Synthetic Study on Gymnomitrol. II.[1] A Synthesis of (±)-Isogymnomitrol

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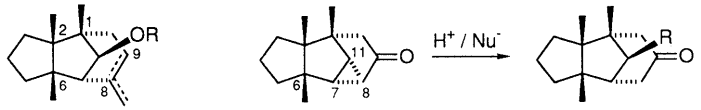
(±)-Isogymnomitrol (1b) and (±)-*O*-methylgymnomitrol (1c) were synthesized starting from the 1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undecan-9-one derivative 4 *via* 1,2-carbonyl transposition from C(9) to C(8) as a key step.

Keywords gymnomitrol; *O*-methylgymnomitrol; isogymnomitrol; tricyclo[5.3.1.$0^{2,6}$]undecane; 1,2-carbonyl transposition; demethylation

Gymnomitrol (**1a**), isolated from the river wort *Gymnomitrion obtusum* (LINDB.) Pears in 1970 by Connolly *et al.*,[2] is a kind of diquinane sesquiterpenoid having a unique 1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undecane skeleton. Because of its unusual framework, it has attracted much attention from organic synthetic chemists and several groups have reported syntheses of gymnomitrol (**1a**)[3] and its isomer, isogymnomitrol (**1b**),[3a,d,e] which could be obtained by acid-catalyzed isomerization of **1a**.[2b] 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-trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one (**2**) to give the 11-substituted 1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]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 transposition[4] 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 phenylthio 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 ^{1}H-NMR spectrum. Reduction of **7** with lithium aluminum hydride ($LiAlH_4$) 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 pyridine[5] smoothly took



1a: R=H, Δ_{exo} : gymnomitrol
1b: R=H, $\Delta_{8\text{-}9}$: isogymnomitrol
1c: R=Me, Δ_{exo} : *O*-methygymnomitrol

2

3: R=Nu
4: R=OMe

Chart 1

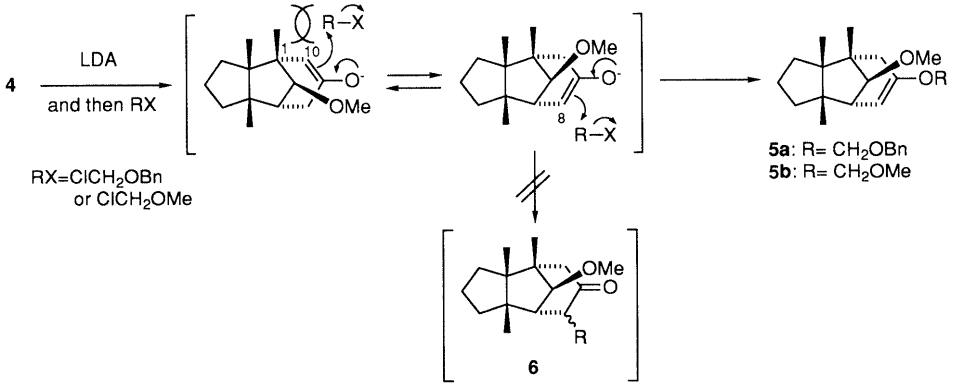
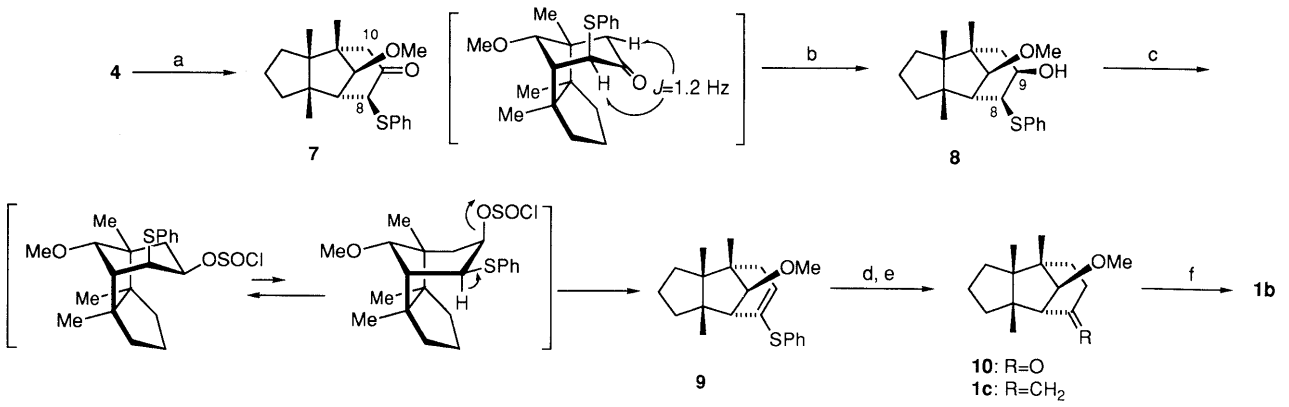


