C-Nucleosides. 2. Synthesis of 3-(β-D-Ribofuranosyl)phthalimide

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The synthesis of 3-(β-D-ribofuranosyl)phthalimide (**19**) from 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**1**) is described. One sequence started by aromatizing Diels–Alder reaction adduct **2** to dimethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate (**3**) with titanium tetrachloride–lithium aluminum hydride. Treatment of this with sodium hydroxide solution followed by dehydration with acetic anhydride and trifluoroacetic acid gave 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)phthalic anhydride (**12**). However, conversion of **12** into the phthalimide *C*-nucleoside was unsuccessful. The second sequence, which was brought to completion, made use of the adduct 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (**17**) as the starting material. Treatment of this with sulfuric acid in dichloromethane yielded phthalimide **18**, which on deblocking with sodium methoxide gave the desired phthalimide *C*-nucleoside **19**.

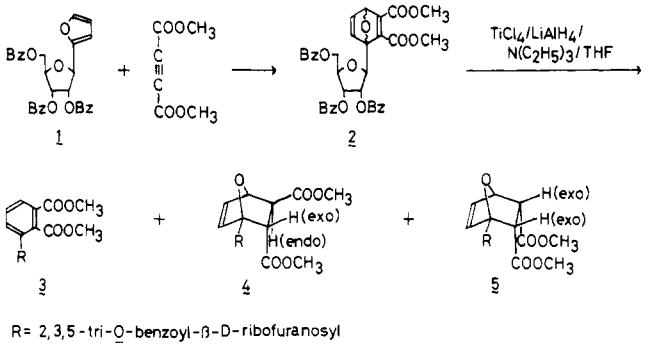
Because of their biological importance, considerable effort has been directed toward the synthesis of *C*-nucleosides during the past several years.[1] In a previous report[2] from our laboratory, we described the preparation of the key intermediate, 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**1**) (Scheme I), and utilization in the synthesis of pyridazine *C*-nucleosides by the Clauson–Kaas method. We now report here the synthesis of 3-(β-D-ribofuranosyl)phthalimide (**19**) from a versatile precursor **1**. The procedure for conversion of the furan ring of **1** into a phthalimide utilized the propensity of furans to undergo the Diels–Alder reaction. Two different approaches were investigated in our efforts to prepare **19**.

Treatment of **1** with dimethyl acetylenedicarboxylate at 100 °C for 5 h afforded the adduct **2** as a mixture of diastereomeric isomers in 94% yield. These isomers could not be separated by preparative TLC, but the mixture was entirely satisfactory for the next step. The synthetic route adopted for the aromatization of **2** was based on the method reported by Xing and Haung[3] for the deoxygenation of 7-oxabicyclo[2.2.1]hepta-2,5-diene and 7-oxabicyclo-[2.2.1]hept-2-ene systems to substituted benzene by titanium tetrachloride–lithium aluminum hydride under relatively mild conditions. Deoxygenation of **2** under these conditions afforded three products, which could be separated by preparative TLC. The desired product, dimethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate (**3**), was obtained in 57.5% yield accompanied by the unexpected partial reductive compounds **4**[4] and **5** in 14% and 19% yield, respectively. Extending the reaction time decreased the yield of the desired compound **3**. Attempted deoxygenation of **4** and **5** into **3** under a variety of acidic conditions, however, proved unsuccessful, leading to degradation of the starting material.

