C-Nucleosides and related compounds. XIII. Synthesis of D,L-2′-deoxyshowdomycin (1*d*)

GEORGE JUST AND MU-ILL LIM
Department of Chemistry, McGill University, Montreal, P.Q., Canada H3C 3G1

Received September 23, 1976[1]

GEORGE JUST and MU-ILL LIM. Can. J. Chem. **55**, 2993 (1977).

Starting from the Diels–Alder adduct of furan and methyl β-nitroacrylate, the synthesis of the title compound is described.

GEORGE JUST et MU-ILL LIM. Can. J. Chem. **55**, 2993 (1977).

Partant de l'adduit de Diels–Alder du furanne avec le β-nitroacrylate de méthyle, on décrit une synthèse du composé mentionné dans le titre.

[Traduit par le journal]

We have recently described the synthesis of the 2′-epimer **1***b* of D,L-showdomycin **1***a* (1), and of the carbocyclic analogues of D,L-showdomycin **1***c* (2) and D,L-2′-deoxypyrazofurin A (3), starting from the Diels–Alder adducts of methyl β-nitroacrylate and furan or β-bromoacrylic acid and cyclopentadiene, respectively.

We now should like to describe a similar sequence of reactions leading to D,L-2′-deoxyshowdomycin **1***d* (see Scheme 1).

Because of some variability in the ratio of adducts **2** and **3** obtained in the initial Diels–Alder reaction, the reaction was studied in some detail. At 45°C, the concentration of the *endo*-nitro adduct **2** reached a maximum after 8 h (**2**:**3** = 2). After 4 days, an equilibrium was reached in which the *exo*-nitro adduct **3** predominated (**2**:**3** = 0.5).

Konig and co-workers reported the similar result that the *endo*-nitro isomer predominated in early stages of the Diels–Alder reactions of furan or 2,5-dimethyl furan with nitroethylene (4).

Hydroboration of the *exo*-nitro adduct **3** and oxidation of the resulting organoborane with alkaline hydrogen peroxide (5) was unsatisfactory. However, reaction of **3** with diborane in tetrahydrofuran at 0°C, followed by oxidation with triethylamine *N*-oxide dihydrate as reported by Kabalka and Hedgecock (6), resulted in the formation of the isomeric mixture of the alcohols **4***a* in 42% yield after chromatography on silicic acid.

The resulting isomeric alcohols **4***a* could not be separated. Direct acetylation of the alcohol using acetic anhydride and *p*-toluenesulfonic acid monohydrate afforded the acetates **4***b* in good yield. All attempts to separate the isomeric acetates failed. It is interesting to note here that acetylation with acetic anhydride in pyridine led to decomposition products, as already noted for similar bicyclic systems (1).

