Phytochemistry, 1975, Vol 14 pp 2647–2650 Pergamon Press Printed in England

TWO NEW IRIDOID GLUCOSIDES FROM *IXORA CHINENSIS**

YOSHIO TAKEDA, HIROSHI NISHIMURA and HIROYUKI INOUYE

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, Japan

(*Revised Received* 14 *February* 1975)

Key Word Index—*Ixora chinensis*, Rubiaceae, iridoid glucosides, ixoroside, ixoside, 7,8-dehydroforsythide

Abstract—From leaves and twigs of *Ixora chinensis*, two new iridoid glucosides, ixoroside (**1**) and ixoside (7,8-dehydroforsythide) (**2**) along with known geniposidic acid (**3**) have been isolated and their structures have been established.

INTRODUCTION

We have previously isolated eight iridoid glucosides from *Gardenia jasminoides* Ellis forma *grandiflora* (Lour) Makino and have established their structures [1,2]. This paper describes the results obtained by the examination of the iridoid glucosides of *Ixora chinensis* Lam. (Rubiaceae) which belongs to the Ixoreae, a tribe closely related to the tribe Gardenieae.

RESULTS AND DISCUSSION

The concentrated methanolic extract of leaves and twigs of *Ixora chinensis* was diluted with H_2O, washed with ethyl acetate and evaporated. Residue was fractionated as described in the Experimental and two new iridoid glucosides, ixoroside (**1**) and ixoside (**2**) were isolated along with geniposidic acid (**3**) [1,3].

Ixoroside (**1**) was obtained as an amorphous powder, $C_{16}H_{24}O_9 . 2\ H_2O$. The NMR spectrum (in D_2O) of **1** shows singlets at δ 9·16 and 1·32 assignable to an aldehyde and a tertiary methyl group, respectively. Acetylation of **1** with acetic anhydride–pyridine gave the tetraacetate (**4**), $C_{24}H_{32}O_{13} . 1/2\ H_2O$, which shows NMR signals assignable to four acetyl groups (δ 1·92–2·10) and a tertiary hydroxy group which disappears on the addition of D_2O. Further acetylation of **4** with acetic anhydride–boron trifluoride gave the pentaacetate (**5**), $C_{26}H_{34}O_{14}$, the NMR spectrum of which displays signals (δ 1·90–2·11) assignable to five acetyl groups. The signal arising from the methyl group at δ 1·51 is shifted downfield (0·19 ppm) compared to the corresponding signal in **4**. From these facts it can be deduced that the tertiary hydroxy group is located at C-8 in an iridoid glucoside structure.

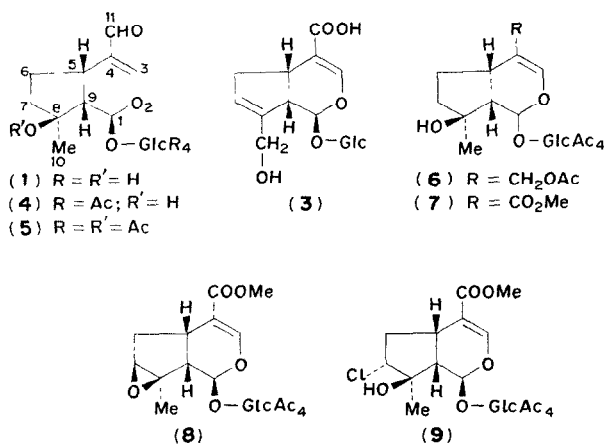
$NaBH_4$ reduction of **4** followed by conventional acetylation gave 11-dihydroixoroside pentaacetate (**6**), $C_{26}H_{36}O_{14} . 1/2\ H_2O$, with an NMR-spectrum displaying signals from five acetyl groups at δ 2·00–2·09. Since the C-3 proton signal appeared at δ 6·29, an upfield shift compared to that from **4** (δ 7·11), the aldehyde group must be located at C-4. Accordingly, the only remaining problem in the structure of glucoside (**1**) is the configuration of the tertiary hydroxy group at C-8. Previously, we have suggested that the configuration of this group in iridoid glucosides could be deduced from comparisons of the chemical shifts of C-1 and C-9 protons in the 8-hydroxy and the corresponding acetoxy compound [2]. In the NMR spectrum of the *tert*-acetoxy compound (**5**), the C-1 proton signal appears downfield by 0·42 ppm compared with that of the original 8-hydroxy compound (**4**). Although the C-9 proton signal of **5** is difficult to assign because of overlapping with other signals, it has obviously under-

