Synthesis of the E-D-C Trisaccharide Unit of Aureolic Acid Cytostatics

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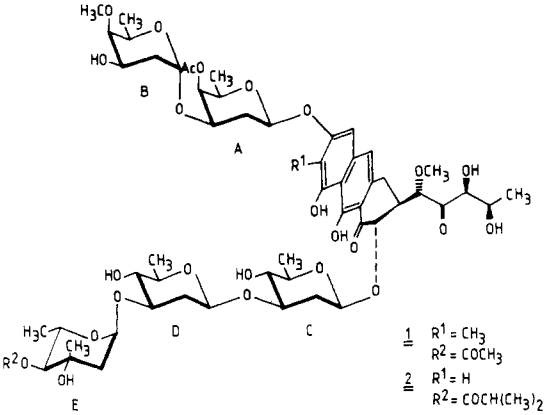
Various transformations of the disaccharide glycosides **3** and **4** led to a series of partially blocked as well as reduced disaccharide derivatives **5–15**. In *N*-iodosuccinimide glycosylations of L-olivomycal **21** some of these (**5**, **6**, **13**) showed an extremely low reactivity which surprisingly led to self-condensation of **21** and formation of disaccharide glycal **22** with an unusual interglycosidic linkage at the branching point. By a model reaction between the arabino monosaccharide compound **23** and the glycal **21** the E–D disaccharide subunit could be obtained regioselectively. A corresponding *N*-iodosuccinimide glycosylation of **21** with the D–C disaccharide precursor **14** was accomplished with exclusive formation of an α,1→3 interglycosidic linkage. This gave the E–D–C trisaccharide unit **26**, which represents a derivative of the "lower" oligosaccharide chain of the aureolic acid cytostatics.

Introduction

The cytostatic agents of the aureolic acid group chromomycin A_3 (**1**), olivomycin A (**2**), and mithramycin are the best known compounds among those which presently enjoy selected clinical application.[2] Although they exhibit a cytostatic activity which considerably exceeds that of the more popular and widely used anthracycline glycosides,[3] their clinical application is hampered by severe toxic side effects.[4] Earlier structural studies revealed the gross structure, the monosaccharide composition and, after more extensive studies, the structure of the similar aglycones chromomycinone in **1** and olivin in **2**, respectively.[5-7] More recently work in our laboratory has proved the complete structure with respect to the sugar sequence as well as to direction and type of their interglycosidic linkages.[8-10]

Recent interest in compounds of the aureolic acid group has focused on various attempts toward the synthesis of the aglycones.[11] We have so far been engaged mainly in designing approaches to syntheses of the complex oligodeoxy disaccharides B–A of **1** and **2**[12] and the different B–A component in mithramycin,[10] devised methods giving access to the E–D[13] as well as the D–C subunits of the trisaccharide chain,[14] the latter being present in every member of the aureolic acid group, and were able to introduce a new stereoselective approach for the synthesis of β,1→3 interglycosidically linked D–C tetradeoxy disaccharide precursors.[15,16] The present contribution describes further progress along these lines and the first successful synthesis of the oligodeoxy trisaccharide unit E–D–C of chromomycin A_3 (**1**) and olivomycin A (**2**).



Results and Discussion

We have previously reported preparation of the crystalline methyl (**3**)[15] and benzyl glycosides (**4**)[16] of D–C disaccharide derivatives. These syntheses were specifically designed to remove the formyloxy group blocking the 3′-position selectively. The disaccharide components prepared in this way were expected to be ideally suited for condensation with a methyl-branched glycal (cf. for this approach ref 13) following our *N*-iodosuccinimide procedure.[17] This, however, required further deblocking and modification reactions and led to a series of disaccharide glycosides (A: methyl and B: benzyl) of the olivosyl-β,1→3-olivose types (D–C) **5–15** (Scheme I).

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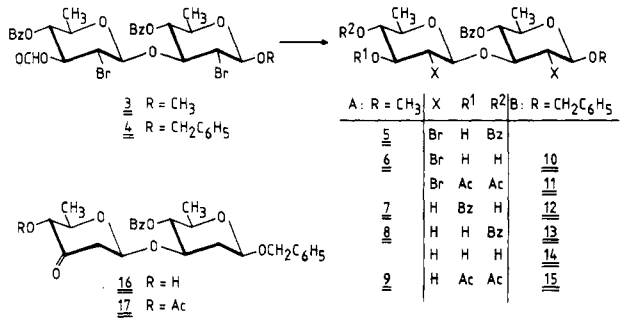
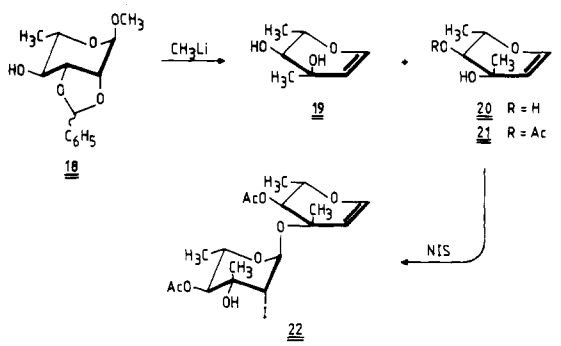
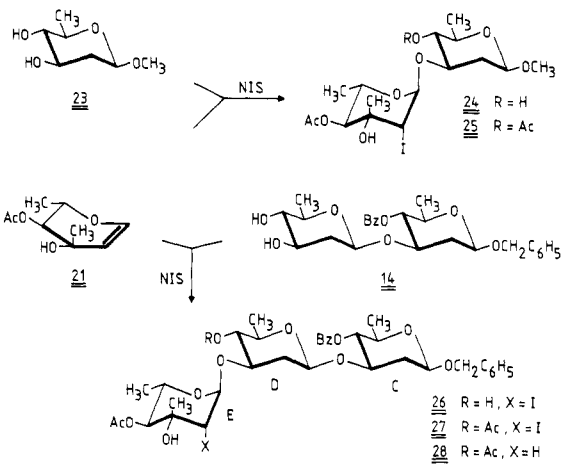
Scheme I



