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# Short total synthesis of the spiro[4.5]decane sesquiterpene (−)-gleenol

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**Abstract**—The spirocyclic sesquiterpene (−)-gleenol was prepared in five steps starting from (−)-methone via a di-olefin. The final spiro-ring system was made using the olefin metathesis reaction. The resulting ketone was selectively reduced to the natural product. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

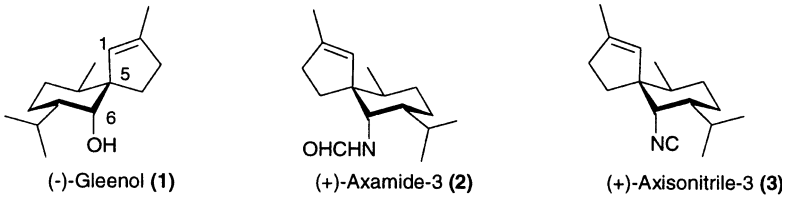
The sesquiterpenoide alcohol (−)-gleenol (**1**) has been isolated from *Picea glehnii*, Yakusugi bogwood,[1] and *Juniperus oxycedrus*,[2] labdanum oil,[3] the brown alga *Taonia atomaria*,[4] and *Helichrysum stoechas*.[5] Its enantiomer (+)-**1** was found in sponges from the genus *Eurypon*.[6] This compound shows the following biological activities: termiticidal, antihelmintic (in folk medicine)[7] and growth regulation effects on plant seeds. Its structure was elucidated by X-ray analysis of the corresponding epoxidation product.[8] This sesquiterpene belongs to a series of compounds which all have a spiro[4.5]decane skeleton (Scheme 1). Some of these compounds possess the opposite chirality. (+)-Axisonitril-3 (**3**) and related compounds are part of the defence and/or communication chemistry of marine organisms.[9]

(−)-Gleenol (**1**) and its C-6 epimer has been synthesized by two different routes.[10,11] Our retro-synthetic consideration leads to the building block **A** and **B** and further to the starting compounds methyl vinyl ketone and formyl menthone (**4**) (Scheme 2).

## 2. Results and discussion

We hereby report on a direct total synthesis of the alcohol (−)-**1** by starting from (−)-menthone. This synthesis is rather straightforward and this short sequence is suitable for isotope labelling. Key step is the ring closure by the olefin metathesis reaction (Scheme 3).[12] Accordingly, the marine sesquiterpene alcohol (+)-**1**[4] could be made from (+)-menthone.

Formylation of (−)-menthone with methyl formate under basic condition gave the enol **4** according to literature.[13] Treatment of enol **4** with methyl vinyl ketone in the presence of triethylamine gave a 1:2 mixture of epimers of the trioxo compound **5a**.[14] Separation of the diastereomers at this stage of the synthesis was not convenient. We considered the McMurry coupling (17 equiv. $TiCl_3$/35 equiv. $C_8K$, DME, 85°C)[15] for the spiro ring closure which would have led directly to the spiro ketone **6** and **7** but we could not observe the formation of the desired product using GC–MS analysis. Wittig olefination using potassium *tert*-butoxide as base[16] in dry toluene of the trioxo compound **5a** gave chemoselectively the di-olefin **5b** (60%).




(-)-Gleenol (**1**) (+)-Axamide-3 (**2**) (+)-Axisonitrile-3 (**3**)

**Scheme 1.**

*Keywords*: Michael addition; olefin metathesis; reduction; spiro[4.5]decane; sesquiterpene.

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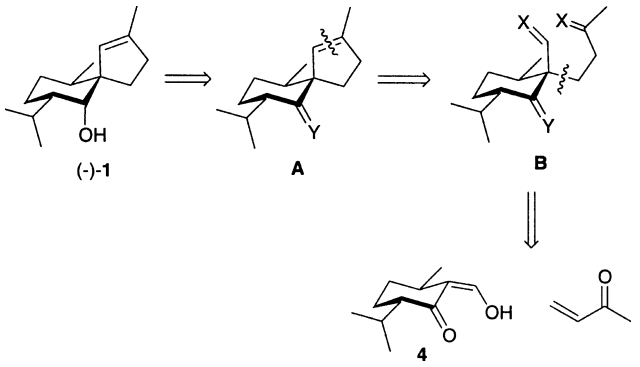



