Synthesis of Antirrhinolide, a New Lactone from *Antirrhinum Majus*

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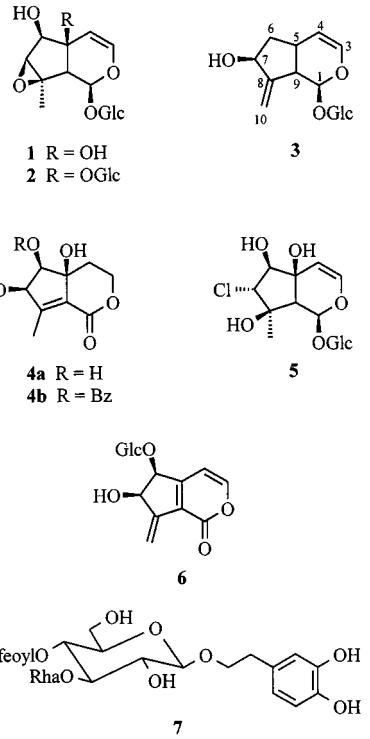
In addition to the known iridoid glucosides antirrhinoside (**1**), antirrhide (**3**), linarioside (**5**) and chaenorrhinoside (**6**), a novel nonglucosidic iridoid lactone was isolated in trace amount from *Antirrhinum majus* (Scrophulariaceae). This lactone, named antirrhinolide (**4a**) was synthesised from 5,6-*O*-isopropylidene-dihydroantirrhinoside aglucone (**7**) in two steps. Thus, its absolute stereochemistry was proven unequivocally.

Introduction

Antirrhinum majus (Scrophulariaceae) belongs to the Scrophularioideae−Antirrhineae,[1] and its content of iridoid glucosides has been investigated repeatedly. Thus, antirrhinoside (**1**),[2] 5-glucosylantirrhinoside (**2**),[3] and antirrhide (**3**)[4] have been reported from this species. During the course of our present work concerning the use of **1** as a building block for cyclopentanoid biologically active compounds[5][6] we have performed large-scale extraction of different varieties of *Antirrhinum majus*. In the present work, we have also examined the minor components in the commercial variety "Bright Eyes".

Results and Discussion

An ethanolic extract of dried aerial parts of *Antirrhinum majus* was subjected to further solvent partitioning. Since the primary aim was to obtain large quantities of **1**, the water-soluble part was extracted with ethyl acetate to remove possible apolar constituents. Reverse phase chromatography of this ethyl acetate fraction yielded first a novel non-glucosidic compound **4a**, followed by the known iridoid glucosides **1**, **3**, linarioside (**5**)[7] and chaenorrhinoside (**6**),[8] also, verbascoside (**7**) was obtained, this being the most apolar compound. The ^{13}C NMR spectrum (see Table 2) of **4a** showed nine signals, suggesting the compound to be a decarboxylated iridoid aglucone. The co-occurrence of **4a** and **6** led us to the assumption that the former similarly might be related to either **1** or **3**.



The structural elements deduced from the ^{13}C NMR spectrum (Table 2) were: one methyl group (δ = 15.2), two −CHOH− groups, one −C(OH)< group, two methylene groups, and an α,β-unsaturated ester or lactone functionality (δ = 161.2, 129.3 and 166.2). Inspection of the ^{1}H NMR spectrum (Table 1) revealed only two spin-coupling systems, namely the two hydroxymethine protons (AB-system at δ = 4.18 and 3.74), and two connected methylene groups (ABXY system at δ = 4.67/4.38 and 2.12/1.84), the latter apparently being part of the ester or lactone. One way to combine these substructures is given in the formula **4a**. ^{1}H homodecoupling of the methyl group effected a sharpening of the hydroxymethine proton signal at δ = 4.18. This taken together with the low field chemical shifts of these protons suggested that they were all placed in an allylic position to the double bond as in the proposed structure **4a**. Finally, the mass spectrum gave an M^+ ion at *m/z* 208, which also points to the chemical composition $C_9H_{12}O_5$. Benzoylation under mild conditions afforded a dibenzoate **4b**, while ketalization with acetone yielded a major (**10a**) and a minor (**10b**) product. Of these, **10b** proved identical with the 5,6-isopropylidene derivative obtained by synthesis (see below), while **10a** was the 6,7-isopropylidene ketal as

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seen by the ^{1}H NMR spectrum (Table 1) in which H-7 showed an significant downfield shift (0.51 ppm) when compared to **10b**. This showed that the three hydroxy groups at C-5, C-6 and C-7 in **4a** were consecutive and in an all-*cis* configuration.

