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INTERMEDIACY OF 6-HYDROXYLOGANIN IN THE RING CLEAVAGE COURSE OF LOGANIN TO SECOLOGANIN*†

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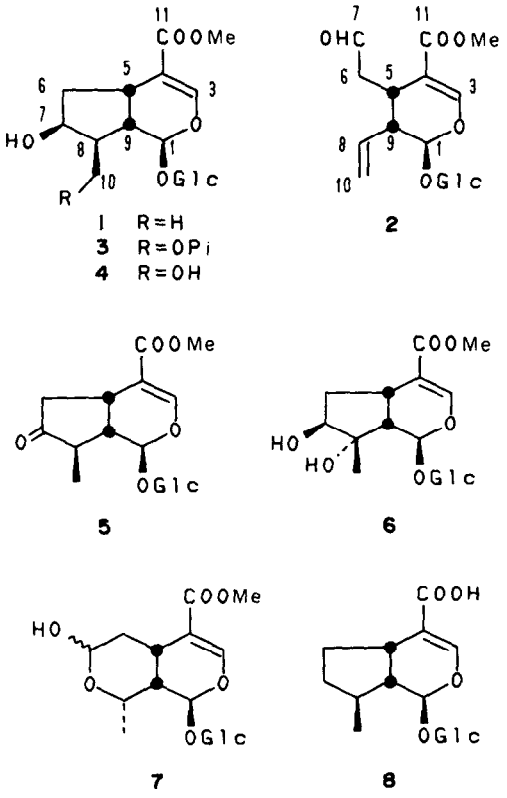
Key Word Index—Biosynthesis; ring cleavage; loganin; 6,7-stereoisomer of 6-hydroxyloganin; secologanin; stereochemical course of the reduction; deuterium labelling.

Abstract—A possible biosynthetic pathway from loganin to secologanin through ring cleavage of 6-hydroxyloganin was ruled out in feeding experiments in which *Eustoma russellianum, Swertia japonica, Lonicera morrowii* and *Adina pilulifera* were each presented with three C-6 and C-7 stereoisomers of 6-hydroxy [7-^{2}H] loganin as well as [6,6,7,8-$^2H_4$]- and [6,6,7,8, carbomethoxy-$^2H_7$]-loganin. In an associated experiment, the reduction of the aldehyde group of secologanin leading to sweroside was shown to proceed by hydride ion attack from the *si* face.

INTRODUCTION

Loganin (**1**) and secologanin (**2**) are important intermediates in the biosynthesis of secoiridoid glucosides and monoterpenoid indole alkaloids [1–4]. The ring cleavage of loganin (**1**) to form secologanin (**2**) had been believed to proceed via 10-phosphoryloxyloganin (**3**) [5] until feeding and dilution experiments with tritium labelled 10-hydroxyloganin (**4**) and related compounds showed this not to be the case [6, 7]. Other possible pathways such as a Baeyer–Villiger type oxidation of 7-dehydrologanin (**5**) or cleavage between the C-7 and C-8 vicinal hydroxyl groups of 8-hydroxyloganin (**6**) can also be ruled out for the following reasons: [7-^{3}H] loganin (**1**) is incorporated into secologanin (**2**), morroniside (**7**) and indole alkaloids such as ajmalicine with retention of the label [8–10]; [7,8-$^3H_2$] loganic acid (**8**) is also incorporated into **2** and **7** with retention of both labels [11]; and finally, [6,6,8-$^3H_3$] loganin (**1**) is incorporated into camptothecin with retention of 8-^{3}H [12].

In this study, we examined another possible cleavage route of **1** to secologanin (**2**), which proceeds via 6-hydroxyloganin (**9**) or its stereoisomers (or corresponding phosphates). In addition, we have obtained stereochemical evidence pertaining to the reduction process of the aldehyde group of **2** leading to sweroside (**11**).



RESULTS AND DISCUSSION

Of the postulated intermediates mentioned above, 6β-hydroxyloganin (**9a**) [13] or its phosphate (**10a**) best seemed to satisfy the stereochemical requirements. In preparing the labelled compounds to be used for the feeding experiments, we tried to synthesize not only **9a**, but also its three stereoisomers (**9b**, **9c**, **9d**) at C-6 and C-7.

7-*O*-Tosyl-7-epiloganin tetraacetate (**12**) prepared from loganin (**1**) through several steps [14, 15] was treated with 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) in THF to

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†A part of this work has been reported in a review [1].

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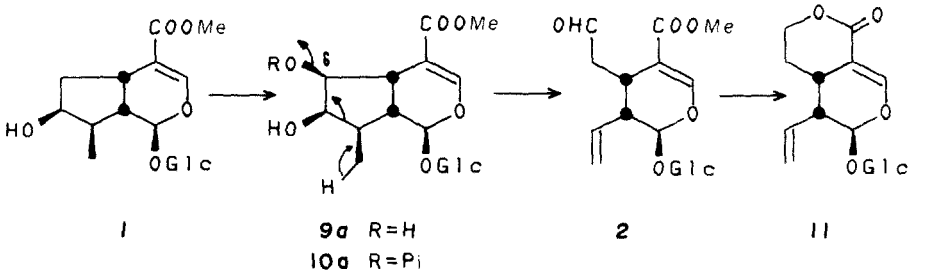

Fig. 1.

give 6,7-dehydro- (**13**) and 7,8-dehydrodeoxyloganin tetraacetate (**14**) in a ratio of 5:1. This mixture of dehydrated products, without separation, was subjected to *cis*-hydroxylation with osmium tetroxide to give the *cis*-diols **15** and **16** in a ratio of 22:5 along with a small amount of 8-hydroxy-8-epiloganin (**17**). The ^{1}H NMR spectrum of **15** exhibited signals of H-6 and H-7 at δ3.73 (*dd*, $J_{5,6}=7.1$ Hz, $J_{6,7}=4.4$ Hz) and 3.96 (*dd*, $J_{6,7}=4.4$ Hz, $J_{7,8}=3.7$ Hz), while that of **16** exhibited signals at δ4.27 (*t*, $J_{5,6}=J=_{6,7}=4.0$ Hz) and 3.69 (*dd*, $J_{7,8}=8.5$ Hz, $J_{6,7}=4.0$ Hz). In agreement with a previous generalization about 6-hydroxylated iridoids [16], it was difficult to determine the configurations at C-6 and C-7 of either compound only from ^{1}H NMR data. Therefore, **15** and **16** were converted into hexaacetates **18** and **19**, respectively. In NOE experiments, **18** showed 8% NOE between H-5 and H-9 and no effect between H-5 and H-6, whereas **19** showed 8% NOE between H-5 and H-6. Thus, it was concluded that **15** and **18** were respectively the tetra- and hexaacetate of 6β-hydroxyloganin (**9a**), and **16** and **19** the respective acetates of 6α-hydroxy-7-epiloganin (**9b**). This conclusion was supported by the appearance of the H-1 signal of hexaacetate **18** at δ5.28 as a doublet with $J=2.4$ Hz, as well as that of acetate **19** at δ5.07 as a doublet with $J=8.1$ Hz. These finding were also in accord with the report by Jensen *et al.* [16] that the $J_{1,9}$ value of iridoid glucosides having 6α-hydroxy or 6α-acetoxy group is larger than 8 Hz. Zemplén reaction of tetraacetates **15** and **16** gave 6β-hydroxyloganin (**9a**) and 6α-hydroxy-7-epiloganin (**9b**), respectively.

Next, we tried to obtain 6β-hydroxy-7-epiloganin (**9c**) and 6α-hydroxyloganin (**9d**) both having 6,7-*trans*-dihydroxy groups. Oxidation of a mixture of 6,7-dehydro- (**13**) and 7,8-dehydrodeoxyloganin tetraacetate (**14**) with *m*-chloroperbenzoic acid in CH_2Cl_2 gave 6,7-epoxydeoxyloganin tetraacetate (**20**) as the sole product. Its ^{1}H NMR spectrum showed doublets ($J=2.7$ Hz) due to H-6 and H-7 at δ3.78 and 3.27 respectively, and gave no clue as to the

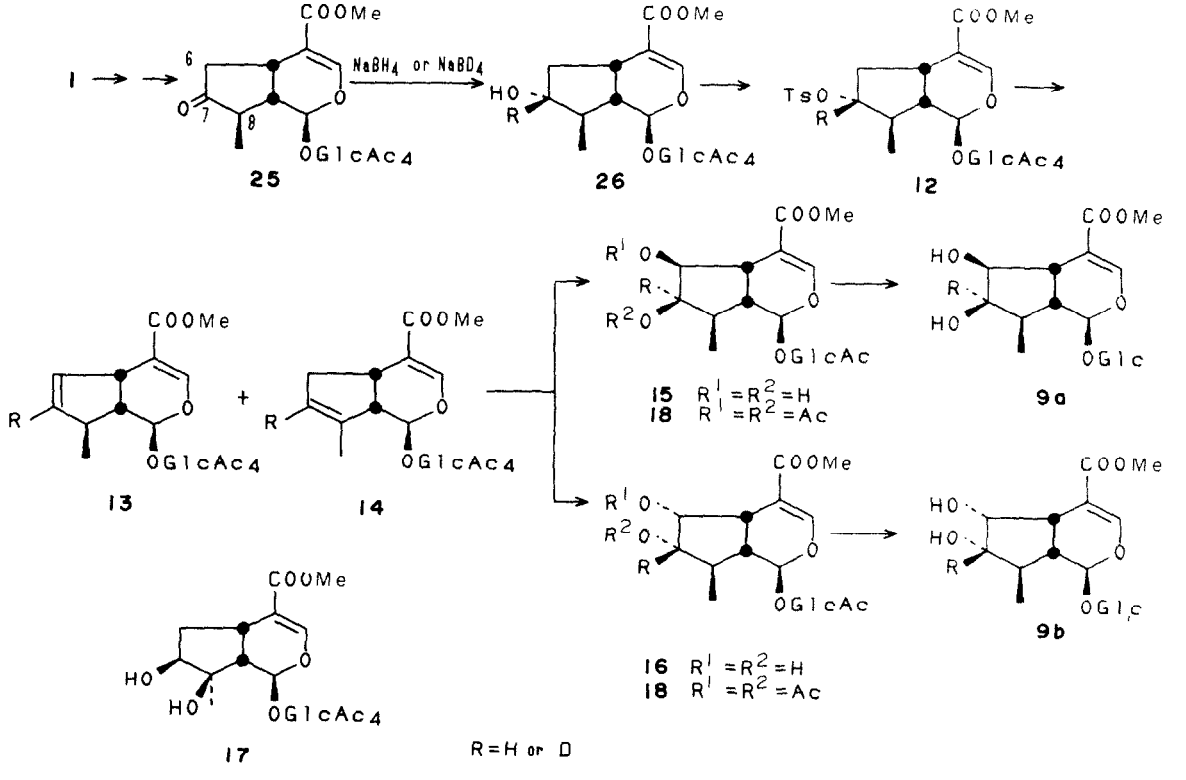

Fig. 2.