**Scheme 2.**

The carbonyl at C-1 was obviously too hindered to react under this condition. We obtained also up to 10% of the unwanted Robinson anneletion product **8** (formed after deformylation of **5a**) as determined by GC–MS. The spiro ketone **6** (and its diastereomer **7**) was formed very readily from the di-olefin **5b** using the olefin metathesis reaction with Grubbs catalyst {[MesIm][$(Cy)_3P$]$RuCl_2CHPh$} (**9**)[17] in boiling dichloromethane. No cyclization was observed with {$[(Cy)_3P]_2RuCl_2CHPh$} under the same condition within 24 h.[18] The chromatographic separation of the ketone **6** from its undesired diastereomer **7** was accomplished by chromatography using silver impregnated silica gel (10% silver nitrate) with dichloromethane as an eluent.[19] The ketone **6** was eluted first. According to NOESY measurements, cross peak analysis between 1-H and 7-H revealed the expected (5*S*)-configuration. The undesired ketone **7** was not further characterized.

Reduction of the ketone **6** with LAH in diethyl ether at 0°C led to a 1:1 mixture of the C-6 epimeric alcohols, in addition, reduction with L-selectride at −80°C in THF gave also a mixture of the unwanted equatorial and the desired axial alcohol of **1** in a 6:4 ratio. The formation of the unwanted equatorial alcohol was suppressed when the reduction was carried out using L-selectride at room temperature. Both workup procedures i.e. addition of carboxylic acids or oxidation with alkaline aqueous hydrogen peroxide caused the formation of byproducts. However, quenching of the reaction mixture with pyridin-*N*-oxide gave cleanly (−)-gleenol (**1**) in 77% yield.

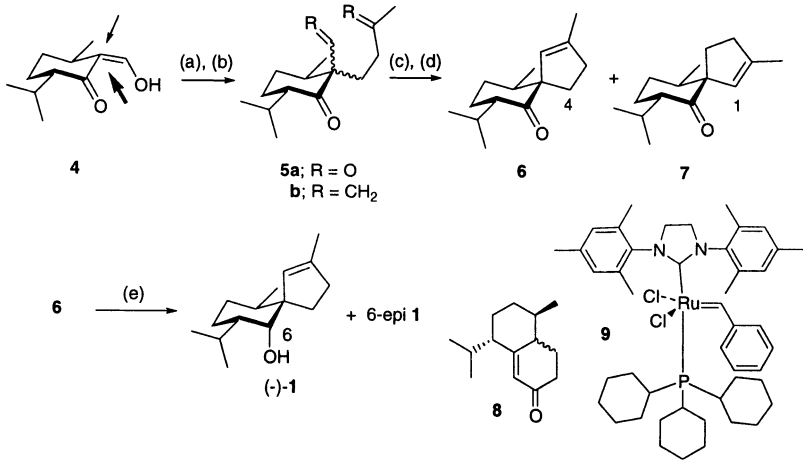
## 3. Experimental

### 3.1. General

THF and toluene were dried over benzophenone/sodium and distilled prior to use. Dichloromethane was dried over $P_4O_{10}$ and distilled prior to use. The Grubbs catalyst {[MesIm]-[$(Cy)_3P$]$RuCl_2CHPh$} (**9**) was purchased from Strem Chemicals GmbH, Kehl, Germany. All reactions have been performed under argon. $^1H$ NMR and $^{13}C$ NMR: Varian $^{Unity}$INOVA-300, at 300 ($^1H$) and 75.42 MHz ($^{13}C$) and $^{Unity}$INOVA-500 at 500 MHz, respectively. IR: Perkin–Elmer FT-IR Paragon 1000. Optical rotation: Perkin–Elmer Polarimeter 241. CD: Jasco Spektropolarimeter J-500A, Xenon-lamp. MS: Varian MAT 311A, EI, 70 eV, low and high resolution. GC: GC 8000 Series, Fisons Instruments, fused silica capillary column: DB 1, 10 m, methylsilicon rubber, nitrogen as carrier gas. TLC: DC-aluminium foil, silica gel 60 $F_{254}$, Merck, Darmstadt, Germany. Column chromatography: silica gel 60, 0.063–0.200 mm (70–220 mesh ASTM), Merck, Darmstadt, Germany. Short path distillation: Kugelrohr GKR-50, Fa. Büchi, Buchs, Switzerland. Temperatures are path temperatures.

