Linear Fused Pyran-Dioxane-Cyclohexane Tricycles: Synthesis of the Five Linkage Isomers and Ensuing Reactions[‡]

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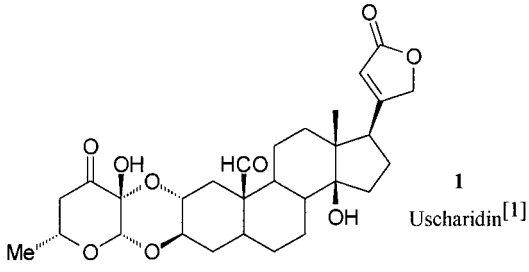
Keywords: Carbohydrates / Glycosylation / Ulosyl bromides / Trioxa-perhydroanthracenes

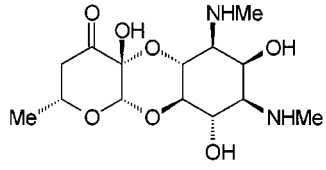
A systematic investigation of the mono-*O*-glycosylation of *meso*-, (*S*,*S*)-, and (*R*,*R*)-cyclohexane-1,2-diol with the D-glucose-derived 2-ketohexosyl bromide **5** is presented. In each instance, simple Königs–Knorr conditions not only elicit the exclusive formation of the respective β-2-ketoglycosides, but also effect their subsequent intramolecular hemiketalization to provide tricycles with a 1,5,10-trioxa-perhydroanthracene framework. The linkage geometries of the products – two each from the *meso*- (→ **10**, **12**) and (*S*,*S*)-diols (→ **16**, **17**), and only one from the (*R*,*R*)-isomer (→ **26**) – are determined in the hemiketalization step by an interplay of the anomeric effect and steric factors, favoring those isomers in which the pyran ring oxygen and the ketal-OH are in a *trans*-diaxial disposition. The most propitious case with respect to uniformity of reaction and yield (87%) turned out to the (*R*,*R*)-diol-derived *cis-cisoid-trans*-fused **26** as steric and stereoelectronic factors operate concertedly in the hemiketalization step. In each of these pyran-dioxane-cyclohexane tricycles, the acetalic hydroxyl group could be removed by BF_3-mediated reduction with triethylsilane, the ^1H NMR spectroscopic data of the respective products **14**, **15**, **18** and **28** being instrumental in assigning their linkage geometries. Slightly basic conditions (nBu_4NOAc in acetonitrile) elicit highly stereoselective rearrangements in the pyran ring, for example **16** → **23** and **26** → **30**; the tricycles have the structurally and stereochemically correct framework of a variety of cardenolides, in which a 2-ketosugar is doubly linked to a steroidal aglycon-diol. Thus, the methodology elaborated here shows high promise to provide a first, preparatively satisfactory access to this type of cardiac glycosides as well as to spectinomycin type antibiotics.

Introduction

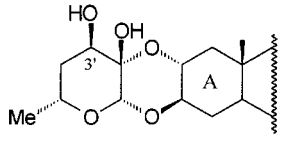
Various genera of the milkweed family (Asclepiadaceae) as well as *Streptomyces spectabilis* generate glycosides in which the sugar portion − a 4,6-dideoxy-D-hexos-2,3-diulose in **1** and **2** or its epimeric C-3 reduction products in **3** and **4**, respectively − is attached to the cyclohexanoid aglycon-diol by both a β-glycosidic bond and a hemiketal linkage, thereby engendering an additional 1,4-dioxane ring (Figure 1).



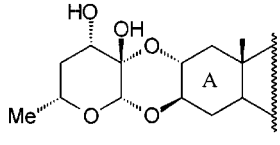
1 Uscharidin[1]



2 Spectinomycin[2]



3 Calactin, Calotoxin[1] Gomphoside, Afroside[3] Syriobioside[4]



4 Calotropin[1] 3'-Epigomphoside[3] Humistratin[5]

Figure 1. Naturally occurring glycosides in which the sugar portion is attached to a cyclohexanoid diol aglycon by a glycosidic and a hemiacetal bond thereby engendering a central dioxane ring

[‡] Sugar-Derived Building Blocks, 36. Part 35: See ref.[7]

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For linear fused pyran-dioxane-cyclohexane tricycles of this type − they de facto comprise the framework of 1,5,10-trioxa-perhydroanthracenes − five basic linkage geometries are possible, yet in the natural products only the *cis-cisoid-trans* form[6] is realized (Figure 2). This is obviously due to the fact that in the biosynthetic key steps, the 2-ketohexose (or a precursor thereof) is β-glycosidated by one of the cyclohexane hydroxy groups and then undergoes intramolecular hemiketalization with the other, which, due to operation of the anomeric effect, exclusively occurs from the upper face of the pyran ring to generate an axially disposed tertiary OH.

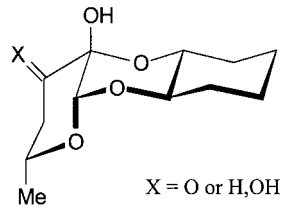
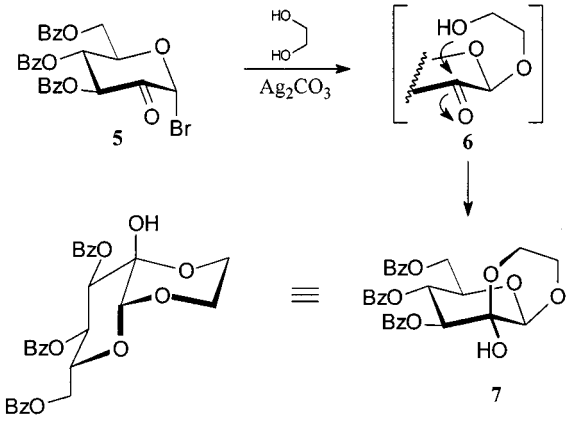


Figure 2. The linkage geometry in various cardiac glycosides and in the antibiotic spectinomycin is invariably *cis-cisoid-trans*[7]

Some recent model experiments on the silver carbonate promoted glycosidation of ulosyl bromide **5** with glycol[7] have shown that this step not only proceeds in a β-specific manner (**5** → **6**) but is spontaneously followed by an intramolecular hemiketalization from the upper face of the pyran ring (arrows in **6**) to give the *cis*-annulated trioxadecalin **7**, in which dipolar interactions between the pyranoid ring oxygen and the ketal-OH are minimized by their *trans*-diaxial disposition (Scheme 1).



Scheme 1

As the molecular geometry of **7** corresponds to that of the pyrano-dioxane portion of the natural products **1**−**4**, this "ulosyl donor approach"[8] offers the potential to provide a straightforward methodology towards their total syntheses, − especially, as none of the cardenolides has yet been synthesized and the strategies followed in two syntheses of spectinomycin[9] are unsuited for general application.[10] Before engaging in the total synthesis of the natural products by the "ulosyl donor approach", we opted to first explore its feasibility with (*S*,*S*)-, *meso*- and (*R*,*R*)-1,2-cyclohexanediol as the aglycons for gaining insight into the stereochemical subtleties of linear-fused pyran-dioxane-cyclohexane tricycles. The results are the subject of this report.

