Halohydrins and Polyols Derived from Antirrhinoside: Structural Revisions of Muralioside and Epimuralioside

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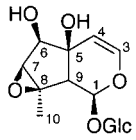
Treatment of the iridoid glucoside antirrhinoside (**1**) with pyridinium chloride in dimethylformamide gave rise to the two possible *trans*-halohydrins, linarioside (**4**) and isolinarioside (**5**). Pyridinium bromide gave the two analogous bromohydrins. It is shown that the iridoid glucosides 8-*epi*-muralioside from *Linaria arcusangeli* and 7,8-*epi*-antirrhinoside from *Linaria dalmatica* are both identical with isolinarioside, and therefore, these names are redundant. The structure of muralioside isolated from *Cymbalaria muralis* is revised to that of its 8-epimer (**8**), while the structure of an isomeric, new iridoid glucoside from *Paulownia tomentosa* has been elucidated to be 7*β*-hydroxyharpagide (**3**), the structure originally assigned to **8**. In addition, 7α-hydroxyharpagide (**2**), the known product from the base-catalyzed hydrolytic opening of **1**, has been isolated from *Antirrhinum majus* and thus shown to be a natural product.

Hydrolytic opening of the epoxide ring in the iridoid glucoside antirrhinoside (**1**), the main constituent of *Antirrhinum majus* L., has been demonstrated to take place under both alkaline and acidic conditions, giving rise to two different products. Under base catalysis,[1,2] an S_N2 nucleophilic attack takes place at the least hindered position to give the expected trans-opened 7α-hydroxyharpagide (**2**). Conversely, acid-catalyzed hydrolysis[3] yields the compound muralioside, which, on the basis of NMR evidence, was assigned structure **3** with an 8α-methyl configuration. The epoxide ring in **1** was thus assumed to have opened cis-wise by a carbocation mechanism with retention of configuration at C-8. In both cases, only a single product was obtained, and accordingly, opening of the epoxide ring by nucleophilic attack seemed a promising way to prepare derivatives of **1**.



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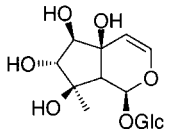

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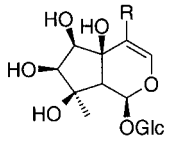

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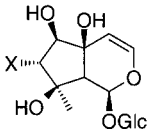
10 R = COOMe



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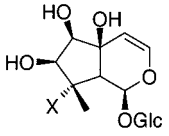

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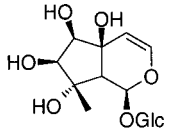
7 X = Br



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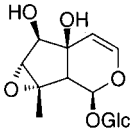

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Results and Discussion

In order to investigate the formation of halohydrins from **1**, this was treated with pyridinium chloride[4] in dimethylformamide, the latter chosen as solvent due to the poor solubility of **1** in chloroform. As monitored by reversed-phase HPLC, a slow conversion of **1** took place, and two new compounds with considerably longer retention times were observed. After 24 h, the reaction was stopped, and the products were worked up to give the isomeric chlorohydrins **4** (45 %) and **5** (11 %) as well as recovered antirrhinoside (**1**; 23 %). Similarly, reaction of **1** with pyridinium bromide for 6 days gave a pair of bromohydrins **6** and **7**.

The major chlorohydrin **4** proved identical to linarioside, first isolated from *Linaria japonica*, by comparison with the published ^{1}H and ^{13}C NMR spectra[5,6] of this compound. Negative-mode high-resolution FAB-MS of **5** showed that this had the same elemental composition, and it was therefore named isolinarioside. Complete assignment of all ^{1}H and ^{13}C NMR signals for both **4** and **5** was performed using HSQC and HMBC experiments (see the Experimental Section and Table 1). The ^{1}H NMR spectrum of **5** displayed a methyl signal at δ 1.75 compared to that of δ 1.20 in **4**, and the downfield position proved that the chlorine atom in **5** was attached to C-8. The coupling constant ($J_{6,7}$ = 4.5 Hz) showed that H-6 and H-7 were cis; it was identical to that reported for phlomiol[7] (**10**) and lamalbide[8] and was significantly different from the 9−10.5 Hz coupling constant seen[3] for the 6,7-trans compounds **2** and **4**. This left only the configuration at C-8 to be settled in **5**. A NOESY experiment showed effects between the C-10 methyl group and H-1, H-7, and H-9, and since the