Scheme II



Scheme III



In fact, the formyloxy group of **3** could be removed under mild acidic conditions and gave the crystalline derivative **5** in high yield. In basic medium (sodium carbonate in methanol) only the two ester groups in the nonreducing moiety were split and **6** was obtained as a sirup. By hydrogenolytic cleavage of the 2,2′-dibromo substituents in the presence of triethylamine a benzoate migration occurs. Thus the 4,3′- (**7**) and the 4,4′-dibenzoates (**8**) were obtained in the ratio 5:3. Further removal of the benzoates in the nonreducing moiety (for unknown reasons these Zemplén type conditions did not transesterify the 4-benzoate group) and subsequent peracetylation led to the fully acyl-blocked olivosyl-β,1→3-olivoside component **9**.[15]

Transformations of the benzyl glycoside **4** are quite attractive with respect to the projected attachment of a trisaccharide unit to olivin or modified derivatives thereof. Basic cleavage of the ester functions in the nonreducing ring led in high yield to **10**, which was characterized as the diacetate **11**. Its hydrogenolysis under the same conditions described above, i.e., with triethylamine to neutralize HBr and to partially poison the catalyst in order to prevent the cleavage of the anomeric benzyloxy function, gave a mixture of the regioisomeric dibenzoates **12** and **13** which were separated by preparative TLC and characterized by NMR (**12**, H-3′ δ 4.65 ddd and **13**, H-4′ δ 4.63 dd).

Hydrogenolytic cleavage of the 2,2′-dibromide **10** gave two compounds in the ratio 5:2. The former was the expected olivosyl-β,1→3-olivoside (**14**) which was further substantiated by the NMR spectrum of its peracylated derivative **15**.[16] NMR analysis of the second compound surprisingly revealed the formation of a 3′-keto derivative **16**, the expected H-3′ signal was missing in the nonreducing sugar ring of **16** and its peracetate **17** and the signals of H-4′, H-2a′, and H-2e′ displayed simpler patterns with coupling constants $J_{1',2a'} = 9.2$, $J_{1',2e'} = 2.5$, $J_{2a',2e'} = 14.0$, $J_{2a'4'} = 1.5$, $J_{4',5'} = 9.7$, $J_{4',OH\text{-}4'} = 3.4$ Hz; also the ^{13}C NMR of **16** showed a carbonyl resonance at δ 205.5. The unexpected formation of **16** in a hydrogenolysis can be rationalized as a result of a triethylamine-induced isomerization of **10** followed by elimination of hydrogen bromide to an intermediate enol which subsequently leads to the 3′-ulose.

As was demonstrated previously[13] the methyl-branched saccharide unit E (L-olivomycose) can be attached via the glycal **21**[18] through use of our *N*-iodosuccinimide procedure.[17] Recently Jung and Klemer[19] have described an advantageous preparation for L-olivomycal **20** and its epimer L-mycaral **19** by treatment of methyl 2,3-*O*-alkylidene-L-rhamnoside **18** with methyllithium (Scheme II) which we adopted in our work.

Reaction of the 4-acetate **21**[18] and the 3′-hydroxy disaccharide **5** in acetonitrile in the presence of *N*-iodosuccinimide under anhydrous conditions for 3 weeks at room temperature gave no trisaccharide, although there was only minor decomposition of the very labile methyl-branched glycal (cf. ref 18). No condensation was observed when the conditions were varied or when the 3′,4′-deblocked dibromo disaccharide **6** or the reduced 3′-hydroxy derivative **13** was employed as aglycone unit. However, extensive preparative TLC led in moderate yield to a new dissacharide component **22** (Scheme II) which contained in part the elements expected for the wanted compound. In the NMR spectrum chemical shifts and coupling constants (doublets for H-1′ at 5.62, H-2′ at 4.23, and H-5′ at 5.18, $J_{1',2'} = 3.5$, $J_{4',5'} = 7.6$ Hz) were only compatible with a 3-branched nonreducing moiety in the α-L-manno configuration, that is a precursor of an L-olivomycose unit. The doublet of the anomeric enol ether proton at δ 6.06 gave evidence of the intact glycal structure (L-olivomycal moiety) at the reducing position. Thus there had occurred a quite surprising disaccharide condensation via a tertiary allylic hydroxy group which, to the best of our knowledge, is without precedent in the synthesis of oligosaccharides. This fascinating side reaction also shed some light on the extremely low nucleophilicity of the secondary 3′-hydroxy group in the compounds **5**, **6**, and **13**.

The condensation could have been induced by the neighboring 2′-bromo substituent or the 4′-benzoate ester group or both. It was of interest therefore to check this assumption with a more easily accessible monosaccharide model which should contain the essential features of the D unit and was choosen to be methyl 2,6-dideoxy-β-D-*arabino*-hexopyranoside (**23**).[5b,20] As it turned out there was no problem in the *N*-iodosuccinimide condensation between 4-*O*-acetyl-L-olivomycal (**21**) and **23**, which gave

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the E–D disaccharide model **24** in good yield. Reacetylation to **25** resulted in a most noticable completely regiospecific glycosylation at position 3 of the sugar aglycon moiety (Scheme III).

