Synthesis of ^{13}C-Labeled Possible Intermediates in the Biosynthesis of Phenylethanoid Derivatives, Cornoside and Rengyosides

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In order to clarify the biosynthetic pathway of C_6–C_2 unit compounds containing salidroside, cornoside, and rengyosides A and B in oleaceous plants, ^{13}C-labeled putative precursors, 4-hydroxyphenylethanol, salidroside and cornoside, were prepared.

Key words quinol glucoside; cornoside; cyclohexylethanoid; 4-hydroxyphenylethanol; salidroside; ^{13}C-labeled compound

In the course of phytochemical and biosynthetic studies on secoiridoid glucosides, we have been investigating the chemical constituents of several oleaceous plants.[1] Oleaceae is a rich source of oleoside (**1**)-type secoiridoid glucosides, such as oleuropein (**2**) and ligstroside (**3**), which contain an esterified phenylethanol group in their molecules. In our search for glucoside constituents of the fresh leaves of *Abeliophyllum distichum* (Japanese name, Uchiwanoki) of this family, we have isolated a quinol-type phenylethanoid, cornoside (**4**) and three related compounds containing halleridone (**5**).[1] On the other hand, Seya *et al.* have isolated the cyclohexylethanoids rengyosides A (**6**), B (**7**) and C (**8**), along with **4**, **5** and salidroside (**9**) from the fruits of *Forsythia suspensa* of the same family, and have proposed a biosynthetic pathway leading from 4-hydroxyphenylethanol (**10**) *via* salidroside (**9**) and cornoside (**4**) to the above cyclohexylethanoids, based on their co-occurrence.[2] However, no unequivocal evidence for the biosynthesis of these aromatic and aliphatic C_6–C_2 compounds has so far been reported. Moreover, dihydrocornoside (**11**), along with **4**, **6**, **7** and **9**, was recently isolated from *Millingtonia hortensis* (Bignoniaceae) by Hase *et al.*[3] In the present paper, we describe the synthesis of ^{13}C-labeled cornoside (**4**), rengyosides A (**6**), B (**7**) and salidroside (**9**), which are indispensable for experiments to confirm the proposed biosynthetic pathway. Additionally, the synthesis of **11** pertaining to the reduction process of **4** to **7** was examined.

Synthesis of ^{13}C-Labeled 4-Hydroxyphenylethanol (10) and Salidroside (9) We planned to introduce the ^{13}C-label into the C-8 position of C_6–C_2 compounds by carboxylation of a benzylmagnesium halide. Carbon dioxide (prepared from $BaCO_3$ and sulfuric acid) was passed into 4-methoxybenzylmagnesium chloride (prepared from 4-methoxybenzyl chloride and metallic Mg) in tetrahydrofuran (THF) to give the acid **12** in 75% yield based on $BaCO_3$.[4a–c] Demethylation of **12** with BBr_3 gave **12a**.[5] The attempted reduction of **12a** with $LiAlH_4$ under several conditions was unsuccessful, but the methyl ester **12b** obtained by methylation of **12a** with HCl–MeOH was smoothly reduced with $NaBH_4$–H_2O[6] to give the desired alcohol **10** in 90% yield. Selective acetylation of **10** was performed with 1-acetyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridine

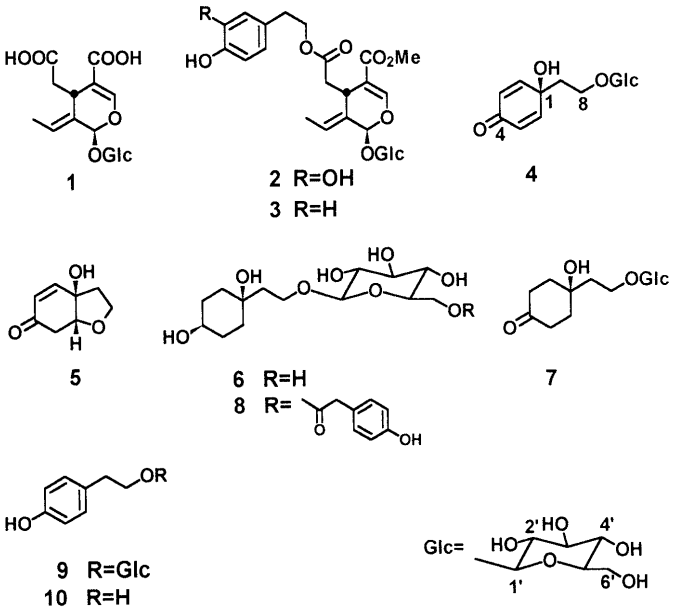

Fig. 1

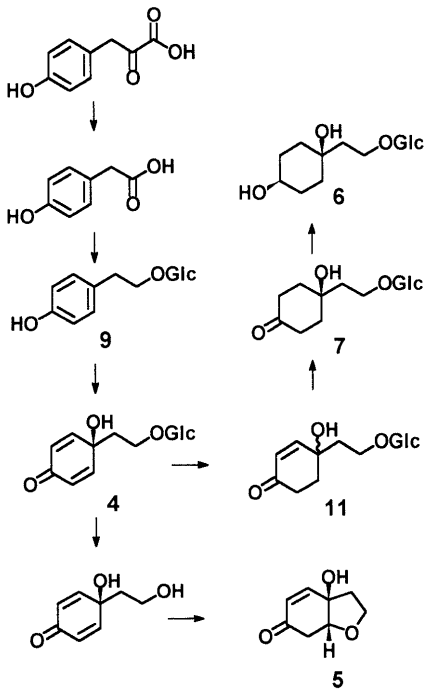

Chart 1

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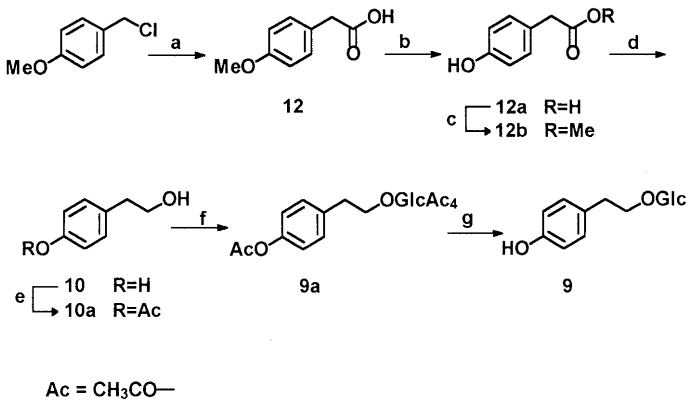
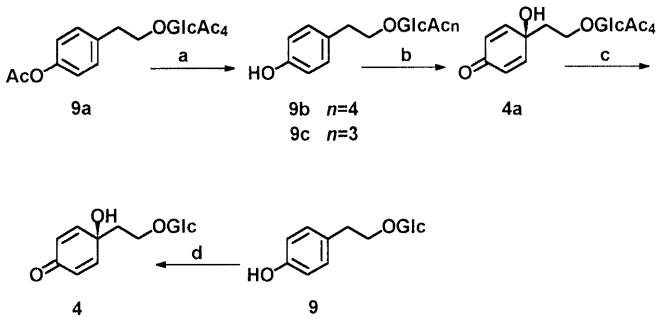


a) i : Mg / THF, ii : CO_2 ; b) BBr_3, CH_2Cl_2, −78 °C ; c) HCl / MeOH ; d) $NaBH_4$ / H_2O
e) 1-acetyl-1*H*-1,2,3-triazolo [4,5-*b*] pyridine / 0.1 N NaOH ; f) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, Ag_2CO_3, Drierite, I_2 / Et_2O ; g) NaOMe–MeOH

