matography using a Hewlett-Packard Model 402 gas chromatograph with a flame-ionization detector (3% SP2250 column, 2 mm i.d. × 1.80 m, 260 °C). High-resolution mass spectra were recorded on an MS-30 instrument by a direct probe inlet system at the University of Minnesota. Low-resolution mass spectra were recorded on a Hewlett-Packard 5970 series mass spectrometer system with a 5890 GC apparatus for sample introduction and a Hewlett-Packard 9133 system for data acquisition. Fourier transform ^1H NMR spectra were recorded on a Nicolet Magnetic Corporation NMC-300 spectrometer equipped with a 1280 data system. All spectra were referenced to $CHCl_3$ (7.259 ppm). Commercial reagents and solvents were analytical grade or were purified by standard procedures[22] prior to use. Radioactivity was determined with a Beckman LZ7500 liquid scintillation counter through the courtesy of Prof. R. D. Simoni of the Biology Department at Stanford University.

Incorporation of Radiolabeled Precursors. *J. stellifera* (Carter, 1879) was obtained from 10 to 15 m at two reefs (John Brewer and Rib) located in the central section of the Australian Great Barrier Reef. Portions of sponges were attached underwater to PVC plastic plaques with nylon cable ties and were left for at least 1 week to allow reattachment to the plaques. Precursors were then incorporated into sponge transplants (June and October 1985) with methods modified after Catalan et al.[7] and Carballeira et al.[23] The precursors were transferred to 4-L glass containers containing 2–3 L of unfiltered seawater in 2 mL of ethanol. The contents were continuously aerated via a glass outlet and were maintained under dim natural light at ambient ocean surface temperature (approximately 25 °C). After 30 min of aeration, a single sponge transplant was placed in each aquarium for 6 to 12 h. The transplants were then returned to their original sites of collection for 30 days. Finally the sponges were frozen, lyophilized, and shipped to Stanford for analysis.

Isolation and Purification of Sterols. The sterol fraction of the sponge samples from the incorporation experiments was obtained according to our standard procedure.[7]

Acknowledgment. Financial support was provided by NIH Grants GM-06840 and GM-28352. Use of the 300-MHz NMR spectrometers at Stanford University was made possible by NSF Grant CHE 81-09064. We thank Prof. R. D. Simoni for the use of his liquid scintillation counter and Dr. Peter Murphy, Libby Evans, and Jane Fromont for field assistance. This is contribution no. 369 from the Australian Institute of Marine Science.

Registry No. 2, 52936-69-3; 3, 71486-08-3; 4, 38636-50-9; 7, 69081-87-4; 8, 69081-88-5.

Stereoselective Formation of a Steroidal 20-Hydroxy-24-oic Lactone by a Novel Reaction of Dichloroketene with an Epoxy Olefin

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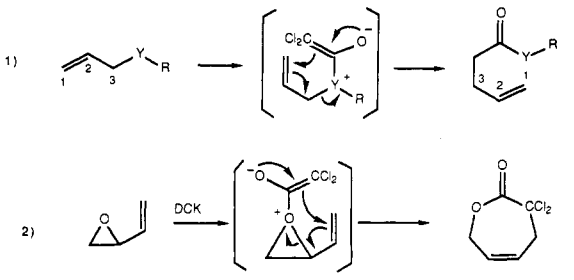
Received February 16, 1988

Reaction of dichloroketene (DCK) (generated from trichloroacetyl chloride and zinc dust) with the 20-methylene derivative of 16α,17α-epoxy-3β-acetoxy-5-pregnene (1) gave (20*R*)-3β-acetoxy-23,23-dichloro-20-hydroxy-5,16-choladien-24-oic lactone (4) in high yield. Zinc dust dechlorination of 4 gave lactone **6b**, which was converted to triol **9a** on treatment with lithium aluminum hydride. A single-crystal X-ray analysis of 5, a monodechlorinated derivative of 4, established the structure and C-20 configuration of all these five-membered lactones. The expected product from the reaction of DCK with 1 was a dichloro seven-membered lactone, 2, which is proposed as an intermediate in the formation of 4. On treatment with zinc chloride, 1 was rapidly transformed to an allylic chloro alcohol, 7, which also gave lactone 4 on subsequent reaction with DCK. Alkylation of 7 with dimethyl malonate produced a seven-membered lactone ester (11), analogous to the proposed intermediate 2. Treatment of 11 with zinc chloride induced a facile rearrangement to an isomeric five-membered lactone (12), which on hydrolysis and decarboxylation gave **6a**, identical in all respects with the hydrolysis product (3β-alcohol) from **6b**.

The chemistry of dichloroketene (DCK) and its use in synthesis have been studied and reviewed by Brady and co-workers.[1] This in situ generated reagent has been used chiefly in 2π + 2π cycloaddition reactions with olefins, and recent improvements in its preparation from di- or trichloroacetyl chloride[2] are such that DCK merits serious consideration as a convenient ketene equivalent despite the large mass loss due to discarded chlorine.

The scope of dichloroketene cycloadditions is limited in part by the tendency of allyl ethers and allyl sulfides to rearrange as shown in eq 1.[3] In a recently reported synthesis of (±)-lineatin,[4] this rearrangement was suppressed by substitution of 1,2-dimethoxyethane (glyme) for phosphorus oxychloride as a sequestering solvent in the reaction of zinc dust with trichloroacetyl chloride.