On the basis of these results a comparable reaction using the 3′,4′-unblocked olivosyl-β,1→3-olivoside **14** with **21** in the presence of *N*-iodosuccinimide could be expected. In fact, there was obtained the trisaccharide derivative **26** regiospecifically in 62% yield. In the ^{1}H NMR spectrum of its peracetate **27** the H-4′ triplet at δ 4.61 ($J_{3',4'}$ = 9.3, $J_{4',5'}$ = 9.5 Hz) clearly proved that the glycal **21** was linked to position 3 of the preterminal saccharide unit D. Chemical shifts and coupling constants of the terminal unit in **27** (doublets for H-1″ at 5.16, H-2″ at 4.03, and H-5″ at 5.26, $J_{1'',2''}$ = 2.9, $J_{4'',5''}$ = 9.1 Hz) were in accord with an α-L-manno configuration as previously deduced in the case of compound **22**. Hydrogenolytic cleavage of the 2″-iodo substituent completed the synthesis of the partly blocked trisaccharide **28** with the natural sequence as well as configurations and regiodirected interglycosidic linkages of the E–D–C trisaccharide unit in aureolic acids.

Experimental Section

Reactions were monitored by TLC on silica gel foils FG_{254} (Merck) and spots were detected by ultraviolet light or by spraying with concentrated sulfuric acid and subsequent heating to 150 °C. Preparative thin-layer chromatography was done on silica gel plates (0.25 mm, 0.5 mm, and 2.0 mm with and without concentrating zone, Merck). For column chromatography silica gel 60 (Merck) was used. Melting points were determined with a Leitz melting point microscope or a Mettler FP-61 apparatus and are uncorrected.

Methyl 4-*O*-Benzoyl-3-*O*-(4-*O*-benzoyl-2-bromo-2,6-dideoxy-β-D-glucopyranosyl)-2-bromo-2,6-dideoxy-β-D-glucopyranoside (5). The disaccharide derivative **3** (90 mg, 0.13 mmol) dissolved in dry methanol (5 mL) was treated with a drop of concentrated hydrochloric acid and left at room temperature for 7 h. The mixture was evaporated, and the residue taken up in dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$), concentrated, and crystallized from ether/*n*-hexane to give 77 mg (89%) of colorless crystals: mp 191 °C; $[\alpha]^{20}_D$ +4.2 (*c* 0.58, dichloromethane); ^{1}H NMR (270 MHz, C_6D_6) δ 4.24 (d, H-1), 4.06 (dd, H-2), 4-15 (dd ~ t, H-3), 5.09 (dd ~ t, H-4), 3.32 (dq, H-5), 1.15 (d, CH_3-6), 5.15 (d, H-1′), 3.48 (dd, H-2′), 3.63 (dd ~ t, H-3′), 4.69 (dd ~ t, H-4′), 3.14 (dq, H-5′), 0.74 (d, CH_3-6′), 3.26 (s, OCH_3), 7.02–7.20 and 8.00–8.25 (m, 10H, aryl-H), $J_{1,2}$ = 8.4, $J_{2,3}$ = 9.8, $J_{3,4}$ = 9.6, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.6, $J_{1',2'}$ = 8.3, $J_{2',3'}$ = 10.2, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.6, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{27}H_{30}Br_2O_9$ (658.3): C, 49.26; H, 4.59. Found: C, 49.25; H, 4.62.

Methyl 4-*O*-Benzoyl-2-bromo-3-*O*-(2-bromo-2,6-dideoxy-β-D-glucopyranosyl)-2,6-dideoxy-β-D-glucopyranoside (6). Compound **3** (50 mg, 0.073 mmol) dissolved in dry methanol (7 mL) was treated with dry sodium carbonate (10 mg) and stirred for 4 h at room temperature. Following filtration the mixture was concentrated in vacuo and subjected to column chromatography (ethyl acetate/*n*-hexane 2:1) to give 22 mg (55%) as a colorless syrup: $[\alpha]^{20}_D$ +33.9, (*c* 0.71, ethyl acetate); ^{1}H NMR (270 MHz, C_6D_6) δ 4.20 (d, H-1), 4.07 (dd, H-2), 4.11 (dd ~ t, H-3), 5.07 (dd ~ t, H-4), 3.27 (dq, H-5), 1.11 (d, CH_3-6), 5.09 (d, H-1′), 3.50 (dd, H-2′), 3.28 (mc, H-3′), 2.64 (dd ~ t, H-4′), 3.04 (dq, H-5′), 0.88 (d, CH_3-6′), 3.31 (s, OCH_3), 7.02–7.19 and 8.00–8.25 (m, 5 H, aryl-H), $J_{1,2}$ = 8.6, $J_{2,3}$ = 9.7, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.2, $J_{5,6}$ = 6.2, $J_{1',2'}$ = 8.3, $J_{2',3'}$ = 10.3, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 9.8, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{20}H_{26}Br_2O_8$ (554.2): C, 44.34; H, 4.73. Found: C, 44.82; H, 4.72.

Methyl 4-*O*-Benzoyl-3-*O*-(3- and -4-*O*-Benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside 4,3′-Dibenzoate (7) and 4,4′-Dibenzoate (8). The dibromo disaccharide **3** (10.5 mg, 0.015 mmol) in dry dimethoxyethane (5 mL) was treated with 2 drops of triethylamine and 10% palladium on charcoal (20 mg) and hydrogenolyzed for 24 h at room temperature. After filtration over Celite and concentration the isomers were separated by PTLC (double development, ethyl acetate/*n*-hexane 1:4) to give 4.1 mg (54%) of **7** [$[\alpha]^{20}_D$ −9.3 (*c* 0.21, CH_2Cl_2)] and 2.4 mg (32%) of **8** [$[\alpha]^{20}_D$ −23.3 (*c* 0.12, CH_2Cl_2)] both as colorless syrups.