Chart 2



a) Zn / MeOH ; b) TTP / CH_2Cl_2 ; c) NaOMe–MeOH ; d) i : *hν* / O_2, ii : Me_2S

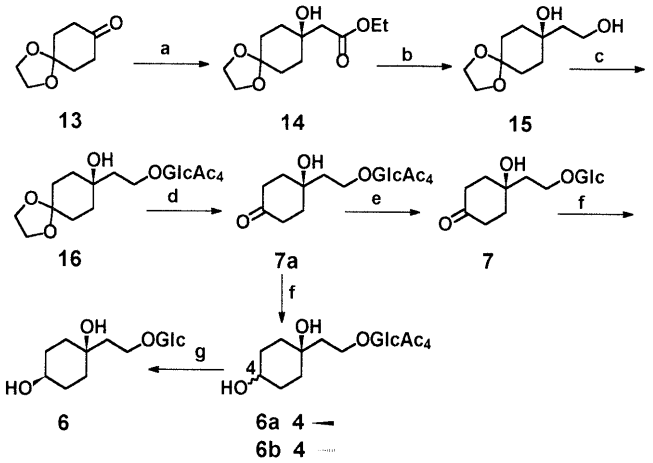
Chart 3

in aqueous NaOH[7] to afford the desired monoacetate **10a** in 73% yield. The acetate **10a** was subjected to a Konig–Knorr reaction[8] with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of Ag_2CO_3 to afford salidroside pentaacetate (**9a**). The configuration of the glycosidic linkage of **9a** was determined to be *β* from the coupling constant of the anomeric proton. **9a** was deacetylated with MeONa–MeOH[9] to give salidroside (**9**) in the overall yield of 25% based on $BaCO_3$. Next, we carried out the same experiments using $^{13}CO_2$ instead of CO_2 and obtained [8-^{13}C]-4-hydroxyphenylethanol (**10**) (enrichment factor: 97.6%, calculated on the basis of EI-MS data) and [8-^{13}C]salidroside (**9**), respectively.

Biomimetic Conversion of [8-^{13}C]Salidroside (9) to [8-^{13}C]Cornoside (4) In the biosynthesis of cornoside (**4**), salidroside (**9**) or its aglucone, 4-hydroxyphenylethanol (**10**), was supposed to be oxygenated to a quinol compound. Thus, we examined the oxygenation of salidroside (**9**) derivatives according to two methods. The tetraacetate **9b** prepared from the pentaacetate (**9a**) by treatment with zinc in MeOH[10] was subjected to oxygenation with thallium triperchlorate (TTP) in CH_2Cl_2[11a–c] to give the quinol acetate **4a** in a low yield of 12%. On the other hand, the photosensitized oxygenation of **9b** in MeOH in the presence of Rose Bengal did not proceed at all, whereas the oxygenation of **9** under the conditions described above gave the peroxide **4b**, without the formation of any by-product, and **4b** was subsequently reduced with dimethyl sulfide (Me_2S) to yield cornoside (**4**) in 49% isolated yield.[12] By applying the latter procedure, [8-^{13}C]salidroside (**9**) was converted to [8-^{13}C]cornoside (**4**).

Synthesis of [7-^{13}C]Rengyosides A (6), B (7) and [7-^{13}C]Dihydrocornoside (11) Although the direct conversion of cornoside (**4**) into rengyoside B (**7**) *via* hydrogenation catalyzed by palladium on activated carbon has been reported,[12] the yield of the product was unsatisfactory. Thus, we planned the preparation of ^{13}C-labeled **7** by means of the Reformatsky reaction[13a–c] of a cyclohexanone derivative and ethyl bromoacetate. The condensation of 1,4-cyclohexanedione monoethyleneketal (**13**) with ethyl bromoacetate in the presence of zinc was examined in various solvents. The best yield (77%) of the desired ester **14** was obtained in dry benzene. On reduction of **14** with $LiAlH_4$ in dry THF,[14a,b] the alcohol **15** was formed in 83% yield. The glycosidation of **15** in a manner analogous to the preparation of salidroside (**9**) gave the ketal **16**, which was subjected to deprotection by *p*-toluenesulfonic acid (*p*-TsOH) in acetone[15] to afford the corresponding ketone **7a**. This in turn gave rengyoside B (**7**) in 35% overall yield from the ketal **13** on decetylation with NaOH in acetone. [7-^{13}C]Rengyoside B (**7**) was prepared as described above starting from [2-^{13}C]ethyl bromoacetate and 1,4-cyclohexanedione monoethyleneketal (**13**).

In order to prepare rengyoside A tetraacetate (**6a**), rengyoside B tetraacetate (**7a**) was reduced with $NaBH_4$ in EtOH to give a separable mixture of two alcohols **6a** and **6b** in a ratio of 3 : 1. Their ^{1}H-NMR spectra showed different configurations of the newly generated hydroxy group at C-4 of **6a** and **6b**. It was concluded on the basis of the width of the H-4 signal that **6a** has the equatorial hydroxy group at C-4 [axial H-4 ($W_{1/2}$ = 20 Hz) at *δ* 3.55—3.62] and **6b** the axial one [equatorial H-4 ($W_{1/2}$ = 13 Hz) at *δ* 3.90—3.96] in accordance with the data reported previously.[2,16] However, the reduction of **7a** to



a) Zn, $BrCH_2CO_2Et$ / C_6H_6 ; b) $LiAlH_4$ / THF ; c) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, Ag_2CO_3, Drierite, I_2, / $CHCl_3$; d) *p*-TsOH / Me_2CO ; e) 0.2 N NaOH-Me_2CO ; f) $NaBH_4$ / EtOH ; g) NaOMe-MeOH

Chart 4

the desired alcohol **6a** resulted in a poor yield of 27%, probably because **6a** was further hydrolyzed to more polar deacetylated compounds during the reaction. So, rengyoside B (**7**) was reduced in the same way as above to give stereoselectively rengyoside A (**6**) in quantitative yield; this product was identical with the deacetylated compound of **6a**. Next, [7-^{13}C]rengyoside B (**7**) was reduced in the same way as above to give [7-^{13}C]rengyoside A (**6**).

Finally, we tried to prepare a dihydro derivative of **4**, dihydrocornoside (**11**). Cornoside (**4**) was subjected to partial hydrogenation by using Pd/C to afford **11** in 39% yield as a diastereomeric mixture in a ratio of 1 : 1 as judged from the ^{1}H- and ^{13}C-NMR spectra, along with rengyoside B (**7**). [8-^{13}C]Cornoside (**4**) was subjected to the above hydrogenation to afford [8-^{13}C]dihydrocornoside (**11**). Feeding experiments with these ^{13}C-labeled compounds are in progress.

Experimental

The melting points were measured on a Yanagimoto MP-32 micro-melting point apparatus and are uncorrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Hitachi Model 260-30 IR spectrophotometer. The NMR experiments were performed with a JEOL JNM-GX 500 or JNM-GSX 270 spectrometer, with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-HX 100 instrument. For FAB-MS, glycerol was used as the matrix. For TLC, Silica gel 60 GF_{254} was used and spots were visualized under UV light or by exposure to I_2 vapor or by spraying anisaldehyde–H_2SO_4 reagent followed by heating. For preparative TLC (PTLC), Silica gel 60 PF_{254} was used and bands were detected under UV light or by exposure to I_2 vapor. For column chromatography, Silica gel BW-820 (Fuji Silysia Chemical Ltd.) and highly porous polymer Diaion SP207 (Mitsubishi Chemical Co. Ltd.) were used. Solvent ratios are expressed by volume. All extracts were dried over anhydrous $MgSO_4$.

