[Chem. Pharm. Bull. 26(9)2805—2810(1978)]

UDC 547.918.02 : 581.192

Studies on the Constituents of Aceraceae Plants. II.[1] Structure of Aceroside I, a Glucoside of a Novel Cyclic Diarylheptanoid from *Acer nikoense* Maxim.[2]

Masahiro Nagai, Masayoshi Kubo, Masao Fujita, Takao Inoue,[3a] and Mitsuyoshi Matsuo[3b]

Hoshi College of Pharmacy[3a] and Tokyo Metropolitan Institute of Gerontology[3b]

(Received March 18, 1978)

The structure of aceroside I, $C_{25}H_{32}O_8$, mp 170—171° (acetone), $[\alpha]_D^{20}$ −7.7°, which was isolated from the stem bark of *Acer nikoense* Maxim. (Aceraceae), was established to be acerogenin A β-D-glucopyranoside represented by formula **1**. Acerogenin A, $C_{19}H_{22}O_3$, mp 151—152°, $[\alpha]_D^{20}$ +57.3°, was concluded to be a *m*-, *p'*-bridged diphenyl ether type diarylheptanoid (**2**) on the basis of chemical and spectroscopic (especially NMR) evidences. The stereostructure of **2** was determined by derivation of acerogenin A (**2**) into (*S*)-1-(*p*-hydroxyphenyl)-7-(*p*-methoxyphenyl)-heptan-3-ol. Acerogenin A (**2**) is the first example of a novel type of diarylheptanoid—20-oxa-[7,1]-metapara-cyclophane.

Keywords——*Acer nikoense*; Aceraceae; aceroside I; acerogenin A; diarylheptanoid glucoside; diphenyl ether; [7,1]-cyclophane; NMR

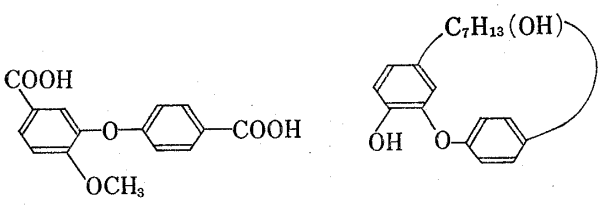
Previously we reported the isolation and characterization of several compounds including two new glycosides designated as epirhododendrin and aceroside I from the leaves and the stem bark of *Acer nikoense* Maxim. (Aceraceae), which has been used as a folk medicine in Japan. The structure of epirhododendrin has been elucidated to be (*S*)-4-(*p*-hydroxyphenyl)-butan-2-ol 2-β-D-glucopyranoside. This report deals with the detail of structure elucidation of aceroside I, a glucoside of a novel cyclic diarylheptanoid isolated from the stem bark.

Aceroside I (**1**) has a molecular formula $C_{25}H_{32}O_8$, mp 170—171°, and $[\alpha]_D^{20}$ −7.7°. On acid hydrolysis, it was split into glucose and an aglycone named acerogenin A (**2**), $C_{19}H_{22}O_3$, mp 151—152°, $[\alpha]_D^{20}$ +57.3°. This fact indicated that aceroside I (**1**) is a monoglucoside of acerogenin A (**2**). The genin (**2**) was detected in an ether-soluble fraction of methanolic extract of the plant bark.[1]

Acerogenin A (**2**) showed hydroxy and aromatic ring absorptions in its infrared (IR) spectrum. It has an ultraviolet (UV) absorption maximum at 278 nm (ε=2390), and the maximum exhibited a bathochromic shift on addition of alkali. In carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of acerogenin A (**2**), twelve sp^2 and seven sp^3 carbon signals were observed. The sp^2 carbon signals comprised seven doublets and five singlets—three (at δ_C 145.1, 150.7 and 156.6 ppm) out of these singlets are probably assignable to carbons bearing an oxygen atom on each of them. The sp^3 carbons were ascribable to a methine bound to an oxygen function and six methylene groups. Acerogenin A (**2**) yielded a diacetate (**3**) on acetylation, and a monomethyl ether (**4**) on methylation with diazomethane. The methyl ether (**4**) afforded an optically inactive ketone (**5**) on oxidation with Jones' reagent. Thus the presence of a phenolic and a secondary alcoholic hydroxyls was concluded in the molecule (**2**).

