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# Studies on the Constituents of Aceraceae Plants. VI.[1] Revised Stereochemistry of (−)-Centrolobol, and New Glycosides from *Acer nikoense*

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Two diarylheptanoid glycosides, named aceroside VII (**8**), $C_{25}H_{34}O_8$, mp 144—145 °C, $[\alpha]_D^{15}$ −28.4°, and aceroside VIII (**9**), $C_{30}H_{42}O_{12}$, $[\alpha]_D^{15}$ −64.8° were isolated from the stem bark of *Acer nikoense* MAXIM. (Aceraceae). On acid hydrolysis **8** yielded (−)-centrolobol (**10**) and glucose, while **9**, on partial hydrolysis, gave **8** and apiose. Acerosides VII (**8**) and VIII (**9**) were determined to be the 3-*O*-*β*-D-glucopyranoside and the 3-*O*-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside of (−)-centrolobol (**10**), respectively, on the basis of carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) spectral analyses and additional chemical data.

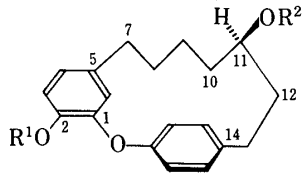
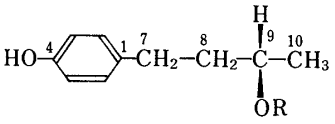
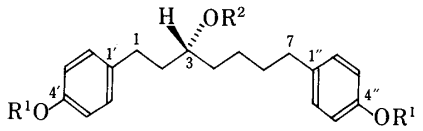
The absolute configuration *S* for (−)-centrolobol (**10**) has been claimed, but the authors propose its revision to *R*(−) on the basis of Brewster's empirical rule on the correlation between absolute configuration and optical rotation. The stereochemistries of some compounds related to **10** such as acerogenin A (**1**) and (−)-centrolobin should also be revised. At the same time, partial revision of the $^{13}$C-NMR signal assignments for acerosides III (**3**) and VI (**4**) is also necessary.

**Keywords**——*Acer nikoense*; diarylheptanoid; *R*(−)-centrolobol; aceroside (VII, VIII); Brewster's empirical rule; absolute configuration revision

From the stem bark of *Acer nikoense* MAXIM., several cyclic diarylheptanoids such as acerogenins A (**1**),[3,4] B,[5] and C,[6] and their glycosides, acerosides I (**2**),[3,4] III (**3**),[1] IV[6] and VI (**4**)[1] have been isolated, along with (+)-rhododendrol (**5**)[3] and its glycosides, epi-rhododendrin (**6**)[3] and apiosylepirhododendrin (**7**)[1] (Chart 1). On further examination of the ethyl acetate solubles from the methanol extract, two new glycosides of a linear diarylheptanoid, named aceroside VII (**8**) and aceroside VIII (**9**), were isolated. This paper deals with structure elucidation of these glycosides and proposes a revision of the absolute configuration of their common aglycone, (−)-centrolobol (**10**), and related compounds.

Aceroside VII (**8**), $C_{25}H_{34}O_8$, was obtained as a white crystalline powder, mp 144—145 °C, $[\alpha]_D^{15}$ −28.4°, and gave positive coloration (blue) with ferric chloride reagent. It has ultraviolet (UV) absorption maxima at 224 and 279 nm, which exhibited bathochromic shifts on addition of alkali. In the infrared (IR) spectrum, it showed broad absorptions due to hydroxyl groups at 3100—3630 $cm^{-1}$ and aromatic ring absorptions at 1610, 1598 and 1515 $cm^{-1}$. These properties suggested that **8** is a glycoside of a phenolic compound. On hydrolysis with dilute hydrochloric acid, aceroside VII (**8**) afforded an aglycone (**10**) and glucose. The aglycone (**10**), colorless needles, mp 129—130 °C, $[\alpha]_D^{15}$ −10.2°, showed positive coloration (blue) with ferric chloride reagent, and gave a molecular ion at *m/z* 300 corresponding to $C_{19}H_{24}O_3$ in its mass spectrum (MS). On the basis of these data together with other spectrometric evidence, **10** was presumed to be (−)-centrolobol, previously isolated from *Centrolobium robustum* (Leguminosae).[7]

The carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) spectra of aceroside VII (**8**) and

**1**: $R^1=R^2=H$
**2**: $R^1=\beta$-D-glucopyranosyl, $R^2=H$
**3**: $R^1=H$, $R^2=\beta$-D-apiofuranosyl-(1→6)-$\beta$-D-glucopyranosyl
**4**: $R^1=H$, $R^2=\beta$-D-glucopyranosyl
**5**: R=H
**6**: R=$\beta$-D-glucopyranosyl
**7**: R=$\beta$-D-apiofuranosyl-(1→6)-$\beta$-D-glucopyranosyl
**8**: $R^1=H$, $R^2=\beta$-D-glucopyranosyl
**9**: $R^1=H$, $R^2=\beta$-D-apiofuranosyl-(1→6)-$\beta$-D-glucopyranosyl
**10**: $R^1=R^2=H$
**11**: $R^1=CH_3$, $R^2=H$

Chart 1

TABLE I. $^{13}$C-Chemical Shifts ($\delta$ ppm) in $C_5D_5N$

| | Carbon | 9 | 8 | 10 | Carbon | 5 | Carbon | 3 | 4 | 1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Genin | 1′ and 1″ | 133.7 | 133.4 | 133.7 | 1 | 133.3 | 1 | 150.6 | 150.6 | 150.7 |
| | | 133.3 | 133.2 | 133.4 | | | 2 | 145.1 | 145.1 | 145.1 |
| | 2′, 6′ and 2″, 6″ | 130.0 | 129.9 | 129.9 | 2, 6 | 129.7 | 3 | 117.1 | 117.1 | 117.1 |
| | | 129.7 | 129.6 | 129.8 | | | 4 | 122.3 | 122.3 | 122.5 |
| | 3′, 5′ and 3″, 5″ | 116.0 | 116.0 | 116.1 | 3, 5 | 115.9 | 5 | 132.5 | 132.5 | 132.8 |
| | 4′, 4″ | 156.7 | 155.6 | 156.8 | 4 | 156.6 | 6 | 116.7 | 116.5 | 116.7 |
| | 1 | 31.2 | 31.0 | 31.9 | 7 | 31.8 | 7 | 32.2 | 32.0 | 32.0 |
| | 2 | 37.8 | 37.5 | 40.7 | 8 | 42.2 | 8 | 28.2 | 28.3 | 28.5 |
| | 3 | 78.4[a] | 78.3[a] | 70.3 | 9 | 66.3 | 9 | 25.1 | 25.2 | 25.3 |
| | 4 | 34.6 | 34.3 | 38.4 | 10 | 24.2 | 10 | 36.9 | 36.5 | 39.7 |
| | 5 | 25.0 | 24.8 | 26.0 | | | 11 | 78.0 | 77.8[a] | 69.8 |
| | 6 | 32.4 | 32.3 | 32.5 | | | 12 | 39.6 | 39.5 | 40.9 |
| | 7 | 35.2 | 35.2 | 35.5 | | | 13 | 32.2 | 32.3 | 32.7 |
| | | | | | | | 14 | 140.1 | 140.1 | 139.7 |
| | | | | | | | 15, 19 | 130.3 | 130.3 | 130.3 |
| | | | | | | | | 132.5 | 132.5 | 131.8 |
| | | | | | | | 16, 18 | 123.3 | 123.2 | 123.0 |
| | | | | | | | | 124.3 | 124.2 | 124.2 |
| | | | | | | | 17 | 156.6 | 156.5 | 156.6 |
| Glucosyl | 1 | 103.4 | 103.3 | | | | 1 | 103.8 | 103.5 | |
| | 2 | 75.1 | 75.1 | | | | 2 | 74.8 | 74.8 | |
| | 3 | 78.6[a] | 78.4[a] | | | | 3 | 78.7 | 78.2[a] | |
| | 4 | 71.5 | 71.7 | | | | 4 | 71.2 | 71.6 | |
| | 5 | 76.7 | 77.8 | | | | 5 | 76.3 | 77.9[a] | |
| | 6 | 68.5 | 62.8 | | | | 6 | 68.1 | 62.8 | |
| Apiosyl | 1 | 110.8 | | | | | 1 | 110.5 | | |
| | 2 | 77.7 | | | | | 2 | 77.4 | | |
| | 3 | 80.3 | | | | | 3 | 80.1 | | |
| | 4 | 74.9 | | | | | 4 | 74.8 | | |
| | 5 | 65.6 | | | | | 5 | 65.4 | | |

