Natural Product Synthesis

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A Concise and General Method for Doubly Attaching 2-Ketosugars to Aglycon Diols: Synthesis of the Gomphosides and Spectinomycin**

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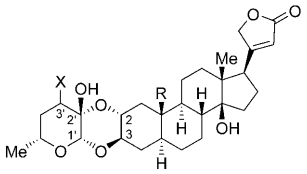
Dedicated to Professor András Lipták on the occasion of his 70th birthday

Whereas the cardiac glycosides from *Digitalis* and *Strophantus* species carry one to five sugar units linked through the 3-OH of the steroid aglycon,[1] those produced by plants from the milkweed family *Asclepiadacea*, such as **1**–**6** (Table 1),[2–4]

Table 1: Cardenolide glycosides (**1**–**6**) isolated from the milkweed family *Asclepiadaceae*.



	Compound	3′-C–X	R	Reference
1	gomphoside	◄OH	Me	[2]
2	3′-*epi*-gomphoside	····OH	Me	[3]
3	3′-dehydrogomphoside	=O	Me	[3]
4	calactin	◄OH	CHO	[4]
5	calotrophin	····OH	CHO	[4]
6	usacharidin	=O	CHO	[4]

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invariably contain a single sugar—the rare 4,6-dideoxy-D-hexos-2,3-diulose or its epimeric C-3 reduction products—in a unique "dioxanoid" attachment. The common β-glycosidic bond to the steroidal 3-OH is complemented by a hemiacetal linkage between the 2-carbonyl group of the sugar and the 2-OH group of the aglycone to result in a *cis,cisoid,trans*-fusion of pyran, dioxane, and cyclohexane rings. The antibiotic spectinomycin (**7**) and its dihydro derivative **8**, elaborated by *Streptomyces spectabilis*, contain the same 2-ketosugars in an analogous double attachment to actinamine, an *N*-methylated diaminoinositol (Figure 1).[5]

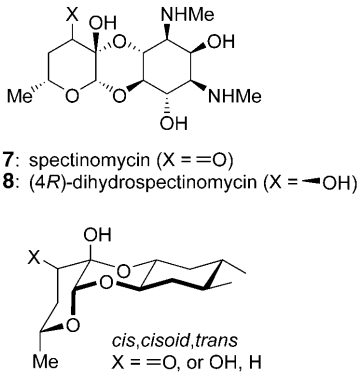
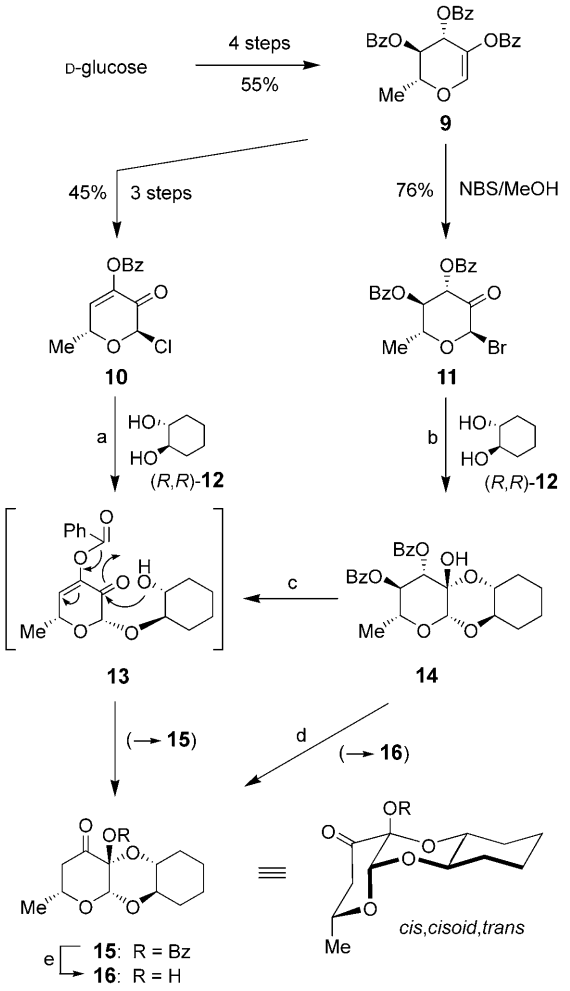


Figure 1. Two antibiotics (**7**, **8**) produced by *Streptomyces spectabilis*, each comprising a 4,6-dideoxy-2-ketohexose moiety doubly attached to a cyclohexanoid aglycone-diol in *cis,cisoid,trans* fusion.