4-Methoxyphenylacetic Acid (12) 4-Methoxybenzyl chloride (5.7 ml, 42.0 mmol) was added dropwise to a stirred mixture of Mg (1.0 g, 42.0 mmol) and THF (84.0 ml) under argon over a period of 40 min at 20 °C, and stirring was continued for an additional 30 min. Carbon dioxide [generated from $BaCO_3$ (5.0 g, 25 mmol) and excess concentrated H_2SO_4] was passed into the reaction mixture over a period of 1.5 h at 10—25 °C with stirring. After acidification of the mixture by adding 1 N HCl, the residue obtained by removal of the solvent *in vacuo* was extracted with Et_2O. The Et_2O layer was extracted with 2 N NaOH, and the aqueous layer was acidified with concentrated H_2SO_4 and extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated *in vacuo* to give **12** (3.2 g, 75.0% based on $BaCO_3$). Compound **12** was identical with an authentic sample of 4-methoxyphenylacetic acid.

4-Methoxybenzyl chloride (5.7 ml, 42.0 mmol) and $^{13}CO_2$ generated from $Ba^{13}CO_3$ (5.0 g, 25.0 mmol) (^{13}C-enrichment 99%, CIL) were subjected to a Grignard reaction as described above to give [8-^{13}C]-**12** (3.1 g, 72.7%). [8-^{13}C]-**12**: ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, d, $^2J_{CH}$ = 7.6 Hz, H-7), 3.79 (3H, s, OCH_3), 6.86 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-3, -5), 7.19 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-2, -6). EI-MS (70 eV) *m/z*: 167 $[M]^+$. ^{13}C-enrichment factor: 97.8% (calculated on the basis of EI-MS data). The ^{13}C-NMR spectrum of [8-^{13}C]-**12** exhibited a strongly enriched ^{13}C signal arising from the carbonyl carbon of C-8 at 177.60. In the C-8-labeled compounds mentioned as follows, it was confirmed by examination of their ^{13}C-NMR spectra that the C-8 carbon signals were enhanced.

4-Hydroxyphenylacetic Acid (12a) A solution of BBr_3 (4.2 ml, 44.4 mmol) in dry CH_2Cl_2 (34.0 ml) was added dropwise to a stirred solution of **12** (3.2 g, 19.3 mmol) in dry CH_2Cl_2 (50.0 ml) at −78 °C and the mixture was stirred for 30 min. After decomposition of the excess reagent by adding H_2O under ice-cooling, CH_2Cl_2 was removed *in vacuo* and the aqueous layer was extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated *in vacuo* to give **12a** (2.7 g, 93.0%). **12a** was identical with an authentic sample of 4-hydroxyphenylacetic acid.

[8-^{13}C]-**12** (3.2 g) was demethylated in the same way as above to give [8-^{13}C]-**12a** (2.3 g, 85.6%). [8-^{13}C]-**12a**: ^{1}H-NMR (DMSO-d_6) δ: 3.42 (2H, d, $^2J_{CH}$ = 7.5 Hz, H_2-7), 6.70 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-3, -5), 7.04 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-2, -6). EI-MS (70 eV) *m/z*: 153 $[M]^+$.

Methyl 4-Hydroxyphenylacetate (12b) A solution of **12a** (2.7 g, 17.7 mmol) in MeOH (40 ml) was acidified with 3 drops of concentrated HCl and the mixture was refluxed for 30 min. After neutralization of the mixture with 10% aqueous $NaHCO_3$ under ice-cooling, the solution obtained by removal of MeOH *in vacuo* was extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated *in vacuo* to give **12b** (2.8 g, 95.0%), which was identical with an authentic sample of methyl 4-hydroxyphenylacetate.

[8-^{13}C]-**12a** (3.2 g) was methylated in the same manner as described above to give [8-^{13}C]-**12b** (3.3 g, 94.4%). [8-^{13}C]-**12b**: ^{1}H-NMR ($CDCl_3$) δ: 3.56 (2H, d, $^2J_{CH}$ = 7.9 Hz, H_2-7), 3.70 (3H, d, $^3J_{CH}$ = 4.0 Hz, $^{13}COOCH_3$), 6.74 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-3, -5), 7.11 (2H, AA'BB' pattern, J_{ortho} = 8.8 Hz, H-2, -6). EI-MS (70 eV) *m/z*: 167 $[M]^+$.

4-Hydroxyphenylethanol (10) A stirred suspension of **12b** (2.8 g, 16.8 mmol) in H_2O (50.0 ml) was treated with $NaBH_4$ (4.7 g, 127.0 mmol) and stirring was continued for 8 h at room temperature. After decomposition of the excess reagent by adding 2 N HCl under ice-cooling, the mixture was extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated *in vacuo*. The resulting residue was recrystallized from $CHCl_3$ to give 4-hydroxyphenylethanol (**10**) as colorless needles (2.1 g, 90.0%). This compound was identical with an authentic sample of 4-hydroxyphenylethanol.

[8-^{13}C]-**12b** (2.5 g) was reduced with $NaBH_4$ as described above to give [8-^{13}C]-4-hydroxyphenylethanol (**10**) (1.9 g, 91.0%). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (2H, td, J = 7.0 Hz, $^2J_{CH}$ = 5.0 Hz, H_2-7), 3.67 (2H, dt, $^1J_{CH}$ = 142.5 Hz, J = 7.0 Hz, H_2-8), 6.69 (2H, AA'BB' pattern, J_{ortho} = 8.3 Hz, H-3, -5), 7.02 (2H, AA'BB' pattern, J_{ortho} = 8.3 Hz, H-2, -6). EI-MS (70 eV) *m/z*: 139 $[M]^+$.

4-*O*-Acetylphenylethanol (10a) A solution of 1-acetyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridine (324.8 mg, 2.0 mmol) in dry THF (8.0 ml) was added dropwise to a solution of 4-hydroxyphenylethanol (**10**) (276.3 mg, 2.0 mmol) in 1 N NaOH (2.0 ml) and the mixture was stirred for 1 h at room temperature. After having been neutralized with 2 N HCl, the mixture was extracted with Et_2O. The Et_2O layer was washed with H_2O, dried and concentrated *in vacuo* to give the residue (282.6 mg), which was subjected to PTLC ($CHCl_3$: MeOH = 9 : 1) to yield 4-*O*-acetylphenylethanol (**10a**) as a colorless oil (263.2 mg, 73.0%). IR (neat) cm^{-1}: 3330, 1745, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, CH_3CO), 2.84 (2H, t, J = 6.7 Hz, H_2-7), 3.76—3.87 (2H, m, H_2-8), 7.02 (2H, AA'BB' pattern, J_{ortho} = 8.5 Hz, H-2, -6), 7.21 (2H, AA'BB' pattern, J_{ortho} = 8.5 Hz, H-3, -5). FAB-MS *m/z*: 181 $[M+H]^+$.

[8-^{13}C]-**10** (2.1 g) was subjected to selective acetylation with 1-

acetyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridine as described above to give [8-^{13}C]-**10a** (1.98 g, 72.3%). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, CH_3CO), 2.85 (2H, td, J=6.7 Hz, $^2J_{CH}$=5.0 Hz, H_2-7), 3.82 (2H, br dt, $^1J_{CH}$=142.0 Hz, J=7.0 Hz, H_2-8), 7.02 (2H, AA'BB' pattern, J_{ortho}=8.2 Hz, H-2, -6), 7.21 (2H, AA'BB' pattern, J_{ortho}=8.2 Hz, H-3, -5). FAB-MS m/z: 182 $[M+H]^+$.

