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Synthetic studies toward the preparation of (4*R*,5*R*)-(−)-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-cyclopenten-2-one: an important synthetic intermediate for carbanucleosides

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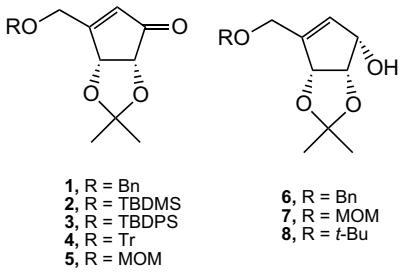
Abstract—The carbocyclic compound (4*R*,5*R*)-(−)-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone **1** is an important synthetic intermediate to access a variety of carbanucleosides. Herein, synthetic studies that lead to this valuable compound employing inexpensive D-ribose as the chiral source are presented.

1. Introduction

In common with conventional nucleosides, their corresponding isosteric analogues carbanucleosides display a wide range of biological properties especially as antiviral and antitumor agents.[1–6] The title compound (4*R*,5*R*)-(−)-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone **1**,[7,8] and other closely related compounds such as **2**,[9] **3**,[9] **4**,[9,10] **5**,[11] **6**,[7,8,12] **7**,[11,13] and **8**[14,15] are versatile synthetic intermediates that have been used for the preparation of a significant number of carbocyclic nucleosides (Fig. 1).



1, R = Bn
2, R = TBDMS
3, R = TBDPS
4, R = Tr
5, R = MOM

6, R = Bn
7, R = MOM
8, R = *t*-Bu

Figure 1.

In spite of having at hand many synthetic methods for the preparation of these intermediates, most of them suffer from some disadvantages such as low overall yields, partial racemization, numerous synthetic steps, and nonviable scale up preparations that make these processes impractical from the synthetic point of view. Very recently, Jeong et al. solved this problem to some extent by a new excellent and elegant synthetic approach that allows a straightforward access to these compounds.[10] With this strategy, that employs D-ribose as a chiral starting material, it is possible to obtain the respective silyl ether and trityl derivatives of compound **1**, namely, compounds **2**–**4**, respectively, in very good yields.[10] On the other hand, the benzyl protecting group has been widely used in nucleoside chemistry and presents some advantages over silyl and trityl protecting groups, such as stability in acidic media and facile removal.[16] However, this strategy does not work when the benzyl protecting group is required to protect the hydroxymethyl group (compound **1**). This failure is due to one of the key steps for this method, which is the facial diastereoselectivity exhibited by synthetic intermediate **9a** toward the attack of a Grignard reagent onto the corresponding carbonyl group. The presence of bulky groups like *tert*-butyldiphenylsilyl or trityl moiety block more efficiently the *Si* face of the carbonyl group of compounds **9b**–**d** than the benzyl ether does. Therefore, in the presence of these bulky groups, the preferred side for nucleophilic attack in compounds **9b**–**d** is the *Re* face of the carbonyl moiety. With the appropriate

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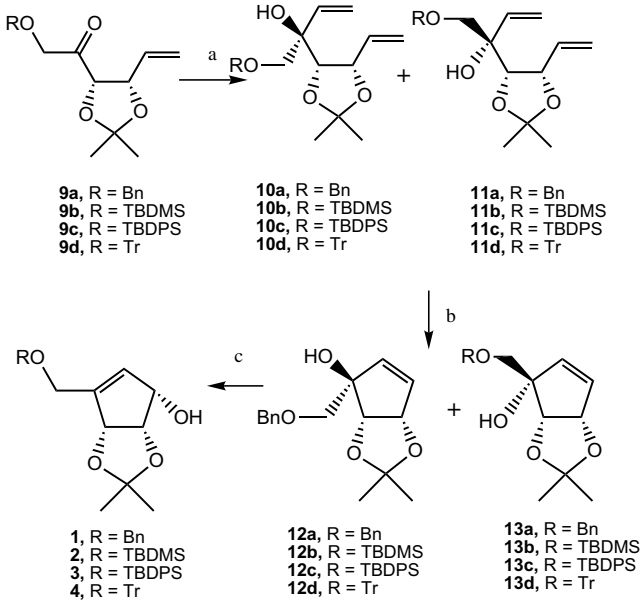
stereochemistry, the resulting dienes **10a–d** are able to be converted into the desired carbocyclic rings (**12a–d**) by a Grubbs ring closure metathesis reaction[17] (Scheme 1).



Scheme 1. Reagents and conditions: (a) $CH_2CHMgBr$, THF, −78 °C, 1 h; (b) Grubbs catalyst, CH_2Cl_2, rt, 2 d; (c) PDC, MS, DMF, rt, 18 h.