Synthetically, the double attachment of a 2-ketosugar to a natural aglyconediol has only been addressed in the case of spectinomycin (**7**), for which two total syntheses (one in 9 steps from L-glucose,[6a] and the other in 23 steps from D-glucose[6b]) have been reported that comprise monoglycosylation of a readily accessible *N*-protected actinamine and subsequent gradual elaboration of the 2-carbonyl group of the sugar. In the case of cardenolide glycosides of type **1**–**6**, however, the aglycons are only laboriously available. Thus for annulation of their sugar portion, alternatives that are capable of reaching this objective more directly became imperative. On the basis of our previous studies on the extension of the "ulosyl donor approach"[7] to glycol and (*R*,*R*)-1,2-cyclohexanediol, which smoothly led to *cis*-fused pyranodioxanes[8] and to pyran-dioxane-cyclohexane tricycles[9] in *cis,cisoid,trans* fusion, we inferred that the D-glucose-derived 2-ketohexosyl donors **10** and **11** would be particularly well-adjusted for targeting natural products with annulated sugar components. The donors not only contain the 2-carbonyl function, which is essential for generation of the cyclohemiacetal linkage, but in the case of **10**, an enol-ester-protected carbonyl at C-3 is also present thereby closely matching the tricarbonyl sugar units in **3**, **6**, and **7**. Furthermore, these donors are fairly well accessible from D-glucose through the 6-deoxy-2-hydroxyglucal ester **9**:[10] ulosyl bromide **11** can be obtained in five, large-scale adaptable steps from D-glucose[11,12] versus seven steps for its unsaturated chloro analogue **10**,[12] with overall yields of 42 and 25%, respectively (Scheme 1).

The feasibility of advancing from donors **10** and **11** to cardenolides of type **1**–**6** was first probed with (*R*,*R*)-1,2-cyclohexanediol (**12**) as a model aglycon. On exposure of **12** to equimolar amounts of Ag_2CO_3 and donor **10**, a single product was obtained (TLC) and isolated in high yield (81%) which on the basis of cogent NMR evidence proved to be *cis,cisoid,trans*-fused pyran-dioxane-cyclohexane tricycle **15**. Thus, an essentially β-specific mono-*O*-glycosylation of diol **12** to glycosidulose **13** is spontaneously followed by a cascade reaction in which the second OH group engages in hemiacetal formation and the 3-*O*→2-*O*-benzoyl group (arrows in **13**) subsequently shifts, with seemingly exclusive preference for OH→C=O attack occurring from the lower (axial) face of the pyran ring.[13] Here, electronic interactions are minimized by *trans*-diaxial disposition of the oxygen of the pyran ring and the benzoyloxy acetal group—a consequence of the anomeric effect—and steric interactions are at a minimum due to chair conformations of the three rings.



