fluorophenylalanine isopropyl ester: mp 39–40 °C; IR ($CHCl_3$) $\nu$ 3450 (m, NH), 2970, 2930 (m, CH), 1740–1710 (s, two C=O), 1495 (s), 1375 (s), 1280–1170 (br s, COO), 1110 (s), 1070 (m), 1040 (m), 985 (m), 920 (m), 865 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ ($Me_4Si$) 1.15–1.53 (m, 16 H, 2-$C_3H_7$, $t$-$C_4H_9$), 4.40–5.40 (overlapping m, 3 H, $H_\alpha$, NH, -$CHMe_2$), 5.90 (dd, 1 H, $H_\beta$, $J$ = 45 Hz, $J_{H_\alpha-H_\beta}$ = 3.7 Hz), 7.27 (m, 5 H, aromatic H); mass spectrum, $m/z$ 326 ($M^+$ + H), 325 ($M^+$), 269 ($M^+ - C_4H_8$), 215 ($M^+ - C_6H_7F$), 182 ($C_9H_9O_2NF$), 138 ($C_8H_9NF$), 116 ($NHCO_2C_4H_9$), 109 ($C_7H_6F$), 73 ($C_4H_9OH$), 57 ($C_4H_9$).

Anal. Calcd for $C_{17}H_{24}O_4NF$: C, 62.75; H, 7.43; N, 4.30; F, 5.84. Found: C, 63.06; H, 7.66; N, 4.29; F, 5.98.

Enzymatic hydrolysis of the esster to *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine was carried out as follows. Into the DMF solution of the N-protected amino ester [975 mg (3 mmol)/145 Ml of DMF] were sequentially added 145 mL of water and the enzyme, chymotrypsine dissolved in 5 mL of water just prior to use, with vigorous stirring at room temperature. As soon as the enzyme was added, the pH meter monitoring the progress of hydrolysis showed a quick shfit toward the acidic value of 6.0. Aqueous hydroxide solution (0.5 N) was immediately added to adjust the pH value of the solution to 7.2–7.5. This operation was repeated for 6 h until the rate of hydrolysis became markedly sluggish when half of the starting material had been hydrolyzed. At this stage, 3.16 mL of 0.5 N aqueous sodium hydroxide solution had been consumed to neutralize the acidic product liberated. Next, aqueous sodium hydroxide was added to the solution to change its pH value to 11.0. After the 500 mg of unreacted material was removed from the solution with ether extraction for three times, the aqueous layer was acidified with 0.5 N hydrogen chloride to a pH value of around 1.5. From this aqueous solution, the desired acidic hydrolysis product was removed by extraction three times with ethyl acetate using the salting out technique. The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure, leaving 203 mg of the oily product in 48.7% yield. After recrystallization from hexane–ether, the product gave the following data: mp 141–142 °C; $[\alpha]^{21.5}_D$ 0.0 ($c$ 0.547, $CHCl_3$–1% EtOH); $[\alpha]^{365}_{21.5}$ +9.9 ± 0.9 ($c$ 0.547, $CHCl_3$–1% EtOH); $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$ ($Me_4Si$) 1.28 (s, 9 H, $C_4H_9$), 4.58 (m, 1 H, $H_\alpha$, $J_{H_\beta-F}$ = ca. 29 Hz), 6.02 (q, 1 H, $H_\beta$, $J_{H_\beta-H_\alpha}$ = ca. 3.5 Hz, $J_{H_\beta-F}$ = 46 Hz), 7.35 (m, 5 H, aromatic H).

The amino group was deprotected by sequentially adding 0.308 mL (20 molar equiv) of trifluoroacetic acid and 0.30 mL of anisol with stirring at 0 °C to the dichloromethane solution of the acid obtained above [114 mg (0.40 mmol)/1.5 mL of $CH_2Cl_2$]. The reaction temperature was gradually raised to room temperature and maintained for 4 h to complete the reaction. Concentration of this reaction mixture under reduced pressure left a crude oily product, the trifluoroacetic acid salt of *threo*-3-fluorophenylalanine. This salt was converted into the desired free amino acid *threo*-3-fluorophenylalanine by treatment with acidic ion exchange resin, Dowex 50W-X8, as in the case of the erythro diastereomer. After recrystallization from aqueous 2-propanol, the pure product was obtained: mp 150–152 °C dec. with evolution of gas; IR $\nu$ 3400–2400 (br s, $NH_3^+$ and aromatic), 1640–1560 (three peaks s, $COO^-$ and $C_6H_5$), 1500 (m, $NH_3^+$ and aromatic), 1475 (w), 1405 (m, $COO^-$), 1345 (m), 1255 (w), 1223 (w), 1150 (w), 1130 (w), 990 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 4.14 (dd, 1 H, $H_\alpha$, $J_{H_\alpha-F}$ = 27.3 Hz, $J_{H_\alpha-H_\beta}$ = 4.3 Hz), 6.14 (dd, 1 H, $H_\beta$, $J_{H_\beta-F}$ = 45 Hz), 7.47 (m, 5 H, aroamtic H); $^{19}F$ NMR $\delta$ –25.3 ($J$ = 45 Hz, $J$ = 27.3 Hz); mass spectrum, $m/z$ 276 (M + $H^+$ + glycerin), 184 (M + $H^+$), 164 ($M^+$ – F).

