Ozonolysis of Protected Iridoid Glucosides

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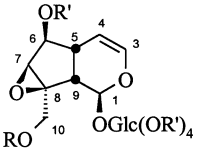
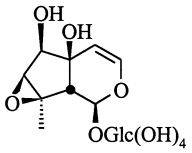
Scutellaria subvelutina was found to be an excellent source of the catalpol ester scutellarioside I (**3**) and this was chemically converted into 5,7-dideoxycynanchoside. The partially protected iridoid glucosides, 8,10:4′,6′-di-*O*-isopropylidene-5,7-dideoxycynanchoside (**6**) and 6,2′,3′,6′-tetra-*O*-benzoylantirrhinoside (**10**), as well as the fully protected 5,6-*O*-isopropylidene-2′,3′,4′,6′-tetra-*O*-acetylantirrhinoside (**8a**) were subjected to ozonolysis with reductive work-up using sodium tetrahydridoborate. Using a large excess of reductant, the reaction mixtures from **6** and **8a** were reduced completely to give the respective polysubstituted cyclopentanols, while reduction of the ozonolysis product from **10** could be stopped at the hemiacetal **11** by employing a smaller amount of reductant.

Previous reports on the utilization of iridoid glucosides as chiral building blocks have focused on a few groups of cyclopentanoid target molecules. So far, only three iridoids, namely aucubin, catalpol (**1**) and asperuloside have been thoroughly examined in this respect. Most previous studies have dealt with conversions into prostaglandins[1][2][3][4][5] or into analogs of the Corey lactone intermediate.[6][7] However, syntheses of methyl jasmonate from **1** have also been reported,[8][9] and finally, **1** has been employed as starting material in a multi-step preparation of the triquinane sesquiterpene (−)-hypnophilin.[10][11]



1 R = H, R' = H
3 R = *t*-Cinnamoyl, R' = H
4 R = *t*-Cinnamoyl, R' = Ac



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Since it is the aglucone part of the iridoid glucosides which are used as building blocks for semi-total syntheses of natural cyclopentanoids or other bioactive compounds, the removal of the sugar moiety becomes a crucial step. For this, three methods have commonly been employed: (i) enzymatic cleavage, (ii) acid-catalyzed hydrolysis,[12] and (iii) periodate oxidation of the sugar.[13] A general limitation with these methods is that it is usually not possible to protect the aglucone before removal of the sugar moiety. Therefore, we decided to investigate ozonolysis of partially and fully protected iridoid glucosides as a more versatile route to cyclopentanoid building blocks having only one-carbon side chains.

Ozonolysis of iridoid derivatives has apparently only been used twice, viz. in the structural elucidation of loganin,[14] and in an early study of the biosynthesis of cornin (verbenalin) where degradation was necessary to establish the distribution of labelling.[15] In both these cases, ozonolysis was performed on *C*-4-carboxylated iridoid glucosides and no experimental details were given.

Our initial experiments with iridoids unsubstituted at C-4, i.e. peracylated derivatives of **1** and of antirrhinoside (**2**), showed a fast reaction with ozone at −78°C. An attempt to employ a two-step reductive work-up procedure, in which the ozonolysis product was treated first with dimethyl sulfide[16] and then was reduced in situ with sodium tetrahydridoborate, gave a complex reaction mixture. Accordingly, we tried a direct reduction of the initial ozonolysis product with sodium tetrahydridoborate,[17] and this was found to give a single product derived from the aglucone.

In the course of the present work we sought easily grown plant sources with iridoids suitable as starting materials. A number of *Scutellaria* species (Lamiaceae) were investigated for their content of iridoids and the Israeli *S. subvelutina* Rech fil. was found to be the most promising, since it contained only one major iridoid glucoside in the water-soluble part of the crude ethanolic extract. This compound proved to be the 10-cinnamoyl ester of **1**, scutellarioside I[18] (**3**), and it was sufficiently apolar to allow a simple isolation procedure. Thus, a semi-continuous extraction from a concentrated aqueous solution of the water-soluble extract into ethyl acetate gave a 1.3% yield of crude **3** (fresh weight). Acetylation of this crude product afforded the pentaacetate **4** in a purity that allowed direct crystallization of the pentaacetate in 37% yield leaving a mother liquor with a purity of approximately 80%. Reduction of pure **4** with lithium aluminum hydride in tetrahydrofuran[19] yielded 5,7-dideoxycynanchoside[20] (**5**) in 94% yield after chromatography. Subsequent acetalization of **5** with 2,2-dimethoxypropane in acetone using pyridinium *p*-toluenesulfonate (PPTS) as a

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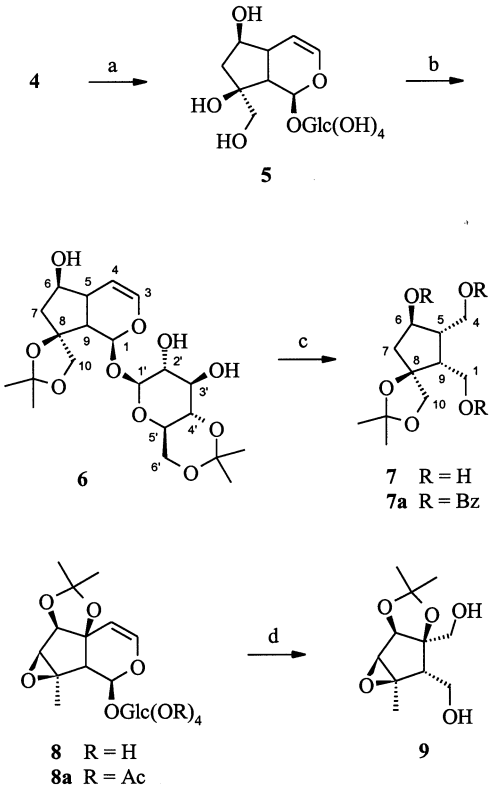
mild catalyst[21] gave diacetonide **6** in 81% yield. Ozonolysis of **6** at −78°C in a methanol/ethanol mixture for 15 min gave full conversion to a less polar product as seen by TLC. Reduction of this product with sodium tetrahydridoborate appeared to proceed via two increasingly more polar unidentified intermediates (as judged by TLC) to finally yield the polar triol **7** (iridoid numbering is maintained throughout for all the derived compounds in Schemes 1−2). Complete conversion to triol **7** as well as full deacetylation of the sugar-derived component required an extended reaction time of 2 days; the latter greatly facilitating the isolation of the aglucone derivative. Although the overall reaction thus involves several steps, the reaction proceeded remarkably cleanly, and the product **7** was isolated in 82% yield.