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Table 1. ^{13}C NMR Data of Iridoid Glucosides in D_2O

	1	**3**	**10**[a]	**8**[b]	**5**	**7**	**2**	**4**	**6**
C-1	95.0	93.4	94.1	93.2	93.5	94.3	91.9	91.7	91.9
C-3	143.0	141.9	154.2	142.2	141.2	140.9	140.0	140.1	140.0
C-4	107.0	107.5	112.9	107.2	107.8	108.0	109.4	108.9	108.9
C-5	74.4	68.3	68.3	68.5	68.6	68.6	64.1	65.4	66.1
C-6	76.7	78.0	77.5	77.8	77.1	81.6	82.5	80.0	80.3
C-7	66.3	76.5	75.2	79.6	81.1	77.1	78.8	71.6	64.7
C-8	65.1	77.8	75.9	79.3	73.8	67.9	74.9	74.8	74.4
C-9	52.0	57.0	56.6	55.2	56.8	57.7	56.2	57.1	57.0
C-10	17.0	21.9	20.9	24.7	27.7	29.1	16.6	18.1	19.6
C-11			168.7						
11-OMe			52.6						
C-1′	99.3	99.0	99.1	100.0	98.8	98.8	98.6	98.6	98.7
C-2′	73.4	73.3	73.1	73.3	73.4	73.4	73.3	73.3	73.3
C-3′	76.4	76.1	76.1	76.2	76.2	76.2	76.1	76.1	76.1
C-4′	70.4	70.5	70.4	70.5	70.5	70.5	70.5	70.5	70.5
C-5′	77.1	77.1	77.0	77.0	77.2	77.3	77.0	77.0	77.0
C-6′	61.5	61.5	61.5	61.5	61.5	61.5	61.5	61.5	61.5

[a] Data from ref 6. [b] Data from ref 3.

last effect was the strongest, a position on the β-face was indicated. The otherwise convenient method[9] of using the C-9 chemical shift value to determine the configuration at C-8 cannot be used for compounds with only a single electronegative substituent present at either C-8 or C-10, which is the case here. However, the trans disposition of the 8-chloro atom to the 7β-OH group was finally demonstrated chemically by the facile conversion of **5** into **1**. This was performed in excess sodium deuteroxide in deuterium oxide at room temperature to allow monitoring by ^1H NMR. The epoxide formation took less than 10 min, and the mechanism is an intramolecular S_N2 substitution by the C-7 oxygen atom with inversion at C-8.[10a] This proved isolainarioside to have the structure **5**. Likewise, linarioside (**4**) was converted into **1**, but in this case full conversion took about 30 min.

The above NOESY experiment on **5** showed NOE effects of the same intensity between H-1 and the C-10 methyl group as between H-1 and H-9, but similar effects were also seen for **4**. In fact, Dreiding models of **4** and **5** with the dihydropyrane ring in the distorted boat conformation ($B_{O,5}$) could accomodate the required dihedral angle $\angle H_1H_9 \approx 90°$ ($J_{1,9} = 0$ Hz), and moreover, the cyclopentane ring would readily adopt the ^7V envelope conformation.[8] Inspection of this model showed that the distances between H-1 and either of the two C-8 substituents was nearly the same, consistent with the observed effects. This molecular arrangement also gave a reasonable fit with the coupling contants measured for $J_{6,7}$, namely 10.5 Hz in **4** ($\angle H_6H_7 \approx 170°$) and 4.5 Hz in **5** ($\angle H_6H_7 \approx 30°$). Consequently, an NOE effect seen between H-1 and the C-10 protons cannot be used as proof of the 8α-position of this group. In fact, the structure of the iridoid glucoside 10-hydroxyepihastatoside,[11] first assigned by such an NOE effect, has recently been revised to its 8-epimer 10-hydroxyhastatoside by chemical correlation.[12]

The structures of the two bromohydrins were similarly shown to be **6** and **7**, and in both cases, the conversion back to **1** was complete in less than 3 min. The 8-halo compounds proved to be rather unstable at room temperature, and they must be stored in the freezer. Thus, when **7** was dried under vacuum with the aim of measuring the optical rotation, it turned dark in a few hours and obviously was degraded.