**Single-Crystal X-ray Analysis. Crystal Data for *threo*-*N*-Acetyl-3-fluorophenylalanine Isopropyl Ester (6).** $C_{14}H_{18}NO_3F$, monoclinic, $P2_1/c$, $a$ = 5.167 (1) Å, $b$ 22.089 (2) Å, $c$ = 12.856 (1) Å, $\beta$ = 103.85 (1)°, $Z$ = 4. A crystal, with dimensions of 0.15 × 0.15 × 0.15 mm, was used for data collection on a Rigaku diffractometer (monochromated Cu $K_\alpha$ radiation) and 2130 independent reflections were measured in the range $\theta \leq 60°$. No absorption correction was made. The structure was solved by direct methods (MULTAN76).[30] After a few cycles of anisotropic block diagonal least-squares refinement, difference synthesis showed all the hydrogen atoms, which were included in the refinement with isotropic temperature factors. The final $R$ value was 0.041 for 1768 reflections. The atomic scattering factors were taken from the International Table for X-ray Crystallography (1974).[31] The weighting scheme employed was $w = 1/\sigma^2(F_o)$ for $|F_c| \geq \sigma(F_o)$ and $w = 0$ for $|F_c| < \sigma(F_o)$ or $|\Delta F| > 3\sigma(F_o)$. $\sigma(F_o)$ was estimated by the relation $\sigma(F_o) = [\sigma_1^2(F_o) + 0.00082|F_o|^2]^{1/2}$, where $\sigma_1(F_o)$ is the esd based on the counting errors.[32]

**Crystal Data for *erythro*-*N*-Acetyl-3-fluorophenylalanine (7).** $C_{11}H_{12}NO_3F$, orthorhombic, $P2_12_12_1$, $a$ = 11.899 (7) Å, $b$ = 16.714 (8) Å, $c$ = 5.615 (2) Å, $Z$ = 4. A crystal, with dimensions of 0.10 × 0.10 × 0.20 mm, was used for data collection and 1250 independent reflections were measured in the range $\theta \leq 70°$. The crystal structure was solved and refined as described above. The final $R$ value was 0.044 for 1033 reflections.

**Acknowledgment.** We express our thanks to Dr. H. Tanida for the opportunity to perform this work and Dr. Y. Nakagawa for the mass spectroscopic measurements.

**Registry No.** **1a**, 79617-87-1; **1b**, 80817-87-4; **1c**, 80817-88-5; **2**, 76582-49-5; **3a** (X = H, R = Me), 80540-55-2; **3b** (X = Cl, R = Me), 80540-56-3; **3c** (X = $NO_2$, R = Et), 80540-57-4; **4a** (X = H, R = Me), 76532-83-7; **4b** (X = Cl, R = Me), 79547-04-9; **4c** (X = $NO_2$, R = Me), 88867-08-7; **5a** (X = H, M = Na), 76532-84-8; **5b** (X = Cl, M = H), 88867-09-8; **5b** (X = Cl, M = Na), 88867-10-1; **5c** (X = $NO_2$, M = H), 88867-11-2; **5c** (X = $NO_2$, M = Na), 88867-12-3; **6**, 88928-87-4; **7**, 88867-13-4; *threo*-3-fluorophenylalanine isopropyl ester, 79617-86-0; *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine isopropyl ester, 88867-14-5; *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine, 88867-15-6; *threo*-3-fluorophenylalanine·trifluoroacetic acid salt, 88867-16-7.

**Supplementary Material Available:** Table 2A and 2B, interatomic distances, angles and torsion angles; Table 3A and 3B, final positional and isotropic thermal parameters; Table 4A and 4B, anisotropic thermal parameters (10 pages). Ordering informations is given on a current masthead page.

(30) Main, P.; Woolfson, M. M.; Lessinger, L.; Germain, G.; Declerc, J. P. "MULTAN76, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Biffraction Data"; University of York and Louvain, 1976.

(31) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol IV.

(32) Grandt, D. F.; Killean, R. C. G.; Laurence, J. L. *Acta Crystallogr., Sect. B* **1969**, *B-25*, 374.

(33) Presented at the third French-Japanese Symposium on Medicinal and Fine Chemistry, Sept 4–7, 1983, Shizuoka, Japan.

# Total Synthesis of 2,6-Epoxy-1(2*H*)-benzoxocin Sugar Analogues

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An expedient route for construction of sugar analogues of 2,6-epoxy-1(2*H*)-benzoxocins is described.

The anthracycline antibiotic nogalamycin (**1a**) is the only known example of a glycosidic natural product containing a perhydroxylated epoxyoxocin ring system.[2] Conceptually this fragment originates from the dual at-

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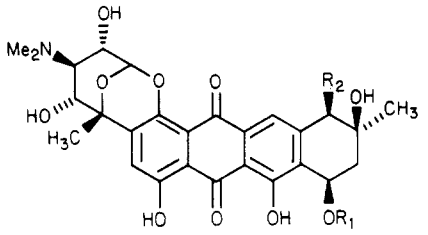
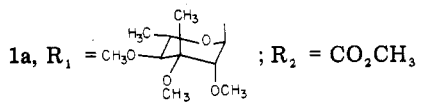




1a, $R_1$ = ; $R_2 = CO_2CH_3$

1b, $R_1 = CH_3$; $R_2 = H$

tachment of a single deoxyamino sugar residue to the aglycon through both carbon–carbon and carbon–oxygen bonds. The absence of precedents for preparing perhydroxylated epoxyoxocin ring systems[3] led us to explore various procedures for their fabrication prior to undertaking total synthesis of **1a** and the semisynthetic derivative 7-con-*O*-methylnogarol (**1b**).[2b,4]