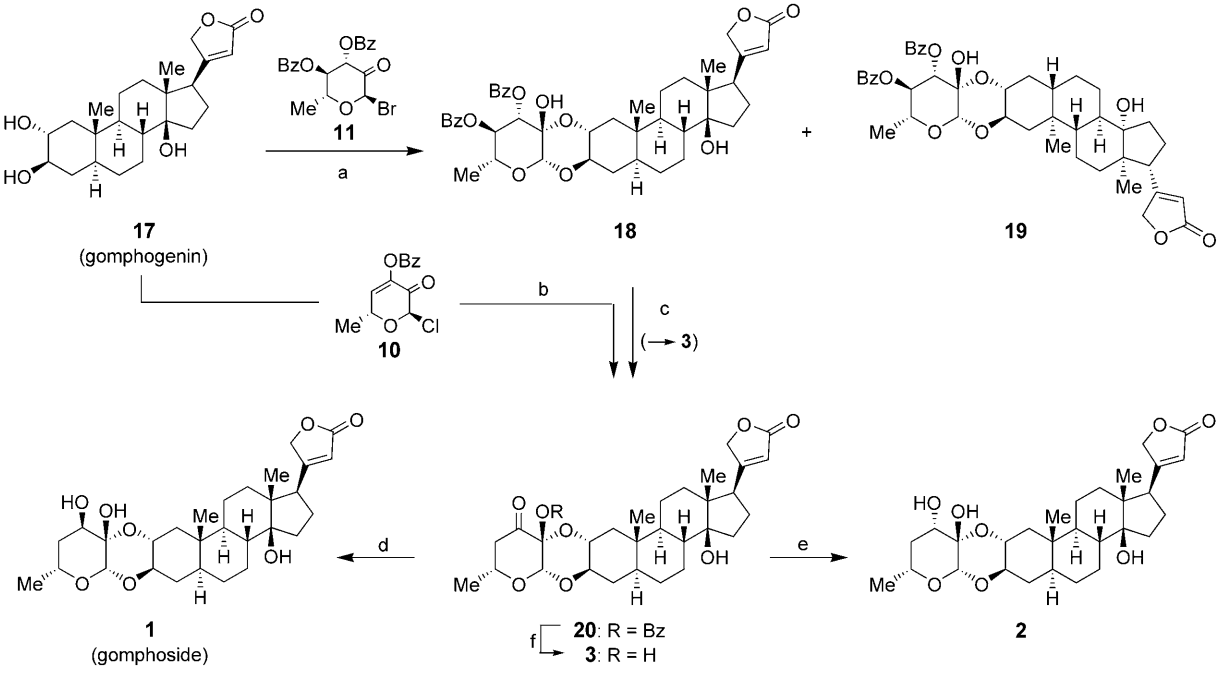
Scheme 1. Synthesis of linear fused pyran-dioxane-cyclohexane tricycles that correspond to dioxanoid cardenolide glycosides in structure and linkage geometry. Reagents and conditions: a) **12** (1.0 equiv), Ag_2CO_3 (1.0 equiv), molecular sieves, CH_2Cl_2, 40°C, 8 h, 81%; b) **12** (1.0 equiv), Ag_2CO_3 (1.0 equiv), CH_2Cl_2, 25°C, 20 h, 87%; c) nBu_4NOAc, CH_2Cl_2, 25°C, 20 h, 85% (**15**); d) nBu_4NOAc, moist MeCN, 25°C, 6 h, 81% (**16**); e) K_2CO_3, MeOH, 25°C, 10 min, 87%. Bz = benzoyl; NBS = *N*-bromosuccinimide.

In the case of the ulosyl bromide **11**, the Ag_2CO_3-mediated glycosylation of one OH group of diol **12** expectedly[7,12] proceeded in β-specific fashion and was similarly followed by sterically uniform hemiketalization with the other OH group to provide the *cis,cisoid,trans*-interconnected tricycle **14**, with the high yield (87%) emphasizing the extent of stereocontrol in the two reactions involved. Owing to its free ketalic OH group, **14** is prone to react in the ring-opened glycosidulose form, particularly under basic conditions. Thus, on stirring **14** with tetra-*n*-butylammonium acetate in CH_2Cl_2, 3,4-elimination of benzoic acid to the enolone ester **13** was induced; however, the ester was not isolable under these conditions, as hemiketalization and migration of the *O*-benzoyl group readily took place (arrows in **13**; see Scheme 1), thereby elaborating the tricyclic ketone **15** (85%). When β elimination of **14**→**13** was attempted with nBu$_4$NOAc in aqueous acetonitrile, the benzoyl migration step was intercepted by hydrolysis to afford instead the free hemiketal **16** in crystalline form[14] and 81% yield. Expectedly, **16** was also obtained on de-*O*-benzoylation of **15** (87%).