*a*) Assignments in each column may be reversed, but those given are preferred.

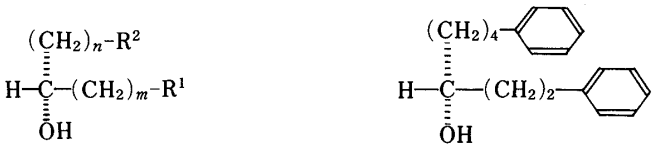
its genin (**10**) in comparison with those of aceroside VI (**4**) and its genin, acerogenin A (**1**) (Table I) revealed that the glucose moiety of **8** is bound to the alcoholic hydroxyl of **10** as the $\beta$-anomer.[8] In order to confirm the structures **8** and **10**, **8** was methylated with diazomethane

and then hydrolyzed with dilute hydrochloric acid. A methylated genin (**11**) was obtained as colorless needles, mp 57—58 °C, $[\alpha]_D^{15}$ −9.1 °, and was identical with an authentic sample of (−)-di-*O*-methylcentrolobol derived from acerogenin A (**1**).[4] On the basis of these results, aceroside VII (**8**) was concluded to be (−)-centrolobol 3-*O*-*β*-D-glucopyranoside (Chart 1).

The other glycoside, aceroside VIII (**9**), was obtained as a colorless film, $[\alpha]_D^{15}$ −64.8 °, and gave positive coloration (blue) with ferric chloride reagent. In the UV spectrum, it showed the same absorption maxima and bathochromic shifts on addition of alkali as aceroside VII (**8**). The $^{13}$C-NMR spectrum of aceroside VIII (**9**) suggested that it is a glycoside of centrolobol and that its sugar moiety is a disaccharide consisting of a pentose and a hexose (Table I). On complete hydrolysis with dilute hydrochloric acid, **9** gave apiose, glucose and centrolobol, while on partial hydrolysis with aq. acetic acid, **9** yielded aceroside VII (**8**) and apiose. In the $^{13}$C-NMR spectrum, the anomeric carbon signal of the apiose residue in **9** appeared at the same chemical shift ($\delta_C$ 110.8) as that in aceroside III (**3**) ($\delta_C$ 110.5), and a signal ascribable to C-6 of the glucose residue in **9** was observed at $\delta_C$ 68.5, almost the same chemical shift as that in aceroside III (**3**) ($\delta_C$ 68.1), which was observed at lower magnetic field by 5.7 ppm[1] than in the case of aceroside VII (**8**) ($\delta_C$ 62.8). On the basis of these results, the structure of aceroside VIII (**9**) was elucidated to be (−)-centrolobol 3-*O*-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside (Chart 1).

Concerning the absolute configuration of (−)-centrolobol (**10**), Craveiro and his coworkers[7] proposed *S* on the basis of the correlation between molecular rotation and absolute configuration developed by Brewster.[9] However, we think that they erroneously applied Brewster's empirical rule, and we would like to revise the configuration to *R* for (−)-centrolobol (**10**) on the basis of the following discussion.