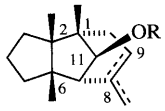
Chart 2



a) LDA, HMPA, $(PhS)_2$ b) $LiAlH_4$ c) $SOCl_2$, pyridine d) 10% HCl, MeCN e) CH_2I_2, Zn, $TiCl_4$ f) BBr_3, NaI, 15-crown-5

Chart 3

TABLE I. ^{1}H-NMR Data for Gymnomitrol (**1a**), *O*-Methylgymnomitrol (**1c**), and Isogymnomitrol (**1b**)



gymnomitrol (**1a**): R=H, Δ_{exo}
isogymnomitrol (**1b**): R=H, Δ_{8-9}
O-methylgymnomitrol (**1c**): R=Me, Δ_{exo}

	1a[a]	**1c**	**1b**	Authentic **1b**[a]
1,2,6-Me	0.96	0.92	0.98	0.92
	1.09	1.03	1.05	0.99
	1.25	1.13	1.21	1.15
8-Me	—	—	1.66	1.62
7-H	2.33	2.52	1.80	1.76
11-H	3.72	3.16	4.01	3.97
C(8)=CH_2	4.64, 4.66	4.63, 4.66	—	—
9-H	—	—	5.07	5.05

a) Spectral data were taken from reference 2*b*.

place to afford the vinyl sulfide **9** in 90% yield as a sole product with no detectable formation of the regioisomer, 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.

Methylenation of **10** by use of the Wittig reaction[6] or Peterson reaction[7] resulted in failure, but the desired *O*-methylgymnomitrol (**1c**) was obtained in 89% yield when the organotitanium reagent reported by Nozaki's group[8] was used. Demethylation of **1c** was successfully achieved in quantitative yield when **1c** was treated with a boron tribromide (BBr_3)–sodium iodide (NaI)–15-crown-5 system,[9] but isomerization of the *exo*-methylene group also took place to afford isogymnomitrol (**1b**). The structures of *O*-methylgymnomitrol (**1c**) and isogymnomitrol (**1b**), thus obtained, were confirmed by comparison of the ^{1}H-NMR spectra with those of authentic gymnomitrol and isogymnomitrol[2] as summarized in Table I.

Experimental

The infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H-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.

Attempt to Introduce the C-1 Unit at C(8) of 4 by Alkylation Using Benzyl Chloromethyl Ether A solution of **4** (20 mg, 0.085 mmol) in tetrahydrofuran (THF, 1 ml) was added dropwise to a solution of LDA in THF (0.5 ml) [prepared from diisopropylamine (13 mg, 0.13 mmol) and *n*-butyllithium (1.6 M in hexane, 0.08 ml, 0.13 mmol)] at −78 °C and the whole was stirred for 15 min at the same temperature. Hexamethylphosphoric triamide (HMPA, 1 ml) was added to the reaction mixture and stirring was continued for 15 min, then benzyl chloromethyl ether (21 mg, 0.13 mmol) was added dropwise. The whole was stirred for 1 h at −78 °C, 4 h at 0 °C, and 12 h at room temperature. After addition of saturated NH_4Cl solution, the mixture was extracted with ether (5 ml × 3). The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (20 : 1) to give **5a** (13 mg, 43%) as a colorless oil.

