Synthesis of (+)-galiellalactone. Absolute configuration of galiellalactone

Supporting Information

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EXPERIMENTAL

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. THF was dried by refluxing over sodium / benzophenone ketyl immediately prior to use. CH_2Cl_2 and triethylamine were distilled from calcium hydride prior to use. MeOH was dried by distilling from magnesium / iodine. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. EIMS spectra (direct inlet, 70 eV) were recorded with a JEOL SX102 spectrometer, and the NMR spectra (in $CDCl_3$) with a Bruker DRX 400 spectrometer at 400 MHz (^{1}H) and at 100 MHz (^{13}C) and with a Bruker ARX 500 spectrometer at 500 MHz (^{1}H) and at 125 MHz (^{13}C). All flash chromatography was performed on 60 Å 35-70 µm Matrex silica gel (Grace Amicon). TLC analyses were made on Silica Gel 60 F_{254} (Merck) plates and visualised with anisaldehyde / sulphuric acid and heating.

[(3R,5R)-3-(2-1,3-Dioxolan-2-yl-ethyl)-5-methyl-cyclohex-1-enyloxy]-trimethyl-silane, 3

575 mg (23.6 mmol) of magnesium turnings were stirred over night under a nitrogen flow before 11 ml THF was added. To this mixture was then added a crystal of iodine and a drop of 1,2-dibromoethane. A solution of 2826 µl (23.6 mmol) 2-(2-bromoethyl)-1,3-dioxolane in 26 ml THF was added dropwise under 30 min. mainting the temperature below 20°C with a water bath. The waterbath was removed and the mixture was stirred for an additional 1 h. The mixture was added to a solution of 3260 mg (26.7 mmol) DMAP and 494 mg (2.4 mmol) CuBr·DMS in 20 ml THF at –78°C. The resulting solution was stirred at –78°C for 1 h. before 3250µl (25.6 mmol) TMSCl and 1300 mg (11.8 mmol) (R)-5-methyl-cyclohex-2-enone in 20 ml was added dropwise. The reaction was complete after 30 min at –78°C and 10ml TEA was added. The solution was brought to room temperature and diluted with 50 ml heptane and 25 ml water. The resulting slurry was filtered through celite which was then washed with heptane / ether 1:1. The phases were separated and the water phase was extracted with ether. The combined organix extracts were dried and concentrated. Flash chromatography (heptane / ether 10:1 1%TEA) afforded 2575 mg (77%) **3**.
$[\alpha]_D^{20}$= +48.7° (c=3.9 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 0.16 (9H, s), 0.94 (3H, d, J=6.7 Hz), 1.34 (2H, m), 1.41 (2H, m), 1.62 (1H, dt, J_1=1.8, J_2=7.6 Hz), 1.70 (1H, m), 1.92 (1H, m), 2.05 (1H, dd, J_1=5.5 Hz, J_2=11.2 Hz), 2.17 (1H, m), 3.84 (2H, m), 3.95 (2H, m), 4.82 (1H, d, J=1.7 Hz), 4.83 (1H, t, J=4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 0.7, 21.3, 25.9, 31.3, 32.3, 32.9, 35.8, 38.5, 65.2, 105.2, 108.4, 150.1; HRMS (EI) calcd for $C_{15}H_{28}O_3Si$ 284.1808, found 284.1810

(R)-3-(2-1,3-Dioxolan-2-yl-ethyl)-5-methyl-cyclohex-2-enone, 4

To a ice-cold solution of 3980 mg (13.99 mmol) of trimethylsilyl enolether **3** in 42 ml THF was added 2738 mg (15.39 mmol) *N*-bromosuccinimide. The solution was stirred for 20 min before 20 ml $NaHCO_3$ (sat.) and 20 ml brine was added. The phases were separated and the water phase was extracted with ether. The combined extracts were dried and concentrated. The crude product was dissolved 20 ml dry DMF and added to a slurry of dry LiBR and Li_2CO_3 in 64 ml dry DMF at 120°C. The temperature was maintained between 120 and 130°C for 50 min. The reaction mixture was cooled to room temperature and diluted with 120 ml NH_4Cl (sat.). The mixture was extracted with ether twice. The organic phases were combined, washed with brine, dried and the solvents removed. Flash chromatography ($CHCl_3$ / MeOH 100:1) gave 1889 mg (64%) of the α,β-unsaturated ketone **4.**
$[\alpha]_D^{20}$= -58.4° (c=1.8 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, d, J=6.5 Hz), 1.84 (2H, m), 2.03 (2H, m), 2.15 (1H, m), 2.31 (3H, m), 2.41 (1H, dd, J_1=4.0, J_2=16.3 Hz), 3.84 (2H, m), 3.94 (2H, m), 4.87 (1.87, t, J=4.9 Hz), 5.85 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.6, 31.4, 32.3, 38.5, 45.9, 65.4, 103.1, 125.8, 165.0, 200.3; HRMS (EI) calcd for $C_{12}H_{18}O_3$ 210.1256, found 209.1174 ($M-H^+$)