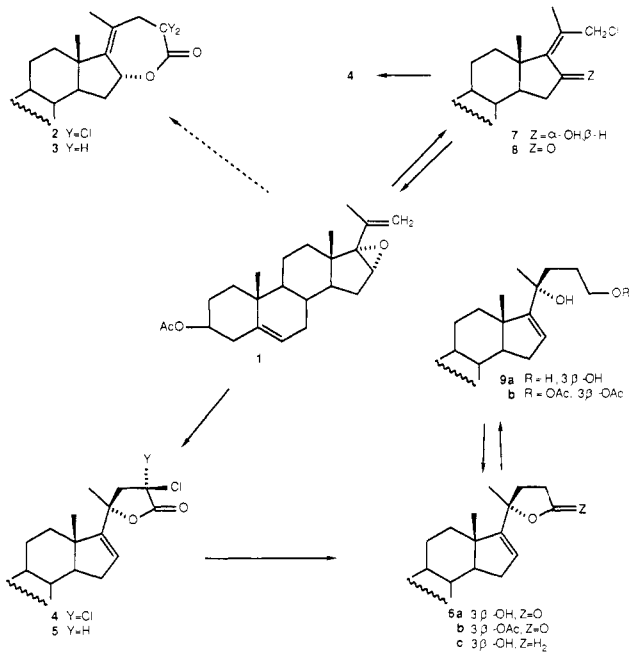


Our interest in dichloroketene lay in part on our expectation that it would react with conjugated epoxy olefins to form seven-membered lactones under mild conditions, as shown in eq 2. The substrate we chose to examine first in this respect was the 20-methylene derivative 1 of 16α,17α-epoxypregnenolone acetate. Dechlorination of the anticipated product (2) from reaction of 1 with DCK

(1) (a) Brady, W. T. *Tetrahedron* **1981**, 37, 2949. (b) Brady, W. T. *The Chemistry of Ketenes, Allenes and Related Compounds, Part I*; Patai, S., Ed.; Wiley: New York, 1980.
(2) (a) Krepski, L.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, *15*, 991.
(3) (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (b) Rossisi, G.; Spineti, E.; Foresti, E.; Pradella, G. *J. Org. Chem.* **1981**, *46*, 2228. (c) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860.
(4) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114.

0022-3263/88/1953-3469$01.50/0

Scheme I



should give lactone **3**, which we believed could be elaborated with good configurational control at C-20 (Scheme I). The reaction of **1** with DCK took an unexpected course, however, giving instead of **2** the five-membered lactone **4** as the only isolated product (65–75% yield from glyme solution and over 85% from ether). Carbonyl absorption at 1791 cm^{-1} provided the first clue to the identity of this compound, and off-resonance decoupling of the olefinic ^{13}C NMR signals demonstrated the presence of two trisubstituted double bonds. Final confirmation of structure **1** was eventually accomplished by examination of monodechlorinated derivative **5** (vide infra). It is noteworthy that the heterocyclic oxygen atom in **4** is no longer bonded to either of the carbon atoms (16 and 17) where it originated in epoxy olefin **1**.

Dechlorination of **4** by zinc dust/acetic acid gave **6** as a mixture of isomers, presumed to be epimeric at C-20 (doubling of ^1H NMR signals from protons on C-16, C-18, and C-21). This unwelcome epimerization could be prevented by conducting the dechlorination reaction in methanol saturated with ammonium chloride, and in this fashion **6** was obtained in almost quantitative yield. The sensitivity of **6** to acid-catalyzed epimerization was demonstrated by brief exposure to zinc chloride (acetic acid solution), whereupon a 50:50 mixture of C-20 epimers was obtained. Lactones of this kind are relatively rare,[5] the only previous synthesis being from 3β-methoxy-5-androsten-17-one in four steps with poor stereoselectivity (20*R* in overall 21% yield and 20*S* in 8% yield).[6] Saturated 24,20-lactones were prepared earlier by Sarel et al.,[7] again with poor stereoselectivity, and were used in a synthesis of 14α-bufadienolides.

During our study of dechlorination reactions, we treated **4** with tributyltin hydride, as described in the Experimental Section. A good yield of the selectively monodechlorinated lactone **5** resulted, and this yielded crystals suitable for X-ray analysis. Figure 1 displays an ORTEP diagram of **5**, determined in the course of its structure solution and refinement. Clearly the 20*R* configuration disclosed by this study establishes the corresponding configurations of **4** and **6**. Furthermore, the stereoselective dechlorination of **4** by the action of tributyltin hydride appears to proceed with loss of the less hindered chlorine atom to give **5**. The structure displayed in Figure 1 reflects this assertion and resembles closely the most stable C-17:C-20 rotamer found by MM2 calculations[8] on structure **6**.

