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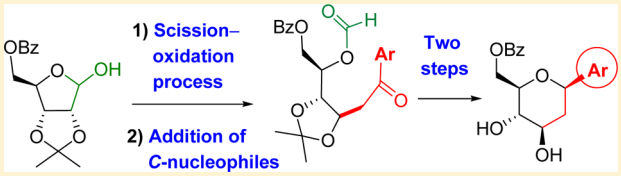
Stereoselective Conversion of Sugar Derivatives into *C*-nucleosides

Javier Miguélez, Venkateswara Rao Batchu, and Alicia Boto*

Instituto de Productos Naturales y Agrobiología del CSIC, Avda. Astrofísico Francisco Sánchez 3, 38206-La Laguna, Tenerife, Spain

Supporting Information

ABSTRACT: A two-step process for the transformation of readily available carbohydrate derivatives into acyclic *C*-nucleosides is described. The carbohydrate undergoes a scission process that is followed by the addition of aryl ketone derivatives, allowing the introduction of a variety of aryl rings. The resulting acyclic *C*-nucleosides are transformed into 2-deoxy cyclic pyranosides in good yield and excellent stereoselectivity.



The preparation of *C*-nucleosides has attracted much interest[1] since many of these compounds display a potent biological activity. For instance, the acyclic nucleosides **1** (Figure 1) present antibiotic and anti-inflammatory activity,[2]

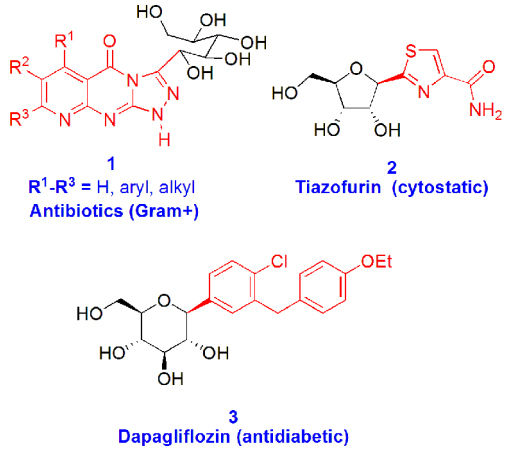


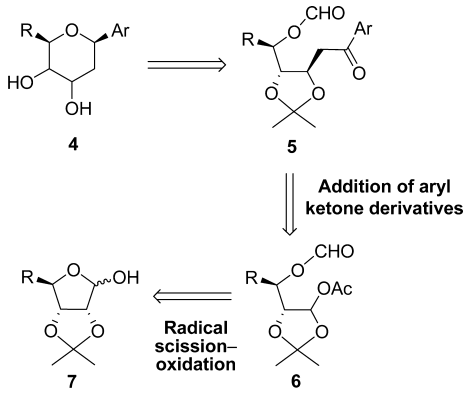
Figure 1. Bioactive *C*-nucleosides.

while cyclic products tiazofurin **2**[1a,3] and dapagliflozin **3**[4] are cytostatic and antidiabetic drugs, respectively. The stability of *C*-nucleosides to in vivo hydrolysis is an important advantage for their therapeutical use.

Therefore, the development of stereoselective routes to these compounds has attracted the interest of medicinal chemists and the pharmaceutical industry.[5] Herein we report a highly stereoselective route to *C*-nucleosides from readily available carbohydrates. In the example shown in Scheme 1, the cyclic *C*-nucleosides **4** are obtained by reduction and cyclization of the acyclic precursors **5**, which are formed by addition of aryl ketones or their silyl enol ethers to the acetals **6**. These acetals are formed from carbohydrate derivatives **7** using a sequential radical scission–oxidation process.[6] These steps proceed under mild conditions and good yields.

The conversion of carbohydrate derivatives into acyclic *C*-nucleosides was studied with rhamnose derivative **8**[7] (Scheme 2) and the ribofuranose **9**.[6d] Following our previously reported radical scission–oxidation procedure,[6d] substrates **8** and **9** were treated with (diacetoxyiodo)benzene (DIB) and iodine under irradiation with visible light to give the oxycarbenium intermediates **10** and **11**, respectively. These intermediates were trapped by acetate from the reagent (DIB), affording the acetoxy acetals **12** or **13**. The rhamnose-derived acetal **12** was treated with silyl enol ethers to give the arylketone derivatives **14** (89%), **15** (80%), and **16** (46%). In a similar way, the ribose-derived acetal **13**[6d] was transformed into ketone **17** (48%). In all cases, the stereocontrol exerted by the substituted dioxolane ring provided the acyclic *C*-nucleosides with excellent 1,2-*trans* stereoselectivity (dr >98:2).

Scheme 1. Retrosynthetic Approach for the Preparation of *C*-Nucleosides from Carbohydrate Derivatives



The introduction of halogenated aromatic rings is particularly interesting since they often display potent biological activities and are also precursors of other aryl systems.[8] For instance, compound **14** can be transformed into product **15** by sp^2–sp^2 coupling.

Also interesting is the introduction of methoxy-substituted phenyl rings, since they are found in bioactive nucleoside

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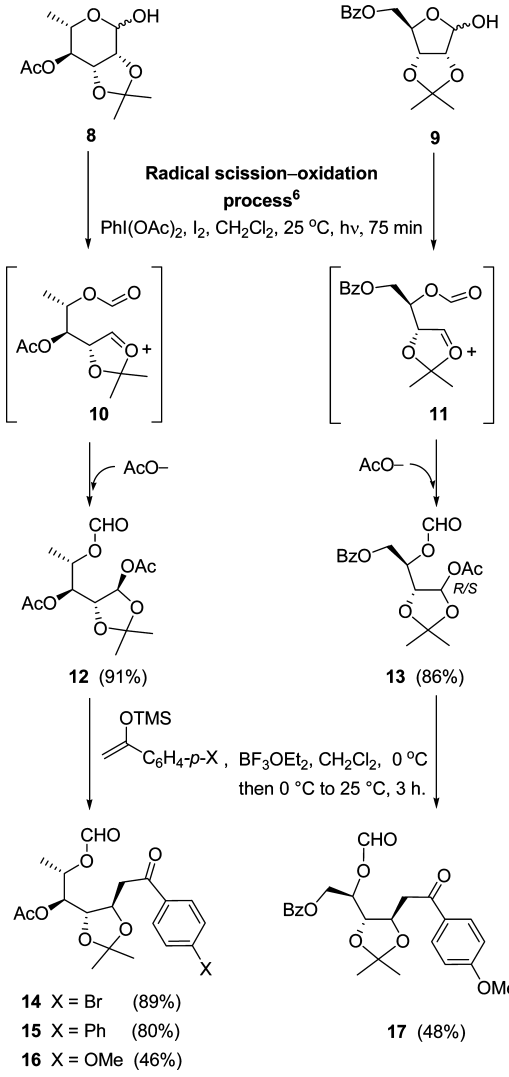
Scheme 2. Study of the Scission and Alkylation Process