1) Part I: T. Inoue, Y. Ishidate, M. Fujita, M. Kubo, M. Fukushima, and M. Nagai, *Yakugaku Zasshi*, **98**, 41 (1978).
2) A part of this study was reported briefly in *Chem. Commun.*, **1976**, 338 by M. Nagai, M. Kubo, M. Fujita, T. Inoue, and M. Matsuo.
3) Location: *a) Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan; b) Sakaecho 35-2, Itabashi-ku, Tokyo 173, Japan.*

On further oxidation with permanganate, the ketone (**5**) yielded a dicarboxylic acid, mp 298—300°, which was directly identified as 3-carboxy-6-methoxyphenyl-4-carboxyphenyl ether (**6**).[4] This proves not only the presence of a diphenyl ether structure in the molecule (**2**), but also the location of the substituents on the aromatic rings. The diphenyl ether structure accounts well for the sp^2 carbon signals observed in the ^{13}C-NMR spectrum of **2** (*vide supra*).



6 **A**

Chart 1

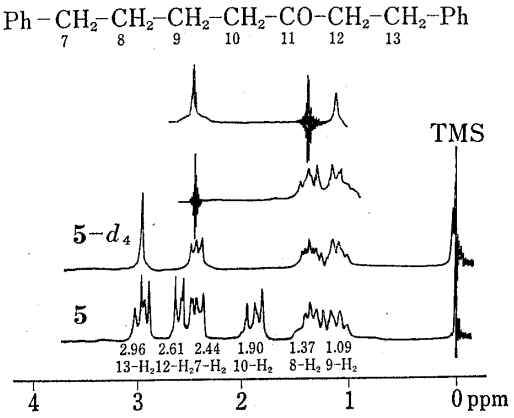


Fig. 1. ^{1}H-NMR Spectra of Ketone (**5**) and 10, 12-Tetradeuteriated Ketone (**5**-d_4)

These data led to the structure (**A**) in Chart 1 for acerogenin A (**2**), since **2** must have a seven-carbon bridge composed of six methylenes and one secondary carbinyl carbon across the *m*- and *p'*-positions of a diphenyl ether.

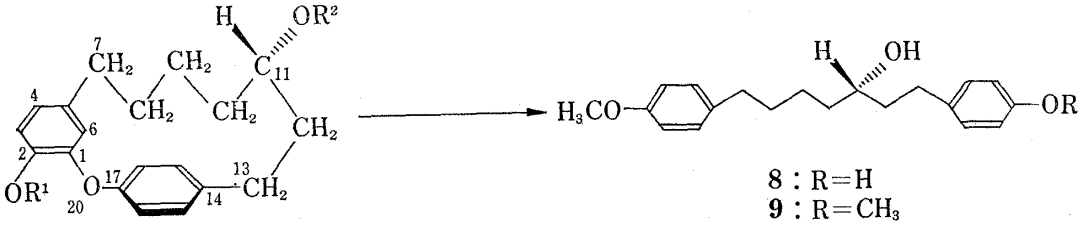
In proton nuclear magnetic resonance (^{1}H-NMR) spectrum, the ketone (**5**) showed an AA'BB' quartet centered at δ_H 7.11 ppm (J=9 Hz) [1,4-disubstituted benzene], an ABX pattern at δ_H 5.65 ppm (6-H, d, J=2 Hz), 6.63 ppm (4-H, d-d, J=2 and 8 Hz), and 6.82 ppm (3-H, d, J=8 Hz) [1,2,5-trisubstituted benzene], and six two-proton multiplets in region δ_H 1—3 ppm. The 1—3 ppm region of the spectrum of **5** and that of a tetradeuteriated ketone (**5**-d_4) prepared by treatment of **5** with sodium methoxide in methanol-d_1 are shown in Fig. 1. Two multiplets observed at δ_H 1.90 and 2.61 ppm in **5** disappeared in the case of **5**-d_4, and they are ascribable to methylenes α to the carbonyl function. A multiplet at δ_H 2.96 ppm in **5** became a broad singlet in **5**-d_4. From this ^{1}H-NMR data the multiplets at δ_H 2.61 and 2.96 ppm are coupled with each other and not with any other proton. In other words, the seven-carbon chain of **5** is separated by the ketonic carbon into adjacent two methylenes and linearly arranged four methylenes. In nuclear magnetic double resonance (NMDR) experiments on **5**-d_4, two multiplets at δ_H 1.09 and 2.44 ppm changed into two broad singlets upon irradiation of a multiplet at δ_H 1.37 ppm, while the two multiplets in high field became a symmetric four-proton multiplet upon irradiation of the methylene at δ_H 2.44 ppm which is assignable to a benzylic methylene from its chemical shift. These NMR experiments permitted us to assign all the methylene signals of the ketone (**5**) as shown in Fig. 1.

