

Stereoselective Hydrogenation and Ozonolysis of Iridoids. Conversion into Carbocyclic Nucleoside Analogues

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Stereoselective hydrogenation of the iridoids geniposide (**9**) and aucubin (**19**) was achieved by using the 1-methyl-1-methoxyethyl ether as a protecting group for the allylic alcohol, as it enhanced the stereoselectivity and prevented undesired hydrogenolysis. Ozonolysis of the hydrogenation product from **9**, adoxoside (**11**), with reductive workup, afforded either a chiral lactone (**25**) or a chiral polyol (**26**), depending on the reduction conditions. Polyol **26** was subjected to protecting-group manipulation and subsequent oxidation and reductions to yield cyclopentane building blocks (**29–34**), which, by Mitsunobu couplings with purines, afforded carbocyclic nucleoside analogues (**7**, **8**, and **35**).

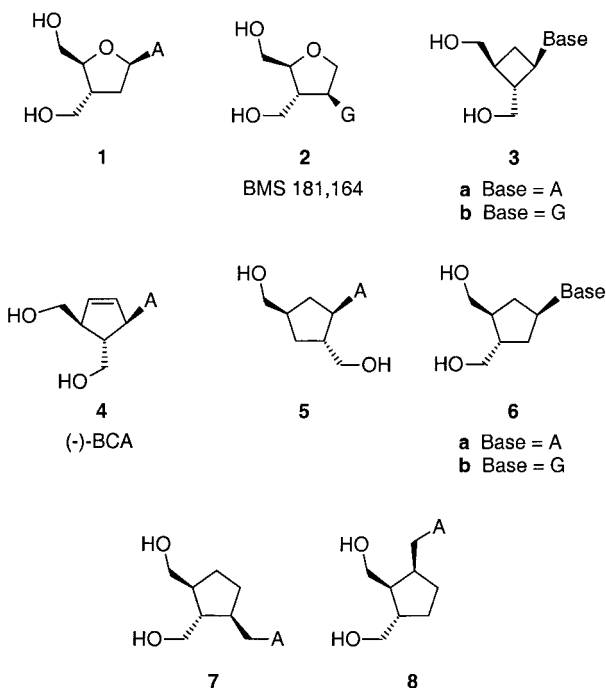
The iridoids aucubin (**19**), catalpol, and asperuloside have previously been used synthetically as precursors of cyclopentanoids such as prostaglandins,^{1–3} methyl jasmonate,⁴ and triquinanes.⁵ Also, the aglucone of geniposide (**9**), genipin, has been the starting material in semisyntheses of diterpenes from marine algae.^{6–8} In addition, iridoid aglucones have been converted into pyridine monoterpene alkaloids⁹ and monoterpene piperidines.¹⁰ Although β -glucosidase is often used for sugar removal, simple acid-catalyzed hydrolysis of the glucoside bond or oxidative degradation¹¹ of the sugar moiety may also be employed to obtain iridoid aglucones. Recently it was demonstrated that ozonolytic cleavage (with reductive workup) of the enol ether bond in protected iridoids lacking C-11 gives concomitant loss of the sugar moiety to produce partially

protected cyclopentane derivatives.¹² In the present work, we extend this method to the 4-carboxymethyl-substituted iridoid, adoxoside (**11**; derived from **9**), to obtain polyhydroxylated cyclopentane building blocks suitable for the conversion into carbocyclic nucleosides. So far, only two such interconversions have been reported.^{13,14} A number of hydroxymethyl-substituted nucleosides (e.g., compounds **1–4**, listed by Mansour and Storer¹⁵), exhibit a variety of antiviral activities, while compounds **5**¹⁶ and **6**¹⁷ are inactive against HIV. Hence, the objective was to prepare the novel carbocyclic homo-*N*-nucleoside analogues **7** and **8**, which seem structurally related to the active compounds **2–4**.

Results and Discussion

Selective Hydrogenations. To avoid a competing ozonolytic cleavage of both double bonds in geniposide (**9**), the first step was to hydrogenate the 7,8-double bond selectively to obtain adoxoside (**11**). However, this did not prove to be straightforward. Hydrogenation of olefin **9** with Pt as a catalyst gave 8-epiadoxoside (**10**) and adoxoside (**11**) in a 5:1 ratio.¹⁸ Conversely, our initial hydrogenation of olefin **9** in the presence of Pd/C in ethanolic triethylamine afforded almost equal amounts of the epimers **10** and **11** in addition to hydrogenolysis products, as earlier reported.¹⁹ In recent synthetic work on iridoids,^{10,12} acetonides were found to be convenient protecting groups for polyfunctional iridoids. In the present study, iridoid glucosides having allylic alcohol groups proved prone to forming stable 1-methyl-1-methoxyethyl ethers (also referred to as methoxyisopropylidene: MIP) at these positions. Thus, the MIP group was tried as an inexpensive, easily introduced, and readily removed protecting group for glucoside **9** during its hydrogenation. Treatment of **9** with excess 2,2-dimethoxypropane (DMP) in dry acetone, with pyridinium *p*-toluenesulfonate (PPTS) as catalyst, afforded five isolable products, namely acetonides **12–16**, of which **13**, **14**, and **16** carried a MIP group on the primary allylic alcohol (See Scheme 1).

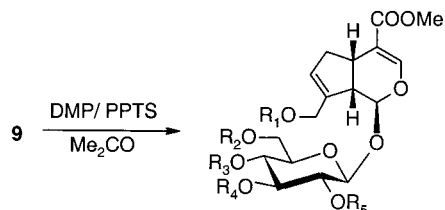
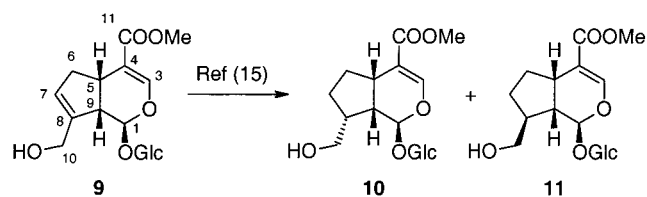
To improve the yield of acetonides **14** and **16** (63% and 3%, respectively), more forcing conditions involving subsequent heating of the (above) reaction mixture with 2-methoxypropene were attempted. In this case, acetonides **12** and **13** were separated and subjected to repeated acetonation under mild conditions. This procedure resulted



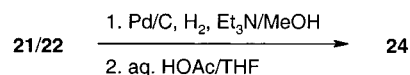
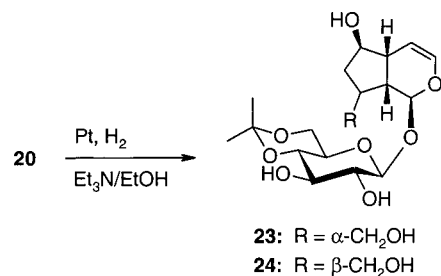
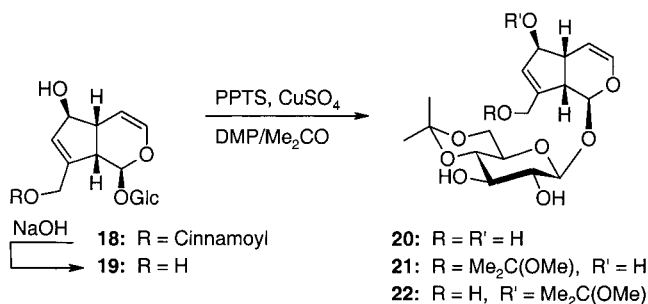
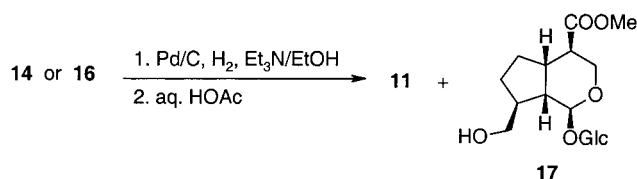
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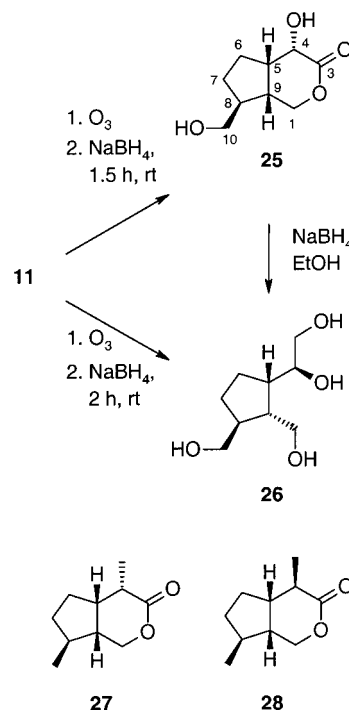
[‡] Colorado State University.

Scheme 1. Hydrogenation of Allylic MIP Ethers

- 12:** R₁ = H, R₂, R₃ = Me₂C, R₄ = R₅ = H
13: R₁ = R₂ = Me₂C(OMe), R₃ = R₄ = R₅ = H
14: R₁ = Me₂C(OMe), R₂, R₃ = Me₂C, R₄ = R₅ = H
15: R₁ = H, R₂, R₃ = R₄, R₅ = Me₂C
16: R₁ = Me₂C(OMe), R₂, R₃ = R₄, R₅ = Me₂C



in 68% and 27% overall yields of 10-MIP acetonides **14** and **16**, respectively. The sequence of protection appeared to involve an initial introduction of a MIP group on the primary 6'-position²⁰ in the glucose moiety, followed by rapid cyclization to the 4',6'-acetonide (i.e., to give **12**), and then protection of the allylic 10-position to give **14**. The five-membered *trans*-2',3'-acetonides (e.g., **16**) formed only when forcing conditions were applied. Hydrogenation of acetonides **14** and **16** in the presence of Pd/C and triethyl-

Scheme 2. Ozonolysis of Adoxoside (**11**)

amine in ethanol proceeded almost exclusively (>98%), with addition of hydrogen to the more hindered concave side, but hydrogenation of the 3,4-enol ether was also a significant side-reaction. Separation of the 7,8-dihydro and 3,4,7,8-tetrahydro compounds was difficult, but was also unnecessary because the mixture (after deprotection to **11** and **17**) could be used in the subsequent ozonolysis.