(3S,5R)-3-(2-1,3-Dioxolan-2-yl-ethyl)-5-methyl-cyclohexanone, 5
1646 mg (7.83 mmol) of the α,β-unsaturated ketone **4** was dissolved in 32 ml THF and 150 mg 10% Pd / C catalyst was added. After stirring under 1 atmosphere of hydrogen at room temperature for 6 h the catalyst was removed by filtration through celite. The celite was washed with ethyl acetate. The filtrate was removed under reduced pressure to give 1660 mg (quant. yield) of **5** which was used without further purification in the next step.
$[\alpha]_D^{20}$= +5.68° (c=1.9 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J=6.4 Hz), 1.03 (1H, m), 1.45 (1H, m), 1.66 (1H, m), 1.76 (1H, m), 1.86-1.97 (3H, m), 2.35 (2H, m), 3.83 (2H, m), 3.94 (2H, m), 4.83 (1H, t, J=4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 22.8, 31.37, 31.40, 33.4, 38.2, 40.9, 47.8, 50.1, 65.3, 104.7, 211.5; HRMS (EI) calcd for $C_{12}H_{20}O_3$ 210.1256, found 211.1334 ($M+H^+$)

(6R,7aS)-6-Methyl-1,2,5,6,7,7a-hexahydro-inden-4-one , 6
1374 mg (6.47 mmol) **5** was dissolved in 68 ml THF and 6.8 ml 1N HCl was added. The solution was stirred at room temperature for 3 days and then refluxed for 1 h. The solution was cooled and diluted with $NaHCO_3$ (sat.). The aqueous mixture was extracted twice with ether. After drying and concentration the crude product was purified with flashchromatography (heptane / ethyl acetate 8:1) giving 847mg (87%) of the bicyclic ketone **6**.
$[\alpha]_D^{20}$= +35.80° (c=1.6 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J=6.3 Hz), 1.03 (1H, m), 1.53 (1H, m , J_1=2.1 Hz, J_2=9.8), 1.89 (1H, dABd, J_1=12.4 Hz, J_2=16.7 Hz), 2.00 (2H, m), 2.26 (1H, m), 2.39 (2H, m), 2.48 (1H, dq, J_1=2.4 Hz, J_2=16.7 Hz, J_3=3.7 Hz), 2.87 (1H, m), 6.58 (1H, d, J=2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 31.9, 32.2, 33.5, 41.0, 45.6, 49.4, 138.5, 144.8, 199.5; HRMS (EI) calcd for $C_{10}H_{14}O$ 150.1045, found 150.1046

Trifluoro-methanesulfonic acid (6R,7aS)-6-methyl-2,6,7,7a-tetrahydro-1[H]-inden-4-yl ester, 7

To stirred solution of 888 µl (6.28 mmol) diisopropylamine in 5.5 ml THF was added dropwise 2.38 ml (5.71 mmol) *n*-BuLi (2.0 M in hexanes) at 0° C. The LDA solution was stirred for 10 min before beeing cooled to –78°. A solution of 780 mg (5.19 mmol) of the bicyclic ketone **6** in 3.6 ml THF was added slowly. The solution turned yellow and after 40 min 2000 mg (5.61 mmol) *N*-phenyltriflurosulfonimide in 5.5 ml THF was added. The reaction mixture was allowed to reach room temperature while stirring for 1 h. The reaction was quenched by the addition of 5 ml NH_4Cl (sat.). After dilution with water and ether the phases were separated and the water phase was extracted with ether. The organic phases were combined, washed with brine, dried and concentrated. Flash chromatography (heptane / ether 30:1) gave 1128 mg (77%) of the enol-triflate **7**.
$[\alpha]_D^{20}$= +107.3° (c=2.3 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.03 (1H, m), 1.13 (1H. d. J=7.2 Hz), 1.47 (1H, m, J_1=2.3 Hz, J_2=10.2 Hz), 2.05 (1H, dt, J_1=4.6 Hz, J_2= 12.6 Hz), 2.20 (1H, 1H, m, J_1=6.2 Hz, J_2=11.4), 2.55 (2H, m), 2.70 (1H, m), 2.89 (1H, m), 5.57, (1H ,s), 5.85 (1H, d, J=2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 32.0, 32.7, 32.9, 38.7, 45.5, 117.4 (J_{C-F}=320 Hz), 125.5, 126.1, 136.9, 144.5; HRMS (EI) calcd for $C_{11}H_{13}F_3O_3S$ 282.0538, found 282.0540