Salidroside Pentaacetate (9a) A solution of **10a** (4.2 g, 23.3 mmol) in dry Et_2O (120.0 ml) was stirred, and Ag_2CO_3 (12.8 g, 46.4 mmol) and Drierite (33.0 g) were added to it at room temperature. After 10 min, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (19.2 g, 46.6 mmol) and I_2 (680 mg) were added to the mixture and stirring was continued for 14 h in the dark. The insoluble material was filtered off through a Celite layer, which was washed with Et_2O. The combined filtrate and washings were concentrated *in vacuo* to give the residue (16.0 g), which was purified by silica gel column chromatography (C_6H_6 : Et_2O=4 : 1) to afford **9a** as a colorless oil (6.2 g, 70.0%). IR (neat) cm^{-1}: 1765, 1740, 1500. ^{1}H-NMR ($CDCl_3$) δ: 1.91, 2.00, 2.08, 2.17, 2.28 (15H, each s, CH_3CO), 2.86 (1H, br ddd, J=14.5, *ca.* 7.0, *ca.* 6.0 Hz, H-7a), 2.92 (1H, br ddd, J=14.5, 8.0, *ca.* 7.0 Hz, H-7b), 3.65 (1H, ddd, J=9.5, 8.0, 6.6 Hz, H-8a), 3.68 (1H, ddd, J=9.5, 4.6, 2.5 Hz, H-5'), 4.13 (1H, ddd, J=9.5, 6.8, 6.0 Hz, H-8b), 4.20 (1H, dd, J=12.0, 2.5 Hz, H-6'a), 4.26 (1H, dd, J=12.0, 4.6 Hz, H-6'b), 4.48 (1H, d, J=8.0 Hz, H-1'), 4.99 (1H, dd, J=9.5, 8.0 Hz, H-2'), 5.08 (1H, t, J=9.6 Hz, H-4'), 5.18 (1H, t, J=9.5 Hz, H-3'), 6.99 (2H, AA'BB' pattern, J_{ortho}=8.6 Hz, H-2, -6), 7.20 (2H, AA'BB' pattern, J_{ortho}=8.6 Hz, H-3, -5). FAB-MS m/z: 511 $[M+H]^+$.

A solution of [8-^{13}C]-**10a** (1.9 g) was prepared in dry Et_2O (60 ml), and Ag_2CO_3 (5.8 g) and Drierite (15.0 g) were added to it. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (8.7 g) and I_2 (308 mg) were added to the solution, and the mixture was worked-up as described above to yield [8-^{13}C]-**9a** (3.0 g, 75.0%). ^{1}H-NMR ($CDCl_3$) δ: 1.91, 2.00, 2.08, 2.17, 2.28 (15H, each s, CH_3CO), 2.82—2.95 (2H, m, H_2-7), 3.66 (1H, dddd, $^1J_{CH}$=143.2 Hz, J=9.5, 7.9, 6.6 Hz, H-8a), 3.68 (1H, ddd, J=9.5, 4.6, 2.5 Hz, H-5'), 4.13 (1H, dddd, $^1J_{CH}$=143.2 Hz, J=9.5, 6.8, 6.0 Hz, H-8b), 4.20 (1H, dd, J=12.0, 2.5 Hz, H-6'a), 4.25 (1H, dd, J=12.0, 4.6 Hz, H-6'b), 4.48 (1H, dd, J=8.0 Hz, $^3J_{CH}$=4.5 Hz, H-1'), 4.98 (1H, dd, J=9.5, 8.0 Hz, H-2'), 5.08 (1H, t, J=9.6 Hz, H-4'), 5.18 (1H, t, J=9.5 Hz, H-3'), 6.99 (2H, AA'BB' pattern, J_{ortho}=8.6 Hz, H-2, -6), 7.20 (2H, AA'BB' pattern, J_{ortho}=8.6 Hz, H-3, -5). FAB-MS m/z: 512 $[M+H]^+$.

Salidroside (9) Methanolic NaOMe (0.1 N, 4.3 ml) was added to a solution of **9a** (401.2 mg, 0.86 mmol) in dry MeOH (4.2 ml) and the mixture was stirred for 1 h at room temperature. After neutralization of the mixture by adding Amberlite IR 120B (H^+ form), the resin was filtered off and washed with MeOH. The combined filtrate and washings were concentrated *in vacuo* to give a syrupy residue, which was recrystallized from *n*-hexane–EtOH to give colorless needles (251.1 mg, 97.7%) of **9**. $[\alpha]_D^{23}$ −40.6° (c=0.65, H_2O) [lit.,[12] $[\alpha]_D$ −30.0° (c=1.78, H_2O)]. mp 163—165.5 °C. IR (KBr) cm^{-1}: 3250, 1610, 1510. ^{1}H-NMR (CD_3OD) δ: 2.81 (1H, br ddd, J=14.0, 8.0, *ca.* 7.0, H-7a), 2.84 (1H, dt, J=14.0 Hz, 7.0 Hz, H-7b), 3.17 (1H, dd, J=9.0, 8.0 Hz, H-2'), 3.24 (1H, ddd, J=9.5, 5.5, 2.0 Hz, H-5'), 3.27 (1H, t, J=9.5 Hz, H-4'), 3.34 (1H, t, J=9.0 Hz, H-3'), 3.67 (1H, dd, J=11.6, 5.5 Hz, H-6'a), 3.69 (1H, ddd, J=9.0, 8.0, 6.5 Hz, H-8a), 3.85 (1H, dd, J=11.6, 2.0 Hz, H-6'b), 4.02 (1H, ddd, J=9.0, 8.0, *ca.* 7.0 Hz, H-8b), 4.28 (1H, d, J=8.0 Hz, H-1'), 6.68 (2H, AA'BB' pattern, J_{ortho}=8.8 Hz, H-3, -5), 7.06 (2H, AA'BB' pattern, J_{ortho}=8.8 Hz, H-2, -6). FAB-MS m/z: 301 $[M+H]^+$.

Methanolic NaOMe (0.1 N, 29.5 ml) was added to a solution of [8-^{13}C]-**9a** (3.0 g) in dry MeOH (30.0 ml) and the mixture was deacetylated as described above to give [8-^{13}C]-**9** (1.65 g, 93.5%). ^{1}H-NMR (CD_3OD) δ: 2.81 (1H, m, H-7a), 2.84 (1H, m, H-7b), 3.17 (1H, dd, J=9.0, 8.0 Hz, H-2'), 3.25 (1H, ddd, J=9.5, 5.5, 2.0 Hz, H-5'), 3.28 (1H, t, J=9.5 Hz, H-4'), 3.34 (1H, t, J=9.0 Hz, H-3'), 3.66 (1H, dd, J=11.6, 5.5 Hz, H-6'a), 3.69 (1H, dddd, $^1J_{CH}$=143.5 Hz, J=9.0, 8.0, 6.5 Hz, H-8a), 3.86 (1H, dd, J=11.6, 2.0 Hz, H-6'b), 4.02 (1H, dddd, $^1J_{CH}$=143.5 Hz, J=9.0, 8.0, *ca.* 7.0 Hz, H-8b), 4.28 (1H, dd, J=8.0 Hz, $^3J_{CH}$=4.2 Hz, H-1'), 6.68 (2H, AA'BB' pattern, J_{ortho}=8.8 Hz, H-3, -5), 7.06 (2H, AA'BB' pattern, J_{ortho}=8.8 Hz, H-2, -6). FAB-MS m/z: 302 $[M+H]^+$.