The high diastereoselectivity exhibited by **9b** with vinyl magnesium bromide has also been observed by Chu et al.[18,19] The benzyl ether derivative **10a** is obtained by this protocol in only 17% yield,[10] therefore this process is not viable from the synthetic point of view. In addition, Jacobson et al. have described another interesting synthetic approach to obtain **1** starting from 5-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropyliden-D-ribose (compound **14**) as advanced starting material. This strategy uses also a Grubbs reaction as the key step. However, this article suffers from some discrepancies about the origin of the chiral starting material **14**. In spite of being mentioned in the main text and the corresponding scheme that **14** is prepared from D-ribono-1,4-lactone **15** in four synthetic steps, the authors cite the work of Ohira et al. that uses 5-*O*-trityl-2,3-*O*-isopropyliden-D-ribose **16** as the starting material, which in turn, is readily available from D-ribose **17** (Fig. 2).[9] In any case, if compound **16** is employed, the trityl protecting group should be replaced by the benzyl ether. The use

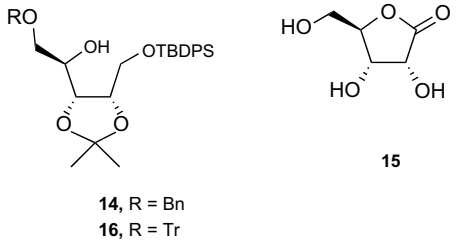


Figure 2.

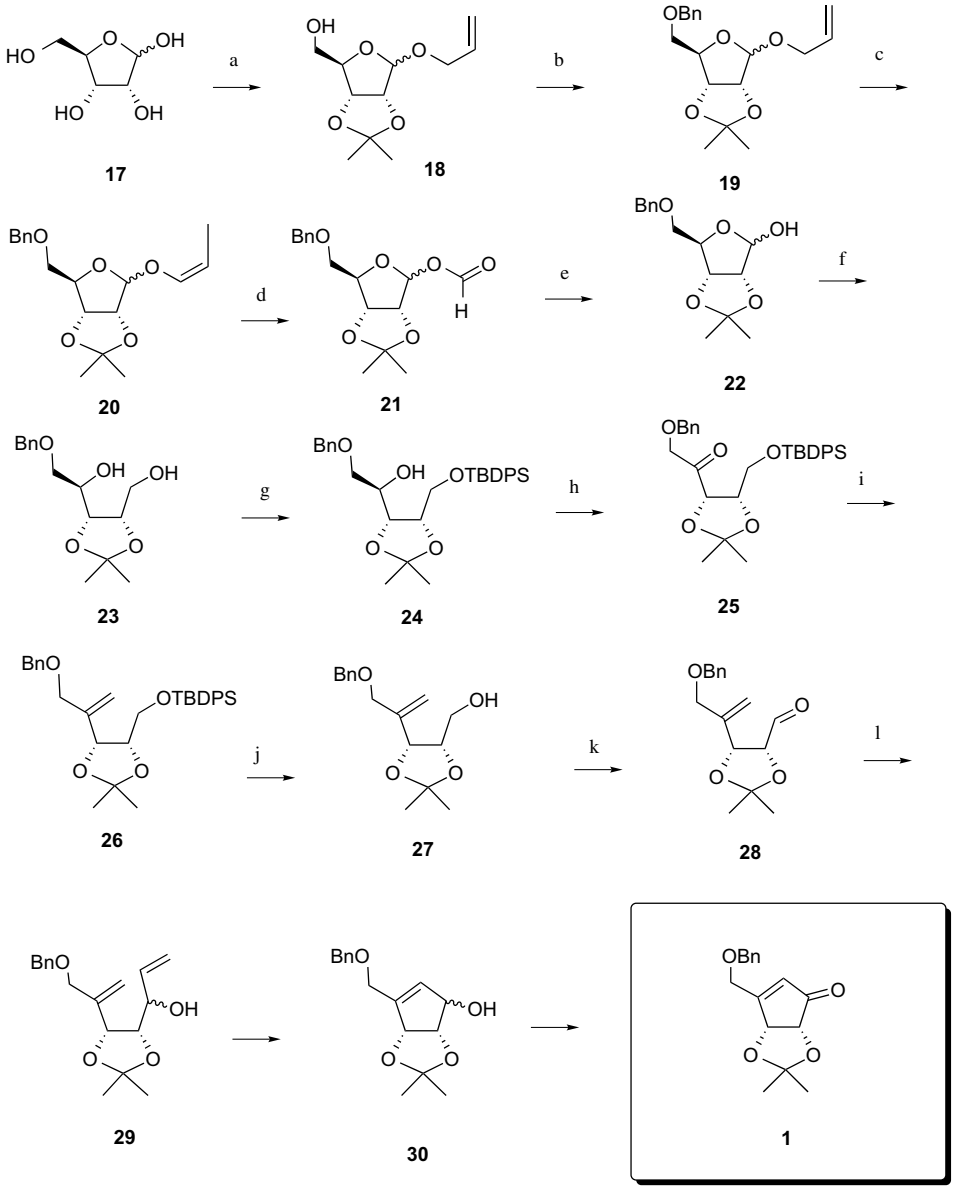
of D-ribono-1,4-lactone presents a number of difficulties in terms of the introduction of the benzyl group to protect the primary alcohol at the C-5 position that are associated with lactone ring opening. In fact, we experienced these problems during the total synthesis of neplanocin C and neplanocin F employing **1** as synthetic intermediate.[8,20] Consequently, a large scale and reliable method for the preparation of **1** is still lacking. In this work we report a straightforward access to **1** from readily available and inexpensive D-ribose.

