Synthetic Study on Gymnomitrol. II.* A Synthesis of (±)-Isogymnomitrol

Takeshi IMANISHI,* Masayuki YAMASHITA, Yoshimi HIROKAWA, Tetsuaki TANAKA, Kazuyuki MIYASHITA, and Chuzo IWATA

Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka 1-6, Suita, Osaka 565, Japan.
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(±)-Isogymnomitrol (1b) and (±)-O-methylgymnomitrol (1c) were synthesized starting from the 1,2,6-trimethyltricyclo[5.3.1.0².⁶]undecan-9-one derivative 4 via 1,2-carbonyl transposition from C(9) to C(8) as a key step.

Keywords: gymnomitrol; O-methylgymnomitrol; isogymnomitrol; tricyclo[5.3.1.0².⁶]undecane; 1,2-carbonyl transposition; demethylation

Gymnomitrol (1a), isolated from the river wort Gymnomitron obtusum (LINDL.) Pears in 1970 by Connolly et al.,² was a kind of diquinane sesquiterpenoid having a unique 1,2,6-trimethyltricyclo[5.3.1.0².⁶]undecane skeleton. Because of its unusual framework, this compound has attracted much attention from organic synthetic chemists and several groups have reported syntheses of gymnomitrol (1a)³ and its isomer, isogymnomitrol (1b),³,⁴,⁶,⁷ which could be obtained by acid-catalyzed isomerization of 1a.²⁸ As is clear from the structures, one of the most important problems in the total synthesis of 1 is to construct the basic skeleton. In the previous paper,¹ we reported the interesting cyclopropane ring opening reaction of 1,2,6-trimethyltetrahydrotricyclo[5.3.1.0².⁶][⁷.¹¹]undecan-9-one (2) to give the 11-substituted 1,2,6-trimethyltricyclo[5.3.1.0².⁶]undecan-9-one derivative 3, which has the same carbon skeleton as 1 except for the one-carbon unit at the C(8) position. As an application of this reaction, we describe here the synthesis of isogymnomitrol (1b) and O-methylgymnomitrol (1c) starting from 4.

Apparently, the crucial step is the regioselective introduction of the one-carbon unit at the C(8) position, and it was expected that the electrophilic introduction of the one carbon unit into the enolate generated from 4 would regioselectively occur at the C(8) position to give 6 because of the steric hindrance of the C(1) position. But attempts to introduce the one carbon unit by the reaction of the enolate generated from 4 with an electrophile such as benzyl chloromethyl ether or chloromethyl methyl ether resulted in failure and the O-alkylated derivative (5a or b) was obtained as the only product in moderate yield.

Next, 1,2-carbonyl transposition⁴ was examined according to the route shown in Chart 3. The lithium enolate, prepared from 4 with 2 eq of lithium diisopropylamide (LDA), reacted with diphenyl disulfide to afford the phenythio derivative 7 as a sole product in 93% yield, via an antiparallel attack of diphenyl disulfide at the less hindered C(8) position. The stereochemistry of 7 was assigned as shown based on the ¹H-NMR spectrum. Reduction of 7 with lithium aluminum hydride (LiAlH₄) stereoselectively afforded the alcohol 8 in 67% yield (87% yield based on the consumed starting material 7). The stereochemistry of the C(9) position was supposed to be as shown from a consideration of a molecular model of 7 and was confirmed by the following transformation. Dehydration of 8 with thionyl chloride in pyridine⁵ smoothly took
place to afford the vinyl sulfide 9 in 90% yield as a sole product with no detectable formation of the regiosomer, indicating that the relation between the C(8) phenylthio group and the C(9) hydroxyl group is cis as shown. This also confirmed the stereochemistry of 8. Compound 9 was hydrolyzed to the desired ketone 10 in 96% yield by treatment with aqueous acid.

Methyleneation of 10 by use of the Wittig reaction or Peterson reaction resulted in failure, but the desired O-methylgymnomiotril (1c) was obtained in 89% yield when the organotin(IV) reagent reported by Nozaki's group was used. Demethylation of 1c was successfully achieved in quantitative yield when 1c was treated with a boron tribromide (BBr3)–sodium iodide (NaI)–15-crown-5 system, but isomerization of the exo-methylene group also took place to afford isogymnomiotril (1b). The structures of O-methylgymnomiotril (1c) and isogymnomiotril (1b), thus obtained, were confirmed by comparison of the 1H-NMR spectra with those of authentic gymnomiotril and isogymnomiotril as summarized in Table I.

### Experimental

The infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. 1H-NMR spectra were measured on a Hitachi R-22 (90 MHz) or a JEOL FX-90Q (90 MHz) with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution MS (high MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS-D300 mass spectrometer. For column chromatography, silica gel 60 (E. Merck) was used. After being dried over anhydrous sodium sulfate or magnesium sulfate, all organic extracts were concentrated under reduced pressure.