The utility of the MIP protecting group during hydrogenation using Pd/C was studied further on a mixture of aucubin acetonides **21/22**. Again, the approach of hydrogen took place at the more hindered concave face to give acetonide **24** in high yield (90%; the only isolable product) after the facile and selective removal of the MIP groups. Thus, the present protection scheme was shown to be superior to alternate analogous hydrogenations.^{21,22} To rule out that the above-observed selectivity was due to a steric effect exerted by the protected sugar moiety, both Pt- and Pd/C-catalyzed hydrogenations were performed on olefin **20**. As expected, the 8α-epimer **23** was predominant when Pt was used (α:β ratio 10:1), while Pd/C catalysis in this case only afforded an α:β ratio of 1:3 (i.e., between **23** and **24**). The ¹³C NMR signals for C-9 and C-10 were more lowfield in 8β-epimer **24** as compared to 8α-epimer **23**, in accordance with data for related iridoid epimers.²³

The induction of high stereoselectivity with MIP as protecting group has also been observed in a hydroxyalkylation²⁴ and in a carbanion addition to a ketone.²⁵ The MIP group has been used as a protecting group during hydroboration.²⁶ Its simultaneous use as a protecting group (to avoid hydrogenolysis) and as an aid to enhance stereoselectivity during hydrogenation is, to our knowledge, unprecedented.

Ozonolysis of an Unprotected Iridoid. Next, we examined the ozonolysis of unprotected adoxoside (**11**) and the subsequent in situ reduction of the ozonolysis product. This proceeded through several less polar intermediates toward a very polar end-product. At first, the sodium borohydride reduction was stopped when an intermediate of moderate polarity prevailed in the product mixture. This compound was an aglucone-derived C₉-lactone (**25**), the

structure of which (except for the orientation of the 4-OH group) was evident from its NMR spectra. Comparison with the ^1H NMR data of the two 4-epimers (\pm)-iridomyrmecin (**27**; $J_{1a,1b} = 11.8$ Hz, $J_{1a,9} = 2.6$ Hz, $J_{1b,9} \approx 0$)²⁷ and (\pm)-isoiridomyrmecin (**28**; $J_{1a,1b} = 11.0$ Hz, $J_{1a,9} = 6.3$ Hz, $J_{1b,9} = 11.0$ Hz)²⁸ indicated the 4-OH to be α -positioned in lactone **25** ($J_{1a,1b} = 12$ Hz, $J_{1a,9} = 4$ Hz, $J_{1b,9} \approx 0$). Final structural proof for **25** was obtained by an X-ray structure determination. Tetrol **26** was then obtained in good yield after a slightly longer reduction period for the ozonolysis mixture, and by the direct reduction of lactone **25** (See Scheme 2).

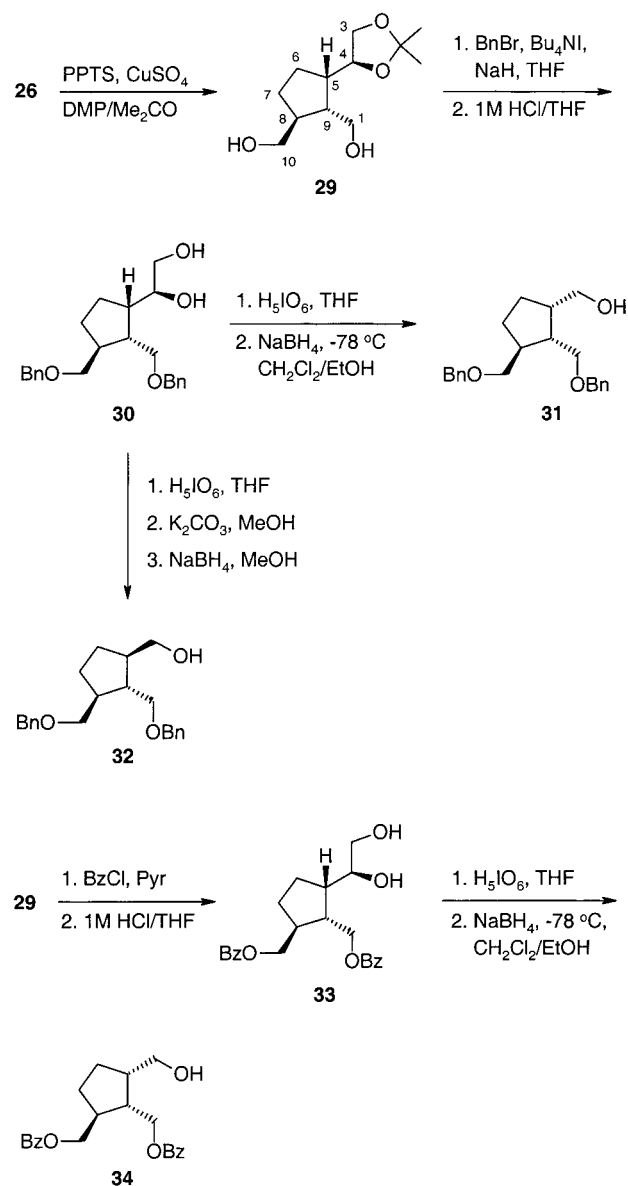
Conversion into Carbocyclic Nucleoside Analogues.

To distinguish between the three primary hydroxyl groups, the vicinal 3,4-diol system was protected as an acetonide (i.e., to give **29**; 79% yield). Subsequent benzylation²⁹ and acetonide deprotection afforded the crystalline **30**. Oxidative cleavage of the 3,4-diol system in **30** was accomplished with periodic acid to yield an aldehyde, which was reduced directly to the corresponding alcohol. With sodium borohydride in methanol at room temperature, extensive epimerization was observed. A change of solvent to dichloromethane-ethanol and a lowering of the reaction temperature resulted in an excellent yield (92.5%) of pure epimer **31**. Next, a deliberate epimerization of the intermediate aldehyde was attempted, and potassium carbonate in methanol or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane were found to work equally well. Subsequent sodium borohydride reduction (one-pot) of the above methanolic reaction mixture gave the epimeric benzyl-protected alcohol **32** in 94% yield. In a similar way, the unepimerized benzoate-protected alcohol **34** was obtained in an overall yield of 68% from acetonide **29** (See Scheme 3).

Then, a Mitsunobu coupling on acetonide **29** was performed to prepare a homo-*N*-nucleoside analogue, we hoped, with the nucleobase attached to the least-hindered carbon (i.e., C-10). However, the use of two equivalents of triphenylphosphine, diethyl azodicarboxylate (DEAD), and 6-chloropurine surprisingly gave a protected bisnucleoside as the predominant product, but in low yield (ca. 40%). Increasing the amounts of reagents to four equivalents improved the yield to ca. 70%. Successive ammonolysis and deprotection with aqueous acid afforded bisnucleoside analogue **35**. Mitsunobu coupling of 6-chloropurine to alcohol **34** yielded only the expected product, which, after ammonolysis, gave nucleoside analogue **8**. By contrast, both a Mitsunobu coupling of **31** with 6-chloropurine and an attempted preparation of the corresponding triflate resulted in formation of tetrahydrofuran **37** as the main product. Anchimeric assistance of an appropriately situated benzyloxy group has previously been observed in displacements of tosylates, mesylates, and triflates, and occasionally in Mitsunobu reactions.^{30–32} Mitsunobu coupling of adenine and alcohol **32** afforded benzylated analogue **38**, and subsequent debenylation with borontrichloride yielded nucleoside analogue **7** (See Scheme 4.)

These studies provide additional examples of the usefulness of iridoids as chiral synthons. We have shown that the MIP group serves as an excellent inducer of stereoselectivity in hydrogenations of certain allylic alcohols. Also, an unprotected iridoid (i.e., **11**) was ozonolyzed and subsequently reduced stereoselectively into either a chiral lactone (**25**) or a polyol building block (**26**). These types of lactones are synthetic precursors of iridoid lactones of the iridomyrmecin type (e.g., **27** and **28**),³³ thus establishing a formal synthesis of substituted analogues. The nucleoside

Scheme 3. Preparation of Building Blocks

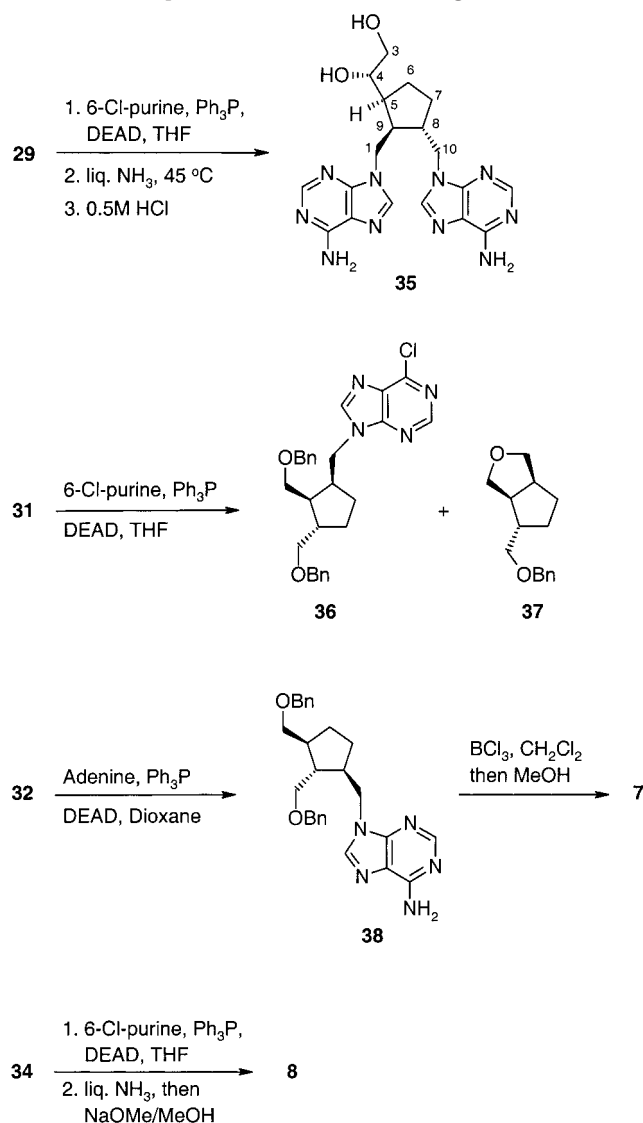


analogues prepared here have been tested in HIV and HSV-1 assays, but they did not exhibit significant antiviral or cytotoxic activities.