During the structure elucidation of isolinarioside (**5**), its ^{13}C NMR data were compared with those of the C-8-epimeric pair muralioside (from *Cymbalaria muralis* P. Gaertn., B. Mey. & Scherb.)[3] and epimuralioside (from *Linaria arcusangeli* Atzei et Camarda),[13] presumed to have the structures **3** and **8**, respectively. Surprisingly, the published NMR spectra of epimuralioside proved identical to those of **5**. A comparison of epimuralioside and synthetic **5** (performed in Rome by Prof. Bianco's group) by reversed-phase HPLC showed that the two compounds had identical retention times. This, together with a direct comparison of ^1H and ^{13}C NMR spectra, proved without doubt that the structure of epimuralioside is that attributed to **5**. It was also demonstrated that considerable degradation of "epimuralioside" had taken place at room temperature. This also explains the difference in optical rotation between the natural compound (−50°) and the freshly prepared synthetic isolinarioside (−159°). Regarding the published MS data,[13] the experimental conditions for the FAB-MS experiment have evidently given rise to substitution of chlorine with hydroxyl, thus affording incorrect MS data. In view of the above evidence, epimuralioside is identical to isolinarioside, and we consider that only the name isolinarioside should be retained.

We also discovered that another compound, which had been isolated together with antirrhinoside (**1**) and linarioside (**4**) from *Linaria dalmatica* (L.) Mill.[14] and had been assigned the structure 7,8-*epi*-antirrhinoside, also had NMR data identical to those of **5**. In addition, the NMR signals supposed to arise from the epoxide functionality ($\delta_{C-7} = 81.1$ ppm and $\delta_{C-8} = 73.8$ ppm, Table 1) seemed to be at abnormally low field for such a structure and would comply much better with an open form. The mass spectrum reported for this compound was recorded by CI-MS, and it proved almost identical to that of **1** also previously reported.[14] This would be consistent with a breakdown of the compound to **1** either before or in the process of recording the mass spectrum. Unfortunately, no sample of the compound was left, but reversed-phase HPLC (performed in Sofia by Dr. Handjieva) using the original conditions further proved the identity. Consequently, we conclude that isolinarioside is present in *L. dalmatica*, and therefore, the name 7,8-*epi*-antirrhinoside is also redundant.

Chlorohydrins of iridoid glucosides have indeed been particularly capricious in their structural elucidation. In the past, the compounds thunbergioside from *Thunbergia mysorensis* (Wight) T. Anders.[15] and avicennioside (= linarioside (**4**)) from *Avicennia officinalis* L.[16] were both initially published as the corresponding hydroxylated analogues.

The above results obliged us to reinvestigate the structure of muralioside, which had been assigned the structure

3.[3] Comparison of the ^{13}C NMR spectrum of muralioside (**9**, Table 1) with that of phlomiol[6] (**10**) showed less similarity than would be expected in view of the identical substitution pattern in the five-ring. Particularly, the signals for C-7, C-8, C-9, and C-10 were quite dissimilar, indicating that these two compounds were stereochemically different at C-8. In muralioside, the small size of the coupling constant $J_{1,9} = 0.7$ Hz[17] as well as the value for the chemical shift difference between δ_{C-3} and δ_{C-4} (35 ppm)[9] demonstrated the β-position of the 6-OH group. Also, the coupling constant $J_{6,7} = 5.7$ Hz showed the cis disposition of the 6- and 7-OH substituents. With regard to the stereochemistry at C-8, this was believed to have the methyl group in the 8α position. The main arguments for this structural assignment were the presence of an NOE effect between H-1 and the 10-methyl group and the fact that the compound was formed by acid-catalyzed hydrolysis[3] of **1**. Above, we have already argued that this particular NOE effect is insufficient for the purpose of determining the stereochemistry at C-8. Furthermore, the acid-catalyzed hydrolysis of **1** would more likely proceed with inversion of configuration at the most substituted carbon to give **8**, although an S_N1 mechanism leading to **3** might be a possibility.[10b] In conclusion, muralioside must have the structure **8**, which was ironically first assigned to epimuralioside.