However, two alternative structures **5** and **B** are still possible for the ketone (**5**). In NMDR experiments on **5**, irradiation on 7-H_2, 9-H_2 and 13-H_2 resulted in increase of signal intensity of 4-H (6.63 ppm) by 11%, 6-H (5.65 ppm) by 13%, and 15, 19-H_2 (7.20 ppm) by 12%, respectively. These nuclear Overhauser effect (NOE) showed that C-6 and C-9 protons as well as C-4 and C-7 protons are sterically close to each other. This finding indicated that the ketone has structure **5**, because the alternative structure **B** cannot explain the NOE.

4) E. Fujita and T. Tomimatsu, *Yakugaku Zasshi*, **79**, 1256 (1959).

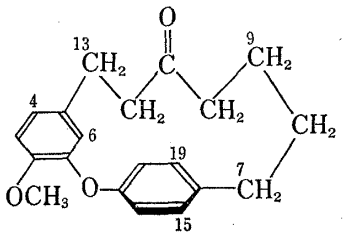
In order to confirm the assignment of structure **2**, including its configuration at C-11, the diphenyl ether linkage was reductively cleaved. Sowa, *et al.*[5] reported a reaction and its mechanism to cleave diphenyl ethers with alkali metal in liquid ammonia. Tomita and his colleagues[6] applied this reaction to bis-coculaurine alkaloids in good results, and Cannon, *et al.*[7] employed the reaction on the way to structure determination of robustol, a macrocyclic phenol. We first took the methyl ether (**4**) as a starting material for the cleavage reaction but obtained a complex mixture of products. Secondly the tetrahydropyranyl ether (**7**) of **4** was cleaved with lithium in liquid ammonia. The phenol (**8**), mp 80.5—81.5°, $[\alpha]_D^{20}$ −7.5°, obtained after removal of the tetrahydropyranyl group by acid treatment, was identified with an authentic sample of (−)-O-methylcentrolobol [=(*S*)-1-(*p*-hydroxyphenyl)-7-(*p*-methoxyphenyl)-heptan-3-ol].[8] Physico-chemical data of its methyl ether (**9**) also showed a good agreement with those reported on (−)-di-O-methylcentrolobol.

These findings described above established structure **2** for acerogenin A, a novel cyclic diarylheptanoid. The 6-H signals in compounds (**2**—**5**) were observed at abnormally high magnetic field, because this proton is located above the plane of the other benzene ring and thus is subject to shielding effect of the ring current.[9] A Dreiding model of **5** showed that the two benzene rings are approximately perpendicular to each other.



8 : R=H
9 : R=CH_3

1: R^1=β-D-glucopyranosyl, R^2=H
2: R^1=R^2=H, 11(*S*)
3: R^1=R^2=$COCH_3$
4: R^1=CH_3, R^2=H
5: R^1=CH_3, 11-oxo
7: R^1=CH_3, R^2=tetrahydropyranyl