Experimental Section

General Experimental Procedures. PPTS was purchased from Aldrich Chemical Co.; DMP, BnBr, adenine, and 6-chloropurine were from Fluka Chemie AG; and Ph₃P was from Merck. Geniposide (**9**) was a gift from Glico Foods Corporation. Acetone was distilled and then stirred with CaCl₂, filtered, and stored over 3 Å molecular sieves. THF and dioxane were freshly distilled from Na. All concentrations were performed in vacuo. Elemental analyses were performed by Microanalytical Laboratory, Institute of Physical Chemistry, Vienna, by Desert Analytics, Tucson, Arizona or by the Microanalytical Department at the H. C. Ørsted Institute (University of Copenhagen). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. TLC was performed on Merck Si gel 60 F₂₅₄ aluminum sheets with detection by charring with H₂SO₄, or by UV light when applicable. MPLC was performed on Merck Lobar Lichroprep RP₁₈ columns. Vacuum-liquid chromatography (VLC) was performed on predried (120 °C; > 24 h) Merck Si gel 60H; the column size is given as height × diameter (cm).

Scheme 4. Preparation of Nucleoside Analogues



NMR spectra were recorded on Bruker AM-500 or AC-300P and Varian Inova 500 or Mercury 300 spectrometers. Chemical shifts are given in parts per million (ppm) using the solvent peaks as internal standards (CDCl_3 : $\delta_{\text{H}} = 7.27$, $\delta_{\text{C}} = 77.0$, methanol- d_4 : $\delta_{\text{H}} = 3.31$, $\delta_{\text{C}} = 49.0$, DMSO- d_6 : $\delta_{\text{H}} = 2.50$, $\delta_{\text{C}} = 39.5$). Coupling constants are given in Hertz. For all compounds ^1H NMR signals were assigned by homonuclear decoupling experiments or by COSY, while ^{13}C NMR signals were assigned from HETCOR spectra or HSQC spectra. In the NMR spectra a prime (') denotes sugar positions in the glucosides, while (') and (") denote the purine moieties in the nucleoside analogues. Carbocyclic nucleoside analogues were tested against HIV and HSV-1 virus at the Department of Virology, The Danish Serum Institute, Copenhagen.^{34,35}

Geniposide Acetonides 12–16. Geniposide (9, 10.0 g) and PPTS (1.0 g) were suspended in dry Me_2CO –DMP (1:1, 200 mL), and the mixture was stirred at room temperature for 12 h, when more DMP (50 mL) was added. After an additional 24 h, Et_3N (2 mL) was added and the mixture concentrated. The residue was purified on a VLC column (5.5 × 8.5 cm). Elution with hexanes– Me_2CO (10:1 to 1.5:1) yielded, successively, acetonides **16** (0.45 g, 3%), **15** (0.17 g, >95% purity, 1.4%), **14** (8.08 g, 63%), and a mixture of **12** and **13** (2.82 g, 26%). The last fraction was further purified by VLC eluting with hexanes– Me_2CO (3:1 to 1.8:1) to give **13** (0.35 g, >95% purity), **12** (1.72 g, >95% purity), and pure **12** (0.74 g). Similarly, analytical samples of **13** and **15** were obtained by repeated VLC.

4',6'-O-Isopropylidene-geniposide (12): white hygroscopic foam, $[\alpha]_{\text{D}}^{25} -13^\circ$ (c 1.1, MeOH); ^1H NMR (methanol- d_4 , 500 MHz) δ 7.51 (1H, d, $J_{3,5} = 1$ Hz, H-3), 5.80 (1H, br s, H-7), 5.01 (1H, d, $J_{1,9} = 8$ Hz, H-1), 4.28 (1H, br d, $J_{a,b} = 14$ Hz, H-10a), 4.17 (1H, br d, $J_{a,b} = 14$ Hz, H-10b), 3.71 (3H, s, 11-MeO), 3.18 (1H, q-like, $J = 8.5$ Hz, H-5), 2.83 (1H, br dd, $J_{a,b} = 16$ Hz, $J_{5,6a} = 8.5$ Hz, H-6a), 2.70 (1H, t, $J_{1,9} = J_{5,9} = 8$ Hz, H-9), 2.06 (1H, br dd, $J_{a,b} = 16$ Hz, $J_{5,6b} = 8$ Hz, H-6b); sugar signals essentially as for **14**; ^{13}C NMR (methanol- d_4 , 125 MHz) δ 169.4, 153.2, 144.8, 128.5, 112.6, 98.6, 61.4, 51.8, 46.8, 39.8, 36.7; sugar moiety 101.1, 100.8, 75.7, 74.8, 74.7, 68.8, 63.1, 29.4, 19.3; anal. C 55.90%, H 6.37%, calcd for $\text{C}_{20}\text{H}_{28}\text{O}_{10}$, C 56.06%, H 6.60%.

10,6'-Di-O-(1-methoxy-1-methylethyl)-geniposide (13): white foam, $[\alpha]_{\text{D}}^{25} +22^\circ$ (c 0.7, MeOH); ^1H NMR (methanol- d_4 , 500 MHz) δ 7.54 (1H, d, $J_{3,5} = 1$ Hz, H-3), 5.76 (1H, br s, H-7), 5.07 (1H, d, $J_{1,9} = 8$ Hz, H-1), 4.12 (1H, br d, $J_{a,b} = 13.5$ Hz, H-10a), 4.08 (1H, br d, $J_{a,b} = 13.5$ Hz, H-10b), 3.72 (3H, s, 11-MeO), 3.17 (1H, q-like, $J = 8$ Hz, H-5), 2.83 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6a} = 8.5$ Hz, H-6a), 2.67 (1H, t, $J_{1,9} = J_{5,9} = 8$ Hz, H-9), 2.00 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6b} = 9$ Hz, H-6b), 3.22, 1.35, 1.34 (each 3H, s, 10-[$\text{Me}_2\text{C}(\text{OMe})$]), 4.70 (1H, d, $J_{1',2'} = 8$ Hz, H-1'), 3.73 (1H, obsc., H-6a'), 3.49 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{5',6b'} = 6.5$ Hz, H-6b'), 3.37 (1H, t, $J_{2',3'} = J_{3',4'} = 9.5$ Hz, H-3'), 3.36 (1H, obsc., H-5'), 3.26 (1H, t, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4'), 3.25 (1H, br t, $J = 9$ Hz, H-2'), 1.31, 1.30 (each 3H, s, 4',6'- Me_2C); ^{13}C NMR (methanol- d_4 , 500 MHz) δ 169.5, 153.4, 142.7, 129.0, 112.4, 101.3, 98.5, 60.6, 51.7, 49.1, 46.8, 39.9, 37.0, 24.8; sugar moiety 101.4, 100.3, 78.1, 76.9, 74.9, 71.8, 61.8, 48.8, 24.7; anal. C 56.37%, H 7.54%, calcd for $\text{C}_{25}\text{H}_{40}\text{O}_{12}$, C 56.37%, H 7.58%.

4',6'-O-Isopropylidene-10-O-(1-methyl-1-methoxyethyl)-geniposide (14): white foam, $[\alpha]_{\text{D}}^{25} +2.6^\circ$ (c 1.2, MeOH); ^1H NMR (methanol- d_4 , 500 MHz) δ 7.51 (1H, d, $J_{3,5} = 1$ Hz, H-3), 5.82 (1H, br s, H-7), 5.03 (1H, d, $J_{1,9} = 8$ Hz, H-1), 4.17 (1H, br d, $J_{a,b} = 13.5$ Hz, H-10a), 4.05 (1H, br d, $J_{a,b} = 13.5$ Hz, H-10b), 3.71 (3H, s, 11-MeO), 3.18 (1H, q-like, $J = 8$ Hz, H-5), 2.82 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6a} = 8.5$ Hz, H-6a), 2.70 (1H, t, $J_{1,9} = J_{5,9} = 8$ Hz, H-9), 2.06 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6b} = 8$ Hz, H-6b), 3.21, 1.36, 1.35 (each 3H, s, 10-[$\text{Me}_2\text{C}(\text{OMe})$]), 4.78 (1H, d, $J_{1',2'} = 8$ Hz, H-1'), 3.85 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{5',6a'} = 5.5$ Hz, H-6a'), 3.74 (1H, t, $J_{a,b} = J_{5',6b'} = 10.5$ Hz, H-6b'), 3.53–3.47 (2H, m, H-3' and H-4'), 3.33–3.25 (2H, m, H-2' and H-5'), 1.50, 1.36 (each 3H, s, 4',6'- Me_2C); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 169.4, 153.2, 142.4, 129.1, 112.6, 101.6, 98.8, 60.5, 51.8, 49.1, 47.1, 39.8, 36.6, 24.8; sugar signals 101.3, 100.8, 75.7, 74.9, 74.7, 68.7, 63.1, 29.4, 19.3; anal. C 57.41%, H 7.60%, calcd for $\text{C}_{24}\text{H}_{36}\text{O}_{11}$, C 57.58%, H 7.26%.

2',3':4',6'-Di-O-isopropylidene-geniposide (15): white foam, $[\alpha]_{\text{D}}^{25} -18^\circ$ (c 0.8, MeOH); ^1H NMR (methanol- d_4 , 500 MHz) δ 7.52 (1H, d, $J_{3,5} = 1$ Hz, H-3), 5.81 (1H, br s, H-7), 5.06 (1H, d, $J_{1,9} = 7.5$ Hz, H-1), 4.26 (1H, br d, $J_{a,b} = 14$ Hz, H-10a), 4.17 (1H, br d, $J_{a,b} = 14$ Hz, H-10b), 3.72 (3H, s, 11-MeO), 3.19 (1H, q-like, $J = 8.5$ Hz, H-5), 2.84 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6a} = 8.5$ Hz, H-6a), 2.70 (1H, t, $J_{1,9} = J_{5,9} = 8$ Hz, H-9), 2.07 (1H, br dd, $J_{a,b} = 16.5$ Hz, $J_{5,6b} = 8$ Hz, H-6b); sugar signals essentially as for **16**; ^{13}C NMR (methanol- d_4 , 125 MHz) δ 169.3, 153.0, 144.7, 128.6, 112.6, 98.6, 61.3, 51.8, 46.8, 39.7, 36.7; sugar signals 112.9, 100.8, 99.6, 78.9, 73.8, 71.2, 63.1, 29.3, 26.9, 26.6, 19.5; anal. C 58.95%, H 7.09%, calcd for $\text{C}_{23}\text{H}_{32}\text{O}_{10}$, C 58.95%, H 6.90%.