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-9-Benzyloxymethoxy-11-methoxy-1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undec-8-ene (**5a**): IR ($CHCl_3$): 3060, 3010, 1665, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.98 and 1.03 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.8—2.4 (9H, m), 3.28 (3H, s, OMe), 3.40 (1H, s, 11-H), 4.25 and 4.62 (each 1H, ABq, J=12 Hz, $C\underline{H}_2Ph$), 4.63 (1H, m, 8-H), 4.94 and 5.00 (each 1H, ABq, J=18 Hz, $OC\underline{H}_2O$), 7.33 (5H, s, aromatic H).

Attempt to Introduce the C-1 Unit at C(8) of 4 by Alkylation Using Chloromethyl Methyl Ether Compound **4** (129 mg, 0.547 mmol) was reacted with chloromethyl methyl ether (53 mg, 0.65 mmol) by the same method described above to give **5b** (69 mg, 45%) as a colorless oil.

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-11-Methoxy-9-methoxymethoxy-1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undec-8-ene (**5b**): ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.98 and 1.04 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.1—2.4 (9H, m), 3.23 (3H, s, OMe), 3.35 (3H, s, OMe), 3.36 (1H, s, 11-H), 4.54 (1H, br s, =C$\underline{H}$), 4.78 and 4.88 (each 1H, ABq, J=6 Hz, $OC\underline{H}_2O$).

(1*RS*,2*RS*,6*RS*,7*SR*,8*SR*,11*RS*)-11-Methoxy-1,2,6-trimethyl-8-phenylthiotricyclo[5.3.1.$0^{2,6}$]undecan-9-one (7) A solution of **4** (303 mg, 1.28 mmol) in THF (4 ml) was added dropwise to a solution of LDA in THF (3 ml) [prepared from diisopropylamine (286 mg, 2.83 mmol) and *n*-butyllithium (1.6 M in hexane, 1.80 ml, 2.88 mmol)] at −78 °C under a nitrogen atmosphere and the mixture was stirred for 30 min at the same temperature. HMPA (2 ml) was added and the whole was stirred at room temperature for 30 min. A solution of diphenyl disulfide (421 mg, 1.93 mmol) in THF (4 ml) was added dropwise to the reaction mixture, which was stirred overnight at room temperature. After addition of saturated NH_4Cl solution, the mixture was extracted with ether (15 ml × 3). The combined extracts were washed with saturated $NaHCO_3$ solution, and brine, dried, and evaporated. The residue was chromatographed on silica gel with benzene–hexane (2 : 1) to give **7** (410 mg, 93%) as a pale yellow oil. IR ($CHCl_3$): 3060, 1715, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00, 1.06 and 1.13 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.4—2.0 (6H, m), 2.28 (1H, dd, J=17, 1.2 Hz, 10-H), 2.55 (1H, d, J=2.6 Hz, 7-H), 2.74 (1H, d, J=17 Hz, 10-H), 3.32 (3H, s, OMe), 3.71 (1H, s, 11-H), 3.83 (1H, dd, J=2.6, 1.2 Hz, 8-H), 7.0—7.6 (5H, m, aromatic H). MS *m/z*: 344 (M^+, 100), 235 (38). High MS: 344.1794 (M^+, Calcd for $C_{21}H_{28}O_2S$: 344.1807).