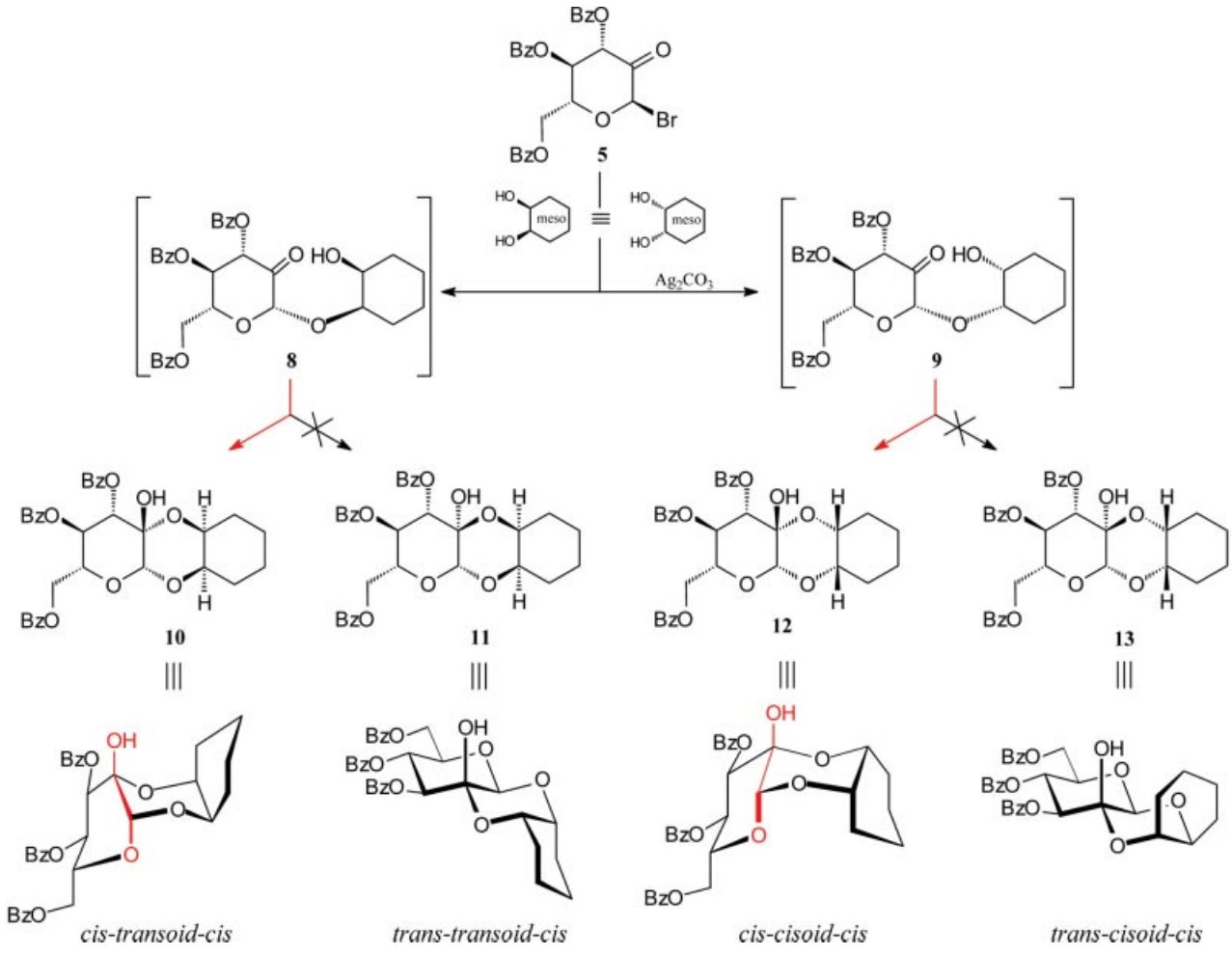
Results and Discussion

meso-1,2-Cyclohexanediol: Glycosidation and Hemiketalization

As the silvercarbonate-promoted glycosidation of ulosyl bromides proceeds in an essentially β-specific manner,[11] the reaction of the most readily accessible[11b] **5** with *meso*-1,2-cyclohexanediol is expected to generate the diastereomeric β-D-glycosiduloses **8** and **9** (Scheme 2), depending on which of the OH groups is glycosylated. Each of these glycosiduloses can then undergo cyclo-hemiketalization in two stereochemically different ways: addition of the hydroxyl onto the pyran carbonyl from the axial side (β-face) resulting in products **10** (from intermediate **8**) and **12** (from **9**), each having the hemiacetal-OH generated in *trans*-diaxial disposition to the pyranoid ring oxygen (Scheme 2); the alternate possibility comprises attack of the cyclohexane-OH to the pyranoid carbonyl from the equatorial side (α-face), i.e. **8** → **11** and **9** → **13**, both products carrying the hemiacetal-OH in a gauche disposition to either of the anomeric oxygens.

When performing the reaction, only two of the four theoretically possible β-linked pyran-dioxane-cyclohexane isomers are obtained, namely **10** and **12**, isolable in crystalline form, and in yields of 38 and 35%, respectively. The ^{1}H and ^{13}C NMR spectroscopic data clearly show them to be pyran-dioxane-cyclohexane-fused products with the pyranoid portion in a $^{4}C_{1}$ chair geometry based on the large couplings within the ring (Table 1). Their linkage geometries, however, could be established by detailed NOE studies not only on **10** and **12** but on the products obtained on reductive removal of the hemiacetal-OH through brief exposure to triethylsilane/BF_3-etherate in dichloromethane (Scheme 3), i.e. **14** (from **10**) and **15** (from **12**).

The linkage geometry assignments rest on the following pieces of evidence: (i) **10** and **14** show distinct NOEs between the axially oriented pyranoid protons 2-H, 4-H and 10a-H (Scheme 3, left), yet none between the dioxane ring hydrogen atoms; as the coupling constants $J_{4,4a}$ and $J_{4a,10a}$ are both small (Table 1), pyran and dioxane rings are *cis*-annulated, entailing the *cis-transoid-cis* fusion with all rings in chair conformations; (ii) **12** and **14** exhibit the same NOEs within the pyranoid ring, as expected (Scheme 3, right), yet in **15** an additional one between 4a-H and 5a-H clearly indicates their *cis-cisoid-cis* linkage geometries − a conclusion corroborated by the small $J_{4,4a}$ and $J_{4a,10a}$ couplings observed (Table 1). Additional validity for these assignments is derived from the fact that the alternative products **11** and **13**, respectively, should (upon triethylsilane-promoted removal of their acetalic OH) give $J_{4,4}$ and $J_{4a,10a}$ values in the range 9−10 Hz, which is clearly not the case.



Scheme 2

The essentially complete stereoselection observed in the reaction of ulosyl bromide **5** with *meso*-cyclohexanediol undoubtedly lies in the cyclo-hemiketalization step following the β-specific glycosidation: due to operation of the anomeric effect, the intermediate β-D-glycosiduloses **8** and **9** cyclize such that the cyclohexane-OH → carbonyl addition occurs from the β-face (axial side) of the pyran ring (Scheme 2) to exclusively generate the two products with the pyranoid ring oxygen and ketalic OH in a *trans*-diaxial disposition. That each of the products can have the three linear-fused six-membered rings in chair conformations with the outer rings *cis*-annulated to the central 1,4-dioxane is an additional stereochemical asset towards their formation.

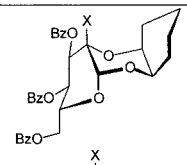
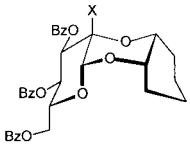
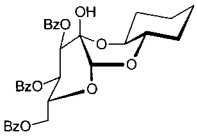
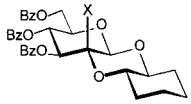
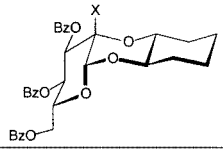
(*S*,*S*)-1,2-Cyclohexanediol

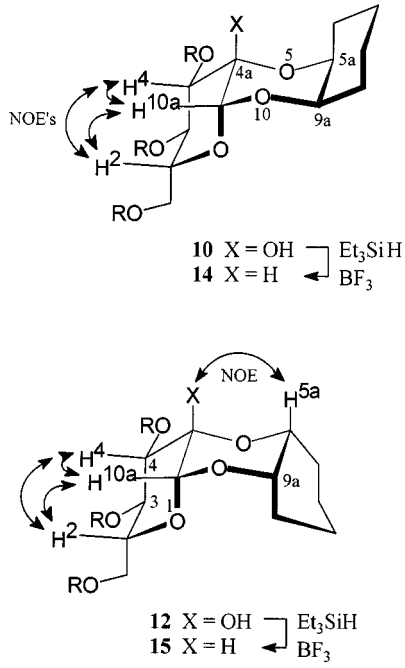
Ag_2CO_3-promoted mono-glycosylation of (*S*,*S*)-1,2-cyclohexanediol with ulosyl bromide **5** under standard conditions (CH_2Cl_2, 2 h, 40 °C) resulted in quantitative conversion into an approximate 1:1-mixture of two products (^{1}H NMR), of which one crystallized well and was isolated in 44% yield. On the basis of its X-ray structural analysis (Figure 3), itwas confirmed to be the *cis*-*transoid*-*trans*-interconnected tricycle **16** (Scheme 4). This linkage geometry necessitates the central dioxane ring to adopt a skew-boat conformation, its unfavorable steric interactions obviously being overruled by minimization of the dipolar interactions through the *trans*-diaxial disposition of the pyranoid ring oxygen and the ketalic OH group.