2. Results and discussion

The synthesis of **28** was successfully carried out starting from readily available and inexpensive D-ribose as the chiral source. This compound treated with acetone in the presence of sulfuric acid[21,22] followed by addition of allylic alcohol afforded, via a Fischer glycosidation reaction, the desired allyl 2,3-*O*-isopropylidene-β-D-ribofuranoside **18** in 96% yield in a one-pot procedure. Nuclear magnetic resonance analysis of **18** indicated the β-configuration of the furanosic form for this compound. The anomeric proton appeared as a broad singlet at 5.12 ppm in the proton NMR spectrum, while the anomeric carbon was observed at 108.0 ppm in the corresponding ^{13}C NMR spectrum. The protection of the free primary hydroxyl group at C-5 in compound **18** as a benzyl ether derivative was conducted by treatment with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide at 0 °C[23] to give **19** in 61% yield. Allyl group cleavage was conducted in three steps: (a) isomerization of the allyl moiety to form the corresponding enol ether;[24] (b) oxidative double bond cleavage to produce the respective formyl glycoside; (c) removal of the formyl group to obtain the free sugar. Therefore, on reaction with potassium *tert*-butoxide in methyl sulfoxide at 100 °C **19** was converted into isomerized product **20** in 92% yield, which treated with ozone in methylene chloride at −78 °C followed by addition of triphenylphosphine[25] afforded compound **21** in 95% yield. The resulting formyl glycoside was removed by treatment with methanolic triethylamine to produce **22** in theoretical yield. Hydrolysis of prop-1-en-1-yl glycoside **20** was also attempted either by hydrolysis in mild acidic conditions,[26] or by the use of iodine.[27] Neither of these methods was effective in terms of the reaction yield. Deprotection of the anomeric center was more efficiently performed by the use of palladium chloride in methanol.[28] Therefore, on reaction with palladium chloride compound **19** was straightforwardly converted into free sugar **22** in 72% yield. Kinetics for this reaction was a critical point in this transformation because long reaction times led to isopropylidene cleavage as well. The optimum reaction time was 4 h at room temperature. This strategy straightforwardly allowed access to sugar **22** with the free anomeric center. As mentioned before, it is not possible to protect the C-5 position as a benzyl ether without previous glycoside formation due to undesired lactol ring-opening provoked by benzylation procedures. Compound **22** treated with lithium aluminum hydride afforded the corresponding alditol **23** in 88% yield, which was regioselectively protected by

treatment with one equivalent of *tert*-butylchlorodiphenylsilane dissolved in *N*,*N*-dimethylformamide in the presence of imidazole to give the corresponding silyl ether derivative **24** exclusively in almost quantitative yield (Scheme 2).

Once the *tert*-butyldiphenylsilyl ether **24** was at hand, a somewhat analogous strategy outlined by Jacobson et al. was followed.[12] This compound underwent Swern oxidation[29] by treatment with oxalyl chloride and methyl sulfoxide at −70 °C followed by addition of triethylamine to produce the expected keto derivative **25**. Treatment of keto derivative **25** with methyltriphenylphosphonium bromide and *n*-butyllithium at 0 °C gave rise to corresponding alkene **26** that after silyl ether cleavage by treatment with tetrabutyl ammonium fluoride in acetonitrile at room temperature afforded the respective pentitol **27** in 97% yield. On treatment with methyl sulfoxide/oxalyl chloride under Swern reaction conditions, **27** was converted into aldehyde **28** in 100% yield. This compound treated with vinylmagnesium bromide produced the desired allylic alcohol **29** as a diastereomeric mixture. NMR analysis of **29** indicated the presence of two diastereomers with the diagnostic signals for the vinylic proton bonded to the hydroxylated carbon: a double double of doublets centered at 5.76 ppm and coupling constants of 16.7, 10.5, 5.7 Hz, respectively, for the major isomer and a double double of doublets centered at 6.00 ppm and coupling constants of 16.1, 10.5, 5.7 Hz, respectively, for the minor isomer



Scheme 2. Reagents and conditions: (a) i. H_2SO_4, acetone, 0 °C, 2 h, ii. allylic alcohol, rt, 3 d, 96%; (b) BnBr, NaH, DMF, 0 °C, 3 h, 61%; (c) ^tBuOK, DMSO, 100 °C, 16 h, 92%; (d) O_3, CH_2Cl_2, −78 °C → PPh_3, rt, 95%; (e) MeOH, NEt_3, rt, 16 h, 100%; (f) $LiAlH_4$, THF, rt, 2 h, 88%; (g) TBDPSCl, imidazole, DMF, rt, 16 h, 98%; (h) i. $(ClCO)_2$, DMSO, CH_2Cl_2, −70 °C, ii. NEt_3, 5 min, 100%; (i) $[PPh_3CH_3]^+Br^-$, *n*-BuLi, THF, 0 °C, 30 min → **25**, rt, 16 h, 92%; (j) $(n\text{-}Bu)_4NF$, MeCN, rt, 2 h, 97%; (k) i. $(ClCO)_2$, DMSO, CH_2Cl_2, −70 °C, ii. NEt_3, 5 min, 98%; (l) vinyl magnesium bromide, THF, −78 °C, 8%.

(data not shown). However the desired transformation occurred in very low yield employing either a commercial tetrahydrofuran solution of vinylmagnesium bromide or a freshly prepared Grignard reagent from vinyl bromide, and, unexpectedly, the isolated main product turned out to be the reduction product alcohol **27**. The problems associated to this synthetic step could be to some extent overcome with the use of a recently prepared tetrahydrofuran solution of vinyllithium. Efforts aimed at optimizing the addition of vinyl lithium or vinyl magnesium bromide onto **28** are currently being pursued in our laboratory. Conversion of **29** into **1** is direct and could be carried out by Jacobson protocol.