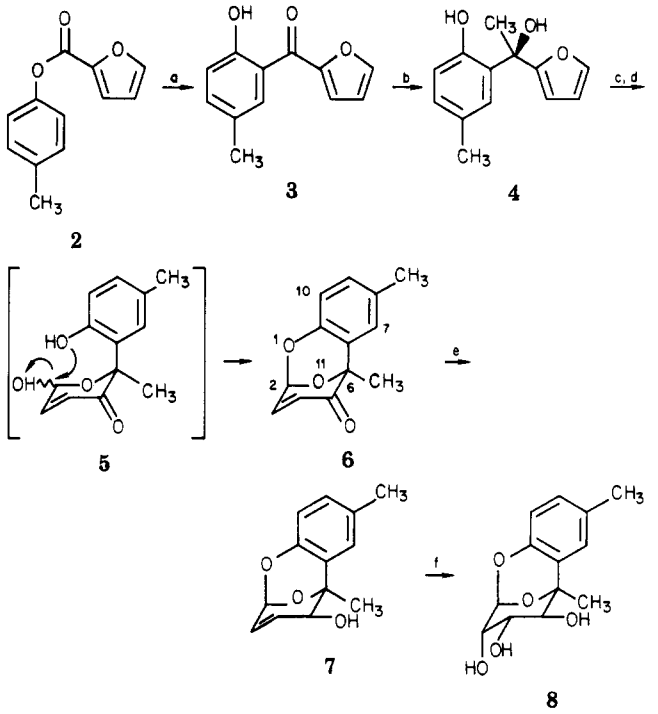
This paper describes a novel and expedient procedure for the preparation of the 2,6-epoxy ketobenzoxocin **6** and the subsequent conversion to racemic sugar analogues with the manno (**8**), talo (**13**), altro (**14**), and galacto (**17**) configurations.

The synthetic plan leading to **6** is shown in Scheme I and was devised in part from the finding of Achmatowicz and co-workers that furancarbinols can be oxidatively transformed to unsaturated pyrones.[5] This procedure was employed to convert the furan **4** to the pyrone **5**. Since the anomeric hydroxyl in the pyrone fragment of **5** is suitably disposed to a neighboring phenolic group, intramolecular ring closure to furnish the oxocin **6** was expected. The product of conjugate addition of the phenolic group to the unsaturated enone fragment was also a possiblity; however, thermodynamic considerations indicated that the oxocin would be the ultimate product.[6]

The presence of the phenyl group in the rigid bicyclic epoxyoxocin ring system creates a strong diastereofacial bias in the enone fragment of **6**. As a consequence, further transformation of **6** to sugar analogues through manipulation of the enone fragment was anticipated to occur in a highly stereoselective, if not stereospecific, manner.

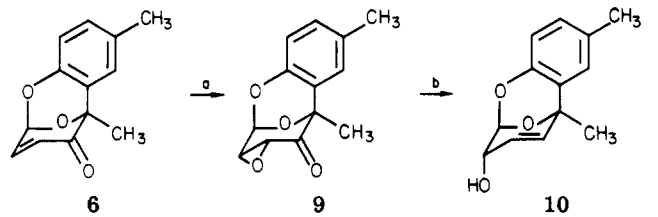
The preparation of the tertiary carbinol precursor **4** to the ketooxocin **6** was accomplished as shown in Scheme I. Fries rearrangement of the *p*-cresol ester of 2-furoic acid (**2**) in molten aluminum chloride (2 equiv, 165 °C, 30 min) furnished the ketone **3** in 87% yield.[7] Reaction of **3** with excess methyl lithium (3 equiv) gave the tertiary carbinol **4** in 92–95% yield. Although **4** was reasonably stable, it

Scheme I[a]



[a] a, $AlCl_3$, 165 °C, 30 min (87%); b, $CH_3Li$, $Et_2O$ (92–95%); c, $Br_2$, MeOH; d, $H_2SO_4$, HOAc (79%); e, LAH, $Et_2O$ (96%); f, TMNO, $OsO_4$ (92%).

Scheme II[a]



[a] a, NaOCl, dioxane (36%); b, $H_2NNH_2$, HOAc (5–10%).

underwent dehydration on attempted chromatography; therefore, it was not purified but directly used in the next step.

A qualitative examination of the reagents known to effect transformation of furans to pyrones was performed.[8] The procedure described by Achmatowicz et al.[5] was found to be superior. Treatment of **4** with bromine in methanol proceeded smoothly to give the expected methanol adduct as a mixture of diastereoisomers. Isolation of the adduct and then hydrolysis in acetic acid containing a trace of sulfuric acid directly furnished the crystalline benzoxocin **6** in 79% yield.

The conversion of **6** to the benzoxocin sugar analogue **8** with the manno configuration was readily accomplished. Reduction of **6** with either lithium aluminum hydride or cerium borohydride[11] furnished the endo alcohol **7** as the sole product of reaction (96%). Cis hydroxylation of **7** with trimethylamine *N*-oxide and a catalytic amount of osmium tetroxide[12] also occurred stereospecifically to give the triol

(1) Recipient of a Career Development Award, 1978–83, from the National Cancer Institute of the National Institutes of Health.

(2) (a) Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; MacKellar, F. R.; Mizsak, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 542. (b) Wiley, P. F. *J. Nat. Prod. Chem.* **1979**, *42*, 569.

(3) (a) The only previously reported route which was employed to prepare an unfunctionalized 2,6-epoxy-2*H*-1-benzoxocin was described by Roffey, P.; Sargent, M. V.; Knight, J. A. *J. Chem. Soc. C* **1967**, 2328. A similar sequence was employed by Townsend et al. in a synthesis of averafin: Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (b) While this manuscript was in preparation, Bates and Sammes published a synthesis of an amino glucose benzoxocin analogue: Bates, M. A.; Sammes, P. G. *J. Chem. Soc., Chem Commun.* **1983**, 896.

(4) Stezowski, J. J.; Wiley, P. F. *Tetrahedron Lett.* **1980**, *21*, 507.

(5) Achmatowicz, O., Jr.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973.

(6) Conjugate addition to the enone fragment was expected to be a reversible process and regenerate **5**.

(7) This method for preparation of **3** proceeds in much higher yield than previously published procedures. Sen, A. B.; Bhattacharji, S. *J. Indian Chem. Soc.* **1954**, *31*, 581.