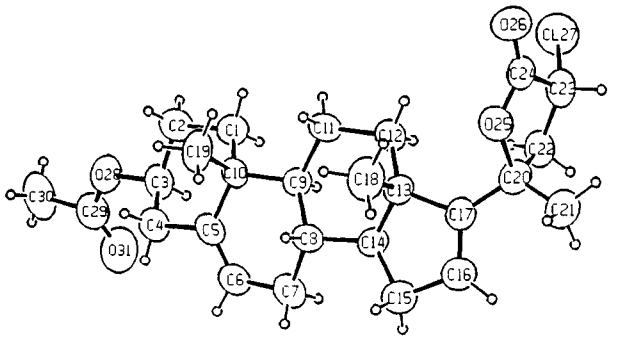


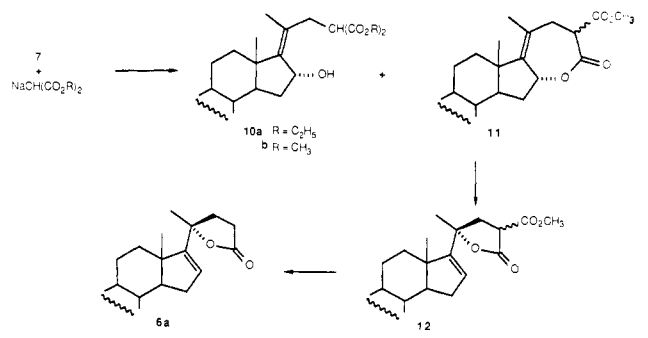
Figure 1. ORTEP diagram of compound **5**.

Our initial speculation regarding the mechanism of the DCK reaction with **1** focused on the possibility that **2** was an intermediate. A suprafacial 1,3-shift of oxygen from C-16 to C-20 (presumably acid catalyzed) would then account for the configuration of **4**. We were, however, concerned by the absence of **2** in our product mixtures. A new factor emerged with the isolation and identification of chloro alcohol **7** from reactions in which an excess of DCK (relative to **1**) was not used. In some experiments **7** was the major product, and it was also obtained in poorer yield on exposure of **1** to zinc chloride alone. Key steps in the identification of **7** were its oxidation to cyclopentenone **8**, conversion to epoxide **1b** on treatment with base, and alkylation with malonic ester. The *Z* configuration of the double bond in **7** was established by chemical shift changes on converting **7** to **8**[9] and by the lactonization of the malonic ester alkylation product. We suggest that the stereoselectivity of the reaction giving **7** from **1** reflects a cyclic S_N2' mechanism, involving an initial coordination of zinc chloride with the epoxide oxygen followed by suprafacial attack of the associated chloride at the olefin terminus. Since treatment with DCK converted **7** to **4**, either the former compound is an intermediate in the addition of DCK to **1** or it is the product of a fast but reversible and nonproductive side reaction of **1**.

The potential usefulness of lactone **6b** as an intermediate in side-chain synthesis was probed by a study of selected reduction reactions. Attempts to convert **6b** to the corresponding lactol (or hydroxy aldehyde) by reaction with diisobutylaluminum hydride (DIBALH) failed. With 1 equiv of reducing agent, cleavage of the acetoxy group at C-3 proved to be the chief reaction. In order to effect reduction of the lactone function, it was necessary to use an excess of DIBALH in refluxing ether. Unfortunately, these conditions led to overreduction and dehydration, giving tetrahydrofuran **6c** in good yield, accompanied by some epimerization at C-20. Reduction of **6b** with lithium aluminum hydride gave an excellent yield of triol **9a**, but

(5) Two trisnordammarane lactones from *Cabralea polytricha* (Meliacae) have a 20*S*,24 lactone function. Cascon, S. C.; Brown, K. S. *Tetrahedron* **1972**, *28*, 315.
(6) Kocor, M.; Bersz, B. *Tetrahedron* **1985**, *41*, 197.
(7) (a) Shalon, Y.; Yanuka, Y.; Sarel, S. *Tetrahedron Lett.* **1969**, 957. (b) Sarel, S.; Shalon, S.; Yanuka, Y. *Chem. Commun.* **1970**, *80*, 81.
(8) MM2 calculations were run on an IBM-AT computer using programs distributed by Serena Software, Box 3076, Bloomington, IN 47402. These programs were adapted from the original MM programs of N. L. Allinger by J. J. Gajewski and K. E. Gilbert.
(9) For an example of chemical shift differents of *E* and *Z* isomers of 17-alkylidene-16-keto steroids, see: Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.

Scheme II



this compound was very sensitive to traces of acid. Conversion of **9a** to the diacetate derivative **9b** served to block the facile dehydration of the former to **6c**. Oxidative allylic rearrangement of **9b** produced a single unsaturated ketone, assigned the *Z* configuration on the strength of its ^{1}H NMR characteristics.

Our failure to isolate the seven-membered lactone **2** from any reactions of **1** with DCK casts doubt on its proposed role as an intermediate in the formation of **4**. Fortunately, the isolation of **7** provided us with a means of testing this putative rearrangement (**2** → **4**). Alkylation of **7** with the conjugate base of dimethyl malonate gave lactone **11**, together with a small amount of diester **10b** (Scheme II). Interestingly, a similar reaction with diethyl malonate gave only the diester **10a**. Although compound **11** does not have dichlorosubstitution at C-23, the electron-withdrawing ester function should exert a similar inductive influence. Consequently, we considered **11** to be a good model for studying the lactone rearrangement. In the event, **11** was isomerized to **12** in high yield on treatment with zinc chloride or the in situ generation of DCK. Since **12** proved to be a mixture of isomers, it was saponified and decarboxylated to remove the unwanted ester function at C-23 (a possible site of diastereoisomerism). The product was a single isomer which proved to be identical with compound **6a**. The postulated intermediacy of **2** in the formation of **4** from **1** is therefore sound.