7: ^{1}H NMR (270 MHz, C_6D_6) δ 4.11 (d, H-1), 1.87 (ddd, H-2a), 2.27 (ddd, H-2e), 4.11 (ddd, H-3), 5.28 (dd ~ t, H-4), 3.38 (mc, H-5), 1.32 (d, CH_3-6), 4.34 (dd, H-1′), 1.39 (mc, H-2a′), 1.87 (mc, H-2e′), 4.65 (ddd, H-3′), 3.38 (mc, H-4′), 3.38 (mc, H-5′), 1.14 (d, CH_3-6′), 3.31 (s, OCH_3), 7.41–8.05 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.8, $J_{1,2e}$ = 2.1, $J_{2a,2e}$ = 12.0, $J_{2a,3}$ = 12.0, $J_{2e,3}$ = 5.5, $J_{3,4}$ = 9.6, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.3, $J_{1',2a'}$ = 7.6, $J_{1',2e'}$ = 3.4, $J_{2a',3'}$ = 10.4, $J_{2e',3'}$ = 4.8, $J_{3',4'}$ = 9.2, $J_{5',6'}$ = 6.2 Hz.

8: ^{1}H NMR (270 MHz, C_6D_6) δ 4.14 (dd, H-1), 1.83 (ddd, H-2a), 2.23 (ddd, H-2e), 4.04 (ddd, H-3), 5.26 (dd ~ t, H-4), 3.36 (dq, H-5), 1.31 (d, CH_3-6), 4.29 (dd, H-1′), 1.41 (ddd, H-2a′), 1.92 (ddd, H-2e′), 3.47 (ddd, H-3′), 4.64 (dd ~ t, H-4′), 3.16 (dq, H-5′), 1.09 (d, CH_3-6′), 3.33 (s, OCH_3), 7.38–8.02 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.5, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.4, $J_{2a,3}$ = 11.9, $J_{2e,3}$ = 5.2, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.1, $J_{1',2a'}$ = 9.5, $J_{1',2e'}$ = 2.0, $J_{2a',2e'}$ = 12.6, $J_{2a',3'}$ = 11.8, $J_{2e',3'}$ = 5.2, $J_{3',4'}$ = 9.1, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{27}H_{32}O_9$ (500.5): C, 64.79; H, 6.44. Found for **7**: C, 64.52; H, 6.35. Found for **8**: C, 64.40; H, 6.66.

Benzyl 4-*O*-Benzoyl-2-bromo-3-*O*-(2-bromo-2,6-dideoxy-β-D-glucopyranosyl)-2,6-dideoxy-β-D-glucopyranoside (10). A solution of **4** (200 mg, 0.26 mmol) in dry methanol (30 mL) was stirred with sodium methylate (10 mg) for 5 h at room temperature. After treatment with ion exchange resin (Amberlite IR 120, H^+) the eluent was concentrated, taken up in ethyl acetate, filtered, and again concentrated to give 157 mg (96%) as a colorless syrup: $[\alpha]^{20}_D$ +1.9 (*c* 1.19, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.41 (d, H-1), 4.12 (dd, H-2), 4.03 (dd ~ t, H-3), 5.05 (dd ~ t, H-4), 3.21 (dq, H-5), 1.26 (d, CH_3-6), 5.10 (d, H-1′), 3.59 (dd, H-2′), 3.39 (dd ~ t, H-3′), 2.75 (dd ~ t, H-4′), 3.10 (dq, H-5′), 1.12 (d, CH_3-6′), 4.50 and 4.76 (AB pattern, J = 12.2 Hz, PhCH_2), 7.02–7.47 and 8.10–8.17 (m, 10 H, aryl-H), $J_{1,2}$ = 8.6, $J_{2,3}$ = 9.8, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.1, $J_{1',2'}$ = 8.2, $J_{2',3'}$ = 10.3, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 9.8, $J_{5',6'}$ = 6.1 Hz.

Anal. Calcd for $C_{26}H_{30}Br_2O_8$ (630.3): C, 49.54; H, 4.80. Found: C, 49.01; H, 4.52.

Benzyl 3-*O*-(3,4-Di-*O*-acetyl-2-bromo-2,6-dideoxy-β-D-glucopyranosyl)-4-*O*-benzoyl-2-bromo-2,6-dideoxy-β-D-glucopyranoside (11). Disaccharide **10** (10 mg, 0.016 mmol) in dry pyridine (2 mL) was left with acetic anhydride (1 mL) for 24 h at 5 °C. After quenching with solid sodium bicarbonate (10 mg) the mixture was codestilled with toluene several times and then filtered over silica gel. Crystallization from ether/*n*-hexane gave 11 mg (97%) of colorless crystals: mp 187 °C; $[\alpha]^{20}_D$ +6.6 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 4.38 (d, H-1), 4.06 (dd, H-2), 3.99 (dd, H-3), 5.07 (dd ~ t, H-4), 3.21 (dq, H-5), 1.12 (d, CH_3-6), 5.05 (d, H-1′), 3.59 (dd, H-2′), 5.37 (dd, H-3′), 4.46 (dd ~ t, H-4′), 2.97 (dq, H-5′), 0.62 (d, CH_3-6′), 4.49 and 4.75 (AB pattern, J = 11.8 Hz, PhCH_2), 1.58 and 1.67 (each s, OAc), 7.14, 7.38 and 8.12 (each mc, 10 H, aryl-H), $J_{1,2}$ = 8.5, $J_{2,3}$ = 9.8, $J_{3,4}$ = 8.8, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.2, $J_{1',2'}$ = 8.5, $J_{2',3'}$ = 10.7, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.7, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{30}H_{34}Br_2O_{10}$ (714.4): C, 50.44; H, 4.80. Found: C, 50.68; H, 4.85.

