Synthesis of (−)-Galiellalactone

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Nature offers a wide variety of chiral compounds suitable as starting materials for the synthesis of enantiomerically pure molecules[1]. However, in cases when both enantiomers are required, the usefulness of this "chiral pool" is limited as normally only one enantiomer is occurring naturally. On the contrary, when chiral reagents or catalysts are utilised to induce asymmetry, both enantiomers can be obtained depending on which form of the reagents is used[2].

(−)-Galiellalactone (**1**), a fungal metabolite isolated from the ascomycetes *Galiella rufa* strain A75-86[3] and A111-95[4], is a selective and potent inhibitor of interleukin-6 (IL-6) signalling in HepG2 cells[5], and its biological characterisation requires larger amounts than what is readily available from fermentations. Our first attempt to synthesise **1** made use of (5*R*)-5-methylcyclohex-2-en-1-one (**2**), derived from the monoterpene (*R*)-(+)-pulegone, as an important chiral intermediate. However, as the initially proposed absolute configuration of **1** was wrong this approach furnished us with the unnatural enantiomer (+)-galiellalactone[6]. The same synthetic scheme starting from (*S*)-(−)-pulegone would give **1**, but although (*S*)-(−)-pulegone is commercially available it is expensive and not a convenient starting material. An asymmetric synthesis of (5*S*)-5-methylcyclohex-2-en-1-one has been reported[7], but was not considered suitable for our purposes as the overall length of the synthesis would be significantly increased. Instead, inspired by NANGIA and PRASUNA who showed that both enantiomers of 3,5-dimethylcyclohex-2-en-1-one can be made in an enantiodivergent fashion from (*R*)-(+)-pulegone[8], we utilised the ability of 5-methylcyclohex-2-en-1-one to undergo both 1,2- and 1,4-additions. In this way, also **1** is available from (*R*)-(+)-pulegone.

The acetal-containing Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane can be used for both 1,2- and 1,4-additions just by altering the reaction temperature, without the need for any special additives[9]. Addition of the Grignard reagent to the enone **2** at room temperature afforded the alcohol **3** as a 4 : 1 mixture of epimers in a fair yield. 1,4-Addition is predominant below 0°C. The tertiary allylic alcohol **3** undergoes an oxidative rearrangement when treated with PCC, to give the 3,5-disubstituted cyclohex-2-en-1-one **4**[10]. Following the previously reported procedure which gave the enantiomer of **1** from the enantiomer of **4** (summarised in Scheme 1)[6], gave us **1** with identical optical rotation as the natural product. All intermediates showed identical spectroscopic data but opposite optical rotation compared to the previously reported intermediates[6]. A slight modification was made for the generation of the enol triflate **7**, KHMDS[11] was found to be a superiour base compared to LDA for the enolisation of **6**. This completed an enantiodivergent synthesis of both enantiomers of galiellalactone starting from (*R*)-(+)-pulegone.

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. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. 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. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded at room temperature. The spectra were recorded in $CDCl_3$, and the solvent signals (7.26 and 77.0 ppm, respectively) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (J) in Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker XWIN-NMR software (rev. 010101). Mass spectra were recorded with a Jeol SX102 spectrometer, while the UV and the IR spectra were recorded with a Varian Cary 2290 and a Perkin Elmer 298 spectrometer. The melting point (uncorrected) were determined with a Reichert microscope, and the optical rotations were measured with a Perkin-Elmer 141 polarimeter at 20°C.

1-(2-[1,3]-Dioxolan-2yl-ethyl)-5-methyl-cyclohex-2-en-1-ol, **3**. Magnesium turnings (530 mg, 21.8 mmol) were

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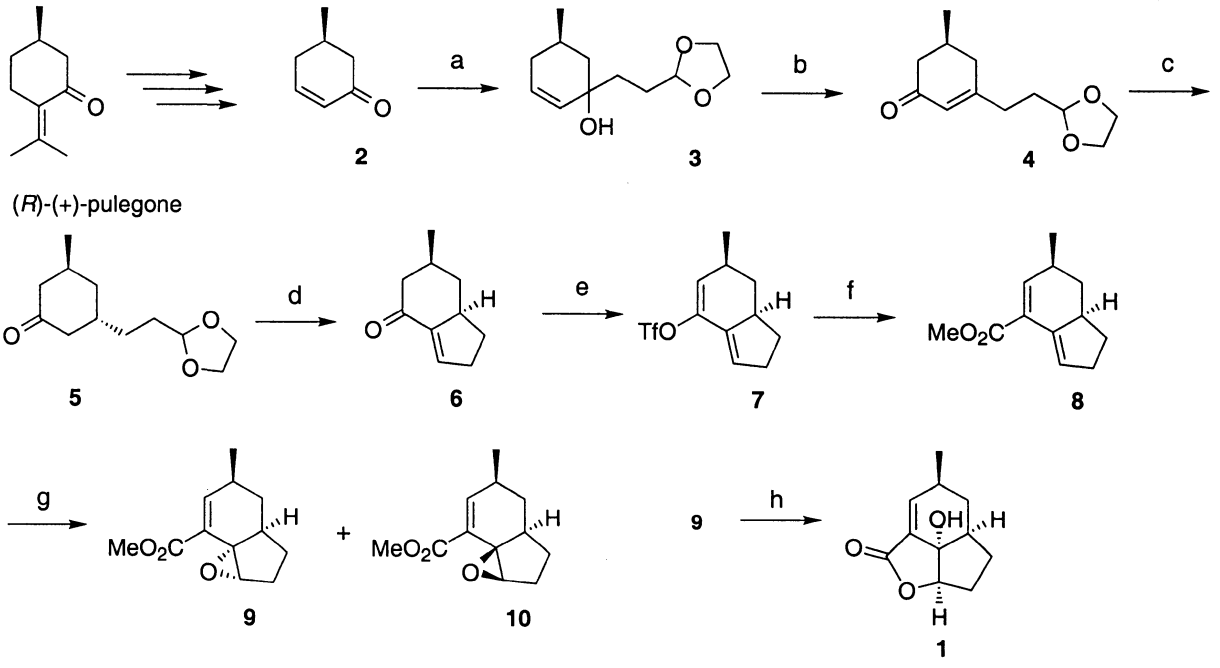
Scheme 1.