Accidentally, during earlier work on *Paulownia tomentosa* Koch.[18] we isolated another tetrahydroxylated iridoid glucoside (**3**) as a minor constituent, but at that time it was not properly characterized. Assignment of all ^1H and ^{13}C NMR signals for **3** has now been performed using HMQC and HMBC experiments (see Experimental Section and Table 1). The ^{13}C NMR spectrum was partly similar to that of muralioside (**8**), except for the signals arising from C-6−C-10, which only showed a moderate match. Conversely, this latter part of the spectrum was more similar to that of phlomiol (**10**) with an 8α-methyl group. In fact, the signals from C-9 and C-10 (which usually are the most informative[9] regarding the stereochemistry at C-8) were within 1 ppm from those of **10**, indicating the presence of an 8α-methyl group in **3**. The ^1H NMR data proved the cis disposition of H-6 and H-7 ($J_{6,7} = 4$ Hz). Furthermore, a NOESY experiment showed strong NOE effects between the methyl group (C-10) and the protons at C-1, C-6, and C-7, while only a weak effect was seen between the methyl group and H-9, consistent with the α-disposition of C-10. Consequently, the new compound was assigned the structure 7β-hydroxyharpagide (**3**), and it is the 8-epimer of muralioside (**8**).

As stated in the introduction, 7α-hydroxyharpagide (**2**) has long been known as the product of the base-catalyzed hydrolytic opening of **1**.[1,2] We now also report it as a minor natural constituent in *Antirrhinum majus*, at least in the commercial variety White Wonder. During reversed-phase chromatography, compound **2** is so polar that it elutes with the often substantial fraction of sugars and thus escapes detection. We have now discovered that adsorption of the glucosides in the aqueous extract of the plant on activated carbon allows selective removal of all free sugars, and subsequently, **2** could be isolated from the resulting crude glucoside fraction. The compound was identified by comparison of its NMR data with those published (see Experimental Section).

Experimental Section

General Experimental Procedures. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 instrument in D_2O using the solvent peak (δ 4.75) or the C-6′ peak (δ 61.5)[9] as the internal standards, respectively. The signals of compounds **3**−**5** were assigned using HSQC and HMBC spectra. Also, for these three compounds NOESY spectra were recorded. FAB high-resolution mass spectra were recorded in the negative mode, using bis(2-hydroxyethyl)disulfide as matrix. Preparative reversed-phase chromatography was performed on a Merck Lobar Lichroprep RP-18 (size B) or on a column (size D) packed with Polygoprep. C_{18} (50-60 μm; 1.5 kg; from Macherey-Nagel). VLC (vacuum liquid chromatography) was performed on predried (120 °C, >24 h) Merck silica gel 60H.

Chlorohydrins of Antirrhinoside (1). Compound **1** (2.92 g) was dissolved in DMF (13 mL), and pyridinium chloride (2.92 g) was added with stirring and gentle heating until complete dissolution. After 24 h at room temperature, analytical RP-HPLC showed that most **1** was converted into two products with considerably longer retention times. The reaction mixture was poured onto a VLC column (11 × 4 cm), and most DMF and pyridine were removed by elution with hexane (1 L), followed by $CHCl_3$ (1.8 L). The glucosides were then eluted with $CHCl_3$−MeOH (3:1; 1.8 L) to give a crude iridoid mixture (4.94 g). Reversed-phase chromatography (D-column) eluting with H_2O−MeOH (20:1−7:1) gave, in order of elution, **1** (660 mg, 23%), linarioside (**4**, 1420 mg, 45%), and isolinarioside (**5**, 360 mg, 11%).

Bromohydrins of antirrhinoside (1). Treatment of **1** (770 mg) in DMF (5 mL) with pyridinium bromide (770 mg) as above was continued for 6 days. Purification with proportional amounts of solvents gave bromolinarioside (**6**, 520 mg) and bromoisolinarioside (**7**, 95 mg).