**3.1.1. Formyl menthone (4).** This compound was prepared according to the literature from 16.0 g (0.104 mol) of (−)-menthone and methyl formate. Yield: 12.7 g (68%), oil (150°C, 20 Torr, kugelrohr; lit. cit.[13] 122.5°C, 14 Torr).

**3.1.2. Michael addition—ketone (5a).** Ketone **5a** (as a 1:2 mixture of 2*R*/2*S* epimers, determined by GC) was made from 12.0 g (66 mmol) of formyl menthone **4**, methyl vinyl ketone and triethylamine according to the literature.[20] Yield: 14.5 g (87%), oil (140°C, 0.03 Torr). The major isomer of **5a** was separated from the mixture on a small scale by chromatography (silica gel, petroleum ether/diethyl ether, 4:1). IR (film): $\tilde{\nu}$=2958 $cm^{-1}$ (CH), 2872 (CH), 1719 (C=O). $^1H$ NMR ($CDCl_3$): $\delta$=0.93 (d, $J$=6.8 Hz, 3H, $CH_3$), 0.95 (d, $J$=6.8 Hz, 3H, $CH_3$), 1.05 (d, $J$=6.8 Hz,




**Scheme 3.** (a) Methyl vinyl ketone, triethylamine, 0–25°C, 3 d, 87%; (b) $Ph_3PCH_2$ (from $Ph_3PCH_3Br$ and KO*t*Bu, 100°C), toluene, 25°C, 3 d, 60%; (c) {[Meslm][$(Cy)_3P$]$RuCl_2CHPh$} (**9**), $CH_2Cl_2$, 23 h, 40°C; (d) separation, silica gel (10% $AgNO_3$, $CH_2Cl_2$, 64% [(c)+(d)]; (e) L-selectride, THF, room temperature, 6 h, pyridine-*N*-oxide, 77%.

3H, C$H_3$), 1.62 (m, 1H), 1.78 (m, 1H), 1.98–2.47 (m, 9H), 2.12 (s, C$H_3$), 10.08 (d, $J$=0.8 Hz, 1H, C$H$O). $^{13}$C NMR ($CDCl_3$): $\delta$=15.9 (q, $C$H$_3$), 18.4 (q, $C$H$_3$), 20.9 (q, $C$H$_3$), 25.8 [d, $C$H(CH$_3$)$_2$], 23.1, 26.6 and 28.2 (t, C-4, C-5 and C-1″), 39.9 (q, $C$H$_3$), 28.3 (t, C-2″), 39.6 (d, C-3), 52.6 (d, C-6), 64.7 (s, C-2), 205.0 (d, $C$HO), 207.2 (s, C-3″), 214.1 (s, C-1). MS (70 eV); $m/z$ (%)=252 (5) [M$^+$], 234 (40), 224 (60) [M$^+$−CO], 209 (60), 191 (55), 167 (55).