* Part 28 in the series *Studies on monoterpene glucosides and related natural products* For Part 27 see [1]

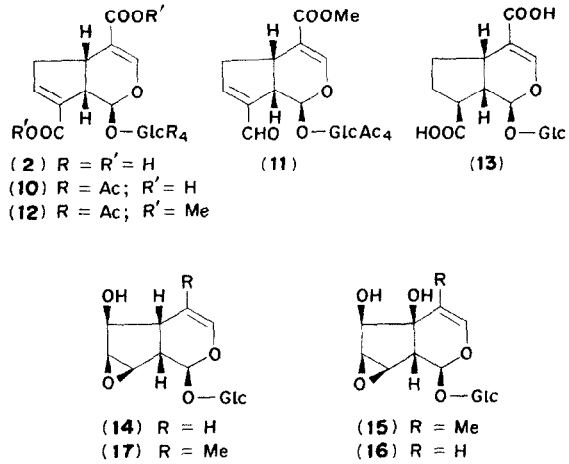
gone a downfield shift compared with the corresponding signal of **4** appearing at δ 2·32 (*dd*, *J* 10·0 & 3·3 Hz). From this, it can be deduced that the tertiary hydroxy group in ixoroside is in the β-position. The structure **1** can thus be assigned to the compound, which was confirmed by the chemical correlation described below.

A carboxylic acid methyl ester, $C_{25}H_{34}O_{14}$ 1/2 H_2O, was obtained by oxidation of the tetraacetate (**4**) with Jones reagent or argentic (II) oxide followed by methylation. This ester was found to be identical to the alcohol (**7**), obtained by catalytic hydrogenation (Pd-C, $HClO_4$) of the β-epoxide (**8**). The latter compound has been prepared in several steps from asperuloside [4,5]. The chlorohydrin (**9**) [4] was obtained in addition to **7**. Accordingly, not only the β-configuration of the tertiary hydroxy group, but also the absolute structure of **1** was confirmed. The structure of this substance (**1**) is biosynthetically interesting since iridoid glucoside bearing an aldehyde group at C-4 are rare [6].

Ixoside (**2**) was obtained as a powder, $C_{16}H_{20}O_{11}$ 1/2 H_2O. The NMR-spectrum (in D_2O) displays typical iridoid signals arising from the proton at C-3 (δ 7·57) and C-1 (δ 5·72, *d*, *J* 5·0 Hz). In addition to these signals, an absorption arising from a β-positioned conjugated olefinic proton is found at δ 7·03. Acetylation of **2** afforded the tetraacetate (**10**), $C_{24}H_{28}O_{15}$. 1/2 H_2O, which shows NMR signals assignable to four acetyl groups (δ 1·95–2·08) and a conjugated olefinic proton (δ 6·84). Previously, we have noticed that the C-7 proton signal of 10-dehydro-



Scheme 1



Scheme 2

geniposide tetraacetate (**11**) bearing an aldehyde group at C-8 appears at δ 6·93 [1]. Since the NMR spectra of **2** and **10**, however, lack any signals assignable to an aldehyde proton, it can be assumed that both compounds possess a carboxy group at C-8. In fact, methylation of **10** gave a tetraacetate dimethyl ester (**12**), $C_{26}H_{32}O_{15}$, showing signals at δ 3·70 and 3·74, assignable to two carbomethoxy groups. Ixoside and its acetate could thus be represented by the structures **2** and **10**, respectively. To verify this, compound **11** [1] was subjected to Jones oxidation followed by methylation affording **12**, identical to ixoside tetraacetate dimethyl ester. Accordingly, structure **2** can be assigned to ixoside.

As stated above, *Ixora chinensis* also contains geniposidic acid (**3**). Thus it would be reasonable to presume that ixoside (**2**) is biosynthesized by an oxidation of geniposidic acid (**3**). Ixoside (**2**) is a glucoside of rather novel type, featuring a 10-carboxy group. Although there is a possibility that substances lacking the C-10 carbon such as unedoside (**14**) [7,8], scabroside (**15**) [9], stilbericoside (**16**) [8] and deutzioside (**17**) [10] could be synthesized through a 10-carboxy compound, forsythide (**13**) [11] is the only compound of this type so far reported.