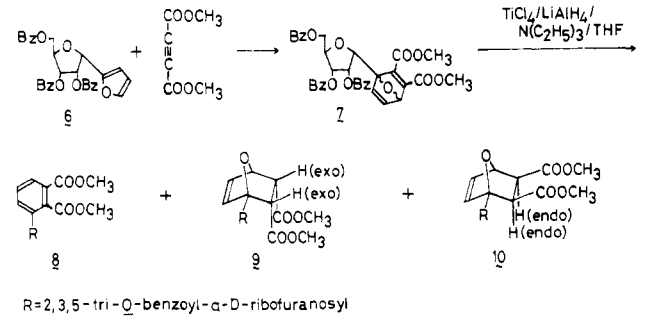
To establish the anomeric configuration of the benzene derivative **3**, we also prepared the α isomer, starting from **6** (Scheme II) by the same procedure. Deoxygenation of the adduct **7** afforded three products which could be separated by preparative TLC. Compound **8** was obtained in 49.2% yield accompanied by the partial reductive compounds **9** and **10** in 3.7% and 7.3% yield, respectively. The assignment of the anomeric configuration at C-1′ to **3**, **5**, **8**, and **9** were based on a comparison of their ^{1}H NMR spectra. The spectra of **8** and **9** exhibited a signal for H-1′ appearing further downfield (δ 5.71 and 5.01) than that for **3** and **5** (δ 5.49 and 4.96). The ^{1}H NMR data showed that no epimerization had occurred at the sugar glycosidic position during the Diels–Alder deoxygenation sequence, that is, the β-ribofuranoside configuration had been preserved.

Treatment of **3** with 5% sodium hydroxide in MeOH gave 3-(β-D-ribofuranosyl)phthalic acid (**11**) in 95.2% yield.

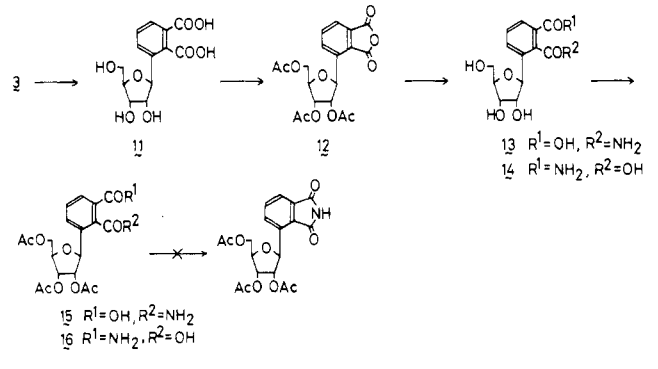
Scheme I



Scheme II



Scheme III



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(4) The structure of the substituent at C-1′ of this compound is possible to be represented by the formula **4** or its mirror image. The same relationships are present in compounds **5**, **9**, and **10**.

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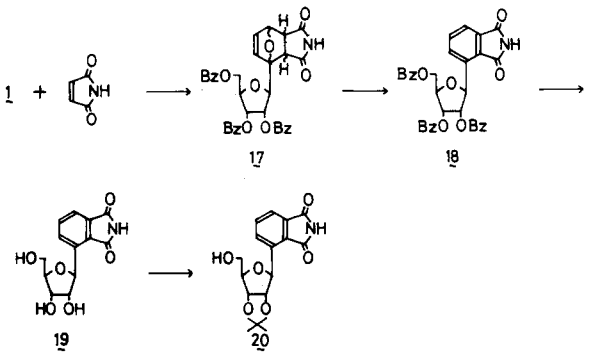
Scheme IV



Reaction of the phthalic acid **11** with acetic anhydride and trifluoroacetic acid at 40 °C for 6 h afforded 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)phthalic anhydride (**12**)(Scheme III) in quantitative yield. Attempts to purify **12** were found not practical owing to decomposition of this product on the silica gel column. The phthalic anhydride **12** reacted readily with ammonia in ether at room temperature to produce the inseparable mixture of phthalamic acids **13** and **14**, whose precise structure was not determined. Treatment of **13** and **14** with acetic anhydride afforded the protected phthalamic acid **15** and **16** which could be separated by preparative TLC. The assignments of the anomeric configuration of **12**, **15**, and **16** are based on ^{1}H NMR studies. The ^{1}H NMR spectra of the per-*O*-acetylated β-nucleosides contain signals for AcO-2′ at $\delta >$ 2.05, whereas per-*O*-acetylated α-nucleosides usually have this resonance at $\delta <$ 1.95.[5] The AcO-2′ values obtained for **12**, **15**, and **16** were $\delta >$ 2.05 (see Experimental Section), and therefore all of these were assigned the β-configuration. Unfortunately, we have been unable to effect cyclization of **15** and **16** by treatment with EPP[6] or acetyl chloride in DMF.[7] We did not go as far as the cyclization of **15** or **16**, since at this point we set aside the first approach in favor of another that was progressing smoothly and showing considerable promise. But the phthalic anhydride **12** may be used as a versatile intermediate for the synthesis of new types of *C*-nucleosides (for example, phthalazine,[8] benzimidazole,[9] and benzoxazine[10]).