**Table I. 1H-NMR Data for Gymnomiotril (1a), O-Methylgymnomiotril (1c), and Isogymnomiotril (1b)**

<table>
<thead>
<tr>
<th></th>
<th>1a</th>
<th>1c</th>
<th>1b</th>
<th>Authentic 1b</th>
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<tbody>
<tr>
<td>1,2,6-Me</td>
<td>0.96</td>
<td>0.92</td>
<td>0.98</td>
<td>0.92</td>
</tr>
<tr>
<td>1,2,6-Me</td>
<td>1.00</td>
<td>1.08</td>
<td>1.05</td>
<td>0.99</td>
</tr>
<tr>
<td>1,2,6-Me</td>
<td>1.25</td>
<td>1.13</td>
<td>1.21</td>
<td>1.15</td>
</tr>
<tr>
<td>7-H</td>
<td>2.52</td>
<td>2.52</td>
<td>1.80</td>
<td>1.76</td>
</tr>
<tr>
<td>11-H</td>
<td>3.72</td>
<td>3.16</td>
<td>4.01</td>
<td>3.97</td>
</tr>
<tr>
<td>C(8)=CH3</td>
<td>4.64, 4.66</td>
<td>4.63, 4.66</td>
<td>—</td>
<td>5.07, 5.05</td>
</tr>
</tbody>
</table>

a) Spectral data were taken from reference 2b.
(1R,2S,5R,6S,7R,8S,9R,11R)-11-Methoxy-1,2,6-trimethyl-8-phenylthiochromene [5,3.1.0^-2]jundecan-9-ol (8) LiAlH₄ (47.0 mg, 1.24 mmol) was added portionwise to a solution of 7 (215 mg, 0.625 mmol) in ether (5 mL) at 0°C and the whole was stirred for 2 h at 0°C. After addition of saturated potassium sodium tartrate solution, stirring was continued for 30 min and the precipitate was filtered off. The filtrate was dried and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (35:1) to give the starting material 7 (41 mg, 19%) and 8 (145 mg, 67%) as a colorless oil. IR (CHCl₃): 3500, 1650, 1580 cm⁻¹.

1H-NMR (CDCl₃) δ: 0.91, 1.03, 1.34, and 1.41 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.27-2.7 (8H, m), 2.41 (1H, d, J = 3 Hz, 7-H), 2.87 (1H, br, s, OEt), 3.16 (1H, s, 11-H), 3.33 (2H, s, OMe), 3.51 (1H, dd, J = 7, 3 Hz, 8-H). 3.97 (1H, m, 9-H), 7.1-7.5 (5H, aromatic H). MS m/z: 346 (M⁺, 100), 149 (99).

High MS: 346.199 (M⁺, Calcd for C₁₉H₂₃O₂S: 346.196).

(1R,2S,5S,6S,7R,8S,9R,11R)-11-Methoxy-1,2,6-trimethyl-8-phenylthiochromene [5,3.1.0^-2]jundec-8-ene (9) Thiophenyl chloride (0.04 ml, 0.52 mmol) was added to a solution of 8 (106 mg, 0.306 mmol) in pyridine (5 mL) at 5°C and the whole was stirred for 30 min at 5°C. After addition of water, the mixture was extracted with ether (10 mL × 3) and the combined extracts were washed with saturated copper II sulfate solution (10 mL × 3) and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (50:1) to afford 9 (90 mg, 90%) as a colorless oil. IR (CHCl₃): 3020, 1590 cm⁻¹. 1H-NMR (CDCl₃) δ: 0.97, 0.98, 1.05 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.83–2.0 (6H, m), 2.17 (1H, s, 7-H), 2.05 and 2.31 (each 1H, dd, J = 19, 3 Hz, 10-H), 3.14 (3H, s, OMe), 3.48 (1H, s, 11-H), 5.54 (1H, t, J = 3 Hz, 9-H), 6.9–7.5 (5H, aromatic H). MS m/z: 328 (M⁺, 23), 219 (44), 57 (100). High MS: 328.1849 (M⁺, Calcd for C₂₁H₂₀OS: 328.1859).

(1R,2S,5S,6R,7R,8S,9R,11S)-11-Methoxy-1,2,6-trimethyl-thiochromene [5,3.1.0^-2]jundecan-9-ol (10) A mixture of 9 (90 mg, 0.27 mmol) in acetonitrile (10 mL) and 10% HCl solution (5 mL) was refluxed for 3 d. After removal of the acetonitrile under reduced pressure, the reaction mixture was extracted with ether (10 mL × 3). The combined extracts were washed with saturated NaHCO₃ solution and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (50:1) to afford 10 (62 mg, 95%) as a colorless powder. IR (CHCl₃): 1715 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.08, 1.09 and 1.18 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.6–2.6 (10H, m), 2.66 (1H, s, 7-H), 3.26 (3H, s, OMe), 3.38 (1H, s, 11-H). MS m/z: 236 (M⁺, 14), 204 (12), 149 (100). High MS: 236.1769 (M⁺, Calcd for C₁₉H₂₁O₂: 236.1774).

(±)-O-Methyl-glycinnitro (1c) Diiodomethane (499 mg, 1.86 mmol) was added to a suspension of zinc powder (214 mg, 3.27 mg atom) in THF (2.5 mL) at room temperature and the whole was stirred for 30 min. Titanium (IV) chloride (10% in CH₂Cl₂, 0.4 mL, 0.36 mmol) was added dropwise to the mixture at 0°C and the whole was stirred for an additional hour at room temperature. A solution of 10 (19 mg, 0.081 mmol) in THF (1 mL) was added to the resulting solution and stirring was continued for 15 min. After being diluted with ether, the reaction mixture was washed with 1N HCl solution and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (20:1) to give 1c (17 mg, 89%) as a colorless amorphous powder. IR (CHCl₃): 3080, 1650, 895 cm⁻¹.

1H-NMR (CDCl₃) δ: 0.92, 1.03 and 1.12 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.8–2.4 (10H, m), 2.52 (1H, s, 7-H), 3.15 (1H, s, 11-H), 3.25 (3H, s, OMe), 4.63 and 4.66 (each 1H, s, =C=O). MS m/z: 234 (M⁺, 27), 219 (28), 38 (100). High MS: 234.1992 (M⁺, Calcd for C₁₉H₂₃O₂: 234.1984).

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References