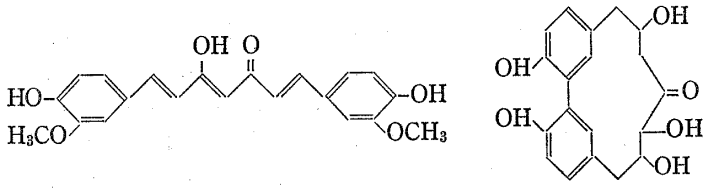
B

Chart 2

Aceroside I (**1**), a monoglucoside of acerogenin A (**2**), has a UV maximum at 265 nm, and the maximum never shifted at all on addition of alkali. This indicated that the glucosyl of **1** is linked to the phenolic hydroxyl but not to the alcoholic one of acerogenin A (**2**). The permethylate (**10**) of aceroside I (**1**), prepared by Hakomori's methylation procedure,[10] yielded methyl 2,3,4,6-tetra-O-methyl-α-, and -β-D-glucopyranoside on methanolysis. Enzymatic hydrolysis of **1** using emulsin furnished its aglycone (**2**). These data indicated that aceroside I (**1**) is represented as acerogenin A 2-β-D-glucopyranoside.

5) A.L. Kranzfelder, J.J. Verbanc, and F.J. Sowa, *J. Am. Chem. Soc.*, **59**, 1488 (1937).
6) M. Tomita, Y. Inubushi, and H. Niwa, *Yakugaku Zasshi*, **72**, 206 (1952).
7) J.R. Cannon, P.W. Chow, M.W. Fuller, B.H. Hamilton, B.W. Metcalf, and A.J. Power, *Aust. J. Chem.*, **26**, 2257 (1973).
8) A.A. Craveiro, A.C. Prado, O.R. Gottlieb, and P.C. Welerson de Albuquerque, *Phytochemistry*, **9**, 1869 (1970).
9) D.G. Farnum and C.F. Wilcox, *J. Am. Chem. Soc.*, **89**, 5379 (1967).
10) S. Hakomori, *J. Biochem.*, **55**, 205 (1964).

Acerogenin A (2) is the first example of a novel type of diarylheptanoid— a diphenyl ether derivative. After our preliminary communication on the structure of acerogenin A,[2] Malterud, *et al.*[11] isolated galeon and hydroxygaleon from *Myrica gale* L. These two compounds are further examples of this type of diarylheptanoid. Two other types of diarylheptanoid have been known so far—one, linear type such as curcumin[12] and the other, biphenyl type such as asadanin.[13] Whiting and his co-workers studied on the biosynthesis of curcumin,[14] but the general biosynthetic route of diarylheptanoid has not been established yet. Oxidative coupling of a suitable diarylheptanoid precursor may explain the biosynthesis of a *m*-, *m'*-bridged biphenyl type and *m*-, *p'*-bridged diphenyl ether type diarylheptanoids (Fig. 2). Anyway, a series of diarylheptanoids including biphenyl and diphenyl ether types, might be interesting from biosynthetic consideration.



curcumin asadanin

Chart 3

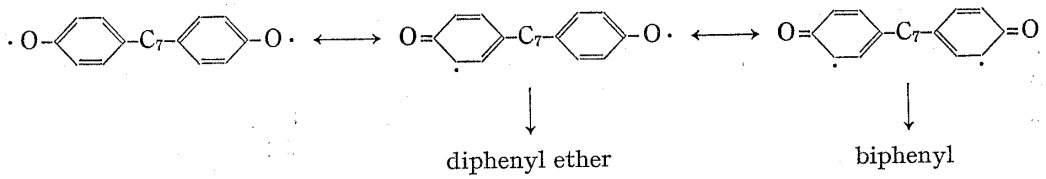


Fig. 2. Hypothetic Scheme of Oxidative Coupling of Diarylheptanoid

Experimental

All melting points were taken on a Shimadzu micro melting point apparatus and uncorrected. IR spectra were obtained with a Shimadzu-IR-400 and a Hitachi-IR-215 spectrometer. Mass spectrum (MS) was measured with a Hitachi RSM-4. Gas–liquid chromatography (GLC) was run on a Shimadzu GC-4A with a hydrogen flame ionization detector. UV spectra were recorded on a Shimadzu UV-200. Circular dichroism (CD) spectra were taken with a JASCO J-40A. Thin–layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (Merck) and detection was carried out by UV-254 and by spraying 10% H_2SO_4 followed by heating. NMR spectra were measured with a Varian XL-100 and a JEOL FX-100 using tetramethylsilane (TMS) as an internal standard.