2',3':4',6'-Di-O-isopropylidene-10-O-(1-methyl-1-methoxyethyl)-geniposide (16): white foam, $[\alpha]_{\text{D}}^{25} -2.8^\circ$ (c 0.9, MeOH); ^1H NMR (methanol- d_4 , 500 MHz) δ 7.52 (1H, d, $J_{3,5} = 1$ Hz, H-3), 5.83 (1H, br s, H-7), 5.05 (1H, d, $J_{1,9} = 8$ Hz, H-1), 4.13 (1H, br d, $J_{a,b} = 13$ Hz, H-10a), 4.07 (1H, br d, $J_{a,b} = 13$ Hz, H-10b), 3.72 (3H, s, 11-MeO), 3.18 (1H, q-like, $J = 8.5$ Hz, H-5), 2.83 (1H, br dd, $J_{a,b} = 16$ Hz, $J_{5,6a} = 9$ Hz, H-6a), 2.69 (1H, t, $J_{1,9} = J_{5,9} = 8$ Hz, H-9), 2.06 (1H, br dd, $J_{a,b} = 16$ Hz, $J_{5,6b} = 8.5$ Hz, H-6b), 3.22, 1.36, 1.35 (each 3H, s, 10-[$\text{Me}_2\text{C}(\text{OMe})$]), 5.22 (1H, d, $J_{1',2'} = 8$ Hz, H-1'), 3.95 (1H, t, $J_{3',4'} = J_{4',5'} = 9$ Hz, H-4'), 3.88 (2H, m, 2 × H-6'), 3.72 (1H, t, $J_{2',3'} = J_{3',4'} = 9$ Hz, H-3'), 3.42 (1H, dd, $J_{2',3'} = 9$ Hz, $J_{1',2'} = 8$ Hz, H-2'), 3.34 (1H, m, H-5'), 1.53, 1.36 (each 3H, s, 4',6'- Me_2C), 1.45, 1.44 (each 3H, s, 2',3'- Me_2C); ^{13}C NMR (methanol- d_4 , 125

(MHz) δ 169.3, 153.0, 142.3, 129.7, 112.7, 101.5, 98.5, 60.5, 51.8, 49.2, 46.9, 39.8, 36.7, 24.9, 24.8; sugar moiety 113.0, 100.8, 99.4, 78.9, 73.9, 71.2, 63.2, 29.4, 26.9, 26.7, 19.5; *anal.* C 60.14%, H 7.67%, calcd for $C_{27}H_{40}O_{11}$, C 59.98%, H 7.47%.

Alternate Preparation of Geniposide Acetonides 14 and 16. Geniposide (**9**, 12.0 g) and PPTS (1.5 g) in dry Me_2CO -DMP (1:1, 300 mL) was kept for 14 h at room temperature followed by 1.5 h at 50 °C, when more DMP (50 mL) and PPTS (1.0 g) were added. After a further 3 h at 50 °C, followed by 12 h at room temperature, 2-methoxypropene (9 mL) was added in three portions over the next 6 h. Then the mixture was heated to 50 °C for 1.5 h, when Et_3N (10 mL) was added. Concentration gave a residue that was purified by VLC as above to give **16** (3.62 g, 22%) and **14** (8.51 g, 55%). Fractions of **12** and **13** were combined (4.00 g) and then dissolved in dry Me_2CO -DMP (1:1.25, 125 mL) with PPTS (0.50 g) added. After the mixture was stirred at room temperature for 45 h and subsequently at 50 °C for 1 h, Et_3N (2.5 mL) was added, and the mixture was concentrated. The residue was purified by VLC to give additional amounts of **16** (0.91 g, 5%) and **14** (2.01 g, 13%).

Adoxoside (11) from Acetonide 14. Acetonide **14** (13.3 g) in EtOH (150 mL) and Et_3N (15 mL) was hydrogenated for 4.5 h in the presence of 5% Pd/C (0.75 g). The catalyst was filtered off on activated charcoal over Celite, and the cake was eluted further with EtOAc (500 mL). The filtrates were concentrated and the residue heated to 45–50 °C in 5% aqueous HOAc for 3 h. The solvent was removed and the residue purified by MPLC. Elution with H_2O -MeOH (2:1) yielded **11** (7.13 g, 69%).³⁶

Adoxoside (11) from Acetonide 16. Compound **16** (4.77 g) was hydrogenated as above for 24 h to give a crude product (4.60 g), which was deprotected as above for 3 h to give a crude 5:1 mixture of adoxoside (**11**) and the 3,4-dihydro compound **17** (3.45 g), which was used directly for ozonolysis (see below).

10-Cinnamoylaucubin (18, Isoscrophularioside). Fresh aerial parts of *Penstemon teucrioides* (1.5 kg)³⁷ were homogenized with 95% EtOH (6.5 L). After filtration, the cake was eluted with MeOH (3.0 L). The combined filtrates were concentrated and the residue partitioned in H_2O - Et_2O (1:1, 1.6 L). The aqueous layer was concentrated to ca. 200 mL and was then extracted with EtOAc (8 \times 400 mL). Concentration of the organic layers gave a residue (29.5 g), that was treated with Al_2O_3 (400 g) on a Büchner funnel. Elution with H_2O (2.0 L) and concentration of the filtrates gave a residue, which was dissolved in MeOH (250 mL) and filtered through activated charcoal (ca. 5 g). Removal of the solvent gave crude **18** (13.9 g).³⁷

Aucubin (19). To crude **18** (4.46 g) in H_2O (30 mL) was added 1M NaOH (15 mL), and the mixture was stirred at room temperature for 2 h. Then HOAc was added till pH 6.5, and then solid $NaHCO_3$ was added until pH 8.5. The mixture was then purified by MPLC. Elution with H_2O -MeOH (15:1) yielded **19** (2.20 g, 68%).

Aucubin Acetonides 20 and 21/22. Aucubin (**19**, 527 mg, 1.52 mmol) and anhydrous $CuSO_4$ (527 mg) were suspended in dry Me_2CO (40 mL), and then PPTS (53 mg, 0.21 mmol) was added. The mixture was cooled to 0 °C, and DMP (2.0 mL, 16.3 mmol) was added. Stirring at 0–5 °C was continued for 4 days. Then Et_3N (0.2 mL) was added, and the mixture was diluted with EtOAc and filtered through a layer of Na_2SO_4 . The filtrate was concentrated to give a residue that was purified on a VLC column (3 \times 3 cm). Elution with hexanes- Me_2CO (4:1 to 1:1) yielded a 4:1 mixture of acetonides **21/22** (217 mg, 31%) and **20** (238 mg, 40%).

4',6'-O-Isopropylidene-aucubin (20): white foam, $[\alpha]^{20}_D$ -124° (c 0.7, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 6.32 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.76 (1H, m, H-7), 5.12 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.79 (1H, d, $J_{1,9}$ = 7.5 Hz, H-1), 4.42 (1H, ddt, J = 5.5, 4, 2 \times 2 Hz, H-6), 4.31 (1H, br d, $J_{a,b}$ = 15.5 Hz, H-10a), 4.15 (1H, br d, $J_{a,b}$ = 15.5 Hz, H-10b), 2.87 (1H, br t, J = 7.5 Hz, H-9), 2.64 (1H, dddd, J = 7.5, 5.5, 4, 2 Hz, H-5), 1.50, 1.37 (each 3H, s, 4',6'- Me_2C); other sugar signals as for **21**; ^{13}C NMR (methanol- d_4 , 125 MHz) δ 147.8, 141.6, 130.5, 105.8, 98.1, 82.9, 61.5, 47.9, 46.6; sugar

signals essentially as for **21**; *anal.* C 55.56%, H 6.75%, calcd for $C_{18}H_{26}O_9$, C 55.94%, H 6.80%.

4',6'-O-Isopropylidene-10-O-(1-methyl-1-methoxyethyl)-aucubin (21): 1H NMR (methanol- d_4 , 500 MHz) δ 6.32 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.78 (1H, m, H-7), 5.11 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.81 (1H, d, $J_{1,9}$ = 8 Hz, H-1), 4.41 (1H, ddt, J = 5.5, 4, 2 \times 2 Hz, H-6), 4.23 (1H, br d, $J_{a,b}$ = 14.5 Hz, H-10a), 3.99 (1H, br d, $J_{a,b}$ = 14.5 Hz, H-10b), 2.86 (1H, t, J = 8 Hz, H-9), 2.64 (1H, dddd, J = 7.5, 5.5, 4, 2 Hz, H-5), 3.21, 1.36, 1.35 (each 3H, s, 10-[$Me_2C(OMe)$]), 4.74 (1H, d, $J_{1',2'}$ = 8 Hz, H-1'), 3.86 (1H, dd, $J_{a,b}$ = 10.5 Hz, $J_{5',6a'}$ = 5.5 Hz, H-6a'), 3.74 (1H, t, $J_{a,b}$ = $J_{5',6b'}$ = 10.5 Hz, H-6b'), 3.53–3.46 (2H, H-3' and H-4'), 3.32–3.24 (2 H, H-2' and H-5'), 1.49, 1.38 (each 3H, s, 4',6'- Me_2C); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 145.5, 141.5, 130.9, 105.8, 101.6, 98.2, 82.9, 60.4, 49.1, 48.2, 46.3, 24.8, 24.7; sugar moiety 100.8 (2 C), 75.8, 74.9, 74.8, 68.6, 63.1, 29.4, 19.2.

4',6'-O-Isopropylidene-6-O-(1-methyl-1-methoxyethyl)-aucubin (22): 1H NMR (methanol- d_4 , 500 MHz) δ 6.31 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.77 (1H, m, H-7), 5.06 (1H, dd, $J_{3,4}$ = 6.5 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.86 (1H, d, $J_{1,9}$ = 8 Hz, H-1), 4.49 (1H, ddt, J = 5.5, 4, 2 \times 2 Hz, H-6), 4.30 (1H, br d, $J_{a,b}$ = 15.5 Hz, H-10a), 4.15 (1H, br d, $J_{a,b}$ = 15.5 Hz, H-10b), 2.89 (1H, m, H-9), 2.73 (1H, m, H-5), 3.25, 1.36, 1.35 (each 3H, s, 6-[$Me_2C(OMe)$]), sugar signals as for **21**; ^{13}C NMR (methanol- d_4 , 125 MHz) δ 148.1, 141.5, 129.7, 105.7, 101.6, 97.7, 82.1, 61.4, 49.1, 47.5, 44.4, 25.7, 25.6; remaining signals as for **21**; acetonides **21/22**: white foam, $[\alpha]^{21}_D$ -99° (c 0.2, MeOH); *anal.* C 57.38%, H 7.51%, calcd for $C_{22}H_{34}O_{10}$, C 57.63%, H 7.47%.