**3.1.3. Di-olefin (5b).** A mixture of 85.65 g (240 mmol) of triphenylmethylphosphonium bromide, 24.65 g (220 mmol) potassium *tert*-butoxide in 400 ml of dry toluene was stirred under Ar at 100°C for 4 h. To the ice-cold yellow suspension was added under stirring a solution of 25.20 g (100 mmol) of ketone **5a** (as mixture) in 50 ml of anhydrous toluene. Stirring was continued at room temperature for 3 d. The reaction mixture was filtered. The filtrate was concentrated to a semisolid, which was suspended in 300 ml of diethyl ether. The suspension was kept in the refrigerator over night, filtrated, the filtrate diluted with pentane to precipitate the triphenylphosphine oxide. The filtrate was concentrated and then chromatographed (silica gel, diethyl ether as eluent). The main fraction concentrated and the resulting oily residue distilled (100°C, 0.04 Torr, kugelrohr). Yield: 15.04 g (60%), colourless oil, mixture of epimers. An analytical sample was obtained by chromatography on silver impregnated silica gel (10% $AgNO_3$, petroleum ether/diethyl ether, 4:1). IR (film): $\tilde{\nu}$=3074 cm$^{-1}$ (CH), 2957 (CH), 2932 (CH), 2870 (CH), 1706 (C=O), 1648 (C=C), 1458, 1378, 919, 884. $^1$H NMR ($CDCl_3$): $\delta$=0.87 (d, $J$=6.7 Hz, 3H, C$H_3$), 0.93 (d, $J$=6.7 Hz, 3H, C$H_3$), 1.01 (d, $J$=6.7 Hz, 3H, C$H_3$), 1.30–1.58 (m, 2H, 4-H, 5-H), 1.73 (m, 2H, 1″-H), 1.8–2.6 [m, 6H, 4-H, 5-H, 2″-H, 3-H, C$H$(CH$_3$)$_2$], 1.88 (s, 3H, CH$_3$), 2.43 (dt, $J$=5.4 Hz, $J$=13.5 Hz, 1H, 6-H), 4.73 and 4.76 (br s, 1H, 4″-H), 4.97 (d, $J$=17.6 Hz, 1H, 2′-H), 5.24 (d, $J$=11.0 Hz, 1H, 2′-H), 6.18 (dd, $J$=17.6, 11.0 Hz, 1H, 1′-H). $^{13}$C NMR ($CDCl_3$): $\delta$=15.8 (q, $C$H$_3$), 18.9 (q, $C$H$_3$), 21.4 (q, $C$H$_3$), 22.8 (q, $C$H$_3$), 26.5 [d, $C$H(CH$_3$)$_2$], 28.0 (t, C-5), 30.5 (t, C-1″), 32.1 (t, C-4), 33.1 (t, C-2″), 38.9 (d, C-3), 53.1 (d, C-6), 59.2 (s, C-2), 109.7 (t, C-4″), 117.5 (t, C-2′), 138.9 (d, C-1′), 147.0 (s, C-3′), 212.3 (s, C-1). MS (70 eV); $m/z$ (%)=248 (10) [M$^+$], 234 (5) [M$^+$−CH$_2$], 220 (3), 206 (5), 192 (5), 180 (40). $C_{17}H_{28}O$ (248.4): HRMS calcd. 248.2140; found 248.2156.

**3.1.4. Olefin metathesis reaction, spiroketone (6).** To a solution of 0.32 g (1.1 mmol) of **5b** (as a mixture) in 2 ml of anhydrous and oxygen-free dichloromethane 50 mg (59 μmol) of Grubbs catalyst {[MesIm][(Cy)$_3$P]-RuCl$_2$CHPh} (**9**) was added and the mixture refluxed. Another portion of 20 mg (23 μmol) of the catalyst was added after 15 h and heating continued for an additional 8 h. The catalyst was removed by filtration using silica gel, petroleum ether/diethyl ether, 4:1. The filtrate was then concentrated and the resulting ketone mixture separated using chromatography (silica gel containing 10% $AgNO_3$, $CH_2Cl_2$). Yield: 0.74 g (64%). IR (film): $\tilde{\nu}$=2956 cm$^{-1}$, 2930, 2955, 2870 (CH), 1704 (C=O), 1652 (C=C), 1460, 1376, 113. $^1$H NMR ($CDCl_3$): $\delta$=0.89 (d, $J$=8.4 Hz, 3H, C$H_3$), 0.92 (d, $J$=6.6 Hz, 6H, C$H_3$), 1.37 (ddd, $J$=12.8, 12.8, 3.8 Hz, 1H, 8-H), 1.50–1.75 (m, 4H, 10-H, 9-H, 4-H), 1.75 (br s, 3H, C$H_3$), 2.05–2.40 [m, 5H, 3-H, 8-H, 7-H, C$H$(CH$_3$)$_2$], 2.84 (ddd, $J$=13.4, 9.4, 5.2 Hz, 1H, 4-H), 5.35 (s, 1H, 1-H). $^{13}$C NMR ($CDCl_3$): $\delta$=16.9 (q, $C$H$_3$), 17.2 (q, $C$H$_3$), 19.0 (q, $C$H$_3$), 21.7 (q, $C$H$_3$), 26.5 [d, $C$H(CH$_3$)$_2$], 28.4 (t, C-4), 28.8 (t, C-8), 32.0 (t, C-9), 36.3 (t, C-3), 43.8 (d, C-10), 53.6 (d, C-7), 69.9 (s, C-5), 123.3 (d, C-1), 145.1 (s, C-2), 212.8 (s, C-6). MS (70 eV); $m/z$ (%)=220 (25) [M$^+$], 192 (14) [M$^+$−C=O], 149 (12), 121 (100), 108 (62). CD (methanol): $\lambda_{max}$ ($\Theta/\Delta\varepsilon$)=294 nm (−5250/−1.59). $C_{15}H_{24}O$ (220.4): HRMS calcd 220.1827; found 220.1821.