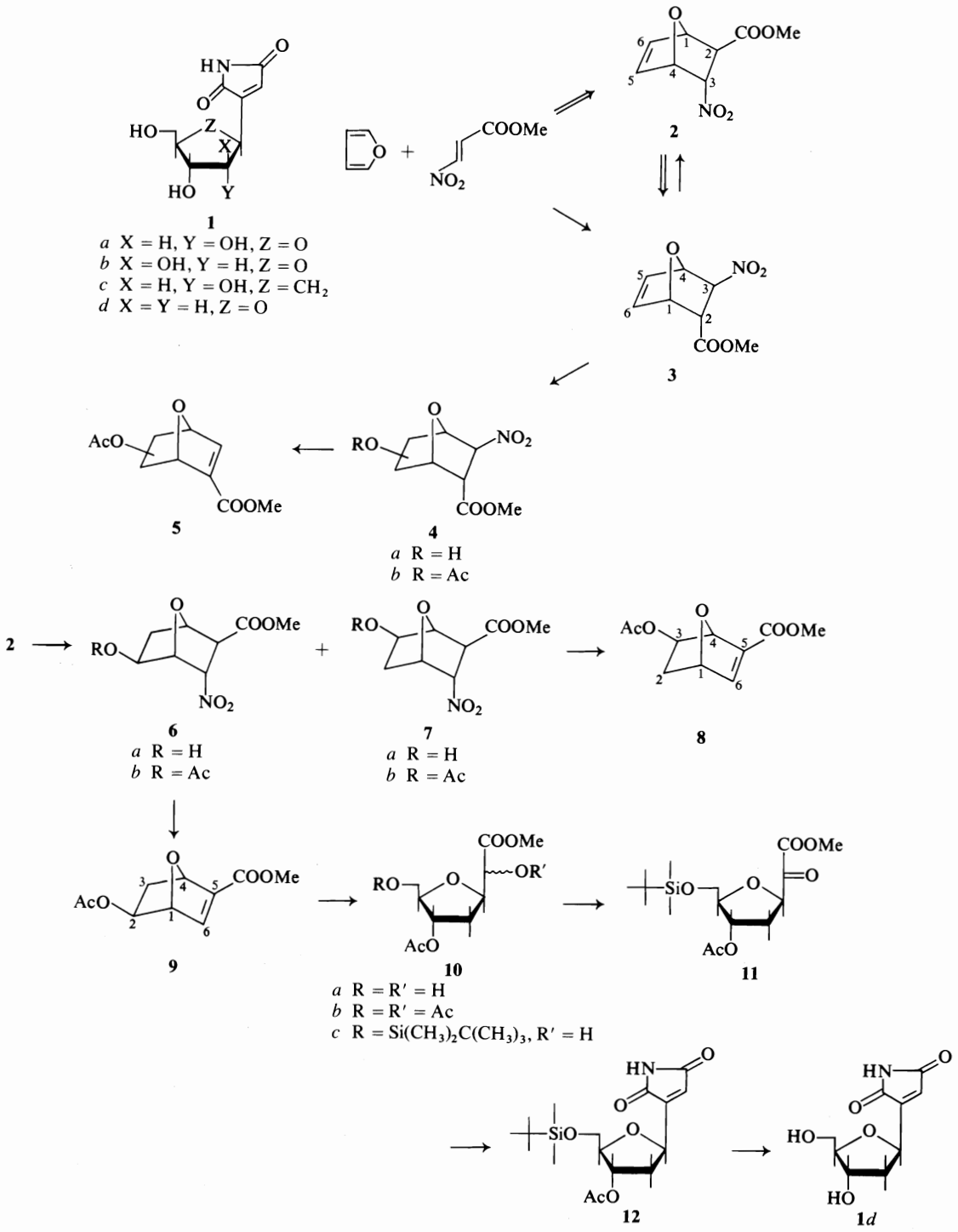
The acetates **4***b* were treated with diazabicyclo[5.4.0]undec-5-ene (DBU) in methylene chloride under reflux for 1 h to give the olefin esters **5** (7). The products consisted of a 1:1 mixture of isomers according to the nmr spectral data and could not be separated.

The above synthetic route was repeated starting with the *endo*-nitro adduct **2**. Hydroboration of **2** and oxidation of the resulting borane with triethylamine *N*-oxide dihydrate, under conditions identical to those described above, gave the isomeric alcohols **6***a* and **7***a* which were obtained in 46% yield after column chromatography on silicic acid. Without separation of the isomers, the mixture was acetylated with acetic anhydride and *p*-toluenesulfonic acid monohydrate in 82% yield. Both isomers were formed in approximately equal amounts, based on the nmr spectral data of **6***b*, **7***b*.

It was possible to separate the two isomers by fractional crystallization from hexane – carbon tetrachloride. One isomer, mp 113–114°C, was later identified to be the desired acetate **6***b* and the other, mp 67–68°C, to be the undesired acetate **7***b*. At this stage, we were unable to confirm the structures by nmr spectroscopy.