configuration of the epoxide ring. On treatment with a few drops of conc sulphuric acid, epoxide **20**, in acetic acid solution, gave two products (**21** and **22**). The ^{1}H NMR spectra of these compounds were similar, except for the chemical shifts of signals due to H-6 and H-7 and the presence of one extra acetyl group in the spectrum of **22**. Furthermore, both compounds yielded the same hexaacetate (**23**) on acetylation. Thus, it was demonstrated that **22** was a monoacetate of **21**. The extra acetoxy group of **22** was assigned to C-7, because the ^{1}H NMR spectrum of **22** showed the signal of H-6 at δ3.86 (*dd*, $J_{6,7}=5.6$ Hz, $J_{5,6}=3.9$ Hz) and that of H-7 at δ4.80 (*dd*, $J_{7,8}=9.3$ Hz, $J_{6,7}=5.6$ Hz). The J values of these signals, the presence of a 13% NOE between H-5 and H-9 and the absence of a NOE between H-5 and H-6 led us to presume that **22** represented 6β-hydroxy-7-*O*-acetyl-7-epiloganin tetraacetate and hence **21** was 6β-hydroxy-7-epiloganin tetraacetate. Compound **20** was presumed to be 6β,7β-epoxydeoxyloganin tetraacetate, since both **21** and **22** were assumed to be formed by the attack of OH^- or AcO^- from the α-side at C-7 of **20**. **21** yielded 6β-hydroxy-7-epiloganin (**9c**) on Zemplén reaction. Attempts to obtain the remaining stereoisomer of **9**, 6α-hydroxyloganin (**9d**), by Walden inversion of the 6-*O*-tosylate of **15** or the 7-*O*-tosylate of **16**, and reduction of the 6-oxologanin tetraacetate (**24**) with sodium borohydride were proved unsuccessful.

Compounds **9a–c** labelled with deuterium on C-7 were obtained as described above starting from 7-*O*-tosyl-7-epi [7-^{2}H]loganin tetraacetate (**12**) which had been obtained from 7-dehydrologanin tetraacetate (**25**) by NaB^2H_4 reduction and subsequent tosylation. Because the feeding experiments required loganin (**1**), which is fully deuteriated on C-6, C-7 and C-8, [6,6,7,8-$^2H_4$]loganin (**1**) and [6,6,7,8,*carbomethoxy*-$^2H_7$]-**1** were prepared in the following way: 7-[6,7,8-$^2H_3$]dehydrologanin (**5**) obtained by treating 7-dehydrologanin (**5**) with sodium methoxide–methanol-d_1 was acetylated and the product reduced with NaB^2H_4 to afford 7-epi[6,6,7,8-$^2H_4$]loganin tetraacetate (**26**). This compound was converted into its tosylate ([6,6,7,8-$^2H_4$]-**12**) and then treated with tetraethylammonium acetate in acetone solution.

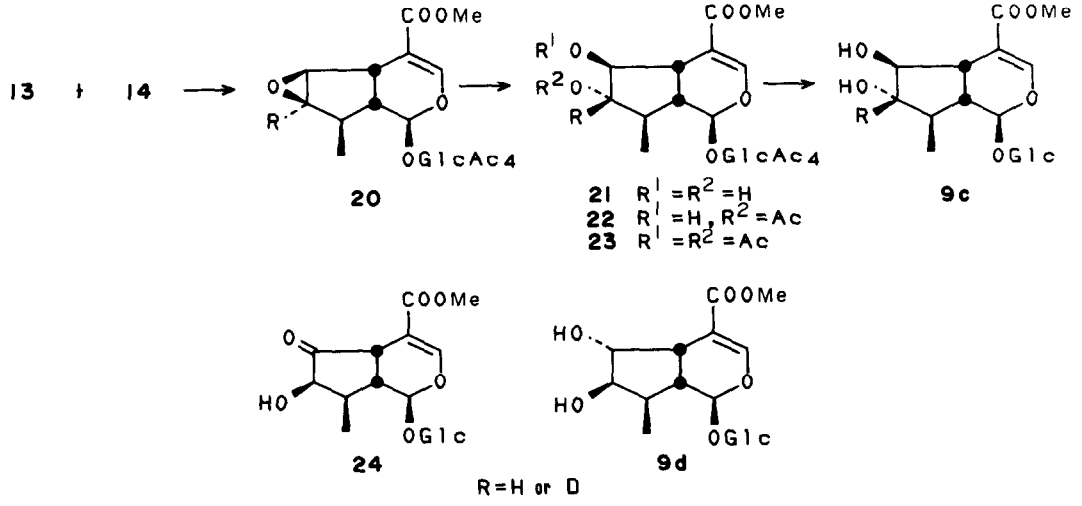

Fig. 3.

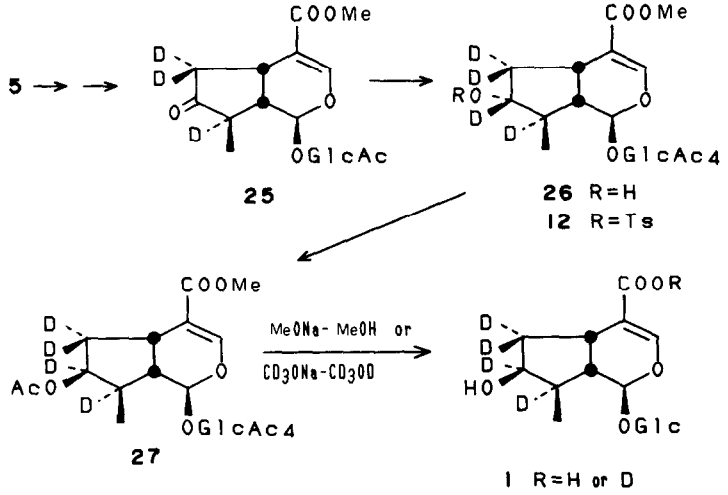

Fig. 4.

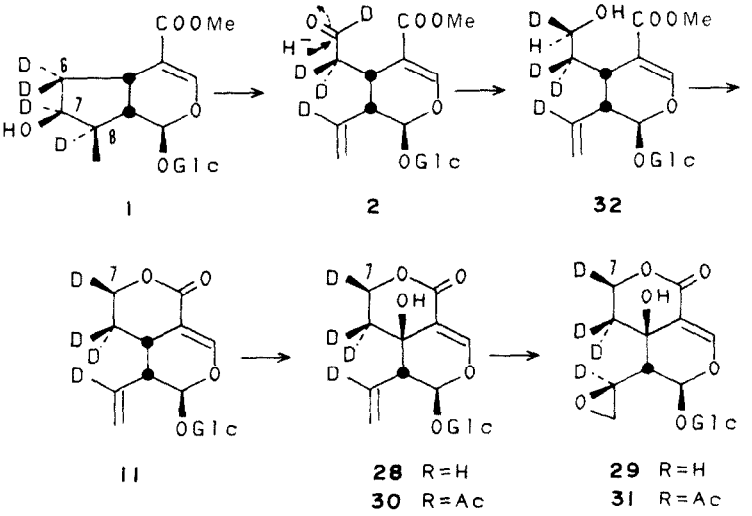

Fig. 5.

The resulting [6,6,7,8-$^2H_4$]loganin pentaacetate (**27**) was finally subjected to Zemplén deacetylation in sodium and sodium methoxide-d_3–CD_3OD to give [6,6,7,8-$^2H_4$]loganin (**1**) and [6,6,7,8,*carbomethoxy*-$^2H_7$]-**1**, respectively.

The application of these deuteriated compounds to several plants was performed in the following way: 6β-[7-^{2}H]hydroxyloganin (**9a**) and 6α-hydroxy-7-epi[7-^{2}H]loganin (**9b**) were administered to *Adina pilulifera* by the hydroponic method and to *Swertia japonica* by the cotton-wick method. However, neither morroniside (**7**) isolated from *Adina*, nor swertiamarin (**28**) obtained from *Swertia* contained any deuterium. Likewise, on treatment of *Eustoma rusellianum* and *S. japonica* with 6β-hydroxy-7-epi[7-^{2}H] loganin (**9c**), no deuterium was detected either in eustomoside (**29**) or swertiamarin (**28**). The non-incorporation of **9a** into these secoiridoid glucosides seemed to rule out the intermediacy of 6-hydroxyloganin (**9**), but in order to draw a unequivocal conclusion, a feeding experiment with 7-deuteriated 6α-hydroxyloganin (**9d**) should also be done.

If, however, 6-hydroxyloganin (**9**) is a biosynthetic intermediate, one of the C-6 methylene protons of loganin should be lost during the ring cleavage process. Thus, we examined the fate of deuteriums on C-6 of loganin (**1**) by feeding [6,6,7,8,*carbomethoxy*-$^2H_4$]-**1** to *E. russellianum* and *S. japonica* and [6,6,7,8,*carbomethoxy*-$^2H_7$]-**1** to *A. pilulifera* and *Lonicera morrowii*. The ^{2}H NMR spectra of isolated **29**, **28**, **7** and **2** as well as their acetates showed that two deuteriums were retained at C-6 and one deuterium at C-7 and C-8 of each of the above secoiridoid glucosides, and that the incorporations of the fed glucosides into them were 1.59, 0.90, 1.23 and 1.61%, respectively. Accordingly, the ring cleavage mechanism involving **9** could be ruled out. Thus the cyclopentane ring of **1** seems most likely to be cleaved directly through a radical or ionic process. Tietze *et al.* [7] suggested that ring cleavage might occur via the thio-analogue of 10-hydroxyloganin (**4**). Likewise, the 6-thio-analogue of 6-hydroxyloganin (**9**) might have been a conceivable intermediate, but this possibility has also been excluded with the above results.