Aceroside I (1)——Colorless needles from acetone, mp 170—171°, $[\alpha]_D^{20}$ −7.65° (c=1.0, EtOH). *Anal.* Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00. Found: C, 65.18; H, 7.03. IR ν_{max}^{KBr} cm^{-1}: 3350, 2950, 2850, 1584, 1510, 1500. UV λ_{max}^{EtOH} nm (log ε); 265 (3.374), 270 (inf.). λ_{min}^{EtOH} 240. UV $\lambda_{max}^{EtOH+NaOH}$ unchanged. TLC: solvent, $CHCl_3$–MeOH (5:1); *Rf* 0.57.

Hydrolysis of 1 with 5% HCl in Aqueous MeOH——To a solution of **1** (10 mg) in MeOH (3 ml) was added 10% HCl (3 ml) and the mixture was refluxed for 2 hr. After cooling the reaction mixture was diluted with water (20 ml) and extracted with ether and then with EtOAc. The organic layers were combined and evaporated *in vacuo*. The residue was purified by recrystallization from MeOH to give acerogenin A (2) as colorless needles, mp 151—152°, $[\alpha]_D^{20}$ +57.3° (c=0.8, EtOH). *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.50; H, 7.31. MS *m/e*: 298 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3460, 3170, 2935, 2853, 1593, 1517, 1500. UV λ_{max}^{EtOH} nm (log ε): 278 (3.378), 290 (inf.). UV $\lambda_{max}^{EtOH+NaOH}$ nm: 285—300 (bathochromic shift). ^{1}H-NMR $\delta_{ppm}^{C_5D_5N}$: 0.68—1.12 (9-H_2), 1.12—1.48 (8-H_2), 1.48—1.84 (12-H_2), 1.84—2.24 (10-H_2), 2.24—2.52 (7-H_2), 2.52—2.99 (13-H_2), 3.24—3.56 (11-H) (all m); 5.84 (6-H, d, J=2 Hz), 6.64 (4-H, d-d, J=2 and 8 Hz), 6.93 (3-H, d, J=

11) K.E. Malterud, T. Anthonsen, and J. Hjortås, *Tetrahedron Lett.*, **1976**, 3069.
12) J. Milobedzka, St. v. Kostanecki, and V. Lampe, *Chem. Ber.*, **43**, 2163 (1910).
13) M. Yasue, *J. Japan Wood Res. Soc.*, **11**, 146 (1965); *idem, ibid.*, **11**, 153 (1965).
14) P.J. Roughley and D.A. Whiting, *J. Chem. Soc. Perkin I*, **1973**, 2379.

8 Hz) (1,2,5-trisubstituted benzene); 7.06—7.22 (16,18-H and 15,19-H, complex multiplet, aromatic protons). ^{13}C-NMR $\delta_{ppm}^{C_5D_5N}$: 25.3, 28.5, 32.0, 32.7, 39.7, 40.9 (all t) (6×-$\underline{C}H_2$-); 69.8 (d, -$\underline{C}$H(OH)-); 116.7, 117.1, 122.5, 123.0, 124.2, 130.3, 131.8 (all d) (7×Ar$\underline{C}$H); 132.8, 139.7 (all s) (2×Ar$\underline{C}$-C); 145.1, 150.7, 156.6 (all s) (3×Ar$\underline{C}$-O). The aqueous layer was neutralized with Ag_2CO_3 and concentrated *in vacuo*. Glucose was detected in the residue by TLC. TLC: solvent, BuOH–acetone–H_2O (4: 5: 1); *Rf* 0.49 (glucose).

Hydrolysis of 1 with Emulsin——To the solution of **1** (30 mg) in 1/10 N AcOH–1/10 M AcONa buffer (pH 5.0, 10 ml) was added emulsin (1 mg), and the mixture was allowed to stand for 3 days at 30°. The reaction mixture was extracted repeatedly with ether and the organic layers were combined, washed with water, and then evaporated. The residue was examined on TLC. TLC: solvent, C_6H_6–EtOAc (4: 1); *Rf* 0.42 (acerogenin A). The aqueous layer was concentrated under reduced pressure. The residue was examined on PPC. PPC: paper, Toyo Roshi No. 50; solvent, BuOH–AcOH–H_2O (6: 1: 2); coloring reagent, aniline hydrogen phthalate; *Rf* 0.22 (glucose).