10 α -4',6'-O-Isopropylidene-3,4,7,8-tetrahydroaucubin (23). Acetonide **20** (493 mg) in EtOH (5 mL) and Et_3N (50 μ L) was hydrogenated for 12 h in the presence of Pt (from 25 mg PtO_2). The catalyst was filtered off on activated charcoal/Celite, eluting the cake with Me_2CO (50 mL). Concentration of the filtrates gave a residue (487 mg) that was purified on a VLC column (3 \times 3 cm). Elution with hexane- Me_2CO (2:1 to 1:1.3) gave first a 1:1.5 mixture of acetonides **23/24** (121 mg, 24%); then came pure **23** (311 mg, 62%): mp 157–158 °C (from Me_2CO -hexanes), $[\alpha]^{20}_D$ -120° (c 0.9, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 5.15 (1H, d, $J_{1,9}$ = 4 Hz, H-1), 4.04 (1H, br dd, J = 9, 4 Hz, H-6), 3.97 (1H, ddd, J = 12, 8.5, 3.5 Hz, H-3a), 3.75 (1H, dd, $J_{a,b}$ = 11 Hz, $J_{8,10a}$ = 7 Hz, H-10a), 3.53 (1H, obsc., H-10b), 3.50 (1H, obsc., H-3b), 2.47 (1H, br sextet, J = 8 Hz, H-8), 2.30 (1H, m, H-9), 2.27 (1H, m, H-5), 1.85 (1H, br d, J = 9 Hz, H-7a), 1.84 (1H, dd, J = 9, 1.5 Hz, H-7b), 1.62 (1H, m, H-4a), 1.37 (1H, m, H-4b), 4.67 (1H, d, $J_{1',2'}$ = 8 Hz, H-1'), 3.88 (1H, dd, $J_{a',b'}$ = 10.5 Hz, $J_{5',6a'}$ = 5.5 Hz, H-6a'), 3.76 (1H, t, J = 10.5 Hz, H-6b'), 3.54–3.46 (2H, m, H-3' and H-4'), 3.28 (1H, dd, $J_{2',3'}$ = 9 Hz, $J_{1',2'}$ = 8 Hz, H-2'), 3.25 (1H, m, H-5'), 1.51, 1.38 (each 3H, s, 4',6'- Me_2C); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 95.5, 76.3, 65.6, 60.2, 45.0, 43.1, 42.2, 38.0, 26.2; glucose moiety 99.5, 75.8, 75.0, 74.8, 68.6, 63.1, 29.4, 19.3; *anal.* C 55.56%, H 7.56%, calcd for $C_{18}H_{26}O_9$, C 55.36%, H 7.76%.

Hydrogenation of Acetonide 20 with Pd/C as Catalyst. Acetonide **20** (100 mg) in MeOH (5 mL) and Et_3N (0.14 mL) was hydrogenated (as described below for **24**) for 24 h in the presence of 5% Pd/C (15 mg). NMR of the crude product (101 mg, quant.) showed a 1:3 ratio between **23** and **24** (data given above and below).

10 β -4',6'-O-Isopropylidene-3,4,7,8-tetrahydroaucubin (24). A mixture of acetonides **21/22** (176 mg) in MeOH (10 mL) and Et_3N (0.28 mL) was hydrogenated for 24 h in the presence of 5% Pd/C (25 mg). The mixture was filtered on charcoal over Celite eluting further with EtOAc (75 mL). Concentration of the filtrate gave a residue (181 mg), which was treated with 1% aqueous HOAc-THF (1:1, 10 mL) for 2 days. Then Et_3N (0.2 mL) was added, and the mixture was concentrated. The residue was purified as described for **23** to give acetonide **24** (135 mg, 90%): mp 187–188 °C (from MeOH-EtOH-hexanes), $[\alpha]^{20}_D$ -98° (c 0.8, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 5.13 (1H, br s, H-1), 4.00 (1H, dt, $J_{a,b}$ = $J_{3a,4b}$ = 11.5 Hz and $J_{3a,4a}$ = 2.5 Hz, H-3a), 3.91 (1H, br d, J = 5.5 Hz, H-6), 3.57 (1H, dd, $J_{a,b}$ = 10.5 Hz, $J_{8,10a}$ = 6 Hz, H-10a), 3.51 (1H,

dd, $J_{a,b} = 10.5$ Hz, $J_{8,10b} = 6.5$ Hz, H-10b), 3.48 (1H, obsc., H-3b), 2.29 (1H, m, H-7a), 2.28 (1H, m, H-5), 2.21 (1H, m, H-8), 1.98 (1H, br dd, $J = 9, 7$ Hz, H-9), 1.47 (1H, m, H-4a), 1.39 (1H, m, H-7b), 1.30 (1H, m, H-4b), 4.64 (1H, d, $J_{1,2'} = 8$ Hz, H-1'), 3.86 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{5',6a'} = 5.5$ Hz, H-6a'), 3.76 (1H, t, $J_{a',b'} = J_{5',6b'} = 10.5$ Hz, H-6b'), 3.52–3.48 (2H, m, H-3' and H-4'), 3.30 (1H, dd, $J_{2,3'} = 9$ Hz, $J_{1,2'} = 8$ Hz, H-2'), 3.24 (1H, ddd, $J_{5',6b'} = 10.5$ Hz, $J_{4',5'} = 9.5$ Hz and $J_{5',6a'} = 5.5$ Hz, H-5'), 1.50, 1.38 (each 3H, s, 4',6'-Me₂C); ¹³C NMR (methanol-*d*₄, 125 MHz) δ 96.6, 77.7, 67.2, 59.3, 44.1, 43.5, 41.7, 37.1, 25.5; sugar signals 100.7, 99.4, 75.9, 75.2, 74.9, 68.6, 63.2, 29.4, 19.3; *anal.* C 55.32%, H 7.76%, calcd for C₁₈H₂₆O₉, C 55.36%, H 7.76%.

Lactone 25; Preparation from Acetonide 14. Acetonide **14** (5.60 g) in EtOH (185 mL) and Et₃N (5.60 g) was hydrogenated for 12 h in the presence of 5% Pd/C (0.28 g). Workup and deprotection, as described for **11**, afforded a crude 5:1 mixture of **11** and **17** (4.64 g). An aliquot (3.95 g, 10.2 mmol) of this mixture was dissolved in CH₂Cl₂-MeOH (2:1, 90 mL), cooled to -78 °C, and then treated with O₃ for 15 min. After purging the solution with Ar for 15 min, NaBH₄ (0.92 g, 24.3 mmol) and EtOH (50 mL) were added. After 2.5 h, the cooling was stopped, and, after an additional 1.5 h at room temperature, HOAc (4 mL) was added. When a clear solution was obtained, it was concentrated, and the residue was partitioned between EtOAc (200 mL) and brine-saturated NaHCO₃ (2:1, 90 mL). The aqueous layer was extracted further with EtOAc (5 × 150 mL). The organic layers were dried (Na₂SO₄) and concentrated to a residue (1.31 g), which was purified on a VLC column (4 × 4 cm). Elution with hexane-Me₂CO (10:1 to 2:1) and then Me₂CO afforded impure lactone **25** (273 mg, 16% from **14**), lactone **25** (885 mg, 53%), and then a mixture (112 mg) containing **17** and a small amount of tetrol **26** (see below). Recrystallization from Me₂CO-hexane gave an analytical sample of **25**: mp 154–155 °C, $[\alpha]_D^{25} +196^\circ$ (c 0.8, MeOH); ¹H NMR (methanol-*d*₄, 500 MHz) δ 4.60 (1H, d, $J_{4,5} = 7$ Hz, H-4), 4.42 (1H, dd, $J_{a,b} = 12$ Hz, $J_{1a,9} = 4$ Hz, H-1a), 4.26 (1H, br d, $J_{a,b} = 12$ Hz, H-1b), 3.62 (1H, dd, $J_{a,b} = 11$ Hz, $J_{8,10a} = 6$ Hz, H-10a), 3.56 (1H, dd, $J_{a,b} = 11$ Hz, $J_{8,10b} = 6.5$ Hz, H-10b), 2.88 (1H, m, H-5), 2.24 (1H, ddd, $J = 12, 9.5, 4$ Hz, H-9), 1.98 (1H, m, H-8), 1.93 (1H, m, H-6a), 1.79 (1H, m, H-7a), 1.24 (1H, m, H-7b), 1.19 (1H, m, H-6b); ¹³C NMR (methanol-*d*₄, 125 MHz) δ 177.3, 69.7 (2 C), 65.6, 47.9, 42.9, 42.0, 30.0, 29.7; *anal.* C 58.11%, H 7.57%, calcd for C₉H₁₄O₄, C 58.04%, H 7.59%.