Secologanin (**2**) formed by the ring cleavage of loganin (**1**) yields sweroside (**11**) through the reduction of the aldehyde group followed by lactonization, while **11** leads to eustomoside (**29**) via swertiamarin (**28**) [1, 2, 17]. The incorporation of [6,6,7,8-$^2H_4$]loganin (**1**) into sweroside (**11**) type secoiridoid glucosides gave stereochemical evidence of the reduction process of the aldehyde group. Thus, in the ^{2}H NMR spectra of swertiamarin tetraacetate (**30**) and eustomoside tetraacetate (**31**) obtained in the above experiments, signals of C-7 deuterium were observed at δ5.12 and 5.14, respectively. By contrast the ^{1}H NMR spectra of the unlabelled compounds **30** and **31**, the β-configurated C-7 axial protons appeared at δ4.85 and 4.90, respectively, and the α-orientated C-7 equatrial protons at δ4.30 and 4.40, respectively.* These findings establish beyond doubt that the C-7 aldehyde group of **2** is attacked by the hydride ion from the *si* face to give secologanol (**32**), which is then lactonized to form sweroside (**11**).

EXPERIMENTAL

General. Mps: uncorr; ^{1}H and ^{13}C NMR: 200 and 50.10 MHz resp, TMS as int. standard; ^{2}H NMR: deuterium signal (δ7.27 or 4.85) of the solvent ($CHCl_3$ or H_2O) as int. standard; TLC: silica gel 60 GF_{254} (Merck), spots visualized by irradiation under UV light, or by exposure to I_2 vapour; prep. TLC: silica gel 60 PF_{254} (Merck), bands detected under UV light, CC: silica gel 60 (70–230 mesh, Merck) and activated charcoal for chromatography (Wako); ^{2}H-enrichments: labelled compounds chemically prepared were measured by FABMS or FD-MS and those of the glucosides isolated from the plants were calculated from intensity of ^{2}H signals.

7-[6,6,7,8-$^2H_3$] *Dehydrologanin* (**5**). A soln of **5** [18] (2.0 g) in MeOD (100 ml) (^{2}H-enrichment 99%, CEA) was added under ice-cooling and a N_2 stream to a stirred soln of NaOMe–MeOD prepared from Na (1.1 g) and MeOD (50 ml). After stirring for 4 hr at room temp, D_2O (16 ml) was added to the mixture and

*The discrepancy in the shift values of the signals due to the 7-^{2}H and 7-^{1}H in both compounds can be ascribed to (i) the broad form of the deuterium signals and (ii) the different standards used for the measurements.

the whole was neutralized with 10% D_2SO_4–D_2O. The resulting ppts were filtered off and washed with MeOH (20 ml × 2), combined with the washings, and concd *in vacuo* to *ca* 40 ml. The soln was the subjected to chromatography on activated charcoal (20 g) and eluted successively with H_2O (500 ml) and MeOH (2 l). The residue (853 mg) from the MeOH eluate, on concn *in vacuo*, was recrystallized from EtOH to give [6,6,8-$^2H_3$]-**5** as colourless needles (770 mg). Mp 193–195.5°; ^{1}H NMR (CD_3OD) δ: 1.14 (3H, *s*, 10-H_3), 2.33 (1H, *dd*, J = 7.0 and 3.0 Hz, 9-H)*; FABMS *m/z*: 392 $[M+H]^+$ (M: $C_{17}{}^2H_3H_{21}O_{10}$); ^{2}H-enrichment: 78.7%.

7-*Dehydro*[6,6,8-$^2H_3$]*loganin tetraacetate* (**25**). [6,6,8-$^2H_3$]-**5** (2.8 g) was acetylated with pyridine–Ac_2O (each 28 ml) in the usual way and the product (3.0 g) was recrystallized from EtOH to give [6,6,8-$^2H_3$]-**25** as colourless needles (2.3 g). mp 151°; ^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, *s*, 10-H_3), 2.32 (1H, *dd*, J = 7.5 and 2.0 Hz, 9-H), 3.15 (1H, *dd*, J = 7.5 and 1.5 Hz, 5-H); FABMS *m/z*: 560 $[M+H]^+$ (M: $C_{25}{}^2H_3H_{29}O_{14}$); ^{2}H-enrichment: 70.9%.

7-*Epi*[6,6,7,8-$^2H_4$]*loganin tetraacetate* (**26**). A soln of NaB^2H_4 (200 mg) (^{2}H-enrichment 97%, CEA) in H_2O (1.5 ml) was added to a soln of [6,6,8-$^2H_3$]-**25** (1.97 g) in dioxane (35 ml) and the mixture was stirred for 30 min at room temp. After decomposition of the excess reagent by adding a few drops of AcOH under ice-cooling, the mixture was diluted with H_2O (75 ml) and extracted with $CHCl_3$ (150 ml × 3). The $CHCl_3$ layer was washed with H_2O, dried and concd *in vacuo* to give a residue (1.89 g), which was recrystallized from EtOH to give [6,6,7,8-$^2H_4$]-**26** as colourless needles (1.50 g). Mp 160–162°; ^{1}H NMR ($CDCl_3$) δ: 1.10 (3H, *s*, 10-H_3), 1.83 (1H, *dd*, J = 8.5 and 4.5 Hz, 9-H), 2.81 (1H, *dd*, J = 8.5 and 1.5 Hz, 5-H); FABMS *m/z*: 563 $[M+H]^+$ M: $C_{25}{}^2H_4H_{30}O_{14}$); ^{2}H-enrichment: 72.8%.

7-*Epi* [7-^{2}H]*loganin tetraacetate* (**26**). **25** (6.90 g) was reduced with NaB^2H_4 (701 mg) as described above to give [7-^{2}H]-**26** (5.20 g). ^{1}H NMR ($CDCl_3$) δ: 1.45 (1H, *dd*, J = 14.0 and 6.5 Hz, 6-H_{eq}), 1.75 (1H, *dq*, J = 8.5 and 7.0, 8-H), 2.58 (1H, *dd*, J = 14.0 and 8.5 Hz, 6-H_{ax}); FABMS *m/z*: 560 $[M+H]^+$ (M: $C_{25}{}^2HH_{33}O_{14}$); ^{2}H-enrichment: 93.5%.

7-O-*Tosyl-7-epi* [6,6,7,8-$^2H_4$]*loganin tetraacetate* (**12**). *p*-TsCl (4.48 g) was added to a soln of [6,6,7,8-$^2H_4$]-**26** (1.48 g) in pyridine (23 ml) and the mixture was allowed to stand for 48 hr at room temp. It was then poured into ice-H_2O and extracted with $CHCl_3$ (240 ml × 3). The $CHCl_3$ layer was washed successively with 1 M HCl, satd $NaHCO_3$ and H_2O, dried and concd *in vacuo*. The residue was recrystallized from EtOH to give [6,6,7,8-$^2H_4$]-**12** as colourless needles (1.57 g). Mp 114°; ^{1}H NMR ($CDCl_3$) δ: 1.10 (3H, *s*, 10-H_3), 1.83 (1H, *dd*, J = 8.0 and 3.0 Hz, 9-H), 2.80 (1H, *dd*, J = 8.0 and 1.5 Hz, 5-H); FABMS *m/z*: 717 $[M+H]^+$ (M: $C_{32}{}^2H_4H_{36}O_{16}S$); ^{2}H-enrichment: 60.3%.

7-O-*Tosyl-7-epi*[7-^{2}H]*loganin tetraacetate* (**12**). [7-^{2}H]-**26** (4.60 g) was tosylated with *p*-TsCl (14.00 g) in pyridine (50 ml) as described above to give [7-^{2}H]-**12** as colourless needles (5.30 g). The C-7 signal in ^{1}H NMR ($CDCl_3$) was missing as expected. FABMS *m/z*: 714 $[M+H]^+$ (M: $C_{32}{}^2HH_{39}O_{16}S$); ^{2}H-enrichment: 87.7%.

6,7-*Dehydrodeoxyloganin tetraacetate* (**13**) *and* 7,8-*dehydrodeoxyloganin tetraacetate* (**14**). To a soln of **12** (2.90 g) in THF (25 ml) was added DBU (25 ml) and the mixture was refluxed for 67 hr. It was then concd *in vacuo*, the oily residue dissolved in $CHCl_3$ (30 ml), washed successively with 1 M HCl, brine and H_2O, and dried. The residue (2.50 g) obtained by removal of the solvent *in vacuo* was subjected to silica gel (51 g) CC, and eluted successively with C_6H_6 (50 ml), C_6H_6–Et_2O (95:5) (315 ml), (92.5:7.5) (340 ml), (9:1) (635 ml) and (4:1) (215 ml). Fractions of 5 ml each were collected. Frs. 135–270 were combined and concd *in vacuo* to give a mixture (559.9 mg) of **13** and **14** as a white powder [based on the intensity of the two methyl signals observed at δ 1.12 (3H, *d*, J = 6.8 Hz, 10-H_3) and 1.78 (3H, *s*, 10-H_3), the ratio of the two compounds in this mixture was estimated to be 5:1]. The mixture was then used for further reaction without separation.

IR ν_{max}^{KBr} cm^{-1}: 1750, 1700, 1635. **13**: ^{1}H NMR ($CDCl_3$) δ: 1.12 (3H, *d*, J = 6.8 Hz, 10-H_3), 1.94, 1.99, 2.01 and 2.08 (each *s*, OAc), 2.15 (1H, *ddd*, J = 8.0, 3.7 and 2.5 Hz, 9-H), 2.73 (1H, *qtd*, J = 6.8, 2.5 and 1.7 Hz, 8-H), 3.51 (1H, *dddd*, J = 8.0, 2.5, 1.7 and 1.5 Hz, 5-H), 3.71 (3H, *s*, COOMe), 3.75 (1H, *ddd*, J = 10.0, 4.6 and 2.4 Hz, 5'-H), 4.13 (1H, *dd*, J = 12.5 and 2.4 Hz, 6'-H_S), 4.31 (1H, *dd*, J = 12.5 and 4.6 Hz, 6'-H_R), 4.86 (1H, *d*, J = 8.1 Hz, 1'-H), 5.01 (1H, *dd*, J = 9.3 and 8.1 Hz, 2'-H), 5.10 (1H, *dd*, J = 10.0 and 9.3 Hz, 4'-H), 5.16 (1H, *d*, J = 3.7 Hz, 1-H), 5.19 (1H, *t*, J = 9.3 Hz, 3'-H), 5.57 (1H, *dt*, J = 5.6 and 1.7 Hz, 7-H), 5.88 (1H, *dt*, J = 5.6 and 2.5 Hz, 6-H), 7.34 (1H, *d*, J = 1.5 Hz, 3-H).