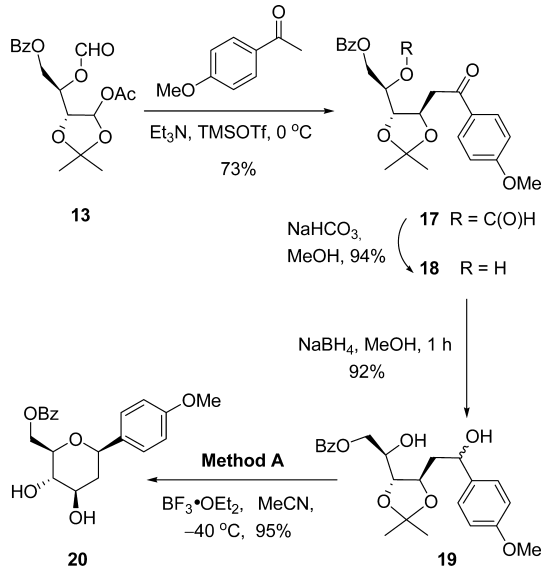


analogues such as chaetiacandin,[9a] papulacandin,[9a] and the hypotensive agent codonopsin.[9b] However, the acyclic nucleosides **16** and **17**, containing the *p*-methoxyphenyl rings, were obtained in moderate yield (46% and 48% respectively), probably because of the reagent's degradation. Therefore, an alternative procedure was explored using ketones as the nucleophiles in the presence of an amine base and a Lewis acid (Scheme 3). Although these conditions were described for the nucleophilic addition to aldehydes,[10] their application to highly functionalized acetoxy acetals such as **13** is new.

Thus, compound **13** was treated with methyl *p*-methoxyphenyl ketone, triethylamine, and TMSOTf, affording compound **17** in good yield (73% versus 48% with the previous procedure) and excellent stereoselectivity. This method not only increased the yields but also simplified the addition procedure, avoiding the preparation of the silyl enol ether. In addition, production costs are reduced, since many methylaryl ketones are commercial and relatively inexpensive products.

The formate group of compound **17** was selectively hydrolyzed, affording hydroxy ketone **18**.[6b] The reductive cyclization of this compound was tried using different conditions,[8a,b,11] but side products (dihydroxy derivatives, furan rings, etc) were often isolated. A change in the procedure

Scheme 3. New Conditions for the Alkylation Reaction and Intramolecular Cyclization To Give *C*-Nucleoside 20



was carried out by reduction of the ketone and treatment of the resulting alcohol **19** with a Lewis acid[12] to afford the 2-deoxy 1,5-*cis* *C*-nucleoside **20** in excellent yield and stereoselectivity (95%, dr >98:2).[13] The causes for this high stereolectivity will be discussed later. Although some examples of this cyclization procedure have been reported with simpler diols,[12] the result described herein is noteworthy because of the high functionalization of substrate **20** and the conformational constraints imposed by the dioxolane ring.

With this result in hand, other *C*-nucleosides were prepared (Scheme 4). Thus, compound **13** was treated with commercial methyl biphenyl ketone to give the acyclic nucleoside **21** (67%). The one-pot hydrolysis of the formate and the reduction of the ketone were carried out, affording the dihydroxy compound **22**. On treatment with boron trifluoride at −20 °C, the cyclization[12,13] and deprotection of the isopropylidene group took place to give the *C*-nucleoside **23** in good yield and excellent diastereomeric ratio (78%, dr >98:2).

In a similar way, compound **13** and commercial methyl 2-naphthyl ketone reacted to give the acyclic *C*-nucleoside **24** in good yield (72%) as a single isomer (1,2-*trans* product). The one-pot formate hydrolysis and ketone reduction provided compound **25**, which underwent the cyclization reaction. Because of solubilty problems of compound **25**, the cyclization under the previous conditions (BF_3OEt_2, MeCN, −20 °C) proceeded in moderate yields (38%). Therefore, the solvent was changed to $MeNO_2$, and after some optimization, the temperature was slightly increased (−10 °C) and boron trifluoride was replaced by TMSOTf. Under these conditions, the cyclization proceeded with excellent stereoselectivity to give compound **26** (71%, dr >98:2).[13] The introduction of polycyclic aryl rings in nucleoside and oligonucleotide analogues has been explored recently in order to develop new materials such as fluorescent sensors and biological probes.[14]

A possible explanation of the high stereoselectivity of the intramolecular cyclization is given in Scheme 5. On treatment of substrate **19** with the Lewis acid, an intermediate **27** could be formed, followed by generation of a cation stabilized by the *p*-