The second product, isolable from the mother liquor by chromatography, proved to be the *trans*-*cisoid*-*trans*-linked isomer **17**, obtained as a syrup only (33%). It appears to be the energetically more stable isomer of the two, since **16**, on standing in chloroform at ambient temperature, undergoes gradual equilibration to **17**. After three weeks, a 5:1 mixture had formed (^{1}H NMR), from which the major product **17** could be isolated in 65% yield.

The *all*-*trans*-annulation of the three rings in **17** followed − aside from being the only alternative to **16** − from a clear-cut NOE between 9a-H and 10a-H across the dioxane ring, and the large coupling constants ($J_{4,4a}$ and $J_{4a,10a}$) observed for the triethylsilane reduction product **18** (Table 1).

Table 1. Selected ^{1}H NMR spectroscopic data (300 MHz, $CDCl_3$) of the linear fused pyran-dioxane-cyclohexane isomers

Compound		chemical shifts (ppm)							coupling constants (Hz)			
		2-H	3-H	4-H	4a-H	5a-H	9a-H	10a-H	$J_{2,3}$	$J_{3,4}$	$J_{4,4a}$	$J_{4a,10a}$
	**10** X = OH	4.13	5.78	5.19	–	3.78	4.57	5.03	9.8	10.0	–	–
	14 X = H	4.05	5.97	5.36	4.52	3.76	4.52	5.04	10.1	10.0	3.4	0
	**12** X = OH	3.98	5.97	5.24	–	4.56	3.73	4.92	9.9	10.0	–	–
	15 X = H	3.92	6.08	5.40	4.27	3.82	3.65	5.00	10.1	10.1	3.4	1.2
	**16**	4.08	5.88	5.35	–	4.08	4.08	5.06	9.8	9.9	–	–
	**17** X = OH	4.23	5.90	5.68	–	3.76	3.52	4.82	9.7	9.7	–	–
	18 X = H	4.21	5.62	5.71	–	3.24	3.46	4.70	9.6	9.6	9.8	7.8
	**26** X = OH	4.11	5.88	5.31	–	3.90	3.90	4.94	10.0	10.0	–	–
	28 X = H	4.07	6.01	5.42	4.29	3.21	3.84	5.03	10.1	10.1	3.4	0.7



Scheme 3

That the *trans-cisoid-trans* fusion of the three rings in **17** is energetically more stable than the alternate *cis-transoid-trans* geometry in **16**, also finds its expression in the monoglycosylation of (*S*,*S*)-cyclohexanediol with the 3,4-unsaturated analog of **5**, the enolone bromide **19** (Scheme 5). Un-

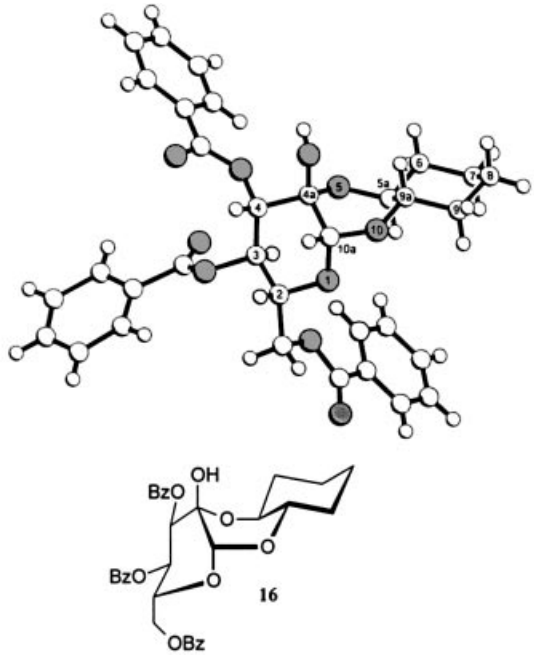
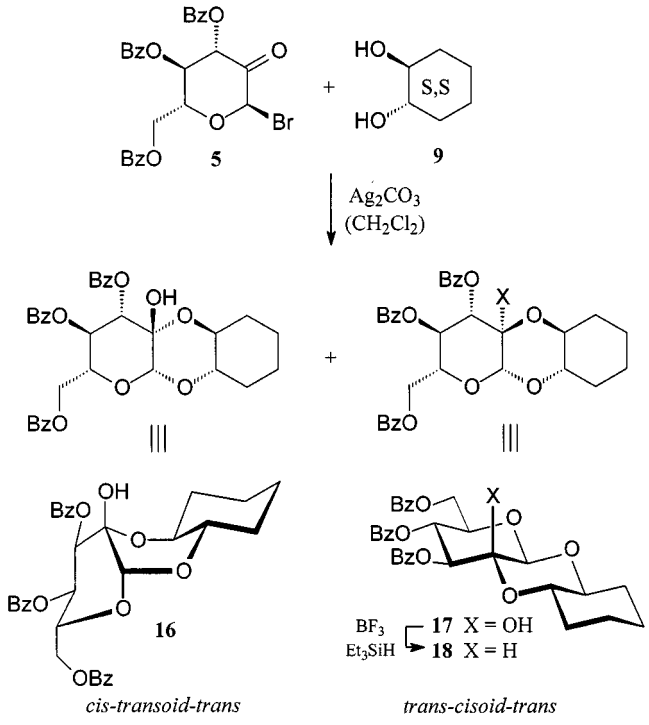


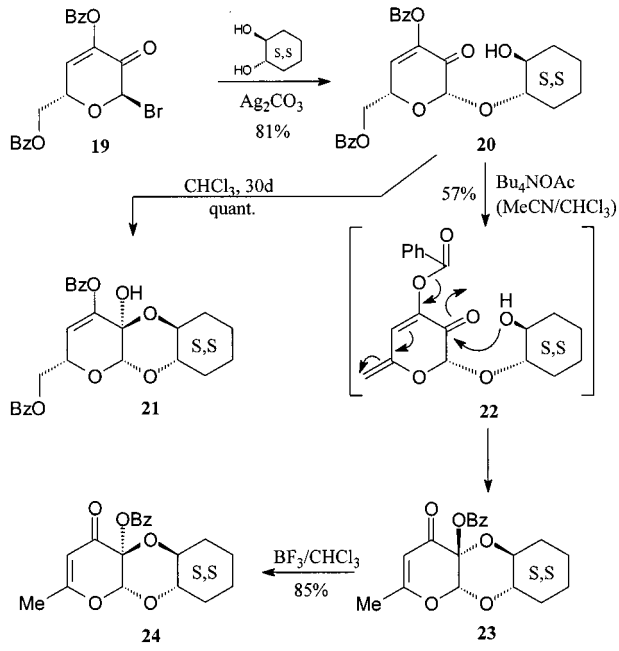
Figure 3. X-ray structure of the *cis-transoid-trans*-interconnected tricycle **16**[13] resulting from reaction of ulosyl bromide **5** with (*S*,*S*)-1,2-cyclohexanediol; the chair conformations of the pyran and cyclohexane rings are contrasted by the central dioxane in a distorted boat form; selected torsional angles: O1−C10a−C4a−O4a 176.6, O1−C10a−C4a−O5 −63.4, O5−C4a−C10a−O10 55.7, O5−C5a−C9a−O10 61.5



Scheme 4

der conditions analogous to those for the **5** → **16**/**17** conversion (Ag_2CO_3/CH_2Cl_2, 2 h, room temp.), however, only β-glycosidation took place, allowing the isolation of the enolone glycoside **20** in crystalline form (81%) with no other product detectable in the reaction mixture (TLC, ^1H NMR). Thus, the steric predispositions in **20** for an ensuing cyclo-hemiketalization are considerably impaired by the half-chair conformation of the dihydropyranone relative to the $^4C_1$ chair geometries of the pyran rings in the analogous uloside precursors, which spontaneously cyclized to **16** and **17**. Only on extended standing of **20** in chloroform solution, gradual cycloketalization to the *trans-cisoid-trans*-fused product **21** occurred; the conversion was essentially quantitative after 30 days.