(1*RS*,2*RS*,6*RS*,7*SR*,8*SR*,9*RS*,11*RS*)-11-Methoxy-1,2,6-trimethyl-8-phenylthiotricyclo[5.3.1.$0^{2,6}$]undecan-9-ol (8) $LiAlH_4$ (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 ($CHCl_3$): 3500, 1650, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91, 1.03 and 1.16 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.2—2.7 (8H, m), 2.41 (1H, d, J=3 Hz, 7-H), 2.87 (1H, br s, OH), 3.16 (1H, s, 11-H), 3.23 (3H, s, OMe), 3.53 (1H, dd, J=7, 3 Hz, 8-H), 3.97 (1H, m, 9-H), 7.1—7.5 (5H, m, aromatic H). MS m/z: 346 (M^+, 100), 149 (99). High MS: 346.1959 (M^+, Calcd for $C_{21}H_{30}O_2S$: 346.1964).

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-11-Methoxy-1,2,6-trimethyl-8-phenylthiotricyclo[5.3.1.$0^{2,6}$]undec-8-ene (9) Thionyl 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 ($CHCl_3$): 3020, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97, 0.98, 1.05 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.85—2.0 (6H, m), 2.18 (1H, s, 7-H), 2.09 and 2.31 (each 1H, dd, J=19, 3 Hz, 10-H), 3.14 (3H, s, OMe), 3.48 (1H, s, 11-H), 5.45 (1H, t, J=3 Hz, 9-H), 6.9—7.5 (5H, m, aromatic H). MS m/z: 328 (M^+, 23), 219 (44), 57 (100). High MS: 328.1849 (M^+, Calcd for $C_{21}H_{28}OS$: 328.1859).

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-11-Methoxy-1,2,6-trimethyltricyclo-[5.3.1.$0^{2,6}$]undecan-8-one (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 $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (30 : 1 then 20 : 1) to afford **10** (62 mg, 96%) as a colorless powder. IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08, 1.09 and 1.18 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.0—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 $C_{15}H_{24}O_2$: 236.1774).

(±)-*O*-Methylgymnomitrol (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 CH_2Cl_2, 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 1 N 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 ($CHCl_3$): 3080, 1650, 895 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92, 1.03 and 1.13 (each 3H, s, 1-Me, 2-Me and 6-Me), 0.8—2.4 (10H, m), 2.52 (1H, s, 7-H), 3.16 (1H, s, 11-H), 3.25 (3H, s, OMe), 4.63 and 4.66 (each 1H, s, =CH$_2$). MS m/z: 234 (M^+, 27), 219 (28), 58 (100). High MS: 234.1992 (M^+, Calcd for $C_{16}H_{26}O$: 234.1984).

(±)-Isogymnomitrol (1b) Boron tribromide (1 M solution in CH_2Cl_2, 0.04 ml, 0.004 mmol) was added at 0 °C to a solution of **1c** (1.6 mg, 0.0068 mmol) in a mixture of CH_2Cl_2 (0.2 ml) and an ether solution (0.3 ml) of 15-crown-5 (19.8 mg, 0.09 mmol) which had been saturated with NaI. The whole was stirred for 15 h at room temperature. After being neutralized with saturated $NaHCO_3$ solution, the reaction mixture was extracted with chloroform (5 ml × 3) and the combined extracts were washed with saturated sodium thiosulfate solution, water, and brine, dried, and evaporated. The residue was chromatographed on silica gel with ether–hexane (1 : 10) to give **1b** (1.5 mg, 100%) as a colorless amorphous powder (lit.[2b] mp 82—84 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.98, 1.05 and 1.21 (each 3H, s, 1-Me, 2-Me and 6-Me), 1.66 (3H, d, J=1.3 Hz, 8-Me), 1.80 (1H, s, 7-H), 4.01 (1H, s, 11-H), 5.07 (1H, br s, 9-H). MS m/z: 220 (M^+, 1.0), 167 (41), 149 (100). High MS: 220.1823 (M^+, Calcd for $C_{15}H_{24}O$: 220.1825).

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