3,4-Dihydrodoxoside (17): Repeated VLC gave an analytical sample: mp 147–148 °C (from MeOH), $[\alpha]_D^{23} -49^\circ$ (c 0.6, MeOH); ¹H NMR (methanol-*d*₄, 500 MHz) δ 5.26 (1H, br s, H-1), 4.03 (1H, t, $J_{a,b} = J_{3a,4} = 11$ Hz, H-3a), 3.68 (3H, s, 11-MeO), 3.63 (1H, dd, $J_{a,b} = 11$ Hz, $J_{3b,4} = 4.5$ Hz, H-3b), 3.56 (1H, dd, $J_{a,b} = 11$ Hz, $J_{8,10a} = 5.5$ Hz, H-10a), 3.50 (1H, dd, $J_{a,b} = 11$ Hz, $J_{8,10b} = 6.5$ Hz, H-10b), 2.60 (1H, m, H-5), 2.53 (1H, dt, $J_{3a,4} = J_{4,5} = 11$ Hz, $J_{3b,4} = 4.5$ Hz, H-4), 2.16 (1H, m, H-8), 1.93 (1H, m, H-7a), 1.80 (1H, br dd, $J = 10, 6$ Hz, H-9), 1.68 (1H, ddd, $J = 13, 9.5, 5.5$ Hz, H-6a), 1.63 (1H, m, H-6b), 1.47 (1H, dddd, $J = 13, 9.5, 6, 3$ Hz, H-7b), 3.86 (1H, dd, $J_{a',b'} = 12$ Hz, $J_{5',6a'} = 2$ Hz, H-6a'), 3.63 (1H, dd, $J_{a',b'} = 12$ Hz, $J_{5',6b'} = 5.5$ Hz, H-6b'), 3.37 (1H, br t, $J = 9$ Hz, H-3'), 3.28 (1H, br t, $J = 9.5$ Hz, H-4'), 3.27 (1H, obsc., H-5'), 3.23 (1H, dd, $J_{2,3'} = 9$ Hz, $J_{1,2'} = 8$ Hz, H-2'); ¹³C NMR (methanol-*d*₄, 125 MHz) δ 175.1, 95.9, 66.4, 60.2, 52.3, 46.4, 43.4, 42.3, 38.6, 30.2, 26.4; glucose moiety 99.0, 74.8, 78.0, 71.6, 78.1, 62.7; *anal.* C 51.87%, H 7.35%, calcd for C₁₇H₂₈O₁₀, C 52.02%, H 7.21%.

X-ray Crystallographic Analysis of 25.³⁸ Compound **25** crystallized in the trigonal space group *P*₃₂ *a* = 7.5812 (4), *c* = 13.4709 (9) Å, *V* = 670.51 (7) Å³, *Z* = 3 and with a calculated density of 1.383 g/cm³. The structure was solved by direct methods (Bruker AXS SHELXTL vers. 5.03) and refined on *F*², using all data by a full-matrix, weighted least-squares process (*R* = 0.054 and *wR*₂ = 0.112). Intensity data were collected on a Bruker AXS SMART CCD system using Mo-*K*_α (λ = 0.7107). Intensities were integrated from a series of frames covering more than a hemisphere of reciprocal space. Absorption corrections were applied by using SADABS (*T*_{max} = 0.98 and *T*_{min} = 0.61). The reflections obtained were merged

to provide 2091 unique reflections (*R*_{int} = 0.024). All non-hydrogen atoms were refined by using anisotropic displacement parameters. Hydrogen atoms were defined in idealized positions.

Tetrol 26; Ozonolysis of Adoxoside (11). Pure glucoside **11** (5.29 g, 13.6 mmol) in CH₂Cl₂-MeOH (2:1, 120 mL) was cooled to -78 °C and then treated with O₃ for 30 min. Then N₂ was passed through the solution for 15 min, at which time NaBH₄ (1.54 g, 40.7 mmol) and EtOH (60 mL) were added. After 1.5 h, the cooling to -78 °C was stopped, and after an additional 2 h at room temperature, HOAc (6 mL) was added. Repeated concentration with MeOH gave a residue that was purified by VLC. Elution with hexane-Me₂CO (1:1) gave tetrol **26** (1.80 g, 70%) as a hygroscopic syrup: $[\alpha]_D^{21} -18^\circ$ (c 0.5, MeOH); ¹H NMR (methanol-*d*₄, 500 MHz) δ 3.78 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{8,10a} = 7.5$ Hz, H-10a), 3.68–3.63 (2H, m, H-3a and H-4), 3.50–3.42 (3H, m, 2 × H-1 and H-3b), 3.44 (1H, obsc., H-10b), 2.13–2.02 (2H, m, H-5 and H-9), 1.89–1.82 (2H, m, H-7a and H-8), 1.65 (1H, m, H-6a), 1.34 (1H, m, H-6b), 1.27 (1H, m, H-7b); ¹³C NMR (methanol-*d*₄, 125 MHz) δ 73.9, 67.1, 66.7, 63.9, 46.2, 46.1 (2 C), 29.1, 28.9.

Tetrol 26; Reduction of Lactone 25. To lactone **25** (955 mg, 5.13 mmol) in EtOH (40 mL) was added NaBH₄ (194 mg, 5.13 mmol). After the mixture was stirred at room temperature for 2.5 h, HOAc (1 mL) was added. The mixture was then concentrated, and the residue was concentrated twice with MeOH. The resulting residue was purified by VLC to yield tetrol **26** (910 mg, 93%).

Tetrol Acetonide 29. Tetrol **26** (3.56 g, 18.7 mmol) was dissolved in dry Me₂CO (220 mL), and PPTS (165 mg), anhydrous CuSO₄ (2.20 g), and DMP (1.65 mL) were added. After 6 h, the mixture was concentrated to ca. 50 mL. The residual solution was then diluted with EtOAc (150 mL) and washed with brine-saturated NaHCO₃ (1:1, 60 mL). The aqueous layer was extracted with more EtOAc (2 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified on a VLC column (6 × 7 cm). Elution with hexane-Me₂CO (10:1 to 6:1) yielded acetonide **29** (3.48 g, 81%): colorless oil, $[\alpha]_D^{23} -1.3^\circ$ (c 0.9, MeOH); ¹H NMR (methanol-*d*₄, 500 MHz) δ 4.10 (1H, ddd, $J_{4,5} = 10$ Hz, $J_{3b,4} = 8$ Hz, $J_{3a,4} = 5.5$ Hz, H-4), 4.03 (1H, dd, $J_{a,b} = 8$ Hz, $J_{3a,4} = 5.5$ Hz, H-3a), 3.85 (1H, dd, $J_{a,b} = 11$ Hz, $J_{1a,9} = 5.5$ Hz, H-1a), 3.53 (1H, dd, $J_{a,b} = 11$ Hz, $J_{1b,9} = 7.5$ Hz, H-1b), 3.52 (1H, obsc., H-10a), 3.51 (1H, t, $J_{a,b} = J_{3b,4} = 8$ Hz, H-3b), 3.49 (1H, obsc., H-10b), 2.11 (1H, m, H-5), 2.05 (1H, m, H-8), 2.02 (1H, m, H-9), 1.90 (1H, m, H-7a), 1.62 (1H, m, H-6a), 1.35 (1H, m, H-7b), 1.33 (1H, m, H-6b), 1.37, 1.33 (each 3H, s, 3,4-Me₂C); ¹³C NMR (methanol-*d*₄, 125 MHz) δ 110.0, 77.7, 70.4, 67.0, 63.7, 47.8, 47.1, 46.4, 29.4, 28.7, 27.1, 26.1; *anal.* C 62.29%, H 9.76%, calcd for C₁₂H₂₂O₄, C 62.58%, H 9.63%.

Di-O-benzyl-tetrol 30. To acetonide **29** (1.49 g, 6.47 mmol) in dry THF (40 mL) was added NaH (0.93 g, 50% oil-suspension, 19.4 mmol) under Ar and cooling to 0 °C. After 15 min at 0 °C and then 15 min at room temperature, Bu₄Ni (717 mg, 1.94 mmol) and BnBr (2.31 mL, 19.4 mmol) in THF (10 mL) were added. The mixture was stirred at room temperature for 2 days, when additional amounts of NaH (186 mg, 50% oil-suspension, 3.87 mmol), Bu₄Ni (72 mg, 0.19 mmol), and BnBr (0.23 mL, 1.94 mmol) were added. After an additional 1 day, the mixture was diluted with EtOAc (100 mL), and then brine (50 mL) was added cautiously. The aqueous layer was extracted with more EtOAc (100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was hydrolyzed in a mixture of 1M HCl (50 mL) and THF (100 mL) for 1 day at room temperature. The mixture was then concentrated to ca. 100 mL, diluted with EtOAc (100 mL), and saturated NaHCO₃ (50 mL) was added. The organic layer was washed with brine-saturated NaHCO₃ (1:1, 2 × 50 mL) and was then dried (Na₂SO₄) and concentrated. The residue was purified on a VLC column (4 × 4 cm). Elution with hexane-Me₂CO (9:1) yielded diol **30** (1.86 g, 77.5%): needles (hexane-EtOAc), mp 67–68 °C, $[\alpha]_D^{23} +6.7^\circ$ (c 0.9, MeOH). ¹H NMR (methanol-*d*₄, 500 MHz) δ 3.66 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1a,9} = 7$ Hz, H-1a), 3.62 (2H, obsc., H-3a and H-4), 3.50 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1b,9} = 5.5$ Hz, H-1b), 3.42 (1H, dd, $J_{a,b} = 9.5$ Hz,

$J_{8,10a} = 7$ Hz, H-10a), 3.41 (1H, obsc., H-3b), 3.37 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{8,10b} = 7$ Hz, H-10b), 2.27 (1H, m, H-9), 2.13 (1H, m, H-8), 2.04 (1H, m, H-5), 1.87 (1H, m, H-7a), 1.62 (1H, m, H-6a), 1.33 (1H, m, H-6b), 1.28 (1H, m, H-7b), 7.33–7.24 (10H, m, $2 \times PhCH_2$), 4.51, 4.48 (each 2H, s, $2 \times PhCH_2$); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 139.9, 139.5, 129.4, 128.9, 128.8, 75.7, 74.3, 73.9, 72.6, 66.8, 46.3, 44.1, 43.4, 29.3, 28.9; *anal.* C 74.86%, H 8.30%, calcd for $C_{23}H_{30}O_4$, C 74.56%, H 8.16%.

