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Synthesis of (+)-Galiellalactone. Absolute Configuration of Galiellalactone

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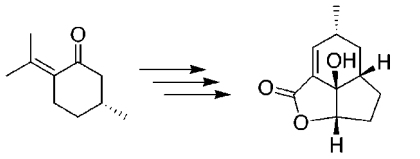
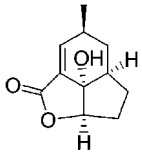
ABSTRACT



(+)-*R*-Pulegone (+)-Galiellalactone

(+)-Galiellalactone was synthesized starting from (*R*)-(+)-pulegone. Natural and synthetic galiellalactone have opposite optical rotations, demonstrating that the structure of the natural product is 1a.

The fungal metabolite galiellalactone (**1a**) is a potent (IC_{50} 250 nM) and highly selective inhibitor of interleukin-6 (IL-6) signaling in HepG2 cells.[1] It was originally isolated from *Galiella rufa* during a screening for new plant growth regulators produced by fungi;[2] galiellalactone was found to inhibit gibberillic acid-induced synthesis of α-amylase, but has since also been obtained from other fungal strains.



1a

Prompted by the activity of galiellalactone toward IL-6 signaling and its potential as a tool for studying this signal pathway or as a lead compound for developing new drugs to treat ailments linked to IL-6 signaling, we decided to undertake a total synthesis. On the basis of previous spectroscopic studies,[3] the absolute configuration of natural galiellalactone was suggested to be **1b** (see Scheme 1), and this enantiomer was consequently the target for our synthesis.

A synthetic sequence starting from a preformed six-membered ring followed by an annulation to form the second carbon ring was anticipated to be successful (Scheme 1). An intramolecular Diels−Alder approach to form the cyclohexene ring was considered to be more difficult because of the requirement of absolute stereocontrol. Similar ring systems[4] have been made, but those routes do not provide an easy way to introduce the tertiary hydroxyl group once the rings are formed.

A major goal of the total synthesis was to establish the absolute configuration of the natural compound, and (*R*)-(+)-pulegone was chosen as an appropriate chiral starting material as it is cheap, readily available, and would give us the suggested configuration of the methylated carbon (C-7). (*R*)-(+)-Pulegone is easily converted to the α,β-unsaturated ketone (5*R*)-5-methylcyclohex-2-en-1-one (**2**) in four steps.[5]

(1) Weidler, M.; Rether, J.; Anke, T.; Erkel, G. *FEBS Lett.* **2000**, *484*, 1.

(2) Hautzel, R.; Anke, H. *Z. Naturforsch.* **1990**, *45c*, 68.

(3) (a) Anke, H.; Hautzel, R.; Sheldrick, W. S.; Casser, I.; Steglich, W. *Abstracts of Papers*, 7th International Congress of Pesticide Chemistry, VCH; New York, 1991; Vol. 1, p 1. (b) Schneider, M. Ph.D. Dissertation, Ludwig-Maximilians-Universität Munich, 1996.

(4) (a) Dulcère, J.-P.; Crandall, J. K. *J. Chem. Soc., Chem. Commun.* **1990**, 561. (b) Mandai, T.; Suzuki, S.; Ikawa, A.; Murakami, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, *32*, 7687.

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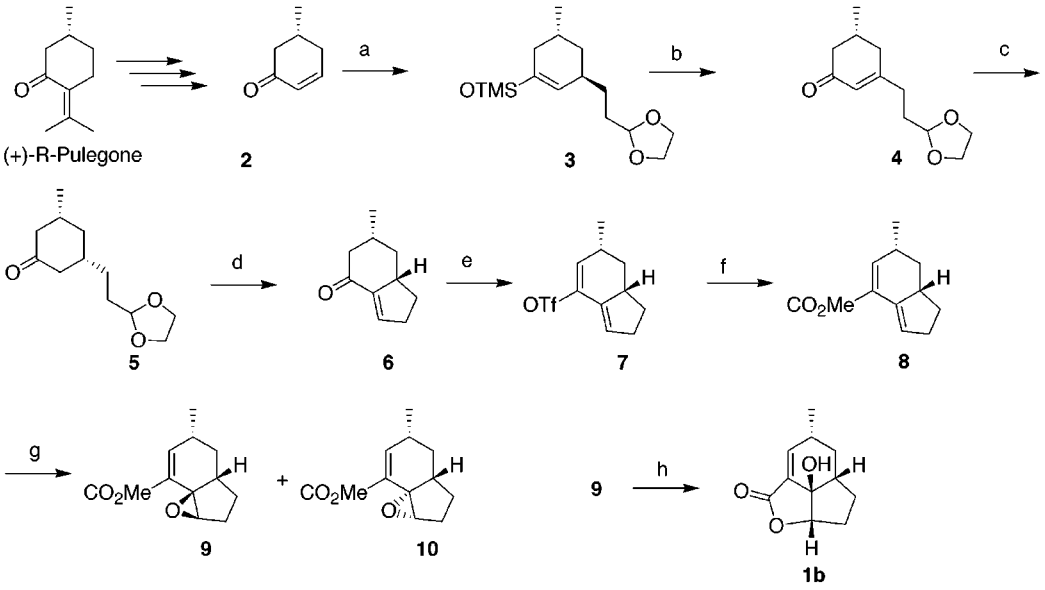
Scheme 1[a]