Scheme 1. Syntheses of cyclopentanoid compounds **7** and **9**



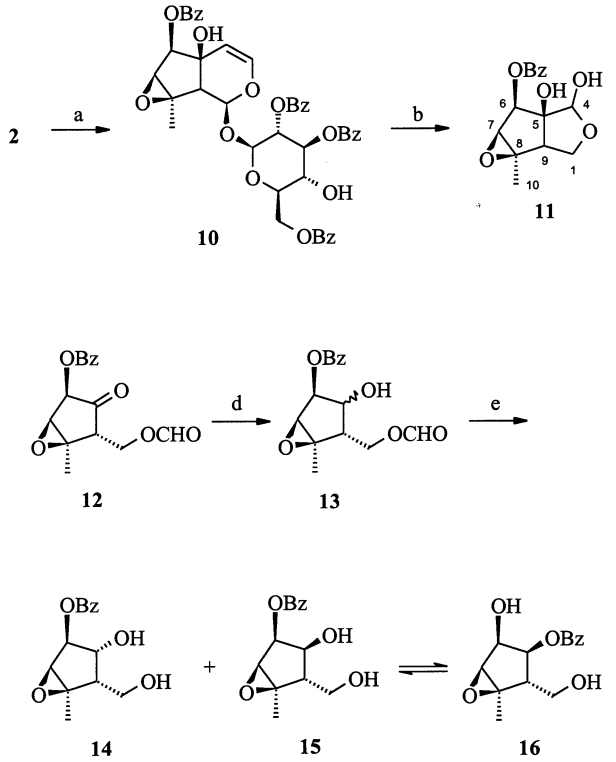
(a) $LiAlH_4$ in THF, reflux, 4 h, then room temp. 16 h. − (b) 2,2-Dimethoxypropane, PPTS, acetone, room temp., 2.5 h. − (c) O_3 in EtOH/MeOH, −78°C, 15 min, excess $NaBH_4$, 2 d. − (d) O_3 in CH_2Cl_2/MeOH, −78°C, 15 min, excess $NaBH_4$, 3 h.

As suggested by Stermitz[22], antirrhinoside (**2**) might also be exploited as a useful cyclopentanoid chiral synthon. In order to facilitate the isolation of its ozonolysis product, the 5,6-diol moiety was protected as an acetonide followed by acetylation to give the fully protected **8a**[23]. Again, the ozonolysis of compound **8a** proceeded rapidly at −78°C with dichloromethane/methanol as solvent and reduction gave the diol **9** (via a less polar intermediate) in 76% yield. In this case, complete deacetylation of the sugar moiety was ensured by a subsequent treatment with sodium methoxide in methanol. Compounds **7** and **9** were both benzoylated to confirm their structures as a triol and a diol, respectively (see Table 1 and Table 2.).

In the next experiment, partial benzoylation of antirrhinoside (**2**) gave the readily crystallized tetrabenzoate **10** as the main product (55%, no optimization was attempted). In this case we investigated whether the reduction of the initial ozonolysis product could be performed in a way that allowed the isolation of an intermediate aglucone derivative. Hence, it was found that lowering the amount of sodium tetrahydridoborate to three mol-equivalents resulted in the selective formation of a crystalline compound still retaining the 6-*O*-benzoyl group and having a (hemi)acetalic carbon atom (signal at δ = 98.8; see Table 3). The structure of this product (obtained in ca. 70% yield) was determined to be **11**, in accordance with the ^{1}H-NMR spectrum which showed the presence of an ether- (or acetal-)linked methylene group due to signals at δ = 3.74 and 4.33, both with strong couplings to the C-9 proton signal at δ = 2.84. Furthermore, coupled signals at δ = 3.69 and 5.29 were assumed to constitute the 6-H/7-H pair, leaving only an isolated hemiacetalic proton signal at δ = 5.52 in agreement with the proposed structure. Additional proof was obtained by periodate oxidation at elevated temperature (ca. 55°C) for 1 hour to give the ketone **12** with a formyloxy substituent at C-1. At room temperature no reaction occurred even after a prolonged reaction time (16 h) indicating a *trans* relationship of the 4- and 5-OH groups in the major anomer of hemiacetal **11**. To avoid any undesired epimerizations of the chiral ketone **12**, it was used immediately in the next step without purification. First, reduction of **12** was attempted with one mol of sodium tetrahydridoborate in methanol at room temperature, but this gave rise to a complex reaction mixture. Thus, more carefully controlled reaction conditions were necessary. Reduction with sodium cyanotrihydridoborate and two mol-equivalents of boric acid under cooling to 0°C proved adequate for obtaining a reasonable selectivity for the epimer mixture **13** (α/β ratio 2:1), which was isolated in 69% overall yield from hemiacetal **11**. However, the epimers **13** proved inseparable both by VLC (vacuum liquid chromatography) and MPLC, so the labile formyl group was removed by a brief treatment (15 min) with one mol-equivalent of sodium tetrahydridoborate in methanol. Surprisingly, the resulting mixture contained three separable (MPLC) monobenzoylated products, namely the main product **14** (61%) and the two minor components **15** and **16** (13% and 9%, respectively), the two latter apparently being in an equilibrium by benzoyl migration. This established that the 5-OH and 6-OH groups in this pair were *cis*-configurated.