Compound **14**. 1.78 (3H, *s*, 10-H_3), 1.96, 1.99, 2.01 and 2.07 (each *s*, OAc), 2.65–2.83 (3H, *m*, 6-H_2 and 9-H), 3.16 (1H, *tdd*, J = 8.0, 5.0 and 1.0 Hz, 5-H), 3.74 (3H, *s*, COOMe), 4.16 (1H, *dd*, J = 12.5 and 2.5 Hz, 6'-H_S), 4.33 (1H, *dd*, J = 12.5 and 4.5 Hz, 6'-H_R), 4.92 (1H, *d*, J = 8.0 Hz, 1'-H), 5.05 (1H, *dd*, J = 9.3 and 8.0 Hz, 2'-H), 5.14 (1H, *dd*, J = 9.8 and 9.3 Hz, 4'-H), 5.23 (1H, *d*, J = 5.0 Hz, 1-H), 5.27 (1H, *t*, J = 9.3 Hz, 3'-H), 5.48 (1H, *br t*, J = 1.5 Hz, 7-H), 7.44 (1H, *d*, J = 1.0 Hz, 3-H). [7-^{2}H]-**12** (3.6 g) was treated with DBU (2.8 ml) as described above to give a mixture (684 mg) of [7-^{2}H]-**13** and **14**.

[7-^{2}H]-**13**. ^{1}H NMR ($CDCl_3$) δ: 2.73 (1H, *qt*, J = 6.8 and 2.5 Hz, 8-H), 3.51 (1H, *ddd*, J = 8.0, 2.5 and 1.5 Hz, 5-H), 5.92 (1H, *t*, J = 2.5 Hz, 6-H); [7-^{2}H]-14: 7-H proton was not found.

6*β-Hydroxyloganin tetraacetate* (**15**) *and* 6*α-hydroxy-7-epiloganin tetraacetate* (**16**). A soln of OsO_4 (263 mg) in Et_2O (17 ml) containing pyridine (0.1 ml) was added dropwise to a soln of the mixture (560 mg) of **13** and **14** in Et_2O (3 ml) over 3 min with stirring. The resulting black ppt. was separated from the soln by centrifugation, washed with Et_2O (10 ml × 4) and dissolved in EtOH (10 ml). After introduction of H_2S to the soln for 20 min under ice-cooling, the resulting ppt. was filtered off and washed with EtOH (3 ml × 4). The combined filtrate and washings were concd *in vacuo* and the resulting residue (350 mg) was subjected to prep. TLC ($CHCl_3$–MeOH, 100:3, 2 developments). Of the two major bands, the less polar one was extracted with $CHCl_3$–MeOH (95:1, 50 ml) and the extract evapd *in vacuo*. The residue (130.4 mg) yielded colourless needles (117.6 mg) of **15** on recrystallization from EtOH. Mp 138–141°; $[\alpha]_D^{13}$ − 67.3° ($CHCl_3$; *c* 1.04); UV λ_{max}^{EtOH} nm (log ε): 235 (3.97); IR ν_{max}^{KBr} cm^{-1}: 3470, 1755, 1700, 1640; ^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, *d*, J = 6.8 Hz, 10-H_3), 1.97, 2.01, 2.03 and 2.09 (12H, each *s*, OAc), 2.35 (1H, *td*, J = 10.3 and 4.2 Hz, 9-H), 2.83 (1H, *ddd*, J = 10.3, 6.8 and 1.0 Hz, 5-H), 3.73 (1H, *dd*, J = 7.1 and 4.4 Hz, 6-H), 3.76 (3H, *s*, COOMe), 3.96 (1H, *dd*, J = 4.4 and 3.7 Hz, 7-H), 4.15 (1H, *dd*, J = 12.5 and 2.4 Hz, 6'-H_S), 4.28 (1H, *dd*, J = 12.5 and 4.4 Hz, 6'-H_R), 4.86 (1H, *d*, J = 7.8 Hz, 1'-H), 4.99 (1H, *dd*, J = 9.0 and 7.8 Hz, 2'-H), 5.04 (1H, *d*, J = 4.2 Hz, 1-H), 5.11 (1H, *dd*, J = 9.5 and 9.3 Hz, 4'-H), 5.23 (1H, *dd*, J = 9.3 and 9.0 Hz, 3'-H), 7.39 (1H, *d*, J = 1.0 Hz, 3-H); FABMS *m/z*: 575 $[M+H]^+$. Found: C, 52.13; H, 6.04; $C_{25}H_{34}O_{15}$ requires: C, 52.26; H, 5.97%. On the other hand, the more polar band upon treatment in the same way as described above a residue (100.7 mg), which was subjected to further prep. TLC ($CHCl_3$–MeOH, 100:3, 10 developments) to give two bands. The less polar one yielded **16** as a white powder (26.7 mg), and the more polar one colourless needles (10.3 mg) of **17** on recrystallization from EtOH.

Compound **16**. $[\alpha]_D^{20}$ −65.4° ($CHCl_3$; *c* 0.52); UV λ_{max}^{EeOH} nm (log ε): 235 (4.09); IR ν_{max}^{KBr} cm^{-1}: 3460, 1750, 1720, 1630; ^{1}H NMR

*Only the proton signals which were changed through the introduction of deuteriums are shown.

($CDCl_3$) δ: 1.19 (3H, *d*, J = 6.5 Hz, 10-H_3), 1.64–1.96 (2H, *m*, 8-H and 9-H), 2.00, 2.03, 2.04 and 2.09 (12H, each *s*, OAc), 2.88 (1H, *ddd*, J = 8.5, 4.0 and 1.5 Hz, 5-H), 3.69 (1H, *dd*, J = 8.5 and 4.0 Hz, 7-H), 3.72 (3H, *s*, COOMe), 4.20 (1H, *dd*, J = 12.5 and 2.5 Hz, 6'-H_S), 4.27 (1H, *t*, J = 4.0 Hz, 6-H), 4.34 (1H, *dd*, J = 12.5 and 4.5 Hz, 6'-H_R), 4.87 (1H, *d*, J = 8.0 Hz, 1'-H), 5.03 (1H, *dd*, J = 9.0 and 8.0 Hz, 2'-H), 5.12 (1H, *t*, J = 9.0 Hz, 4'-H), 5.25 (1H, *t*, J = 9.0 Hz, 3'-H), 7.57 1H, *d*, J = 1.5 Hz, 3-H); FABMS *m/z*: 575 $[M+H]^+$. Found: C, 52.22; H, 6.10; $C_{25}H_{34}O_{15}$ requires: C, 52.26; H, 5.97%.

Compound **17**: $[\alpha]_D^{13}$ −102.7° ($CHCl_3$; *c* 0.74); UV λ_{max}^{EtOH} nm (log ε): 237 (3.89); IR ν_{max}^{KBr} cm^{-1}: 3500, 1760, 1705, 1625. This compound was identical with an authentic sample [15].

A soln of OsO_4 (303 mg) in Et_2O (20 ml)–pyridine (0.5 ml) was added to a soln of the mixture (650 mg) of [7-^{2}H]-**13** and **14** in Et_2O (4 ml) and worked-up as described above to yield [7-^{2}H]-**15** (254 mg) and [7-^{2}H]-**16** (66.1 mg), respectively. [7-^{2}H]-**15**: ^{1}H NMR ($CDCl_3$) δ: 1.82 (1H, *dq*, J = 10.3 and 6.8 Hz, 8-H), 3.73 (1H, *d*, J = 7.0 Hz, 6-H); FABMS *m/z*: 576 $[M+H]^+$ (M: $C_{25}{}^2HH_{33}O_{15}$); ^{2}H-enrichment: 95.1%. [^{2}H-7]-**16**: ^{1}H NMR ($CDCl_3$) δ: 4.27 (1H, *d*, J = 4.0 Hz, 6-H); FABMS *m/z*: 576 $[M+H]^+$ (M: $C_{25}{}^2HH_{33}O_{15}$); ^{2}H-enrichment: 94.0%.

6β-Hydroxyloganin hexaacetate (**18**). Tetraacetate **15** (45 mg) was acetylated with pyridine–Ac_2O (each 0.5 ml) in the usual way and the product (52 mg) was recrystallized from EtOH to give **18** as colourless needles (32.5 mg). Mp 131–132° (lit. [13] 130–131.5°); $[\alpha]_D^{13}$ −88.0° ($CHCl_3$; *c* 1.00), lit. [13] −91.4°, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε): 232 (4.01); IR ν_{max}^{KBr} cm^{-1}: 1740, 1720 (sh), 1635; ^{1}H NMR ($CDCl_3$) δ: 1.05 (3H, *d*, J = 6.8 Hz, 10-H_3), 1.90, 2.01, 2.03, 2.05, 2.07 and 2.10 (18H, each *s*, OAc), 2.95 (1H, *td*, J = 9.0 and 2.4 Hz, 9-H), 2.99 (1H, *ddd*, J = 9.0, 4.6 and 1.2 Hz, 5-H), 3.68 (3H, *s*, COOMe), 3.74 (1H, *ddd*, J = 9.3, 4.6 and 2.4 Hz, 5'-H), 4.14 (1H, *dd*, J = 12.5 and 2.4 Hz, 6'-H_S), 4.33 (1H, *dd*, J = 12.5 and 4.6 Hz, 6'-H_R), 4.83 (1H, *d*, J = 8.1 Hz, 1'-H), 4.98 (1H, *dd*, J = 9.0 and 8.1 Hz, 2'-H), 5.10 (1H, *t*, J = 9.5 Hz, 4'-H), 5.20 (1H, *dd*, J = ~5.6 and 4.6 Hz, 7-H), 5.22 (1H, *t*, J = 4.6 Hz, 6-H), 5.23 (1H, *t*, J = 9.4 Hz, 3'-H), 5.28 (1H, *J* = 2.4 Hz, 1-H), 7.36 (1H, *d*, J = 1.2 Hz, 3-H); FABMS *m/z*: 659 $[M+H]^+$. Found: C, 52.68; H, 5.78. Calc. for $C_{29}H_{38}O_{17}$: C, 52.89; H, 5.78%.

