number of methyl, methylene, methine, and quaternary carbons, large numbers of cases result. This comes about because GENOA is forced to construct all cases in what is a large "labeling" problem; there are many ways of allocating the carbons in various ways about the skeleton in the absence of other constraints! It is difficult to anticipate such situations and, in general, difficult even to predict the size of problems in terms of eventual numbers of cases or final structures. These limitations represent areas where further program development is needed for GENOA to become a program of true utility to a broad community of investigators.

The completely thorough and unbiased exploration of structural possibilities for an unknown carried out by GENOA (and CONGEN) suggests another useful application of the programs. There are several chemical journals which devote significant space to reports of structure elucidation of new natural products. We suggest that our computer programs could be made a useful adjunct to preparing papers for such publications. For those unknowns where structural assignment is based on X-ray determination, unambiguous synthesis, or relation to previously characterized structures, the programs are obviously not necessary. For the remaining problems, however, it would be quite simple to determine, based on reported spectroscopic and chemical data and the structural inferences derived therefrom, whether or not a proposed structure was in fact the only structure allowed by the data. If other structural possibilities were found which could be eliminated by additional experiments, reported structural assignments could be made on much firmer ground.

E. Experimental Section

GENOA is implemented in the ALGOL-like BCPL programming language[14] on a Digital Equipment Corporation KI-10 computer at the SUMEX-AIM facility at Stanford University. The program is available to an outside community of collaborators via a nationwide computer network (TYMNET), to the limits of available resources. Export of the program to other DEC PDP-10 or PDP-20 systems is possible. Information on the possibility of export to the other types of computers or on additional algorithmic details can be obtained from us.

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Supplementary Material Available: This material (23 pages, including six tables, two figures, structures, and references) describes in some detail the key algorithms in GENOA which are necessary for constructive substructure search. Ordering information is given on any current masthead page.

Notes

DAST-Induced Epimerization of a 2-(Acetoxymethyl)myoinositol

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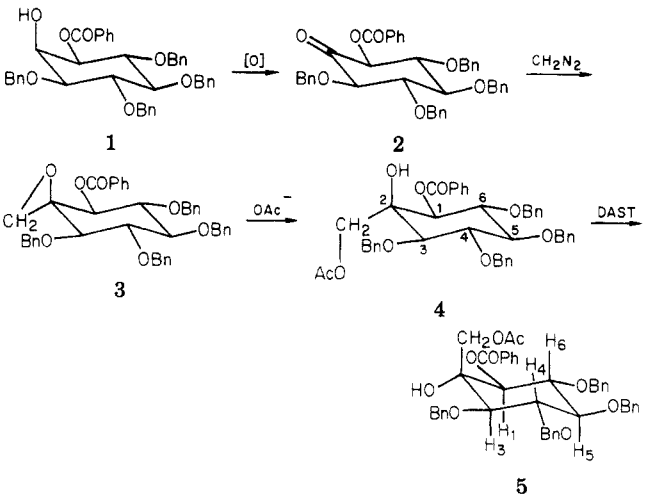
Diethylaminosulfur trifluoride (DAST)[1] has recently been introduced as an excellent reagent for converting ROH to RF. More recently application has been extended to steroids[2-4] and carbohydrates.[5,6] In contrast to the considerable interest in synthesis and chemistry of fluorinated carbohydrates, no fluoro analogues of cyclitols have been reported. While pursuing synthetic studies aimed at preparation of ring-fluorinated inositols,[7] we observed an unusual epimerization. When DL-2-*C*-(acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylmyoinositol (**4**) (prepared from DL-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylmyoinositol (**1**)[8,9] in three steps as shown in Scheme I) was treated with DAST in methylene chloride at 0 °C, a new

Scheme I[10]