Diacetate (3)——**2** (150 mg) was dissolved in a mixture of pyridine (0.5 ml) and Ac_2O (0.5 ml), and the solution was allowed to stand for a day at room temperature. The reaction mixture was worked up in usual way and the product was purified by recrystallization from MeOH to give **3** as colorless needles (169 mg), mp 116—118°, $[\alpha]_D^{20}$ +21.7° (c=0.8, EtOH). *Anal.* Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.36; H, 7.04. MS *m/e*: 382 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2920, 2858, 1762, 1724, 1590, 1510, 1502. ^{1}H-NMR $\delta_{ppm}^{CCl_4}$: 0.95 (2×-$\underline{CH_2}$-, m), 1.30 (-$\underline{CH_2}$-, m), 1.72 (-$\underline{CH_2}$-, m), 1.97 (-OCO$\underline{CH_3}$, s), 2.32 (-OCO$\underline{CH_3}$, s), 2.52 (-$\underline{CH_2}$-, m), 2.84 (-$\underline{CH_2}$-, m), 4.26 (AcO-$\underline{CH}$, m); 5.69 (6-H, d, J=2 Hz), 6.54 (4-H, d-d, J=2 and 8 Hz), 6.79 (3-H, d, J=8 Hz), 6.98—7.32 (16,18-H and 15,19-H, complex multiplet, aromatic protons).

Methyl Ether (4)——**2** (100 mg) in a mixture of ether (15 ml) and MeOH (2 ml) was treated at 0° with an excess of diazomethane in ether for several days. The solvent was evaporated off and the residue was purified by recrystallization from MeOH to give **4** as colorless needles (105 mg), mp 124—125°, $[\alpha]_D^{20}$ +36.1° (c=0.9, EtOH). *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.82; H, 7.66. MS *m/e*: 312 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3500, 3415, 2920, 2852, 1512, 1500. CD (c=3.3×10^{-3}, MeOH) $[\theta]^{23}$ (nm): −7.0×10^3 (283), +3.24×10^4 (240), −1.24×10^4 (219). ^{1}H-NMR $\delta_{ppm}^{CDCl_3}$: 1.02 (9-H_2 and 8-H_2), 1.38 (10-H_2), 1.46—2.04 (12-H_2), 2.44 (7-H_2), 2.52—3.14 (13-H_2), 3.28 (11-H) (all m); 3.93 (-O-$\underline{CH_3}$, s); 5.65 (6-H, d, J=2 Hz), 6.63 (4-H, d-d, J=2 and 8 Hz), 6.82 (3-H, d, J=8 Hz) (1,2,5-trisubstituted benzene); 6.88—7.28 (16,18-H and 15,19-H, complex multiplet, aromatic protons).

Ketone (5)——To the solution of **4** (100 mg) in acetone was added Jones' reagent until an orange color persisted and the mixture was permitted to stand for 10 min at room temperature. The reaction mixture was poured into water. The crude crystals were obtained by salting-out technique. The precipitates were collected by filtration, washed with water, and purified by recrystallization from MeOH to give **5** as colorless needles (92 mg), mp 124—125°, $[\alpha]_D^{20}$ 0° (c=1.0, EtOH). *Anal.* Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.20; H, 7.16. MS *m/e*: 310 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2948, 2920, 2841, 1693, 1607, 1598, 1573, 1510, 1500. ^{1}H-NMR $\delta_{ppm}^{CDCl_3}$: 3.93 (-O-$\underline{CH_3}$, s); 7.01 (16 and 18-H), 7.20 (15 and 19-H) (AA'BB' q, J=9 Hz, 1,4-disubstituted benzene) (See text for other signals).