6α-Hydroxy-7-epiloganin hexaacetate (**19**). Tetraacetate **16** (6.4 mg) was acetylated in the usual way and the product (8.3 mg) was purified by prep. TLC ($CHCl_3$–MeOH, 25:1, 4 developments) to give **19** as a white powder (5.0 mg). $[\alpha]_D^{20}$ −115.1° ($CHCl_3$; *c* 0.73); UV λ_{max}^{EtOH} nm (log ε): 232 (4.07); IR ν_{max}^{KBr} cm^{-1}: 1750, 1710, 1630; ^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, *d*, J = 6.8 Hz, 10-H_3), 2.01, 2.02, 2.04, 2.05 and 2.08 (18H, each *s*, OAc), 3.09 (1H, *ddd*, J = 9.5, 3.9 and 1.5 Hz, 5-H), 3.71 (3H, *s*, COOMe), 3.77 (1H, *dt*, J = 10.0 and 3.7 Hz, 5'-H), 4.22 (2H, *d*, J = 3.7 Hz, 6'-H_2), 4.82 (1H, *dd*, J = 10.3 and 3.9 Hz, 7-H), 4.95 (1H, *d*, J = 7.8 Hz, 1'-H), 5.05 (1H, *dd*, J = 9.0 and 8.1 Hz, 2'-H), 5.07 (1H, *d*, J = 8.1 Hz, 1-H), 5.13 (1H, *dd*, J = 10.0 and 9.8 Hz, 4'-H), 5.26 (1H, *dd*, J = 9.8 and 9.0 Hz, 3'-H), 5.58 (1H, *t*, J = 3.9 Hz, 6-H), 7.51 (1H, *d*, J = 1.5 Hz, 3-H); FABMS *m/z*: 659 $[M+H]^+$. Found: C, 52.70; H, 5.81; $C_{29}H_{38}O_{17}$ requires: C, 52.89; H, 5.82%.

6β-Hydroxyloganin (**9a**). Methanolic NaOMe (1M, 0.1 ml) was added to a soln of **15** (106.3 mg) in abs. MeOH (1 ml) and the mixture was stirred for 30 min at room temp. After neutralization of the mixture by adding Amberlite IR-120 B (H^+ form), the resin was filtered off and washed with MeOH (1 ml × 4). The filtrate and washings were combined and concd *in vacuo* to give a syrupy residue (75.2 mg), which was purified by prep. TLC ($CHCl_3$–MeOH, 6:1, 2 developments). The residue (50.8 mg) obtained by work-up of the main band gave on recrystallization from MeOH–H_2O colourless needles (31.2 mg) of **9a**. Mp 225–227° (lit. [13] 220–222°, EtOH–H_2O); $[\alpha]_D^{14}$ −103.3° (MeOH; *c* 0.90), (lit. [13] −107.2°, MeOH); UV λ_{max}^{MeOH} nm (log ε): 238 (4.07); IR ν_{max}^{KBr} cm^{-1}: 3380, 1690, 1640, 1630; ^{1}H NMR (CD_3OD) δ: 1.12 (3H, *d*, J = 7.1 Hz, 10-H_3), 1.92 (1H, *dqd*, J = 8.5, 7.1 and 4.9 Hz, 8-H), 2.16 (1H, *br td*, J = 9.0 and 4.6 Hz, 9-H), 2.93 (1H, *dd*, J = 9.3, 5.9 and 1.2 Hz, 5-H), 3.13-3.41 (4H, *m*, 2'-, 3'-, 4'- and 5'-H), 3.64 (1H, *dd*, J = 12.0 and 5.4 Hz, 6'-H_R), 3.73 (3H, s, COOMe), 3.83 (1H, *dd*, J = 5.9 and 4.2 Hz, 6-H), 3.89 (2H, *dd*, J = 4.9 and 4.2 Hz, 7-H, and *br d*, J = 12.0 Hz, 6'-H_S), 4.63 (1H, *d*, J = 7.8 Hz, 1'-H), 5.27 (1H, *d*, J = 4.6 Hz, 1-H), 7.47 (1H, *d*, J = 1.2 Hz, 3-H); FABMS *m/z*: 407 $[M+H]^+$. Found: C, 50.20; H, 6.57. Calc. for $C_{17}H_{26}O_{11}$: C, 50.24; H, 6.45%.

Methanolic NaOMe (1M, 0.04 ml) was added to a soln of [7-^{2}H]-**15** (24.8 mg) in abs. MeOH (0.2 ml) and the mixture was treated as described above to give [7-^{2}H]-**9a** (15.6 mg). ^{1}H NMR (CD_3OD) δ: 1.92 (1H, *dq*, J = 9.0 and 7.1 Hz, 8-H), 3.83 (1H, *d*, J = 5.9 Hz, 6-H); FABMS *m/z*: 408 $[M+H]^+$ (M: $C_{17}{}^2HH_{25}O_{11}$); ^{2}H-enrichment: 95.0%.

6α-Hydroxy-7-epiloganin (**9b**). Methanolic NaOMe (1M, 0.04 ml) was added to a soln of **16** (36.6 mg) in abs. MeOH (0.3 ml). After stirring for 15 min at room temp, the mixture was worked-up in the usual way and the product (25.8 mg) subjected to prep. TLC ($CHCl_3$–MeOH, 10:3, 5 developments) to yield **9b** as a white powder (16.4 mg). $[\alpha]_D^{12}$ −100.0° (MeOH; *c* 0.93); UV λ_{max}^{MeOH} nm (log ε): 238 (4.03); IR ν_{max}^{KBr} cm^{-1}: 3325, 1690, 1630; ^{1}H NMR (CD_3OD) δ: 1.16 (3H, *d*, J = 7.0 Hz, 10-H_3), 1.74 (1H, *td*, J = 8.8 and 5.1 Hz, 9-H), 1.95 (1H, *tq*, J = 9.5 and 7.0 Hz, 8-H), 2.84 (1H, *ddd*, J = 8.8, 3.1 and 1.5 Hz, 5-H), 3.22 (1H, *dd*, J = 8.8 and 8.1 Hz, 2'-H), 3.25-3.50 (3H, *m*, 3'-, 4'- and 5'-H), 3.63 (1H, *dd*, J = 9.5 and 3.3 Hz, 9-H), 3.71 (3H, *s*, COOMe), 3.87 (1H, *dd*, J = 11.7 and 0.7 Hz, 6'-H_S), 4.16 (1H, *t*, J = 3.1 Hz, 6-H), 4.68 (1H, *d*, J = 7.7 Hz, 1'-H), 5.29 (1H, *d*, J = 8.8 Hz, 1-H), 7.60 (1H, *d*, J = 1.5 Hz, 3-H); FABMS *m/z*: 407 $[M+H]^+$. Found: C, 48.92; H, 6.30. $C_{17}H_{26}O_{11} \cdot 1/2H_2O$ requires: C, 49.16; H, 6.31%.

Methanolic NaOMe (1M, 0.04 ml) was added to a soln of [7-^{2}H]-**16** (32.0 mg) in abs. MeOH (0.3 ml) and the mixture was worked up as described above to give [7-^{2}H]-**9b** (18.3 mg). ^{1}H NMR (CD_3OD) δ: 1.94 (1H, *qd*, J = 6.8 and 5.1 Hz, 8-H), 4.16 (1H, *d*, J = 3.1 Hz, 6-H); FABMS *m/z*: 408 $[M+H]^+$ (M: $C_{17}{}^2HH_{25}O_{11}$); ^{2}H-enrichment: 95.2%.

6,7-*Epoxydeoxyloganin tetraacetate* (**20**). *m*-CPBA (97.3 mg) was added to a soln of the mixture (177.7 mg) of **13** and **14** in abs. CH_2Cl_2 (2.5 ml) and the soln was allowed to stand for 5 hr at room temp in the dark. After successive washings with satd $NaHCO_3$ and H_2O, the CH_2Cl_2 layer was dried, concd *in vacuo* and the residue (151 mg) was subjected to prep. TLC (Et_2O). The crude product obtained from the band around R_f 0.5 gave on recrystallization from EtOH colourless needles (105 mg) of **20**, mp 191–192°; $[\alpha]_D^{20}$ −71.7° ($CHCl_3$; *c* 0.60); UV λ_{max}^{EtOH} nm (log ε): 233 (3.97); IR ν_{max}^{KBr} cm^{-1}: 1735, 1700, 1625; ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, *d*, J = 6.4 Hz, 10-H_3), 1.84 (1H, *br d*, J = 6.6 Hz, 9-H), 1.89, 2.00, 2.02 and 2.10 (12H, each *s*, OAc), 3.12 (1H, *br d*, J = 6.4 Hz, 5-H), 3.27 (1H, *d*, J = 2.7 Hz, 7-H), 3.74 (4H, *s*, COOMe, and *ddd*, J = 9.5, 4.4 and 2.4 Hz, 5'-H), 3.78 (1H, *br d*, J = 2.7 Hz, 6-H), 4.13 (1H, *dd*, J = 12.5 and 2.4 Hz, 6'-H_S), 4.30 (1H, *dd*, J = 12.5 and 4.4 Hz, 6'-H_R), 4.81 (1H, *d*, J = 8.1 Hz, 1'-H), 4.95 (1H, *dd*, J = 9.3 and 8.1 Hz, 2'-H), 5.09 (1H, *dd*, J = 9.5 and 9.3 Hz, 4'-H), 5.21 (1H, *t*, J = 9.3 Hz, 3'-H), 5.30 (1H, *br s*, 1-H), 7.46 (1H, *d*, J = 1.5 Hz, 3-H); FABMS *m/z*: 557 $[M+H]^+$. Found: C, 53.69; H, 5.80; $C_{25}H_{32}O_{14}$ requires: C, 53.96; H, 5.80%.

m-CPBA (79 mg) was added to a soln of the mixture (145 mg) of [7-^{2}H]-**13** and 14 in abs. CH_2Cl_2 (2 ml) and the mixture worked-up as described above to give [7-^{2}H]-**20** (87.2 mg). ^{1}H NMR ($CDCl_3$) δ: 3.76 (1H, *s*, 6-H); FABMS *m/z*: 558 $[M+H]^+$ (M: $C_{25}{}^2HH_{31}O_{14}$); ^{2}H-enrichment: 86.8%.