Bn = CH_2Ph

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(7) Synthesis of 1-fluoro-1-deoxyscylloinositol will be reported elsewhere.
(8) D. E. Kiely, G. D. Abruscato, and V. Baburao, *Carbohydr. Res.*, **34**, 307 (1974).
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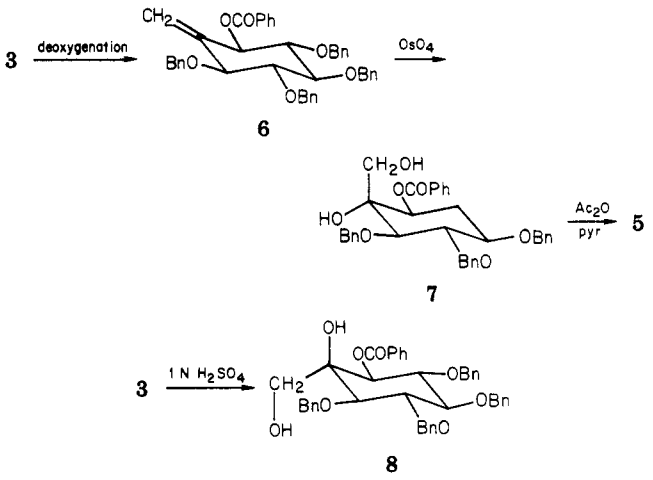
(10) For convenience, D-myoinositol configurations were used to denote DL-myoinositol throughout Schemes I–III.

0022-3263/81/1946-1718$01.25/0

Scheme II[10]

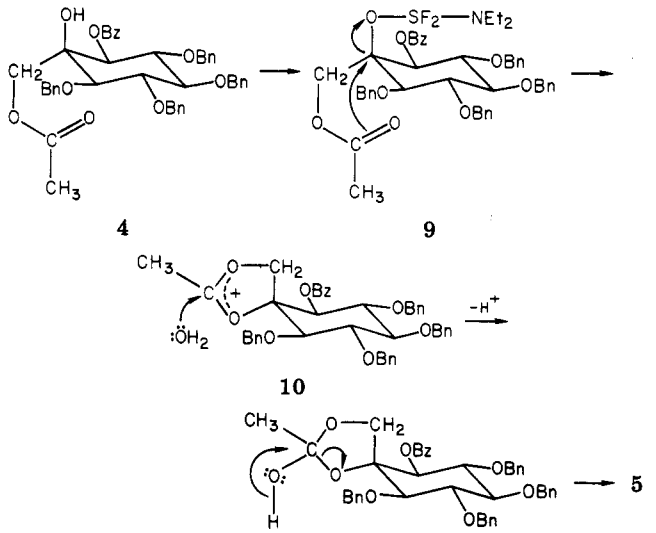


compound which still contained acetoxymethyl, benzoate, and tertiary hydroxy moieties but was devoid of fluorine was isolated in 50% yield. Mass spectra of both starting material 4 and product 5 showed very similar fragmentation patterns [m/e (% intensity 4; 5) 716 (M^+, 0.4; 0.4), 698 ($M^+ - H_2O$, 0.4; 0.3), and 625 ($M^+ - PhCH_2$, 100; 100)], suggesting isomers. The 300-MHz NMR spectra ($CDCl_3$) of 4 and 5 exhibited almost identical chemical shifts on one face of the ring at C-1, C-3, and C-5 axial ring protons while dramatic chemical shift changes were exhibited by methine protons on the opposite face at C-2 OH (2.46 ppm for 4 vs. 3.08 ppm for 5), C-4-H (4.04; 3.81), C-6-H (4.12; 3.90), and the methylene group C–CH_2–O as an AB q (3.86 and 4.02; 4.37 and 4.55). These data are in good agreement with product 5 being epimeric with 4 at C-2. Therefore, 5 was assigned as DL-2-*C*-(acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylscylloinositol.