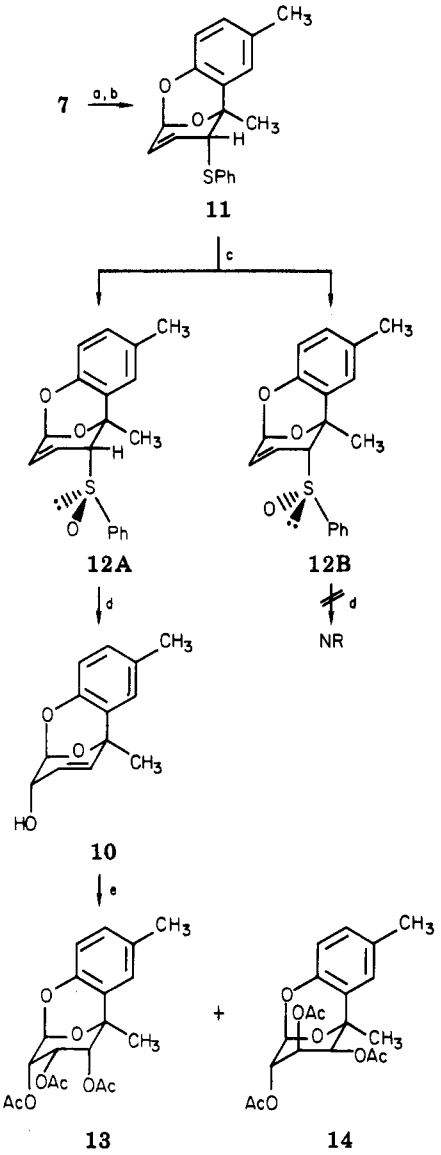
(8) The use of aqueous bromine[9] gave a complex product mixture containing less than 5% of **6** whereas the use of MCPA[10] gave a 17% yield of **6**.

(9) Weeks, P. D.; Brennan, T. M.; Brannegan, D. P.; Kuhla, D. E.; Elliott, M. L.; Watson, H. A.; Wlodecki, B.; Breitenbach, R. *J. Org. Chem.* **1980**, *45*, 1109.

(10) Lefebvre, Y. *Tetrahedron Lett.* **1972**, *2*, 133.

(11) Luche, J. L.; Hahn, L. R.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

Scheme III[a]

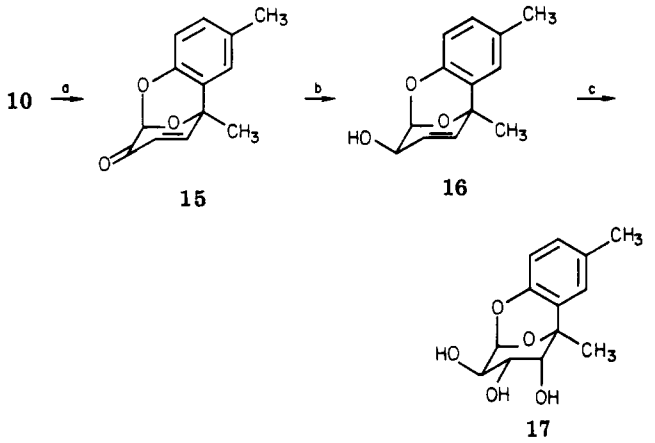


[a] a, $CH_3SO_2Cl$, Py (86%); b, PhSH, $K_2CO_3$, DMF, Δ (48%); c, MCPBA (**12A**, 49%; **12B**, 40%); d, $(MeO)_3P$, $CH_3OH$ (88%); e, catalyst $OsO_4$, TMNO-$Ac_2O$-Py (**13**, 47%; **14**, 18%).

8. Since the chemical shifts for the individual protons on carbons C-2 through C-5 were well separated in the $^1H$ NMR spectrum of **8**, analysis of the spin couplings permitted definitive assignment of the stereochemistry. A notable feature of the spectrum was the upfield location of the C-4 proton (dd, $J$ = 9.7 and 3.7 Hz) at 3.24 ppm which is a consequence of its proximity to the shielding cone of the aromatic ring.

In order to access other sugar configurations, inversion of the regiochemistry of functionalization in the epoxyoxocin ring system was necessary. initially, the route shown in Scheme II was investigated. Although the olefinic entity in **6** proved to be resistant to epoxidation with $NaOH-H_2O_2$,[13] Triton B-*t*-BuOOH,[14] and MCPBA, reaction with NaOCl in dioxane[15] produced the desired epoxide **9** in modest yield (36%). Subsequent Wharton fragmentation[16] of **9** (HOAc, $H_2NNH_2$), though successful, gave only a 5–10% yield of the allyl alcohol **10**.

Scheme IV[a]



[a] a, ClCOCOCl, $Me_2SO$, $Et_3N$ (74%); b, LAH, $Et_2O$ (94%); c, catalyst $OsO_4$, TMNO (72%).

Because of the successive low yields encountered previously, the sequence shown in Scheme III was investigated as an alternative route to sugar analogues. This plan utilizes the finding by Evans et al.[17] that allyl sulfoxides in refluxing methanol in the presence of trimethyl phosphite undergo thermal rearrangement and reductive cleavage to allyl alcohols. The alcohol **7** was converted to the mesylate derivative and then reacted with benzene thiol and potassium carbonate in DMF to furnish the sulfide **11** (48% yield). Oxidation of **11** with sodium metaperiodate in methanol gave a 4:5 ratio of diastereoisomeric sulfoxides **12a** and **12b** which were readily separated by chromatography. Although the $^1H$ NMR spectra of the individual sulfoxide isomers were very different, assignment of the relative stereochemistry was not possible.