A second route to **19**, the Diels–Alder reaction of glycosylfuran **1** with maleimide followed by aromatization, was examined. Treatment of **1** with maleimide in methanol at room temperature for 20 days afforded the adduct **17** (Scheme IV) as a diastereomeric mixture in 93.8% yield. Aromatization of **17** with sulfuric acid in dichloromethane gave the phthalimide **18** in 30% yield. Deblocking of **18** with sodium methoxide in methanol led to the desired phthalimide *C*-nucleoside **19** in 81.5% yield.

The identity of **19** was ascertained from its ^{1}H NMR spectrum, which exhibited a broad NH signal at δ 11.29 and three OH signals at δ 4.68–5.08 (all exchangeable with D_2O), as well as the aromatic proton signals appearing as an ABX type. The IR spectrum of **19** showed absorption bands at 1765 and 1730 cm^{-1} attributed to the imide carbonyl group. Due to the uncertainties of using ^{1}H NMR $J_{1',2'}$ values for the assignment of the anomeric configuration of *C*-nucleosides, the data obtained from the 2′,3′-*O*-isopropylidene derivative of **19** were used as a basis for the determination. The ^{1}H NMR chemical shift differential value ($\Delta\delta$) of the methyl groups in the isopropylidene derivative **20** (0.3 ppm) is indicative of β stereochemistry in accordance with the Imbach's rules.[11] In addition, the H-4′ resonance in **20** gave an apparent quartet which also was supportive of the β-configuration, according to a recent publication.[12] Examination of the biological activities of two compounds (**11** and **19**) is now under investigation.

Experimental Section

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Mass spectra were measured with Hitachi M-52 spectrophotometer and ^{1}H NMR spectra with a JEOL JNM-PS-100 spectrometer, with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Analytical thin-layer chromatography was performed on glass plates coated with a 0.25-mm layer of silica gel GF_{254} (Merk). The compounds were detected with a UV light (254 nm). Column chromatography was performed on silica gel C-200 (74-149μ, Wakogel). All reactions were repeated at least once to check for reproducibility.

Dimethyl 1-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (2 and 7). Dimethyl acetylenedicarboxylate (1.5 mL, 6.1 mmol) and glycosylfuran **1** (1.0 g, 2.0 mmol) were stirred at 100 °C for 6 h under nitrogen atmosphere. The reaction mixture was chromatographed over a column of silica gel with chloroform–hexane (1:3) as the eluent. The yield of the diastereomeric mixture **2** was 1.2 g (94%) as a colorless syrup. This mixture showed only a single spot on TLC in various solvent systems: R_f 0.17 ($CHCl_3$); MS, *m/e* 654 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.66, 3.70, 3.77, 3.87 (each s, CH_3), 4.38–4.80 (m, 3, H-4′, H-5′), 5.22 (d, 1, H-1′, $J_{1',2'}$ = 2 Hz), 5.53 (d, 1, H-4, $J_{4,5}$ = 2 Hz), 5.60–5.88 (m, 2, H-2′, H-3′), 6.98 (dd, 1, H-5, $J_{4,5}$ = 2 Hz, $J_{5,6}$ = 6 Hz), 7.15–8.05 (m, 16, Ar H and H-6); ^{13}C NMR ($CDCl_3$, partial) δ 83.71, 84.12 (C-4), 95.53, 96.99 (C-1); IR ($CHCl_3$) 3000, 1720, 1620 cm^{-1}.

In the same manner 1.2 g (94%) of the isomer **7** was obtained as a colorless syrup from 1.0 g of **6**: R_f 0.12 ($CHCl_3$); MS, *m/e* 654 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.68, 3.74 (each s, 3 each, CH_3), 4.60–4.84 (m, 3, H-4′, H-5′), 5.40 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.72 (d, 1, H-4, $J_{4,5}$ = 2 Hz), 5.87, 6.19 (each t, H-2′, H-3′, $J_{1',2'} = J_{2',3'} = J_{3',4'}$ = 6 Hz), 7.05–8.20 (m, 17, Ar H, H-5 and H-6); ^{13}C NMR ($CDCl_3$, partial) δ 84.06, 84.30 (C-4), 96.88, 97.93 (C-1); IR ($CHCl_3$) 3000, 1720, 1620 cm^{-1}.