Thus, having established the utility of donors **10** and **11** for the dioxanoid annulation of 4,6-dideoxy-2-ketosugar units—the *cis,cisoid,trans*-fused **15** has all the structural and stereochemical essentials of the natural products—the methodology developed for (*R*,*R*)-1,2-cyclohexanediol was then applied to gomphogenin (**17**),[15] the steroid aglycone of gomphosides **1**–**3**. As **17** is an unsymmetric diol, it was expected to give two products as Ag_2CO_3-mediated *O*-glycosylation with donors **10** or **11** followed by folding of the hemiketal can occur on either of the OH groups. Fortunately, it appeared that the 3-OH group of gomphogenine is the more reactive of the two OH groups from the fact that the major components of the 3:1 mixtures obtained in each case proved to be the naturally fused products **18** (from ulosyl bromide **11**) and **20** (from donor **10**). These products were purified by preparative HPLC to afford **18** and **20** in yields of 61 and 54%, respectively (Scheme 2). De-*O*-benzoylation of **20** was readily effected by exposure to mild base to provide crystalline cardenolide **3** in excellent yield (95%). In analogy to the model conversion **14**→**16**, **3** could also be obtained from **18** by stirring with nBu$_4$NOAc in hydrous acetonitrile (81% yield). Compound **3** as synthesized here was identical in all respects with the 3′-dehydrogomphoside derived from *Asclepias fruticosa*[3] with respect to the melting point (300–301 °C; lit.: 302–304 °C[3]) and ^{1}H and ^{13}C NMR spectroscopic characteristics.

The integrity of synthetic **3** could further be verified through conversion into the epimeric 3′-hydroxy analogues. Hydrogenation over 5% Rh/C[16] led to a mixture of gomphoside (**1**) and its 3′-epimer **2**, from which **1** was secured in 80% yield and proved to be identical to the natural product[2b,17] with respect to melting point and spectral data. Reduction of **3** with $NaBH_4$ proceeded stereospecifically to afford 3′-*epi*-gomphoside (**2**) as a crystalline solid,[18] whose structure was analyzed by X-ray diffraction and clearly exposes the *cis,cisoid,trans* interconnection of the pyran, dioxane, and ring A cyclohexane rings (Figure 2).

The methodology developed so far for the dioxanoid annulation of sugars to cyclic 1,2-diols was also probed with *N*,*N*-bis(benzyloxycarbonyl)actinamine (**21**), the aglycon of spectinomycin in an accessible and suitably *N*,*N*-protected form.[19] As the bulky *N*-protecting groups impede glycosylation at the vicinal hydroxy groups through steric shielding,[6] a highly regioselective attack of donors **10** or **11** at 3-OH was anticipated. However, the acceptor reactivity of this 3-hydroxy group proved to be considerably lower than that in



Scheme 2. Reagents and conditions: a) **11** (2 equiv), Ag_2CO_3 (1 equiv), molecular sieves, CH_2Cl_2, 25 °C, 16 h, 61% (**18**), 14% (**19**); b) **10** (1.0 equiv), Ag_2CO_3 (1.0 equiv), molecular sieves, CH_2Cl_2, 40 °C, 2 h, 54% (**20**); c) nBu$_4$NOAc, MeCN/water 50:1, 25 °C, 15 h, 89% (**3**); d) 5% Rh/C, MeOH/water 9:1, 25 °C, 24 h, 80%; e) $NaBH_4$ (1.0 equiv), dry MeOH, 0 °C, 10 min, 81%; f) K_2CO_3, MeOH, 25 °C, 10 min, 95%.