Elimination of nitrous acid from the acetate **6***b* by means of DBU in refluxing methylene chloride gave the 2-acetate olefin ester **9** in 91% yield. Using the same conditions as above,

[1]Revision received April 21, 1977.



SCHEME 1

nitrous acid elimination from the acetate **7***b* afforded, after chromatography, a good yield of the 3-acetate olefin ester **8**. Both isomers had virtually identical ir and mass spectra but different nmr spectra.

In the nmr spectrum of the 2-acetate **9**, the C-4 proton gave a doublet at δ 5.16 (J = 4 Hz) due to coupling with the C-3 *exo* proton. A doublet for the C-6 proton at δ 6.92 resulted from $J_{6,1}$ = 2 Hz. Decoupling of the C-6 proton readily allowed identification of the C-1 proton at δ 5.00 (J = 2 Hz) because irradiation of the doublet for the C-6 proton collapsed the doublet for the C-1 proton to a singlet. The C-2 proton signal was split into a doublet of doublets with $J_{2,3endo}$ = 6 Hz and $J_{2,3exo}$ = 2 Hz (X part of AMX). The C-3 protons appeared as a complex multiplet at δ 1.73–2.20. The remaining two singlets for the carbomethoxy and acetyl protons were found at δ 3.70 and 2.03, respectively.

In the case of the acetate **8**, a singlet for the C-4 proton could be expected since there is no coupling between the C-4 proton and C-3 *endo* proton. In fact, a one-proton singlet overlapped with a one-proton multiplet at δ 4.90–5.10. Irradiation of the multiplet collapsed a doublet for the C-6 proton at δ 7.03 (J = 2 Hz) to a singlet. Therefore, it was obvious that a singlet arose from the C-4 proton and a multiplet from the C-1 proton which coupled with the C-6 and C-2 protons. Like the C-2 *endo* proton in the 2-acetate, the C-3 *endo* proton showed a doublet of doublets with $J_{3,2endo}$ = 6 Hz and $J_{3,2exo}$ = 2 Hz.

Ozonolysis of the olefin ester **9** in methylene chloride at low temperature, followed by mild reduction with dimethyl sulfide (7), afforded the crude aldehydo keto ester and its hydrated form in a ratio of 1:3, as established by nmr.

Since we knew from previous experience that the aldehyde could not be reduced selectively (1), the aldehydo keto ester was treated with 4 equiv. of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at 0°C for 4 h to give the diol ester **10***a* in 62% yield after column chromatography on silicic acid. The structure of the diol ester was confirmed by acetylation to **10***b*.

Selective silylation of the diol ester **10***a* with 1 equiv. of *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide (9) at room temperature for 20 h provided the hydroxy ester **10***c* in 77% yield after purification by column chromatography on silicic acid.

Several different methods were examined for the oxidation of the hydroxy ester **10***c* to the keto ester **11**. By far the best results were obtained using dimethyl sulfoxide – acetic anhydride (10).

The keto ester **11** obtained by oxidation with dimethyl sulfoxide – acetic anhydride was treated with 1 equiv. of carbamoylmethylenetriphenylphosphorane (11) in chloroform at room temperature for 2 h. The reaction gave a single major product together with a considerable amount of polar products. By chromatography of the products on silica gel plates, the maleimide **12** was isolated in an overall yield of 38% from the hydroxy ester **10***c*. In agreement with the maleimide structure, this product showed a strong uv absorption characteristic for the maleimide chromophore at 222 nm in ethanol. The ir spectrum showed a broad absorption at 3420 cm^{-1} (NH) and the typical absorptions at 1780, 1740, 1725, and 1655 cm^{-1} (C=O, C=C). In the mass spectrum the major peak was found at m/e 312 ($M^+ - C(CH_3)_3$). The nmr spectrum displayed a single NH proton at δ 6.55. Similar reaction sequences in related systems indicate that no epimerization took place at the 'anomeric' center.[2]