They pointed out that an alcohol of absolute configuration **12** (Chart 2), in which $m-n=2$, should have the molecular rotation of −24 ° according to the empirical rule. This is correct when $m=n=1$, $R^1$ = isopropyl and $R^2$ = methyl, but incorrect in most other cases. According to Brewster, the molecular rotation of **12** can be expressed as a difference of radical rotations, $[M]$ (**12**) $=\Delta M[(CH_2)_n-R^2]-\Delta M[(CH_2)_m-R^1]$, provided only that $R^1$ and $R^2$ do not interact (as by hydrogen bonding). According to Brewster's definition, the radical rotations of $(CH_2)_2$-Ph and $(CH_2)_4$-Ph can be calculated as 43.3 ° and 35.6 ° respectively[9]; thus the calculated molecular rotation of (*S*)-1,7-diphenylheptan-3-ol (**13**) should be +7.7 °. It follows that the enantiomer (**14**) of **13** should have a negative rotation and that centrolobol with negative rotation (**10**) should have *R* configuration because of its structural similarity to **14** (Chart 2).




**12** **14**

Chart 2

Kimura and Yonemitsu[10a] prepared (+)-1,7-diphenylheptan-3-ol without assignment of its absolute configuration, and this structure corresponds to **13** (*S* configuration). Kuroyanagi *et al.*[10d] isolated 1,7-diphenylhept-6-en-3-ol (**15**) from an *Alpinia* plant. Since **15** showed no optical rotation at 589 nm, **15** from the plant seems to be, they suggested, a racemate. But according to Brewster's empirical rule, both enantiomers of **15** have approximately zero rotation, and so **15** with a negligible rotation is not necessarily a racemate.

Acerogenin A (**1**) has been chemically converted into (−)-*O*-methylcentrolobol and (−)-di-*O*-methylcentrolobol (**11**)[4] which were firstly derived from (−)-centrolobin and (−)-

centrolobol (**10**), respectively.[7] Since the absolute configuration of **10** was revised to *R* as discussed above, we have to propose revision of the configuration at C-11 to *R* for acerogenin A (**1**) (Chart 1) and a revised stereochemistry of (2*S*,6*R*)-2-(*p*-methoxyphenyl)-6-[β-(*p*-hydroxyphenyl)-ethyl]-tetrahydropyran for (−)-centrolobin.[11] At the same time, the signal assignments for C-10 and C-12 in the $^{13}$C-NMR spectra of the two glycosides, acerosides III (**3**) and VI (**4**),[1] should be partly revised as listed in Table I, because they were based on the erroneous absolute configuration (11*S*) for **1**. Application of Lindeman–Adams' rule[12] and the glucosidation shifts reported by Tanaka[8a] and Seo *et al.*[8b] in $^{13}$C-NMR spectroscopy to *R*(−)-centrolobol (**10**) and its glycosides (**8** and **9**) in comparison with the spectra of (+)-rhododendrol (**5**), acerosides III (**3**) and VI (**4**)[1] permitted assignment of all the carbon signals in the spectra of the former three compounds (Table I).

Diarylheptanoids have been found in plants belonging to several families, Betulaceae,[13] Zingiberaceae,[10] Myricaceae,[14] Leguminosae,[7] Aceraceae,[1,3-6] and Dioscoreaceae.[15] Their structures are classified into linear, cyclic biphenyl and diphenyl ether types, and the two cyclic types may be formed from the linear type by oxidative phenolic coupling. Thus, co-occurrence of linear and cyclic diphenyl ether types, (−)-centrolobol (**10**) and acerogenin A (**1**) in *Acer nikoense*, is of interest in view of their putative biosynthetic relationship.