Reaction conditions. a) 2-(2-Bromoethyl)-1,3-dioxolane, Mg, I_2, 1,2 dibromoethane, 42%; b) PCC, CH_2Cl_2, 73%; c) 10% Pd/C, H_2, THF, 100%; d) 1 M HCl, THF, 87%; e) KHMDS, *N*-phenyltrifluoromethylsulfonimide, THF, 94%; f) CO, $Pd(OAc)_2$, PPh_3, diisopropylethylamine, MeOH, 74%; g) 70% *m*-CPBA, CH_2Cl_2, 0°C, 93% (**9**/**10** 3.5 : 1); h) i) $LiOH \cdot H_2O$, THF/water (1 : 1), ii) 10% H_2SO_4, 40°C, 55%.

stirred over night under a nitrogen flow before THF (16 ml) was added. To this mixture was then added a crystal of iodine and a drop of 1,2-dibromoethane. A solution of 2-(2-bromoethyl)-1,3-dioxolane (2.60 ml, 21.8 mmol) in THF (5.5 ml) was added dropwise under 30 minutes maintaining the temperature at 20°C with a water bath. The water bath was removed and the mixture was stirred for an additional 1 hour. (*R*)-5-Methyl-cyclohex-2-enone (1.20 g, 10.9 mmol) in THF (5.5 ml) was then added dropwise to the grey solution. The solution was stirred for 15 minutes. The reaction was quenched by the addition of NH_4Cl (sat.) (5 ml). 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 with Na_2SO_4 and concentrated. Flash chromatography (heptane/EtOAc 4 : 1) gave 967 mg (42%) of an 4 : 1 epimeric mixture of the allylic alcohols **3** as a colorless oil. IR ν_{max} (Nujol) cm^{-1} 3447, 2952, 1710, 1653, 1217, 1021; Major isomer: ^1H NMR δ 0.96 (3H, d, J=6.4), 1.60 (2H, m), 1.75 (2H, m), 1.85 (2H, m), 2.05 (2H, m), 3.86 (2H, m), 3.98 (2H, m), 4.90 (1H, t, J=4.4), 5.59 (1H, ddt, J_1=10.1, J_2=1.4), 5.69 (1H, ddd, J_1=10.1, J_2=4.8); ^{13}C NMR δ 22.0, 27.6, 27.7, 33.8, 35.3, 64.2, 71.5, 104.6, 127.6, 133.0; HRMS (CI-CH_4) calcd for $C_{12}H_{19}O_3$ (M−H) 211.1334, found 211.1333.

(*S*)-3-(2-1,3-Dioxolan-2-yl-ethyl)-5-methyl-cyclohex-2-enone, **4**. To a mixture of PCC (1.45 g, 6.8 mmol) in CH_2Cl_2 (14 ml) was added **3** (689 mg, 3.3 mmol) in CH_2Cl_2 (14 ml). The solution quickly darkened. After 1 hour stirring the reaction mixture was diluted with diethyl ether (35 ml) and filtered through celite. The filter was washed three times with diethyl ether. The filtrate was concentrated under reduced pressure. Flash chromatography (heptane/EtOAc 3 : 1) gave 500 mg (73%) of the disubstituted cyclohexenone **4** as a colorless oil. $[\alpha]_D^{20}$=+57.8 (c=1.8, $CHCl_3$); IR ν_{max} (Nujol) cm^{-1} 3015, 2958, 2360, 1658, 1377, 1217, 1142, 1032; ^1H NMR δ 1.04 (3H, d, J=6.5), 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), 3.84 (2H, m), 3.94 (2H, m), 4.87 (1.87, t, J=4.9), 5.85 (1H, s); ^{13}C NMR 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 $C_{12}H_{17}O_3$

$(M-H^+)$ 209.1178, found 209.1174.

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