Kooiman, in his paper on the chemotaxonomy of Rubiaceae reported that plants belonging to the tribe Ixoreae seem to be devoid of asperulosidic glucosides [12]. The findings presented here imply, however, that his methods of detection are of limited value. With improvement of detection

methods as well as of isolation procedures, it appears possible to find new as well as known iridoids in plants previously reported to lack these substances.

EXPERIMENTAL

General procedures Mp's were uncorrected TLC was on Si gel G and spots were visualized by exposure to I_2 vapour or with a mixture of anisaldehyde (0·5 ml), conc H_2SO_4 (0·5 ml), HOAc (few drops) and 95% EtOH (9 ml) followed by heating Column chromatography was carried out using carbon or Si gel as adsorbents

Isolation procedure Dry leaves and twigs of *Ixora chinensis* (1·5 kg) collected in Iriomote Island (Okinawa Pref) in January and were extracted with 9 l MeOH (×3) under reflux MeOH extracts were combined and concentrated *in vacuo* Residue was dissolved in H_2O (4 l) and insoluble material removed by filtration through Celite The filtrate was washed with EtOAc (3 × 1 l) and concentrated *in vacuo* to about 0·5 l This soln was then chromatographed on a charcoal column and eluted with increasing concs of aq MeOH The fraction eluted with 30–50% MeOH was evaporated *in vacuo* to leave a residue (22·8 g) A fraction of this residue (1·5 g) was dissolved in H_2O (30 ml), made alkaline (pH 8) with aq NH_4OH, adsorbed on a Dowex 1 × 8 column (200–100 mesh, OAc- form, 350 ml) and eluted with H_2O, then with 0·1 N HOAc The H_2O eluate was evaporated to give ixoroside (**1**) (0·2 g) as a powder $[\alpha]_D^{22}$ −102·6 (*c*, 0·64, MeOH), UV λ_{max}^{MeOH} 249 nm (log ε = 4·09); IR ν_{max}^{KBr} 3400, 1730, 1640 cm^{-1}, NMR (D_2O) δ 1·32 (3 H, *s*, C-10 H), 5·73 (1 H, *d*, *J* 3·5 Hz, C-1 H), 7·48 (1 H, broad *s*, C-3 H), 9·16 (1 H, *s*, C-11 H) (Found C, 48·66, H, 6·81 $C_{16}H_{24}O_9$ $2H_2O$ requires C, 48·48, H, 7·12%) The 0·1 N HOAc eluate was evaporated *in vacuo* to afford geniposidic acid (**3**) (0·5 g) $[\alpha]_D^{24}$ +19·3° (*c*, 1·01, MeOH), UV λ_{max}^{MeOH} 237 nm (log ε = 3·64), IR ν_{max}^{KBr} 3500, 1680, 1630 cm^{-1}, NMR (D_2O) δ 5·25 (*d*, *J* 7·0 Hz, C-1 H), 5·92 (*m*, C-7 H), 7·56 (*s*, C-3 H) (Found C, 49·49, H, 5·93 Calc for $C_{16}H_{22}O_{10}$ H_2O C, 49·15, H, 6·17%) This substance was found to be identical with an authentic sample of geniposidic acid by comparison of their IR(KBr) and NMR (D_2O) spectra The fraction eluted with 70% MeOH from the charcoal column was evaporated *in vacuo* to give ixoside (**2**) (0·1 g) as a powder $[\alpha]_D^{24}$ +33·6° (*c*, 1·15, H_2O), UV $\lambda_{max}^{H_2O}$ 219 nm (log ε = 4·16), IR ν_{max}^{KBr} 3400, 1700, 1620 cm^{-1}, NMR (D_2O) δ 5·72 (1 H, *d*, *J* 5·0 Hz, C-1 H), 7·03 (1 H, *m*, C-7 H), 7·57 (1 H, *s*, C-3 H) (Found C, 47·94, H, 5·48 $C_{16}H_{20}O_{11}$ ½ H_2O requires C, 48·35, H, 5·33%)