Deoxygenation of 2 by Titanium Tetrachloride–Lithium Aluminum Hydride. To a solution of **2** (444 mg, 0.67 mmol) in absolute THF (8 mL) was slowly added 8 mL of lithium aluminum hydride–titanium tetrachloride–triethylamine in THF at room temperature. The reaction mixture was stirred at room temperature for about 20 h, and then it was poured into 20% aqueous potassium carbonate solution (20 mL). The resulting mixture was filtered, and the filter cake was washed thoroughly with chloroform. The filtrate was extracted with chloroform (3 × 10 mL). The combined chloroform solution was dried over anhydrous magnesium sulfate and evaporated to dryness in vacuo. TLC (chloroform–ethanol 40:1) showed that the light yellow syrup contained three major components (R_f 0.47, 0.41, and 0.37). The mixture was chromatographed over a column of silica gel with chloroform–hexane (1:3) as the eluent. The first compound eluted, **dimethyl 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate (3)** (249 mg, 57.5%, corresponding to R_f 0.47 on TLC), was obtained as a colorless syrup: MS, *m/e* 607 ($M - OCH_3$, calcd *m/e* 607.1574, found *m/e* 607.1571); ^{1}H NMR ($CDCl_3$) δ 3.78, 3.86 (each

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s, 3 each, CH_3), 4.56–5.02 (m, 3, H-4′, H-5′), 5.49 (d, 1, H-1′, $J_{1',2'}$ = 5 Hz), 5.63–5.88 (m, 2, H-2′, H-3′), 7.23–8.23 (m, 18, Ar H); ^{13}C NMR ($CDCl_3$) δ 52.47 (CH_3), 63.82 (C-5′), 71.78, 77.04, 79.79, 79.91 (C-1′, C-2′, C-3′, C-4′), 128.35–136.25 (Ar C), 164.97, 165.21, 165.91, 166.14, 168.54 (C=O).

Anal. Calcd for $C_{36}H_{30}O_{11}\cdot{}^1/_2H_2O$: C, 66.77; H, 4.82. Found: C, 66.88; H, 4.69.

Dimethyl 2-*endo*-3-*exo*-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (4) was eluted as the second fraction (62 mg, 14%, corresponding to R_f 0.41 on TLC) as a colorless syrup: ^1H NMR ($CDCl_3$) δ 3.29 (dd, 1, H-3, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 4 Hz, becomes a doublet when the H-4 is irradiated), 3.61 (s, 6, CH_3), 3.67 (d, 1, H-2, $J_{2,3}$ = 10 Hz), 4.36–4.85 (m, 4, H-1′, H-4′, H-5′), 4.99 (br s, 1, H-4), 5.81 (m, 2, H-2′, H-3′), 6.51 (dd, 1, H-5, $J_{4,5}$ = 2 Hz, $J_{5,6}$ = 6 Hz), 6.65 (d, 1, H-6, $J_{5,6}$ = 6 Hz), 7.20–8.20 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 46.92, 49.43 (C-2, C-3), 51.83 (CH_3), 63.12 (C-5′), 71.78, 74.12, 79.10, 80.03, 80.38 (C-1′, C-2′, C-3′, C-4′, C-4), 90.91 (C-1), 128.29–133.38 (Ar C), 134.84, 135.55 (C-5, C-6), 165.21, 166.21, 170.41, 170.82 (C=O).

Anal. Calcd for $C_{36}H_{32}O_{12}$: C, 65.85; H, 4.91. Found: C, 65.76; H, 5.06.