The protected 2′-deoxyshowdomycin **12** was subjected to treatment with 0.1 *N* methanolic hydrochloric acid at room temperature for 26 h to remove the acetyl and silyl groups. Subsequent purification by a column of silicic acid using acetone – ethyl acetate (3:7) led to crystalline D,L-2′-deoxyshowdomycin **1***d*, mp 122–124°C, in 68% yield. Kalvoda (13) and Nakagawa *et al.* (14) used the same conditions to remove the acetyl groups of 2′,3′,5′-tri-*O*-acetylshowdomycin. The mass spectrum clearly indicated the complete removal of the protecting groups. A molecular ion was found at m/e 213 (M^+) and a major fragment corresponding to loss of water from the molecular ion at m/e 195 ($M^+ - H_2O$). The uv spectrum showed an absorption at 222 nm (log ε 4.18) like showdomycin and 2′-epishowdomycin and the molar extinction coefficient was also in accordance with that of known examples (1, 14), thus confirming the structure of the aglycon moiety of **1***d*. Furthermore, the elemental analysis confirmed the purity of the final product.

The synthetic route described seems to be

[2]From ref. 12 and unpublished results of T. J. Liak.

quite simple and straightforward, and should be applicable to other 2′-deoxy-analogues of *C*-nucleosides. No further work is at present being undertaken in this area.

Experimental

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra were obtained on an AE1-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer. Infrared spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 ir spectrophotometer. Ultraviolet spectra were determined with a Unicam SP-800 spectrophotometer. Microanalyses were carried out by Dr. C. Daessle, Montreal.

*A Mixture of 2-exo-Carbomethoxy-5-exo-hydroxy-3-endo-nitro-7-oxabicyclo[2.2.1]heptane and 2-exo-Carbomethoxy-6-exo-hydroxy-3-endo-nitro-7-oxabicyclo[2.2.1]heptane (**6***a*, **7***a*)*

A solution of **2** (858 mg, 4.3 mol) in dry tetrahydrofuran (10 ml) was cooled to 0°C by means of an ice-water bath. To the reaction mixture was added 3 ml of 1 *M* diborane solution (3 mmol) in tetrahydrofuran and the mixture was stirred for 2.5 h under nitrogen. After evaporation to dryness *in vacuo* the residue and triethylamine *N*-oxide dihydrate (658 mg, 4.3 mmol) were dissolved in dry tetrahydrofuran (20 ml). The reaction mixture was heated under reflux for 2.5 h. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with 0.1 *N* hydrochloric acid, water, and with brine, dried, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform afforded 416 mg (46%) of the isomeric mixture of **6***a* and **7***a* as an oil; ir ($CHCl_3$) 3650, 3500 (OH), 1735 (C=O), 1735 (C=O), 1578 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.33–2.40 (m, 2H), 2.90 (m, 1H), 3.26 (m, 1H), 3.73 (s, 3H), 4.03 (m, 1H), 4.60–5.10 (m, 2H), 5.10–5.30 (m, 1H). *Anal.* calcd. for $C_8H_{11}NO_6$: C 44.24, H 5.11, N 6.45; found: C 44.35, H 5.10, N 6.78.

*5-exo-Acetoxy-2-exo-carbomethoxy-3-endo-nitro-7-oxabicyclo[2.2.1]heptane (**6b**) and 6-exo-Acetoxy-2-exo-carbomethoxy-3-endo-nitro-7-oxabicyclo[2.2.1]-heptane (**7b**)*

A mixture of the isomeric alcohols **6***a* and **7***a* (504 mg, 2.32 mmol) and acetic anhydride (4 ml) containing 1 equiv. of *p*-toluenesulfonic acid monohydrate was stirred overnight at room temperature. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform, washed with water, and dried over sodium sulfate. Following evaporation of the solvent chromatography of the residue on a column of silicic acid using chloroform afforded 495 mg (82%) of the isomeric mixture of **6***b* and **7***b* as an oil.