Salidroside Tetraacetate (9b) Activated zinc[17] (114.0 g) was added to a solution of **9a** (8.4 g, 16.4 mmol) in MeOH (100 ml) and the mixture was stirred for 4.2 h at room temperature. The zinc was filtered off through a Celite layer. The Celite layer was washed successively with $CHCl_3$ and MeOH. The combined filtrate and washings were concentrated *in vacuo* to give the residue, which was subjected to column chromatography (C_6H_6 : Et_2O=1 : 1) onsilica gel to afford **9b** (3.3 g, 43.3%) and **9c** (2.4 g, 34.2%), each as a colorless oil. **9c** was identified as the 3'-deacetylated derivative of **9b** (^{1}H-NMR, FAB-MS). Compound **9b**: IR (neat) cm^{-1}: 3310, 2910, 1740, 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.92, 1.99, 2.02, 2.09 (12H each s, CH_3CO), 2.80 (1H, br ddd, J=14.0, *ca.* 7.0, *ca.* 6.0 Hz, H-7a), 2.83 (1H, dt, J=14.0, 7.5 Hz, H-7b), 3.62 (1H, dt, J=9.5, 7.5, H-8a), 3.67 (1H, ddd, J=9.6, 5.0, 2.5 Hz, H-5'), 4.08 (1H, ddd, J=9.5, 7.0, 6.0 Hz, H-8b), 4.13 (1H, dd, J=12.3, 2.5 Hz, H-6'a), 4.26 (1H, dd, J=12.0, 5.0 Hz, H-6'b), 4.48 (1H, d, J=8.0, H-1'), 4.99 (1H, dd, J=9.5, 8.0 Hz, H-2'), 5.08 (1H, t, J=9.6 Hz, H-4'), 5.18 (1H, t, J=9.5 Hz, H-3'), 6.74 (2H, AA'BB' pattern, J_{ortho}=8.3 Hz, H-3, -5), 7.05 (2H, AA'BB' pattern, J_{ortho}=8.3 Hz, H-2, -6). FAB-MS m/z: 469 $[M+H]^+$. Compound **9c**: ^{1}H-NMR ($CDCl_3$) δ: 1.93, 2.08, 2.12 (9H, each s, CH_3CO), 2.78 (1H, ddd, J=14.0, 7.0, 6.0 Hz, H-7a), 2.82 (1H, dt, J=14.0, 7.5 Hz, H-7b), 3.50 (1H, ddd, J=9.6, 5.0, 2.5 Hz, H-5'), 3.58 (1H, t, J=9.5 Hz, H-3'), 3.61 (1H, ddd, J=9.5, 7.5, 7.0 Hz, H-8a), 4.07 (1H, ddd, J=9.5, 7.0, 6.0 Hz, H-8b), 4.32 (1H, dd, J=12.1, 2.1 Hz, H-6'a), 4.45 (1H, d, J=8.0, H-1'), 4.47 (1H, dd, J=12.1, 4.3 Hz, H-6'b), 4.92 (1H, dd, J=9.5, 8.0 Hz, H-2'), 5.03 (1H, t, J=9.5 Hz, H-4'), 6.74 (2H, AA'BB' pattern, J_{ortho}=8.5 Hz, H-3, -5), 7.04 (2H, AA'BB' pattern, J_{ortho}=8.5 Hz, H-2, -6). FAB-MS m/z: 427 $[M+H]^+$.

Cornoside Tetraacetate (4a) A solution of **9b** (3.0 g, 6.4 mmol) was prepared in CH_2Cl_2 (140.0 ml), and to it were added H_2O (140.0 ml) and TTP (1.0 mmol), which was prepared from Tl_2O_3 (3.0 g) and 60% $HClO_4$ (50.0 ml). The mixture was vigorously stirred for 15 min and the CH_2Cl_2 layer was separated and washed successively with saturated aqueous $NaHCO_3$, H_2O and brine, and concentrated *in vacuo*. The residue (1.0 g) was purified by silica gel column chromatography (C_6H_6 : Et_2O=1 : 1) to give **4a** as a colorless oil (358.0 mg, 11.5%). IR (neat) cm^{-1}: 3420, 3300, 1760, 1665, 1650, 1625. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.07 (2H, m, H_2-7), 2.01, 2.04, 2.06, 2.10 (12H, each s, CH_3CO), 3.70 (1H, ddd, J=10.2, 7.0, 5.5 Hz, H-8a), 3.71 (1H, ddd, J=9.6, 5.0, 2.5 Hz, H-5'), 4.09 (1H, ddd, J=10.2, 7.0, 5.5 Hz, H-8b), 4.18 (1H, dd, J=12.5, 2.5 Hz, H-6'a), 4.25 (1H, dd, J=12.5, 5.0 Hz, H-6'b), 4.52 (1H, d, J=8.0, H-1'), 5.00 (1H, dd, J=9.5, 8.0 Hz, H-2'), 5.09 (1H, t, J= 9.6 Hz, H-4'), 5.21 (1H, t, J=9.5 Hz, H-3'), 6.13—6.19 (2H, m, H-3, -5), 6.87—6.92 (2H, m, H-2, -6). FAB-MS m/z: 485 $[M+H]^+$.

Cornoside (4) A (Photooxygenation of **9**): A mixture of **9** (100 mg, 0.33 mmol) and Rose Bengal (9.4 mg) in MeOH (28.0 ml) was irradiated under a halogen lamp (Ushio, JPD 100V-500 WC) in a Pyrex reactor with bubbling O_2 for 3 h at 20 °C. The reaction mixture was treated with Me_2S (0.062 ml, 0.83 ml) with stirring for 4 h and then concentrated *in vacuo* to give a residue (158.8 mg), which was purified by PTLC (C_6H_6 : EtOAc : EtOH : H_2O=1 : 4 : 1 : 0.5) to yield **4** as a powder (52.1 mg, 49.4%) and recovered **9** (38.7 mg).

B (Zemplén Deacetylation of **4a**): Methanolic NaOMe (0.1 N, 1.8 ml) was added to a solution of **4a** (40.3 mg, 0.077 mmol) in dry MeOH (2.0 ml) and the mixture was worked-up as described above. The product (28.5 mg) was purified by PTLC ($CHCl_3$: MeOH : H_2O : AcOH=10 : 7 : 2 : 0.1) to give **4** (14.8 mg, 61.1%), which was identical with an authentic sample of cornoside. $[\alpha]_D^{23}$ −19.1° (c=0.99, EtOH) [lit.,[1] $[\alpha]_D$ −20.3° (c=1.13, EtOH), lit.,[12] $[\alpha]_D$ −10.5° (c=0.42, MeOH)]. FAB-MS m/z: 315 $[M-H]^-$.

[8-^{13}C]-**9** (100.0 mg) was photooxygenated followed by reduction with Me_2S as described above to give [8-^{13}C]-**4** (47.5 mg, 45.0%). ^{1}H-NMR (CD_3OD) δ: 2.04 (2H, td, $^2J_{CH}$=7.0 Hz, J=6.5 Hz, H_2-7), 3.13 (1H, dd, J=9.0, 8.0, H-2'), 3.26 (1H, t, J=9.0 Hz, H-4'), 3.33 (1H, t, J=9.0 Hz, H-3'), 3.62 (1H, ddt, $^1J_{CH}$=141.5 Hz, J=10.0, 6.5 Hz, H-8a), 3.64 (1H, dd, J=12.0, 5.5 Hz, H-6'a), 3.84 (1H, dd, J=12.0, 2.0 Hz, H-6'b), 3.99 (1H, ddt, $^1J_{CH}$=145.5 Hz, J=10.0, 6.5 Hz, H-8b), 4.21 (1H, dd, J=8.0 Hz, $^3J_{CH}$=4.0 Hz, H-1'), 6.11 (1H, dd, J=10.0, 2.0 Hz, H-3 or -5), 6.12 (1H, dd, J=10.0, 2.0 Hz, H-3 or -5), 7.02 (2H, d, J=10.0 Hz, H-2, -6). FAB-MS m/z: 318 $[M+H]^+$.