Acid treatment of 6,7-*epoxydeoxyloganin tetraacetate* (**20**). A soln of epoxide **20** (370 mg) in HOAc (5 ml)–H_2O (2.5 ml) containing conc. H_2SO_4 (5 drops) was stirred for 48 hr at room

temp. The soln was then stirred with $CHCl_3$ (10 ml), and the $CHCl_3$ layer washed successively with satd $NaHCO_3$ and H_2O, dried and evapd *in vacuo*. The resulting residue (324 mg) was subjected to prep. TLC (C_6H_6–Et_2O–MeOH, 10:8:1, 3 developments) to give two major bands. The more polar band gave a residue (136 mg), which yielded on recrystallization from EtOH colourless needles (109.6 mg) of **21**. Mp 172–173.2°; $[\alpha]_D^{12}$ −102.8° ($CHCl_3$; *c* 1.09); UV λ_{max}^{EtOH} nm (log ε): 235 (4.01); IR ν_{max}^{KBr} cm^{-1}: 3400, 1735, 1635; ^1H NMR ($CDCl_3$) δ: 1.15 (3H, *d*, *J* = 6.3 Hz, 10-H_3), 1.60–1.80 (1H, *m*, 8-H), 1.94, 2.01, 2.03 and 2.10 (12H, each *s*, OAc), 2.64 (1H, *br dd*, *J* = 9.3 and 4.9 Hz, 5-H), 3.52–3.68 (2H, *m*, 6-H and 7-H), 3.75 (3H, *s*, COOMe), 4.16 (1H, *dd*, *J* = 12.5 and 2.4 Hz, 6′-H_S), 4.28 (1H, *d*, *J* = 12.5 and 4.4 Hz, 6′-H_R), 4.84 (1H, *d*, *J* = 8.1 Hz, 1′-H), 4.97 (1H, *d*, *J* = 9.3 and 8.1 Hz, 2′-H), 5.10 (1H, *dd*, *J* = 9.5 and 9.3 Hz, 4′-H), 5.18 (1H, *d*, *J* = 3.4 Hz, 1-H), 5.23 (1H, *t*, *J* = 9.3 Hz, 3′-H), 7.35 (1H, *d*, *J* = 1.0 Hz, 3-H). FABMS *m/z*: 575 $[M+H]^+$. Found: C, 52.39; H, 5.96; $C_{25}H_{34}O_{15}$ requires: C, 52.26; H, 5.97%.

The less polar band gave a residue (83.8 mg), which was recrystallized from *n*-hexane–EtOH to give **22** as colourless needles (72.6 mg). Mp 127–128.5°; $[\alpha]_D^{13}$ −119.2° ($CHCl_3$; *c* 1.20); UV λ_{max}^{EtOH} nm (log ε): 232 (4.00); IR ν_{max}^{KBr} cm^{-1}: 3450, 1750, 1720 (sh), 1700 (sh), 1635; ^1H NMR ($CDCl_3$) δ: 1.12 (3H, *d*, *J* = 6.6 Hz, 10-H_3), 1.98, 2.00, 2.03, 2.07 and 2.10 (15H, each *s*, OCOMe), 2.22 (1H, *ddd*, *J* = 11.0, 9.0 and 2.9 Hz, 9-H), 2.77 (1H, *ddd*, *J* = 9.0, 3.9 and 1.5 Hz, 5-H), 3.72 (1H, *ddd*, *J* = 9.8, 4.4 and 2.4 Hz, 5′-H), 3.75 (3H, *s*, COOMe), 3.86 (1H, *dd*, *J* = 5.6 and 3.9 Hz, 6-H), 4.14 (1H, *dd*, *J* = 12.5 and 2.4 Hz, 6′-H_S), 4.31 (1H, *dd*, *J* = 12.5 and 4.4 Hz, 6′-H_R), 4.80 (1H, *dd*, *J* = 9.3 and 5.6 Hz, 7-H), 4.85 (1H, *d*, *J* = 8.1 Hz, 1′-H), 4.97 (1H, *dd*, *J* = 9.3 and 8.1 Hz, 2′-H, 5.10 (1H, *dd*, *J* = 9.8 and 9.3 Hz, 4′-H), 5.23 (1H, *t*, *J* = 9.3 Hz, 3′-H), 5.25 (1H, *d*, *J* = 2.9 Hz, 1-H) 7.35 (1H, *d*, *J* = 1.5 Hz, 3-H); FABMS *m/z*: 617 $[M+H]^+$. Found: C, 51.53; H, 5.81; $C_{27}H_{36}O_{16}\cdot 1/2H_2O$ requires: C, 51.84; H, 5.96%.

A soln of [7-^{2}H]-**20** (77.8 mg) in AcOH (1 ml)-H_2O (0.5 ml) containing a drop of conc. H_2SO_4 was worked-up as described above to give [7-^{2}H]-**21** (18.5 mg) and [7-^{2}H]-**22** (10.3 mg), respectively. [7-^{2}H]-**21**: ^1H NMR ($CDCl_3$) δ: 1.73 (1H, *dq*, *J* = 11.2 and 6.6 Hz, 8-H), 3.61 (1H, *d*, *J* = 5.9 Hz. 6-H); FABMS *m/z*: 576 $[M+H]^+$ (M: $C_{25}{}^2HH_{33}O_{15}$); ^{2}H-enrichment: 84.5%. [7-^{2}H]-**22**: ^1H NMR ($CDCl_3$) δ: 3.86 (1H, *d*, *J* = 4.0 Hz, 6-H); FABMS *m/z*: 618 $[M+H]^+$ (M: $C_{27}{}^2HH_{35}O_{16}$); ^{2}H-enrichment: 87.3%.

6β-Hydroxy-7-epiloganin hexaacetate (**23**). Compound **21** (109.5 mg) was acetylated with pyridine–Ac_2O in the usual way and the product (121.0 mg) was recrystallized from EtOH to give **23** as colourless needles (82.4 mg). Mp 134–135°; $[\alpha]_D^{13}$ −90.6° ($CHCl_3$; *c* 1.06); UV λ_{max}^{EtOH} nm (log ε): 231 (3.98); IR ν_{max}^{KBr} cm^{-1}: 1740, 1700, 1640. ^1H NMR ($CDCl_3$) δ: 1.14 (3H, *d*, *J* = 6.6 Hz, 10-H_3), 1.89, 2.01, 2.03, 2.07 and 2.10 (18H, each *s*, COOMe), 2.28 (1H, *ddd*, *J* = 11.2, 8.8 and 2.2 Hz, 9-H), 2.90 (1H, *ddd*, *J* = 8.8, 2.9 and 1.5 Hz, 5-H), 3.69 (3H, *s*, COOMe), 3.75 (1H, *ddd*, *J* = 9.8, 4.4 and 2.4 Hz, 5′-H), 4.14 (1H, *dd*, *J* = 12.5 and 2.4 Hz, 6′-H_S), 4.32 (1H, *dd*, *J* = 12.5 and 4.4 Hz, 6′-H_R), 4.80 (1H, *br dd*, *J* = ~8.0 and ~3.9 Hz, 7-H), 4.86 (1H, *d*, *J* = 8.1 Hz, 1′-H), 4.98 (1H, *dd*, *J* = 9.3 and 8.1 Hz, 2′-H), 5.10 (1H, *dd*, *J* = 9.8 and 9.3 Hz, 4′-H), 5.16 (1H, *dd*, *J* = ~3.9 and 2.9 Hz, 6-H), 5.23 (1H, *t*, *J* = 9.3 Hz, 3′-H), 5.23 (1H, *d*, *J* = 2.2 Hz, 1-H), 7.35 (1H, *d*, *J* = 1.5 Hz, 3-H); FABMS *m/z*: 659 $[M+H]^+$. Found: C, 53.01; H, 5.93; $C_{29}H_{38}O_{17}$ requires: C, 52.89; H, 5.82%. This compound **23** was identical with the hexaacetate obtained by acetylation of **22** in the ususal way (mmp, IR and ^1H NMR).

6β-Hydroxy-7-epiloganin (**9c**). Methanolic NaOMe (1M, 0.1 ml) was added to a soln of **21** (176.0 mg) in abs. MeOH (2 ml) and the mixture was stirred for 30 min at room temp. The reaction mixture was treated in the usual manner and the obtained crude product (121 mg) was purified by prep. TLC ($CHCl_3$–MeOH, 4:1, 5 developments) to give a white powder (94.4 mg) of **9c**. $[\alpha]_D^{14}$ −117.4° (MeOH; *c* 1.29); UV λ_{max}^{MeOH} nm (log ε): 236 (4.01); IR ν_{max}^{KBr} cm^{-1}: 3400, 1690, 1645, 1635; ^1H NMR (CD_3OD) δ: 1.15 (3H, *d*, *J* = 6.6 Hz, 10-H_3), 1.69 (1H, *ddq*, *J* = 9.3, 8.5 and 6.6 Hz, 8-H), 2.03 (1H, apparently *td*, *J* = 9.3 and 3.9 Hz, 9-H), 2.74 (1H, *ddd*, *J* = 9.0, 5.9 and 1.5 Hz, 5-H), 3.16 (1H, *dd*, *J* = 8.5 and 7.8 Hz, 2′-H), 3.20–3.50 (3H, *m*, 3′-, 4′- and 5′-H), 3.46 (1H, *dd*, *J* = 8.5 and 5.9 Hz, 7-H), 3.63 (1H, *dd*, *J* = 12.2 and 5.4 Hz, 6′-H_R), 3.70 (1H, *t*, *J* = 5.9 Hz, 6-H), 3.73 (3H, *s*, $COOCH_3$), 3.89 (1H, *dd*, *J* = 12.2 and 1.7 Hz, 6′-H_S), 4.63 (1H, *d*, *J* = 7.8 Hz, 1′-H), 5.39 (1H, *d*, *J* = 4.2 Hz, 1-H), 7.43 (1H, *d*, *J* = 1.5 Hz, 3-H); FABMS *m/z*: 407 $[M+H]^+$. Found: C, 47.59; H, 6.47; $C_{17}H_{26}O_{11}\cdot 5/4H_2O$ requires: C, 47.60; H, 6.40%.

Methanolic MeONa (1N, 0.01 ml) was added to a soln of [^{2}H-7]-**21** (10 mg) in abs. MeOH (0.1 ml) and worked-up as described above to give [7-^{2}H]-**9b** (6.0 mg). ^1H NMR (CD_3OD) δ: 1.69 (1H, *dq*, *J* = 9.3 and 6.6 Hz, 8-H), 3.70 (1H, *d*, *J* = 5.9 Hz, 6-H); FABMS *m/z*: 408 $[M+H]^+$ (M: $C_{17}{}^2HH_{25}O_{11}$); ^{2}H-enrichment: 87.0%.