Di-*O*-benzyl-triol 31. Diol **30** (270 mg, 0.729 mmol) was dissolved in dry THF (10 mL), and then H_5IO_6 (183 mg, 0.802 mmol) in dry THF (10 mL) was added. The mixture was stirred at room temperature for 15 min and then diluted with EtOAc (100 mL), and saturated aqueous $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with more EtOAc (100 mL). The combined EtOAc phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (25 mL), and the solution was cooled to $-78^\circ C$. Then EtOH (7 mL) and $NaBH_4$ (30 mg, 0.802 mmol) were added. After 1 h at $-78^\circ C$, more $NaBH_4$ (45 mg, 1.20 mmol) was added. The temperature was then allowed to reach $10^\circ C$ during the next 19 h, at which point the mixture was neutralized with HOAc (0.25 mL), and then CH_2Cl_2 (50 mL) and aqueous saturated $NaHCO_3$ (35 mL) were added. The aqueous layer was extracted with more CH_2Cl_2 (50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on a VLC column (3×3 cm). Elution with hexane–EtOAc (10:1 to 7:1) yielded **31** (237 mg, 95.5%), $[\alpha]^{23}_D +29^\circ$ (c 0.8, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 3.67 (1H, dd, $J_{a,b} = 11$ Hz, $J_{4a,5} = 7$ Hz, H-4a), 3.54 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1a,9} = 7.5$ Hz, H-1a), 3.50 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1b,9} = 5.5$ Hz, H-1b), 3.47 (1H, dd, $J_{a,b} = 11$ Hz, $J_{4b,5} = 7.5$ Hz, H-4b), 3.46 (1H, dd, $J_{a,b} = 9$ Hz, $J_{8,10a} = 6.5$ Hz, H-10a), 3.38 (1H, dd, $J_{a,b} = 9$ Hz, $J_{8,10b} = 6.5$ Hz, H-10b), 2.22 (1H, m, H-5), 2.11 (1H, m, H-9), 2.07 (1H, m, H-8), 1.88 (1H, m, H-7a), 1.73 (1H, m, H-6a), 1.45 (1H, m, H-6b), 1.33 (1H, m, H-7b), 7.33–7.24 (10 H, m, $2 \times PhCH_2$), 4.48, 4.47 (each 2H, s, $2 \times PhCH_2$); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 140.0, 139.7, 129.4, 128.9, 128.8, 128.5, 75.6, 74.2, 74.0, 72.0, 63.5, 45.5, 45.0, 43.4, 29.3, 29.2; *anal.* C, 77.61%, H 8.29%, calcd for $C_{22}H_{28}O_3$, C 77.39%, H 8.35%.

Di-*O*-benzyl-triol 32. Diol **30** (0.90 g, 2.43 mmol) was oxidized as above. The crude aldehyde was dissolved in MeOH (100 mL) and then anhydrous K_2CO_3 (1.00 g) was added. After the mixture was stirred at room temperature for 4 h (clear solution), $NaBH_4$ (100 mg, 2.65 mmol) was added. After an additional 16 h, HOAc (1 mL) was added, and then the mixture was concentrated. The residue was dissolved in EtOAc (150 mL), which was washed twice with brine–saturated $NaHCO_3$ (1:1, 80 mL). The EtOAc-phase was dried (Na_2SO_4) and concentrated. The residue was purified on a VLC column (4×4 cm). Elution with hexane and then hexane– Me_2CO (20:1 and 15:1) gave di-*O*-benzyl-triol **32** (0.78 g, 94%): $[\alpha]^{22}_D +19.5^\circ$ (c 1.1, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 3.54 (1H, dd, $J_{a,b} = 9$ Hz, $J_{1a,9} = 6$ Hz, H-1a), 3.52 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{4a,5} = 6$ Hz, H-4a), 3.47 (1H, dd, $J_{a,b} = 9$ Hz, $J_{8,10a} = 6$ Hz, H-10a), 3.44 (1H, dd, $J_{a,b} = 9$ Hz, $J_{1b,9} = 6.5$ Hz, H-1b), 3.41 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{4b,5} = 7$ Hz, H-4b), 3.36 (1H, dd, $J_{a,b} = 9$ Hz, $J_{8,10b} = 7.5$ Hz, H-10b), 2.02 (1H, m, H-8), 1.92 (1H, m, H-5), 1.74 (2H, m, H-6a and H-7a), 1.61 (1H, m, H-9), 1.46 (2H, m, H-6b and H-7b), 7.48–7.22 (10 H, m, $2 \times PhCH_2$), 4.48–4.45 (4H, m, $2 \times PhCH_2$); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 139.9, 139.8, 129.4, 129.3, 128.7, 128.6, 128.5, 75.2, 74.9, 74.1, 74.0, 66.7, 47.6, 47.0, 44.4, 29.6, 29.4; *anal.* C 77.27%, H 8.44%, calcd for $C_{22}H_{28}O_3$, C 77.61%, H 8.29%.

Di-*O*-benzoyl-tetrol 33. Acetonide **29** (1.06 g, 4.60 mmol) was dissolved in CH_2Cl_2 –pyridine (4:1, 15 mL), and then BzCl (1.34 mL, 11.5 mmol) was added. The mixture was kept at $4^\circ C$ for 19 h and subsequently at room temperature for 2 h. Ice was then added to the reaction mixture, and after 30 min, the mixture was diluted with CH_2Cl_2 (50 mL) and then washed successively with 2M H_2SO_4 , H_2O , and saturated $NaHCO_3$ (each 40 mL). Concentration of the organic layer yielded a residue (2.23 g), which was treated with 1M aqueous HCl (30 mL) in THF (70 mL) at room temperature for 34 h. Then EtOAc (150 mL) was added to the mixture; the organic layer was separated and washed twice with brine–saturated $NaH-$

CO_3 (1:1, 50 mL). The EtOAc-phase was dried (Na_2SO_4) and concentrated. The residue (2.02 g) was purified on a VLC column (3.5×4 cm). Elution with hexane and then hexane– Me_2CO (8:1 to 5:1) afforded **33** (1.47 g, 80%) as a colorless syrup: $[\alpha]^{23}_D +4.3^\circ$ (c 0.3, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 4.68 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{1a,9} = 4$ Hz, H-1a), 4.36 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{1b,9} = 9$ Hz, H-1b), 4.31 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{8,10a} = 6$ Hz, H-10a), 4.24 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{8,10b} = 8$ Hz, H-10b), 3.68 (1H, dd, $J_{a,b} = 11$ Hz, $J_{3a,4} = 3$ Hz, H-3a), 3.64 (1H, m, H-4), 3.47 (1H, dd, $J_{a,b} = 11$ Hz, $J_{3b,4} = 6$ Hz, H-3b), 2.59 (2H, m, H-8 and H-9), 2.28 (1H, m, H-5), 2.11 (1H, m, H-7a), 1.80, 1.53 (each 1H, m, $2 \times H-6$), 1.50 (1H, m, H-7b), 8.00–7.40 (10H, m, $2 \times Ph-CO$); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 168.2, 168.1, 134.2, 131.5, 130.5, 129.6, 73.6, 69.3, 67.1, 66.7, 45.4, 43.2, 29.0, 28.7; *anal.* C 69.24%, H 6.49%, calcd for $C_{23}H_{26}O_6$, C 69.33%, H 6.58%.

Di-*O*-benzoyl-triol 34. Dibenzoate **33** (0.61 g, 1.53 mmol) was dissolved in THF (20 mL), and then H_5IO_6 (0.38 g, 1.67 mmol) in dry THF (30 mL) was added. The mixture was stirred at room temperature for 30 min and then diluted with EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (75 mL). The organic layer was washed with brine (75 mL), dried (Na_2SO_4), and concentrated. The residue (0.71 g) was dissolved in CH_2Cl_2 (60 mL), and the solution was cooled to $-78^\circ C$. Then EtOH (25 mL) and $NaBH_4$ (64 mg, 1.68 mmol) were added, and after 1.5 h at $-78^\circ C$, more $NaBH_4$ (32 mg, 0.84 mmol) was added. After an additional 1 h at $-78^\circ C$, HOAc (0.6 mL) was added. The mixture was allowed to reach room temperature during 4 h, when the mixture was diluted with CH_2Cl_2 (100 mL) and then washed with brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue (0.65 g) was purified on a VLC column (3×3 cm). Elution with hexane and then hexane– Me_2CO (10:1 and 9:1) yielded **34** (0.48 g, 85%) as a colorless syrup: $[\alpha]^{22}_D +19^\circ$ (c 0.7, MeOH); 1H NMR (methanol- d_4 , 500 MHz) δ 4.52 (1H, dd, $J_{a,b} = 11$ Hz, $J_{1a,9} = 5.5$ Hz, H-1a), 4.38 (1H, dd, $J_{a,b} = 11$ Hz, $J_{1b,9} = 6.5$ Hz, H-1b), 4.32 (2H, d, $J_{8,10} = 6.5$ Hz, $2 \times H-10$), 3.74 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{4a,5} = 6.5$ Hz, H-4a), 3.61 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{4b,5} = 7$ Hz, H-4b), 2.43 (1H, m, H-8), 2.42 (1H, m, H-9), 2.41 (1H, m, H-5), 2.06 (1H, m, H-7a), 1.90, 1.61 (each 1H, m, $2 \times H-6$), 1.50 (1H, m, H-7b), 7.98 (4H, br d, $J = 8.5$ Hz, $Ph-CO$), 7.56 (2H, br t, $J = 8.5$ Hz, $Ph-CO$), 7.42 (4H, m, $Ph-CO$); ^{13}C NMR (methanol- d_4 , 125 MHz) δ 168.0, 134.1, 131.4, 130.4, 129.5, 69.2, 66.4, 63.2, 45.3, 44.1, 42.8, 29.2, 28.8; *anal.* C 71.58%, H 6.60%, calcd for $C_{22}H_{24}O_5$, C 71.72%, H 6.57%.

Bisnucleoside Analogue 35. Acetonide **29** (144 mg, 0.625 mmol), Ph_3P (656 mg, 2.50 mmol), and 6-chloropurine (387 mg, 2.50 mmol) in dry THF (7 mL) were cooled to $0^\circ C$, when a solution of DEAD (0.38 mL, 2.45 mmol) in dry THF (3 mL) was added dropwise. After 15 min, the cooling bath was removed, and after a total of 2 h the mixture was concentrated (to ca. 2 mL) and loaded onto a VLC column (3.5×3 cm). Elution with hexane– Me_2CO (6:1 to 2:1) gave protected bisnucleoside (226 mg, 72%) contaminated with ca. 5% Ph_3PO . 1H NMR (DMSO- d_6 , 500 MHz) δ 4.34 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{1a,9} = 6$ Hz, H-1a), 4.10 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{1b,9} = 11$ Hz, H-1b), 4.08 (1H, obsc., H-4), 4.04 (1H, obsc., H-3a), 4.01 (1H, obsc., H-10a), 3.99 (1H, obsc., H-10b), 3.55 (1H, t, $J_{a,b} = J_{3b,4} = 7.5$ Hz, H-3b), 2.69 (1H, m, H-9), 2.40 (1H, m, H-8), 2.33 (1H, m, H-5), 2.04 (1H, m, H-7a), 1.70 (1H, m, H-6a), 1.50 (1H, m, H-6b), 1.38 (1H, m, H-7b), 1.31, 1.18 (each 3H, s, 3,4- Me_2C), 8.48, 8.42 (each 1H, s, H-8' and H-8''), 8.46, 8.43 (each 1H, s, H-2' and H-2''); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 108.2, 75.1, 68.6, 47.8, 44.5, 44.1, 42.2, 41.0, 27.8, 26.7, 26.2, 25.5; purine signals 151.4, 151.1, 150.8, 148.8, 148.7, 147.3, 146.9, 130.5, 130.3. An aliquot of the protected nucleoside (140 mg) was treated with liquid NH_3 (20 mL) in a steel vessel at $50^\circ C$ for 3 days. After evaporation of the NH_3 , the residue was treated with 0.5M aqueous HCl (10 mL) at $4^\circ C$ for 1.5 days. After neutralization with solid $NaHCO_3$, the mixture was concentrated to 5 mL and loaded onto an MPLC column. Elution with H_2O – $MeOH$ (2:1) afforded unprotected bisnucleoside **35** (94 mg, 80%): mp 185–186 $^\circ C$ (from H_2O – $MeOH$), $[\alpha]^{20}_D -107^\circ$ (c 0.5, H_2O); 1H NMR (DMSO- d_6 , 500 MHz) δ 4.67 (1H, d, $J = 5$ Hz, 4-OH), 4.52 (1H, t, $J = 5.5$ Hz,