Synthesis of 5 was thus undertaken in order to confirm the structure deduced solely from ^1H NMR and mass spectra. Deoxygenation[11] of the spiroepoxide 3 with zinc/sodium acetate/sodium iodide in aqueous acetic acid gave the olefinic derivative 6 in 76% yield. Attempted epoxidation of 6 with *m*-chloroperbenzoic acid gave only 3 quantitatively without any trace of desired inverted spiroepoxide. Preparation of inverted epoxide from ketone 2 with dimethylsulfonium methylide[12] also failed. Dihydroxylation of 6 with potassium permanganate was unsuccessful but with osmium tetroxide in pyridine[13] afforded 75% yield of DL-2-*C*-(hydroxymethyl)scylloinositol 7. Compound 7 showed a distinctively different NMR spectrum from that of its isomeric diol 8 obtained from mild acid ring opening of the spiroepoxide 3. Mild acetylation of 7 gave a 65% yield of the desired final product 5, the spectra of which were identical with those of the rearrangement product (Scheme II).

A possible mechanistic course for epimerization of 4 is postulated in Scheme III. Fluorination of 4 with DAST reagent is expected to give a transient labile ester 9 which could undergo intramolecular nucleophilic displacement by the neighboring acetoxy group to form a stable 1,3-dioxolan-2-ylium ion[14] 10 with inversion at C-2. Ion 10 is not attacked by fluoride ion in the reaction medium but rather during workup is attacked by water to give 5.

Scheme III[10]



Bz = COPh

Experimental Section

General. All melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B or 267 spectrophotometer as Nujol mulls. Proton nuclear magnetic resonance spectra were recorded at 300 MHz with a Varian SC-300 NMR spectrometer with Me_4Si as an internal standard. Only ring protons as well as selected others are reported. The accuracy of the coupling constants is approximately ±0.3 Hz. Mass spectra were determined on an LKB-9000 spectrometer. Preparative TLC plates were purchased from Analtech, Newark, DE, and were 20 × 20 cm.

DL-1-***O*-Benzoyl-3,4,5,6-tetra-*O*-benzylmyoinositol (1).** 1 was prepared according to the known method:[8,9] mp 144–145 °C (lit.[9] mp 143–145 °C); NMR (300 MHz, $CDCl_3$) δ 3.61 (t, 1 H, J = 9.5 Hz, C-5-H), 3.63 (dd, 1 H, J = 9.5, 2 Hz, C-3-H), 4.01 (t, 1 H, J = 9.5 Hz, C-4-H), 4.24 (t, 1 H, J = 10.0 Hz, C-6-H), 4.43 (t, 1 H, J = 2 Hz, C-2-H), and 5.12 (dd, 1 H, J = 10.0, 2 Hz, C-1-H); mass spectrum, m/e 644 (M^+), 553 ($M^+ - CH_2Ph$).

DL-1-***O*-Benzoyl-3,4,5,6-tetra-*O*-benzylmyoinosose-2 (2).** 2 was prepared by a modification of the Shevchenko method.[9,15] To a solution of 21.35 g of 1 (33 mmol) in 3.5 L of acetone at 5–6 °C under nitrogen was added 36.0 mL of 8/3 M Jones reagent (96 mmol) during 0.5 h. The reaction mixture was stirred at 5 °C for ca. 6 h until oxidation was complete and quenched slowly during 10 min with 100 mL of 2-propanol. The mixture was further stirred at 5 °C for an additional 1 h and then at ambient temperature overnight. Solid inorganic salts were removed by filtration. The filtrate was concentrated in vacuo to a residue which was triturated with 200 mL of ether at 0–5 °C for 1 h to dissolve most impurities. The insoluble solid product was collected, redissolved in hot chloroform, and filtered. Repetition of the evaporation of the filtrate and trituration of the residue afforded 17.1 g of 2 (80% yield): mp 167.5–169 °C; IR (Nujol) 1742 and 1724 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.70 (t, 1 H, J = 9.6 Hz, C-5-H), 3.85 (t, 1 H, J = 10.0 Hz, C-4-H), 4.04 (t, 1 H, J = 9.2 Hz, C-6-H), 4.39 (dd, 1 H, J = 10.0, 2 Hz, C-3-H), and 5.60 (dd, 1 H, J = 10.0, 2 Hz, C-1-H); mass spectrum, m/e 642 (M^+), 551 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{41}H_{38}O_7$: C, 76.61; H, 5.96. Found: C, 76.36; H, 5.86.