Table 1. ^{1}H NMR data (500 MHz, in CD_3OD except for **4b** in $CDCl_3$) of related lactones and derivatives of **4a**.

	11[a]	**4a**	**4b**	**10a**	**10b**
3a-H	4.57 (dd, 11.9, 2.0)	4.67 (ddd, 12.5, 11.0, 3.0)	4.75 (ddd, 12.5, 11.5, 3.0)	4.72 (ddd, 12.5, 11.0, 4.0)	4.62 (ddd, 12.0, 11.0, 4.0)
3b-H	4.51 (dd, 11.9, 3.5)	4.38 (ddd, 11.0, 5.0, 2.0)	4.40 (ddd, 11.5, 5.5, 1.5)	4.42 (ddd, 11.0, 6.0, 1.5)	4.46 (ddd, 11.0, 6.0, 1.5)
4a-H	3.14 (ddd, 5.5, 3.5, 2.0)	2.12 (ddd, 14.0, 3.0, 2.0)	2.37 (overlapped)	2.08 (ddd, 13.5, 4.0, 1.5)	2.19 (ddd, 14.0, 4.0, 1.5)
4b-H		1.84 (ddd, 14.0, 12.5, 5.0)	2.06 (ddd, 14.0, 12.5, 5.5)	1.92 (ddd, 13.5, 12.5, 6.0)	2.11 (ddd, 14.0, 12.0, 6.0)
5-H	3.60 (m)				
6a-H	2.37 (m)	3.74 (d, 6.0)	5.35 (d, 6.0)	4.50 (d, 6.5)	4.55 (d, 6.0)
6b-H	2.06 (m)				
7a-H	4.52 (m)	4.18 (d, 6.0)	5.95 (br d, 6.0)	4.88 (br d, 6.5)	4.37 (br d, 6.0)
7b-H					
10-Me	2.18 (dd, 2.6, 0.6)	2.27 (br s)	2.36 (br s)	2.13 (br s)	2.10 (br s)
$Me_2C<$				1.50 (s)	1.42 (s)
				1.41 (s)	1.40 (s)
Ph-C=O			(10H) 8.07−7.23		

[a] Data from ref.[10].

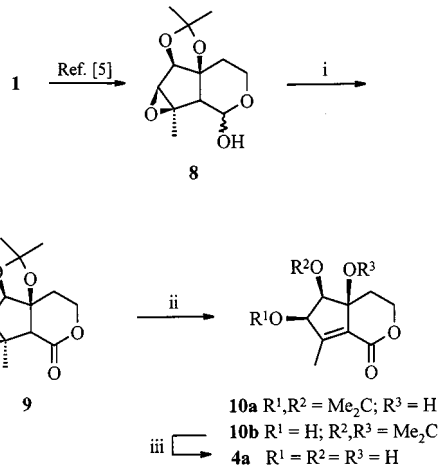
Table 2. ^{13}C NMR (125 MHz, CD_3OD) for related lactones and derivatives.

	11[a]	**4a**	**10b**	**4b**[b]
C-1	165.9	166.2	165.7	162.6
C-3	71.3	68.0	68.6	66.4
C-4	44.0	34.6	33.6	34.2
C-5	43.9	78.1	89.6	77.8
C-6	37.0	75.6	80.6	73.8
C-7	79.8	77.9	77.2	77.1
C-8	158.9	161.2	158.4	154.1
C-9	126.8	129.3	126.9	131.1
C-10	14.4	15.2	13.5	15.0
C-11	172.4			
$Me_2C<$			112.8	
$Me_2C<$			27.8	
			27.7	
Ph-C=O				165.7
				165.4

[a] Data from ref.[10]. − [b] In $CDCl_3$.