One isomer, the 5-acetoxy heptane **6***b*, was crystallized from hexane–carbon tetrachloride to give 220 mg, mp 113–114°C; ir (KBr) 1735 (C=O), 1550 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.70–2.60 (m, 5H), 3.36 (d, 1H, J = 4 Hz), 3.70 (s, 3H), 4.70–5.03 (m, 3H), 5.30 (m, 1H); ms *m/e* 228 ($M^+ - OCH_3$), 213 ($M^+ - HNO_2$), 171, 153, 128, 43. *Anal.* calcd. for $C_{10}H_{13}NO_7$: C 46.33, H 5.06, N 5.40; found: C 46.53, H 5.26, N 5.43.

Upon evaporation the residue contaminated with **6***b* was chromatographed on a column of silicic acid using chloroform–hexane (1:1), giving 121 mg of the 6-acetoxy heptane **7***b* as an oil. The product solidified on standing, mp 67–68°C; ir (KBr) 1735 (C=O), 1550 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.70–2.30 (m, 5H), 3.37 (d, 1H, J = 4 Hz), 3.70 (s, 3H), 4.70–5.06 (m, 3H), 5.20 (m, 1H); ms *m/e* 228 ($M^+ - OCH_3$), 213 ($M^+ - HNO_2$), 169, 127, 81. *Anal.* calcd. for $C_{10}H_{13}NO_7$: C 46.33, H 5.06, N 5.40; found: C 46.23, H 5.30, N 5.21.

*2-exo-Acetoxy-5-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene (**9**)*

A solution of **6***b* (605 mg, 2.34 mmol) and DBU (444 mg, 281 mmol) in methylene chloride (20 ml) was refluxed for 1.5 h. The mixture was diluted with methylene chloride, washed with 0.1 *N* hydrochloric acid and water, dried, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform–hexane (3:1) afforded 453 mg (91%) of **9** as an oil which solidified on standing, mp 62–63°C; ir (KBr) 1725, 1710 (C=O), 1610 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.73–2.20 (s + m, 5H), 3.70 (s, 3H), 4.76 (q, 1H, J = 3 Hz, H-2), 5.00 (d, 1H, $J_{1,6}$ = 2Hz, H-1), 5.16 (d, 1H, $J_{4,3exo}$ = 4 Ha, H-4), 6.92 (d, 1H, $J_{6,1}$ = 2 Hz, H-6); ms *m/e* 212 (M^+), 181 ($M^+ - OCH_3$), 169 ($M^+ - COCH_3$), 152 ($M^+ - CH_3COOH$), 137, 127, 109. *Anal.* calcd. for $C_{10}H_{12}O_5$: C 56.50, H 5.70; found: C 56.45, H 5.36.

*3-exo-Acetoxy-5-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene (**8**)*

A mixture of **7***b* (189 mg, 0.73 mmol) and DBU (122 mg, 0.8 mmol) in methylene chloride was heated under reflux for 1.5 h. After the usual work-up chromatography of the residue on a column of silicic acid using chloroform–hexane (3:1) gave 108 mg (70%) of **8** as an oil which was crystallized from hexane–carbon tetrachloride, mp 119–120°C; ir (KBr) 1725, 1710 (C=O), 1610 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.70–2.10 (s + m), 3.70 (s, 3H), 4.75 (q, 1H, J = 3 Hz, H-3), 4.90–5.10 (s + m, 2H, H-4 and H-1), 7.03 (d, 1H, $J_{6,1}$ = 2 Hz, H-6); ms *m/e* 197 ($M^+ - CH_3$), 181 ($M^+ - OCH_3$), 169 ($M^+ - COCH_3$), 152 ($M^+ - CH_3COOH$), 127, 95, 43. *Anal.* calcd. for $C_{10}H_{12}O_5$: C 56.50, H 5.70; found: C 56.46, H 5.58.