DL-1-***O*-Benzoyl-2-oxiranyl-3,4,5,6-tetra-*O*-benzylmyoinositol (3).** To a solution of 9.0 g of 2 (14.0 mmol) in 200 mL of chloroform and 40 mL of absolute ethanol at 0–5 °C was added 120 mL of 3/5 M diazomethane ether solution[16] (ca. 70 mmol, generated from 12.3 g of *N*-nitrosomethylurea without distillation).

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The solution was stirred at 0–5 °C for 4 h and then at room temperature overnight. The insoluble impurities were removed by filtration. The filtrate was evaporated to dryness and the residue was recrystallized from ether–hexane to give 8.7 g of the epoxide **3** (94%): mp 147–148 °C; IR (Nujol) 1725 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.67 (d, 1 H, J = 5.0 Hz, CH_2), 2.97 (d, 1 H, J = 5.0 Hz, CH_2), 3.76 (t, 1 H, J = 9.2 Hz, C-5-H), 3.83 (d, 1 H, J = 9.5 Hz, C-3-H), 3.92 (t, 1 H, J = 9.4 Hz, C-4-H), 4.01 (t, 1 H, J = 9.5 Hz, C-6-H), and 5.47 (d, 1 H, J = 10.2 Hz, C-1-H); mass spectrum, m/e 656 (M^+), 565 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{40}O_7$: C, 76.81; H, 6.14. Found: C, 76.57; H, 6.06.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylmyoinositol (4). The method of Posternak[17] was used for preparation of **4**. In a mixture of 3.2 mL of glacial acetic acid and 0.6 g of anhydrous sodium acetate was refluxed 400 mg of **3** (0.61 mmol) for 10 min and the mixture was cooled to room temperature. After treatment with cold water, the solid product was collected and recrystallized from absolute ethanol to give 400 mg of **4** (90%): mp 177–179 °C; IR (Nujol) 3540, 1745, 1730 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3 H, CH_3), 2.46 (s, 1 H, OH), 3.70 (d, 1 H, J = 9.2 Hz, C-3-H), 3.71 (t, 1 H, J = 9.4 Hz, C-5-H), 3.86 and 4.02 (AB q, 2 H, J = 11.0 Hz, CH_2O), 4.04 (t, 1 H, J = 10.0 Hz, C-4-H), 4.12 (t, 1 H, J = 10.0 Hz, C-6-H), 5.42 (d, 1 H, J = 9.8 Hz, C-1-H); mass spectrum, m/e 716 (M^+), 625 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.86; H, 6.27.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylscylloinositol (5) from *DAST* and 4. To a solution of 0.2 mL of diethylaminosulfur trifluoride[1] (ca. 1.2 mmol) in 5 mL of methylene chloride at 0–5 °C under nitrogen was added a solution of 190 mg of **4** (0.27 mmol) in 5 mL of methylene chloride. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was purified via preparative TLC using 2000-μm silica gel plates developed twice with 20% acetone in hexanes. Rearrangement product **5** (95 mg) was obtained in 50% yield. An analytical sample was recrystallized from EtOH–hexane (1:4): mp 113–115 °C; IR (Nujol) 3480, 1740, 1725 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 3 H, CH_3), 3.08 (s, 1 H, OH), 3.70 (d, 1 H, J = 9.3 Hz, C-3-H), 3.75 (t, 1 H, J = 9.0 Hz, C-5-H), 3.81 (t, 1 H, J = 9.0 Hz, C-4-H), 3.90 (t, 1 H, J = 9.0 Hz, C-6-H), 4.37 and 4.55 (AB q, 2 H, J = 11.7 Hz, CH_2O), 5.40 (d, 1 H, J = 10.0 Hz, C-1-H); mass spectrum, m/e 716 (M^+), 625 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.64; H, 6.21.