Dimethyl 2-*endo*-3-*endo*-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (5) was eluted as the third fraction (86 mg, 19%, corresponding to R_f 0.37 on TLC) as a white solid, mp 125–127 °C; ^1H NMR ($CDCl_3$) δ 3.58–3.62 (m, 8, CH_3, H-2, H-3), 4.38–4.85 (m, 3, H-4′, H-5′), 4.96 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 5.12 (br s, 1, H-4, becomes a doublet when the H-5 is irradiated, $J_{3,4}$ = 2 Hz), 5.61–5.91 (m, 2, H-2′, H-3′), 6.45 (dd, 1, H-5, $J_{4,5}$ = 2 Hz, $J_{5,6}$ = 6 Hz), 6.66 (d, 1, H-6, $J_{5,6}$ = 6 Hz), 7.20–8.19 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 48.62, 50.08 (C-2, C-3), 51.83 (CH_3), 63.53 (C-5′), 72.43, 72.60, 79.10, 79.86, 81.14 (C-1′, C-2′, C-3′, C-4′, C-4), 91.32 (C-1), 128.23–133.38 (Ar C), 134.90, 135.08 (C-5, C-6), 165.27, 166.14, 170.30, 170.65 (C=O).

Anal. Calcd for $C_{36}H_{32}O_{12}\cdot 3H_2O$: C, 61.01; H, 5.12. Found: C, 61.09; H, 4.67.

Deoxygenation of 7 by Titanium Tetrachloride–Lithium Aluminum Hydride. The same procedure was used as for the reaction of 2 with titanium tetrachloride–lithium aluminum hydride.

Dimethyl 3-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-phthalate (8): colorless syrup, 49.2%; R_f 0.39 (chloroform–ethanol 40:1); ^1H NMR ($CDCl_3$) δ 3.81, 3.85 (each s, 3 each, CH_3), 4.48–4.90 (m, 3, H-4′, H-5′), 5.71 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 5.80–6.14 (m, 2, H-2′, H-3′), 7.08–8.12 (m, 18, Ar H).

Anal. Calcd for $C_{36}H_{30}O_{11}\cdot 5H_2O$: C, 59.33; H, 5.53. Found: C, 59.75; H, 5.38.

Dimethyl 2-*endo*-3-*endo*-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (9): colorless syrup, 3.7%; R_f 0.32 (chloroform–ethanol 40:1); ^1H NMR ($CDCl_3$) δ 3.63–3.67 (m, 8, CH_3, H-2, H-3), 4.48–4.86 (m, 3, H-4′, H-5′), 5.01 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 5.12 (br s, 1, H-4, becomes a doublet when the H-5 is irragiated, $J_{3,4}$ = 2 Hz), 5.86 (m, 1, H-3′), 6.18 (m, 1, H-2′), 6.44 (dd, 1, H-5, $J_{4,5}$ = 2 Hz, $J_{5,6}$ = 5 Hz), 6.57 (d, 1, H-6, $J_{5,6}$ = 5 Hz), 7.12–8.10 (m, 15, Ar H).

Anal. Calcd for $C_{36}H_{32}O_{12}$: C, 65.85; H, 4.91. Found: C, 65.66; H, 5.07.

Dimethyl 2-*exo*-3-*exo*-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (10): colorless syrup, 7.3%; R_f 0.34 (chloroform–ethanol 40:1); ^1H NMR ($CDCl_3$) δ 3.45 (d, 2, H-2, H-3, $J_{3,4}$ = 2 Hz, becomes a singlet when the H-4 is irragiated), 3.54, 3.57 (each s, 3 each, CH_3), 4.60–4.82 (m, 3, H-4′, H-5′), 4.92 (d, 1, H-1′, $J_{1',2'}$ = 3 Hz), 5.03 (m, 1, H-4), 5.84 (q, 1, H-3′, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 8 Hz), 6.21 (q, 1, H-2′, $J_{1',2'}$ = 3 Hz, $J_{2',3'}$ = 5 Hz), 6.49 (dd, 1, H-5, $J_{4,5}$ = 2 Hz, $J_{5,6}$ = 6 Hz), 6.74 (d, 1, H-6, $J_{5,6}$ = 6 Hz), 7.20–8.20 (m, 15, Ar H).

Anal. Calcd for $C_{36}H_{32}O_{12}\cdot H_2O$: C, 64.09; H, 5.08. Found: C, 63.80; H, 5.20.