*Methyl 2-(3-O-Acetyl-2-deoxy-β-D,L-ribofuranosyl)-glycolate (**10***a*)*

To a solution of **9** (483 mg, 2.28 mmol) in dry methylene chloride at −78°C was bubbled ozone until a blue color persisted. Excess ozone was flushed with nitrogen and dimethyl sulfide (0.5 ml) was added. The reaction mixture was allowed to come to room temperature over a period of 5 h. The solution was then washed with brine three times, dried over magnesium sulfate, and evaporated. To a solution of the residue in dry tetrahydrofuran (20 ml) at 0°C was added lithium tri-*tert*-butoxyaluminum hydride (2.3 g, 9.1 mmol). The reaction mixture was stirred at 0°C for 4 h and a solution of ammonium sulfate (1.5 g) in water (2 ml) was added. After filtration over a layer of Celite and evaporation, the residue was dissolved in ethyl acetate, washed with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid using chloroform–ethyl acetate (1:2), giving 349 mg (62%) of **10***a* as an oil; ir ($CHCl_3$) 3500 (OH), 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.73–

2.56 (s + m, 5H), 3.43–4.16 (m, 7H), 4.16–4.80 (m, 3H), 5.10 (m, 1H). *Anal.* calcd. for $C_{10}H_{16}O_7$: C 48.38, H 6.50; found: C 48.49, H 6.28.

*Methyl 2-O-Acetyl-2-(3,5-di-O-acetyl-2-deoxy-β-D,L-ribofuranosyl)glycolate (**10***b*)*

The diol **10***a* (157 mg) was acetylated with acetic anhydride (1 ml) and pyridine (2 ml). After the usual work-up chromatography of the crude product on a column of silicic acid using chloroform–hexane (1:1) afforded 149 mg (70%) of **10***b* as an analytically pure oil; ir (neat) 1745 cm^{-1} (C=O), no hydroxyl group; nmr (CCl_4) δ 1.80–2.70 (m, 11H), 3.63 (m, 3H), 3.76–4.06 (m, 3H), 4.30 (m, 1H), 4.73–5.06 (m, 2H); ms *m/e* 332 (M^+), 301 ($M^+ - OCH_3$), 273 ($M^+ - CH_3COO$), 259, 201, 152, 81. *Anal.* calcd. for $C_{14}H_{20}O_9$: C 50.60, H 6.07; found: C 50.38, H 6.26.

*Methyl 2-(3-O-Acetyl-5-O-tert-butyldimethylsilyl-2-deoxy-β-D,L-ribofuranosyl)glycolate (**10***c*)*

To a solution of **10***a* (242 mg, 0.98 mmol) in dimethylformamide (5 ml) was added *tert*-butyldimethylsilyl chloride (148 mg, 0.98 mmol) and imidazole (166 mg, 2.45 mmol). The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform gave 276 mg (77%) of **10***c* as an oil; ir (neat) 3450 (OH), 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 1.76–2.53 (s + m, 5H), 3.23 (m, 1H), 3.53–3.97 (m, 6H), 4.10–4.46 (m, 2H), 5.03 (m, 1H). *Anal.* calcd. for $C_{16}H_{30}O_7Si$: C 53.04, H 8.29; found: C 53.27, H 8.05.

*2-(3-O-Acetyl-5-O-tert-butyldimethylsilyl-2-deoxy-β-D,L-ribofuranosyl)maleimide (**12**)*