3. Conclusions

In conclusion, the formal synthesis of the key intermediate **1** is presented with a full characterization of all the respective intermediates until keto derivative **28** that were not available in the literature. The novelty in this synthetic approach was the facile access to free sugar **22**, in which it was possible to modify the oxidation state of the anomeric center.

4. Experimental

4.1. General methods

Unless otherwise noted, chemicals were commercially available and used without further purification. Air and/or moisture sensitive reactions were carried out under a dry argon atmosphere in flame dried glassware. Solvents were distilled before use. Methylene chloride was distilled from phosphorus pentoxide and stored over freshly activated 3 Å molecular sieves; methyl sulfoxide was distilled from calcium hydride and stored over freshly activated 3 Å molecular sieves, and tetrahydrofuran was distilled from sodium benzophenone ketyl. Anhydrous *N*,*N*-dimethylformamide was used as supplied from Aldrich.

Nuclear magnetic resonance spectra were recorded using a Bruker AM-500 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Melting points were determined using a Fisher–Johns apparatus and are uncorrected. Column chromatography separations were run using E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical thin layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel 60 F_{254}) and was visualized by 254 nm UV or by immersion into an ethanolic solution of 5% H_2SO_4. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia. The results were within ±0.4% of the theoretical values except where otherwise stated.

4.2. Allyl 2,3-*O*-isopropylidene-β-D-ribofuranoside 18

A mixture of D-ribose **17** (10.09 g, 67.2 mmol) in acetone (300 mL) cooled at 0 °C was treated with concentrated sulfuric acid (4.0 mL) dropwise. The reaction mixture was stirred at room temperature for 2 h. Then, allylic alcohol (10.0 mL) was added and the mixture was stirred at room temperature for 3 days. The reaction was quenched by addition of ammonium hydroxide until pH = 7.0. The resulting ammonium sulfate was filtered off and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (9:1) to afford 14.81 g (96% yield) of pure compound **18** as a colorless oil: R_f 0.45 (hexane–EtOAc, 3:2); $[\alpha]_D^{23} = -69.9$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, J = 17.4, 10.4, 6.1, 5.5 Hz, 1H, $CH_2CH{=}CH_2$), 5.31 (dq, J = 17.6, 1.5 Hz, 1H, $CH_2CH{=}CH_{trans}H$), 5.24 (dq, J = 10.3, 1.3 Hz, 1H, $CH_2CH{=}CHH_{cis}$), 5.12 (br s, 1H, H-1), 4.85 (d, J = 5.9 Hz, 1H, H-3), 4.63 (d, J = 5.9 Hz, 1H, H-2), 4.42 (t, J = 2.8 Hz, 1H, H-4), 4.24 (ddt, J = 12.7, 5.4, 1.4 Hz, 1H, $CH_aHCH{=}CH_2$), 4.07 (ddt, J = 12.7, 5.9, 1.4 Hz, 1H, $CHH_bCH{=}CH_2$), 3.53 (dt, J = 12.6, 2.5 Hz, 1H, H-5$_a$), 3.47 (ddd, J = 12.5, 10.5, 3.4 Hz, 1H, H-5$_b$), 3.16 (dd, J = 10.4, 2.8 Hz, 1H, *OH*), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1 ($CH_2CH{=}CH_2$), 118.3 ($CH_2CH{=}CH_2$), 112.1 ($C(CH_3)_2$), 108.0 (C-1), 88.5 (C-4), 86.0 (C-2), 81.5 (C-3), 69.0 ($CH_2CH{=}CH_2$), 64.0 (C-5), 26.4 (CH_3), 24.7 (CH_3). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.51; H, 7.98.

4.3. Allyl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside 19

A solution of compound **18** (14.81 g, 64.3 mmol) in anhydrous *N*,*N*-dimethylformamide (25 mL) cooled at 0 °C was treated with benzyl bromide (9.6 mL, 80.7 mmol) under argon atmosphere. Then, a 60% sodium hydride dispersion (3.76 g, 94.1 mmol) was added portionwise over 15 min while the temperature was maintained at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (150 mL). The mixture was extracted with methylene chloride (3 × 75 mL), and the combined organic layers were washed with brine (5 × 75 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (19:1) as eluent to give 12.52 g of pure **19** (61% yield) as a colorless oil: R_f 0.37 (hexane–EtOAc, 9:1); $[\alpha]_D^{23} = -15.3$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph), 5.84 (m, 1H, $CH_2CH{=}CH_2$), 5.24 (dq, J = 17.3, 1.6 Hz, 1H, $CH_2CH{=}CH_{trans}H$), 5.16 (dq, J = 10.3, 1.5 Hz, 1H, $CH_2CH{=}CHH_{cis}$), 5.11 (s, 1H, H-1), 4.69 (dd, J = 5.9, 0.7 Hz, 1H, H-3), 4.62 (d, J = 5.9 Hz, 1H, H-2), 4.56 (d, J = 12.1 Hz, 1H, OCH_bHPh), 4.52 (d, J = 11.8 Hz, 1H, OCH_aHPh), 4.40 (distorted t, J = 7.2 Hz, 1H, H-4), 4.13 (ddt, J = 13.0, 5.1, 1.4 Hz, 1H, $CH_aHCH{=}CH_2$), 3.93 (ddt, J = 13.0, 6.1, 1.4 Hz, 1H, $CHH_bCH{=}CH_2$), 3.53 (dd, J = 9.7, 6.8 Hz, 1H, H-5$_a$), 3.47 (dd, J = 9.7, 8.1 Hz, 1H, H-5$_b$), 1.48 (s, 3H, CH_3),