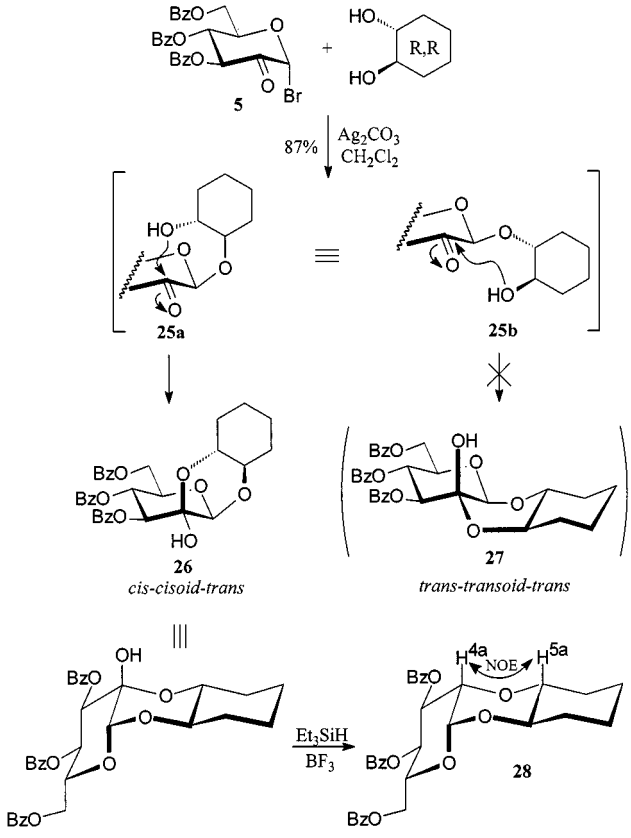
Cyclo-hemiketalization of enolone glycoside **20** could also be effected by stirring with *n*-butylammonium acetate in acetonitrile/chloroform (room temp., 15 h), leading to the *cis-transoid-trans*-fused **23**, isolable in crystalline form in 57% yield, by a remarkable series of successive reactions. In analogy to similar transformations in enolone esters of this type,[7,9a,15] this conversion is surmised to be initiated by base-induced elimination of benzoic acid from the terminal positions to the dienone intermediate **22**, followed by *cis*-hemiketalization and migration of the enolic benzoyl group to the acetalic oxygen (arrows in **22**), thereby liberating the C-4-carbonyl group with concomitant shifts of the two double bonds. The degree of stereocontrol exercised in intermediate **22** is remarkable, as attack of the cyclohexane-OH on the carbonyl group occurs − obviously steered by the anomeric effect − such that the acetalic OH and the pyranoid ring oxygen come into a *trans*-diaxial disposition, hence resulting in product **23**. The alternative product **24** − detectable only in trace amounts in the reaction mixture **20** → **23** by TLC − could be prepared from **23** in 85% yield by exposure to boron trifluoride in chloroform; the epimerization at the C-4a ring junction occurring either through BF_3-promoted removal and subsequent re-addition of benzoate, or by C-4a−O-5 dioxane ring opening and closure. This smooth epimerization also attests to the fact that the *all-trans*-fusion of the three rings in **24** (or **17**) is energetically more favored than the *cis-transoid-trans* arrangement in **23** (or **16**).



Scheme 5

(*R*,*R*)-1,2-Cyclohexanediol

Unlike the reactions of ulosyl bromide **5** with *meso*- and with (*S*,*S*)-cyclohexanediol, which gave two tricyclic products each due to opposing steric and polar effects in the intramolecular hemi-acetalization step, (*R*,*R*)-cyclohexanediol gave only one: Ag_2CO_3-promoted β-glycosidation generated the glycosidulose intermediate **25**, which exclusively cyclized by OH → C=O attack from the axial (upper) face of the pyran ring (arrows in **25a**) to elaborate the *cis-cisoid-trans*-fused product **26**, isolable in 87% yield (Scheme 6). Here, steric and electronic effects obviously augment each other since polar interactions are minimized by the *trans*-diaxial disposition of the pyran ring oxygen and acetalic OH − a consequence of the anomeric effect − and steric interactions are at a minimum due to chair conformations of the three rings. The alternative possibility, cycloketalization from the equatorial (lower) face of the pyran ring (arrows in **25b**), is not realized as this would lead to the *trans-transoid-trans* interconnected **27**, in which the central dioxane ring is forced into a sterically unfavorable boat conformation, and the ketalic OH is in an *a*,*e*-arrangement to the pyran as well as dioxane ring oxygen.



Scheme 6

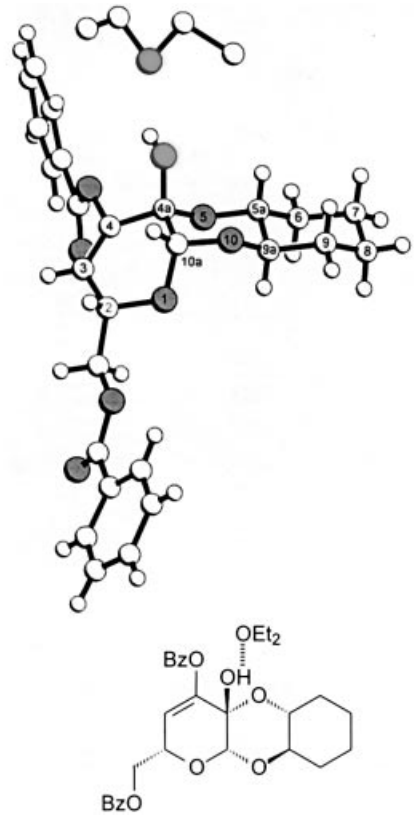
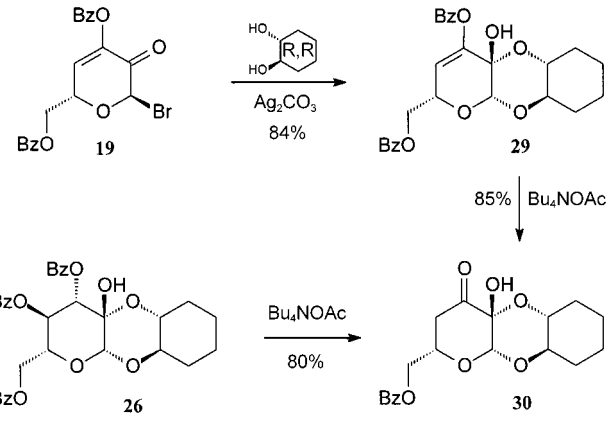


Figure 4. X-ray structure of the *cis-cisoid-trans*-fused **29** mono-etherate: due to the presence of a double bond, the pyran ring adopts the typical half-chair geometry versus nearly perfect chair conformations of the dioxane and cyclohexane parts. The acetalic 4a-OH and the pyranoid oxygen are in a *trans*-diaxial disposition (O1−C10a−C4a−O4a: 164.8°)[16]



Scheme 7

The pronouncedly uniform course of the conversion **5** → **26** was paralleled by the Ag_2CO_3-promoted reaction of enolone bromide **19** with (*R*,*R*)-cyclohexanediol: β-glycosidation and subsequent hemiacetal formation gave a single product, which could be isolated as well-formed prisms in a yield of 84%. It proved to be *cis-cisoid-trans*-fused **29** in the form of a mono-etherate with the ether oxygen uniquely hydrogen-bonded to the acetalic hydroxy group (Figure 4).

The enolic benzoyloxy group in **29**, expectedly sensitive towards mild basic conditions, was cleaved already by stirring with tetrabutylammonium acetate in moist acetonitrile (3 h, room temp.) to give the respective tricyclic ketone **30** (85%). Interestingly, the same product could be obtained from the ulosyl bromide-derived **26** on exposure to the same treatment, here hemiketal opening and elimination of benzoic acid leading to **29** and then **30**.