Benzyl 4-*O*-Benzoyl-3-*O*-(3- and -4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside 4,3′-Dibenzoate (12) and 4,4′-Dibenzoate (13). Compound **4** (20.4 mg, 0.027 mmol) was similarly hydrogenolyzed, worked up, and separated as described for the isomers **7** and **8**. Yields: 5.7 mg (37%) of **12** [$[\alpha]^{20}_D$ −21.8 (*c* 0.29, CH_2Cl_2)] and 3.5 mg (23%) of **13** [$[\alpha]^{20}_D$ −40.0 (*c* 0.18, CH_2Cl_2)], both colorless syrups.

12: ^{1}H NMR (270 MHz, C_6D_6) δ 4.35 (dd, H-1), 2.01 (mc, 3 H, H-2a, H-2a′, H-2e′), 2.28 (ddd, H-2e), 4.04 (ddd, H-3), 5.29 (dd ~ t, H-4), 3.36 (mc, 3 H, H-5, H-4′, H-5′), 1.34 (d, CH_3-6), 4.30 (dd, H-1′), 4.65 (ddd, H-3′), 1.12 (d, CH_3-6′), 4.48 and 4.88 (AB pattern, J = 12.0 Hz, PhCH_2), 7.36–8.09 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.7, $J_{1,2e}$ = 1.8, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 11.9, $J_{2e,3}$ = 5.2, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 7.6, $J_{1',2e'}$ = 3.4, $J_{2a',3'}$ = 10.4, $J_{2e',3'}$ = 4.7, $J_{3',4'}$ = 9.3, $J_{5',6'}$ = 6.2 Hz.

13: ^{1}H NMR (270 MHz, C_6D_6) δ 4.25 (dd, H-1), 2.01 (ddd, H-2a), 2.24 (ddd, H-2e), 3.97 (ddd, H-3), 5.28 (dd, t, H-4), 3.34 (dq, H-5), 1.33 (d, CH_3-6), 4.34 (dd, H-1′), 1.42 (ddd, H-2a′), 2.02 (ddd, H-2e′), 3.50 (ddd, H-3′), 4.63 (dd ~ t, H-4′), 3.14 (dq, H-5′),

1.07 (d, CH_3-6′), 4.49 and 4.87 (AB pattern, J = 12 Hz, PhCH_2), 7.42–8.01 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.6, $J_{1,2e}$ = 2.1, $J_{2a,2e}$ = 12.6, $J_{2a,3}$ = 11.8, $J_{2e,3}$ = 5.0, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.8, $J_{1',2e'}$ = 1.9, $J_{2a',2e'}$ = 12.8, $J_{2a',3'}$ = 12.2, $J_{2e',3'}$ = 5.2, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.3, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{33}H_{36}O_9$ (576.6): C, 68.74; H, 6.29. Found for **12**: C, 68.58; H, 6.35. Found for **13**: C, 68.98; H, 6.41.

Benzyl 4-*O*-Benzoyl-3-*O*-(2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside (14) and Benzyl 4-*O*-Benzoyl-3-*O*-(2,6-dideoxy-β-D-*erythro*-hexopyranos-3-ulosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside (16). Disaccharide **10** (70 mg, 0.11 mmol) in ethyl acetate (10 mL) was hydrogenolyzed with 10% palladium/charcoal (20 mg) for 24 h at room temperature in the presence of 6 drops of triethylamine. After filtration the mixture was concentrated and purified by column chromatography (ethyl acetate/*n*-hexane 1:1). The first fraction was the ulose **16**: 11 mg (21%), $[\alpha]^{20}_D$ −39.3 (*c* 0.8, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.25 (dd, H-1), 1.75 (ddd, H-2a), 2.01 (ddd, H-2e), 3.76 (ddd, H-3), 5.20 (dd ~ t, H-4), 3.25 (dq, H-5), 1.28 (d, CH_3-6), 4.08 (dd, H-1′), 2.09 (ddd, H-2a′), 2.35 (dd, H-2e′), 3.10 (ddd, H-4′), 2.84 (dq, H-5′), 1.20 (d, CH_3-6′), 4.42 and 4.83 (AB pattern, J = 12.0 Hz, PhCH_2), 3.33 (d, OH-4′), 7.13, 7.31 and 8.20 (each mc, 10 H, aryl-H), $J_{1,2a}$ = 9.6, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.3, $J_{2a,3}$ = 11.9, $J_{2e,3}$ = 5.3, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.2, $J_{1',2e'}$ = 2.5, $J_{2a',2e'}$ = 14.0, $J_{2a',4'}$ = 1.5, $J_{4',5'}$ = 9.7, $J_{4',OH-4'}$ = 3.4, $J_{5',6'}$ = 5.9 Hz; ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 97.9, 99.0 (C-1 and C-1′), 36.8 (C-2), 46.7 (C-2′), 205.5 (C-3′), 17.9, 18.6 (C-6 and C-6′), 70.4–79.1 (C-3, C-4, C-5, C-4′, C-5′, PhCH_2).

Anal. Calcd for $C_{26}H_{30}O_8$ (470.5): C, 66.37; H, 6.43. Found: C, 66.42; H, 6.37.