[a] Reaction conditions: (a) 2-(2-bromoethyl)-1,3-dioxolane, Mg, I_2, 1,2-dibromoethane, CuBr·DMS, DMAP, TMSCl, THF, −78 °C, 77%; (b) (i) NBS, THF, (ii) LiBr, Li_2CO_3, DMF, 125 °C, 64%; (c) 10% Pd/C, H_2, THF, 100%; (d) 1 M HCl, THF, 87%; (e) (i) diisopropylamine, *n*-BuLi, THF, −78 °C, (ii) *N*-phenyltrifluoromethylsulfonimide, THF, 77%; (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·H_2O, THF/water (1:1), (ii) 10% H_2SO_4, 40 °C, 55%.

The optical activity of **2** prepared in this investigation was identical to that previously reported.[6] Annulation of the five-membered ring can be carried out by a conjugate addition of the acetal-containing Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane followed by acid-catalyzed hydrolysis and condensation.[7] As expected, the Grignard reagent attacked the 5-substituted cyclohexenone axially from the least hindered face[8] giving the wrong stereochemical relationship between the methyl group on C-7 and the 2-ethyldioxolane group. However, by capturing the intermediate enol in the conjugate addition as a trimethylsilyl enol ether (**3**), this problem could be overcome. Treating enol ether **3** with NBS followed by dehydrobromination with LiBr and Li_2CO_3 reintroduced the conjugated double bond, which could be reduced by hydrogenation of **4** to give the saturated ketone **5** as the desired diastereomer (only one isomer was detected with NMR). Compound **6** was then obtained by stirring the acetal for 3 days in THF/HCl, and the stereochemistry of **6** was confirmed by an NOESY experiment which showed a strong correlation between the bridgehead proton and the proton on C-7. Treatment of the bicyclic ketone with LDA followed by the triflating agent *N*-phenyltrifluoromethylsulfonimide afforded the enol triflate **7**, and palladium-catalyzed carbonylation[9] of the enol triflate in methanol in the presence of a base gave the methyl ester **8** in a good yield. Subsequent epoxidation of the cyclopentene double bond was expected to be selective, only from the least hindered β-face of **8**, but with *m*-CPBA in dichloromethane a mixture of the β- and α-epoxides **9** and **10** was obtained (3.5:1). The two epoxides could be separated by chromatography, and the isolated yield of **9** was 72%. No epoxidation of the cyclohexene double bond was observed. Epoxidation with dimethyldioxirane gave a slightly improved diastereomeric ratio (4:1) but a considerably lower total yield (50%).

The final step was the opening of the epoxide of **9** and the closing of the lactone ring to give **1b**. A one-step procedure using lithium peroxide in ethanol[10] was attempted but led to decomposition. Treating the epoxide (**9**) with 20% formic acid gave a mixture of diols which were difficult to separate. However, hydrolysis of the ester group with LiOH followed by acid-catalyzed opening of the epoxide and subsequent lactonization afforded the desired product. The overall yield of **1b** was 3.4% from (*R*)-(+)-pulegone and 10% from (5*R*)-5-methylcyclohex2-en-1-one (**2**).

(5) (a) Nangia, A.; Prasuna, G. *Synth. Commun.* **1994**, *24*, 1989. (b) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125. (c) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974.

(6) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.

(7) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

(8) Paquette, L. A.; Wang, X. *J. Org. Chem.* **1994**, *59*, 2052.

(9) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(10) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Teterahedron* **2001**, *57*, 2185.

(11) **(4*R*,5a*S*,7a*S*,7b*R*)-5,5a,6,7,7a,7b-Hexahydro-7b-hydroxy-4-methylindeno[1,7-*bc*]furan-2(4*H*)-one, (+)-galiellalactone (1b)**, was obtained as white crystals, mp 58−61 °C. $[\alpha]^{20}_D$ = +51.8° (*c* = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) 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 = 7.4 Hz, 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 ($CDCl_3$, 125 MHz) 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.

The synthetic galiellalactone thus obtained was identical[11] with the natural product in all respects except for its optical activity. The optical rotation of the synthetic product ($[\alpha]^{20} = +51.8°$ ($c = 0.45$, $CHCl_3$) was the opposite of that measured for the natural compound ($[\alpha] = -52.8°$ ($c = 0.24$, $CHCl_3$). Since our synthesis starts with (*R*)-(+)-pulegone and goes via (5*R*)-5-methylcyclohex-2-en-1-one (**2**), two compounds with established absolute configurations, and as the synthetic steps could not inverse the configuration of C-7, the previously suggested absolute configuration of (−)-galiellalactone (**1a**) should be revised. With (*S*)-(−)-pulegone or (5*S*)-5-methylcyclohex-2-en-1-one,[12] the synthesis reported here would consequently yield the natural enantiomer **1a**.

(12) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 3640.

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Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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