The *cis-cisoid-trans* linkage geometry of **26** could readily be delineated from its ^{1}H NMR spectroscopic data and those of the triethylsilane reduction product **28** (Table 1). The latter exhibits small, hence, *e,a*-couplings for the pyranoid ring hydrogens 4H/4a-H and 4a-H/10a-H versus large ones for the others, and shows a particularly relevant NOE across the dioxane ring (4a-H ⇄ 5-H). Further unequivocal proof is provided by an X-ray structural analysis of **29**, crystallizing as the mono-etherate (Figure 4): the junction of the pyran and dioxane rings is *cis*, with the tertiary hydroxy group and the pyranoid ring O atom in axial orientations relative to the dioxane ring. A characteristic feature of the structure is the location of the ether molecule: it is hydrogen bonded to the tertiary hydroxy group with a comparatively short distance between 4a-OH and OEt_2 (1.995 Å), thus providing a unique "horse-saddle" arrangement.

Conclusion

The trioxa-perhydroanthracene framework of **26**, **29** and **30** with the *cis-cisoid-trans* fusion of the three rings and their substituent pattern (most notably in **30**) has close structural analogies to the natural products **1**−**4** with their doubly attached sugar portions. The remarkable ease and efficiency with which these tricyclic products are elaborated from a simple 2-ketohexosyl donor renders this methodology highly promising for the syntheses of these natural products, inasmuch as this approach may be considered biomimetic.[17] These prospects call for the elaboration of ulosyl donors − or their 3,4-unsaturated analogs − from 6-deoxy-D-glucose, and their use for β-selective mono-*O*-glycosylation of steroidal diols or of an *N*-blocked actinamine, as the resulting β-D-glycosiduloses are expected to self-elaborate the stereoelectronically most favorable *cis-cisoid-trans*-annulated cyclo-hemiketal scaffold realized in the natural cardenolides and in spectinomycin. Efforts towards this end are to be reported.

Experimental Section

General Methods: Melting points were determined with a Bock hot-stage microscope and are uncorrected, optical rotations on a Perkin−Elmer 241 polarimeter at 20 °C with a cell of 1 dm path length; concentration (*c*) in g/100 mL and solvent are given in parentheses. ^{1}H and ^{13}C NMR spectra were recorded in the solvent indicated at 300 and 75.5 MHz, respectively. Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were acquired on Varian MAT 311 and MAT 212 spectrometers, microanalyses on a Perkin−Elmer 240 elemental analyzer. TLC was performed on precoated Merck plastic sheets (0.2 mm silica gel F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70−230 mesh) using the specified eluents.

(2*R*,3*R*,4*S*,4a*S*,5a*S*,9a*R*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*cis-transoid-cis* Isomer) (10): A mixture of *meso*-1,2-cyclohexanediol (1.16 g, 10 mmol), Ag_2CO_3 (2.76 g, 10 mmol), molecular sieves (4 Å, 3 g) and CH_2Cl_2 (150 mL) was stirred for 15 min, followed by addition of ulosyl bromide **5**[11b] (5.53 g, 10 mmol) and refluxing for 3 h. Filtration and removal of the solvent from the filtrate left a syrup consisting of an approximate 1:1 mixture (^{1}H NMR, TLC with toluene/EtOAc, 4:1) of **10** (R_f = 0.58) and **12** (0.37). Trituration with methanol resulted in crystallization of **10**, which was filtered with suction (mother liquor containing **12** vide infra) to give 2.21 g (38%) of **10**. M.p. 117−118 °C. $[\alpha]_D^{20}$ = −1.9 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H), 3.78 (m, 1 H), 4.13 (ddd, *J* = 2.9, 4.9, 10.0 Hz, 1 H), 4.57 (m, 1 H), 5.03 (s, 1 H), 5.19 (d, *J* = 9.8 Hz, 1 H), 5.30 (s, OH), 5.78 (dd, *J* = 9.8, 10.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.2, 24.5, 29.2, 30.0 (four *C*H_2), 63.4 (*C*H_2OBz), 65.9 (C-9a), 67.9 (C-2), 71.7 (C-3), 72.6 (C-5a), 81.1 (C-4), 90.5 (C-4a), 97.2 (C-10a), 165.3, 167.5, 168.2 (3 C_6H_5*C*O) ppm. MS (FD, 15 mA): *m*/*z* (%) = 588 (100) [M^+]. $C_{33}H_{32}O_{10}$ (588.6): calcd. C 67.33, H 5.48; found C 67.23, H 5.43.

(2*R*,3*R*,4*S*,4a*S*,5a*R*,9a*S*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*cis-cisoid-cis* Isomer) (12): The methanolic mother liquor remaining after isolation of **10** was evaporated to dryness, the syrup was applied to a silica gel column (2 × 15 cm) and eluted with toluene/EtOAc (4:1). The first fractions (R_f = 0.58, toluene/EtOAc, 4:1) contained residual **10**, those eluted next **12** (R_f = 0.37). Evaporation of the respective eluates in vacuo, dissolution of the syrup in a little methanol and standing for several days eventually resulted in crystallization of 2.10 g (35%) of **12** as colorless crystals. M.p. 140−142 °C. $[\alpha]_D^{20}$ = −8.3 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H), 3.73 (m, 1 H), 3.98 (ddd, *J* = 2.8, 3.1, 12.2 Hz, 1 H), 4.56 (m, 1 H), 4.92 (s, 1 H), 5.24 (d, *J* = 9.9 Hz, 1 H), 5.36 (s, OH), 5.97 (t, *J* = 9.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.3, 24.4, 29.5, 30.2 (4 *C*H_2), 62.0 (*C*H_2OBz), 65.6 (C-5a), 67.2 (C-2), 71.3 (C-3), 72.5 (C-9a), 79.6 (C-4), 92.5 (C-4a), 95.4 (C-10a), 165.1, 166.0, 168.6 (3 C_6H_5*C*O) ppm. MS (FD, 15 mA): *m*/*z* (%) = 588 (100) [M^+]. $C_{33}H_{32}O_{10}$ (588.6): calcd. C 67.33, H 5.48; found C 67.30, H 5.38.

(2*R*,3*R*,4*S*,4a*S*,5a*S*,9a*R*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (14): To a cooled (0 °C) solution of **10** (1.0 g, 1.7 mmol) in CH_2Cl_2 (80 mL) was added triethylsilane (5.4 mL, 34 mmol) and BF_3−diethyl ether (4.3 mL, 34 mmol) consecutively, and the mixture was stirred for 30 min at 0 °C and then allowed to come to room temperature. Dilution with CH_2Cl_2 (200 mL), washing with saturated $NaHCO_3$ solution (50 mL) and water (2 × 50 mL), drying (Na_2SO_4), and evaporation to dryness in vacuo gave 0.79 g (81%) of **14** as colorless crystals. M.p. 175−177 °C. $[\alpha]_D^{20}$ = −15.1 (*c* = 0.7, $CHCl_3$). ^{1}H NMR: Table 1. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.5, 23.0, 24.0, 29.8 (4 CH_2), 63.4 (*C*H_2OBz), 64.9 (C-9a), 66.0 (C-4a), 66.3 (C-3), 72.4 (C-2), 72.8 (C-5a), 73.1 (C-4), 94.2 (C-10a), 165.4, 166.0, 166.2 (3 C_6H_5*C*O) ppm. $C_{33}H_{32}O_{10}$ (572.6): calcd. C 69.22, H 5.63; found C 68.98, H 5.57.

(2*R*,3*R*,4*S*,4a*S*,5a*R*,9a*S*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (15): A mixture of **12** (500 mg, 0.85 mmol), Et_3SiH (2.7 mL, 17 mmol) and BF_3−diethyl ether (2.1 mL, 17 mmol) in CH_2Cl_2 (50 mL) was stirred at 0 °C for 1.5 h and processed as described for **10** → **14**. The syrup obtained was purified by fast elution from a silica gel column (2 × 15 cm) with toluene/EtOAc (8:1). In vacuo removal of the solvents from the respective eluates gave 219 mg (45%) of **15** as a colorless foam (R_f = 0.66, toluene/EtOAc, 4:1). $[\alpha]_D^{20}$ = −20.1 (*c* = 0.8, $CHCl_3$). ^{1}H NMR: Table 1. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.2, 24.7, 29.4, 31.0 (4 CH_2), 62.3 (*C*H_2OBz), 66.0 (C-3), 72.2 (C-2), 73.0 (C-4, C-9a), 74.3 (C-4a), 74.6 (C-5a), 92.8 (C-10a), 165.4, 166.1, 166.2 (3 C_6H_5-*C*O) ppm. MS (FD: *m*/*z* = 572 [M^+]. $C_{33}H_{32}O_{10}$ (572.6): calcd. C 69.22, H 5.63; found C 69.15, H 5.59.