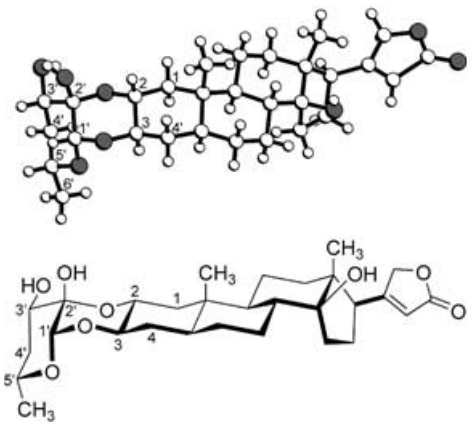
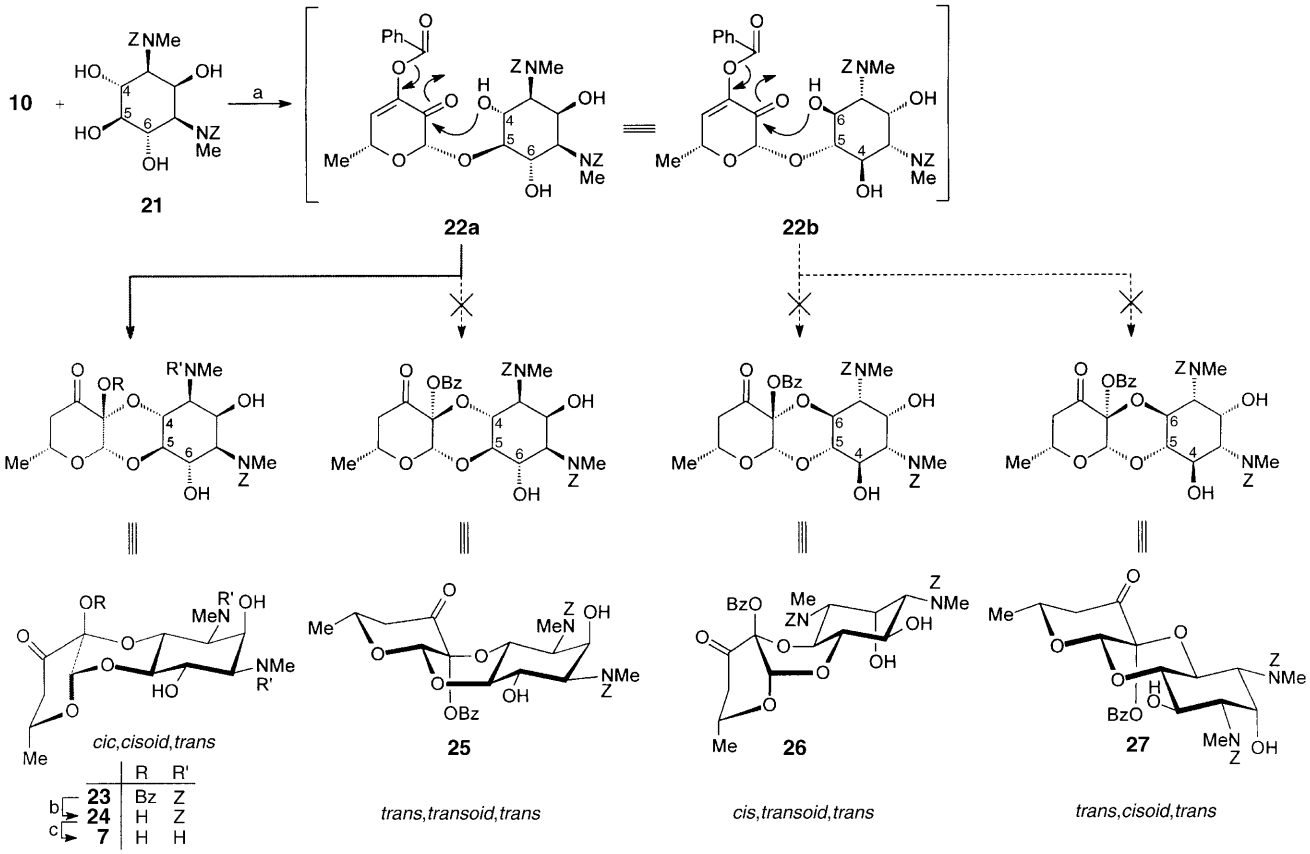