In summary, we have shown that ozonolysis is an efficient, simple and cheap method for removing the sugar moiety of protected iridoid glucosides with concomitant loss of the C-3 carbon atom. Furthermore, when applying the present ozonolysis method on 5-hydroxylated iridoids (e.g. **2**), it allows a convenient two-step removal of an entire two-carbon chain (i.e. C-3 and C-4). Moreover, a wide range of protecting groups including acid-sensitive acetals and base-sensitive esters (e.g. benzoates) may survive the reaction conditions leading to partially protected cyclopentanoid synthons. This facilitates the possible subsequent

Scheme 2. Synthesis of the cyclopentanoid compound **14**



(a) BzCl, CH_2Cl_2/pyridine. − (b) O_3 in CH_2Cl_2/MeOH, 78°C, 15 min, 3 mol-equiv. $NaBH_4$, EtOH, 2 h. − (c) $NaIO_4$, acetone/water, 55°C, 1 h. − (d) $NaCNBH_3$, $H_3B_3O_3$, MeOH, 0°C to room temp., 1.5 h. − (e) $NaBH_4$, MeOH, room temp., 15 min.

additional selective protection of the remaining hydroxy groups, before conversion into biologically interesting compounds. We are currently investigating the conversion of these compounds into carbocyclic nucleoside analogs, novel bicyclic pyrrolidines and aminocyclopentitols.

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Experimental Section

General: Antirrhinoside (**2**) was isolated[24] from *Antirrhinum majus*. THF was distilled from sodium and stored over 4-Å molecular sieves; acetone was distilled and stirred with $CaCl_2$ for 16 h, filtered and stored over 3-Å molecular sieves. − Elemental analyses: Microanalytical Deptartment at the H. C. Ørsted Institute (University of Copenhagen). − Optical rotations: Perkin Elmer 241 polarimeter. − Melting points are uncorrected. − TLC: Merck Silica Gel 60 F_{254} aluminum sheets with detection by UV and/or by charring with sulfuric acid. − MPLC was performed on a Merck Lobar Lichroprep RP-18 (40−63 μm) Fertigsäule (size C) 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 (5−40 μm); the column size is given as height × diameter (cm). − NMR: Bruker AM-500 or HX-250. Chemical shifts are given in ppm, using the solvent peaks as internal standards ([D_6]acetone: δ = 2.05, [D_4]methanol: δ = 3.31, D_2O: δ = 4.75, $CDCl_3$: δ = 7.27). *J* values are given in Hz. Assignments of ^{1}H-NMR spectra were based on 1D homonuclear decoupling experiments, while ^{13}C-NMR spectra were assigned using carbon-proton shift-correlation spectra. − Ozonolyses were performed with a Fischer OZ 500 ozone generator, using a flow of 50−70 l/h (with a setting of 33% or 66% of full ionization power).

Isolation of **3** *from Scutellaria subvelutina:* Frozen plant material (5.5 kg) was homogenized with EtOH (25 l). Concentration gave a crude extract, which was partitioned between H_2O (700 ml) and Et_2O (500 ml). The aq. layer was washed with Et_2O (200 ml), and then concentrated to a syrup (403 g). The plant material was extracted again with EtOH (8 l) for 2 d to give additional water-solubles (49 g). The combined extracts were dissolved in H_2O (350 ml), and continuous extraction with EtOAc (15 l) for 4 d yielded, upon concentration, residue A (25.2 g, from the first 2 l of extract) and slightly impure **3** (55.1 g). Residue A (containing a substantial amount of 6′-*p*-coumaroyl mussaenosidic acid[25] as an impurity) was dissolved in EtOAc (1.1 l), and was then extracted with aq. satd $NaHCO_3$ (100 ml). The aq. layer was extracted back with EtOAc (1.0 l) and then saturated with NaCl, and extracted again with EtOAc (1.0 l). The combined EtOAc layers were concentrated to yield crude, syrupy **3** (total 74.2 g) − virtually pure as seen by NMR and by HPLC.

Pentaacetate **4**: Crude **3** (51.5 g; > 95% purity) was dissolved in pyridine (260 ml), and Ac_2O (190 ml) was added under ice-cooling. The mixture was stirred at room temp. for 2.5 h. Excess Ac_2O was hydrolyzed with ice (280 g) until it was melted, then CH_2Cl_2 (800 ml) was added. After washing successively with 2 M H_2SO_4, H_2O and aq. satd $NaHCO_3$ (each 800 ml), the organic layer was dried (Na_2SO_4) and concentrated. The residue was concentrated with toluene (2 × 300 ml) yielding crude pentaacetate **4**[18] (69.1 g, 94%), which was dissolved in EtOH (1.5 l) and treated with act. carbon (13 g). The mixture was heated to boiling and then filtered hot. During standing overnight at room temp., crystals had precipitated. Then H_2O (60 ml) was added and under vigorous stirring crystallization was continued for 2 h. Filtration and drying gave crystals (27.5 g) of m.p. 148−150°C (ref.[18]: 151°C).