(2*R*,3*R*,4*S*,4a*S*,5a*S*,9a*S*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*cis-transoid-trans* Isomer) (16): A slurry of (*S*,*S*)-1,2-cyclohexanediol (1.16 g, 10 mmol), Ag_2CO_3 (2.76 g, 10 mmol), molecular sieves (4 Å, 3 g) and ulosyl bromide **5** (5.53 g, 10 mmol) in CH_2Cl_2 (150 mL) was gently refluxed for 2 h (at approximately 40 °C) and then filtered through kieselguhr. The filtrate, on removal of the solvent in vacuo, gave a colorless foam, consisting of an approximate 1:1-mixture (^{1}H NMR) of the *cis-transoid-trans* (**16**) and the *all-trans* isomer **17** with nearly identical R_f values (0.55 in toluene/EtOAc, 8:1). Trituration with methanol resulted in crystallization of 2.59 g (44%) of **16** (for mother liquor containing **17**, see below). M.p. 154−156 °C. $[\alpha]_D^{20}$ = −43.7 (*c* = 1, $CHCl_3$). ^{1}H NMR

(300 Hz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H), 4.08 (m, 3 H), 4.44 (dd, J = 3.1, 12.1 Hz, 1 H), 4.66 (dd, J = 4.4, 12.1 Hz, 1 H), 4.70 (s, 1 H, OH), 5.06 (s, 1 H), 5.35 (d, J = 9.8 Hz, 1 H), 5.88 (dd, J = 9.8, 9.9 Hz, 1 H), 7.2−8.1 (m, 15 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 123.7, 23.8, 31.3, 31.6, 63.2, 68.5, 71.8, 74.9, 75.7, 78.6, 93.1, 97.4, 128−133, 165.3, 166.1, 167.8 ppm. MS (FD, 15 mA): m/z (%) = 588 (100) [M^+]. $C_{33}H_{32}O_{10}$ (588.59): calcd. C 67.33, H 5.48; found C 67.19, H 5.39.

Keeping a methanolic solution of **16** at room temperature overnight allowing slow evaporation gave good quality crystals suitable for an X-ray analysis, which showed two independent, yet nearly identical molecular forms. Only one is depicted in Figure 1.

Table 2. Crystal data and structure refinement for **16**

Empirical formula	$C_{33}H_{32}O_{10}$
Molecular mass	588.59
Temperature (K)	293(2)
Wavelength (Å)	1.54180
Crystal system, space group	orthorhombic, *P* 21 21 21
Unit cell dimensions	
a (Å)	45.21(2)
b (Å)	13.622(10)
c (Å)	9.820(10)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	6047(8)
Z	8
Calculated density (Mg·m^{-3})	1.293
Absorption coefficient (mm^{-1})	0.797
F(000)	2480
Crystal size (mm)	0.5 × 0.05 × 0.02
$\theta_{max.}$ (°) for data collection	4.38 to 59.57
Limiting indices	$0 \le k \le 14$, $0 \le l \le 8$
Reflections collected/unique	4129/4129 [*R*(int) = 0.0000]
Completeness to θ = 59.57	82.8%
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	4129/748/778
Goodness-of-fit on F^2	1.269
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0894, *wR*2 = 0.2494
R indices (all data)	*R*1 = 0.1036, *wR*2 = 0.2809
Absolute structure parameter	0(10)
Extinction coefficient	0.0033(6)
Largest diff. peak and hole (e·A^{-3})	0.391 and −0.430

(2*R*,3*R*,4*S*,4a*R*,5a*S*,9a*S*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*trans-cisoid-trans* Isomer) (17): The methanolic mother liquor remaining after isolation of **16** was evaporated to dryness in vacuo, and the syrupy residue, mainly consisting of **17**, was purified by rapid elution from a silica gel column (2 × 20 cm) with toluene/EtOAc (10:1). Removal of the solvents from the respective eluates gave 1.95 g (33%) of **17** as a colorless syrup. $[\alpha]_D^{20}$ = −20.5 (c = 1, $CHCl_3$). ^1H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H), 3.52 (m, 1 H), 3.76 (m, 1 H), 4.23 (ddd, J = 2.8, 4.9, 9.7 Hz, 1 H), 5.68 (d, J = 9.7 Hz, 1 H), 5.90 (t, J = 9.7 Hz, 1 H), 7.2−8.2 (m, 15 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.9, 24.0, 29.3, 29.6, 63.1, 69.4, 72.4, 73.9, 81.1, 92.1, 98.6, 128−133 (C_6H_5), 165.3, 166.2, 167.7 ppm. MS (FD, 15 mA): m/z = 588 [M^+]. $C_{33}H_{32}O_{10}$ (588.59): calcd. C 67.33, H 5.48; found C 67.28, H 5.40. The standing of **16** in chloroform at room temperature, as noticed with an NMR sample, induced gradual equilibration to the more stable *all-trans* isomer **17**, which after 20 days resulted in a 5:1 mixture of **17** and **16**. The major product (**17**) could be secured therefrom by elution from a silica gel column with toluene/EtOAc (10:1) as described above. Yield from 1.0 g of **16**: 650 mg (65%).

(2*R*,3*R*,4*S*,4a*R*,5a*S*,9a*S*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (18): To a solution of (500 mg, 0.85 mmol) of **17** in CH_2Cl_2 (50 mL) was added Et_3SiH (2.7 mL, 17 mmol) and boron trifluoride−diethyl ether (2.1 mL, 17 mmol), and the mixture was stirred for 1.5 h at 0 °C. Workup as described for **10** → **14** and trituration of the syrupy residue with methanol resulted in crystallization of 390 mg (80%) of **18**. M.p. 159−160 °C. $[\alpha]_D^{20}$ = −14.6 (c = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H, 4 CH_2), 3.24, 3.46 (m, 2 H, 5a-H, 9a-H), 3.60 (dd, $J_{4,4a}$ = 9.8, $J_{4a,10a}$ = 7.8 Hz, 4a-H), 4.21 (ddd, J_{2,CH_2} = 3.0, 5.2, $J_{2,3}$ = 9.6 Hz, 2-H), 4.47 and 4.61 (dd, 2 H, 2-CH_2), 4.70 (d, $J_{4a,10a}$ = 7.8 Hz, 10a-H), 5.62 (t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 3-H), 5.71 (dd, $J_{3,4}$ = 9.6, $J_{4,4a}$ = 9.8 Hz, 4-H), 7.2−8.1 (m, 15 H, 3 C_6H_5) ppm. $C_{33}H_{32}O_{10}$ (572.6): calcd. C 69.22, H 5.63; found C 69.15, H 5.51.

(2*R*,6*S*)-4-Benzoyloxy-2-(benzoyloxymethyl)-2-[(*S*,*S*)-(2-hydroxycyclohexyl)oxy]-2*H*-pyran-3(6*H*)-one (20): Silver carbonate (2.75 g, 10 mmol) and molecular sieves (4 Å, 2 g) were added to a solution of (*S*,*S*)-cyclohexanediol (1.16 g, 10 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 20 min, followed by dropwise addition of (2*R*,6*S*)-4-benzoyloxy-6-(benzoyloxymethyl)-6-bromo-2*H*-pyran-3(6*H*)-one[14] (**19**) (2.60 g, 6 mmol) in CH_2Cl_2 (20 mL) over 5 min. After stirring for another 15 min (TLC showed absence of starting material), the mixture was diluted with CH_2Cl_2 (150 mL) and washed with water (3 × 50 mL), dried (Na_2SO_4) and taken to dryness in vacuo. Treatment with ether resulted in crystallization. Recrystallization from ether gave unsaturated glycosiduloside **20** as colorless needles (3.78 g, 81%). M.p. 168−169 °C. $[\alpha]_D^{20}$ = −77.4 (c = 0.65, $CHCl_3$). ^1H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H, 4 CH_2), 3.20 (m, 1 H, OH), 3.31 (m, 2 H, 5a-H, 9a-H), 4.69, 4.73 (dd, 2 H, CH_2OBz), 5.10 (ddd, 1 H, 2-H), 5.41 (s, 1 H, 10a-H), 6.94 (d, 1 H, 3-H), 7.3−8.2 (m, 10 H, 2 C_6H_5) ppm; $J_{2,3}$ = 3.3, J_{3,CH_2} = 6.5, $J_{C,H_2OBzgem}$ = 11.2 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.9, 24.4 (C-7, C-8), 31.8, 32.2 (C-5, C-9), 66.3, 71.1, 74.2 (C-2, C-5a, C-9a, *C*H_2OBz), 100.2 (C-10a), 142.5 (C-4), 166.1, 166.2 (2 BzCO), 183.9 (C-4a) ppm. MS (FD, 15 mA): m/z (%) = 466 (10) [M^+], 320 (100). $C_{26}H_{26}O_8$ (466.5): calcd. C 66.94, H 5.62; found C 66.88, H 5.53.