1.31 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0 (Ph), 133.8 ($CH_2CH{=}CH_2$), 128.4 (Ph), 127.7 (Ph), 117.3 ($CH_2CH{=}CH_2$), 112.4 ($C(CH_3)_2$), 107.3 (C-1), 85.3 (C-2), 85.2 (C-4), 82.2 (C-3), 73.3 (OCH_2Ph), 71.2 (C-5), 67.9 ($CH_2CH{=}CH_2$), 26.5 (CH_3), 25.0 (CH_3). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.69; H, 7.56.

4.4. *Z*-Prop-1-en-1-yl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside 20

A solution of compound **19** (9.72 g, 30.3 mmol) in methyl sulfoxide (10 mL) was treated with potassium *tert*-butoxide (1.36 g, 12.1 mmol) under argon atmosphere, and the reaction mixture was stirred at 100 °C for 16 h. The mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous layer was extracted with methylene chloride (2 × 50 mL). The combined organic layers were washed with brine (5 × 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexane–EtOAc (99:1) to afford 8.91 g (92% yield) of pure compound **20** as a colorless oil: R_f 0.37 (hexane–EtOAc, 9:1); $[\alpha]_D^{23} = -21.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ph), 6.08 (dq, *J* = 6.4, 1.7 Hz, 1H, C*H*=CHCH$_3$), 5.26 (s, 1H, H-1), 4.75 (d, *J* = 6.2 Hz, 1H, H-3), 4.72 (d, *J* = 5.9 Hz, 1H, H-2), 4.58 (d, *J* = 12.1 Hz, 1H, OCHH_aPh), 4.50 (d, *J* = 12.1 Hz, 1H, OCHH_bPh), 4.53 (distorted pentet, *J* = 6.8 Hz, 1H, CH=C*H*CH$_3$), 4.40 (distorted t, *J* = 7.1 Hz, 1H, H-4), 3.50 (dd, *J* = 9.9, 6.4 Hz, 1H, H-5$_a$), 3.47 (dd, *J* = 9.9, 8.0 Hz, 1H, H-5$_b$), 1.50 (dd, *J* = 6.7, 1.7 Hz, 3H, CH=CHC*H*$_3$), 1.49 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.4 (*C*H=CHCH$_3$), 137.9 (Ph), 128.4 (Ph), 127.7 (Ph), 112.6 ($C(CH_3)_2$), 108.0 (C-1), 103.4 (CH=*C*HCH$_3$), 85.7 (C-4), 85.0 (C-2), 82.2 (C-3), 73.4 (OCH_2Ph), 70.7 (C-5), 26.4 (CH_3), 25.0 (CH_3), 9.4 (CH=CH*C*H$_3$). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.24; H, 7.45.

4.5. Formyl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside 21

To a solution of compound **20** (5.64 g, 17.6 mmol) in anhydrous methylene chloride (50 mL) cooled at −78 °C was bubbled ozone until the reaction mixture turned blue. Then, triphenylphosphine (9.30 g, 35.2 mmol) was added and the mixture was allowed to warm to room temperature. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to afford 4.69 g (95% yield) of pure compound **21** as a colorless oil: R_f 0.29 (hexane–EtOAc, 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H, OC*H*O), 7.34 (m, 5H, Ph), 6.27 (s, 1H, H-1), 4.79 (d, *J* = 5.9 Hz, 1H, H-3), 4.72 (d, *J* = 5.9 Hz, 1H, H-2), 4.55 (m*AB*, 2H, OCH_2Ph), 4.50 (dist t, *J* = 6.2 Hz, 1H, H-4), 3.57 (dd, *J* = 10.0, 5.7 Hz, 1H, H-5$_a$), 3.48 (dd, *J* = 10.0, 7.3 Hz, 1H, H-5$_b$), 1.51 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (O*C*HO), 137.7 (Ph), 128.4 (Ph), 127.6 (Ph), 113.1 ($C(CH_3)_2$), 102.6 (C-1), 86.8 (C-4), 85.2 (C-2), 81.7 (C-3), 73.3 (OCH_2Ph), 70.2 (C-5), 26.4 (CH_3), 25.0 (CH_3).