DL-1-*O*-Benzoyl-2-methylene-2-deoxy-3,4,5,6-tetra-*O*-benzylmyoinosose-2 (6). To a mixture[11] of 0.42 g of sodium acetate and 1.26 g of sodium iodide in 3.3 mL of 90% aqueous acetic acid at 0–5 °C was added 1.2 g of zinc dust with stirring followed by dropwise addition of a solution of 1.0 g of **3** (1.52 mmol) in 8.0 mL of tetrahydrofuran and 2.0 mL of acetic acid. The mixture was stirred vigorously for 1 h and filtered at low temperature. The solid residue was washed thoroughly with tetrahydrofuran. The combined filtrate and THF washing solution were concentrated in vacuo and the residue was purified via preparative TLC using 2000-μm silica gel plates developed with 25% ethyl acetate in hexanes. The purified product was further recrystallized from methanol–chloroform to yield 720 mg of **6** (74%): mp 141–143 °C; IR (Nujol) 1720 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.52 (t, 1 H, J = 9.4 Hz, C-5-H), 3.65 (t, 1 H, J = 9.0 Hz, C-4-H), 3.76 (t, 1 H, J = 9.0 Hz, C-6-H), 4.07 (d, 1 H, J = 9.4 Hz, C-3-H), 5.19 (d, 1 H, J = 1 Hz, CH_2=), 5.39 (d, 1 H, J = 1 Hz, CH_2=), 5.59 (d, 1 H, J = 9.6 Hz, C-1-H); mass spectrum, m/e 640 (M^+), 549 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{40}O_6$: C, 78.72; H, 6.29. Found: C, 78.51; H, 6.26.

DL-1-*O*-Benzoyl-2-*C*-(hydroxymethyl)-3,4,5,6-tetra-*O*-benzylscylloinositol (7). To a stirred solution of 64 mg of **6** (0.1 mmol) in 3.0 mL of pyridine was added a solution of 240 mg of osmium tetroxide (0.95 mmol) in 6.0 mL of ether. After 2 h the reaction mixture was treated with 3 g of sodium bisulfite in 15 mL of water and 5 mL of pyridine. The resulting mixture was allowed to stand at room temperature overnight. The crude product was extracted with methylene chloride and purified via preparative TLC using a 1500-μm silica gel plate developed with 30% ethyl acetate in hexanes. The purified product was further recrystallized from aqueous ethanol–hexane to give 41 mg of **7** (75%): mp 135–136 °C; IR (Nujol) 3550, 3470, 1700 cm^{-1}; NMR (300 MHz, C_6D_6) δ 2.53 (dd, 1 H, J = 9.3, 4 Hz, primary OH), 3.36 (s, 1 H, tertiary OH), 3.56 (t, 1 H, J = 9.3 Hz, C-5-H), 3.57 (d, 1 H, J = 9.6 Hz, C-3-H), 3.76 (t, 1 H, J = 9.2 Hz, C-4-H), 3.80 (t, 1 H, J = 10.2 Hz, C-6-H), 3.90 and 3.98 (AB q, 1 H, J = 11.8 Hz, CH_2–O), 3.91 and 4.01 (AB q, 1 H, J = 11.2 Hz, CH_2–O), 5.79 (d, 1 H, J = 10.0 Hz, C-1-H); NMR (300 MHz, $CDCl_3$) δ 3.93 (t, 1 H, J = 11.0 Hz, C-6-H), 4.04 (dd, 1 H, J = 12.0, 2 Hz C-3-H), 5.49 (d, 1 H, J = 10.2 Hz, C-1-H) (the rest of the ring protons appeared at 3.60–3.80 ppm and were unassigned); mass spectrum, m/e 674 (M^+), 583 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{42}O_8 \cdot {}^1/_3H_2O$: C, 74.09; H, 6.32. Found: C, 74.03, H, 6.18.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylscylloinositol (5) from Monoacetylation of 7. To a solution of 35 mg of **7** (0.05 mmol) in 0.5 mL of pyridine at 0–5 °C was added 0.1 mL of acetic anhydride. The mixture was stirred at room temperature for 3 h and then treated with water (0.1 mL). After removal of volatile solvents in high vacuum, the residue was recrystallized from ethanol–hexane to give 25 mg of **5** (60%): mp 113–115 °C; NMR and mass spectra were identical with those of the rearrangement product **5** (see above). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.44; H, 6.19.