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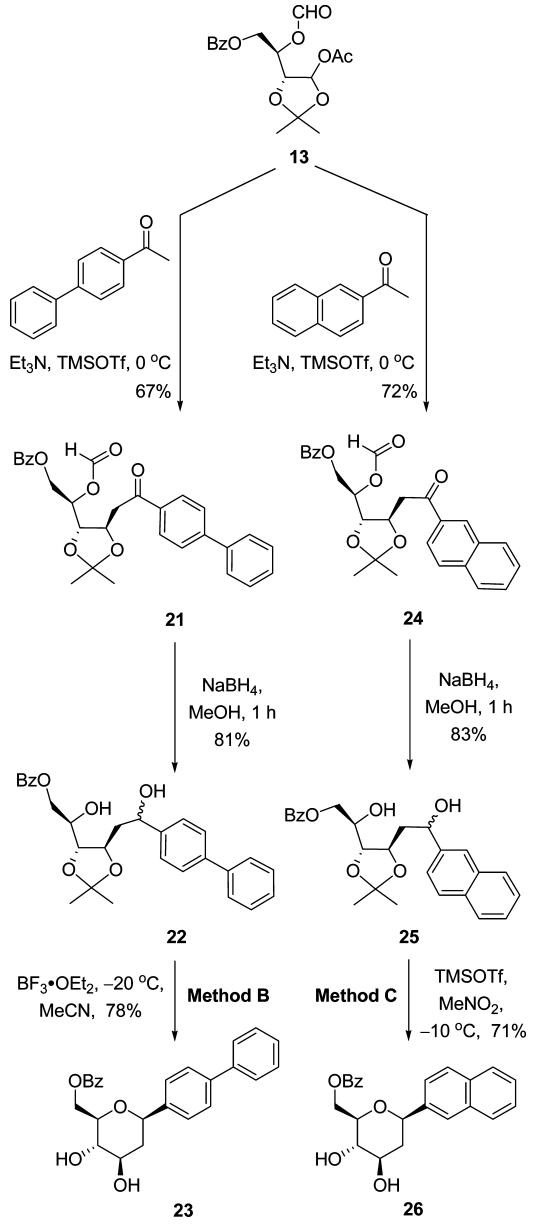
Scheme 4. Conversion of Acetoxy Acetal 13 into *C*-Nucleosides 23 and 26

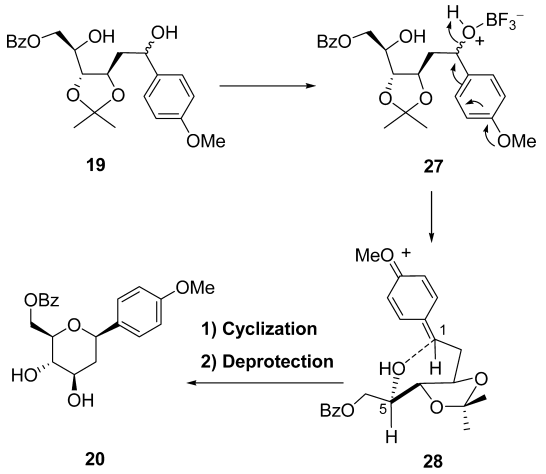


methoxyphenyl group (resonance structure **28** shown).[15] Due to the strain of the *trans*-substituted dioxolane ring, a deformed chair conformation, with two equatorial oxygen functions and equatorial 1-aryl and 5-alkyl substituents, would be adopted. In this conformation, the 5-OH group could get close to the benzylic cation, and the subsequent cyclization would give the 1,5-*cis* isomer.[13b] The cleavage of the isopropylidene protecting group would reduce the strain of the system, yielding the final product **20.**

In the cyclization of related alcohols **22** and **25**, the intermediate cation could be stabilized by resonance with the biphenyl or the naphthyl groups. The cyclization would be similar to the one shown for intermediate **28** to give the *cis*-products **23** or **26**.

In conclusion, a short, highly stereoselective process for the conversion of readily available carbohydrate derivatives into acyclic and cyclic *C*-nucleosides was carried out. Different 2,3-*O*-isopropylidene carbohydrate derivatives were used as

Scheme 5. Mechanism for the Intramolecular Cyclization of Compound 19 To Give *C*-Nucleoside 20



substrates. Using our radical scission–oxidation protocol, followed by the addition of *C*-nucleophiles (aryl ketones or their silyl enol ethers), a variety of 1,2-*trans*-substituted acyclic *C*-nucleosides were produced in good yields and high stereoselectivities and under mild conditions.

The resulting acyclic *C*-nucleosides were transformed into cyclic 2-deoxy *C*-nucleosides in just two steps, in good global yields and excellent diastereoselectivity, to give the 1,5-*cis* products. The application of this cyclization procedure to substrates with high functionalization and conformational constraints, to give the unprotected sugar cores, is remarkable and allows the preparation of potential cytotoxic and antiviral *C*-nucleosides.

EXPERIMENTAL SECTION

General Methods. General Remarks. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature (26 °C) in $CHCl_3$ solutions. NMR spectra were determined at 500 or 400 MHz for ^1H and 125.7 or 100 MHz for ^{13}C in the presence of TMS as internal standard, unless otherwise stated. Mass spectra and HRMS were determined with electronic impact (EI) at 70 eV. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for preparative thin-layer chromatography and column chromatography, respectively. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagent for TLC analysis was 0.5% vanillin in H_2SO_4–EtOH (4:1), and the TLC was heated until development of color.

General Procedure for the Radical Scission–Oxidation. To a solution of the carbohydrate substrate (compounds **8** or **9**, 2.0 mmol) in dry dichloromethane (20 mL) were added iodine (540 mg, 2.11 mmol) and (diacetoxyiodo)benzene (DIB) (820 mg, 2.54 mmol). The reaction mixture was stirred for 75 min at room temperature (26 °C) under irradiation with visible light (80-W tungsten filament lamp). The reaction mixture was then poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to afford the acetoxy acetals (products **12** or **13**).

(1*R*)-1-Acetoxy-3-*O*-acetyl-5-deoxy-4-*O*-formyl-1,2-*O*-isopropylidene-L-arabinitol (12). Obtained from 3-acetyl-1,2-di-*O*-isopropylidene-L-rhamnopyranose (**8**) (492 mg, 2.0 mmol) according to the general procedure for the radical scission–oxidation. After column chromatography (hexanes/EtOAc 70:30), compound **12** (553 mg, 91%) was isolated as a solid: mp 101–103 °C (EtOAc/hexane); IR ($CHCl_3$) 3026, 2993, 2939, 1748, 1725 cm^{-1}; ^1H NMR (500 MHz,

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$CDCl_3$) δ_H 1.28 (3H, d, J = 6.0 Hz), 1.45 (3H, s), 1.46 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 4.38 (1H, dd, J = 2.0, 3.3 Hz), 5.17−5.21 (2H, m), 6.06 (1H, d, J = 2.1 Hz), 8.02 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 15.8, 20.7, 21.1, 26.7, 27.2, 68.8, 71.9, 80.8, 96.8, 113.8, 159.8, 169.9, 170.0; HRMS (EI) calcd for $C_{12}H_{17}O_8$ [$M^+ - CH_3$] 289.0923, found 289.0929. Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.32; H, 6.62. Found: C, 51.07; H, 6.58.

