Synthesis of (-)-Gleenol *via* C-H Insertion Reaction of Alkylidenecarbene

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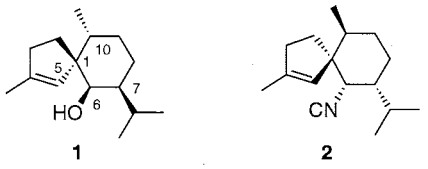
(Received April 27, 1998; CL-980316)

A spiro sesquiterpene alcohol, (-)-gleenol (**1**) was synthesized from (-)-*l*-menthol in 16 steps, using the C-H insertion reaction of the alkylidenecarbene as the key step. The absolute configuration of (-)-**1** was determined to be 1S, 6R, 7S, 10R.

The structure and relative stereochemistry of (-)-gleenol (**1**), a spiro sesquiterpene alcohol isolated from a pine tree *Picea glehnii*, were determined by X-ray analysis of the epoxy derivative.[1] (-)-**1** has been isolated from juniper and cryptmeria trees[2-4] and a marine alga.[5] The enantiomer (+)-**1** was also found in marine sponge,[6] however, their absolute configurations are not known. (+)-Axisonitrile-3 (**2**), which has the same relative stereochemistry as **1**, was isolated from marine sponges,[7] and it was recently found that (+)-**2** shows an antifouling activity against barnacle larvae.[8] The absolute configuration of (+)-**2**[9] was determined by the total synthesis of its enantiomer (-)-**2**.[10] Here, we describe the stereoselective synthesis of (-)-**1** from (-)-*l*-menthol using the C-H insertion reaction of the alkylidenecarbene. The absolute structure of (-)-**1** was determined as shown in the Figure.

Figure



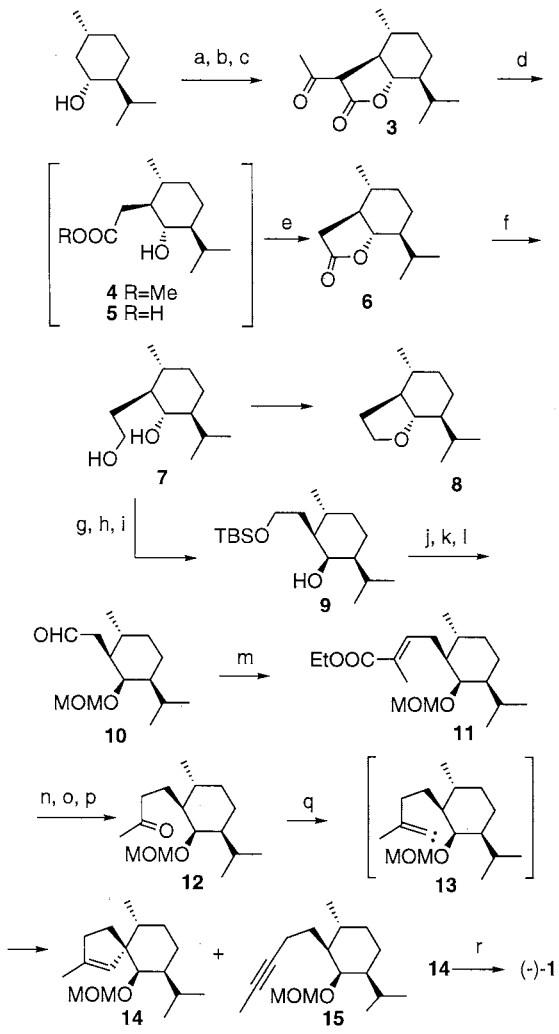
1 **2**

According to the procedure reported by Doyle et al.,[11] (-)-*l*-menthol was converted into the bicyclic *trans* lactone **3** *via* C-H insertion reaction of rhodium carbenoid, catalytically generated from *l*-menthyl diazoacetoacetate. **3** was exposed to sodium methoxide in methanol and the crude reaction mixture, which included methyl ester **4** and carboxylic acid **5**, was treated with *p*-TsOH in CH_2Cl_2 to give the deacylated lactone **6** in good yield. **6** was reduced to the diol **7**, which was easily cyclized to the stable ether **8** under various conditions. Since the free equatorial hydroxyl group, which is close to the equatorial side chain, would possibly make the manipulation of the side chain troublesome, inversion of the stereochemistry and protection of the secondary alcohol were carried out at this stage.

The primary hydroxyl group of the diol **7** was protected as TBS ether. Oxidation of the secondary alcohol with Dess-Martin periodinane followed by reduction with L-Selectride™ exclusively gave the axial alcohol **9**, which possesses the correct configurations for the synthesis of (-)-**1**.