Experimental Section

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere using solvents distilled from appropriate drying agents. Small-scale chromatographic separations were accomplished with the use of 2-mm silica plates (Merck F-254, 20 × 20 cm). Larger scale separations were effected by flash chromatography[10] (40–63-nm silica gel, Merck 9385). Melting points were determined on either a Thomas-Hoover capillary melting point apparatus or a Reichert hot stage microscopic apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 599 grating spectrophotometer. Mass spectra (MS) were obtained with a Finnigan 4000 GC/MS spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were taken in deuteriochloroform solution, using either a Varian T-60 or a Bruker WM 250 spectrometer, and are calibrated in parts per million (δ) from tetramethylsilane (TMS) as an internal standard. Carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker WM 250 spectrometer at 69.8 MHz, using a deuteriochloroform as solvent, and are calibrated in parts per million (δ) from TMS as an internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, MI. High-resolution mass spectra were measured by the Michigan State University, Department of Biochemistry, Mass Spectroscopy Facility, East Lansing, MI.

Conversion of 16α,17α-Epoxypregnenolone Acetate to Epoxy Olefin 1. To a solution of 1.4 mL of diisopropylamine in 7 mL of THF held at 0 °C was added 4 mL of 2.5 M *n*-BuLi. The resulting LDA solution was then transferred by a cannula to a suspension of 3.6 g (10 mmol) of methyltriphenylphosphonium bromide in 15 mL of THF (0 °C). The yellow ylide was stirred at this temperature for a further 2 h, a solution of 2.97 g (8 mmol) of 16α,17α-epoxypregnenolone acetate in 15 mL of THF was then added, and the resulting mixture was allowed to warm to room temperature. Following 4–5 h of stirring, the reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with ether. The combined organic layers were evaporated, and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane). In this manner pure **1** (2.53 g, 86% yield) was obtained, together with 3–4% of unreacted ketone. Characteristic properties of **1**: mp 129–131 °C; ^{1}H NMR δ 5.34 (1 H, d, J = 4.9 Hz), 5.04 (1 H, t, J = 1.5 Hz), 4.98 (1 H, br s), 4.55 (1 H, m), 3.38 (1 H, s), 2.00 (3 H, s), 1.79 (3 H, s), 1.01 (3 H, s), 0.80 (3 H, s); ^{13}C NMR δ 170.89, 140.37, 122.70, 116.37, 74.29, 73.06, 61.44, 50.79, 46.21, 42.50, 38.56, 37.38, 37.24, 32.91, 31.97, 30.96, 28.18, 27.89, 21.83, 21.42, 21.19, 19.71, 16.24; IR ($CDCl_3$) 2950, 2850, 1748 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 370 (0.2), 310 (9.5), 242 (7.8), 198 (15), 43 (100). Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.61; H, 9.26.

Reaction of DCK with Epoxy Olefin 1. To 1.85 g (5 mmol) of **1** were added 6 mL of anhydrous 1,2-dimethoxyethane, 12 mL of ether, and 500 mg of zinc–copper couple. This mixture was stirred under nitrogen while 0.67 mL (6 mmol) of trichloroacetyl chloride in 1 mL of ether was added dropwise. The resulting mixture was refluxed for 24 h, additional portions of the reagents (1 g of zinc–copper couple, 5 mL of glyme, 5 mL of ether, and 0.8 mL of trichloroacetyl chloride) were then added, the latter dropwise, and reflux was continued for an additional 24 h. The reaction mixture was filtered through Celite and extracted with ether. The ether extracts were washed with saturated aqueous bicarbonate and brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the solid residue was then purified by column chromatography (silica gel, ethyl acetate/hexane), giving 1.7 g (71%) of pure **4**. In ether solution alone, with excess DCK, yields of up to 85% have been obtained. Characteristic properties of **4**: mp 128–130 °C; ^{1}H NMR δ 5.67 (1 H, dd, J = 1.5 and 3.0 Hz), 5.36 (1 H, d, J = 4.4 Hz), 4.58 (1 H, m), 3.3–3.0 (2 H, AB quartet), 2.0 (3 H, s), 1.7 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s); ^{13}C NMR δ 172.0 (s), 170.6 (s), 155.6 (s), 140.5 (s), 129.0 (d), 122.2 (d), 85.8, 76.75, 75.1 (d), 59.0, 56.2 (t), 50.7, 48.2, 38.3 (t), 37.7, 37.6, 36.3, 32.5, 31.0, 29.1, 28.9, 22.0 (d), 21.5, 20.0, 18.5; IR ($CDCl_3$) 2900, 2830, 1791, 1730 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 422 (2), 421 (0.7), 420 (3.3) [M – CH_3CO_2H], 105 (10), 91 (13), 43 (100). Anal. Calcd for $C_{26}H_{34}O_4Cl_2$: C, 64.86; H, 7.12; Cl, 14.73. Found: C, 64.76; H, 7.15; Cl, 14.70.