1-Acetoxy-4-*O*-benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-D-erythritol (13). Obtained from 5-benzoyl-2,3-di-*O*-isopropylidene-D-ribofuranose (**9**) (588 mg, 2.0 mmol) according to the general procedure for the radical scission−oxidation. After column chromatography (hexanes/EtOAc 70:30), compound **13** was obtained as a separable mixture of the (1*R*)-**13** (479 mg, 68%) and the (1*S*)-**13** (127 mg, 18%) isomers (global yield, 86%), which have been previously reported.[6d]

General Procedure for the Preparation of Silyl Enol Ethers. The nucleophiles were prepared from their corresponding methyl aryl ketones. Thus, a solution of TMSOTf (0.67 mL, 3.5 mmol) in dichloromethane (3 mL) was added dropwise to a solution of the starting methyl ketone (3.5 mmol) and triethylamine (1.1 mL) in dichloromethane (15 mL), cooled at 0 °C. The mixture was stirred at 0−5 °C for 30 min and then was allowed to reach 26 °C and stirred for 1 h. It was diluted with hexanes and washed with saturated aqueous $NaHCO_3$ solution and water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum to afford the silyl enol ether, which was used without further purification in the next step. The starting amounts for each ketone were as follows: methyl 4-bromophenyl ketone (697 mg, 3.5 mmol), methyl 4-(phenyl)phenyl ketone (686 mg, 3.5 mmol), and methyl 4-methoxyphenyl ketone (525 mg, 3.5 mmol).

General Procedure for Addition of Silyl Enol Ethers. To a solution of the acetoxy acetals (products **12** or **13**, 0.33 mmol) in dry dichloromethane (3 mL) at 0 °C were added the silyl enol ether (1.33 mmol) and boron trifluoride etherate (81 μL, 0.66 mmol). The mixture was stirred until disappearance of the starting material (about 3 h) and then was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After usual solvent drying and evaporation, the residue was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the aryl ketones **14**−**17**.

(1*R*)-3-*O*-Acetyl-4-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(4-bromophenyl)ethyl]-5-deoxy-D-arabinitol (14). Obtained from the acetoxy acetal **12** (100 mg, 0.33 mmol) according to the general procedure for the addition of silyl enol ethers. After column chromatography (hexanes/EtOAc 90:10), compound **14** (130 mg, 89%) was obtained as a solid: mp 99−101 °C (EtOAc/hexane); $[\alpha]_D$ −7.6 (c 0.002, $CHCl_3$); IR ($CHCl_3$) 3015, 1726, 1688, 1588 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.34 (3H, d, J = 6.6 Hz), 1.36 (3H, s), 1.39 (3H, s), 2.16 (3H, s), 3.16 (1H, dd, J = 4.5, 16.7 Hz), 3.26 (1H, dd, J = 7.4, 16.7 Hz), 4.01 (1H, dd, J = 2.3, 7.6 Hz), 4.32 (1H, ddd, J = 4.1, 7.6, 7.6 Hz), 5.18 (1H, dd, J = 2.6, 6.0 Hz), 5.27 (1H, dddd, J = 6.3, 6.6, 6.6, 6.7 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.81 (2H, d, J = 8.9 Hz), 8.02 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 16.0, 20.7, 26.5, 27.4, 41.5, 69.8, 70.9, 72.6, 78.9, 109.7, 128.6, 129.8, 131.9, 135.4, 160.0, 170.3, 195.8; HRMS (EI) calcd for $C_{14}H_{12}O_3{}^{81}Br$ [CH_2=C(OCHO)-CH=CHCH=CHCOC$_6$H$_4$-p-Br]$^+$ 308.9949, found 308.9955; calcd for $C_{14}H_{12}O_3{}^{79}Br$ 306.9970, found 306.9985. Anal. Calcd for $C_{19}H_{23}O_7Br$: C, 51.48; H, 5.23. Found: C, 51.57; H, 5.10.

(1*R*)-3-*O*-Acetyl-4-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(biphenyl-4-yl)ethyl]-5-deoxy-D-arabinitol (15). Obtained from the acetoxy acetal **12** (100 mg, 0.33 mmol) according to the general procedure for the addition of silyl enol ethers. After column chromatography (hexanes/EtOAc 90:10), compound **15** (116 mg, 80%) was obtained as a white solid: mp 136−138 °C (EtOAc/hexane); $[\alpha]_D$ −2.75 (c 0.002, $CHCl_3$); IR ($CHCl_3$) 3019, 1731, 1687, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.36 (3H, d, J = 6.4 Hz), 1.40 (3H, s), 1.42 (3H, s), 2.17 (3H, s), 3.24 (1H, dd, J = 4.5, 16.6 Hz), 3.36 (1H, dd, J = 7.4, 16.6 Hz), 4.06 (1H, dd, J = 2.5, 7.7 Hz), 4.40 (1H, ddd, J = 4.5, 7.5, 7.5 Hz), 5.24 (1H, dd, J = 2.5, 5.8 Hz), 5.30 (1H, dddd, J = 5.7, 6.5, 6.6, 6.7 Hz), 7.40 (1H, dd, J = 7.1, 7.4 Hz), 7.47 (2H, dd, J = 7.6, 8.0 Hz), 7.62 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 8.3 Hz), 8.03 (2H, d, J = 8.5 Hz), 8.04 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 16.0, 20.7, 26.6, 27.5, 41.7, 69.8, 71.0, 72.9, 79.0, 109.7, 127.2, 128.3, 128.9, 135.3, 139.8, 146.0, 160.1, 170.3, 196.4; HRMS (EI) calcd for $C_{24}H_{25}O_7$ [M^+ − Me] 425.1600, found 425.1611. Anal. Calcd for $C_{25}H_{28}O_7$: C, 68.17; H, 6.41. Found: C, 68.52; H, 6.30.