Ixoroside tetraacetate (**4**) **1** (0·1 g) was acetylated (Ac_2O–Py) giving the tetraacetate (**4**) (0·061 g) as needles ex EtOH, mp 156–157° $[\alpha]_D^{33}$ −101·2 (*c*, 1·98, $CHCl_3$), UV λ_{max}^{MeOH} 246 nm (log ε = 4·10), IR ν_{max}^{KBr} 3500, 1750, 1665, 1615 cm^{-1}, NMR ($CDCl_3$) δ 1·32 (3 H, *s*, C-10 H), 1·92–2·10 (4 × OCOMe), 2·32 (1 H, *d*, *d*, *J* 10, 3·3 Hz, C-9 H), 3·05 (1 H, *m*, C-5 H), 5·45 (1 H, *d*, *J* 3·3 Hz, C-1 H), 7·11 (1 H, broad *s*, C-3 H), 9·28 (1 H, *s*, C-11 H) (Found C, 53·53, H, 5·96 $C_{24}H_{32}O_{13}$ ½ H_2O requires C, 53·63, H, 6·19%)

Ixoroside pentaacetate (**5**) To a soln of **4** (0·08 g) in Ac_2O (4 ml) was added BF_3-etherate (4 drops) and the mixture was allowed to stand at room temp for 2 min Iced H_2O was added to the reaction mixture and the resulting ppt was extracted with $CHCl_3$ (3 × 15 ml). $CHCl_3$ extracts were washed with aq soln of 10% $NaHCO_3$ and then with H_2O, dried and evaporated to give a residue (0·084 g), which was recrystallized from EtOH to give pentacetate (**5**) (0·052 g) as needles, mp 95–96° $[\alpha]_D^{36}$ −102·2° (*c*, 0·69, $CHCl_3$), UV λ_{max}^{MeOH} 245 nm (log ε = 4·18), IR ν_{max}^{KBr} 1755, 1675, 1635 cm^{-1}, NMR ($CDCl_3$) δ 1·51 (3 H, *s*, C-10 H), 1·90–2·11 (5 × OCOMe), 5·87 (1 H, *d*, *J* 2·3 Hz, C-1 H), 7·14 (1 H, *d*, *J* 1·0 Hz, C-3 H), 9·28 (1 H, *s*, C-11 H) (Found C, 55·01, H, 6·25 $C_{26}H_{34}O_{14}$ requires C, 54·73, H, 6·01%)

11-Dihydroixoroside pentaacetate (**6**) To a soln of **4** (0·25 g) in dioxane (10 ml) was added a soln of $NaBH_4$ (0·09 g) in H_2O (1 ml) under ice cooling After stirring for 1 hr at room temp, HOAc was added and the solvent was concentrated *in vacuo* Residue was extracted with $CHCl_3$, washed with H_2O, dried and exaporated *in vacuo* The residue (0·194 g) was acetylated (Ac_2O–Py) and the crude product (0·188 g) was purified by chromatography on Si gel (30 g) with Et_2O as eluent and recrystallized from a mixture of Et_2O–petrol to furnish **6** (0·102 g) as needles, mp 120–122° $[\alpha]_D^{34}$ −101·5° (*c*, 0·69, $CHCl_3$), IR ν_{max}^{KBr} 3550, 1750, 1680 cm^{-1}, NMR ($CDCl_3$) δ 1·33 (3 H, *s*, C-10 H), 2·00–2·09 (5 × OCOMe), 2·26 (1 H, *d*, *d*, *J* 9·0, 3·0 Hz, C-9 H), 2·90 (1 H, *m*, C-5 H), 4·47 (2 H, *d*, *J* 14·0 Hz, C-11 H), 5·26 (1 H, *d*, *J* 3·0 Hz, C-1 H), 6·29 (1 H, *d*, *J* 1·0 Hz, C-3 H) (Found C, 53·85, H, 6·41 $C_{26}H_{36}O_{14}$ ½ H_2O requires C, 53·70, H, 6·41%)