Dechlorination of 4 by Tributyltin Hydride. A solution of 115 mg of **4** (0.24 mmol) in 3 mL of toluene was cooled to 0 °C (argon atmosphere) while 0.14 mL (0.53 mmol) of *n*-Bu_3SnH was added. On warming to room temperature, this solution was stirred for 3 h, quenched with water, and extracted with ether. The combined extracts were dried and evaporated to give a solid residue, which was purified by flash chromatography (elution with hexane removes all the tin residues, and further elution with methylene chloride gave a white solid). The product proved to be a single isomer, but one chlorine atom still remained (mass spectroscopy) and the final identification was made by X-ray analysis. Purification gave 85 mg (80%) of **5**, which exhibited the following characteristics: mp 210–212 °C; ^{1}H NMR ($CDCl_3$) δ 5.67 (1 H, dd, J = 1.4 and 3.0 Hz), 5.36 (1 H, d, J = 5.1 Hz), 4.58 (2 H, t overlapping m, J = 9 Hz), 2.72 (2 H, two overlapping doublets), 2.01 (3 H, s), 1.55 (3 H, s), 1.03 (3 H, s), 1.00 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.92, 170.62, 155.88, 140.10, 127.23, 122.18, 84.82, 73.83, 57.91, 50.94, 50.11, 47.70, 44.61, 38.07, 36.81, 36.66, 35.54, 31.30, 31.19, 30.23, 27.65, 27.65, 27.45, 21.38, 20.70, 19.14, 17.53; IR (CCl_4) 3060, 2950, 1785, 1730 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 388 (5), 387 (5), 386 (20) [M – CH_3CO_2H], 371 (11), 253 (14), 159 (13), 157 (13), 145 (24), 43 (100).

Dechlorination of 4 by Zinc in Methanolic Ammonium Chloride. To a solution of 200 mg of **4** in 20 mL of methanol saturated with ammonium chloride was added 250 mg of zinc. This stirred mixture was refluxed under an argon atmosphere for 6 h and on cooling was filtered through a Celite pad followed by

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

an ether wash. The white residue remaining after evaporation of the solvent was treated with cold dilute acid (0.5% sulfuric acid) and extracted with ether. The extracts were washed with brine, dried, and evaporated, yielding 164 mg (95.5%) of **6b**. This compound exhibited the following properties: mp 174–177 °C; ^{1}H NMR δ 5.63 (1 H, dd, J = 1.5 and 3.2 Hz), 5.43 (1 H, d, J = 4.7 Hz), 4.58 (1 H, m), 2.55 (2 H, m), 2.01 (3 H, s), 1.54 (3 H, s), 1.02 (3 H, s), 0.98 (3 H, s); ^{13}C NMR δ 176.92, 170.62, 156.58, 140.07, 126.24, 122.26, 87.02, 73.85, 58.00, 50.14, 47.28, 47.28, 38.07, 36.83, 36.66, 35.63, 34.29, 31.33, 31.04, 30.27, 29.04, 27.86, 27.67, 21.35, 20.70, 19.14, 17.35; IR (CDC_3) 2970, 1765, 1720 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 352 (83) [M – CH_3CO_2H], 337 (33), 253 (23), 99 (88), 43 (100); $[\alpha]_D$ –58.78° (4.1 mg/mL in $CHCl_3$). Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 74.96; H, 8.71.

Hydrolysis of 6b to 6a. To a solution of 20 mg of lactone **6b** in 2 mL of methanol was added 6 mg of potassium carbonate dissolved in 0.6 mL of water. This mixture was stirred for 3 h, the solvent was evaporated, and the residue was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and then evaporated to give a white solid. Purification of this product by column chromatography (silica gel, ethyl acetate/hexane) yielded 16.4 mg (93.8%) of alcohol **6a**. This compound exhibited the following properties: mp 159–162 °C; ^{1}H NMR δ 5.65 (1 H, dd, J = 1.5 and 3.1 Hz), 5.33 (1 H, d, J = 5 Hz), 3.56–3.46 (1 H, m), 1.54 (3 H, s), 1.01 (3 H, s), 0.97 (3 H, s); ^{13}C NMR δ 176.80, 156.46, 141.10, 126.19, 121.23, 87.05, 71.68, 58.09, 50.24, 47.29, 42.24, 37.12, 36.62, 35.74, 34.30, 31.59, 31.38, 31.09, 30.36, 29.09, 27.89, 20.80, 19.26, 17.42; IR ($CDCl_3$) 3600, 2940, 1770 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 370 (2.7), 355 (5.59), 337 (6.1), 271 (16.34), 99 (89.64), 55 (53.52), 43 (100).

Reduction of 6b by Diisobutylaluminum Hydride (DIBALH). A solution of 10 mg of lactone **6b** in 5 mL of ether was mixed with 5 equiv of DIBALH, refluxed for 12 h, and quenched by addition of 3 mL of methanol. A 30% sodium–potassium tartrate solution was added with stirring, and the mixture was then extracted with ether. The organic layers were washed with tartrate solution twice, dried, and evaporated to yield 7.1 mg (82%) of a white solid which proved to be **6c**. From the ^{1}H NMR of **6c** it is clear that the acetate group has been lost in the reduction. Efforts to reduce the lactone selectively without removing the acetate proved unsuccesful, even when the reduction was carried out at lower temperatures with 1 equiv of DIBALH. Furthermore, this reaction appears to cause some epimerization at C-20. Characteristic properties of **6c**: ^{1}H NMR δ 5.61 (1 H, dd), 5.4 (1 H, d), 3.9–3.7 (2 H, m), 3.5 (1 H, m), 1.4 (3 H, s), 1.03 (3 H, s), 0.95 (3 H, s); Mass spectrum (70 eV), m/e (relative abundance) 356 (8), 341 (38), 124 (43), 85 (100).