(1*R*)-3-*O*-Acetyl-4-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(4-methoxyphenyl)ethyl]-5-deoxy-D-arabinitol (16). Obtained from the acetoxy acetal **12** (100 mg, 0.33 mmol) according to the general procedure for the addition of silyl enol ethers. After column chromatography (hexanes/EtOAc 85:15), compound **16** (60 mg, 46%) was obtained as a syrup: $[\alpha]_D$ −1.10 (c 0.002, $CHCl_3$); IR ($CHCl_3$) 3019, 1727, 1677, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.34 (3H, d, J = 6.4 Hz), 1.38 (3H, s), 1.41 (3H, s), 2.16 (3H, s), 3.14 (1H, dd, J = 4.6, 16.4 Hz), 3.28 (1H, dd, J = 7.3, 16.4 Hz), 3.86 (3H, s), 4.03 (1H, dd, J = 2.6, 7.7 Hz), 4.38 (1H, ddd, J = 4.6, 7.4, 7.4 Hz), 5.21 (1H, dd, J = 2.6, 5.8 Hz), 5.28 (1H, dddd, J = 5.8, 6.1, 6.3, 6.5 Hz), 6.93 (2H, d, J = 6.9 Hz), 7.93 (2H, d, J = 6.9 Hz), 8.03 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 16.0, 20.8, 26.7, 27.6, 41.4, 55.5, 69.9, 71.2, 73.1, 79.1, 109.7, 113.8, 129.9, 130.6, 160.1, 163.8, 170.3, 195.3; HRMS (EI) calcd for $C_{19}H_{23}O_8$ [M^+ − Me] 379.1393, found 379.1383. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.68; H, 6.58.

(1*R*)-4-*O*-Benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(4-methoxyphenyl)ethyl]-D-erythritol (17). Obtained from the acetoxy acetal **13** (116 mg, 0.33 mmol) according to the general procedure for the addition of silyl enol ethers. After column chromatography (hexanes/EtOAc 60:40), compound **17** (70 mg, 48%) was obtained as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.44 (3H, s), 1.46 (3H, s), 3.20 (1H, dd, J = 4.8, 16.5 Hz), 3.40 (1H, dd, J = 7.0, 16.6 Hz), 3.87 (3H, s), 4.10 (1H, dd, J = 6.8, 7.1 Hz), 4.50 (1H, dd, J = 6.8, 12.3 Hz), 4.67 (1H, ddd, J = 4.8, 7.1, 7.2 Hz), 4.76 (1H, dd, J = 2.9, 12.3 Hz), 5.50 (1H, ddd, J = 2.9, 6.9, 7.1 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.44 (2H, dd, J = 7.5, 7.9 Hz), 7.57 (1H, dd, J = 7.4, 7.5 Hz), 7.95 (2H, d, J = 8.9 Hz), 8.02 (2H, d, J = 8.4 Hz), 8.07 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.9, 27.3, 42.4, 55.5, 63.2, 71.5, 75.1, 78.9, 110.2, 113.8, 128.5, 129.6, 129.7, 130.6, 133.2, 159.9, 163.8, 166.1, 195.1; HRMS (EI) calcd for $C_{24}H_{27}O_8$ [M^+ + H] 443.1706, found 443.1697.

General Procedure for the Addition of Aryl Ketones. To a stirred solution of acetoxy acetal **13** (400 mg, 1.14 mmol) in dry diclorometane (6 mL) was added the ketone (4.8 mmol) and triethylamine (325 μL, 4.64 mmol). Then TMSOTf (518 μL, 5.7 mmol) was added dropwise for 20 min at 0 °C and the mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. After usual drying and solvent removal, the residue was purified by flash chromatography on silica gel (hexanes/EtOAc) to afford the ketone.

(1*R*)-4-*O*-Benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(4-methoxyphenyl)ethyl]-D-erythritol (17). Obtained from the acetoxy acetal **13** (400 mg, 1.14 mmol) and methyl 4-methoxyphenyl ketone (930 mg, 4.8 mmol) according to the general procedure for the addition of aryl ketones. After column chromatography (hexanes/EtOAc 60:40), compound **17** (362 mg, 73%) was isolated as a clear oil.

(1*R*)-4-*O*-Benzoyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(4-methoxyphenyl)ethyl]-D-erythritol (18). Obtained from aryl ketone **17** (350 mg, 0.79 mmol) by treatment with $NaHCO_3$ (663 mg, 7.9 mmol) in methanol (5 mL). After column chromatography (hexanes/EtOAc 60:40), compound **18** (308 mg, 94%) was obtained as a syrup: $[\alpha]_D$ +8 (c 0.54, $CHCl_3$); IR ($CHCl_3$) 3435, 1720, 1677, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.42 (6H, s), 3.38 (1H, dd, J = 5.4, 17.0 Hz), 3.43 (1H, dd, J = 6.3, 17.0 Hz), 3.85 (1H, dd, J = 7.2, 8.3 Hz), 3.87 (3H, s), 4.09 (1H, m), 4.44 (1H, dd, J = 6.4, 11.8 Hz), 4.67 (1H, dd, J = 2.8, 11.7 Hz), 4.68 (1H, m), 6.93 (2H, d, J = 9.0 Hz), 7.44 (2H, dd, J = 7.6, 8.1 Hz), 7.57 (1H, dd, J = 7.4, 7.5 Hz), 7.97 (2H, d, J = 9.0 Hz), 8.07 (2H, d, J = 7.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 27.0, 27.3, 42.8, 55.5, 67.1, 72.3, 76.2, 80.5, 109.5, 113.8, 128.4, 129.7, 129.8, 130.7, 133.1, 163.8, 167.1, 196.9; HRMS (EI)

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calcd for $C_{22}H_{23}O_7$ [M^+ − Me] 399.1444, found 399.1433. Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.77; H, 6.16.