The second fraction was the disaccharide **14**: 24.2 mg (46%); $[\alpha]^{20}_D$ −72.9 (*c* 1.21, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.35 (dd, H-1), 1.91 (ddd, H-2a), 2.26 (ddd, H-2e), 3.95 (ddd, H-3), 5.21 (dd ~ t, H-4), 3.32 (dq, H-5), 1.30 (d, CH_3-6), 4.32 (dd, H-1′), 1.52 (ddd, H-2a′), 1.98 (ddd, H-2e′), 3.39 (ddd, H-3′), 2.81 (dd ~ t, H-4′), 3.10 (dq, H-5′), 1.20 (d, CH_3-6′), 4.49 and 4.87 (AB pattern, J = 12.0 Hz, PhCH_2), 3.10 and 3.39 (each mc, OH-3′ and OH-4′), 7.16, 7.34 and 8.22 (each mc, 10 H, aryl-H), $J_{1,2a}$ = 9.8, $J_{1,2e}$ = 1.8, $J_{2a,2e}$ = 12.4, $J_{2a,3}$ = 12.0, $J_{2e,3}$ = 5.2, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 10.0, $J_{1',2e'}$ = 1.7, $J_{2a',2e'}$ = 12.3, $J_{2a',3'}$ = 12.4, $J_{2e',3'}$ = 4.8, $J_{3',4'}$ = 8.8, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 6.2 Hz.

Anal. Calcd for $C_{26}H_{32}O_8$ (472.5): C, 66.09; H, 6.83. Found: C, 65.87; H, 6.98.

Benzyl 3-*O*-(4-*O*-Acetyl-2,6-dideoxy-β-D-*erythro*-hexopyranos-3-ulosyl)-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (17). A solution of **16** (11 mg, 0.023 mmol) in dry pyridine (2 mL) was left with acetic anhydride (1 mL) for 24 h at +5 °C and then several times codestilled with toluene, and the residue was dissolved in ethyl acetate and filtered over silica gel to give 10.5 mg (89%) of colorless syrup: $[\alpha]^{20}_D$ −25.4 (*c* 1.0, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.28 (dd, H-1), 1.63 (ddd, H-2a), 2.01 (ddd, H-2e), 3.75 (ddd, H-3), 5.19 (dd ~ t, H-4), 3.29 (dq, H-5), 1.30 (d, CH_3-6), 4.19 (dd, H-1′), 2.13 (ddd, H-2a′), 2.37 (dd, H-2e′), 4.63 (dd ~ d, H-4′), 3.27 (dq, H-5′), 1.01 (d, CH_3-6′), 4.49 and 4.84 (AB pattern, J = 12.1 Hz, PhCH_2), 1.75 (s, OAc), 7.13, 7.30 and 8.20 (each mc, 10 H, aryl-H), $J_{1,2a}$ = 9.6, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 11.9, $J_{2e,3}$ = 5.3, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.2, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.3, $J_{1',2e'}$ = 2.5, $J_{2a',2e'}$ = 14.2, $J_{2a',4'}$ = 0.7, $J_{4',5'}$ = 10.0, $J_{5',6'}$ = 6.0 Hz.

Anal. Calcd for $C_{28}H_{32}O_9$ (512.6): C, 65.61; H, 6.29. Found: C, 65.32; H, 6.01.

Attempted *N*-Iodosuccinimide Condensation of Disaccharide 5 with Glycal 21 and Isolation of 4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl)-1,5-anhydro-2,6-dideoxy-3-*C*-methyl-L-*arabino*-hex-1-enitol (22). A mixture of disaccharide **5** (26 mg, 0.04 mmol) and *N*-iodosuccinimide (55 mg, 0.24 mmol) in dry acetonitrile (2.5 mL) was stirred together with activated molecular sieves (3Å) for 1 h at room temperature under a nitrogen cover. Subsequently a solution of glycal **21** (30 mg, 0.16 mmol) in dry acetonitrile (0.5 mL) was added under nitrogen and the resulting mixture stirred for 4 days at room temperature in the dark. Following addition of dichloromethane (30 mL) and filtration over Celite the mixture was washed with aqueous sodium thiosulfate and water, dried ($MgSO_4$), and purified by PTLC (ethyl acetate/toluene 1:4) to give 10 mg (12% with respect to **21**) of colorless syrup: $[\alpha]^{20}_D$ +4.2 (*c* 0.36, CH_2Cl_2)); ^{1}H NMR (400 MHz, C_6D_6) δ 6.06 (d, H-1), 4.54 (d, H-2), 5.53 (d, H-4), 3.67 (dq, H-5), 1.41 (d, CH_3-6), 1.27 (s, CH_3-3), 5.62 (d, H-1′), 4.23 (d, H-2′), 5.18 (d, H-4′), 4.03 (dq, H-5′), 1.14 (d, CH_3-6′), 1.44 (s, CH_3-3′), 2.31 (s, OH-3′), 1.56 and 1.61 (each s, each 3 H, OAc), $J_{1,2}$ = 6.0, $J_{4,5}$ = 10.3, $J_{5,6}$ = 6.2, $J_{1',2'}$ = 3.5, $J_{4',5'}$ = 7.6, $J_{5',6'}$ = 6.3 Hz.

Anal. Calcd for $C_{18}H_{27}IO_8$ (498.3): C, 43.39; H, 5.46. Found: C, 42.98; H, 5.55.

In substituting **5** with the disaccharide derivatives **6** or **13** similar reactions with NIS and the glycal **21** led to isolation of the disaccharide glycal **22**, which could be also obtained if the addition of any nucleophile was omitted.