Reduction of 6b by Lithium Aluminum Hydride (LAH). A solution of 9 mg of lactone **6b** in 7 mL of ether was mixed with 8 mg of LAH and refluxed for 2 h. The reaction was quenched by the dropwise addition of aqueous sodium hydroxide, and the resulting suspension was filtered. The residue was extracted with ether, the combined ether portions were dried, and the solvent was evaporated. The white solid thus obtained was purified by chromatography, yielding 7 mg (86%) of triol **9a**. As expected, this compound was polar; furthermore, it slowly decomposed to tetrahydrofuran **6c**, especially on exposure to acids (a chloroform solution of **9a** was completely converted to **6c** in a few hours). This dehydration could be prevented by adding a few drops of pyridine during workup, even in chloroform solution. Characteristic properties of **9a**: mp 129–132 °C; ^{1}H NMR δ 5.5 (1 H, dd, J = 3.1 and 1.5 Hz), 5.3 (1 H, d, J = 5 Hz), 3.6 (2 H, t, J = 6 Hz), 3.5 (1 H, m), 1.36 (3 H, s), 1.03 (3 H, s), 0.97 (3 H, s); ^{13}C NMR δ 149.8, 141.1, 124.7, 121.6, 74.7, 71.7, 63.3, 58.2, 50.3, 47.2, 42.3, 39.0, 37.2, 36.7, 36.4, 31.6, 31.5, 31.0, 30.5, 29.1, 27.8, 20.9, 19.3, 17.8; IR ($CDCl_3$) 3610, 3420, 2935, 2850 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 356 (1.7) [M – 18], 341 (16), 315 (16), 124 (46), 91 (33), 85 (100).

Preparation of Diacetate 9b. To a solution of 10 mg of triol **9a** in 4 mL of benzene were added 0.2 mL of pyridine and 0.1 mL of acetic anhydride. This mixture was stirred under an argon atmosphere overnight, quenched with water, and extracted several times with ether. The combined ether layers were dried over anhydrous sodium sulfate and evaporated to give diacetate **9b** as a white solid. Purification by column chromatography (silica gel, ethyl acetate/hexane) yielded 13 mg (94% yield) of pure **9b**, which exhibited the following properties: ^{1}H NMR δ 5.52 (1 H, dd, J = 1.5 and 3.0 Hz), 5.36 (1 H, d, J = 4.5 Hz), 4.03 (2 H, t, J = 6.0 Hz), 2.02 (3 H, s), 2.01 (3 H, s), 1.35 (3 H, s), 1.03 (3 H, s), 0.96 (3 H, s); ^{13}C NMR δ 171.33, 170.71, 159.91, 140.07, 124.88, 122.47, 74.67, 73.96, 64.83, 58.06, 50.22, 47.23, 38.43, 38.14, 36.93, 36.75, 36.28, 31.46, 30.98, 30.41, 28.99, 27.75, 24.01, 21.42, 21.0, 20.89, 19.21, 17.82; IR ($CDCl_3$) 3600, 2975, 2940, 2860, 1728 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 398 (1.2 [M – CH_3COOH], 380 (13.83), 357 (37.03), 297 (90.3), 107 (34.75), 85 (100).

Preparation of Chloro Alcohol 7. To 2 g (5.4 mmol) of epoxy olefin 1 in 100 mL of ether was added 0.5 g (7.5 mmol) of Zn/Cu couple. This mixture was refluxed under an argon atmosphere, and to the refluxing mixture was added dropwise a solution of 0.77 mL (7 mmol) of trichloroacetyl chloride in 50 mL of ether. Reflux was continued for 6 h; the mixture was then filtered through Celite, washed with saturated bicarbonate solution and brine, dried, and evaporated to yield 1.1 g (56.5%) of **7**, 0.68 g (34%) of unreacted starting material, and a small amount of adduct 4. Chloro alcohol **7** exhibited the following properties: mp 120–122 °C; ^{1}H NMR δ 5.37 (1 H, d, J = 5 Hz), 4.72 (1 H, d, J = 4.7 Hz), 4.15 (2 H, AB quartet, J = 10.6 Hz), 2.01 (3 H, s), 1.86 (3 H, s), 1.01 (3 H, s), 0.86 (3 H, s); ^{13}C NMR δ 170.5 (s), 153.2 (s), 139.8 (s), 129.4 (s), 122.3 (d), 73.8 (d), 71.9 (d), 52.5 (overlapping doublets), 49.8 (d), 49.0 (t), 44.5 (s), 38.0 (t), 37.1, 36.9, 36.6, 35.4 (t), 31.6 (t), 30.5 (d), 27.7 (q), 21.4 (q), 21.1 (t), 19.2 (q), 16.5 (q); IR (CCl_4) 3563, 2935, 1730 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 348 (1.9), 346 (5.9) [M – CH_3CO_2H], 328 (1), 310 (13.1), 43 (100). Calculated for $C_{22}H_{31}OCl$: 346.20633. Found: 346.2065.

Hydrolysis of 7 with Potassium Hydroxide. To a solution of 40 mg of **7** in 5 mL of dioxane was added 1 mL of 5% aqueous potassium hydroxide solution. Following a 2.5-h reflux, the reaction mixture was cooled, the solvent evaporated, and the resiude extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated to give a white solid. Purification by flash chromatography (silica gel, ethyl acetate/hexane) yielded 22 mg (80%) of the 3-hydroxy equivalent of 1 (converted to 1 by acetylation) and 1.8 mg (5%) of the 3-hydroxy analogue of **7**.