## Experimental

All melting points were taken on a Shimadzu micro melting point determination apparatus and are uncorrected. IR spectra were obtained with a Hitachi 260-10 spectrometer, and UV spectra were recorded on a Shimadzu UV 250 double-beam spectrometer. MS were measured with a JEOL JMS-D-300 mass spectrometer. Optical rotations were determined with a JASCO DIP-181 automatic polarimeter in a dm tube. $^1$H- and $^{13}$C-NMR spectra were taken with a JEOL JNM FX-100 spectrometer in pyridine-$d_5$, $CDCl_3$ or $(CD_3)_2CO$ as a solvent and with tetramethylsilane as an internal standard. Chemical shifts are given on the δ scale (ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet. Thin layer chromatography (TLC) was performed on Kieselgel 60 $F_{254}$ precoated plates (Merck), and detection was carried out by UV irradiation (254 nm) and by spraying 10% $H_2SO_4$ followed by heating. TLC for sugars was run on Cellulose $F_{254}$ precoated plates (Merck) and spots were visualized by spraying aniline hydrogen phthalate followed by heating at 105 °C for 5—10 min. A mixture of 1% $FeCl_3$ and 1% $K_3Fe(CN)_6$ (1 : 1) was used as the $FeCl_3$ reagent.

**Materials**——The EtOAc extract described in the experimental section of the previous paper[6] was used as the source material in this paper.

**Isolation of Aceroside VII (8)**——The EtOAc extract was separated by chromatography on silica gel with $CHCl_3$–MeOH (9 : 1) to give three fractions (fr. A—C): Fraction A containing mainly aceroside I (**2**), fr. B containing mainly aceroside III (**3**), and fr. C containing more polar compounds. Aceroside I (**2**) was separated from fr. A by crystallization from acetone, while aceroside III (**3**) was isolated from fr. B by crystallization from MeOH. The two mother liquors were combined and concentrated *in vacuo*, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH–$H_2O$ (200 : 55 : 7) to afford fractions containing aceroside VII (**8**). The fractions were combined, concentrated, and then rechromatographed on silica gel using EtOAc to yield aceroside VII (**8**). Repeated recrystallization of **8** from benzene–acetone gave aceroside VII (**8**) as a white crystalline powder (yield, 0.006% of the dried stem bark), mp 144—145 °C, $[\alpha]_D^{20}$ −28.4° (*c* = 0.8, EtOH). $FeCl_3$ reagent: positive (blue). *Anal.* Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 64.82; H, 7.48. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3100—3630, 1610, 1598, 1515. UV $\lambda_{max}^{EtOH}$ nm (log ε): 224 (4.10), 279 (3.43), 283 (sh). UV $\lambda_{max}^{EtOH+NaOH}$ nm: 242, 296 (bathochromic shift). $^{13}$C-NMR: Table I.

**Isolation of Aceroside VIII (9)**——Fraction C described above was chromatographed on silica gel with $CHCl_3$–MeOH–$H_2O$ (20 : 8 : 1). Since crude aceroside VIII (**9**) obtained by this column chromatographic separation was found to be contaminated with apiosylepirhododendrin (**7**) on TLC inspection, the mixture was rechromatographed on silica gel with $CHCl_3$–MeOH–MeOAc–$H_2O$ (5 : 3 : 6 : 1), yielding aceroside VIII (**9**) as a colorless film (yield, 0.25% of the dried stem bark), $[\alpha]_D^{15}$ −64.3° (*c* = 0.6, EtOH). $FeCl_3$ reagent: positive (blue). UV $\lambda_{max}^{EtOH}$ nm: 224, 278, 283 (sh). UV $\lambda_{max}^{EtOH+NaOH}$ nm: 242, 296 (bathochromic shift). $^{13}$C-NMR: Table I.