5,7-Dideoxycynanchoside (**5**): A solution of **4** (32.3 g, 46.0 mmol) in dry THF (120 ml) was added to a suspension of $LiAlH_4$ (10.0 g, 264 mmol, 8 equiv.) in dry THF (1.6 l). The mixture was heated to reflux for 4 h, and stirring was continued at room temp. overnight, and heating to reflux was resumed for 0.5 h. After cooling, excess $LiAlH_4$ was quenched with EtOAc (200 ml). Stirring for an additional 0.5 h was followed by addition of H_2O (300 ml). The reaction mixture was neutralized by passing through CO_2 until pH = 7−8 and filtered. The cake was repeatedly extracted with boiling H_2O (4 × 500 ml). The combined filtrates (organic and aq.) were concentrated to 150 ml, and washed with EtOAc (100 ml). The EtOAc layer was extracted back with H_2O (150 ml). The combined aq. layers were concentrated to yield a crude product (ca. 33 g), which was purified by MPLC (D column, 7 runs). Elution with H_2O/MeOH (25:1) afforded **5**[20] (15.8 g, 94%).

5,7-Dideoxy-8,10:4′,6′-di-O-isopropylidenecynanchoside (**6**): Compound **5** (2.71 g) was concentrated with dry acetone (50 ml). The residue was then suspended in dry acetone (70 ml), and PPTS (0.20 g) and 2,2-dimethoxypropane (14.5 ml) were added. The mixture was stirred at room temp. for 2.5 h, after which triethylamine (0.25 ml) was added. Upon concentration, the residue was chromatographed by MPLC (D column, 3 runs). Elution with H_2O/MeOH (1:1) yielded diacetonide **6** (2.70 g, 81%), hygroscopic foam, $[\alpha]_D^{23} = -158$ (*c* = 0.5, acetone). − ^{1}H NMR (500 MHz, [D_6]acetone): δ = 1.29, 1.32, 1.33 and 1.48 [4 s, each 3 H, 2 × $O_2C(CH_3)_2$], 1.89 (br. dd, *J* = 14.5, 3 Hz, 1 H, 7a-H), 2.09 (dd, *J* = 14.5, 5.5 Hz, 1 H, 7b-H), 2.69 (br s, 2 H, 5-H and 9-H), 3.29 (m, 2 H, 2′-H and 5′-H), 3.52 (m, 2 H, 3′-H and 4′-H), 3.59 (d, *J* = 9 Hz, 1 H,

10a-H), 3.73 (t, J = 10.5 Hz, 1 H, 6a′-H), 3.82 (dd, J = 10.5, 5.5 Hz, 1 H, 6b′-H), 3.94 (br. s, 1 H, 6-H), 4.16 (d, J = 9 Hz, 1 H, 10b-H), 4.73 (d, J = 8 Hz, 1 H, 1′-H), 4.74 (br. dt, J = 6.5, 2 × 2 Hz, 1 H, 4-H), 5.50 (br. d, J = 1 Hz, 1 H, 1-H), 6.18 (dd, J = 6.5, 1.5 Hz, 1 H, 3-H). − ^{13}C NMR: See Table 1. − $C_{21}H_{32}O_{10}\cdot 1/2\ H_2O$ (453.5): calcd. C 55.61, H 7.35; found C 55.58, H 7.09.

Ozonolysis of Diacetonide **6**. − *Cyclopentanoid Triol* **7**: Diacetonide **6** (2.36 g, 5.31 mmol) in EtOH/MeOH (3:1, 40 ml) was cooled to −78°C and treated with an ozone flow for 15 min, at which point a faint blue coloring of the solution was observed. The reaction mixture was purged with nitrogen for 0.5 h and $NaBH_4$ (0.32 g, 8.47 mmol) was added. Stirring at −78°C was continued for an additional 0.5 h, and during the next 0.5 h the mixture was allowed to reach room temp. More $NaBH_4$ (0.20 g, 5.29 mmol) was added, and this was repeated after 1 h. The mixture was then left at 5°C for 2 d. The reaction mixture was diluted with H_2O (30 ml), and HOAc was added until pH = 8. Silica gel (Merck 60H) was added to the solution, and the mixture taken to dryness. The silica-gel residue was concentrated with $CHCl_3$ (50 ml), suspended in $CHCl_3$ (60 ml) and loaded onto a VLC column (5 × 5 cm). Gradient elution with $CHCl_3$/MeOH (15:1 to 10:1) yielded cyclopentanoid triol **7** (1.01 g, 82%) as a syrup, $[\alpha]_D^{23}$ = +8.1 (c = 0.8, MeOH). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.29, 1.30 [2 s, 3 H, $O_2C(CH_3)_2$], 1.83 (dd, J = 13.5, 6.5 Hz, 1 H, 7a-H), 2.20 (dd, J = 13.5, 7.5 Hz, 1 H, 7b-H), 2.33 (m, 1 H, 5-H), 2.45 (m, 1 H, 9-H), 3.65 (d, J = 9 Hz, 1 H, 10a-H), 3.71 (m, 2 H, 1-H), 3.74 (m, 2 H, 4-H), 3.91 (br. d, J = 5 Hz, 1 H, 6-OH), 3.96 (quint, J = 6.5 Hz, 1 H, 6-H), 4.02 (d, J = 9 Hz, 1 H, 10b-H), 4.07 (br. t, J = 5 Hz, 1 H, 1-OH), 4.21 (br. t, J = 5 Hz, 1 H, 4-OH). − ^{13}C NMR: See Table 1. − $C_{11}H_{20}O_5\cdot 1/2\ H_2O$(241.3): calcd. C 54.76, H 8.77; found C 54.66, H 8.80.