Linarioside (4): $[\alpha]^{21}_D = -177°$ (*c* 0.7, MeOH); ^1H NMR (500 MHz, D_2O) δ 6.34 (1 H, d, $J = 6.5$ Hz, H-3), 5.64 (1 H, br s, H-1), 5.21 (1 H, dd, $J = 6.5$, 1 Hz, H-4), 4.76 (1 H, d, partly obscured by solvent peak, H-1′), 4.09 (1 H, d, $J = 10.5$ Hz, H-7), 3.91 (1 H, dd, $J = 2$, 12.5 Hz, H-6a′), 3.72 (1 H, dd, $J = 5.5$, 12.5 Hz, H-6b′), 3.71 (1 H, d, $J = 10.5$ Hz, H-6), 3.49 (1 H, t, $J = 9.5$ Hz, H-3′), 3.48 (1 H, m, H-5′), 3.39 (1 H, t, $J = 9.5$ Hz, H-4′), 3.31 (1 H, dd, $J = 8$, 9.5 Hz, H-2′), 2.48 (1 H, br. s, H-9), 1.20 (3 H, s, 10-Me).

Isolinarioside (5): $[\alpha]^{21}_D = -159°$ (*c* 0.5, MeOH); ^1H NMR (500 MHz, D_2O) δ 6.38 (1 H, d, $J = 6.5$ Hz, H-3), 5.76 (1 H, br s, H-1), 5.20 (1 H, dd, $J = 6.5$, 1 Hz, H-4), 4.76 (1 H, d, partly obscured by solvent peak, H-1′), 4.18 (1 H, d, $J = 4.5$ Hz, H-7), 4.05 (1 H, d, $J = 4.5$ Hz, H-6), 3.93 (1 H, dd, $J = 2$, 12.5 Hz, H-6a′), 3.73 (1 H, dd, $J = 6$, 12.5 Hz, H-6b′), 3.50 (3 H, t, $J = 9.5$ Hz, H-3′), 3.49 (1 H, m, H-5′), 3.41 (3 H, t, $J = 9.5$ Hz, H-4′), 3.31 (1 H, dd, $J = 8$, 9.5 Hz, H-2′), 2.76 (1 H, br s, H-9), 1.75 (3 H, s, 10-Me); LR-FABMS *m*/*z* (rel int) 399, 397 (3:1) $[M - H]^-$; HR-FABMS *m*/*z* 397.089 $[M - H]^-$, calcd for $C_{15}H_{22}ClO_{10}$ 397.090.

Bromolinarioside (6): $[\alpha]^{21}_D = -177°$ (*c* 0.7, MeOH); ^1H NMR (500 MHz, D_2O) δ 6.35 (1 H, d, $J = 6.5$ Hz, H-3), 5.71 (1 H, br s, H-1), 5.22 (1 H, dd, $J = 6.5$, 1 Hz, H-4), 4.76 (1 H, d, $J = 8$ Hz, H-1′), 4.20 (1 H, d, $J = 10.5$ Hz, H-7), 3.92 (1 H, dd, $J = 2$, 12.5 Hz, H-6a′), 3.81 (1 H, d, $J = 10.5$ Hz, H-6), 3.73 (1 H, dd, $J = 6$, 12.5 Hz, H-6b′), 3.51 (3 H, t, $J = 9.5$ Hz, H-3′), 3.50 (1 H, m, H-5′), 3.40 (3 H, t, $J = 9.5$ Hz, H-4′), 3.32 (1 H, dd, $J = 8$, 9.5 Hz, H-2′), 2.50 (1 H, br s, H-9), 1.24 (3 H, s, 10-Me); LR-FABMS *m*/*z* (rel int) 443, 441 (1:1) $[M - H]^-$; HR-FABMS *m*/*z* 441.042 $[M - H]^-$, calcd for $C_{15}H_{22}BrO_{10}$ 441.040.