Figure 2. X-ray crystal structure of 3′-*epi*-gomphoside (**2**). The lactone ring is twofold disordered, as is the solvent molecule CH_2Cl_2 (omitted for clarity). The pyran, dioxane, and cyclohexane rings are all in near-perfect chair conformations. Dihedral angles [°] relevant to the dioxanoid attachment: C2-O2-C2′-C3′ −173.0, C3-O3-C1′-O5′ 64.7, O3-C1′-C2′-C3′ 172.7, O2′-C2′-C1′-O5′ 172.3.

diol **12** or in gomphogenine, seemingly due to the high oxygen substitution in its cyclohexane ring, and entailed sluggish glycosylations when promoted with Ag_2CO_3. After substantial experimentation with various insoluble silver catalysts—the more-reactive soluble promoters such as silver triflate were excluded as they entail α selectivity—silver aluminosilicate[20] in THF/CH_2Cl_2 or in toluene was found to effect β-selective *O*-glycosylation of **21** with donor **10**[21] to give **23** as the major product in 51 % isolated yield after removal of 4-*O*- and 6-*O*-glycosylated analogues (ca. 5 % each) by preparative HPLC (Scheme 3). The integrity of **23**, the 2′-*O*-benzoyl derivative of *N*,*N*-bis-(benzyloxycarbonyl)spectinomycin in its *cis,cisoid,trans*-fused tricyclic framework, was confirmed from its spectral data, its ready de-*O*-benzoylation to the known Boc-protected **24**,[6b,22] as well as from its hydrogenolysis to spectinomycin (**7**), which was found to be identical to the natural product in all respects.

The regioselectivity and β selectivity of the glycosylation reaction are remarkable, whereas the stereocontrol exercised in the hemiketal folding of the glycosidulose intermediate is even more so as it leads from a compound that contains two stereogenic centers to a product that contains nine! As a result of the thermodynamics derived from two anomeric effects and the propensity to form the sterically most favorable linear-fused tricycle, the glycosidulose C=O group in **22** is attacked with high and exclusive preference by the 4*R*-OH group from the axial (lower) face of the pyran ring to elaborate **23**, with the oxygen of the pyranoid ring and the ketalic OBz group positioned in the favorable *trans*-diaxial conformation, as well as chair conformations of the three rings. In contrast, the alternate possibilities—attack of 4*R*-OH from the β (equatorial) face (**22a**→**25**) or of 6*S*-OH in the two conceivable steric modes (**22b**→**26** or **27**)—invariably leads



Scheme 3. Unique stereocontrol in the intramolecular hemiketal folding of glycosidulose intermediate **22** towards the *cis*,*cisoid*,*trans*-fused framework of spectinomycin. Reagents and conditions: a) Ag aluminosilicate (1.2 equiv), toluene, 80 °C, 3 h, 51 %; b) K_2CO_3, MeOH, 25 °C, 10 min, 89 %; c) H_2, 5 % Pd/C, *i*PrOH, 25 °C, 12 h, 90 %. Z = benzyloxycarbonyl.

to thermodynamically less stable products either because the central dioxane ring is forced into a boat conformation (**25** and **26**) or as unfavorable dipolar interactions are operative (**25**, **27**). The ease with which the glycosidulose intermediate spontaneously "folds" into the natural *cis,cisoid,trans* geometry may even be taken as evidence for such a process to be operative in non-enzyme-mediated fashion in the biosynthesis of spectinomycin from D-glucose,[23] with an unprotected form of glycosidulose **22** conceivably being the decisive intermediate.

In summary, the chemistry detailed herein defines a concise and general method for the construction of natural products with a *cis,cisoid,trans*-interconnected pyran-dioxane-cyclohexane framework and has enabled the first syntheses of cardiac glycosides with ring A annulated sugars and an alternate synthesis of the antibiotic spectinomycin. A key feature of the methodology is the monoglycosylation of the respective aglycon diols with 4,6-dideoxy-2-ketohexosyl donors, promoted by an insoluble silver salt, which thereby substantially extends the utility of the "ulosyl donor approach".[7]

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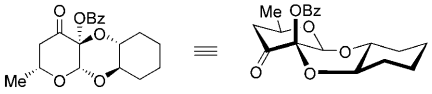

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