3-(β-D-Ribofuranosyl)phthalic Acid (11). To a stirred solution of 3 (144 mg, 0.22 mmol) in methanol (2 mL) was slowly added 2 mL of 5% sodium hydroxide in methanol. After 18 h at room temperature, the reaction solution was neutralized with Dowex 50W-X8 cation-exchange resin (H^+). The resin was collected by filtration and rinsed twice with 10-mL portions of methanol. The combined filtrates were then evaporated to afford a colorless syrup. This syrup purified by filtration through a bed of silica gel in a sintered-glass funnel by eluting first with chloroform to remove the methyl benzoate and then with chloroform–methanol (2:1). This afforded 64 mg of 11 (95.2%) as a white solid, mp 200 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.60–4.25 (m, 5, H-2′, H-3′, H-4′, H-5′) 4.83 (br s, 6, H-1′, OH), 7.46 (m, 1, H-4), 7.85 (m, 2, H-5, H-6); IR (KBr) 3400, 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_8\cdot H_2O$: C, 49.37; H, 5.10. Found: C, 49.77; H, 5.12.

3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)phthalic Anhydride (12). To a stirred solution of 46 mg (0.15 mmol) of 11 in 2 mL of freshly distilled acetic anhydride was added 0.4 mL of trifluoroacetic acid. The mixture was stirred for an additional hour at room temperature and then was heated at 40 °C for 6 h to effect ring closure. Excess of reagent and trifluoroacetic acid were removed by evaporation in vacuo to give the anhydride 12 (60 mg) as a colorless syrup: MS, m/e 406 (M^+); ^1H NMR ($CDCl_3$) δ 2.09, 2.10, 2.13 (each s, 3 each, CH_3), 4.40 (s, 3, H-4′, H-5′), 5.21 (m, 2, H-2′, H-3′), 5.86 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 7.80–8.18 (m, 3, Ar H); IR ($CHCl_3$) 1850, 1770, 1735 cm^{-1}.

3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)phthalamic Acid (15) and 6-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)phthalamic Acid (16). The anhydride 12 (40 mg, 0.1 mmol) was dissolved in dry ether (2 mL), dry ammonia was bubbled through the solution at 0 °C for 10 min, and the mixture was allowed to stand at room temperature for 24 h. Evaporation left the crude deprotected maleamic acid 13 and 14 which were chromatographically inseparable. The crude maleamic acid (45 mg) was dissolved in dry pyridine (1 mL) and acetic anhydride (1 mL), and the mixture was stirred at room temperature for 12 h. The solvent were removed under reduced pressure, and the residue was coevaporated three times with toluene (5 mL). The residue was separated by preparative TLC with chloroform–ethanol (100:3) as the eluent.

Compound 15:[13] colorless foam; 24%, R_f 0.33 (chloroform–ethanol 5:1); ^1H NMR (Me_2SO-d_6) δ 2.10, 2.17 (each s, 9, CH_3), 4.20–4.60 (m, 3, H-4′, H-5′), 5.15–5.36 (m, 3, H-1′, H-2′, H-3′), 5.93 (br, 3, NH_2, OH), 7.52 (t, 1, H-5, $J_{4,5}$ = $J_{5,6}$ = 8 Hz), 7.84 (d, 1, H-4, $J_{4,5}$ = 8 Hz), 8.05 (d, 1, H-6, $J_{5,6}$ = 8 Hz).

Compound 16:[13] colorless foam; 16.8%; R_f 0.22 (chloroform–ethanol 5:1); ^1H NMR (Me_2SO-d_6) δ 2.11, 2.18 (each s, 9, CH_3), 4.40 (m, 3, H-4′, H-5′), 5.23 (m, 3, H-1′, H-2′, H-3′), 5.80 (br, 3, NH_2, OH), 7.40–7.92 (m, 3, Ar H).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-7-oxabicyclo-[2.2.1]hept-5-ene-2,3-dicarboximide (17). A solution of 1 (1.41 g, 2.75 mmol) and maleimide (288 mg, 2.97 mmol) in chloroform (0.1 mL) and methanol (10 mL) was allowed to stir at room temperature for 20 days. The solvent was removed in vacuo below 30 °C to a syrup which was purified on a silica gel column with chloroform as the eluent. This afforded 1.5 g of 17 (93.8%) as a colorless syrup. An analytically pure sample was obtained by preparative TLC; IR ($CHCl_3$) 3010, 1765, 1710, 1600 cm^{-1}.