(2*S*,4a*R*,5a*S*,9a*S*,10a*S*)-4-Benzoyloxy-2-(benzoyloxymethyl)-4a-hydroxy-octahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*trans-cisoid-trans* Isomer) (21): A solution of **20** (200 mg, 0.43 mmol) in $CHCl_3$ (15 mL) was kept at ambient temperature for 30 days, whereafter cycloketalization had occurred nearly quantitatively (^1H NMR). Removal of the solvent in vacuo and filtration of the crystalline residue with ether afforded 175 mg (87%) of **21**. M.p. 155−158 °C. $[\alpha]_D^{20}$ = −53 (c = 0.9, $CHCl_3$). ^1H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.2 (m, 8 H), 3.23 (m, 1 H, 5a-H), 3.34 (m, 1 H, 9a-H), 4.52 and 4.62 (dd, 2 H, CH_2OBz), 4.92 (ddd, 1 H, 2-H), 5.03 (d, 1 H, 10a-H), 6.05 (d, 1 H, 3-H), 6.14 (s, 1 H, OH) ppm; J_{2,CH_2} = 6.4 and 7.0, $J_{2,3}$ = 2.6, $J_{C,H_2OBzgem}$ = 10.8 Hz; NOE between signals at 3.34 and 5.03 (9a-H ⇄ 10a-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.7, 23.9 (C-7, C-8), 29.6, 29.7 (C-5, C-9), 67.1, 71.0, 76.0, 78.2 (C-2, C-5a, C-9a, *C*H_2OBz), 89.0 (C-4a), 96.6 (C-10a), 117.4 (C-3), 143.9 (C-4), 166.2, 167.3 (2 Bz*C*O) ppm. $C_{26}H_{26}O_8$ (466.47): calcd. C 66.94, H 5.62; found C 66.81, H 5.59.

(4a*S*,5a*S*,9a*S*,10a*R*)-4a-Benzoyloxy-2-methyl-octahydro-4*H*-pyrano-[2,3-*b*][1,4]benzodioxin-4-one (*cis-transoid-trans* Isomer) (23): Tetra-

n-butylammonium acetate (2.60 g, 8.6 mmol) was added to a solution of enolone glycoside **20** (2.0 g, 4.3 mmol) in a mixture of acetonitrile (200 mL) and $CHCl_3$ (50 mL), followed by stirring at ambient temperature for 15 h. Subsequent dilution with CH_2Cl_2 (300 mL), washing with water (3 × 200 mL), drying (Na_2SO_4), and evaporation to dryness in vacuo left a syrup, which was purified by elution from a silica gel column with toluene/EtOAc (4:1), to give 1.08 g (73%) of **23** as a colorless syrup. $[\alpha]_D^{20} = -103.6$ (c = 1, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 2.11 (d, J_{3,CH_3} = 0.7 Hz, 3 H, CH_3), 4.02, 4.13 (m, 2 H, 5a-H, 9a-H), 5.48 (dd, $J_{3,10a}$ = 0.4, J_{3,CH_3} = 0.7 Hz, 1 H, 3-H), 6.34 (d, $J_{3,10a}$ = 0.4 Hz, 1 H, 10a-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1 (*C*H$_3$), 23.8 (C-7, C-8), 30.9, 31.3 (C-5, C-9), 78.4 (C-5a, C-9a), 95.1 (C-4a), 97.0 (C-10a), 103.4 (C-3), 164.7 (Bz*C*O), 171.3 (C-2), 183.6 (C-4) ppm. MS (FD, 15 mA): m/z = 344 [M$^+$]. $C_{19}H_{20}O_6$ (344.4): calcd. C 66.27, H 5.85; found C 66.19, H 5.78.

Exposure of *cis-transoid-trans*-linked **16** to Bu_4NOAc treatment in MeCN/$CHCl_3$ as described above followed by analogous workup afforded **23** in 57% yield.

(4a*R*,5a*S*,9a*S*,10a*R*)-4a-Benzoyloxy-2-methyl-octahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (*trans-cisoid-trans* Isomer) (24): BF_3−diethyl ether (1.25 mL, 10 mmol) was added to a cooled (0 °C) CH_2Cl_2 solution of **23** (345 mg, 1 mmol, in 20 mL), and the mixture was stirred at 0 °C for 30 min followed by 1 h at ambient temperature, whereafter **23** (R_f = 0.60 in toluene/EtOAc, 4:1) had isomerized completely to **24** (R_f = 0.50). Dilution with CH_2Cl_2 (200 mL), successive washing with saturated $NaHCO_3$, solution (50 mL), and water (2 × 50 mL), followed by drying (Na_2SO_4), and evaporation to dryness in vacuo gave a syrup, which was purified by elution from a silica gel column (3 × 20 cm) with toluene/EtOAc (20:1). Removal of the solvents from the eluates left colorless crystals of **24** (295 mg, 85%). M.p. 132−134 °C. $[\alpha]_D^{20} = -185.3$ (c = 0.8, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 2.32 (d, $J_{3,Me}$ = 0.7 Hz, 3 H, CH_3), 4.04 (m, 2 H, 5a-H, 9a-H), 5.46 (d, $J_{3,Me}$ = 0.7 Hz, 1 H, 3-H), 6.04 (s, 1 H, 10a-H) ppm; NOE between signals at 4.04 and 6.04 (9a-H ⇄ 10a-H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.2 (*C*H$_3$), 24.0, 24.1 (C-7, C-8), 29.6 (C-5, C-9), 72.3, 76.1 (C-5a, C-9a), 88.5 (C-10a), 100.1 (C-4a), 104.1 (C-3), 164.9 (Bz*C*O), 195.1 (C-4) ppm. $C_{19}H_{20}O_6$ (344.4): calcd. C 66.27, H 5.85; found C 66.23, H 5.81.

(2*R*,3*R*,4*S*,4a*S*,5a*R*,9a*R*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (*cis-cisoid-trans* Isomer) (26): A mixture of (*R*,*R*)-1,2-cyclohexanediol (116 mg, 1 mmol), Ag_2CO_3 (276 mg, 1 mmol), freshly desiccated molecular sieves (4 Å) and CH_2Cl_2 (50 mL) was stirred for 15 min at ambient temperature, followed by addition of ulosyl bromide **5**[11b] (553 mg, 1 mmol) and gentle refluxing for 2 h with the exclusion of light and moisture. Subsequent filtration through kieselguhr and evaporation of the filtrate to dryness in vacuo afforded a syrup, which crystallized on trituration with methanol to give 510 mg (87%) of **26** as colorless crystals. M.p. 196−198 °C. $[\alpha]_D^{20} = -9.5$ (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1−2.0 (br. m, 8 H), 3.90 (m, 2 H), 4.11 (ddd, J = 2.9, 4.6, 10.0 Hz, 1 H), 4.47, 4.68 (dd, J = 2.9, 4.6 Hz, 2 H), 4.94 (s, 1 H), 5.10 (s, OH), 5.31 (d, J = 10.0 Hz, 1 H), 5.88 (t, J = 10.0 Hz, 1 H), 7.2−8.1 (m, 15 H, 3 C_6H_5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.1 (C-7, C-8), 29.5, 29.8 (C-6, C-9), 63.1 (*C*H$_2$OBz), 67.9 (C-3), 71.9 (C-2), 72.2, 72.6 (C-5a, C-9a), 78.6 (C-4), 91.9 (C-4a), 96.1 (C-10a), 165.3, 166.2, 168.2 (3 Bz*C*O) ppm. MS (FD, 15 mA): m/z (%) = 588 (100) [M$^+$]. $C_{33}H_{32}O_{10}$ (588.59): calcd. C 67.33, H 5.48; found C 67.23, H 5.43.