Tosylation of 6β-hydroxyloganin tetraacetate (**15**). **15** (61.7 mg) was tosylated with *p*-TsCl (31.8 mg) in pyridine (1 ml) in the usual way and the product (68.1 mg) was subjected to prep. TLC ($CHCl_3$–MeOH, 50:1, 4 developments). Of the three major bands, the least polar one yielded 7*β*-*O*-tosyloxyloganin tetraacetate as colourless needles (8.7 mg) (from EtOH). Mp 150°; $[\alpha]_D^{26}$ −87.2° ($CHCl_3$; *c* 0.32), and the second polar one gave 6*β*-*O*-tosyloxyloganin tetraacetate as a white powder (22.4 mg). The most polar one was identified as the starting material.

6β-O-Tosyloxyloganin tetraacetate. ^1H NMR ($CDCl_3$) δ: 1.13 (3H, *d*, *J* = 7.0 Hz, 10-H_3), 1.84, 1.99, 2.02 and 2.08 (12H, each *s*, OAc), 2.37 (1H, *br s*, 7-OH), 2.43–2.57 (1H, *m*, 9-H), 2.49 (3H, *s*, arom. Me), 2.98 (1H, *ddd*, *J* = 9.0, 3.5 and 1.2 Hz, 5-H), 3.68 (3H, *s*, COOMe), 3.74 (1H, *ddd*, *J* = 9.5, 4.5 and 2.1 Hz, 5′-H), 4.16 (1H, *dd*, *J* = 5.5 and 3.5 Hz, 7-H), 4.16 (1H, *dd*, *J* = 12.5 and 2.1 Hz, 6′-H_S), 4.32 (1H, *dd*, *J* = 12.5 and 4.5 Hz, 6′-H_R), 4.83 (1H, *d*, *J* = 8.0 Hz, 1′-H), 4.90 (1H, *t*, *J* = 3.5 Hz, 6-H), 4.95 (1H, *dd*, *J* = 9.0 and 8.0 Hz, 2′-H), 5.12 (1H, *dd*, *J* = 9.5 and 9.0 Hz, 4′-H), 5.24 (1H, *t*, *J* = 9.0 Hz, 3′-H), 5.31 (1H, *d*, *J* = 2.5 Hz, 1-H), 7.38 (1H, *d*, *J* = 1.2 Hz, 3-H), 7.43 (2H, AA′BB′ pattern, J_{ortho} = 8.5 Hz, arom. H), 7.93 (2H, AA′BB′ pattern, J_{ortho} = 8.5 Hz, arom. H).

Attempt to obtain 6α-hydroxyloganin (**9d**) *through Walden inversion of 6β-O-tosyloxyloganin tetraacetate*. A soln of 6*β*-*O*-tosyloxyloganin tetraacetate (10.8 mg) and Et_4NOAc (24.0 mg) in dry Me_2CO (1 ml) was worked-up according to the procedure reported by Inouye *et al.* [15]. The crude product (9.2 mg) was subjected to prep. TLC (C_6H_6–Et_2O, 7:3). The band around R_f 0.4 gave dehydro compound (3.0 mg), which was identified with **25** (mmp, IR and ^1H NMR).

Tosylation of 6α-hydroxy-7-epiloganin tetraacetate (**16**). Compound **16** (44.6 mg) was tosylated with *p*-TsCl (23.6 mg) in pyridine (1 ml) in the usual way and the product (50.1 mg) was subjected to prep. TLC (C_6H_6–Et_2O, 1:1). Of the two major bands, the band around R_f 0.60 gave 6*α*-*O*-tosyloxy-7-epiloganin tetraacetate as a white powder (18.6 mg) and the band around R_f 0.25 afforded the starting material. However, the desired 7-*O*-tosylate was not found. 6*α*-*O*-Tosyloxy-7-epiloganin tetraacetate: $[\alpha]_D^{26}$ −76.4° ($CHCl_3$; *c* 0.31); UV λ_{max}^{EtOH} nm (log ε): 228 (4.35), 266 (inf) (2.97), 273 (2.81); IR ν_{max}^{KBr} cm^{-1}: 3450, 1730, 1630; ^1H NMR ($CDCl_3$) δ: 0.95 (3H, *d*, *J* = 7.0 Hz, 10-H_3), 1.68 (1H, *ddd*, *J* = 9.5, 8.5 and 6.0 Hz, 9-H), 1.99, 2.01, 2.02 and 2.06 (12H, each *s*, OAc), 2.11–2.28 (1H, *m*, 8-H), 2.48 (3H, *s*, arom. Me), 2.86 (1H, *ddd*, *J* = 9.5, 3.5 and 1.5 Hz, 5-H), 3.74 (3H, *s*, COOMe), 4.18 (1H, *dd*, *J* = 12.5 and 2.5 Hz, 6′-H_S), 4.28 (1H, *dd*, *J* = 12.5 and 5.5 Hz, 6′-H_R), 4.29 (1H, *dd*, *J* = 8.4 and 3.5 Hz, 7-H), 4.49 (1H, *t*, *J* = 3.5 Hz, 6-H), 4.88 (1H, *d*, *J* = 8.0 Hz, 1′-H), 5.03 (1H, *dd*,

J = 9.2 and 8.0 Hz, 2'-H), 5.10 (1H, *dd*, J = 10.0 and 9.2 Hz, 4'-H), 5.15 (1H, *d*, J = 8.5 Hz, 1-H), 5.26 (1H, *t*, J = 9.2 Hz, 3'-H), 7.36 (2H, AA'BB' pattern, J_{ortho} = 8.5 Hz, arom. H), 7.59 (1H, *d*, J = 1.5 Hz, 3-H), 7.82 (2H, AA'BB' pattern, J_{ortho} = 8.5 Hz, arom. H).

Oxidation of 6,7-*epoxydeoxyloganin tetraacetate* (**20**). A soln of epoxide **20** (315 mg) in DMSO (3.0 ml) containing BF_3etherate (0.025 ml) was stirred for 1 hr at 85° [19]. The soln was then poured into ice-water (50 ml) and extracted with $CHCl_3$ (40 ml × 3). The $CHCl_3$ layer was washed successively with brine and H_2O, dried and evapd *in vacuo*. The resulting residue (315 mg) was subjected to prep. TLC ($CHCl_3$–MeOH, 20:1). The band around R_f 0.6 gave 6β-hydroxy-7-dehydrologanin tetraacetate as colourless needles (119.8 mg) (from EtOH). Mp 135°; $[\alpha]_D^{13}$ −85.4° ($CHCl_3$; *c* 0.82); UV λ_{max}^{EtOH} nm (log ε): 234 (3.87); IR ν_{max}^{KBr} cm^{-1}: 3480, 1740, 1710, 1625; ^1H NMR ($CDCl_3$) δ: 1.23 (3H, *d*, J = 7.0 Hz, 10-H_3), 1.99, 2.02, 2.04 and 2.08 (12H, each *s*, OAc), 2.25–2.44 (2H, *m*, 8-H and 9-H), 3.01 (1H, *ddd*, J = 7.5, 6.5 and 1.5 Hz, 5-H), 3.68 (1H, *br s*, 6-OH), 3.77 (3H, *s*, COOMe), 4.06 (1H, *d*, J = 6.5 Hz, 6-H), 4.15 (1H, *dd*, J = 12.5 and 2.5 Hz, 6'-H_S), 4.28 (1H, *dd*, J = 12.5 and 4.5 Hz, 6'-H_R), 4.92 (1H, *d*, J = 8.0 Hz, 1'-H), 5.03 (1H, *dd*, J = 9.0 and 8.0 Hz, 2'-H), 5.11 (1H, *dd*, J = 9.8 and 9.0 Hz, 4'-H), 5.23 (1H, *d*, J = 5.0 Hz, 1-H), 5.25 (1H, *t*, J = 9.0 Hz, 3'-H), 7.51 (1H, *d*, J = 1.5 Hz, 3-H). HREIMS *m/z*: $C_{25}H_{32}O_{15}$ requires: 572.17419; Found: 572.17004. The desired **24** was not obtained.

[6,6,7,8-$^2H_4$]*Loganin pentaacetate* (**27**). A soln of [6,6,7,8-$^2H_4$]-**12** (1.63 g) and Et_4NOAc (880 mg) in dry Me_2CO (70 ml) was worked-up in the usual way [15] to yield crude product (1.19 g). This was subjected to silica gel (36 g) CC with C_6H_6–Et_2O (7:3) as an eluent, and 100 ml of each fraction was collected. The residue (1.02 g) obtained from Frs. 2–4 gave on recrystallization from EtOH colourless needles (980 mg) of [6,6,7,8-$^2H_4$]-**27**. ^1H NMR ($CDCl_3$) δ: 1.03 (3H, *s*, 10-H_3), 2.23 (1H, *dd*, J = 9.0 and 2.8 Hz, 9-H), 3.01 (1H, *dd*, J = 9.0 and 1.0 Hz, 5-H); FABMS *m/z*: 605 $[M+H]^+$ (M: $C_{27}{}^2H_4H_{32}O_{15}$); ^2H-enrichment: 77.8%.

[6,6,7,8-$^2H_4$]*Loganin* (**1**). Methanolic NaOMe (0.1 M, 0.95 ml) was added to a soln of [6,6,7,8-$^2H_4$]-**27** (1.02 g) in abs. MeOH (26 ml) and the mixture was refluxed for 10 min. The crude product (740 mg) obtained by work-up in the usual way was then subjected to chromatography on silica gel (23 g) with $CHCl_3$–MeOH (9:1) as an eluent, and 100 ml of each fraction was collected. The residue (672 mg) from Frs 2–6 gave on recrystallization from EtOH colourless needles (354 mg) of [6,6,7,8-$^2H_4$]-**1**. ^1H NMR (CD_3OD) δ: 1.10 (3H, *s*, 10-H_3), 2.05 (1H, *dd*, J = 9.0 and 4.5 Hz, 9-H), 3.10 (1H, *dd*, J = 9.0 and 1.0 Hz, 5-H); FDMS *m/z*: 394 (M^+) (M: $C_{17}{}^2H_4H_{22}O_{10}$); ^2H-enrichment: 86.0%.