3-OH), 4.39 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{1a,9} = 4.5$ Hz, H-1a), 3.98 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{1b,9} = 12$ Hz, H-1b), 3.75 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{8,10a} = 8$ Hz, H-10a), 3.64 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{8,10b} = 7.5$ Hz, H-10b), 3.53 (1H, obsc., H-4), 3.52 (1H, obsc., H-3a), 3.36 (1H, obsc. by HDO-peak, H-3b), 2.50 (1H, obsc. by DMSO- d_6 peak, H-9), 2.27 (1H, m, H-8), 2.22 (1H, m, H-5), 1.81 (1H, m, H-7a), 1.70 (1H, m, H-6a), 1.46 (1H, m, H-6b), 1.31 (1H, m, H-7b), 8.05, 7.90 (each 1H, s, H-2' and H-2''), 7.94, 7.73 (each 1H, s, H-8' and H-8''), 7.08, 7.05 (each 2H, br s, 6'-NH₂ and 6''-NH₂); ¹³C NMR (DMSO- d_6 , 125 MHz) δ 71.5, 65.7, 47.1, 43.7, 42.7, 41.0, 27.2, 26.0; purine signals 155.8, 155.7, 152.2, 152.1, 149.8, 149.3, 140.6, 140.3, 118.8, 118.5; *anal.* C 49.59%, H 5.90%, N 30.22%, calcd for C₁₉H₂₄N₁₀O₂·2H₂O, C 49.56%, H 6.13%, N 30.42%.

Protected Nucleoside Analogue 38. A mixture of compound **32** (259 mg, 0.761 mmol), Ph₃P (399 mg, 1.52 mmol), and adenine (206 mg, 1.52 mmol) was stirred in dry dioxane (10 mL) under Ar. Then DEAD (0.23 mL, 1.48 mmol) in dioxane (2 mL) was added. The mixture was stirred at room temperature for 19 h, then concentrated, redissolved in EtOAc (6 mL), and loaded onto a VLC column (3 × 3 cm). Elution with hexane and then hexane–Me₂CO (5:1 to 2:1) gave compound **38** (240 mg, 68.5%): mp 122–123 °C (from hexane–Me₂CO), $[\alpha]_D^{21} +31^\circ$ (c 0.8, MeOH); ¹H NMR (DMSO- d_6 , 500 MHz) δ 4.22 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{4a,5} = 6.5$ Hz, H-4a), 4.05 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{4b,5} = 8.5$ Hz, H-4b), 3.41 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{8,10a} = 5.5$ Hz, H-10a), 3.33 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{8,10b} = 7.5$ Hz, H-10b), 3.31 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1a,9} = 6$ Hz, H-1a), 3.28 (1H, dd, $J_{a,b} = 9.5$ Hz, $J_{1b,9} = 6.5$ Hz, H-1b), 2.35 (1H, pentet-like, $J = 7.5$ Hz, H-5), 1.99 (1H, pentet-like, $J = 7$ Hz, H-8), 1.67 (1H, pentet-like, $J = 6.5$ Hz, H-9), 1.65 (1H, m, H-7a), 1.49 (1H, m, H-6a), 1.45 (1H, m, H-7b), 1.37 (1H, m, H-6b), 8.14 (1H, s, H-2'), 8.09 (1H, s, H-8'), 7.17 (2H, br s, 6'-NH₂), 7.35–7.24 (10H, m, 2 × Ph-CH₂), 4.46, 4.43 (each 1H, d, $J = 13.5$ Hz, Ph-CH₂), 4.36, 4.33 (each 1H, d, $J = 13.5$ Hz, Ph-CH₂); ¹³C NMR (DMSO- d_6 , 125 MHz) δ 138.7, 138.5, 128.2, 127.3, 127.2, 73.3, 72.5, 72.0, 47.0, 45.6, 43.0, 42.4, 28.8, 27.8; purine signals 155.9, 152.3, 149.7, 140.9, 118.7; *anal.* C 70.60%, H 6.69%, N 15.08%, calcd for C₂₇H₃₁N₅O₂, C 70.87%, H 6.83%, N 15.31%.

Nucleoside Analogue 7. Compound **38** (152 mg, 0.332 mmol) in CH₂Cl₂ (16 mL) was cooled to –78 °C, and then 1M BCl₃ in CH₂Cl₂ (4 mL) was added under Ar. The mixture was stirred at –78 °C for 6 h and was subsequently allowed to warm to –25 °C during 1 h. Then MeOH (8 mL) was added, and the cooling bath was removed. When the mixture reached room temperature it was concentrated. The residue was concentrated three times with more MeOH and was then partitioned between EtOAc (50 mL) and H₂O (25 mL). The aqueous layer was concentrated, and the residue was purified on a VLC column (3 × 3 cm). Elution with hexane, CHCl₃, and CHCl₃–MeOH (10:1 to 8:1) yielded nucleoside analogue **7** (89 mg, 97%): mp 169–170 °C (from EtOH–MeOH), $[\alpha]_D^{21} +14.5^\circ$ (c 0.4, H₂O); ¹H NMR (DMSO- d_6 , 500 MHz) δ 4.67 (1H, t, $J = 4.5$ Hz, OH), 4.62 (1H, t, $J = 5$ Hz, OH), 4.19 (1H, dd, $J_{a,b} = 14$ Hz, and $J_{4a,5} = 6$ Hz, H-4a), 4.01 (1H, dd, $J_{a,b} = 14$ Hz, and $J_{4b,5} = 9$ Hz, H-4b), 3.34–3.24 (4H, m, 2 × H-10 and 2 × H-1), 2.24 (1H, sextet-like, $J = 7.5$ Hz, H-5), 1.78 (1H, sextet-like, $J = 6.5$ Hz, H-8), 1.54 (1H, m, H-7a), 1.40 (3H, m, H-6a, H-7b and H-9), 1.29 (1H, m, H-6b), 8.12 (1H, s, H-2'), 8.11 (1H, s, H-8'), 7.17 (2H, br s, 6'-NH₂); ¹³C NMR (DMSO- d_6 , 125 MHz) δ 64.4, 63.7, 48.3, 47.1, 45.2, 42.9, 28.7, 27.4; purine signals 155.8, 152.2, 149.6, 141.0, 118.5; *anal.* C 56.13%, H 6.72%, N 25.11%, calcd for C₁₃H₁₉N₅O₂, C 56.30%, H 6.91%, N 25.25%.

Nucleoside Analogue 8. A mixture of dibenzoate **34** (225 mg, 0.611 mmol), Ph₃P (321 mg, 1.22 mmol), and 6-chloropurine (189 mg, 1.22 mmol) was stirred in dry THF (4 mL). Then DEAD (185 μ L, 1.19 mmol) in THF (1.5 mL) was added under Ar. The mixture was stirred at room temperature for 12 h, when the mixture was concentrated, redissolved in CH₂Cl₂ (4 mL), and loaded onto a VLC column (3 × 3 cm). Elution with hexane and then hexane–Me₂CO (10:1 to 8:1) gave a mixture of product and Ph₃PO (0.42 g), which was treated directly with liquid NH₃ at 45–50 °C for 3 days. The residue

was purified on a VLC column (3 × 3 cm). Elution with hexane, CHCl₃, and CHCl₃–MeOH (10:1 to 8:1) yielded nucleoside analogue **8** (59 mg, 35%) as well as only partially debenzoylated product. The latter was treated with NaOMe–MeOH at room temperature for 2 h, and was purified as above to give an additional amount of nucleoside analogue **8** (75 mg, 44%): mp 167–168 °C (from EtOH–MeOH), $[\alpha]_D^{21} +22^\circ$ (c 0.6, H₂O); ¹H NMR (DMSO- d_6 , 500 MHz) δ 4.70 (1H, t, $J = 4.5$ Hz, 10-OH), 4.58 (1H, t, $J = 5$ Hz, 1-OH), 4.30 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{4a,5} = 5.5$ Hz, H-4a), 4.05 (1H, dd, $J_{a,b} = 13.5$ Hz, $J_{4b,5} = 11$ Hz, H-4b), 3.53 (1H, m, H-1a), 3.48 (1H, dt, $J_{a,b} = 10.5$ Hz, $J = 5$ Hz, H-1b), 3.29 (2H, m, 2 × H-10), 2.56 (1H, m, H-5), 1.87 (2H, m, H-8 and H-9), 1.78 (1H, m, H-7a), 1.30, 1.25 (2H, m, 2 × H-6), 1.18 (1H, m, H-7b); ¹³C NMR (DMSO- d_6 , 125 MHz) δ 64.8, 61.2, 45.8, 43.8, 43.6, 41.7, 28.5, 26.8; purine signals 155.8, 152.2, 149.6, 140.9, 118.6; *anal.* C 56.45%, H 6.86%, N 25.04%, calcd for C₁₃H₁₉N₅O₂, C 56.30%, H 6.91%, N 25.25%.

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Supporting Information Available: Tabulated ¹³C NMR data for all new compounds as well as supplementary reproductions of selected NMR spectra of tetrol **26**, bisnucleoside **35**, and bicyclic tetrahydrofuran **37**; experimental procedure for the preparation of **37**; crystallographic data for lactone **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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