Benzoylation of **7**: Triol **7** (117 mg, 0.504 mmol) was treated with BzCl (0.30 ml, 2.58 mmol) in CH_2Cl_2/pyridine (4:1, 3 ml) at 4°C for 16 h. Work-up and purification on a VLC column (3 × 2 cm) eluting with hexane and then hexane/acetone (20:1) gave tribenzoate **7a** (248 mg, 91%), a syrup, $[\alpha]_D^{23}$ = −37 (c = 0.8, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41, 1.45 [2 s, each 3 H, $O_2C(CH_3)_2$], 2.22 (ddd, J = 15, 4.5, 1 Hz, 1 H, 7a-H), 2.72 (dd, J = 15, 8.5 Hz, 1 H, 7b-H), 2.88 (dt, J = 8, 2 × 5 Hz, 1 H, 9-H), 3.32 (quint, J = 7.5 Hz, 1 H, 5-H), 3.88 (d, J = 9 Hz, 1 H, 10a-H), 4.18 (d, J = 9 Hz, 1 H, 10b-H), 4.48−4.62 (m, 4 H, 2 × 1-H and 2 × 4-H), 5.52 (m, 1 H, 6-H), 7.22−8.18 (m, 15 H, 3 × *Ph*CO). − ^{13}C NMR: See Table 1. − $C_{32}H_{32}O_8$ (544.6): calcd. C 70.58, H 5.92; found C 70.23, H 6.18.

Ozonolysis of **8a**. − *Cyclopentanoid Diol* **9**: Compound **8a**[23a][23b] (6.55 g, 11.5 mmol) was dissolved in CH_2Cl_2/MeOH (4:1, 100 ml). The solution was cooled to −78°C, treated with ozone for 15 min as above and purged with nitrogen, at which point EtOH (50 ml) and $NaBH_4$ (1.30 g, 34.4 mmol) were added. The mixture was stirred for an additional 1.5 h at −78°C followed by addition of the same amount of $NaBH_4$. Stirring of the mixture was continued for an additional 1.5 h at room temp. Neutralization with HOAc (5 ml) and subsequent concentration with MeOH (twice) gave a residue, which was partitioned between EtOAc (150 ml) and satd aq. $NaHCO_3$ (150 ml). The aq. layer was extracted with more EtOAc (2 × 150 ml). The combined EtOAc layers were dried (Na_2SO_4) and concentrated to a crude product (4.23 g) also containing partially protected glucose derivatives. Treatment of this residue with 0.1 M sodium methoxide in MeOH (100 ml) for 2 h at room temp. and subsequent work-up as above afforded an EtOAc-soluble crude sample (2.48 g). Purification on a VLC column (4.5 × 5 cm) eluting first with hexane and then hexane/acetone (10:1 to 5:1) yielded cyclopentanoid diol **9** (2.01 g, 76%) as a syrup, $[\alpha]_D^{23}$ = −38 (c = 0.6, MeOH). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.33, 1.51 [2 s, each 3 H, $O_2C(CH_3)_2$], 1.44 (s, 3 H, 10-H), 2.31 (dd, J = 4, 3 Hz, 1 H, 9-H), 3.24 (d, J = 1.5 Hz, 1 H, 7-H), 3.71 (dd, J = 11.5, 3.5 Hz, 1 H, 4a-H), 3.78 (ddd, J = 11.5, 5, 4 Hz, 1 H, 1a-H), 3.82 (dd, J = 11.5, 8 Hz, 1 H, 4b-H), 4.01 (ddd, J = 11.5, 4, 3 Hz, 1 H, 1b-H), 4.06 (dd, J = 5, 4 Hz, 1 H, 1-OH), 4.16 (dd, J = 8, 3.5 Hz, 1 H, 4-OH), 4.48 (br. d, J = 1.5 Hz, 1 H, 6-H). − ^{13}C NMR: See Table 2. − $C_{11}H_{18}O_5\cdot 1/2\ H_2O$ (239.3): calcd. C 55.22, H 8.00; found C 55.34, H 8.08.

Benzoylation of **9**: Diol **9** (78 mg, 0.34 mmol) was treated with BzCl (0.15 ml, 1.29 mmol) as above for **7**. Purification on a VLC column (4 × 2 cm) eluting with hexane and then hexane/acetone (25:1 to 15:1) gave dibenzoate **9a** (145 mg, 98%), syrup, $[\alpha]_D^{23}$ = −135 (c = 0.2, $CHCl_3$). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.39, 1.59 [2 s, each 3 H, $O_2C(CH_3)_2$], 1.48 (s, 3 H, 10-H), 2.96 (t, J = 4 Hz, 1 H, 9-H), 3.54 (d, J = 2 Hz, 1 H, 7-H), 4.42 (d, J = 12 Hz, 1 H, 4a-H), 4.70 (dd, J = 12, 4 Hz, 1 H, 1a-H), 4.74 (dd, J = 12, 4 Hz, 1 H, 1b-H), 4.83 (d, J = 12 Hz, 1 H, 4b-H), 4.87 (d, J = 2 Hz, 1 H, 6-H), 7.49−8.07 (10 H, 2 × Bz-H). − ^{13}C NMR: See Table 2. − $C_{25}H_{26}O_7$ (239.3): calcd. C 68.48, H 5.98; found C 68.79, H 6.23.