Anal. Calcd for $C_{34}H_{27}NO_{10}$ (mixture): C, 66.99; H, 4.46; N, 2.30. Found: C, 67.21; H, 4.57; N, 2.45.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)phthalimide (18). To a solution of the adduct 17 (200 mg, 0.33 mmol) in CH_2Cl_2 (4 mL) was slowly added 0.2 mL of acetic anhydride and sulfuric acid (10:1) at 0 °C. The mixture was stirred for an additional hour at 0 °C and then was allowed to stand at room temperature for 24 h. Water was added, the mixture was neutralized with $NaHCO_3$, and then the mixture was extracted with chloroform (3 × 30 mL). The dried chlorform solution on evaporation afforded a syrup. The residue was chromatographed over a column of silica gel with chloroform–ethanol (50:1) as the eluent. This afforded 55 mg of 18 (30%) as a white solid, mp 169.5–171 °C; MS, m/e 591 (M^+); ^1H NMR ($CDCl_3$) δ 4.61–5.10 (m, 3, H-4′, H-5′), 5.61 (t, 1, H-3′, $J_{2',3'}$ = $J_{3',4'}$ = 6 Hz), 5.84 (t, 1, H-2′, $J_{1',2'}$, $J_{2',3'}$ = 6 Hz), 6.33 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 7.25–8.36 (m, 19, Ar H, NH); IR ($CHCl_3$) 3420, 3010, 1765, 1725, 1600 cm^{-1}.

Anal. Calcd for $C_{34}H_{25}NO_9\cdot H_2O$: C, 66.99; H, 4.46; N, 2.30. Found: C, 67.39; H, 4.28; N, 2.22.

3-(β-D-Ribofuranosyl)phthalimide (19). Methanolic sodium methoxide (14.3 mg) was added to the protected *C*-nucleoside 18

(13) Although this compound was homogeneous by TLC, we were unable to obtain proper microanalytical data for it.

(26 mg, 0.044 mmol) in 1 mL of absolute methanol. The mixture was allowed to stand at room temperature for 3 h, rendered neutral with Dowex 50W-X8 cation-exchange resin (H^+). The resin was filtered and the solvent was evaporated to dryness in vacuo. The residue was purified by preparative TLC to afford the free *C*-nucleoside **19** (10 mg, 81.5%) as a white solid, mp 180–182 °C; $[\alpha]^{24.3}_D$ +52.9 (*c* 0.59, methanol); MS, *m/e* 279 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.47–4.08 (m, 5, H-2′, H-3′, H-4′, H-5′), 5.68 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 7.67–7.97 (m, 2, H-4, H-5), 8.10 (dd, 1, H-6, $J_{5,6}$ = 6 Hz, $J_{4,6}$ = 2 Hz); ^{13}C NMR (Me_2SO-d_6) δ 61.89 (C-5′), 71.37, 78.39, 78.51, 84.94 (C-1′, C-2′, C-3′, C-4′), 122.15, 128.99, 132.62, 133.09, 134.43 (Ar–C), 169.13, 169.71 (C=O); IR ($CHCl_3$) 3580, 3320, 3210 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91, H, 4.70; N, 5.02. Found: C, 56.07; H, 4.55; N, 4.99.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)phthalimide (20). Ethyl orthoformate (0.1 mL, 0.6 mmol) was added to a well-stirred suspension of **19** (9 mg, 0.032 mmol) in acetone (1 mL) containing *p*-toluenesulfonic acid monohydrate (4.6 mg) and the mixture was allowed to stand at room temperature for 12 h. Then sodium bicarbonate was added, and the mixture was stirred for 15 min. The solid was collected by filtration and thoroughly washed with acetone. The filtrates were combined and evaporated in vacuo to a syrup which was purified by preparative TLC: MS, *m/e* 319 (M^+); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3, isopropylidene CH_3), 1.65 (s, 3, isopropylidene CH_3), 2.94 (br, 1, OH), 3.89 (m, 2, H-5′), 4.23 (q, 1, H-4′, $J_{3',4'}$ = 8 Hz, $J_{4',5'}$ = 4 Hz), 4.68 (t, 1, H-2′, $J_{1',2'}$ = $J_{2',3'}$ = 5 Hz), 4.91 (dd, 1, H-3′, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 8 Hz), 5.69 (d, 1, H-1′, $J_{1',2'}$ = 5 Hz), 7.63–8.04 (m, 3, Ar H), 10.71 (br, 1, NH); IR ($CHCl_3$) 3645, 3410, 2980, 1760, 1720, 1620 cm^{-1}.