(1*R*)-4-*O*-Benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(biphenyl-4-yl)ethyl]-D-erythritol (21). Obtained from the acetoxy acetal **13** and methyl 4-biphenyl ketone (930 mg, 4.76 mmol) according to the general procedure for the addition of aryl ketones. After column chromatography (hexanes/EtOAc 70:30), compound **21** (368 mg, 67%) was obtained as a syrup: $[\alpha]_D$ +20.4 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 1731, 1685, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.46 (3H, s), 1.47 (3H, s), 3.29 (1H, dd, *J* = 4.6, 16.7 Hz), 3.48 (1H, dd, *J* = 7.1, 16.8 Hz), 4.13 (1H, dd, *J* = 6.6, 7.2 Hz), 4.53 (1H, dd, *J* = 6.7, 12.2 Hz), 4.72 (1H, ddd, *J* = 4.6, 7.2, 7.2 Hz), 4.79 (1H, dd, *J* = 2.9, 12.3 Hz), 5.53 (1H, m), 7.40−7.48 (5H, m), 7.56 (1H, dd, *J* = 7.4, 7.5 Hz), 7.62 (2H, d, *J* = 8.0 Hz), 7.68 (2H, d, *J* = 8.2 Hz), 8.03−8.05 (4H, m), 8.10 (1H, brs); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.9, 27.3, 42.7, 63.1, 71.5, 74.9, 78.9, 110.2, 127.2, 128.3, 128.5, 128.8, 128.9, 129.5, 129.7, 133.2, 135.3, 139.7, 146.1, 159.8, 166.1, 196.2; HRMS (EI) calcd for $C_{28}H_{25}O_7$ [M^+ − Me] 473.1600, found 473.1586. Anal. Calcd for $C_{29}H_{28}O_7$: C, 71.30; H, 5.78. Found: C, 71.18; H, 5.80.

(1*R*)-4-*O*-Benzoyl-3-*O*-formyl-1,2-*O*-isopropylidene-1-[2-oxo-2-(2-naphthyl)ethyl]-D-erythritol (24). Obtained from the acetoxy acetal **13** and methyl 2-naphthyl ketone (816 mg, 4.8 mmol) according to the general procedure for the addition of aryl ketones. After column chromatography (hexanes/EtOAc 70:30), compound **24** (378 mg, 72%) was obtained as a syrup: $[\alpha]_D$ +30.4 (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1731, 1685, 1631 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.47 (3H, s), 1.48 (3H, s), 3.40 (1H, dd, *J* = 4.6, 16.7 Hz), 3.59 (1H, dd, *J* = 7.1, 16.6 Hz), 4.17 (1H, dd, *J* = 6.6, 7.3 Hz), 4.53 (1H, dd, *J* = 6.6, 12.2 Hz), 4.75 (1H, ddd, *J* = 4.6, 7.2, 7.2 Hz), 4.79 (1H, dd, *J* = 2.9, 12.2 Hz), 5.54 (1H, dddd, *J* = 0.8, 2.9, 6.5, 6.6 Hz), 7.47 (2H, dd, *J* = 7.6, 8.1 Hz), 7.61 (2H, m), 7.66 (1H, dd, *J* = 7.0, 7.9 Hz), 7.93 (2H, dd, *J* = 8.9, 9.3 Hz), 8.01 (1H, d, *J* = 8.1 Hz), 8.07−8.10 (3H, m), 8.14 (1H, brs), 8.52 (1H, d, *J* = 1.4 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.9, 27.3, 42.7, 63.2, 71.6, 75.0, 78.9, 110.3, 123.7, 126.8, 127.8, 128.4, 128.5, 128.7, 129.5, 129.6, 129.7, 130.1, 132.4, 133.2, 134.0, 135.7, 159.9, 166.1, 196.6; HRMS (EI) calcd for $C_{27}H_{26}O_7$ [M^+] 462.1679, found 462.1680. Anal. Calcd for $C_{27}H_{26}O_7$: C, 70.12; H, 5.67. Found: C, 70.05; H, 5.74.

General Procedure for the Reduction of Aryl ketones. A mixture of the ketone (0.80 mmol) and sodium borohydride (61 mg, 1.60 mmol) in anhydrous methanol (5 mL) was stirred at 0 °C for 90 min. Then saturated aqueous $NaHCO_3$ (2 mL) and EtOAc (10 mL) were added, and the mixture was stirred at 0 °C for 5 min. The reaction mixture was poured into water and extracted with EtOAc. After usual drying and solvent removal, the residue was purified by chromatography (hexanes/EtOAc 70:30) to give the diols.

(1*R*)-4-*O*-Benzoyl-1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-1,2-*O*-isopropylidene-D-erythritol (19). Obtained from the ketone **18** (331 mg, 0.8 mmol) according to the general reduction procedure. After column chromatography (hexanes/EtOAc 70:30), compound **19** (306 mg, 92%) was obtained as a 3:2 diastereomer mixture. Syrup: IR ($CHCl_3$) 3509, 1722, 1612, 1516 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H major isomer 1.41 (3H, s), 1.44 (3H, s), 2.01 (1H, m), 2.23 (1H, ddd, *J* = 3.9, 9.8, 14.5 Hz), 3.79 (3H, s), 3.80 (1H, m), 4.00 (1H, m), 4.33 (1H, ddd, *J* = 3.8, 7.6, 7.6 Hz), 4.39 (1H, m), 4.61 (1H, dd, *J* = 2.5, 6.3 Hz), 4.95 (1H, br d, *J* = 9.6 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 7.28 (2H, d, *J* = 8.6 Hz), 7.45 (2H, dd, *J* = 7.0, 7.8 Hz), 7.57 (1H, dd, *J* = 7.5, 7.8 Hz), 8.06 (2H, d, *J* = 7.5 Hz); minor isomer 1.42 (3H, s), 1.46 (3H, s), 2.05 (1H, m), 2.14 (1H, ddd, *J* = 3.6, 3.6, 14.5 Hz), 3.78 (1H, m), 3.79 (3H, s), 3.99 (1H, m), 4.22 (1H, br ddd, *J* = 3.0, 7.5, 7.6 Hz), 4.37 (1H, m), 4.60 (1H, dd, *J* = 2.5, 6.0 Hz), 4.91 (1H, dd, *J* = 3.6, 9.2 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 7.46 (2H, dd, *J* = 7.5, 7.9 Hz), 7.59 (1H, dd, *J* = 7.2, 7.5 Hz), 8.04 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.91/27.95, 27.26/27.28, 42.9/43.4, 55.2, 67.00/67.06, 71.37/72.66, 72.17/72.00, 77.6/79.1, 80.0/80.2, 109.2/109.6, 113.8/113.9, 126.8/127.0, 128.4/128.5, 129.5/129.7, 133.2/133.3, 136.1/136.4, 159.0, 167.1/167.2; HRMS (EI) calcd for $C_{23}H_{28}O_7$ [M^+] 416.1835, found 416.1833. Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.54; H, 6.86.