To establish the stereochemistry unequivocally, and to rule out any other possible structures, a synthesis of **4a** was undertaken. We have earlier described[5] the preparation of the intermediate **8** (*i.e.* 3,4-dihydro-5,6-*O*-isopropylideneantirrhinoside aglucone) in 61% overall yield from **1**. Oxidation (Scheme 1) of hemiacetal **8** was performed with a catalytic amount of RuO_2 and an excess of $NaIO_4$.[9] Treatment of the initially formed β,γ-epoxylactone intermediate **9** with triethylamine during work-up, accomplished the rearrangement to the γ-hydroxy-α,β-unsaturated lactone **10b**. Thus, hemiacetal **8** was readily transformed into the 5,6-*O*-isopropylidene-protected lactone **10b** in 94% overall yield. Removal of the isopropylidene protecting group proved difficult; traditional methods using aqueous acid and an organic co-solvent or borontrichloride/dichloromethane gave either no reaction or resulted in a complex product mixture. However, deprotection could be achieved using *p*-toluenesulphonic acid in wet chloroform giving the triol **4a** in 32% yield while 67% of starting material was recovered. Attempts for reducing the reaction time by increasing the temperature slightly resulted in the formation of a multitude of by-products. The identity of the synthetic compound and the isolated lactone **4a** was proven by comparison of their NMR spectra and optical rotations.

Scheme 1. Synthesis of lactone **4a** from **1**. − (i) Cat. RuO_4, $NaIO_4$. − (ii) Et_3N. − (iii) $TsOH{\cdot}H_2O$, $CHCl_3$.



The structure of **4a** indicates a biogenetic relationship to **1**, since reduction of the 3,4-enol ether in **1** (or rather in its aglucone), oxidation of C-1 to the carboxylic stage, and a subsequent intramolecular opening of the epoxide by removal of the proton at C-9 might give rise to **4a**. Similar lactones have been reported from the closely related genus *Linaria*. Thus, the esters **11** and **12** of 5-deoxyantirrhinoside have been found in *L. japonica*,[10] while a possible isomer **13** was reported from *L. arcusangeli*.[11] Also two acids isolated from fruits of *Crescentia cujete* (Bignoniaceae)[12] are of related structure.

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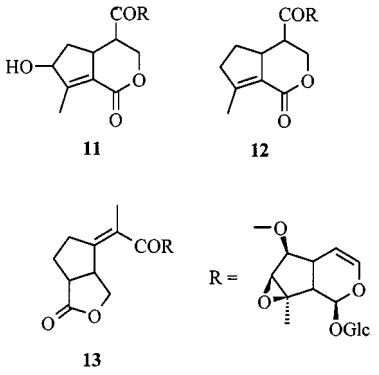

Experimental Section

General: Elemental analyses were performed by the Institute of Physical Chemistry, Vienna. − Optical rotations: Perkin-Elmer 241 polarimeter. − Melting points are uncorrected. − MPLC: Merck Lobar C-18 columns (size B: 25 × 310 mm). − VLC (vacuum liquid chromatography): predried (120°C ; > 24 h) Merck Silica Gel 60H (0.04−0.06 mm), column size is given as height × diameter (cm). − NMR: Bruker AM-500 (500 MHz and 125 MHz for ^1H and ^{13}C, respectively). For ^1H NMR, [D_4]methanol as solvent δ_H = 3.31, $CDCl_3$ δ_H = 7.27; for ^{13}C NMR, [D_4]methanol δ_C = 49.0, $CDCl_3$ δ_C = 77.0. − MS: VG Trio-2 (direct inlet at 150°C).

Work-up of Antirrhinum majus: Dry plant material (3.4 kg) was extracted with MeOH (15 l) for 3 days. The filtrate was concentrated, and the residue partitioned in Et_2O/H_2O (2:1, 1500 ml). The aqueous layer was extracted with EtOAc (3 × 500 ml). Concentration gave a water-soluble extract (231 g) and an EtOAc-soluble extract (3.20 g). Further extraction of the filter-cake (15 l of MeOH for 24 h, twice) and treatment as above yielded additional amounts of water-soluble extract (213 g) and EtOAc-soluble extract (2.87 g).

The first EtOAc extract (3.20 g) was again partitioned between water and EtOAc (1:1, 50 ml). The aqueous layer was concentrated to a small volume and chromatographed by MPLC. Elution with H_2O and then H_2O/MeOH, 25:1, 15:1, 5:1 and 3:2 yielded successively fractions of impure **4a** (30 mg), pure **4a** (43 mg), a mixture (10 mg) of antirrhide (**3**) and antirrhinoside (**1**), **1** (40 mg), linarioside (**5**, 30 mg), a mixture (10 mg) of **5** and chaenorrhinoside (**6**), and verbascoside (**7**, 70 mg).