Reformatsky Reaction of 1,4-Cyclohexanedione Monoethylene Ketal (13) and Ethyl Bromoacetate One-tenth of a solution of ethyl bromoacetate (0.36 ml, 3.2 mmol) in dry C_6H_6 (2.4 ml) was added to a stirred mixture of activated zinc (251.0 mg, 3.8 mg atom) and dry C_6H_6 (1.5 ml) at room temperature under argon. After 15 min, the remaining solution of ethyl bromoacetate was added dropwise and the whole was refluxed for 30 min. It was then the ice-cooled, and a solution of the ketal **13** (500 mg, 3.2 mmol) in dry C_6H_6 (3.2 ml) was added dropwise over a period of 15 min. The reaction mixture was refluxed for 3 h, quenched with ice-water, and filtered through Celite. The residue obtained through concentration of the filtrate *in vacuo* was extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated *in vacuo*. The

resulting residue (706.0 mg) was purified by PTLC (C_6H_6 : Et_2O = 1 : 1) to afford the ester **14** as a pale yellow oil (603.7 mg, 77.3%). IR (neat) cm^{-1}: 3450, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.59 (2H, m, H-2eq, -6eq), 1.68 (2H, td, J = 13.0, 4.5 Hz, H-2ax, -6ax), 1.79 (2H, m, H-3eq, -5eq), 1.95 (2H, td, J = 13.0, 4.5 Hz, H-3ax, -5ax), 2.49 (2H, s, H_2-7), 3.88—3.99 (4H, m, OCH_2CH_2O), 4.18 (2H, q, J = 7.0 Hz, $O\underline{CH_2}CH_3$). EI-MS m/z: 244 $[M]^+$. HR-EI-MS m/z: 244.1307 (Calcd for $C_{12}H_{20}O_5$: 244.1311).

A solution of [2-^{13}C]ethyl bromoacetate (1.0 g, 6.0 mmol) (^{13}C-enrichment 99%, Aldrich) and the ketal **13** (935.0 mg, 6.0 mmol) in dry C_6H_6 (3.5 ml) was added dropwise to a mixture of activated zinc (470.0 mg, 7.2 mg atom) and dry C_6H_6 (3.5 ml) under argon. The mixture was refluxed for 3 h and worked-up according to the same procedure as described above to give the product (1.32 g), which was purified by PTLC to afford [7-^{13}C]-**14** (191.2 mg, 13.6%, The low yield may have been due to insufficient drying of [2-^{13}C]ethyl bromoacetate). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (2H, d, $^1J_{CH}$ = 125.0 Hz, H_2-7). FAB-MS m/z: 246 $[M+H]^+$. ^{13}C-enrichment factor: 97.2% (calculated on the basis of FAB-MS data). The ^{13}C-NMR spectrum of [7-^{13}C]-**14** exhibited a strongly enriched ^{13}C signal arising from the methyl carbon of C-7 at δ 45.24. In the C-7 labeled compounds mentioned below, it was confirmed by examination of their ^{13}C-NMR spectra that the C-7 carbon signals were enhanced.

Reduction of the Ester 14 A solution of **14** (500.0 mg, 2.1 mmol) in dry THF (7.0 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (116.0 mg, 3.0 mmol) in dry THF under argon, and the mixture was stirred for 30 min at room temperature. After decomposition of the excess reagent by adding H_2O under ice-cooling, the mixture was concentrated *in vacuo* and the residue was extracted continuously with CH_2Cl_2. The crystalline residue obtained by the removal of the solvent *in vacuo* was recrystallized from Et_2O to give colorless needles (346.0 mg, 83.8%) of the alcohol **15**. mp 57.5—69.7 °C. IR (KBr) cm^{-1}: 3360, 2940. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (2H, m, H-2eq, -6eq), 1.63 (2H, td, J = 13.0, 4.5 Hz, H-2ax, -6ax), 1.73 (2H, t, J = 6.0 Hz, H_2-7), 1.78 (2H, m, H-3eq, -5eq), 1.90 (2H, td, J = 13.0, 4.5 Hz, H-3ax, -5ax), 3.88 (2H, m, H_2-8), 3.92—3.99 (4H, m, OCH_2CH_2O). FAB-MS m/z: 203 $[M+H]^+$. HR-FAB-MS m/z: 203.1203 (Calcd for $C_{10}H_{19}O_4$: 203.1205).

[7-^{13}C]-**14** (270.0 mg) was reduced with $LiAlH_4$ (62.6 mg) as described above to give a residue (240.2 mg), which was purified by PTLC ($CHCl_3$: MeOH = 19 : 1) to yield [7-^{13}C]-**15** (214.9 mg, 96.4%). ^{1}H-NMR ($CDCl_3$) δ: 1.73 (2H, dt, $^1J_{CH}$ = 124.5 Hz, J = 5.6 Hz, H_2-7). FAB-MS m/z: 204 $[M+H]^+$.

Glycosidation of the Alcohol 15 A mixture of **15** (260.0 mg, 1.3 mmol), Ag_2CO_3 (1.3 g, 4.7 mmol) and Drierite (52.1 g) in dry $CHCl_3$ (50.0 ml) was stirred for 10 min. After addition of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (593.0 mg, 1.7 mmol) and I_2, the mixture was stirred for 22 h. The crude product (894.0 mg) obtained by work-up in the usual way was then subjected to column chromatography on silica gel with $CHCl_3$–MeOH (46 : 1) as an eluent to give **16** as a colorless oil (336.0 mg, 49.0%) and recovered **15** (122.0 mg, 47.0%). IR (neat) cm^{-1}: 3495, 2940, 1760, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.54—1.64 (4H, m, H-2, -6), 1.70 (2H, m, H_2-7), 1.75—1.84 (2H, m, H-3eq, -5eq), 1.92 (2H, m, H-3ax, -5ax), 2.00, 2.02, 2.04, 2.09 (12H, each s, CH_3CO), 3.70 (1H, ddd, J = 9.6, 4.5, 2.5 Hz, H-5′), 3.68—3.72 (1H, ddd, J = 10.0, 6.0, 5.0 Hz, H-8a), 3.90—3.97 (4H, m, OCH_2CH_2O), 4.12 (1H, ddd, J = 10.0, 6.0, 5.0 Hz, H-8b), 4.16 (1H, dd, J = 12.5, 2.5 Hz, H-6′a), 4.26 (1H, dd, J = 12.5, 4.5 Hz, H-6′b), 4.52 (1H, d, J = 8.0 Hz, H-1′), 4.98 (1H, dd, J = 9.5, 8.0 Hz, H-2′), 5.09 (1H, t, J = 9.6 Hz, H-4′), 5.21 (1H, t, J = 9.5 Hz, H-3′). FAB-MS m/z: 533 $[M+H]^+$. HR-FAB-MS m/z: 533.2150 (Calcd for $C_{24}H_{37}O_{13}$: 533.2159).