Oxidation of 5 with $KMnO_4$——To a solution of **5** (100 mg) in pyridine (10 ml) were added 10% NaOH (7.5 ml) and $KMnO_4$ (950 mg) dissolved in water (7.5 ml). The mixture was refluxed for 40 min. An excess of $KMnO_4$ was decomposed with MeOH. After the reaction mixture was acidified with dil. HCl, a saturated solution of $NaHSO_3$ was added to it. The resulting precipitates were filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dil. HCl and extracted repeatedly with ether. The combined ether layers were washed with water and then extracted with aq. $NaHCO_3$. The aqueous layer was acidified with dil. HCl and extracted repeatedly with ether. The ethereal extract was dried, concentrated to a small volume and treated with diazomethane. After evaporation of solvent, the residue was purified by column chromatography on alumina and on silica gel. Elution with benzene afforded colorless needles (30 mg) (=dimethyl ether of **6**), mp 97—98° (from MeOH) (lit. 97—98°).[15] The dimethyl ether (20 mg) was refluxed with ethanolic 5% KOH for 1 hr. The reaction mixture was acidified with dil. HCl and concentrated to a small volume. The resulting precipitates were collected and recrystallized from aq. EtOH to give colorless crystalline powders (**6**) (15 mg), mp 301—302° (lit. 297°).[4] This was identified with an authentic sample of 3-carboxy-6-methoxyphenyl-4-carboxyphenyl ether by the comparison of IR, TLC and mixed fusion.

10,12-Tetradeuteriated Ketone (5-d_4)——To a solution of **5** (50 mg) in methanol-d_1 (5 ml) was added a solution of sodium methoxide (prepared from Na (50 mg) and CH_3OD (0.5 ml)) (0.5 ml) and the mixture was allowed to stand for 6 hr at room temperature. The mixture was concentrated *in vacuo* to a half of the original volume. The resulting precipitates were collected by filtration, washed with D_2O, and recrystallized from methanol-d_1 to give 5-d_4 as colorless needles (39 mg), mp 124—126°. MS *m/e*: 314 (M^+). ^{1}H-NMR $\delta_{ppm}^{CDCl_3}$: 3.93 (-O-$\underline{CH_3}$, s); 5.65 (6-H, d, J=2 Hz), 6.63 (4-H, d-d, J=2 and 8 Hz), 6.82 (3-H, d, J=8 Hz) (1,2,5-trisubstituted benzene); 7.01 (16 and 18-H), 7.20 (15 and 19-H) (AA'BB' q, J=9 Hz, 1,4-disubstituted benzene) (See text for other signals).

15) E. Späth and J. Pikl, *Chem. Ber.*, **62**, 2251 (1929).

Reduction of 4 with Lithium in Liquid Ammonia——A slurry of **4** (890 mg) and dihydropyran (4.5 ml) was treated with two drops of conc. HCl and shaken vigorously for 5 min. After standing for 3 hr at room temperature, a few pellets of sodium hydroxide was added to the reaction mixture to destroy the acid, and the excess of dihydropyran was evaporated under reduced pressure. The residue was extracted with ether, and the ethereal extract was washed with water, then dried and evaporated to give tetrahydropyranyl ether (**7**). A solution of **7** in dry ether (20 ml) was added under stirring to liquid ammonia (200 ml) at −80°. Lithium (2 g) was added in portions to this solution and the mixture was stirred for 6 hr. The reaction mixture was allowed to stand for 12 hr at room temperature to remove NH_3. Water was added cautiously to the residue, which was extracted with ether. The ether layer was washed with water, then dried, and evaporated to give diarylheptanol pyranyl ether. A solution of diarylheptanol ether and *p*-toluenesulfonic acid (100 mg) in EtOH (10 ml) was refluxed for 1 hr, concentrated to two thirds of the original volume *in vacuo*, diluted with water, and then extracted with ether. The extract was washed with water, then dried, and evaporated to dryness. The residue was purified by silica gel chromatography using C_6H_6–EtOAc (9:1) as solvent. Repeated recrystallization from ether–hexane (3:1) afforded a diarylheptanol (**8**), colorless needles (142 mg), which was found to be identical with (−)-O-methylcentrolobol [(*S*)-1-(*p*-hydroxyphenyl)-7-(*p*-methoxyphenyl)-heptan-3-ol] by comparison of $[\alpha]_D$, TLC, GLC, IR spectra and a mixed fusion. mp 80.5—81.5° (lit. 73—75°).[8] $[\alpha]_D^{20}$ −7.5° (c=1.7, MeOH). MS *m/e*: 314 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3400, 3250, 2928, 2900, 2848, 1601, 1510. TLC: i) solvent, C_6H_6–EtOAc (5:1); *Rf* 0.3. ii) solvent, $CHCl_3$–dioxane–acetone–NH_4OH (50:4:4:1); *Rf* 0.45. GLC: 1.5% OV-17 on Shimalite W (80—100 mesh), 4 mm×1.5 m column; column temp. 227°; carrier gas N_2 (1 kg/cm²); t_R (min) 28.2. ^{1}H-NMR $\delta_{ppm}^{CDCl_3}$: 1.20—1.83 (4×–C<u>H</u>$_2$–, m), 2.13—2.79 (2×Ar–C<u>H</u>$_2$–, –CH(O<u>H</u>)– and ArO<u>H</u>, m), 3.56 (–C<u>H</u>(OH)–, m), 3.71 (Ar–O–C<u>H</u>$_3$, s), 6.54—6.97 (2 AA′BB′ systems of aromatic protons, m).