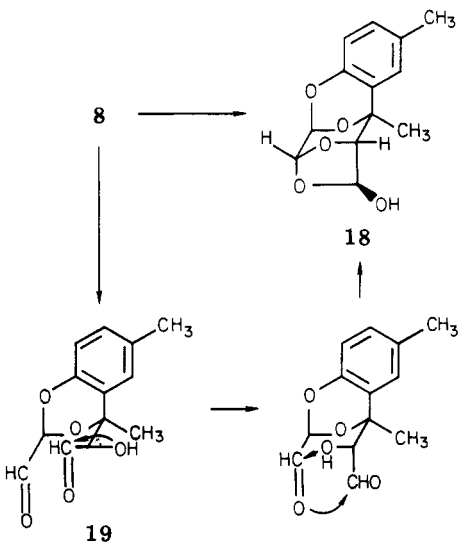
The dichotomy in chemical behavior ultimately delineated the stereochemistry at sulfur; the more polar sulfoxide underwent smooth 3,3-sigmatropic rearrangement and reductive cleavage at reflux in methanol containing trimethyl phosphite to give the allyl alcohol **10** (88%). Under the same conditions, the less polar sulfoxide failed to undergo any reaction and the starting material was recovered. Based on its ability to readily attain a transition state geometry which furnishes the allyl alcohol product **10**, the more polar isomer was assigned structure **12a**. Since the transition state geometry of the less polar sulfoxide results in a severe steric interaction between the ring methyl and the phenyl groups, this isomer fails to undergo reaction and was assigned structure **12b**.

A variety of other oxidizing agents were examined in an attempt to enhance the formation of the sulfoxide diastereoisomer **12a**. The use of MCPBA in methylene chloride (−78 °C) gave the best result, a 5:4 ratio of **12a** to **12b** in 90% yield. Efforts to racemize **12** with hydrochloric acid[18] in dioxane or to invert the configuration of **12b** through alkylation with Merwein's reagent ($Et_3O^+BF_4^-$) followed by hydrolysis[19] were unsuccessful.

Cis hydroxylation of the olefinic entity in **10** was performed with the trimethylamine *N*-oxide/osmium tetroxide (catalyst) reagent combination. The triols which were produced were successfully separated only after conversion to the peracetate derivatives. An analysis of

(12) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.
(13) Wasson, R. L.; House, H. O. "Organic Syntheses"; Wiley: New York, 1963; Collect, Vol. 4, p 552.
(14) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.
(15) Marmor, S. *J. Org. Chem.* **1963**, *28*, 250.
(16) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781.
(17) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1385.
(18) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.
(19) Johnson, C. R. *J. Am. Chem. Soc.* **1963**, *85*, 1020.

Scheme V



the $^1H$ NMR spectrum of the major product (47%) showed it to be isomer **13** with the talo configuration which arises from hydroxylation of the less hindered olefinic face. The minor isomer **14** (18%), with the altro configuration, was identified from its striking $^1H$ NMR spectrum; the methyl of the 4-acetoxyl group is shifted upfield to 1.40 ppm since it lies directly in the shielding cone of the phenyl group. The formation of **14** emphatically demonstrates the sensitivity of osmium tetroxide hydroxylations to environmental factors.

The olefinic alcohol **10** was also employed as shown in Scheme IV to prepare the epoxyoxocin sugar analogue with the galacto configuration. Oxidation of **10** with Swern's reagent[20] (ClCOCOCl, $Me_2SO$, $Et_3N$) gave the unsaturated ketone **15** (74%) which upon reduction (LAH, $Et_2O$) furnished the endo alcohol **16** as the sole product of the reaction. Hydroxylation of **16** (catalyst $OsO_4$, TMNO) proceeded stereospecifically to give **17** with the galacto configuration which was verified by its $^1H$ NMR spectrum.

In order to utilize **8** as a precursor to a 4-amino sugar analogue, the triol moiety would initially be cleaved to a dialdehyde with loss of carbon 4. Subsequent cyclization of the dialdehyde with nitromethane followed by reduction would provide the objective amino sugar. However, treatment of **8** with periodate did not produce the expected dialdehyde, but instead gave the diepoxy-1,4-benzodioxonin **18** shown in Scheme V. This ring system is previously unreported and is striking by virtue of both its stairstep structure and highly oxygenated nature. A rational mechanism for its formation requires an initial cleavage of the *cis*-diol functionality to the hydroxy dialdehyde **20**. Subsequent rotation of the hydroxyaldehyde appendage and two intramolecular closures furnishes **19**.

## Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were obtained on a JEOL FX90Q spectrophotometer. Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ($\delta$ 0.00) as an internal standard. Carbon and hydrogen analyses were performed by Galbraith Laboratories.

Methanol was dried by distillation from magnesium turnings containing a catalytic amount of iodine. A stock solution of osmium tetroxide (1 g $OsO_4$ in 200 mL of 3:1 *tert*-butyl alcohol/carbon tetrachloride) was used for hydroxylations. Methyl lithium in ether (1.6 M) was purchased from Alfa Products, Inc. Reagent grade solvents were used and, unless otherwise noted, were not further purified.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck & Co. Radial preparative thick-layer chromatography was performed on a Chromatotron (Harrison Research) using rotors coated to 4 mm thickness (silica gel 60 PF-254 manufactured by E. Merck & Co.). Silica gel column chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

**2-Furanyl(2-hydroxy-5-methylphenyl)methanone (3).** A mixture of *p*-tolyl 2-furoate (**2**) (29.1 g, 0.14 mol) and aluminum chloride (38.7 g, 0.29 mol) under $N_2$ was immersed in a wax bath at 180 °C and maintained at 160–165 °C for 30 min. The molten slurry solidified after being magnetically stirred for approximately 20 min. After cooling, the flask was chilled in an ice bath and the solid was manually dissolved in 10% hydrochloric acid (500 mL) and methylene chloride (500 mL). The aqueous mixture was extracted (3 × 200 mL) with methylene chloride and the combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum to give a solid. Final purification was accomplished by column chromatography (300 g, silica gel, $CH_2Cl_2$) and furnished 25.4 g (87%) of pure **3** as yellow needles: mp 66–67 °C (lit.[7] mp 74–75 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 2.33 (s, 3 H), 6.61 (dd, $J$ = 1.6 Hz, $J$ = 3.6 Hz, 1 H), 6.93 (d, $J$ = 8.4 Hz, 1 H), 7.33 (d, $J$ = 10.3 Hz, 1 H), 7.35 (s, 1 H), 7.73 (d, $J$ = 1.6 Hz, 1 H), 8.02 (d, $J$ = 3.4 Hz, 1 H).