(1*R*)-4-*O*-Benzoyl-1-[2-hydroxy-2-(biphenyl-4-yl)ethyl]-1,2-*O*-isopropylidene-D-erythritol (22). Obtained from compound **21** (390 mg, 0.8 mmol) using the general reduction procedure. After purification by chromatography (hexanes/EtOAc, 70:30), compound **22** was obtained as a 1:1 diastereomer mixture (299 mg, 81%). Syrup: IR ($CHCl_3$) 3509, 1720, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.43/1.45 (3H, s), 1.46/1.49 (3H, s), 2.08/2.11 (1H, m), 2.22/2.29 (1H, [ddd, *J* = 3.3, 3.3, 14.3 Hz/ddd, *J* = 3.8, 10.3, 13.9 Hz]), 3.80/3.84 (1H, [dd, *J* = 7.6, 7.6 Hz/dd, *J* = 7.6, 7.7 Hz]), 4.02/4.03 (1H, m), 4.30/4.36 (1H, [br ddd, *J* = 3.2, 7.9, 9.5 Hz/ddd, *J* = 3.8, 7.9, 9.5 Hz]), 4.41 (1H, dd, *J* = 6.5, 11.8 Hz), 4.62/4.63 (1H, m/m), 5.02/5.06 (1H, [dd, *J* = 3.2, 9.6 Hz/br d, *J* = 9.5 Hz]), 7.36 (1H, dd, *J* = 7.5, 7.8 Hz), 7.42−7.47 (6H, m), 7.56−7.59 (5H, m), 8.04−8.07 (2H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 27.0, 27.3, 42.8/43.5, 66.9/67.1, 71.5/72.9, 72.2/72.1, 77.6/79.3, 80.0/80.3, 109.3/109.7, 126.0, 126.2, 127.0/127.1, 127.1/127.2, 128.5, 128.7, 129.7, 133.3/133.4, 140.4, 140.8/140.9, 142.9/143.2, 167.2; HRMS (EI) calcd for $C_{27}H_{27}O_6$ [M^+ − Me] 447.1808, found 447.1824. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.80; H, 6.77.

(1*R*)-4-*O*-Benzoyl-1-[2-hydroxy-2-(2-naphthyl)ethyl]-1,2-*O*-isopropylidene-D-erythritol (25). Obtained from compound **24** (369 mg, 0.8 mmol) using the general reduction procedure. After purification by chromatography (hexanes/EtOAc, 70:30), compound **25** was obtained (289 mg, 83%) as a 3:2 diastereomer mixture. Syrup: IR ($CHCl_3$) 3506, 1720, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H major isomer: 1.40 (3H, s), 1.44 (3H, s), 2.11 (1H, m), 2.32 (1H, ddd, *J* = 3.7, 9.7, 14.6 Hz), 3.82 (1H, dd, *J* = 7.7, 7.8 Hz), 3.98 (1H, m), 4.36 (1H, m), 4.39 (1H, m), 4.61 (1H, m), 5.14 (1H, dd, *J* = 2.3, 9.8 Hz), 7.40−7.48 (5H, m), 7.55 (1H, dd, *J* = 7.6, 7.8 Hz), 7.77−7.84 (4H, m), 8.00−8.06 (2H, m); minor isomer: 1.41 (3H, s), 1.47 (3H, s), 2.11 (1H, m), 2.25 (1H, ddd, *J* = 3.5, 3.5, 14.4 Hz), 3.80 (1H, dd, *J* = 7.6, 7.7 Hz), 3.97 (1H, m), 4.26 (1H, ddd, *J* = 3.5, 7.5, 9.0 Hz), 4.39 (1H, m), 4.60 (1H, m), 5.12 (1H, dd, *J* = 3.7, 9.3 Hz), 7.40−7.48 (5H, m), 7.56 (1H, dd, *J* = 7.7, 7.8 Hz), 7.77−7.84 (4H, m), 8.00−8.06 (2H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.9, 27.3, 43.0/43.4, 67.0, 71.9/72.1, 71.8/73.1, 77.6/79.2, 80.0/80.2, 109.2/109.6, 123.8/124.0, 124.1/124.4, 125.7/125.8, 126.0/126.1, 127.6, 127.9/128.0, 128.1/128.2, 128.4/128.5, 129.6, 129.7, 132.8/132.9, 133.2/133.3, 133.2/133.4, 141.2/141.6, 167.1/167.2; HRMS (EI) calcd for $C_{26}H_{28}O_6$ [M^+] 436.1886, found 436.1889. Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.60; H, 6.70.

General Procedures for the Cyclization Reaction. Method A. To a solution containing the diol (0.15 mmol) in dry acetonitrile (3 mL) were added active molecular sieves 4 Å (5 mg) and $BF_3{\cdot}OEt_2$ (19 μL, 0.15 mmol) at −40 °C. The mixture was stirred for 20 min and quenched with aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, dried, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to give the cyclic *C*-nucleoside.