4.6. 5-*O*-Benzyl-2,3-*O*-isopropylidene-α,β-D-ribofuranose 22

Method A. A solution of compound **21** (4.49 g, 14.6 mmol) in methanol (20 mL) was treated with triethylamine (0.5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the product was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (9:1) to yield 4.08 g (100% yield) of pure **22** as a colorless oil: R_f 0.49 (hexane–EtOAc, 7:3); $[\alpha]_D^{23} = -2.92$ (*c* 2.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H, Ph), 5.29 (s, 1H, H-1), 5.27 (s, 1H, H-1, α-anomer), 4.73 (d, *J* = 5.9 Hz, 1H, H-3), 4.64 (d, *J* = 11.6 Hz, 1H, OCH_aHPh), 4.57 (d, *J* = 11.6 Hz, 1H, OCHH_bPh), 4.50 (d, *J* = 5.9 Hz, 1H, H-2), 4.38 (dist t, *J* = 2.2 Hz, 1H, H-4), 3.66 (dd, *J* = 10.0, 2.5 Hz, 1H, H-5$_a$), 3.59 (dd, *J* = 10.0, 2.3 Hz, 1H, H-5$_b$), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1 (Ph), 128.4 (Ph), 128.1 (Ph), 112.0 ($C(CH_3)_2$), 103.8 (C-1), 100.7 (C-1 α-anomer), 87.6 (C-4), 85.6 (C-2), 82.0 (C-3), 74.1 (OCH_2Ph), 71.1 (C-5), 26.5 (CH_3), 24.9 (CH_3). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.25.

Method B. A solution of compound **19** (162 mg, 0.51 mmol) in methanol (10 mL) was treated with palladium chloride as catalyst (3.0 mg). The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through a Celite bed. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 42 mg of **22** and 69 mg of unreacted starting material **19** (72% yield).

4.7. 5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribitol 23

A solution of compound **22** (936 mg, 3.3 mmol) in anhydrous tetrahydrofuran (18 mL) was treated with lithium aluminum hydride (507 mg, 13.4 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with ethyl acetate (1.0 mL). The mixture was partitioned between an aqueous saturated solution of sodium potassium tartrate (100 mL) and methylene chloride (100 mL). The organic layer was washed with the tartrate solution (3 × 70 mL) and water (2 × 70 mL). The solvent was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (4:1) to afford 815 mg (88% yield) of pure compound **23** as a white solid: R_f 0.29 (hexane–EtOAc, 1:1); mp 64–65 °C; $[\alpha]_D^{23} = +26.3$ (*c* 2.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph), 4.59 (m*AB*, 2H, OCH_2Ph), 4.35 (dt, *J* = 7.7, 5.5 Hz, 1H, H-2), 4.10 (dd, *J* = 9.7, 5.8 Hz, 1H, H-3), 3.96 (m, 1H, H-4), 3.88 (ddd, *J* = 11.8, 7.7, 5.0 Hz, 1H, H-1$_a$), 3.80 (m, 1H, H-1$_b$), 3.76 (dd, *J* = 9.6, 3.0 Hz, 1H, H-5$_a$), 3.57 (dd, *J* = 9.6, 6.7 Hz, 1H, H-5$_b$), 3.00 (m, 1H, *OH*), 2.97 (m, 1H, *OH*), 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 137.8 (Ph), 128.5 (Ph), 127.8 (Ph), 108.6 ($C(CH_3)_2$), 85.6 (C-2)*, 82.0 (C-3)*, 73.5 (OCH_2Ph), 71.7 (C-5), 68.7 (C-4), 60.8 (C-1), 27.8 (CH_3), 25.3 (CH_3). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.04; H, 8.12.

4.8. 1-*O*-*tert*-Butyldiphenylsilyl-5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribitol 24

To a solution of compound **23** (1.59 g, 5.63 mmol) in anhydrous dimethylformamide (10 mL) was added imidazole (844 mg, 12.4 mmol) and *tert*-butyldiphenyl chlorosilane (1.61 g, 6.83 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (100 mL) and methylene chloride (100 mL). The aqueous phase was reextracted with methylene chloride (100 mL), and the combined organic layers were washed with brine (5×100 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to give 2.858 g (98% yield) of pure compound **24** as a colorless oil: R_f 0.47 (hexane–EtOAc, 4:1); $[\alpha]_D^{23} = -4.2$ (*c* 3.2 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4H, Ph), 7.46–7.28 (m, 11H, Ph), 4.65 (d, $J = 12.3$ Hz, 1H, OCH_aHPh), 4.61 (d, $J = 12.2$ Hz, 1H, $OCHH_bPh$), 4.34 (m, 1H, H-2), 4.29 (dd, $J = 9.3$, 5.7 Hz, 1H, H-3), 4.07 (m, 1H, H-4), 3.90 (dd, $J = 10.8$, 8.3 Hz, 1H, H-1_a), 3.79 (dd, $J = 10.1$, 2.3 Hz, 1H, H-5_a), 3.72 (d, $J = 3.4$ Hz, 1H, *OH*), 3.67 (dd, $J = 11.0$, 4.1 Hz, 1H, H-1_b), 3.65 (dd, $J = 10.0$, 5.6 Hz, 1H, H-5b), 1.31 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.07 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5 (Ph), 135.6 (Ph), 132.5 (Ph), 132.4 (Ph), 128.3 (Ph), 127.9 (Ph), 127.7 (Ph), 127.5 (Ph), 108.5 ($C(CH_3)_2$), 77.4 (C-2)*, 76.9 (C-3)*, 73.5 (OCH_2Ph), 71.8 (C-5), 69.0 (C-4), 62.9 (C-1), 27.9 (CH_3), 26.9 ($C(CH_3)_3$), 25.4 (CH_3), 19.1 ($C(CH_3)_3$). Anal. Calcd for $C_{31}H_{40}O_5Si$: C, 71.50; H, 7.74. Found: C, 71.69; H, 7.76. *Signal attribution may be interchanged.