[6,6,7,8,carbomethoxy-$^2H_7$]*Loganin* (**1**). To a soln of [6,6,7,8-$^2H_4$]-**27** (130 mg) in CD_3OD (^2H-enrichment: 99.5%, CEA) (3 ml) was added 0.1 M CD_3ONa–CD_3OD (0.8 ml) and the mixture was worked-up as described above. Prep. TLC ($CHCl_3$–MeOH, 4:1, 3 developments) followed by recrystallization from EtOH of the crude product (118 mg) gave colourless needles (65 mg) of [6,6,7,8,*carbomethoxy*-$^2H_7$]-**1**. This compound showed the same ^1H NMR spectrum as that of [6,6,7,8-$^2H_4$]-**1** except for the lack of the signal due to the COOMe group at δ3.70. FDMS *m/z*: 397 $[M]^+$ (M: $C_{17}{}^2H_7H_{19}O_{10}$); ^2H-enrichment: 70.8%.

Feeding experiments with 6-β-*hydroxy* [7-^2H]*loganin* (**9a**), 6α-*hydroxy*-7-*epi*[7-^2H]*loganin* (**9b**) *and* [6,6,7,8,carbomethoxy-$^2H_7$]*loganin* (**1**) *to* Adina pilulifera. A soln of [7-^2H]-**9a** (37.5 mg; ^2H-enrichment: 95.0%) in H_2O (1 ml) was given hydroponically to two twigs (*ca* 20 cm long) of *A. pilulifera* in October. After 4 days, the leaves (7.64 g) were extracted with hot MeOH (200 ml × 3) and the extracts concd *in vacuo*. The combined extracts (1.26 g) were then turbulated with H_2O (50 ml) and the insoluble material was filtered off through a Celite layer. The Celite layer was washed with H_2O (30 ml), and the filtrate and washings were combined and concd *in vacuo* to give 1.24 g of residue which was subjected to chromatography on activated charcoal (5 g) and eluted successively with H_2O (200 ml) and MeOH (300 ml). 100 mg of the residue (480 mg) of the MeOH eluate obtained through concn *in vacuo* was purified by prep. TLC (C_6H_6–EtOAc–EtOH, 1:4:1). The band around R_f 0.27 gave **7** as a white powder (46.8 mg).

[7-^2H]-**9b** (26 mg; ^2H-enrichment: 95.2%) was given to *A. pilulifera* in the same way as above and the MeOH extract of the leaves (5.44 g) was subjected to chromatography on activated charcoal. 100 mg of the residue (470 mg) obtained from the MeOH eluate was purified by prep. TLC to give **7** (50.6 mg). ^2H was not detected in the ^2H NMR spectra of **7** in either experiment.

In the final experiment, [6,6,7,8,*carbomethoxy*-$^2H_7$]-**1** (50 mg; ^2H-enrichment: 70.8%) was given to *Adina* plants in the same way and the leaves (5.38 g) were extracted with MeOH after 4 days. The water-soluble portion (1.16 g) was chromatographed on activated charcoal (5 g) and 200 mg of the residue (550 mg) of the MeOH eluate was purified by prep. TLC to give ^2H-**7** as a white powder (98.6 mg). ^2H NMR (H_2O) δ: 1.88 (2^2H, 6-^2H), 3.73 (3^2H, carbomethoxy-$^2H_3$), 4.00 (1^2H, 8-^2H), 4.85 (7-H_2 and HDO). ^2H-enrichment based on ^2H introduced to the 6-position: 0.87%; Incorporation: 1.23%.

^2H-**7** (73.7 mg) was acetylated with pyridine–Ac_2O (each 0.74 ml) in the usual way and the product (100 mg) was subjected to prep. TLC (C_6H_6–Et_2O, 7:3, 2 developments). Of the two major bands, the less polar one gave ^2H-7*R*-morroniside pentaacetate (29.6 mg), and the more polar one gave ^2H-7*S*-morroniside pentaacetate (9.6 mg), respectively. ^2H-7*R*-morroniside pentaacetate: ^2H NMR ($CHCl_3$) δ: 1.93 (2^2H, 6-^2H), 3.48–3.67 (4^2H, 8-^2H and carbomethoxy-^2H), 5.20 (1^2H, 7-^2H).

Feeding experiments with 6β-*hydroxy* [7-^2H]*loganin* (**9a**), 6α-*hydroxy*-7-*epi*[7-^2H]*loganin* (**9b**), 6β-*hydroxy*-7-*epi*[7-^2H]*loganin* (**9c**) *and* [6,6,7,8-$^2H_4$]*loganin* (**1**) *to* Swertia japonica. A soln of [7-^2H]-**9a** (40 mg; ^2H-enrichment: 95.0%) in H_2O (1 ml) was given by the cotton wick method to two plants of *S. japonica* (*ca* 12 cm high) in October. After 10 days, the leaves, flowers and stems (3.43 g) were extracted with hot MeOH (100 ml × 4). After concn *in vacuo*, the extract was turbulated with H_2O (30 ml), and the insoluble material was filtered off through a Celite layer. The Celite layer was washed with H_2O (50 ml), and the filtrate and washings were combined and lyophilized to give 223 mg of residue which was subjected to chromatography on activated charcoal (1.7 g) and eluted successively with H_2O (100 ml) and MeOH (200 ml). The MeOH eluate was concd *in vacuo* to give a residue (91 mg), which was subjected to prep. TLC ($CHCl_3$–MeOH, 17:3, 3 developments). The residue (39.4 mg) obtained from the major band was further purified by prep. TLC (C_6H_6–EtOAc–EtOH, 1:4:1, 4 developments) to yield **28** as a white powder (24.5 mg). Experiments with [7-^2H]-**9b** (18 mg; ^2H-enrichment: 95.2%) and [7-^2H]-**9c** (11 mg; ^2H-enrichment: 87.0%) were also carried out in this way. None of **28** isolated in the above three experiments indicated any signal in the ^2H NMR spectra in H_2O, but when [6,6,7,8-$^2H_4$]-**1** (39.2 mg; ^2H-enrichment: 86.0%) was given to *S. japonica* and the experiment carried out in the same way as above, the isolated **28** (38.0 mg) gave signals at δ1.97 (2^2H, 6-^2H) and 4.27 (1^2H, 7-^2H). ^2H-enrichment based on ^2H introduced to the 7-position: 0.77%; Incorporation: 0.90%. This compound (37.2 mg) was acetylated with pyridine–Ac_2O (each 0.37 ml) in the usual way and the

product (42 mg) was recrystallized from EtOH to give ^{2}H-30 (31.3 mg). ^{2}H NMR ($CHCl_3$) δ: 5.12 (1^2H, 7-^{2}H).

Administration of 6β-hydroxy-7-epi[7-^{2}H]*loganin* (**9c**) *and* [6,6,7,8^2-H_4]*loganin* (**1**) *to* Eustoma russellianum. A soln of [7-^{2}H]-**9c** (14.1 mg; ^{2}H-enrichment: 87.0%) in H_2O (1 ml) was given by the cotton wick method to two plants (*ca* 30 cm high) of *E. russellianum* in September. After 12 days, the stems and leaves (5.14 g) were extracted with hot MeOH (100 ml × 4), and the extract was concd *in vacuo* and turbulated with H_2O (50 ml). After the insoluble material was separated by filtration through a Celite layer, it was washed with H_2O (70 ml) and the filtrate and washings were combined and concd *in vacuo*. The resulting residue (441 mg) was subjected to CC on activated charcol (3 g), and eluted successively with H_2O (500 ml) and MeOH (200 ml). 90 mg of the residue (176 mg) of the MeOH eluate was subjected to prep. TLC ($CHCl_3$–MeOH, 4:1). The crude substance (35 mg) obtained from the band around R_f 0.35 gave **29** as a white powder (25 mg) on purification by further prep. TLC (C_6H_6–EtOAc–EtOH, 1:4:1, 3 developments). ^{2}H was not detected in the NMR spectrum (H_2O) of this compound, whereas **29** (33 mg) isolated in the experiment with [6,6,7,8-$^2H_4$]-**1** (42 mg; ^{2}H-enrichment: 86.0%) showed ^{2}H signals at δ1.85 (2^2H, 6-^{2}H), 4.21 (1^2H, 7-^{2}H). ^{2}H-enrichment based on ^{2}H introduced to the 7-position: 1.37%; Incorporation: 1.59%.

This substance (18.3 mg) was acetylated with pyridine–Ac_2O (each 0.15 ml) in the usual way and the product was recrystallized from EtOH to give ^{2}H-**31** (17.5 mg). ^{2}H NMR ($CHCl_3$) δ: 1.93–2.19 (3^2H, 6-$^2H_2$ and 8-^{2}H), 5.14 (1^2H, 7-^{2}H).

Administration of [6,6,7,8-carbomethoxy-$^2H_7$]*loganin* (**1**) to Lonicera morrowii. A soln of [6,6,7,8,*carbomethoxy*-$^2H_7$]-1 (51.2 mg; ^{2}H-enrichment: 70.8%) in H_2O (1 ml) was given hydroponically to two twigs (*ca* 30 cm long) of *L. morrowii* in June. After 5 days, the leaves (28.7 g) were cut into pieces and extracted with hot MeOH (300 ml × 3). After concn *in vacuo*, the extract was turbulated with H_2O (50 ml) and the insoluble material was filtered off through a Celite layer. After washing the Celite layer with H_2O (25 ml × 3), the filtrate and washings were combined and concd *in vacuo* to give a residue (3.3 g), which was subjected to chromatography on activated charcoal (13.2 g), and eluted successively with H_2O (300 ml), 10% (300 ml) and 60% MeOH–H_2O (350 ml). 196 mg of the residue (980 mg) obtained from 60% MeOH–H_2O eluate through concn *in vacuo* was subjected to prep. TLC ($CHCl_3$–MeOH, 4:1, 2 developments) to give crude ^{2}H-**2** (118.7 mg), which was further subjected to prep. TLC (C_6H_6–EtOAc–EtOH, 1:4:1). The band around R_f 0.45 gave ^{2}H-**2** as a white powder (76.4 mg). ^{2}H NMR (H_2O) δ: 3.66 (3^2H, carbomethoxy-^{2}H), 5.36 (1^2H, 8-^{2}H), 9.66 (7-^{2}H). ^{2}H-enrichment based on ^{2}H introduced to the carbomethoxy group: 1.14%; Incorporation: 1.61%.

On acetylation with pyridine–Ac_2O (each 0.7 ml) in the usual way followed by purification through prep. TLC (Et_2O), ^{2}H-**2** (70.0 mg) gave ^{2}H-secologanin tetraacetate as a white powder (50.4 mg). ^{2}H NMR ($CHCl_3$) δ: 3.63 (3^2H, carbomethoxy-^{2}H), 5.30 (1^2H, 8-^{2}H), 9.72 (7-^{2}H).

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