Oxidation of 7 with Pyridinium Chlorochromate (PCC). To a solution of 18 mg of **7** in 3 mL of methylene chloride were added 0.5 g of Celite and 40 mg (4 equiv) of pyridinium chlorochromate. The reaction mixture was stirred for 6 h under argon atmosphere, filtered through a Celite pad, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to a solid residue, which was then chromatographed (silica gel, ethyl acetate/hexane) to give 16 mg (89%) of chloro ketone **8**. Characteristic properties of **8**: mp 45–48 °C; ^{1}H NMR δ 5.35 (1 H, d, J = 5 Hz), 4.68 (2 H, s), 4.67–4.5 (1 H, m), 2.0 (3 H, s), 1.99 (3 H, s), 1.04 (6 H, s); IR ($CDCl_3$) 2951, 2863, 1725, 1714, 1625 cm^{-1}; mass spectrum (70 eV), m/e (relative abundance) 362 (3.85), 360 (10.94) [M – CH_3CHO], 346 (11.77), 344 (33.81) [M – CH_3COOH], 331 (31.53), 329 (100), 295 (15.43), 293 (40.31), 129 (54.75).

Alkylation of 7 with Diethyl Malonate. Under an argon atmosphere, diethyl malonate (0.05 mmol) was added to a suspension of sodium hydride (1.2 mg, 0.05 mmol) in 2 mL of tetrahydrofuran. This mixture was stirred for 45 min, following which a solution of 15 mg (0.04 mmol) of **7** in 2 mL of THF was added. The reaction was quenched 5 h later by the addition of saturated ammonium chloride and was then extracted with ether. The combined ether layers were dried and evaporated to give a white solid. Purification by column chromatography yielded 14 mg (71.5%) of **10a** and 3 mg (20%) of recovered **7**. Characteristic properties of **10a**: mp 168–169 °C; ^{1}H NMR δ 5.36 (1 H, d, J = 4 Hz), 4.66 (1 H, d, J = 5 Hz), 4.57–4.64 (1 H, m), 4.22–4.1 (4 H, two overlapping quartets, J = 7 Hz), 3.64 (1 H, dd, J = 6 and 10 Hz), 3.08 (1 H, br s), 2.92 (1 H, dd, J = 10 and 14 Hz), 2.55 (1 H, dd, J = 6 and 14 Hz), 1.99 (3 H, s), 1.68 (3 H, s), 1.23 (6 H, t, J = 7 Hz), 0.99 (3 H, s), 0.84 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 170.51, 170.07, 169.19, 151.34, 127.11, 122.61, 73.88, 71.29, 61.83, 61.59, 52.53, 49.82, 49.78, 44.18, 38.07, 37.51, 36.87, 36.63, 35.59, 34.62, 31.58, 30.45, 27.72, 21.4, 21.22, 19.21, 16.81, 16.48, 14.06, 14.02;

IR ($CDCl_3$) 3480 (br), 2970, 2945, 2910, 1738, 1725 cm^{-1}; mass spectrum (70 eV), *m/e* (relative abundance) 515 (6.6) [M - 15], 452 (23.9) [M - CH_3COOH - H_2O], 437 (22.8), 310 (30.6), 173 (75.3), 160 (100).

Alkylation of 7 with Dimethyl Malonate. To a suspension of 12 mg (0.5 mmol) of sodium hydride in 2 mL of tetrahydrofuran was added 0.06 mL (0.5 mmol) of dimethyl malonate in 2 mL of tetrahydrofuran. After this mixture was stirred for 1 h under an argon atmosphere, a solution of 81 mg (0.2 mmol) of **7** in 1 mL of THF was added. Following a 10-h reaction period, the reaction was quenched by addition of ice water and extracted with ether. Evaporation of the washed and dried extracts gave a white solid, which was chromatographed (silica gel, ethyl acetate/hexane) to yield 70.5 mg (75% yield) of **11** and 6 mg (6%) of a compound tentatively identified as **10b**, based on its similarity to **10a**. Compound **11** exhibited the following properties: mp 185-187 °C; ^1H NMR ($CDCl_3$) δ 5.35 (2 H, two overlapping doublets), 4.6 (1 H, m), 4.29 (1 H, dd, J = 6.3 and 13 Hz), 3.76 (3 H, s), 2.75 (1 H, dd, J = 13 and 18 Hz), 2.49 (1 H, dd, J = 6.3 and 18 Hz), 1.99 (3 H, s), 1.74 (3 H, s), 0.99 (3 H, s), 0.86 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 170.62, 170.41, 169.04, 143.19, 139.64, 128.96, 122.1, 78.53, 73.71, 52.62, 51.59, 49.4, 46.71, 45.95, 37.98, 37.42, 36.75, 34.69, 32.57, 31.24, 30.79, 27.63, 21.36, 21.07, 19.65, 19.19, 16.88; IR ($CDCl_3$) 2950, 1752, 1737, 1726, 1440 cm^{-1}; mass spectrum (70 eV), *m/e* (relative abundance) 410 (75) [M - CH_3COOH], 395 (21), 370 (8.7), 355 (10.4), 295 (46), 157 (67.4), 135 (100). Calculated for $C_{26}H_{34}O_4$: 410.24570. Found: 410.2456.