(6R,7aS)-6-Methyl-2,6,7,7a-tetrahydro-1[H]-indene-4-carboxylic acid methyl ester, 8
To a solution of 186 mg (0.66 mol) **7** in 1.0 ml MeOH was added 170 µl diisopropylethylamine followed by 7.4 mg (0.033 mmol) $Pd(OAc)_2$ and 17.3 mg (0.066 mmol) PPh_3. Carbon monoxide was bubbled through the yellow solution for 15 min and the solution was stirred under an atmoshere of carbon monoxide for 20 h. The resulting red solution was diluted with NH_4Cl (sat.) and ether. The phases were separated and the water phase was extracted with ether. The organic phases were combined, washed with water and brine, dried and concentrated. The residue was purified with flash chromatography (heptane / ether 50:1) to give 93 mg (74%) of the methyl ester **8**.
$[\alpha]_\Delta^{20}$= +85.3° (c=1.3 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 0.99 (1H, q, J=11.1 Hz), 1.12 (3H, d, J=7.3 Hz), 1.36 (1H, m, J_1=2.2 Hz, J_2=10.0 Hz), 2.04 (1H, m, J=4.4 Hz), 2.13 (1H, m), 2.42 (2H, m), 2.58 (1H, bm), 2.73 (1H, bm), 3.78 (3H, s), 6.26 (1H, d, J=2.3 Hz), 6.68 (1H,s);^{13}C NMR ($CDCl_3$) δ 21.2, 31.4, 32.7, 33.4, 39.0, 45.0, 51.9, 127.0, 127.4, 137.7, 146.8, 167.4; HRMS (EI) calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1143

(1aR,3aS,5R,7aR)-5-Methyl-1a,2,3,3a,4,5-hexahydro-1-oxa-cyclopropa[c]indene-7-carboxylic acid methyl ester 9
To a solution of 98 mg (0.51 mmol) **8** in 9 ml CH_2Cl_2 was added 170 mg (0.66 mmol) 70% mCPBA at 0°. The mixture was stirred for 40 min before $Na_2S_2O_3$ (sat.) was added. The phases were separated and the organic phase was washed with $NaHCO_3$ (sat.) before being dried and concentrated. This afforded 98.5 mg (93%) of a 3.3:1 mixture of epoxides **9** and **10.** 91 mg of the mixture was chromatographed on SiO_2 (hexane / ether 10:1) to afford 60 mg (61%) **9**.
$[\alpha]_D^{20}$= -4.2° (c=2.4 , $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.09 (1H, m), 1.17 (3H, d, J=7.3 Hz), 1.27 (1, d, J=12.7 Hz), 1.52 (1, dt, J_1=7.2 Hz, J_2=12.0 Hz), 1.62 (1H, qdd, J_1=1.0 Hz, J_2=7.7, J_3=10.5 Hz), 1.92 (2H, m), 2.03 (1H, dd, J_1=7.7 Hz, J_2=13.8 Hz), 2.52 (1H, m), 3.70 (3H, s), 4.37 (1H, s), 7.14 (1H, d, J=2.4 Hz);^{13}C NMR ($CDCl_3$) 20.8, 23.6, 28.0, 32.8, 34.4, 40.3, 51.9, 63.5, 64.0, 126.6, 154.9, 165.8; HRMS (FAB) calcd for $C_{12}H_{16}O_2$ 208.1099, found 209.1174 (M+H)

(4R,5aS,7aS,7bR)-5,5a,6,7,7a,7b-hexahydro-7b-hydroxy-4-methyl-indeno[1,7-bc]furan-2(4H)-one, (+)-galiellalactone, 1b

11 mg (0.056 mmol) of **9** were dissolved in 0.5 ml THF / water 1:1 and 2.8 mg (0.067 mmol) $LiOH \cdot H_2O$ was added. The resulting solution was stirred for 5 h when an additional 2.8 mg (0.067 mmol) $LiOH \cdot H_2O$ was added. After a total of 7.5 h the solution was diluted with 0.25 ml THF and 0.2 ml 10% H_2SO_4 was added and stirring was continued for 3 days. The solution was diluted with ether and the phases were separated. The organic phase was washed with $NaHCO_3$ (sat.), dried and concentrated. Flashchromatography (heptane / ethyl acetate 2:1) afforded 6 mg (55%) of pure **1b** as white crystals.

$[\alpha]_D^{20}$= +51.8° (c=0.45, $CHCl_3$), mp 58-61 °C, ^{1}H NMR ($CDCl_3$) δ 1.06 (1H, ddd, J_1= 4.6 Hz, J_2= 7.9 Hz, J_3=13.9 Hz), 1.16 (1H, m), 1.18 (3H, d, J=7.3 Hz), 1.73 (1H, ddt, J_1= 2.60 Hz, J_2= 7.0 Hz, J_3=14.7 Hz), 1.85 (1H, dtd, J_1= 2.7 Hz, J_2= 7.2 Hz, J_3=13.4 Hz), 2.07 (1H, m), 2.24 (1H, dt, J_1= 7.4Hz, J_2= 139 Hz), 2.43 (1H, m), 2.63 (1H, qtd, J_1= 3.1 Hz, J_2= 7.4 Hz, J_3=14.7 Hz), 4.77 (1H, dd, J_1= 2.3 Hz, J_2= 7.5 Hz), 7.01 (1H, d, J=3.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 29.0, 31.4, 33.0, 43.1, 81.8, 89.8, 130.7, 150.1, 169.7; HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0945