4.9. (2*S*,3*S*)-1-*O*-*tert*-Butyldiphenylsilyl-5-*O*-benzyl-2,3-*O*-isopropylidene-4-keto-D-*erythro*-pentitol 25

To a solution of oxalyl chloride (1.12 mL, 12.93 mmol) in anhydrous methylene chloride (10 mL) cooled at −70 °C under argon atmosphere was added methyl sulfoxide (2 mL). The mixture was stirred at −70 °C for 5 min, then alcohol **24** (3.06 g, 5.88 mmol) in methylene chloride (10 mL) was added and the reaction was stirred for 15 min. Triethylamine (5.5 mL) was then added and the mixture was stirred for an additional 5 min. The mixture was allowed to warm to room temperature and water (50 mL) was added. The aqueous phase was reextracted with methylene chloride (50 mL). The combined organic layers were washed with brine (4×50 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 3.05 g (100% yield) of pure compound **25** as a colorless oil, which was used in the next step without further purification: R_f 0.42 (hexane–EtOAc, 4:1); $[\alpha]_D^{23} = -34.1$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4H, Ph), 7.38–7.27 (m, 11H, Ph), 4.70 (d, $J = 8.0$ Hz, 1H, H-3), 4.49–4.46 (m, 2H, H-$5_{a,b}$), 4.41–4.34 (m, 2H, OCH_2Ph, H-2), 3.78 (dd, $J = 11.6$, 4.6 Hz, 1H, H-1_a), 3.71 (dd, $J = 11.4$, 4.1 Hz, 1H, H-1_b), 1.55 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.04 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (C-4), 137.3 (Ph), 135.7 (Ph), 135.6 (Ph), 133.2 (Ph), 133.0 (Ph), 129.7 (Ph), 128.4 (Ph), 127.8 (Ph), 127.7 (Ph), 109.7 ($C(CH_3)_2$), 79.7 (C-3), 78.5 (C-2), 74.1 (C-5), 73.2 (OCH_2Ph), 61.9 (C-1), 26.9 ($C(CH_3)_3$), 26.7 (CH_3), 24.6 (CH_3), 19.2 ($C(CH_3)_3$).

4.10. (2*S*,3*R*)-1-*O*-*tert*-Butyldiphenylsilyl-5-*O*-benzyl-2,3-*O*-isopropylidene-4-*C*-methylene-D-*erythro*-pentitol 26

A suspension of methyltriphenylphosphonium bromide (19.32 g, 54.1 mmol) in anhydrous tetrahydrofuran (70 mL) at 0 °C was added *n*-butyllithium (1.6 M in hexane; 28.3 mL, 45.3 mmol) dropwise under argon atmosphere. The mixture was stirred at 0 °C for 30 min. Then, was added a solution of compound **25** (3.08 g, 5.9 mmol) in tetrahydrofuran (10 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (97:3) to afford 2.794 g (92% yield) of pure compound **26** as a colorless oil: R_f 0.28 (hexane–EtOAc, 9:1); $[\alpha]_D^{23} = -36.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H, Ph), 7.42–7.28 (m, 11H, Ph), 5.35 (s, 1H, C=CH_aH), 5.24 (s, 1H, C=CHH_b), 4.81 (d, $J = 5.9$ Hz, 1H, H-3), 4.50 (d, $J = 11.6$ Hz, 1H, OCH_aHPh), 4.40 (d, $J = 11.6$ Hz, 1H, $OCHH_bPh$), 4.33 (q, $J = 6.0$ Hz, 1H, H-2), 4.06 (d, $J = 12.5$ Hz, 1H, H-5_a), 3.99 (d, $J = 12.5$ Hz, 1H, H-5_b), 3.64 (dd, $J = 10.5$, 6.4 Hz, 1H, H-1_a), 3.49 (dd, $J = 10.5$, 5.5 Hz, 1H, H-1_b), 1.40 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.02 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8 (C-4), 138.2 (Ph), 135.7 (Ph), 135.6 (Ph), 133.5 (Ph), 133.3 (Ph), 129.6 (Ph), 128.4 (Ph), 127.6 (Ph), 127.6 (Ph), 113.7 (C=CH_2), 107.8 ($C(CH_3)_2$), 78.3 (C-3), 76.9 (C-2), 72.1 (OCH_2Ph), 71.8 (C-5), 63.5 (C-1), 27.6 (CH_3), 26.8 ($C(CH_3)_3$), 25.3 (CH_3), 19.1 ($C(CH_3)_3$).

4.11. (2*S*,3*R*)-5-*O*-Benzyl-2,3-*O*-isopropylidene-4-*C*-methylene-D-*erythro*-pentitol 27

A solution of the compound **26** (2.62 g, 5.07 mmol) in acetonitrile (30 mL) was added tetrabutyl ammonium fluoride (1.0 M in tetrahydrofuran, 7.0 mL, 7.0 mmol) and the resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated and the product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to afford 1.37 g (97% yield) of pure compound **27** as a colorless oil: R_f 0.26 (hexane–EtOAc, 4:1); $[\alpha]_D^{23} = -49.0$ (*c* 2.0 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H, Ph), 5.44 (s, 1H, C=CH_aH), 5.31 (s, 1H, C=CHH_b), 4.72 (d, $J = 6.4$ Hz, 1H, H-3), 4.53 (m*AB*, 2H, OCH_2Ph), 4.27 (q, $J = 6.4$ Hz, 1H, H-2), 4.03 (d, $J = 11.6$ Hz, 1H, H-5_a), 3.98 (d, $J = 11.6$ Hz, 1H, H-5_b), 3.51 (ddd, $J = 11.4$, 6.1, 5.2 Hz, 1H, H-1_a), 3.43 (dd, $J = 11.4$, 6.0, 5.4 Hz, 1H, H-1_b), 2.36 (t, $J = 6.1$ Hz, 1H, *OH*), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0 (C-4), 137.3 (Ph), 128.4 (Ph), 127.8