**α-Methyl-α-(2-hydroxy-5-methylphenyl)-2-furanmethanol (4).** Methyllithium (23 mL, 1.6 M, 36.8 mmol) was added by syringe over a 15 min period to a magnetically stirred, cold (0 °C) solution of **3** (2.5 g, 12.2 mmol) in anhydrous ether (25 mL) under $N_2$. The reaction was stirred for an additional 20 min, then quenched with saturated aqueous ammonium chloride (50 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the combined extracts were dried, filtered, and evaporated at reduced pressure to yield 2.5 g (93%) of **4** as a colorless oil which was used in the next step without purification because of its tendency to dehydrate: $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (s, 3 H), 2.16 (s, 3 H), 3.84 (s, 1 h), 6.29 (m, 2 H), 6.48 (d, $J$ = 2.0 Hz, 1 H), 6.75 (d, $J$ = 8.2 Hz, 1 H), 6.95 (dd, $J$ = 2.1 Hz, J = 8.3 Hz, 1 H), 7.37 (m, 1 H), 8.70 (s, 1 H).

**DL-6,8-Dimethyl-2,6-epoxy-2*H*-1-benzoxocin-5(6*H*)-one (6).** A solution of bromine (0.6 mL, 11.7 mmol) in methanol (10 mL) was added dropwise over a 15-min addition period to a magnetically stirred, cold (−60 °C) solution of carbinol **4** (2.5 g, 11.4 mmol) in methanol (50 mL) under $N_2$. The reaction was continued for 30 min, then saturated with ammonia gas with gradual warming to 0 °C. The methanol was removed by rotary evaporation and the residue was taken up in benzene (100 mL). The benzene solution was washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated to give the methanol adduct of **4** as an oil.

The adduct was dissolved in acetic acid (15 mL) containing sulfuric acid (6 mL of 0.5 N) and heated at 50 °C overnight with stirring. The reaction was cooled and then poured slowly into a slurry of potassium carbonate hydrate (21 g) in water (50 mL). When the carbon dioxide evolution subsided, the aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried ($MgSO_4$), then filtered, and evaporated under vacuum. Purification of the residue by column chromatography (silica gel, 100 g, 20% EtOAc–hexane) gave 1.95 g (79% based on **4**) of **6** as large colorless crystals after recrystallization from hexane: mp 111–111.5 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.73 (s, 3 H), 2.25 (s, 3 H), 5.93 (d, $J$ = 3.7 Hz, 1 H), 6.15 (d, $J$ = 10.1 Hz, 1 H), 6.76 (d, $J$ = 9.4 Hz, 1 H), 6.81 (dd, $J$ = 10.3 Hz, $J$ = 3.6 Hz, 1 H), 6.91 (d, $J$ = 2.0 Hz, 1 H), 7.05 (dd, $J$ = 8.4 Hz, $J$ = 2.0 Hz, 1 H).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.44; H, 5.70.

**DL-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2*H*-1-benzoxocin-5β-ol (7).**[21] To a magnetically stirred mixture of lithium alu-

(20) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2840.

(21) The use of β designates a cis (endo) relationship of a given functionality with the aromatic ring; an α designates a trans (exo) relationship.

minum hydride (0.17 g, 4.5 mmol) in anhydrous ether (50 mL) under nitrogen was added a solution of **6** (0.65 g, 3.0 mmol) in anhydrous ether (20 mL). The mixture was stirred for 30 min and then heated at reflux for 1 h. The reaction was cooled in an ice bath and the excess hydride was cautiously decomposed by sequential dropwise addition of water (0.2 mL), 15% NaOH (0.6 mL), and water (0.6 mL). The resulting slurry was filtered through celite, and the ether filtrate dried ($MgSO_4$), filtered, and then evaporated under vacuum. Radial chromatography of the residue (Chromatotron, 40% $CH_2Cl_2$/hexane) gave 0.61 g (97%) of pure **7** as a white crystalline solid: mp 105–108 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.63 (s, 3 H), 1.75 (s, 1 H), 2.27 (s, 3 H), 4.24 (d, $J$ = 5.7 Hz, 1 H), 5.68 (m, 3 H), 7.20 (m, 3 H).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.35; H, 6.47.

**1,2′-Anhydro-6-deoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-mannopyranose (8).** A mixture of **7** (0.40 g, 1.8 mmol), acetone (6 mL), water (1 mL), trimethylamine *N*-oxide dihydrate (0.43 g, 3.9 mmol), and osmium tetroxide (1.0 mL) was magnetically stirred overnight at room temperature. The reaction mixture was chilled in an ice bath, quenched with saturated sodium bisulfite (30 mL), and extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was recrystallized from ethyl acetate to furnish 0.42 g (92%) of pure **8** as colorless plates: mp 238–240 °C; $^1H$ NMR ($CD_3OD$) $\delta$ 1.64 (s, 3 H), 2.28 (s, 3 H), 3.24 (dd, $J$ = 3.7 Hz, $J$ = 9.7 Hz, 1 H), 3.78 (d, $J$ = 9.9 Hz, 1 H), 3.97 (dd, $J$ = 3.7 Hz, $J$ = 1.8 Hz, 1 H), 5.42 (d, $J$ = 1.8 Hz, 1 H), 6.80 (m, 3 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.98; H, 6.48.

**DL-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5α-(phenylthio)-2*H*-1-benzoxocin (11).** To a solution of **7** (0.61 g, 2.9 mmol) in ether (75 mL) and pyridine (0.8 mL, 9.9 mmol) chilled in an ice bath under $N_2$ was added methanesulfonyl chloride (0.5 mL, 6.5 mmol) and the mixture was stirred at room temperature for 2 h. Hydrochloric acid (25 mL of 2%) was added to the reaction and the aqueous phase was separated and then extracted with ether (4 × 30 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and then evaporated at reduced pressure. The residue was taken up in ether and filtered through silica to give 0.75 g (86%) of the mesylate as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.70 (s, 3 H), 2.30 (s, 3 H), 3.11 (s, 3 H), 5.40 (d, $J$ = 2.6 Hz, 1 H), 5.75 (s, 1 H), 5.88 (dd, $J$ = 2.6 Hz, $J$ = 1.8 Hz, 1 H), 5.95 (d, $J$ = 1.8 Hz, 1 H), 6.90 (m, 3 H).