[7-^{13}C]-**15** (140.0 mg) was glycosidated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (365.0 mg) as described above to give [7-^{13}C]-**16** (137.7 mg, 37.3%) and recovered [7-^{13}C]-**15** (60.2 mg, 43.1%). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (2H, dm, $^1J_{CH}$ = *ca.* 140 Hz, H_2-7), 3.68—3.73 (1H, dddd, J = 10.0, 6.0, 5.0 Hz, $^2J_{CH}$ = 2.0 Hz, H-8a), 4.12 (1H, dddd, J = 10.0, 6.0, 5.0 Hz, $^2J_{CH}$ = 2.0 Hz, H-8a). FAB-MS m/z: 534 $[M+H]^+$.

Rengyoside B Tetraacetate (7a) A solution of **16** (101.0 mg, 0.2 mmol) in Me_2CO (5.0 ml) was treated with *p*-TsOH · H_2O (10.0 mg, 0.053 mmol) and the mixture was stirred for 18 h. After addition of H_2O (3.0 ml) to the solution, the mixture was neutralized with saturated aqueous $NaHCO_3$ under ice-cooling, concentrated *in vacuo* and extracted with $CHCl_3$. The $CHCl_3$ layer was worked-up in the usual way to give the residue (111.0 mg), which was subjected to PTLC (Et_2O : Me_2CO = 9 : 1). The main product yielded **7a** as colorless needles (65.0 mg, 69.8%) on recrystallization from Et_2O. mp 132.5—134.0 °C. IR (KBr) cm^{-1}: 3420, 1750, 1740, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (2H, tt, J = 13.0, 4.0 Hz, H-2ax, -6ax), 1.87 (2H, t, J = 6.0 Hz, H_2-7), 2.02, 2.04, 2.06, 2.10 (12H, each s, CH_3CO), 2.22 (2H, br ddd, J = *ca.* 15.0, 5.0, 3.0 Hz, H-3eq, -5eq), 2.75 (1H, br dd, J = 13.5, 5.6 Hz, H-3ax or -5ax), 2.80 (1H, br dd, J = 13.5, 5.6 Hz, H-5ax or -3ax), 3.73 (1H, ddd, J = 9.6, 4.5, 2.5 Hz, H-5′), 3.76 (1H, ddd, J = 11.5, 6.0, 5.0 Hz, H-8a), 4.18 (1H, ddd, J = 11.5, 6.0, 5.0 Hz, H-8b), 4.18 (1H, J = 12.5, 2.5 Hz, H-6′a), 4.26 (1H, J = 12.5, 4.5 Hz, H-6′b), 4.53 (1H, d, J = 8.0 Hz, H-1′), 5.00 (1H, dd, J = 9.5, 8.0 Hz, H-2′), 5.10 (1H, t, J = 9.6, H-4′), 5.23 (1H, t, J = 9.5 Hz, H-3′). FAB-MS m/z: 489 $[M+H]^+$.

p-TsOH · H_2O (19.9 mg) was add to a solution of [7-^{13}C]-**16** (200.7 mg) in Me_2CO (10.0 ml) and worked-up as described above to yield [7-^{13}C]-**7a** (139.2 mg, 75.2%). ^{1}H-NMR ($CDCl_3$) δ: 1.88 (2H, dt, $^1J_{CH}$ = 125.0 Hz, J = 6.0 Hz, H_2-7), 3.75 (1H, br dddd, J = 11.5, 6.0, 5.0 Hz, $^2J_{CH}$ = *ca.* 3.0 Hz, H-8a), 4.18 (1H, br dddd, J = 11.5, 6.0, 5.0 Hz, $^2J_{CH}$ = *ca.* 3.0 Hz, H-8b). FAB-MS m/z: 490 $[M+H]^+$.

Rengyoside B (7) 0.2 N NaOH (13.09 ml) was added to a solution of **7a** (300.0 mg, 0.61 mmol) in Me_2CO (9.0 ml) and the mixture was stirred for 4 h at room temperature. After having been neutralized with 0.1 N HCl under ice-cooling, the mixture was evaporated *in vacuo* to give a residue, which was subjected to PTLC (Et_2O : Me_2CO = 9 : 1). The residue obtained from the main band was subjected to column chromatography on SP207 and eluted successively with H_2O and MeOH. The MeOH eluate was concentrated *in vacuo* to give **7** as a colorless oil (164.8 mg, 83.8%). $[\alpha]_D^{23}$ −17.6° (c = 0.46, EtOH) [lit.,[2]) $[\alpha]_D$ −10.4° (c = 0.28, EtOH)]. IR (neat) cm^{-1}: 3250, 2925, 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (2H, br td, J = 13.0, 5.0 Hz, H-2ax, -6ax), 1.90 (2H, t, J = 7.0 Hz, H_2-7), 2.02 (2H, br d, J = 13.0 Hz, H-2eq, -6eq), 2.20 (2H, br dt, J = 15.0, 4.0 Hz, H-3ax, -5eq), 2.63—2.72 (2H, m, H-3eq, -5ax), 3.15 (1H, dd, J = 9.5, 8.0 Hz, H-2′), 3.65 (1H, dd, J = 11.5, 5.0 Hz, H-6′a), 3.76 (1H, dt, J = 10.5, 7.0 Hz, H-8a), 3.86 (1H, dd, J = 11.5, 1.5 Hz, H-6′b), 4.13 (1H, dt, J = 10.5, 7.0 Hz, H-8b), 4.27 (1H, d, J = 8.0 Hz, H-1′). FAB-MS m/z: 321 $[M+H]^+$.

A solution of [7-^{13}C]-**7a** (121.2 mg) in Me_2CO (5.3 ml) was treated with 0.2 N NaOH (3.6 ml) and the mixture was stirred for 4 h at room temperature. It was treated in the same manner as described above to give [7-^{13}C]-**7** (50.3 mg, 63.3%). ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, dt, $^1J_{CH}$ = 126.0 Hz, J = 7.0 Hz, H_2-7), 3.75 (1H, dtd, J = 10.5, 7.0 Hz, $^2J_{CH}$ = 2.5 Hz, H-8a), 4.12 (1H, dtd, J = 10.5, 7.0 Hz, $^2J_{CH}$ = 2.5 Hz, H-8b). FAB-MS m/z: 322 $[M+H]^+$.

Reduction of Rengyoside B Tetraacetate (7a) $NaBH_4$ (17.8 mg, 0.47 mmol) was added to a solution of **7a** (460.0 mg, 0.94 mmol) in EtOH (15.0 ml) and the mixture was stirred for 30 min at room temperature. It was worked-up in the usual way to give the product (205.2 mg), which was subjected to column chromatography on silica gel with Et_2O. Fractions of 10 ml were collected. Fractions 40—99 were concentrated *in vacuo* to give **6b** as a white powder (40.9 mg, 8.9%). ^{1}H-NMR ($CDCl_3$) δ: 1.43—1.53, 1.68—1.95 (10H, m, H-2, 3, 5, 6, 7), 2.00, 2.03, 2.06, 2.10 (12H, each s, CH_3CO), 3.66—3.75 (2H, m, H-8a, -5′), 3.90—3.96 (1H, m, $W_{1/2}$ = 13.0 Hz, H-4), 4.13 (1H, ddd, J = 10.0, 6.5, 5.0 Hz, H-8b), 4.17 (1H, dd, J = 12.5, 2.5 Hz, H-6′a), 4.26 (1H, dd, J = 12.5, 4.5 Hz, H-6′b), 4.52 (1H, d, J = 8.0 Hz, H-1′), 4.98 (1H, dd, J = 9.5, 8.0 Hz, H-2′), 5.09 (1H, t, J = 10.0 Hz, H-4′), 5.21 (1H, t, J = 9.5 Hz, H-3′). FAB-MS m/z: 491 $[M+H]^+$. The residue obtained from Fractions 100—145 was recrystallized from AcOEt to afford **6a** as colorless needles (125.8 mg, 27.2%). mp 125.5—127.0 °C. IR (KBr) cm^{-1}: 3380, 2930, 1740. ^{1}H-NMR ($CDCl_3$) δ: 1.28—1.38, 1.63—1.82 (10H, m, H-2, 3, 5, 6, 7), 2.01, 2.03, 2.05, 2.10 (12H, each s, CH_3CO), 3.55—3.62 (1H, m, $W_{1/2}$ = 20 Hz, H-4), 3.68—3.71 (2H, m, H-8a, -5′), 4.11 (1H, ddd, J = 10.0, 6.5, 5.0 Hz, H-8b), 4.16 (1H, dd, J = 12.5, 2.5 Hz, H-6′a), 4.26 (1H, dd, J = 12.5, 4.5 Hz, H-6′b), 4.51 (1H, d, J = 8.0 Hz, H-1′), 4.98 (1H, dd, J = 9.5, 8.0 Hz, H-2′), 5.09 (1H, t, J = 10.0 Hz, H-4′), 5.21 (1H, t, J = 9.5 Hz, H-3′). FAB-MS m/z: 491 $[M+H]^+$.