Table 1. Selected ^{13}C-NMR data (125 MHz) of 5,7-dideoxycynanchoside and derived compounds

Atom	**5**[a]	**6**[b]	**7**[b]	**7a**[c]
C-1	93.2	93.0	59.2	61.5
C-3	140.1	140.4		
C-4	105.2	104.7	61.4	63.2
C-5	40.7	40.6	51.5	44.4
C-6	76.4	76.3	72.9	75.7
C-7	44.1	46.1	48.0	45.1
C-8	82.1	88.3	88.6	87.8
C-9	50.3	49.0	50.8	47.7
C-10	67.0	71.1	70.5	69.4
$(CH_3)_2C<$		26.5	27.0[f]	26.8
		27.4		26.6
$(CH_3)_2C<$		108.8	108.3	109.3
C-1′	98.9	100.1[d]		
C-2′	73.5	75.6		
C-3′	76.5	74.7[e]		
C-4′	70.4	74.4[e]		
C-5′	77.0	68.3		
C-6′	61.5	62.7		
$(CH_3)_2C<$		19.4		
		29.5		
$(CH_3)_2C<$		100.1[d]		

[a] In D_2O. − [b] In [D$_6$]acetone. − [c] Tribenzoate of **7** in $CDCl_3$. − [d][f] Two distinct, but close signals. − [e] Signals interchangeable.

Table 2. Selected ^{13}C-NMR data (125 MHz, [D$_6$]acetone) of 5,6-*O*-isopropylideneantirrhinoside and derivatives

Atom	**8**	**9**	**9a**
C-1	95.2	59.5	63.3
C-3	142.9		
C-4	109.2	64.7[a]	66.7
C-5	87.8	94.8	92.6
C-6	86.3	83.9	84.0
C-7	63.7	64.7[a]	64.5
C-8	67.6	67.8	67.4
C-9	53.4	53.3	50.3
C-10	18.1	16.9	16.9
$(CH_3)_2C<$	28.1	28.6	28.6
	29.6	30.6	30.2
$(CH_3)_2C<$	114.0	113.4	114.6
C=O			166.5

[a] Two close, but distinct signals.

6,2′,3′,6′-Tetra-O-benzoylantirrhinoside **10**: Antirrhinoside (0.78 g, 2.15 mmol) was dissolved in dry pyridine/CH_2Cl_2 (3:2, 5 ml), and BzCl (1.12 ml, 9.66 mmol) was added under cooling to 0°C. Then additional dry CH_2Cl_2 (10 ml) was added and the mixture was kept at 4°C overnight when excess BzCl was hydrolyzed by addition of water (1 ml) and standing for 0.5 h. Work-up gave a crude product (1.70 g). Chromatography on a VLC column (5 × 5 cm) eluting first with hexane and then hexane/EtOAc (4:1 to 1:1) gave crude pentabenzoate (4:1, 0.20 g, 10%), crystalline tetrabenzoate **10** (2.5:1, 0.91 g, 55%) followed by two tribenzoates: 6,3′,6′-tri-*O*-benzoylantirrhinoside (1.5:1, 0.15 g, 10%) and 6,2′,6′-tri-*O*-benzoylantirrhinoside (1:1, 0.12 g, 8%); the latter two were characterized only by ^{1}H NMR.

Tetrabenzoate **10**: M.p. 221−223°C, $[\alpha]_D^{23}$ = −80 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 3 H, 10-H), 2.53 (d, *J* = 7.5 Hz, 1 H, 9-H), 3.57 (br. s, 1 H, 7-H), 3.63 (d, *J* = 4.5 Hz, 1 H, 4′-OH), 3.88 (ddd, *J* = 10, 4, 2.5 Hz, 1 H, 5′-H), 3.97 (dt, *J* = 2 × 9.5, 4.5 Hz, 1 H, 4′′-H), 4.73 (dd, *J* = 12, 2.5 Hz, 1 H, 6a′-H), 4.82 (d, *J* = 6 Hz, 1 H, 4-H), 4.83 (dd, *J* = 12, 4 Hz, 1 H, 6b′-H), 5.14 (d, *J* = 1.5 Hz, 1 H, 6-H), 5.22 (d, *J* = 8 Hz, 1 H, 1′-H), 5.25 (d, *J* = 7.5 H, 1 H, 1-H), 5.46 (dd, *J* = 10, 8 Hz, 1 H, 2′-H), 5.57 (t, *J* = 9.5 Hz, 1 H, 3′-H), 6.10 (d, *J* = 6 Hz, 1 H, 3-H), 7.35−7.63 (m, 12 H, 4 × 3′′-H, 4 × 4′′-H and 4 × 5′′-H), 7.98 (br. d, *J* = 8 Hz, 4 H, 2 × 2′′-H and 2 × 6′′-H), 8.09, 8.13 (2 br. d, *J* = 8 Hz, each 2 H, 2 × 2′′-H and 2 × 6′′-H). − ^{13}C NMR: See Table 3. − $C_{43}H_{38}O_{14}$ (778.8): calcd. C 66.32, H 4.92; found C 66.03, H 4.75.

6,3′,6′-Tri-O-benzoylantirrhinoside: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, 10-H), 2.51 (d, *J* = 9 Hz, 1 H, 9-H), 3.55 (br. s, 1 H, 7-H), 3.73 (dd, *J* = 9.5, 8 Hz, 1 H, 2′-H), 3.76 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1 H, 5′-H), 3.80 (t, *J* = 9.5 Hz, 1 H, 4′-H), 4.68 (dd, *J* = 12, 2.5 Hz, 1 H, 6a′-H), 4.72 (dd, *J* = 12, 4.5 Hz, 1 H, 6b′-H), 4.93 (d, *J* = 8 Hz, 1 H, 1′-H), 4.98 (d, *J* = 6 Hz, 1 H, 4-H), 5.12 (d, *J* = 9 Hz, 1 H, 1-H), 5.17 (d, *J* = 1 Hz, 1 H, 6-H), 5.28 (t, *J* = 9.5 Hz, 1 H, 3′-H), 6.30 (d, *J* = 6 Hz, 1 H, 3-H), 7.40−7.46 (m, 6 H, 3 × 3′′-H and 3 × 5′′-H), 7.53−7.58 (m, 3 H, 3 × 4′′-H), 8.03, 8.07, and 8.10 (3 br. d, *J* = 8 Hz, each 2 H, 3 × 2′′-H and 3 × 6′′-H).