Methyl 3-*O*-(4-*O*-Acetyl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside (24). To the monosaccharide **23** (11 mg, 0.068 mmol) dissolved in dry acetonitrile (3 mL) was added *N*-iodosuccinimide (50 mg, 0.22 mmol) and activated molecular sieves (3 Å). After stirring for 1 h the mixture was cooled to −40 °C and then treated under nitrogen with a solution of the glycal **21** (25 mg, 0.13 mmol). Following gradual warming to room temperature the mixture was stirred another 2 days, then diluted with dichloromethane (30 mL), filtered over Celite, washed with aqueous sodium thiosulfate and water, dried ($MgSO_4$), and concentrated to give 23 mg (71%) of condensation product: ^{1}H NMR (400 MHz, C_6D_6) δ 4.05 (dd, H-1), 1.80 (ddd, H-2a), 2.17 (ddd, H-2e), 3.16 (mc, 3H, H-3,-4,-5), 1.48 (d, CH_3-6), 5.11 (d, H-1′), 4.19 (d, H-2′), 4.95 (d, H-4′), 3.91 (dq, H-5′), 1.22 (d, CH_3-6′), 1.20 (s, CH_3-3′), 3.34 (s, OCH_3), 3.77 (s, OH-4), 1.59 (s, OAc-4′), $J_{1,2a}$ = 9.7, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.0, $J_{2a,3}$ = 12.3, $J_{2e,3}$ = 4.5, $J_{5,6}$ = 5.6, $J_{1',2'}$ = 5.8, $J_{4',5'}$ = 5.2, $J_{5',6'}$ = 6.5 Hz.

Methyl 4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranoside (25). The above material **24** (23 mg, 0.05 mmol) dissolved in dry pyridine (2 mL) was treated with acetic anhydride (1 mL) for 5 h at room temperature. Repeated coevaporation with toluene and filtration over silica gel gave after concentration in vacuo 20 mg (78%) of colorless syrup: $[\alpha]^{20}_D$ +104.5 (*c* 0.8, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 3.81 (dd, H-1), 3.35 (ddd, H-3), 4.80 (dd ~ t, H-4), 3.04 (dq, H-5), 1.19 (d, CH_3-6), 5.27 (d, H-1′), 3.81 (d, H-2′), 5.75 (d, H-4′), 3.97 (dq, H-5′), 1.25 (d, CH_3-6′), 1.49 (s, CH_3-3′), 3.27 (s, OCH_3), 1.65 and 1.75 (each s, each 3 H, OAc), $J_{1,2a}$ = 9.6, $J_{1,2e}$ = 1.9, $J_{2a,3}$ = 11.6, $J_{2e,3}$ = 5.3, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.3, $J_{1',2'}$ = 1.9, $J_{4',5'}$ = 10.0, $J_{5',6'}$ = 6.3 Hz.

Anal. Calcd for $C_{18}H_{29}IO_9$ (516.3): C, 41.87; H, 5.66. Found: C, 42.21; H, 5.17.

Benzyl 3-*O*-[3-*O*-(4-*O*-Acetyl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl)-2,6-dideoxy-β-D-*arabino*-hexopyranosyl]-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (26). A solution of disaccharide **14** (24 mg, 0.05 mmol) and *N*-iodosuccinimide (25 mg, 0.11 mmol) in dry acetonitrile (2 mL) was stirred with activated molecular sieves (3 Å) for 1 h. Under nitrogen glycal **21** (15 mg, 0.08 mmol) dissolved in dry ether (0.5 mL) was added at room temperature and the mixture stirred another 3 days. Workup as described above (for **24**) with subsequent filtration over silica gel gave 26 mg (62%) of a colorless syrup: $[\alpha]^{20}_D$ −44.5 (*c* 1.3, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.37 (dd, H-1), 1.96 (dd, H-2a), 2.31 (ddd, H-2e), 4.03 (ddd, H-3), 5.30 (dd ~ t, H-4), 3.35 (dq, H-5), 1.34 (d, CH_3-6), 4.25 (dd, H-1′), 3.46 (ddd, H-3′), 2.88 (dd ~ t, H-4′), 3.11 (dq, H-5′), 1.10 (d, CH_3-6′), 5.10 (d, H-1″), 4.10 (d, H-2″), 4.97 (d, H-4″), 3.85 (dq, H-5″), 1.33 (d, CH_3-6″), 1.49 (s, CH_3-3″), 4.51 and 4.89 (AB pattern, J = 11.8 Hz, PhCH_2), 1.59 (s, OAc-4″), 7.05–7.36 and 8.22–8.28 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.8, $J_{1,2e}$ = 1.8, $J_{2a,2e}$ = 12.4, $J_{2a,3}$ = 11.8, $J_{2e,3}$ = 5.3, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.7, $J_{1',2e'}$ = 1.9, $J_{2a',3'}$ = 12.2, $J_{2e',3'}$ = 4.8, $J_{3',4'}$ = 8.8, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 6.0, $J_{1'',2''}$ = 5.3, $J_{4'',5''}$ = 5.5, $J_{5'',6''}$ = 6.2 Hz.

Anal. Calcd for $C_{35}H_{45}IO_{12}$ (784.6): C, 53.58; H, 5.78. Found: C, 53.84; H, 5.32.