Registry No. **1**, 86528-49-6; **2** (isomer 1), 89196-63-4; **2** (isomer 2), 89299-52-5; **3**, 89196-64-5; **4**, 89196-65-6; **6**, 86528-50-9; **7** (isomer 1), 89254-78-4; **7** (isomer 2), 89254-79-5; **8**, 89196-66-7; **9**, 89196-67-8; **11**, 89196-68-9; **12**, 89196-69-0; **13**, 89196-70-3; **14**, 89196-71-4; **15**, 89196-72-5; **16**, 89196-73-6; **17**, 89196-74-7; **18**, 89196-75-8; **19**, 89196-76-9; **20**, 89196-77-0; dimethyl acetylenedicarboxylate, 762-42-5; maleimide, 541-59-3.

Studies of Vitamin D Oxidation. 4. Regio- and Stereoselective Epoxidation of Vitamin D

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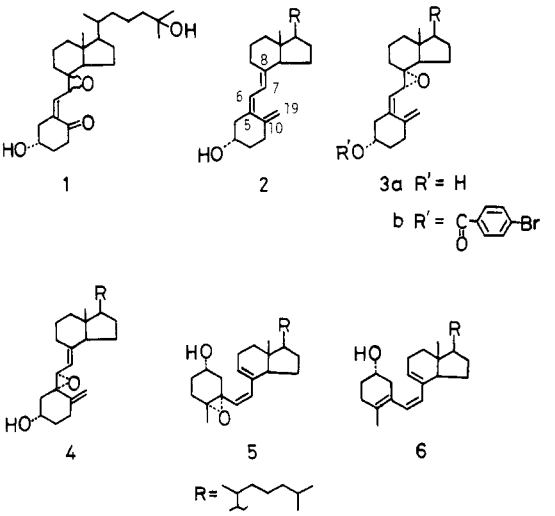
Regio- and stereoselective epoxidations of vitamin D_3 at the 7,8- and 5,6-double bonds were performed. Epoxidation with *m*-chloroperbenzoic acid gave exclusively (7*R*)-7,8-epoxyvitamin D_3 (81%) while epoxidation with *tert*-butyl hydroperoxide catalyzed by $VO(acac)_2$ afforded (5*S*)-5,6-epoxyvitamin D_3 in excellent yield (90%). The structures of the epoxides were confirmed by spectral analysis and by single-crystal X-ray analysis.

By extensive studies of the metabolism of vitamin D, more than twenty metabolites of vitamin D_3 (**2**) have been isolated and identified.[1] The structural alterations of vitamin D by metabolism can be classified into two groups, hydroxylation at the 1α-position under conditions of vitamin D deficiency and oxidation at the side chain mostly under conditions of vitamin D supplementation. Oxidation of the conjugated triene part of vitamin D has not been observed in the metabolites isolated so far, except for 7,8-epoxy-25-hydroxy-19-nor-10-oxovitamin D_3 (**1**),[2] although one may expect such oxidation in vivo as in other unsaturated fat-soluble biological compounds such as fatty acids[3] and vitamin A.[4] We have been studying the oxidation of the conjugated triene part of vitamin D in conjunction with biological oxidation and have reported its oxidation with singlet oxygen.[5]



1 2 3a R′ = H b R′ = 4-bromobenzoyl 4 5 6

Selective epoxidation of vitamin D derivatives is known. It has been reported that epoxidation of 3,5-dinitro-

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