DL-1-*O*-Benzoyl-2-*C*-(hydroxymethyl)-3,4,5,6-tetra-*O*-benzylmyoinositol (8). To a solution of 1.2 g of **3** (1.83 mmol) in 45 mL of dioxane was added dropwise 1.5 mL of 1 N H_2SO_4. The resulting solution was heated at 100 °C for 3.5 h, cooled to room temperature, and poured into 40 mL of cold 5% sodium bicarbonate solution. After removal of dioxane in vacuo, the aqueous mixture was extracted with chloroform (2 × 50 mL). The organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent gave the crude product which was recrystallized consecutively from ethanol, ethanol–hexanes, and ether–hexane to give 0.78 g of pure **8** (63%): mp 152.5–153.5 °C; IR (Nujol) 3560, 3540, 1703 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.27 (d, 1 H, J = 1 Hz, C-2-OH), 3.13 (dd, 1 H, J = 10.2, 5.0 Hz, CH_2–O), 3.28 (dd, 1 H, J = 11.6, 5.0 Hz, CH_2–O), 3.54 (dd, 1 H, J = 11.5, 10.2 Hz, primary OH), 3.65 (t, 1 H, J = 9.6 Hz, C-5-H), 3.88 (d, 1 H, J = 9.5 Hz, C-3-H), 4.01 (t, 1 H, J = 9.8 Hz, C-4-H), 4.22 (t, 1 H, J = 9.8 Hz, C-6-H), 5.23 (d, 1 H, J = 10.0 Hz, C-1-H). Anal. Calcd for $C_{42}H_{42}O_8$: C, 74.76; H, 6.28. Found: C, 74.99; H, 6.23.

Epoxidation of 6 with *m*-Chloroperbenzoic Acid. To a refluxing solution of 40 mg of **6** (0.06 mmol) in 1.0 mL of chloroform was added 12.0 mg of *m*-chloroperbenzoic acid (large excess) in portions until the epoxidation was complete. The mixture was poured into excess cold sodium bicarbonate solution. Extraction of the aqueous mixture with chloroform gave the crude product which was purified via preparative TLC to give 41 mg of pure epoxide (98%). The physical data were identical with those of **3**.

Acknowledgment. We thank Dr. T. Y. Shen and Dr. B. H. Arison for helpful discussions and Messrs. J. L. Smith, J. P. Gilbert, and H. Flynn for their technical assistance.

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An Example of an *N*-Acetyl Group More Labile to Methanolic Hydrogen Chloride than an Analogous *N*-*tert*-Butoxycarbonyl Group. β-Acetyl- and β-[[(Alkoxycarbonyl)amino]oxy]-α-*N*-acetyl-D-alanine Butylamides

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During a recent study of the acylation of bovine serum albumin (BSA) with diacetylcycloserine (D-2-acetyl-4-acetamido-3-isoxazolidone, **1**) it was found that the ε-amino groups of lysine were not only acylated via ring opening

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