Method B. To a solution containing the diol (0.3 mmol) in dry acetonitrile (3 mL) was added $BF_3{\cdot}OEt_2$ (70 μL, 0.60 mmol) at −20 °C. The mixture was stirred for 60 min, followed by workup and purification as in method A.

Method C. To a solution containing the diol (0.1 mmol) in dry nitromethane (1 mL) was added TMSOTf (50 μL, 0.27 mmol) at −10 °C. The mixture was stirred for 60 min, followed by workup and purification as in method A.

(1*R*)-6-*O*-Benzoyl-1-(4-methoxyphenyl)-1,2-dideoxyglucopyranose (20). Obtained from compound **19** (62 mg, 0.15 mmol) as described in the general procedure for cyclization, method A. After purification by chromatography, compound **20** was obtained (51 mg, 95%) as a syrup: $[\alpha]_D$ −43.1 (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3591, 3491, 1707, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.64 (1H, ddd, *J* = 11.6, 11.6, 12.9 Hz), 2.13 (1H, ddd, *J* = 2.0, 4.9, 13.0 Hz), 3.31 (1H, dd, *J* = 9.1, 9.2 Hz), 3.53 (1H, m), 3.71 (3H, s), 3.77 (1H, m), 4.39 (1H, dd, *J* = 1.7, 11.6 Hz), 4.45 (1H, dd, *J* = 2.2, 12.2 Hz), 4.76 (1H, dd, *J* = 3.9, 12.2 Hz), 6.79 (2H, d, *J* = 8.6 Hz), 7.19 (2H, d, *J* = 8.7 Hz), 7.36 (2H, dd, *J* = 7.7, 7.8 Hz), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz), 8.00 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 40.3, 55.3, 64.4, 72.1, 72.6, 77.4, 78.3, 113.8, 127.2, 128.4, 129.6, 129.9, 133.1,

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133.4, 159.2, 167.8; HRMS (EI) calcd for $C_{20}H_{22}O_6$ [M^+] 358.1416; found, 358.1418.

(1*R*)-6-*O*-Benzoyl-1-(biphenyl-4-yl)-1,2-dideoxyglucopyranose (23). Obtained from compound **22** (139 mg, 0.3 mmol) as described in the general procedure for cyclization, method B. After purification by chromatography (hexanes/EtOAc, 60:40), compound **23** was obtained (95 mg, 78%) as a syrup. Compound **22** was also transformed using method A, but the yields of compound **23** were lower (57%): $[\alpha]_D$ −41.9 (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3487, 1716, 1604, 1490 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.77 (1H, ddd, *J* = 11.5, 11.6, 13.1 Hz), 2.31 (1H, ddd, *J* = 2.1, 4.9, 13.1 Hz), 3.40 (1H, dd, *J* = 9.1, 9.2 Hz), 3.65 (1H, ddd, *J* = 2.3, 3.5, 9.6 Hz), 3.91 (1H, ddd, *J* = 4.9, 8.7, 11.4 Hz), 4.54 (1H, dd, *J* = 2.2, 12.2 Hz), 4.60 (1H, dd, *J* = 2.0, 11.6 Hz), 4.94 (1H, dd, *J* = 3.5, 12.3 Hz), 7.34 (1H, dd, *J* = 7.3, 7.6 Hz), 7.40−7.50 (6H, m), 7.58 (4H, d, *J* = 7.8 Hz), 7.60 (1H, dd, *J* = 7.8, 7.9 Hz), 8.11 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 40.3, 64.2, 72.0, 72.5, 77.6, 78.4, 126.4, 127.1, 127.2, 127.3, 128.5, 128.7, 129.5, 129.9, 133.4, 139.9, 140.8, 167.9; HRMS (EI) calcd for $C_{25}H_{24}O_5$ [M^+] 404.1624, found 404.1625. Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.54; H, 6.12.

(1*R*)-6-*O*-Benzoyl-1-(2-naphthyl)-1,2-dideoxyglucopyranose (26). Obtained from compound **25** (44 mg, 0.1 mmol) as described in the general procedure for cyclization, method C. After purification by chromatography (hexanes/EtOAc, 55:45), compound **26** was obtained (27 mg, 71%). Compound **25** was also transformed using methods A and B, but the yields of compound **26** were lower (25% and 38%, respectively), probably due to solubility problems of the starting material. Compound **26**: syrup; $[\alpha]_D$ −44.0 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3480, 1714, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.81 (1H, ddd, *J* = 11.5, 11.6, 12.9 Hz), 2.35 (1H, ddd, *J* = 2.1, 4.9, 13.1 Hz), 3.44 (1H, dd, *J* = 9.0, 9.2 Hz), 3.68 (1H, br b), 3.69 (1H, ddd, *J* = 2.3, 3.6, 9.6 Hz), 3.93 (1H, m), 4.56 (1H, dd, *J* = 2.1, 12.3 Hz), 4.71 (1H, dd, *J* = 1.6, 11.5 Hz), 4.94 (1H, dd, *J* = 3.2, 12.3 Hz), 7.43−7.50 (5H, m), 7.59 (1H, dd, *J* = 7.3, 7.6 Hz), 7.82 (2H, d, *J* = 8.9 Hz), 7.83 (2H, d, *J* = 8.2 Hz), 8.12 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 40.4, 64.3, 72.1, 72.6, 77.8, 78.5, 124.0, 124.6, 125.9, 126.1, 127.6, 128.0, 128.2, 128.5, 129.6, 130.0, 133.0, 133.2, 133.4, 138.3, 167.9; HRMS (EI) calcd for $C_{23}H_{22}O_5$ [M^+] 378.1467, found 378.1485. Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 73.27; H, 6.20.

■ ASSOCIATED CONTENT

Supporting Information

Carbon and proton shifts and NOESY correlations for compounds **14**−**16**, **18**, **20**, **21**, **23**, **24**, and **26**. ^1H and ^{13}C NMR spectra for products **14**−**26**. Mechanistic considerations for the cyclization reaction and molecular-modeling studies with analogues of intermediate **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +34-922-260112 (ext 267). Fax: +34 922260135. E-mail: alicia@ipna.csic.es.

Notes

The authors declare no competing financial interest.

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