Methylation of 8——To the solution of **8** (40 mg) in 10% NaOH was added an excess amount of dimethyl sulfate. The solution was stirred for 5 min and the resulting precipitates were extracted with ether. The extract was dried and concentrated. The residue was recrystallized from ether–hexane (3:1) to give **9** as colorless needles (39 mg), mp 56—58°, $[\alpha]_D^{25}$ −7.2° (c=2.4, EtOH). MS *m/e*: 328 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3325, 3240, 2940, 2855, 1615, 1587, 1518. TLC: solvent, C_6H_6–EtOAc (6:1); *Rf* 0.41. GLC: column temp. 225°; carrier gas N_2 (1.3 kg/cm²); t_R (min) 22.2. ^{1}H-NMR $\delta_{max}^{CDCl_3}$: 1.20—1.82 (4×–C<u>H</u>$_2$–, m), 2.56 (2×Ar–C<u>H</u>$_2$–, m) 3.58 (–C<u>H</u>(OH)–, m), 3.78 (2×Ar–O–C<u>H</u>$_3$, s), 6.77—7.12 (2 AA′BB′ systems of aromatic protons, s).

Permethylation of 1——According to the Hakomori's method, a mixture of NaH (1 g) and dimethylsulfoxide (DMSO 10 ml) was stirred at 65° for 45 min under N_2 gas flow. To this reagent was added **1** (1 g) in DMSO (10 ml) and the mixture was stirred for 1 hr at room temperature under N_2 gas flow. CH_3I (8 ml) was added to it and the reaction mixture was allowed to stand at room temperature for 2 hr with stirring. After dilution with water, the mixture was extracted with $CHCl_3$ and the organic layer was washed with water, dried and concentrated *in vacuo*. The residue was repeatedly methylated under the same condition until the IR spectrum of this product had no absorption in region 3200—3700 cm^{-1}. The final product was extracted with ether–hexane (1:1) mixture, and the extract was washed with water, dried and evaporated to afford a syrup (**10**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2920, 2850, 1720, 1600, 1580, 1500. TLC: solvent, C_6H_6–EtOAc (6:1); *Rf* 0.37.

Methanolysis of Permethylate (10)——A solution of the permethylate in methanolic 10% HCl (30 ml) was refluxed for 2 hr. The reaction mixture was neutralized with Ag_2CO_3 and filtered. The filtrate was evaporated *in vacuo* to afford a syrup, which was separated on preparative TLC (solvent, C_6H_6–acetone (4:1)). The each O-methylsugar was identified with the authentic sample on TLC and GLC. TLC: solvent, C_6H_6–acetone (4:1); *Rf* 0.61 (methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside), 0.47 (methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside). GLC: column temp. 125°; carrier gas N_2 (1 kg/cm²); t_R (min) 5.95 (methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside), 8.75 (methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside).

Acknowledgement The authors express their gratitude to Prof. T. Tomimatsu, Pharmaceutical Faculty, University of Tokushima, for his kind supply of 3-carboxy-6-methoxyphenyl-4-carboxyphenyl ether. Thanks are also due to Prof. A.A. Craveiro, Dept. Quim. Organica, Universidade Federal do Ceará, Brasil, for a gift of (−)-O-methylcentrolobol. A part of this work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, to which author's thanks are also due.