Oxidation of ixoroside tetraacetate (**4**) *followed by methylation* (a) A soln of **4** (0·041 g) in Me_2CO (5 ml) was stirred with Jones reagent (3 ml) under cooling for 3 hr The reaction mixture was dil with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 20 ml) The combined $CHCl_3$ extract was washed with H_2O, dried and evaporated *in vacuo*. The residue was dissolved in MeOH (5 ml) and methylated with CH_2N_2–Et_2O The reaction produce (0·03 g) was purified by chromatography on Si gel (10 g) with Et_2O as eluent and recrystallized from a mixture of Et_2O–petrol to give **7** (0·007 g) as needles, mp 86–87° $[\alpha]_D^{15}$ −82·3° (*c*, 0·78, $CHCl_3$), UV λ_{max}^{MeOH} 236 nm (log ε = 3·95), IR ν_{max}^{KBr} 3500, 1750, 1705, 1640 cm^{-1}, NMR ($CDCl_3$) δ 1·33 (3 H, *s*, C-10 H), 1·93–2·10 (4 × OCOMe), 2·31 (1 H, *d*, *d*, *J* 9·5, 3·0 Hz, C-9 H), 3·03 (1 H, *m*, C-5 H), 3·71 (3 H, *s*, COOMe), 5·33 (1 H, *d*, *J* 3·0 Hz, C-1 H), 7·34 (1 H, *d*, *J* 1·0 Hz, C-3 H) (Found C, 52·54, H, 6·11 $C_{25}H_{34}O_{14}$ ½ H_2O requires C, 52·91, H, 6·22%) (b) To a soln of **4** (0·131 g) in THF–H_2O (9·1) (15 ml) was added AgO (0·126 g) and the mixture was stirred at room temp for 4 days Insoluble material was filtered off and the filtrate was diluted with H_2O, extracted with $CHCl_3$, dried and evaporated *in vacuo* to leave a residue (0·142 g) This residue was methylated with CH_2N_2–Et_2O and the reaction product (0·100 g) was purified by chromatography on Si gel (20 g) with Et_2O as eluent and recrystallized from a mixture of Et_2O–petrol. to give pure **7** (0·022 g)

Catalytic hydrogenation of β-epoxide (**8**) A soln of **8** (0·2 g) in EtOAc (20 ml) was hydrogenated over a Pd–C catalyst prepared from 5% $PdCl_2$ soln (3 ml) and charcoal (0·3 g) in the presence of 60% $HClO_4$ aq soln (1 drop) until the absorption of hydrogen had ceased (18 hr) The catalyst was filtered off and the filtrate was washed with aq 5% NaOH and then with H_2O, dried and evaporated *in vacuo* to leave a residue (0·163 g) This residue was chromatographed on Si gel (20 g) with Et_2O as eluent The first fraction was concentrated *in vacuo* and the residue was recrystallized from a mixture of Et_2O–petrol to give chlorohydrin (**9**) (0·035 g) as needles, mp 163–165° giving a positive Beilstein test $[\alpha]_D^{25}$ −245·9° (*c*, 0·63, $CHCl_3$), IR ν_{max}^{KBr} 3500, 1750, 1710, 1640 cm^{-1}, NMR ($CDCl_3$) δ 1·26 (3 H, *s*, C-10 H), 1·88–2·09 (4 × OCOMe), 3·70 (3 H, *s*, COOMe), 5·51 (1 H, *d*, *J* 1·5 Hz, C-1 H), 7·32 (1 H, *s*, C-3 H) (Found C, 49·31, H, 5·50 Calc for $C_{24}H_{33}O_{14}Cl$ H_2O C, 49·15, H, 5·77%) The second fraction was concentrated *in vacuo* and the residue was recrystallized from a Et_2O–petrol mixture to give colourless needles (0·023 g) mp 86–87° $[\alpha]_D^{33}$

$-83{\cdot}8°$ (*c*, 0·51, $CHCl_3$); IR: ν_{max}^{KBr} 3500, 1750, 1705, 1640 cm^{-1}; NMR ($CDCl_3$): δ 1·33 (3 H, *s*, C-10 H), 1·93–2·10 (4 × OCOMe), 2·31 (1 H, *d*, *d*, *J* 9·5, 3·0 Hz, C-9 H), 3·03 (1 H, *m*, C-5 H), 3·71 (3 H, *s*, COOMe), 5·33 (1 H, *d*, *J* 3·0 Hz, C-1 H), 7·34 (1 H, *d*, *J* 1·0 Hz, C-3 H). (Found: C, 52·49; H, 5·98. Calc. for $C_{25}H_{34}O_{14}\cdot\frac{1}{2}H_2O$: C, 52·91; H, 6·22%). Comparison with an authentic sample of **7** derived from **2** proved the identity and comparisons of IR (KBr) and NMR spectra).