A mixture of **10***c* (152 mg, 0.42 mmol) and acetic anhydride (1 ml) in dry dimethyl sulfoxide (4 ml) was stirred overnight at room temperature. The mixture was diluted with chloroform and washed with an aqueous sodium bicarbonate solution, water, and brine. The organic layer was dried over magnesium sulfate and evaporated to dryness, leaving the crude keto ester **11** as an oil which was contaminated with minor amounts of impurities. Without any further purification this material was directly used in the next step. A solution of the resulting keto ester and carbamoylmethylenetriphenylphosphorane (121 mg, 0.38 mmol) in dry chloroform was stirred at room temperature for 2 h. The solvent was then evaporated. The residue was chromatographed on a silica gel plate using ethyl ether – hexane (1:1), giving 58 mg (38% from **10***c*) of **12** as an oil; ir ($CHCl_3$) 3420 (NH), 1780, 1740, 1725 (C=O), 1645 cm^{-1} (C=C); uv λ_{max} (EtOH) 222 nm; nmr ($CDCl_3$) δ 0.06 (s, 6H), 0.86 (s, 9H), 1.70–2.76 (s + m, 5H), 3.70–3.90 (m, 2H), 4.10 (m, 1H), 4.83–5.23 (m, 1H), 5.33 (m, 1H), 6.55 (t, 1H, C=CH), 8.20 (m, 1H, NH); ms *m/e* 312 ($M^+ - C(CH_3)_3$), 253, 129, 117, 75, 73. *Anal.* calcd. for $C_{17}H_{27}NO_6Si$: C 55.28, H 7.32, N 3.79; found: C 55.12, H 7.35, N 3.68.

*2-(Z-Deoxy-β-D,L-ribofuranosyl)maleimide (**1***d*)*

A solution of **12** (102 mg, 0.28 mmol) in 0.1 *M* methanolic hydrochloric acid (15 ml) was stirred at room temperature for 26 h. After evaporation to dryness, chromatography of the residue on a column of silicic acid using acetone – ethyl acetate (3:7) afforded 40 mg (68%) of **1***d* as an oil which was crystallized from acetone–benzene; mp 122–124°C; ir (KBr) 3510, 3320, 3280, 3100 (OH, NH), 1770, 1700 (C=O), 1640 cm^{-1} (C=C); uv λ_{max} (EtOH) 222 nm (log ε 4.18); ms *m/e* 214 ($M^+ + 1$), 213 (M^+), 195 ($M^+ - H_2O$), 182, 165, 153, 136, 124, 81, 53, 44, 43, 39, 31, 29. *Anal.* calcd. for $C_9H_{11}NO_5$: C 50.70, H 5.20, N 6.57; found: C 50.85, H 5.40, N 6.64.

Acknowledgment

We wish to thank the National Research Council of Canada for financial assistance.

1. M. Lim. Ph.D. Thesis, McGill University, Montreal, P.Q. 1976.
2. G. Just and S. G. Kim. Tetrahedron Lett. 1063 (1976).
3. G. Just and S. G. Kim. Can. J. Chem. **55**, 427 (1977).
4. T. A. Eggelte, H. de Konig, and H. O. Huisman. Heterocycles, **4**, 19 (1976).
5. G. Zweifel and H. C. Brown. Org. React. **13**, 1 (1963).
6. G. N. Kabalka and H. C. Hedgecock. J. Org. Chem. **40**, 1776 (1975).
7. H. Oediger and Fr. Möller. Angew. Chem. Int. Ed. Engl. **6**, 76 (1967).
8. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger. Tetrahedron Lett. 4273 (1966).
9. E. J. Corey and A. Venkateswarlu. J. Am. Chem. Soc. **94**, 6190 (1972).
10. J. D. Albright and L. Goldman. J. Am. Chem. Soc. **89**, 2416 (1967).
11. (*a*) S. Trippett and D. M. Walker. J. Chem. Soc. 3874 (1959); (*b*) G. Trummlitz and J. G. Moffatt. J. Org. Chem. **38**, 1841 (1973).
12. G. Just and S. Kim. Tetrahedron Lett. 1063 (1976); G. P. Donnini. Ph.D. Thesis, McGill University, Montreal, P.Q. 1976.
13. L. Kalvoda, J. Farkas, and F. Sorm. Tetrahedron Lett. 2297 (1970).
14. Y. Nakagawa, H. Kano, Y. Tsukuda, and H. Koyama. Tetrahedron Lett. 4105 (1967).