**3.1.5. (−)-Gleenol (1).** To a solution of 60 mg (0.27 mmol) of ketone **6** in 5 ml THF was added at room temperature 1 ml (1 mmol) of a solution of L-selectride [1.0 M LiBH($s$-Bu)$_3$ in THF] under stirring and the mixture was stirred for 6 h. After this time, 0.5 g (53 mmol) of solid pyridine-*N*-oxide was added. Stirring was continued for another 1 h and the solution concentrated and the residue purified on silica gel (petroleum ether/diethyl ether, 10:1). Yield 46 mg (77%). IR (film): $\tilde{\nu}$=3470 cm$^{-1}$ (OH), 2950 (CH), 1460, 1345, 1110, 1030, 955, 920, 830. $^1$H NMR ($CDCl_3$): $\delta$=0.73 (d, $J$=6.7 Hz, 3H, C$H_3$), 0.92 [d, $J$=6.6 Hz, 3H, CH(C$H$)$_3$], 0.93 [d, $J$=6.6 Hz, 3H, CH(C$H$)$_3$], 1.05 (dddd, $J$=3.7, 12.8, 12.8, 12.8 Hz, 1H, 9-H), 1.15 (m, 1H, 7-H), 1.26 (dddd, $J$=3.7, 12.8, 12.8, 12.8 Hz, 1H, 8-H), 1.45 (m, 1H, 9-H), 1.55 [m, 1H, C$H$(CH$_3$)$_2$], 1.65 (m, 1H, 8-H), 1.70 (m, 1H, 10-H), 1.75 (q, $J$=1.5 Hz, 3H, allylic-C$H_3$), 1.78 (ddd, $J$=12.5, 8.0, 8.0 Hz, 1H, 4-H), 1.88 (ddd, $J$=12.5, 8.0, 8.0 Hz, 1H, 4-H), 2.21 (m, 2H, 3-H), 3.52 (br s, 1H, 6-H), 5.18 (m, 1H, 1-H). $^{13}$C NMR ($CDCl_3$): $\delta$=16.2 (q, $C$H$_3$), 16.9 (q, allylic-$C$H$_3$), 20.7 and 21.2 [q, CH($C$H$_3$)$_2$], 24.4 (t, C-8), 29.3 [d, $C$H(CH$_3$)$_2$], 31.7 (t, C-4), 33.9 (t, C-9), 34.0 (d, C-10), 36.3 (t, C-3), 45.3 (d, C-7), 58.9 (s, C-5), 76.4 (d, C-6), 125.5 (d, C-1), 142.8 (s, C-2). MS (70 eV); $m/z$ (%)=222 (73) [M$^+$], 204 (21) [M$^+$−H$_2$O], 179 (7) [M$^+$−C$_3$H$_7$], 161 (14), 121 (100). $[\alpha]_D^{25}$=−1.6 ($c$=0.044, $CHCl_3$) {lit.: −8.9 ($c$=0.04, $CHCl_3$, 589 nm);[4] for (+)-**1**: +1.3 ($c$=0.6, $CHCl_3$, 589 nm)[6]}.

The $^1$H and $^{13}$C NMR spectra of the synthetic (−)-gleenol (**1**) were identical to those of (+)-**1** isolated from sponges of the genus *Eurypon*.[6]

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20. We observed that the ratio of (2*R*)-**5a** to (2*S*)-**5a** depends on the time for addition of the triethylamine. Addition of triethylamine during 1 h leads to a 1:2 ratio of the (2*R*)/(2*S*)-epimers.