Ixoside tetraacetate (**10**). **2** (0·1 g) was acetylated (Ac_2O–Py) and the product was recrystallized from EtOH to furnish the tetracetate (**10**) (0·095 g) as needles, mp 236–237°. $[\alpha]_D^{35}$ −3·2° (*c*, 0·28, MeOH); UV: λ_{max}^{MeOH} 218 nm (log ϵ = 4·20); IR: ν_{max}^{KBr} 1750, 1615 cm^{-1}; NMR (CD_3OD): δ 1·95–2·08 (4 × OCOMe), 6·08 (1 H, *d*, *J* 2·0 Hz, C-1 H), 6·84 (1 H, *m*, C-7 H), 7·42 (1 H, *s*, C-3 H). (Found: C, 51·19; H, 5·20. $C_{24}H_{28}O_{15}\cdot\frac{1}{2}H_2O$ requires: C, 50·98; H, 5·07%).

Ixoside tetraacetate dimethyl ester (**12**). A methanolic soln of **10** (0·05 g) was methylated with ethereal CH_2N_2. The product was recrystallized from EtOH to give the tetracetate dimethyl ester (**12**) (0·035 g) as needles, mp 165–166°. $[\alpha]_D^{36}$ +7·3° (*c*, 0·71, $CHCl_3$); UV: λ_{max}^{MeOH} 220 nm (log ϵ = 4·22); IR: ν_{max}^{KBr} 1750, 1700, 1640 cm^{-1}; NMR ($CDCl_3$): δ 1·90–2·10 (4 × OCOMe), 3·70 (3 H, *s*, COOMe), 6·02 (1 H, *d*, *J* 2·0 Hz, C-1 H), 6·86 (1 H, *m*, C-7 H), 7·38 (1 H, *s*, C-3 H). (Found: C, 53·52; H, 5·68. $C_{26}H_{32}O_{15}$ requires: C, 53·43; H, 5·52%).

Chemical transformation of 10*-dehydrogeniposide tetraacetate* (**11**) *into ixoside tetracetate dimethyl ester*. A soln of **11** (0·484 g) in Me_2CO (20 ml) was stirred with Jones reagent (10 ml) for 1 hr under ice cooling. The reaction mixture was dil with H_2O, estracted with $CHCl_3$, dried and evaporated *in vacuo* to leave a residue (0·483 g), which was recrystallized from EtOH to give a monocarboxylic acid (0·283 g) as needles, mp 226–228°. $[\alpha]_D^{34}$ +10·5° (*c*, 1·66, $CHCl_3$); IR: ν_{max}^{KBr} 1750, 1705, 1680, 1640 cm^{-1}; NMR ($CDCl_3$): δ 1·90–2·08 (4 × OCOMe), 3·70 (3 H, *s*, COOMe), 6·03 (1 H, *d*, *J* 1·5 Hz, C-1 H), 7·02 (1 H, *m*, C-7 H), 7·58 (1 H, *s*, C-3 H). (Found: C, 52·88; H, 5·30. $C_{25}H_{30}O_{15}$ requires: C, 52·63; H, 5·30%). A portion of the above oxidation product (0·1 g) was methylated with ethereal CH_2N_2 and the reaction product was recrystallized from EtOH to afford ixoside tetracetate dimethyl ester (**12**) (0·075 g) as needles, mp 165–166°. $[\alpha]_D^{15}$ +2·0° (*c*, 1·79, $CHCl_3$); IR: ν_{max}^{KBr} 1750, 1700, 1640 cm^{-1}; NMR ($CDCl_3$): δ 1·90–2·10 (4 × OCOMe), 3·70 (3 H, *s*, COOMe), 3·74 (3 H, *s*, COOMe), 6·02 (1 H, *d*, *J* 2·0 Hz, C-1 H), 6·86 (1 H, *m*, C-7 H), 7·38 (1 H, *s*, C-3 H). (Found: C, 53·16; H, 5·35. Calc. for $C_{26}H_{32}O_{15}$: C, 53·43; H, 5·52%). This substance was found to be identical to an authentic sample of **12** (mmp and comparisons of IR (KBr) and NMR ($CDCl_3$) spectra).

Acknowledgements—This work was partly supported by Grant-in-Aid for Scientific Research from the Ministry of Education which is greatly appreciated. The authors are grateful to Dr. H. Murata and Dr. Y. Ikeshiro for their collaboration to collect plant materials. We are also indebted to Mrs. M. Uobe for measurement of NMR spectra and to the members of the Microanalytical Centre of this University for microanalyses.

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