 (d, *J* = 7.0 Hz, 3 H), 1.02–1.03 (d, *J* = 7.0 Hz, 3 H), 1.28 (d, *J* = 8.0 Hz, 3 H), 1.32–1.43 (m, 2 H), 1.47–1.54 (m, 1 H), 1.61–1.65 (m, 1 H), 1.91–1.97 (m, 1 H), 2.19–2.36 (m, 1 H), 2.43–2.48 (m, 1 H), 3.82 (s, 1 H), 4.36 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 12.8, 14.2, 20.5, 33.6, 35.9, 36.0, 42.5, 72.9, 83.1, 96.1, 174.0.

LC-MS: *m*/*z* = 237 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{22}O_3Na$: 237.1463; found: 237.1461.

(5*R*,6*S*)-3,5-Dimethyl-6-[(*R*)-pentan-2-yl]-5,6-dihydro-2*H*-pyran-2-one (21)

To a stirred soln of **20** (1 g, 4.67 mmol) in anhyd CH_2Cl_2 (10 mL) was added Et_3N (3.6 mL, 25 mmol) and MsCl (1 mL, 10 mmol) at 0 °C; the mixture was stirred at r.t. for 1 h. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo.

DBU (2 mL, 14.5 mmol) was added to the crude product dissolved in anhyd THF (10 mL) at r.t. The mixture was stirred at r.t. for 2 h and then it was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and evaporated to give crude α,β-unsaturated lactone, which was purified by column chromatography to afford pure **19** as a colorless liquid; yield: 0.81 g (88%); R_f = 0.3 (10% EtOAc–hexane); $[\alpha]_D^{25}$ –26.81 (*c* 1.0, $CHCl_3$).

IR (neat): 2961, 1722, 1715, 1456, 1138 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86–0.91 (t, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 7.5 Hz, 3 H), 1.23–1.51 (m, 4 H), 1.71–1.73 (dd, *J* = 1.5, 5.3 Hz, 1 H), 1.88 (s, 3 H), 2.54–2.64 (m, 1 H), 3.93–3.97 (dd, *J* = 2.3, 8.3 Hz, 1 H), 6.32 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 14.0, 16.1, 16.8, 20.3, 30.9, 33.3, 35.5, 86.0, 127.0, 146.4, 166.3.

LC-MS: *m*/*z* = 219 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{20}O_2Na$: 219.1354; found: 219.1355.

(3*R*,5*R*,6*S*)-3,5-Dimethyl-6-[(*R*)-pentan-2-yl]-2*H*-tetrahydropyran-2-one [(–)-Invictolide, (–)-1]

To a stirred soln of **21** (0.1 g, 0.5 mmol) in EtOAc (10 mL), was added 10% Pd/C (cat.) and the mixture was stirred under H_2 atmosphere for 6 h. Then, the mixture was filtered through a small Celite pad and concentrated in vacuo. The crude residue thus obtained was a mixture of (–)-invictolide and its 3-epimer (3:1). The pure isomer **1** could be separated by crystallization (*n*-hexane at –78 °C). The resulting spectral data, specific rotation are in good agreement with the reported data.[3] Colorless oil; yield: 75 mg (80%); R_f = 0.5 (10% EtOAc–hexane); $[\alpha]_D^{25}$ –93.06 (*c* 1.0, $CHCl_3$) [Lit.[3] $[\alpha]_D$ –101 (*c* 0.45, $CHCl_3$)].

IR (neat): 2963, 1741, 1460, 1193 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86–0.96 (m, 6 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 1.30–1.48 (m, 5 H), 1.62–1.74 (t, *J* = 8.3 Hz, 2 H), 1.84–2.04 (m, 1 H), 2.54–2.67 (m, 1 H), 3.86 (dd, *J* = 2.3, 9.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 14.0, 16.4, 17.5, 20.3, 28.3, 32.4, 33.5, 35.2, 36.0, 85.6, 176.7.

LC-MS: *m*/*z* = 221 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{22}O_2Na$: 221.1512; found: 221.1512.

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