**Hydrolysis of Aceroside VII (8) with 5% HCl**——A mixture of **8** (10 mg), MeOH (3 ml) and 10% aqueous hydrochloride (3 ml) was heated for 2 h under reflux. After cooling, the reaction mixture was concentrated to distil off the MeOH, then diluted with water, and extracted with ether. On concentration of the organic layer, the aglycone (**10**) ((−)-centrolobol) was detected in the residue on TLC; solvent, benzene–EtOAc (3 : 1); *Rf* 0.2. The aqueous layer was concentrated *in vacuo*. Glucose was detected in the residue on TLC; solvent, BuOH–AcOH–$H_2O$ (6 : 1 : 2); *Rf* 0.18 (glucose).

**Hydrolysis of Aceroside VII (8) with β-Glucosidase**——A solution of **8** (110 mg) in 1/10 N AcOH–1/10 M AcONa buffer (pH 5.0, 2 ml) was treated with β-glucosidase (Sigma Chemical Co., Ltd., 3 mg) and the mixture was allowed to stand for 3 d at 37 °C, then extracted repeatedly with ether. The organic layers were combined, washed with water, and then concentrated. The residue was recrystallized from benzene–acetone to give **10** (43.2 mg) as colorless needles, mp 129—130 °C, $[\alpha]_D^{15}$ −10.2° ($c=1.0$, EtOH). $FeCl_3$ reagent: positive (blue). MS *m/z*: 300 ($M^+$).

**Methylation of Aceroside VII (8) Followed by Hydrolysis**——An excess of diazomethane in ether was added to a solution of **8** (130 mg) in MeOH (5 ml), and the mixture was allowed to stand for 18 h at room temperature, then concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–EtOH (10 : 1) to give a fraction containing methylated glucoside. This fraction was concentrated *in vacuo*. A solution of the residue in MeOH (10 ml) was refluxed with 5% HCl (10 ml) for 4 h. After cooling, the reaction mixture was diluted with water and extracted with ether. The organic layer was concentrated and the residue was chromatographed on silica gel with benzene–EtOAc (7 : 1) to afford the crude methylated genin (**11**). The product was recrystallized from hexane–ether to give **11** (40 mg) as colorless needles, mp 57—58 °C, $[\alpha]_D^{15}$ −9.1° ($c=0.5$, EtOH). $FeCl_3$ reagent: negative. MS *m/z*: 328 ($M^+$). This product was identical with (−)-di-*O*-methylcentrolobol derived from acerogenin A (**1**) on the basis of mixed melting point, TLC and $^1$H-NMR comparisons.

**Hydrolysis of Aceroside VIII (9) with 5% HCl**——A mixture of **9** (51 mg), MeOH (15 ml) and 10% HCl (15 ml) was heated for 2 h under reflux. After cooling, the reaction mixture was concentrated to distil off the MeOH, then diluted with water and extracted with ether. The organic layer was concentrated. The aglycone (**10**) ((−)-centrolobol) was detected in the residue by TLC; solvent, benzene–EtOAc (3 : 1); *Rf* 0.2. The aqueous layer was concentrated *in vacuo*. Glucose and apiose were detected in the residue on TLC; solvent, BuOH–AcOH–$H_2O$ (6 : 1 : 2); *Rf* 0.18 (glucose), 0.32 (apiose).

**Partial Hydrolysis of Aceroside VIII (9) with Aqueous Acetic Acid**——A mixture of **9** (400 mg) and 50% aqueous acetic acid (20 ml) was heated for 1.5 h under reflux, and then concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with water and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–MeOH–$H_2O$ (200 : 77 : 5) to afford crude partially hydrolyzed product. The product was recrystallized from benzene–acetone to give a white crystalline powder (132.8 mg), mp 144—145 °C, $[\alpha]_D$ −33.3° ($c=1$, EtOH) which was identical with aceroside VII (**8**) isolated from the plant materials on the basis of mixed melting point, IR and TLC comparisons. The aqueous layer was concentrated *in vacuo* and apiose was detected in the residue on TLC, solvent, BuOH–AcOH–$H_2O$ (6 : 1 : 2), *Rf* 0.32 (apiose).

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