Rengyoside A (6) A (Reduction of **7**): $NaBH_4$ (6.6 mg, 0.2 mmol) was added to a solution of **7** (113.4 mg, 0.35 mmol) in EtOH (5.0 ml) and the mixture was stirred for 30 min at room temperature. The mixture was worked-up in the usual way to give the product (164.6 mg), which was purified through PTLC ($CHCl_3$: MeOH : H_2O : AcOH = 7 : 3 : 0.5 : 0.1) to yield **6** (114.6 mg, 100%) as a syrupy compound.

B (Zemplén Deacetylation of **6a**): Methanolic NaOMe (0.1 N, 2.0 ml) was added to a solution of **6a** (125.8 mg, 0.26 mmol) in dry MeOH (2.0 ml). After having been stirred for 40 min at room temperature, the

mixture was worked-up in the usual way to give **6** (87.7 mg, 100%). $[\alpha]_D^{23}$ $-13.5°$ ($c=0.46$, EtOH) [lit.,[12] $[\alpha]_D^{23}$ $-13.3°$ ($c=0.35$, MeOH)]. IR (neat): 3300, 2900. ^{1}H-NMR (CD_3OD) δ: 1.37—1.46, 1.59—1.76 (8H, m, H-2, 3, 5, 6), 1.75 (1H, dt, $J=14.0$, 7.0 Hz, H-7a), 1.78 (1H, dt, $J=14.0$, 7.0 Hz, H-7b), 3.14 (1H, $J=9.0$, 8.0 Hz, H-2′), 3.48—3.55 (1H, m, $W_{1/2}=20.0$ Hz, H-4), 3.65 (1H, dd, $J=12.0$, 5.5 Hz, H-6′a), 3.70 (1H, dt, $J=10.0$, 7.0 Hz, H-8a), 3.86 (1H, dd, $J=12.0$, 1.5 Hz, H-6′b), 4.07 (1H, dt, $J=10.0$, 7.0 Hz, H-8b), 4.25 (1H, d, $J=8.0$ Hz, H-1′). FAB-MS *m/z*: 321 $[M-H]^-$.

A solution of [7-^{13}C]-**7** (30.0 mg) in EtOH (2.0 ml) was reduced with $NaBH_4$ (1.7 mg) according to procedure A to give [7-^{13}C]-**6** (29.5 mg, 97.4%). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (1H, ddt, $^1J_{CH}=125.0$ Hz, $J=14.0$, 7.0 Hz, H-7a), 1.77 (1H, ddt, $^1J_{CH}=125.0$ Hz, $J=14.0$, 7.0 Hz, H-7b), 3.70 (1H, dtd, $J=10.0$, 7.0 Hz, $^2J_{CH}=2.5$ Hz, H-8a), 4.13 (1H, dtd, $J=10.0$, 7.0 Hz, $^2J_{CH}=2.5$ Hz, H-8b). FAB-MS *m/z*: 322 $[M-H]^-$.

Partial Hydrogenation of Cornoside (4) A solution of **4** (41.1 mg, 0.13 mmol) in EtOH (1.5 ml) was hydrogenated in the presence of 5% Pd–C (4.1 mg) and the suspension was stirred for 2.5 h at room temperature with monitoring by TLC (AcOEt : MeOH : $H_2O=10:1.5:0.5$). The catalyst was filtered off and washed with MeOH, then the filtrate and washings were combined and concentrated *in vacuo*. The resulting residue (36.8 mg) was subjected to PTLC (AcOEt : MeOH : $H_2O=10:1.5:0.5$, 4 developments). Of the three major bands, the most polar one gave **7** (7.5 mg, 39.4%), and the less polar one gave **11** as a colorless oil (7.3 mg, 38.6%), which was a diastereomeric mixture in a ratio of 1 : 1 as judged from the ^{1}H- and ^{13}C-NMR data. The least polar one was identified as the starting material (22.3 mg). Compound **11**: $[\alpha]_D^{15}$ $-12.1°$ ($c=1.12$, MeOH). IR (neat) cm^{-1}: 3330, 3300. ^{1}H-NMR (CD_3OD) δ: 1.946—2.046 (2H, m, H-6a), 2.025—2.103 (4H, m, H-7), 2.188—2.260 (2H, m, H-6b), 2.471, 2.473 (each 1H, ddd, $J=17.0$, 11.5, 5.0 Hz, H-5ax), 2.550, 2.552 (each 1H, ddd, $J=17.0$, 6.5, 5.0 Hz, H-5eq), 3.154, 3.156 (each 1H, dd, $J=9.0$, 7.5 Hz, H-2′), 3.64 (3H, m, H-5′, 6′a), 3.772, 3.780 (each 1H, dt, $J=10.0$, 6.0 Hz, H-8a), 3.86 (2H, br dd, $J=12.0$, *ca.* 1.0 Hz, H-6′b), 4.135, 4.141 (each 1H, dt, $J=10.0$, 6.0 Hz, H-8b), 4.277, 4.297 (each 1H, d, $J=7.5$ Hz, H-1′), 5.86 (2H, d, $J=10.0$ Hz, H-3), 6.958, 6.960 (each 1H, dd, $J=10.0$, 1.0 Hz, H-2). FAB-MS *m/z*: 319 $[M+H]^+$.

[8-^{13}C]-**4** (475 mg) was hydrogenated over 5% Pd–C (48 mg) with stirring for 3.5 h as described above to give [8-^{13}C]-**11** (15.4 mg, 7.0%), [8-^{13}C]-**7** (37.4 mg, 17.0%), and 224.6 mg of the starting material. ^{1}H-NMR (CD_3OD) δ: 3.772, 3.780 (each 1H, ddt, $^1J_{CH}=142.5$ Hz, $J=10.0$, 6.0 Hz, H-8a), 4.135, 4.141 (each 1H, ddt, $^1J_{CH}=145.0$ Hz, $J=10.0$, 6.0 Hz, H-8b), 4.270, 4.280 (each 1H, dd, $J=7.5$ Hz, $^3J_{CH}=1.0$ Hz, H-1′), FAB-MS *m/z*: 320 $[M+H]^+$.

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17) Activation of zinc: zinc dust (114.0 g) was stirred for 10 min with 10% aqueous HCl (120.0 ml). The supernatant liquid was decanted and the zinc was washed successively with acetone (100 ml × 2), Et_2O (100 ml × 3) and MeOH (100 ml × 2).