Carbon chain elongation of **9** to the methyl ketone **12** was achieved by a somewhat novel method, using only commercially available reagents.[12] Protection of the secondary alcohol as MOM ether, deprotection of TBS ether and then Swern oxidation of the primary alcohol gave the aldehyde **10**. This was reacted with the lithiated triethyl 2-phosphonopropionate to afford the α,β–unsaturated ester **11** as a mixture of *cis-trans* isomers. Hydrolysis of **11** and Curtius rearrangement of the carboxylic acid under Shioiri's conditions,[13] followed by mild acidic hydrolysis of the isocyanate, produced the methyl ketone **12**, a precursor of the alkylidenecarbene.

Treatment of the ketone **12** with dimethyl diazomethylphosphonate[14] in the presence of *t*-BuOK generated



Scheme. (a) diketene; (b) TsN_3, Et_3N; (c) $Rh_2(OAc)_4$; (d) MeONa, MeOH; (e) p-TsOH, CH_2Cl_2 (77%); (f) $LiAlH_4$, Et_2O (90%); (g) TBSCl, imidazole, DMF (91%); (h) Dess-Martin periodinane, CH_2Cl_2 (83%); (i) L-Selectride, THF (89%); (j) MOMCl, Et_3N, CH_2Cl_2 (74%); (k) TBAF, THF (94%); (l) $(COCl)_2$, DMSO, Et_3N; (m) $(EtO)_2P(O)CH(CH_3)COOEt$, BuLi, THF (83% in two steps); (n) KOH, MeOH; (o) DPPA, Et_3N, CH_2Cl_2; (p) aq HCl, MeOH, rt (53% in three steps); (q) $(MeO)_2P(O)CHN_2$, tBuOK, THF (39%); (r) PPTS, MeOH, 50°C (52%)

the alkylidenecarbene **13**, which underwent 1,5 intramolecular C-H insertion to produce the spiro compound **14** in moderate yield. The rearranged compound **15** was also produced. Removal of the MOM group of **14** gave the final product (-)-**1**. The ^{1}H- and ^{13}C-NMR spectra of the synthetic compound were essentially identical with those of the natural product.[15] The sign of optical rotation {$[\alpha]_D^{22}$ -17° (c 0.50, $CHCl_3$)} was the same as the natural product isolated from plants (-10°[1], -15°[3], -8.9°[4]) and the opposite of the product from the sponge (+1.3°). Thus, the absolute stereochemistry of (-)-gleenol was determined as **1**.

References and Notes

1 P. I. Kurvyakov, Yu. V. Gatilov, V. A. Khan, and Zh.V.Dubovenko, and V. A. Pentegova, *Khim. Prir. Soedin.*, **1979**, 164.

2 V. A. Khan, Zh. V. Dubovenko, and V. A. Pentegova, *Khim. Prir. Soedin.*, **1983**, 109.

3 A. F. Barrero, J. F. Sanchez, J. E. Oltra, J. Altarejos, N. Ferrol, and A. Barragan, *Phytochemistry*, **30**, 1551 (1991).

4 S. D. Rosa, A. D. Giulio, C. Iodice, and N. Zavodink, *Phytochemistry*, **37**, 1327 (1994).

5 S. Nagahama, M. Tazaki, H. Nomura, K. Nishimura, M. Tajima, and Y. Iwasita, *Mokuzai Gakkaishi* , **42**, 1127 (1996).

6 C. J. Barrow, J. W. Blunt, and M. H. G. Munro, *Aust. J. Chem.*, **41**, 1755 (1988).

7 B. D. Blasio, E. Fattorusso, S. Magno, L. Mayol, C. Pedone, C. Santacroce, and D. Sica, *Tetrahedron*, **32**, 473 (1976).

8 H. Hirota, Y. Tomono, and N. Fusetani, *Tetrahedron*, **52**, 2359 (1996).

9 There might be some confusion about the absolute configurations of **1** and **2**, since the opposite enantiomeric forms of (-)-**1** and (+)-**2** are shown in the literature; these refer to the *relative* stereochemistry determined by X-ray analysis.

10 D. Caine and H. Deutsh, *J. Am. Chem. Soc.*, **100**, 8030 (1978).

11 M. P. Doyle, V. Bagheri, M. M. Pearson, and J. D. Edwards, *Tetrahedron Lett.*, **30**, 7001 (1989).; M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, and M. M. Pearson, *J. Am. Chem. Soc.*, **115**, 958 (1993).

12 M. C. Pirrung, W. L. Brown, S. Rege, and P. Laughton, *J. Am. Chem. Soc.*, **113**, 8561 (1991).

13 T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972).

14 D. Seyferth, R. M. Marmar, and P. H. Hilbert, *J. Org. Chem.*, 1971, **36**, 1379 (1971); S. Ohira, *Synth. Commun.*, **19**, 561 (1989).

15 We thank Professor J. W. Blunt of the University of Canterbury, New Zealand for providing us with ^{1}H- and ^{13}C-NMR spectra of (+)-**1**