6,2′,6′-Tri-O-benzoylantirrhinoside: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, 10-H), 2.48 (br. d, *J* = 7.5 Hz, 1 H, 9-H), 3.51 (br. s, 1 H, 7-H), 3.68 (m, 2 H, 4′-H and 5′-H), 3.86 (m, 1 H, 3′-H), 4.64 (br. d, *J* = 12 Hz, 1 H, 6a′-H), 4.75 (dd, *J* = 12, 2.5 Hz, 1 H, 6b′-H), 4.81 (d, *J* = 6 Hz, 1 H, 4-H), 5.04 (d, *J* = 7.5 Hz, 1 H, 1′-H), 5.07 (t, *J* = 8 Hz, 1 H, 2′-H), 5.10 (d, *J* = 1 Hz, 1 H, 6-H), 5.18 (d, *J* = 7.5 Hz, 1 H, 1-H), 6.12 (d, *J* = 6 Hz, 1 H, 3-H), 7.42, 7.43, and 7.46 (3 br. t, *J* = 8 Hz, each 2 H, 3 × 3′′-H and 3 × 5′′-H), 7.53−7.59 (m, 3 H, , 3 × 4′′-H), 8.04, 8.05, and 8.10 (3 br. d, *J* = 8 Hz, each 2 H, 3 × 2′′-H and 3 × 6′′-H).

Ozonolysis of Tetrabenzoate **10**. − *Hemiacetal* **11**: Tetrabenzoate **10** (6.20 g, 7.97 mmol) in CH_2Cl_2/MeOH (4:1, 75 ml) was treated with ozone as above. After purging with nitrogen, EtOH (40 ml) and $NaBH_4$ (0.90 g, 23.8 mmol) were added. The mixture was kept at −78°C with vigorous stirring for 1 h. Cooling was stopped, and stirring of the mixture at room temp. was continued for an additional 1 h. Neutralization of the reaction mixture with HOAc (4 ml) was followed by concentration with MeOH (twice). The obtained residue was partitioned between EtOAc (150 ml) and satd aq. $NaHCO_3$/brine (1:1, 150 ml). The aq. layer was extracted further with EtOAc (2 × 150 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give a crude product (5.98 g), which was chromatographed by MPLC (column size D). Elution with H_2O/MeOH (3:1 to 1:1) afforded crystalline hemiacetal **11** (1:1, 1.53 g, 67%) followed by more, impure (ca. 50%) **11** (0.24 g, 5%). Recrystallization of the former (hexane/acetone 1:1, 50 ml) gave an analytical sample, m.p. 162−163°C, $[\alpha]_D^{23}$ = −5.8 (*c* = 0.2, MeOH). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s , 3 H, 10-H), 2.84 (dd, *J* = 9, 5 Hz, 1 H, 9-H), 3.52 (br. s, 1 H, 4-OH), 3.69 (br. s, 1 H, 7-H), 3.74 (dd, *J* = 9.5, 5 Hz, 1 H, 1a-H), 4.33 (t, *J* = 9.5 Hz, 1 H, 1b-H), 5.29 (d, *J* = 1 Hz, 1 H, 6-H), 5.52 (br. s, 1 H, 4-H), 7.44 (t, *J* = 8 Hz, 2 H, 3′-H/5′-H), 7.57 (br. t, *J* = 8 Hz, 1 H, 4′-H), 8.09 (br. d, *J* = 8 Hz, 2 H, 2′-H/6′-H). − ^{13}C NMR: See Table 3. − $C_{15}H_{16}O_6$ (292.3): calcd. C 61.64, H 5.52; found C 61.43, H 5.39.

Periodate Oxidation of Hemiacetal **11**. − *Monobenzoylated Cyclopentanoid Synthon* **14**: Hemiacetal **11** (252 mg, 0.875 mmol) in warm (55°C) acetone (20 ml) was treated with $NaIO_4$ (206 mg, 0.962 mmol) in H_2O (10 ml). The mixture was stirred at 55°C for 1 h. Ethylene glycol (10 µl) was added, and the acetone was evaporated. The remaining aq. solution was diluted with brine (30 ml) and extracted with EtOAc (3 × 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to yield the crude ketone **12** as a syrup (240 mg, 95% yield, purity > 95%). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, 10-H), 2.79 (m, 1 H, 9-H), 3.90 (dd, *J* = 1.5, 0.5 Hz, 1 H, 7-H), 4.42 (ddd, *J* = 12, 3.5, 1 Hz, 1 H, 1a-H), 4.49 (ddd, *J* = 12, 3.5, 1 Hz, 1 H, 1b-H), 5.81 (dd, *J* = 1.5, 1 Hz, 1 H, 6-H), 7.45 (br. t, *J* = 8 Hz, 2 H, 3′-H/5′-H), 7.59 (br. t, *J* = 8 Hz, 1 H, 4′-H), 8.08 (br. s, 1 H, OC*H*O), 8.10 (br. d, *J* = 8 Hz, 2 H, 2′-H/6′-H).