Lactone **4a**: Amorphous syrup, $[\alpha]_D^{23}$ = −52 (*c* 0.5, MeOH). − ^1H NMR: See Table 1. − ^{13}C NMR: See Table 2. − CI-MS (NH_3 as reagent gas): *m/z* $[M+NH_4]^+$ 218, 201. − $C_9H_{12}O_5$ (200.2): calcd C 54.00, H 6.04; found C 53.97, H, 6.17.

Benzoylation of Lactone **4a**: Lactone **4a** was benzoylated with BzCl in CH_2Cl_2/pyridine for about 12 h. Work-up afforded a crude product, which was purified by VLC eluting with hexane, and then hexane/Me_2CO, 5:1 and 4:1. This yielded dibenzoate **4b** as an amorphous syrup. − ^1H NMR: See Table 1. − ^{13}C NMR: See Table 2. − EI-MS: *m/z* $[M]^+$ 408, 391, 286. − $C_{23}H_{20}O_7$ (408.4).

Ketalization of Lactone **4a**: Pyridinium *p*-toluenesulfonate (PPTS, 2 mg) was added to a stirred solution of **4a** (14 mg, 0.07 mmol) in a mixture of acetone and 2,2-dimethoxypropane (10:1, 2 ml). The reaction mixture was stirred at room temp. for 5.5 h, then kept at 4 °C for 3 days. Analytical HPLC showed the disappearance of **4a** with formation of a less polar product. Saturated aq. $NaHCO_3$ (5 ml) was added to the reaction mixture, and the volume was reduced in vacuo to ca. 5 ml, which were extracted with EtOAc (2 × 20 ml). The organic layers were dried ($MgSO_4$), filtered and the solvent removed in vacuo to yield impure 6,7-isopropylidene lactone (**10a**, 16 mg). Comparison of the analytical HPLC chromatograms showed this to be identical to the apolar by-product from the deprotection of the 5,6-ketal **10b** (see below).

Oxidation of 3,4-Dihydro-5,6-isopropylidene Antirrhinoside Aglucone (**8**): A solution of aglucone **8** (5.0 g, 21 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously with a mixture of $RuO_2{\cdot}H_2O$ (56 mg), $NaIO_4$ (4.5 g, 21 mmol), $NaHCO_3$ (500 mg), and water (50 ml). Additional $NaIO_4$ (500 mg each time) was added until the reaction mixture turned yellow. Then 2-propanol was added in order to quench excess RuO_4. Filtration through a layer of act. charcoal over Celite and evaporation of the solvent yielded a residue which was partitioned between CH_2Cl_2 (100 ml) and water (50 ml). Drying (Na_2SO_4) and concentration gave an oil (mainly containing the labile lactone **9**), which was dissolved in CH_2Cl_2 and Et_3N (1 ml) was added. After 1 h at room temp. the solvent was removed (as full conversion to **10b** was seen by TLC). The residue was partitioned between EtOAc (100 ml) and 0.015 M H_2SO_4 (30 ml). The organic layer was washed with water (20 ml), dried ($MgSO_4$), and then the solvent was removed in vacuo to yield a solid residue. Crystallization from acetone/hexane gave the protected lactone **10b** as needles (4.72 g, 94%), m.p. 97−98°C. − $[\alpha]_D^{24}$ = −21 (*c* = 0.61, MeOH). − ^1H NMR: See Table 1. − ^{13}C NMR: See Table 2. − $C_{12}H_{16}O_5$ (240.3): calcd C 59.99, H 6.71; found C 59.77, H 6.55.

Deprotection of **10b**: To a solution of compound **10b** (234 mg, 0.97 mmol) in $CHCl_3$ (10 ml) was added *p*-TsOH·H_2O (25 mg), and the mixture was stirred at room temp., while following the conversion by analytical HPLC. After 3 days, the formation of a major polar product was detected together with residual apolar starting material and a trace of an even less polar compound (with same retention as the above **10a**). Saturated aq. $NaHCO_3$ (1 ml) and water (1 ml) were added to the reaction mixture, which was concentrated in vacuo to 2 ml. More H_2O (2 ml) was added, and the resulting solution was purified by MPLC to give the desired lactone **4a** (63 mg, 32%) as a colorless oil, $[\alpha]_D^{23}$ = −51 (*c* = 0.7, MeOH), and recovered starting material (157 mg, 67%).

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