(2*R*,3*R*,4*S*,4a*S*,5a*R*,9a*R*,10a*R*)-3,4-Bis(benzoyloxy)-2-(benzoyloxymethyl)-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (28): To a cooled (0 °C) solution of **26** (1.0 g, 1.7 mmol) in CH_2Cl_2 (50 mL) was added triethylsilane (4.0 g, 34 mmol) and BF_3−diethyl ether (4.8 g, 34 mmol) consecutively. The mixture was stirred at 0 °C for 1 h and then allowed to come to room temperature. Workup as described for **10** → **14**, purification by elution from a short silica gel column with toluene/EtOAc (20:1) gave a syrupy residue, which crystallized from MeOH to give 0.67 g (79%) of **28**. M.p. 129−131 °C. $[\alpha]_D^{20} = -17.1$ (c = 0.8, $CHCl_3$). ^{1}H NMR: Table 1. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.0 (C-8, C-7), 29.7, 30.0 (C-6, C-9), 63.2 (*C*H$_2$OBz), 66.4 (C-3), 72.5 (C-2), 72.9 (C-5a, C-9a), 73.1 (C-4a), 79.9 (C-4), 93.8 (C-10a), 165.4, 166.0, 166.2 (3 Bz*C*O) ppm. $C_{33}H_{32}O_{10}$ (572.6): calcd. C 69.22, H 5.63; found C 69.20, H 5.59.

(2*S*,4a*S*,5a*R*,9a*R*,10a*S*)-4-Benzoyloxy-2-(benzoyloxymethyl)-4a-hydroxy-octahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin (29): Molecular sieves (4 Å, 2 g) and Ag_2CO_3 (2.76 g, 10 mmol) were added to a solution of (*R*,*R*)-1,2-cyclohexanediol (1.16 g, 10 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 20 min with the exclusion of moisture and light. A solution of bromo-enolone **19**[14] (2.60 g, 6 mmol) in CH_2Cl_2 (20 mL) was then added dropwise over 5 min. After stirring for another 15 min, TLC (*n*-hexane/acetone/$CHCl_3$, 4:3:3) indicated the absence of **19**; the mixture was filtered through kieselguhr, and the filtrate was diluted with CH_2Cl_2 (150 mL) followed by washing with water (3 × 50 mL), drying (Na_2SO_4), and evaporation to dryness in vacuo. The syrupy residue crystallized on trituration with ether to give 2.73 g (84%) of **29** as the mono-etherate. M.p. 78−80 °C. $[\alpha]_D^{20} = -7.3$ (c = 1, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.2 (m, 8 H), 3.65 (s, 1 H, OH), 3.87, 3.94 (m, 2 H, 5a-H, 9a-H), 4.52 (m, 2 H, CH_2OBz), 4.83 (ddd, 1 H, 2-H), 4.93 (s, 1 H, 10a-H), 5.97 (d, 1 H, 3-H), 7.3−8.2 (m, 10 H, 2 C_6H_5) ppm; $J_{2,3}$ = 1.7, J_{2,CH_2} = 5.1 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.2, 24.3 (C-7, C-8), 29.8, 29.9 (C-6, C-9), 65.9 (*C*H$_2$OBz), 70.5 (C-2), 72.3 (C-5a, C-9a), 88.2 (C-4a), 95.3 (C-10a), 115.5 (C-3), 128−134 (2 *C*$_6$H$_5$), 145.3 (C-4), 164.6, 166.4 (2 C_6H_5*C*O) ppm. MS (FD, 5 mA): m/z (%) = 466 (100) [M$^+$]. $C_{26}H_{26}O_8$·Et_2O (540.66): calcd. C 66.65, H 6.71; found C 66.70, H 6.69.

Recrystallization from diethyl ether afforded well-formed needles suitable for X-ray structural analysis,[16] which proved the presence of an ether molecule.

(2*S*,4a*R*,5a*R*,9a*R*,10a*S*)-2-(Benzoyloxymethyl)-4a-hydroxy-decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (30): To a solution of **29**·Et_2O (270 mg, 0.5 mmol) in acetonitrile (10 mL) was added tetrabutylammonium acetate (450 mg, 1.5 mmol) and 5 drops of water, and the mixture was stirred for 3 h at ambient temperature. Dilution with CH_2Cl_2 (100 mL), washing with water (3 × 50 mL), drying (Na_2SO_4), and evaporation to dryness in vacuo left 155 mg (85%) of **30** as a chromatographically uniform syrup (R_f = 0.12, toluene/EtOAc, 8:1). $[\alpha]_D^{20} = -5.6$ (c = 1, $CHCl_3$). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 1.1−2.0 (m, 8 H, 4 CH_2), 2.59, 3.08 (dd, 2 H, 3-H$_2$), 3.91 (m, 1 H, 2-H), 4.05 (m, 2 H, 5a-H, 9a-H), 4.43 (s, 1 H, OH), 4.51, 4.55 (dd, 2 H, CH_2OBz), 4.73 (s, 1 H, 10a-H), 7.2−8.1 (m, 5 H, C_6H_5) ppm; $J_{3,3}$ = 14.2, $J_{2,3}$ = 2.0 and 12.3, J_{2,CH_2} = 4.6 and 5.0, $J_{C,H_2OBzgem}$ = 11.7 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.1, 24.2 (C-7, C-8), 29.7, 29.8 (C-6, C-9), 39.9 (C-3), 65.7 (*C*H$_2$OBz), 69.3 (C-2), 72.5, 72.8 (C-5a, C-9a), 91.3 (C-4a), 97.3 (C-10a), 128−133 (C_6H_5), 166.1 (Bz−*C*O), 201.2 (C-4) ppm. MS (FD, 15 mA): m/z (%) = 362 (100) [M$^+$]. $C_{19}H_{22}O_7$ (362.4): calcd. C 62.97, H 6.12; found C 62.88, H 6.17.

Exposure of ulosyl bromide-derived **26** (295 mg, 0.5 mmol) to Bu_4NOAc in moist acetonitrile (as described above) afforded 145 mg (80%) of **30**.

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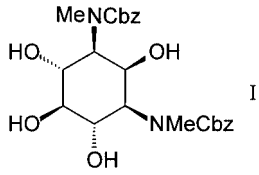

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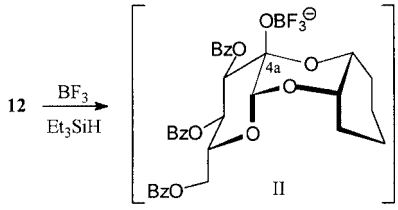
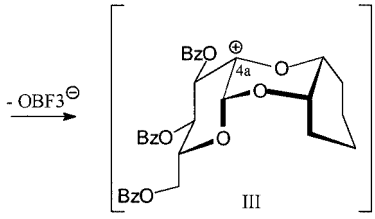
[12] The BF_3-promoted reductive deoxygenation of **10** and **12** cannot occur through S_N2-type hydride attack on the tertiary carbon (C-4a) of the OH-activated intermediate (e.g. II), as the rigidity of the tricyclic ring system precludes inversion at C-4a. The reaction must thus proceed through a carboxonium ion (e.g. III), which adds hydride, e.g. II → III → **15**. Accordingly, the OH groups in **10** and **12** are replaced by hydrogen with retention of configuration, thereby verifying the linkage geometry conclusions drawn from NOE effects of the *cis-transoid-cis* (**10/14**) and the *cis-cisoid-cis* pairs **12/15** (Scheme 3).





[13] CCDC-224773 contains the supplementary crystallographic data for **16**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[17] An attractive possibility for the biosynthesis of cardenolides of type **1, 3** and **4**, as well as of spectinomycin (**2**), implies monoglycosylation of the steroidal diol aglycon or of actinamine, oxidation of the respective 6-deoxy-glycosides to the glycosiduloses which − in nonenzyme-mediated fashion − undergo intramolecular hemiketalization.

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