Benzyl 3-*O*-[3-*O*-(4-*O*-Acetyl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl)-4-*O*-acetyl-2,6-dideoxy-α-D-*arabino*-hexopyranosyl]-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (27). The trisaccharide **26** (9 mg, 11.0 μmol) dissolved in dry pyridine (2 mL) was treated with acetic anhydride (1 mL) for 24 h at +5 °C. After addition of sodium hydrogen carbonate (10 mg), repeated coevaporation with toluene, filtration, and concentration PTLC (ethyl acetate/*n*-hexane 2:3)

gave 5.3 mg (58%) of colorless syrup: $[\alpha]^{20}_D$ -90.2 (c 0.27, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.37 (dd, H-1), 1.94 (ddd, H-2a), 2.27 (ddd, H-2e), 3.96 (ddd, H-3), 5.30 (dd, t, H-4), 3.36 (dq, H-5), 1.35 (d, CH_3-6), 4.08 (dd, H-1'), 1.59 (ddd, H-2a'), 1.68 (ddd, H-2e'), 3.39 (ddd, H-3'), 4.61 (dd ~ t, H-4'), 2.97 (dq, H-5'), 1.04 (d, CH_3-6'), 5.16 (d, H-1''), 4.03 (d, H-2''), 5.26 (d, H-4''), 3.85 (dq, H-5''), 1.21 (d, CH_3-6''), 1.44 (s, CH_3-3''), 4.51 and 4.90 (AB pattern, J = 11.9, PhCH_2), 1.60 and 1.71 (each s, each 3 H, OAc), 7.04-7.39 and 8.20-8.28 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.6, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 12.0, $J_{2e,3}$ = 5.3, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.7, $J_{1'2e'}$ = 1.9, $J_{2a',2e'}$ = 12.3, $J_{2a',3'}$ = 11.8, $J_{2e',3'}$ = 5.3, $J_{3',4'}$ = 9.3, $J_{4',5'}$ = 9.5, $J_{5',6'}$ = 6.2, $J_{1'',2''}$ = 1.9, $J_{4'',5''}$ = 9.1, $J_{5'',6''}$ = 6.3 Hz.

Anal. Calcd. for $C_{37}H_{47}IO_{13}$ (826.7): C, 53.76; H, 5.73. Found: C, 53.46; H, 5.98.

Benzyl 3-*O*-[3-*O*-(4-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-4-*O*-acetyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl]-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (28). Compound **27** (3.1 mg, 3.7 μmol) in ethyl acetate (2 mL) was hydrogenated with 10% palladium/charcoal (10 mg) for 3 h at room temperature in the presence of triethylamine (1 drop). After the mixture was filtered over Celite and silica gel, evaporation led to 2.5 mg (95%) of colorless syrup: $[\alpha]^{20}_D$ -16.6 (c 0.25, ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 4.36 (dd, H-1), 1.91 (ddd, H-2a), 2.25 (ddd, H-2e), 3.96 (ddd, H-3), 5.28 (dd ~ t, H-4), 3.36 (dq, H-5, 1.34 (d, CH_3-6), 4.11 (dd, H-1'), 1.77 (ddd, H-2e'), 3.56 (ddd, H-3'), 4.70 (dd ~ t, H-4'), 3.02 (dq, H-5'), 1.06 (d, CH_3-6'), 4.49 (dd, H-1''), 4.80 (d, H-4''), 3.82 (dq, H-5''), 1.23 (d, CH_3-6''), 1.37 (s, CH_3-3''), 4.50 and 4.89 (AB pattern, J = 11.8, PhCH_2), 1.68 and 1.78 (each s, each 3 H, OAc), 7.05-7.38 and 8.20-8.25 (m, 10 H, aryl-H), $J_{1,2a}$ = 9.7, $J_{1,2e}$ = 1.9, $J_{2a,2e}$ = 12.4, $J_{2a,3}$ = 12.2, $J_{2e,3}$ = 5.1, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2, $J_{1',2a'}$ = 9.6, $J_{1',2e'}$ = 1.9, $J_{2a',2e'}$ = 12.4, $J_{2a',3'}$ = 11.6, $J_{2e',3'}$ = 5.1, $J_{3',4'}$ = 9.4, $J_{4',5'}$ = 9.5, $J_{5',6'}$ = 6.2, $J_{1'',2a''}$ = 3.9, $J_{1'',2e''}$ = 0.7, $J_{4'',5''}$ = 9.6, $J_{5'',6''}$ = 6.2 Hz.

Anal. Calcd for $C_{37}H_{48}O_{13}$ (700.8): C, 63.42; H, 6.90. Found: C, 63.89; H, 6.51.

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One-Pot Conversion of 6-Hydroxy-Δ^7-iridoid Glucosides into *cis*-2-Oxabicyclo[3.3.0]oct-7-enes and Transformation into Corey's Lactone Analogue

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A simple conversion of some iridoid glucosides into *cis*-2-oxabicyclo[3.3.0]oct-7-enes by a three-step "one-pot" sequence is described. Such important prostanoid intermediates have been obtained through intramolecular acid-catalyzed cyclization of the corresponding cyclopentenepolyols. An analogue (**17**) of Corey's lactone has been prepared by PCC oxidation of 2-oxabicyclo[3.3.0]oct-7-ene (**16**) together with other important derivatives.

Various routes have been devised to prepare optically active prostanoid intermediates, starting from naturally occurring materials.[1] In particular several syntheses have appeared using iridoid glucosides including aucubin (**1**).[2]

In this report we describe a one-pot, three-step transformation of 6-hydroxy-Δ^7-iridoid glucosides into *cis*-2-oxabicyclo[3.3.0]oct-7-enes,[3] which implies the easy inversion of the C-O linkage at C-6 from a β to an α configuration. Such bicyclic ethers are considered particularly attractive intermediates[4] for prostaglandin synthesis.[5] Along these lines we carried out the oxidation of the tetrahydrofuran ring to the corresponding lactone and obtained an analogue of Corey's lactone.

Results and Discussion

In previous communications on the reactivity of iridoid aglycons we described the acid-catalyzed rearrangement of aucubigenin (**2**)[6] as well as the $NaBH_4$ reductions in aqueous solution of **2**[7] and its 6-deoxy and 6,10-dideoxy

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