Rearrangement of 11 to 12. To a solution of 50 mg (0.1 mmol) of **11** in 3 mL of diethyl ether was added 9 mg of zinc-copper couple, and this mixture was stirred under an argon atmosphere while a solution of 0.013 mL of trichloroacetyl chloride in 3 mL of ether was added dropwise. Following 4 h at reflux, the reaction mixture was filtered through a Celite pad with additional ether and washed successively with saturated aqueous bicarbonate and brine solutions. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 43.5 mg (87%) of **12**. The ^1H NMR of this product indicated it was a mixture of epimers (4:1), the major isomer showing the following signals: δ 5.68 (1 H, dd, J = 1.5 and 3.0 Hz), 5.34 (1 H, d, J = 4.0 Hz), 4.6 (1 H, m), 3.75 (3 H, s), 3.6 (1 H, dd, J = 6 and 18 Hz), 2.025 (3 H, s), 1.67 (3 H, s), 1.03 (3 H, s), 0.97 (3 H, s); IR ($CDCl_3$) 2950, 1775, 1735, 1720 cm^{-1}.

Hydrolysis and Decarboxylation of 12 to 6a. To a solution of **12** (47 mg, 0.1 mmol) in 2 mL of methanol was added 3 mL of 0.1 M methanolic potassium hydroxide, and this mixture was refluxed for 3 h. The cooled reaction mixture was acidified to pH 5 by addition of 0.1 N HCl and then evaporated to dryness. The residue was mixed with 5 mL of benzene, refluxed for 1 h, cooled, and then partitioned in a water-ether mixture. The ether extracts were washed and dried and on evaporation gave 32 mg (>86%) of **6a**, identical in all respects with the sample prepared by hydrolysis of **6b**.

Acknowledgment. We thank Mr. Ernest Oliver for assistance in obtaining mass spectra.

Supplementary Material Available: X-ray data for **5**, experimental procedures, positional and thermal parameters, bond distances, bond angles, torsion angles, a drawing of a single molecule showing 50% probability ellipsoids, and a stereoview of the unit cell showing 20% probability ellipsoids (23 pages). Ordering information is given on any current masthead page.

Efficient Synthesis of 5-(β-D-Ribofuranosyl)nicotinamide and Its α-Isomer[1]

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Received February 9, 1988

Condensation of 2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-D-ribonolactone (**3**) with 3-cyano-5-lithiopyridine afforded 1-(3-cyanopyridin-5-yl)-2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-β-D-ribofuran-1-ulose (**5a**), which was reduced with $NaBH_4$ to a 1:1 *allo/altro* mixture of 5-[2,3-*O*-isopropylidene-5-*O*-(tetrahydropyranyl)-D-pentitol-1-yl]-3-cyanopyridine (**7a**). The isomers were chromatographically separated. Treatment of *allo*-**7a** with TsOH/MeOH gave 5-(2,3-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-**8a**), which was acetonated to give 5-(2,3:4,5-di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-3-cyanopyridine (*allo*-**9a**). Mesylation of *allo*-**9a** to *allo*-**10** followed by acid hydrolysis with $CF_3CO_2H/CHCl_3$ afforded 5-(α-D-ribofuranosyl)-3-cyanopyridine (**11a**). The β-isomer **1a** was synthesized in a similar manner from *altro*-**7a**. Inversion of the configuration at the C-1 position of 6-(2,3:4,5-di-*O*-isopropylidene-D-*allo*-pentitol-1-yl)-2-bromopyridine (*allo*-**9b**) into the corresponding *altro* isomer *altro*-**9b** was achieved albeit in modest yield (24%) by mesylation of *allo*-**9b** to *allo*-**10b** followed by treatment with potassium superoxide. Interconversion of *altro*-**9a** or **-9b** into the corresponding *allo* derivatives was readily achieved in excellent yield by oxidation with CrO_3/pyridine/Ac_2O to the corresponding keto intermediates **19** followed by borohydride reduction. Treatment of the 1-*O*-mesylate *allo*-**10b** with NaN_3 in DMF afforded the corresponding 1-azido-1-deoxy *altro* derivative (**17**). Similar treatment of the 1-*O*-triflyl derivatives *allo*-**15a,b** with NaN_3 or NaOAc in DMF surprisingly afforded *allo*-**9a,b** in good yield.

Recently an interest in the preparation of analogues of nicotinamide riboside has grown increasingly.[2-5] Biochemical behavior of the nicotinamide adenine dinucleotide (NAD) analogues containing the α-anomer of nicotinamide nucleosides has become of current interest.[3,5] We have reported the synthesis of 5-(β-D-ribofuranosyl)-nicotinamide[6] (**1c**, Scheme I), the C-nucleoside isostere of nicotinamide riboside, by condensation of 2,4:3,5-di-*O*-benzylidene-D-*aldehydo*-ribose[7] with 3-bromo-5-lithiopyridine to an *altro/allo* mixture followed by conversion of the bromopyridine aglycon into the nicotinamide moiety. This procedure, however, was inefficient and not amenable to large-scale preparations due to (i) involvement of a ribose dithioacetal during the preparation of the key starting material, (ii) the formation of an *altro/allo* isom-

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