Without purification, the above ketone (240 mg, 0.84 mmol) and boric acid (104 mg, 1.68 mmol) were dissolved in MeOH (15 ml). At 0°C, sodium cyanotrihydridoborate (53 mg, 0.84 mmol) in MeOH (2 ml) was added. The mixture was stirred at 0°C for 45 min, followed by 45 min while the temp. was allowed to rise to 20°C. Acetone (1 ml) was added followed, after 10 min, by HOAc (0.2 ml). Upon concentration, the resulting residue was partitioned between EtOAc (50 ml) and 5% aq. HOAc/brine (1:1, 40 ml). The aq. layer was extracted with EtOAc (2 × 40 ml). The organic layers were separately washed with satd aq. $NaHCO_3$/brine (1:1, 40 ml). The combined EtOAc phases were dried (Na_2SO_4) and concentrated to yield a crude product (250 mg), which was purified on a VLC column (4.5 × 3 cm). Elution first with hexane and then hexane/acetone (10:1 to 5:1) yielded first a 2:1 mixture of 5α- and 5β-alcohols **13** (174 mg, 0.60 mmol, 69% overall) and next a fraction containing deformylated diols **14**/**15** (29 mg, 13%).

The above fraction of **13** was solely characterized by ^{13}C NMR (Table 3.). It was dissolved in MeOH (7 ml), and $NaBH_4$ (23 mg, 0.60 mmol) was added. After stirring at room temp. for 15 min, HOAc (0.2 ml) was added. The reaction mixture was concentrated twice with MeOH, followed by chromatography on an MPLC column (size C). Gradient elution with H_2O (2:1 and 1.75:1) afforded successively the 5β-benzoate **16** (15 mg, 9%), the 1,5β-diol **15** (21 mg, 13%), and then the 1,5α-diol **14** (98 mg, 61%); the former two proved to undergo partial interconversion due to benzoyl migration and were therefore characterized only by NMR.

1,5α-Diol **14**: $[\alpha]_D^{23}$ = −155 (*c* = 1.1, acetone). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.49 (s, 3 H, 10-H), 2.36 (ddd, *J* = 7, 2 × 3.5 Hz, 1 H, 9-H), 3.53 (d, *J* = 1.5 Hz, 1 H, 7-H), 3.62 (t, *J* = 4.5 Hz, 1 H, 1-OH), 3.84 (dt, *J* = 11, 2 × 3.5 Hz, 1 H, 1a-H), 4.01 (ddd, *J* = 11, 4.5, 3.5 Hz, 1 H, 1b-H), 4.24−4.28 (m, 2 H, 5-H and 5-OH), 5.39 (dd, *J* = 6, 1.5 Hz, 1 H, 6-H), 7.53 (br. t, *J* = 8.5 Hz, 2 H, 3′-H/5′-H), 7.65 (br. t, *J* = 8.5 Hz, 1 H, 4′-H), 8.07 (br. d, *J* = 8.5 Hz, 2 H, 2′-H/6′-H). − ^{13}C NMR: See Table 3. − $C_{14}H_{16}O_5 \cdot 1/4\ H_2O$ (268.8): calcd. C 62.56, H 6.19; found C 62.72, H 6.37.

1,5β-Diol **15**: δ = 1.50 (s, 3 H, 10-H), 2.25 (t, *J* = 4 Hz, 1 H, 9-H), 2.58 (d, *J* = 12, 1 H, 5-OH), 3.69 (d, *J* = 1 Hz, 1 H, 7-H), 3.75−3.90 (m, 2 H, 1-H), 4.04 (t, *J* = 4 Hz, 1 H, 1-OH), 4.17 (dd, *J* = 12, 6.5 Hz, 1 H, 5-H), 5.36 (dd, *J* = 6.5, 1 Hz, 1 H, 6-H), 7.53 (br. t, *J* = 8.5 Hz, 2 H, 3′-H/5′-H), 7.65 (br. t, *J* = 8.5 Hz, 1 H, 4′-H), 8.07 (br. d, *J* = 8.5 Hz, 2 H, 2′-H/6′-H).

5β-Benzoate **16**: δ = 1.45 (s, 3 H, 10-H), 2.33 (t, *J* = 3.5 Hz, 1 H, 9-H), 3.38 (br. s, 1 H, 7-H), 3.76 (d, *J* = 9.5 Hz, 1 H, 6-OH), 3.75−3.90 (m, 2 H, 1-H), 4.00 (t, *J* = 3.5 Hz, 1 H, 1-OH), 4.55 (br. t, *J* = 8.5 Hz, 1 H, 6-H), 5.31 (br. d, *J* = 7 Hz, 1 H, 5-H), 7.53 (br. t, *J* = 8.5 Hz, 2 H, 3′-H/5′-H), 7.65 (br. t, *J* = 8.5 Hz, 1 H, 4′-H), 8.07 (br. d, *J* = 8.5 Hz, 2 H, 2′-H/6′-H).

Table 3. Selected ^{13}C-NMR data (125 MHz) of antirrhinoside (**2**) and derivatives

Atom	**2**[a]	**10**[b]	**11**[b]	**13**[c][d]	**14**[c]	**15**[c]	**16**[c]
C-1	95.0	94.4	66.1	59.7	58.6	61.3	61.5
C-3	143.0	141.5					
C-4	107.0	106.6	98.8				
C-5	74.4	73.4	85.4	72.9	73.9	72.8	76.0
C-6	76.7	78.5	77.7	83.3	83.9	77.5	73.9
C-7	66.1	62.8	64.2	61.4	61.9	64.7	66.7
C-8	65.1	63.2	63.3	62.5	63.2	63.8	63.8
C-9	52.0	52.0	53.2	44.2	47.7	55.2	53.0
C-10	17.0	17.0	16.0	15.9	16.6	15.8	15.9
C-1′	99.3	96.8					
C-2′	73.4	71.3					
C-3′	77.1	76.1					
C-4′	70.4	69.4					
C-5′	76.4	74.8					
C-6′	61.5	62.7					

[a] In D_2O. − [b] In $CDCl_3$. − [c] In [D_6]acetone. − [d] Main isomer; formyl signal at δ = 160.6.

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