A mixture of the mesylate (0.62 g, 2.1 mmol), dimethylformamide (15 mL), thiophenol (0.4 mL, 3.9 mmol), and potassium carbonate (0.7 g, 5.0 mmol) was stirred overnight at 75 °C. The reaction mixture was cooled, diluted with water (50 mL), and extracted with 1:1 ether/hexane (4 × 50 mL). The combined extracts were washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography (Chromatotron, 20% $CH_2Cl_2$/hexane) of the residue furnished 0.31 g (48%) of pure **11** as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.71 (s, 3 H), 2.23 (s, 3 H), 3.68 (dd, $J$ = 5.4 Hz, $J$ = 0.9 Hz, 1 H), 5.63 (dd, $J$ = 2.0 Hz, $J$ = 1.4 Hz, 1 H), 5.72 (dd, $J$ = 3.4 Hz, $J$ = 1.0 Hz, 1 H), 6.12 (m, 1 H), 6.84 (m, 3 H), 7.36 (m, 5 H).

**DL-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5α-(phenylsulfinyl)-2*H*-1-benzoxocins (12A and 12B).** To a mixture of **11** (1.77 g, 5.7 mmol) in methylene chloride (50 mL) at −78 °C under $N_2$ was added solid *m*-chloroperbenzoic acid (1.85 g, 8.6 mmol) and the reaction was stirred for 2 h. Saturated sodium bisulfite (40 mL) was added to the cold reaction and the mixture was allowed to come to room temperature. The methylene chloride layer was separated, washed with saturated sodium bicarbonate (40 mL) and water (40 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Column chromatography of the residue (silica gel, 200 g, 40% EtOAc–hexanes) gave 0.91 g (49%) of **12A** as colorless needles (mp 145–146 °C) and 0.76 g (40%) of **12B** as an oil.

**12A**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.08 (s, 3 H), 2.26 (s, 3 H), 3.09 (dd, $J$ = 5.4 Hz, $J$ = 1.0 Hz, 1 H), 5.45 (dd, $J$ = 9.9 Hz, $J$ = 5.3 Hz, 1 H), 5.86 (d, $J$ = 3.3 Hz, 1 H), 6.17 (ddd, $J$ = 9.9 Hz, $J$ = 3.3 Hz, $J$ = 0.9 Hz, 1 H), 6.84 (m, 3 H), 7.55 (m, 5 H).

**12B**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.74 (s, 3 H), 2.26 (s, 3 H), 3.34 (dd, $J$ = 5.5 Hz, $J$ = 0.9 Hz, 1 H), 5.06 (m, 1 H), 5.68 (t, $J$ = 1.5 Hz, 1 H), 5.76 (dd, $J$ = 3.5 Hz, $J$ = 0.9 Hz, 1 H), 6.80 (m, 3 H), 7.60 (m, 5 H).

Anal. (**12A**) Calcd for $C_{19}H_{18}O_3S$: C, 69.93; H, 5.56. Found: C, 69.79, H, 5.68.

**DL-(2α,5β,6α)-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2*H*-1-benzoxocin-3α-ol (10).** A mixture of **12A** (0.56 g, 1.7 mmol) and trimethyl phosphite (0.8 mL, 6.8 mmol) in methanol (50 mL) was refluxed under $N_2$ for 2 h. The reaction mixture was cooled, then quenched with dilute $NH_4OH$ (50 mL of 5%), and extracted with ether (4 × 60 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography of the residue (Chromatotron, 20% EtOAC–hexane) furnished 0.32 g (88%) of **10** as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.72 (s, 3 H), 1.79 (s, 1 H), 2.27 (s, 3 H), 3.92 (m, 1 H), 5.78 (br s, 1 H), 5.95 (m, 2 H), 6.85 (m, 3 H).

**1,2′-Anhydro-6-deoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-talopyrranose (13) and 1,2′-Anhydro-6-deoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-altropyrranose (14).** A mixture of **10** (0.10 g, 0.5 mmol), acetone (6 mL), water (1 mL), trimethylamine *N*-oxide (0.20 g, 1.8 mmol), and osmium tetroxide (1 mL) was stirred overnight at room temperature. The reaction mixture was quenched with saturated sodium bisulfite (30 mL) and extracted with ethyl acetate (4 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and then evaporated under vacuum. In order to effect separation of the diol mixture the initial product was acetylated. The residue (0.06 g) from the hydroxylation was taken up in acetic anhydride (2 mL) and pyridine (5 mL), then stirred overnight under $N_2$. Saturated sodium bicarbonate solution (25 mL) was added to the reaction which was then extracted with ethyl acetate (4 × 25 mL). The combined extracts were washed with 1 N HCl (2 × 50 mL) and water (50 mL), then dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography (Chromatotron, 20% EtOAc/hexane) furnished 82 mg (47%) of **13**, mp 180.5–182 °C, and 31 mg (18%) of **14** as an oil.

**13**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.59 (s, 3 H), 1.91 (s, 3 H), 2.17 (s, 3 H), 2.21 (s, 3 H), 2.28 (s, 3 H), 5.00 (m, 1 H), 5.28 (m, 2 H), 5.62 (d, $J$ = 1.7 Hz, 1 H), 6.94 (m, 3 H).

**14**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 (s, 3 H), 1.57 (s, 3 H), 2.03 (s, 3 H), 2.18 (s, 3 H), 2.28 (s, 3 H), 5.04 (br s, 1 H), 5.22 (br s, 1 H), 5.33 (br s, 1 H), 5.47 (br s, 1 H), 6.86 (m, 3 H).