Bromoisolinarioside (7): ^1H NMR (500 MHz, D_2O) δ 6.38 (1 H, d, $J = 6.5$ Hz, H-3), 5.74 (1 H, br s, H-1), 5.23 (1 H, br d, $J = 6.5$ Hz, H-4), 4.78 (1 H, d, partly obscured by solvent peak, H-1′), 4.32 (1 H, d, $J = 4$ Hz, H-7), 4.15 (1 H, d, $J = 4$ Hz, H-6), 3.94 (1 H, dd, $J = 2$, 12.5 Hz, H-6a′), 3.74 (1 H, dd, $J = 6$, 12.5 Hz, H-6b′), 3.51 (3 H, t, $J = 9.5$ Hz, H-3′), 3.50 (1 H, m, H-5′), 3.42 (3 H, t, $J = 9.5$ Hz, H-4′), 3.32 (1 H, dd, $J = 8$, 9.5 Hz, H-2′), 2.76 (1 H, br s, H-9), 1.95 (3 H, s, 10-Me); LR-FABMS *m*/*z* (rel int) 443, 441 (1:1) $[M - H]^-$; HR-FABMS *m*/*z* 441.044 $[M - H]^-$, calcd for $C_{15}H_{22}BrO_{10}$ 441.040.

Conversion of 4−7 to 1. Each compound was dissolved in D_2O (0.5 mL) in an NMR tube at 25 °C and the ^1H NMR spectrum recorded. Next, 40% NaOD (ca. 25 μL) was added and the spectrum recorded again within 3 min. At this point, **6** and **7** were completely converted, while **4** was ca. 25% and

5 ca. 80% transformed. Conversions of the last two were complete after 30 and 10 min, respectively.

Workup of *P. tomentosa*. The extract from the leaves of the old specimen published previously[18] gave a fraction (250 mg) eluting immediately after catalpol. Rechromatography on a size B column gave four fractions, namely fractions A (36 mg), B (35 mg), C (32 mg), and D (15 mg). NMR showed that fraction B consisted mainly of a single compound. Rechromatography on a VLC column (2 × 3 cm) eluting with $CHCl_3$−MeOH (5:1−3:1) gave pure **3** (10 mg).

7*β*-Hydroxyharpagide (3): $[\alpha]^{21}_D = -128°$ (*c* 0.5, MeOH); ^{1}H NMR (500 MHz; D_2O) δ 6.38 (1 H, d, J = 6.5 Hz, H-3), 5.74 (1 H, br s, H-1), 5.10 (1 H, dd, J = 6.5, 1.5 Hz, H-4), 4.74 (1 H, d, partly obscured by solvent peak, H-1′), 3.93 (1 H, dd, J = 2.5, 12.5 Hz, H-6a′), 3.76 (1 H, d, J = 4 Hz, H-6), 3.73 (1 H, dd, J = 6, 12.5 Hz, H-6b′), 3.71 (1 H, d, J = 4 Hz, H-7), 3.50 (3 H, t, J = 9.5 Hz, H-3′), 3.50 (1 H, m, H-5′), 3.41 (3 H, t, J = 9.5 Hz, H-4′), 3.32 (1 H, dd, J = 8, 9.5 Hz, H-2′), 2.65 (1 H, br s, H-9), 1.23 (3 H, s, 10-Me); HR-FABMS *m*/*z* 379.123 [M − H]$^-$, calcd for $C_{15}H_{23}O_{11}$ 379.124.

Workup of *A. major* (White Wonder). Dry plant material (200 g) was blended with MeOH (1.3 L) and left to stand for 20 h, and then the extract was taken to dryness. After partitioning in H_2O−Et_2O (each 50 mL), the aqueous phase was extracted with EtOAc (2 × 25 mL) and concentrated to a brown syrup (16.5 g). Sugars and inorganics was removed by redissolving in H_2O (200 mL) followed by adsorption on activated carbon (50 g) under stirring for 1.5 h. After filtering, the filter cake was washed with acetone (20 mL, to remove residual H_2O) and dried overnight by suction. Elution with EtOH (150 mL) gave a crude glucoside mixture (5.0 g). Reversed-phase chromatography (D column) eluting with H_2O−MeOH (20:1 to 10:1) gave as the first fraction impure 7α-hydroxyharpagide (**2**, 0.3 g), followed by antirrhinoside (**1**, 2 g), 5-glucosylantirrhinoside and **1** (1:1, 0.6 g), and linarioside (**4**, 0.8 g). Rechromatography of the first fraction gave pure **2** (0.19 g).

7α-Hydroxyharpagide (**2**) was solely characterized by ^{1}H and ^{13}C NMR data (Table 1), which were essentially identical to those published.[3,6]

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