(Ph), 127.7 (Ph), 115.0 (C=CH_2), 107.9 ($C(CH_3)_2$), 77.9 (C-3), 76.6 (C-2), 72.9 (OCH_2Ph), 71.8 (C-5), 61.9 (C-1), 27.7 (CH_3), 25.2 (CH_3).

4.12. (2*S*,3*R*)-5-*O*-Benzyl-2,3-*O*-isopropylidene-1-keto-4-*C*-methylene-D-*erythro*-pentose 28

To a solution of oxalyl chloride (0.75 mL, 8.6 mmol) in anhydrous methylene chloride (10 mL) cooled at −70 °C under argon atmosphere was added methyl sulfoxide (1.5 mL). The mixture was stirred at −70 °C for 5 min, then compound **27** (1.09 g, 3.92 mmol) in methylene chloride (10 mL) was added and the reaction was stirred for 15 min. Triethylamine (4.0 mL) was then added and the mixture was stirred for an additional 5 min. The mixture was allowed to warm to room temperature and water (50 mL) was added. The aqueous phase was reextracted with methylene chloride (50 mL). The combined organic layers were washed with brine (4 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (9:1) to afford 1.059 g (98% yield) of pure compound **28** as a colorless oil: R_f 0.44 (hexane–EtOAc, 3:2); $[\alpha]_D^{23} = -44.5$ (*c* 1.5, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, J = 2.7 Hz, 1H, H-1), 7.33 (m, 5H, Ph), 5.41 (s, 1H, C=CH_aH), 5.28 (t, J = 1.1 Hz, 1H, C=CHH_b), 4.93 (d, J = 7.4 Hz, 1H, H-3), 4.53 (d, J = 12.0 Hz, 1H, OCHH_aPh), 4.49 (d, J = 11.9 Hz, 1H, OCHH_bPh), 4.46 (dd, J = 7.4, 2.8 Hz, 1H, H-2), 4.02 (m*AB*, 2H, H-5), 1.63 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2 (C-1), 139.1 (C-4), 137.7 (Ph), 128.4 (Ph), 127.8 (Ph), 127.7 (Ph), 114.9 C=CH_2), 110.5 ($C(CH_3)_2$), 81.6 (C-2), 77.6 (C-3), 72.3 (OCH_2Ph), 71.4 (C-5), 27.1 (CH_3), 25.3 (CH_3).

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References

1. Herdewijn, P.; De Clercq, E. In *A Textbook of Drug Design and Development*, 2nd ed.; Krogsgaard-Larsen, P., Liljefors, T., Madsen, U., Eds., Harwood Academic: Amsterdam, 1996; pp 425–459.
2. (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272; (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623.
3. Agrofolio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670.
4. Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1–40.
5. Marquez, V. E. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI: Greenwich, CT, 1996; Vol. 2, pp 89–146.
6. Rodriguez, J. B.; Comin, M. J. *Mini Rev. Med. Chem.* **2003**, *3*, 95–114.
7. Marquez, V. E.; Lim, M.-I.; Tseng, C. K.-H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709–5714.
8. Comin, M. J.; Rodriguez, J. B. *Tetrahedron* **2000**, *56*, 4639–4649.
9. Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1536–1537.
10. Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A.; Dae Hong Shin, D. H.; Jeong, L. S. J. *Org. Chem.* **2004**, *69*, 2634–2636.
11. Bestmann, H. J.; Roth, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 99–100.
12. Lee, K.; Cass, C.; Jacobson, K. A. *Org. Lett.* **2001**, *3*, 597–599.
13. Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1483–1487.
14. Song, G. Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R. W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2001**, *44*, 3985–3993.
15. Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712–4717.
16. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 76–86.
17. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
18. Jin, Y. H.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012–9018.
19. Chu, C. K.; Jin, Y. H.; Baker, R. O.; Huggins, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9–12.
20. Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136.
21. Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *II*, 318.
22. de Belder, A. N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219–301.
23. Marquez, V. E.; Russ, P.; Alonso, R.; Sidiqqui, M. A.; Hernández, S.; George, C.; Nicklaus, M.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119–2129.
24. Gigg, J.; Gigg, R. *J. Chem. Soc. (C)* **1966**, 82–86.
25. Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092–2112.
26. Manthorpe, P. A.; Giggs, R. *Methods Carbohydr. Chem.* **1980**, *8*, 305.
27. Nashed, M. A.; Anderson, L. *J. Chem. Soc., Chem. Commun.* **1982**, 1274–1276.
28. Rosenberg, H. J.; Riñey, A. M.; Correa, V.; Taylor, C. W.; Potter, B. V. L. *Carbohydr. Res.* **2000**, *329*, 7–16.
29. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.