Anal. (**13**) Calcd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.51; H, 6.06.

**DL-6,8-Dimethyl-2,6-epoxy-2*H*-1-benzoxocin-3(6*H*)-one (15).** A mixture of oxalyl chloride (0.15 mL, 1.7 mmol) in methylene chloride (15 mL) was cooled to −78 °C under $N_2$. Dimethyl sulfoxide (0.25 mL, 3.5 mmol) was added and the reaction stirred for 10 min. A mixture of **10** (0.23 g, 1.05 mmol) in methylene chloride (5 mL) was added dropwise over 15 min and then stirred for an additional 30 min. Triethylamine (1.2 mL, 8.6 mmol) was next added dropwise and after 15 min, the cooling bath was removed and the reaction was allowed to come to room temperature over 1 h. The reaction was quenched with saturated sodium bicarbonate (30 mL) and extracted with methylene chloride (3 × 30 mL). The combined extracts were washed with 2% hydrochloric acid (2 × 50 mL), then dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography of the residue (Chromatotron, 20% EtOAc-hexane) furnished 0.17 g (74%) of pure **15** as colorless needles: mp 75–76 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.78 (s, 3 H), 2.28 (s, 3 H), 5.57 (d, $J$ = 0.7 Hz, 1 H), 5.18 (dd, $J$ = 10.2 Hz, $J$ = 0.8 Hz, 1 H), 6.88 (m, 3 H), 6.12 (d, $J$ = 10.3 Hz, 1 H).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.42; H, 5.71.

**DL-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2*H*-1-benzoxocin-3-ol (16).** A mixture of **15** (0.17 g, 0.8 mmol) in ether (10 mL) was added to lithium aluminum hydride (60 mg, 1.6 mmol) in ether (15 mL) at room temperature under $N_2$. The reaction was stirred at room temperature for 1 h, then quenched with 3 N hydrochloric acid (40 mL), and extracted with ether (4 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography (Chromatotron, 25% EtOAc/hexane) of the residue furnished 0.16 g (94%) of **16** as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.68 (s, 3 H), 2.03 (s, 1 H), 2.27 (s, 3 H), 4.26 (dd, $J$ = 11.7 Hz, $J$ = 3.8 Hz, 1 H), 5.73 (m, 2 H), 6.89 (m, 3 H).

**1,2′-Anhydro-6-deoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-galactopyrranose (17).** A mixture of **16** (0.07 g, 0.3 mmol), acetone (6 mL), water (1 mL), trimethylamine *N*-oxide (0.08 g, 0.7 mmol), and osmium tetroxide (1 mL) was stirred overnight at room temperature. The reaction was quenched with saturated sodium bisulfite (30 mL) and extracted with ethyl acetate (4 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was purified by radial chromatography (Chromatotron, EtOAc as eluent) to furnish 0.06 g (72%) of pure **17** as a colorless solid: mp 159–160 °C; $^1H$ NMR ($CD_3OD$) δ 1.62 (s, 3 H), 2.28 (s, 3 H), 3.49 (dd, $J$ = 10.1 Hz, $J$ = 3.5 Hz, 1 H), 3.75 (d, $J$ = 3.5 Hz, 1 H), 3.95 (dd, $J$ = 10.1 Hz, $J$ = 3.5 Hz, 1 H), 6.89 (m, 3 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.01, H, 6.54.

**DL-2,3,6,7-Tetrahydro-7,9-dimethyl-2,7:3,6-diepoxy-5*H*-1,4-benzodioxonin-5-ol (18).** To a mixture of **8** (255 mg, 1.01 mmol) in acetone (40 mL) and acetic acid (20 mL) was added a solution of sodium metaperiodate (410 mg, 1.9 mmol) in water (10 mL) and the mixture was stirred for two days. The reaction was diluted with water (40 mL) and enough sodium bicarbonate was added to neutralize the mixture. The layers were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give a semisolid. Chromatography of the residue (silica gel, 30 g, $CH_2Cl_2$ to 5% EtOAc/$CH_2Cl_2$) followed by recrystallization of the eluate ($CHCl_3$–hexane) gave 130 mg (55%) of pure **19**: mp 140–158 °C; $^1H$ NMR ($CDCl_3$) δ 1.62 (s, 3 H), 2.29 (s, 3 H), 2.93 (d, $J$ = 9.9 Hz, 1 H), 3.92 (d, $J$ = 0.7 Hz, 1 H), 5.05 (dd, $J$ = 0.7 Hz, $J$ = 1.4 Hz, 1 H), 5.27 (d, $J$ = 1.4 Hz, 1 H), 5.84 (d, $J$ = 9.9 Hz, 1 H), 6.7–7.1 (m, 3 H); $^{13}C$ NMR ($CDCl_3$) 19.30, 20.71, 73.09, 86.75, 92.22, 95.09, 100.78, 115.35, 123.80, 124.99, 129.71, 129.87, 149.81.

The acetate derivative was prepared by acetylating **18** (65 mg, 0.26 mmol) with acetic anhydride (5 mL) and pyridine (1 mL) for 15 min at room temperature. Workup and then chromatography (silica gel, $CH_2Cl_2$) furnished an oil which slowly crystallized. Recrystallization (hexane–benzene) of this material furnished 69 mg (91%) of the acetate derivative of **19**: mp 113.5–115 °C; $^1H$ NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.10 (s, 3 H), 2.28 (s, 3 H), 4.10 (d, $J$ = 0.9 Hz, 1 H), 5.10 (dd, $J$ = 0.9 Hz, $J$ = 1.4 Hz, 1 H), 5.60 (d, $J$ = 1.4 Hz, 1 H), 6.64 (s, 1 H), 6.7–7.1 (m, 3 H); $^{13}C$ NMR ($CDCl_3$) 19.35, 20.71, 20.98, 73.37, 85.77, 91.95, 94.17, 101.64, 115.40, 123.86, 124.72, 129.76, 129.98, 149.75, 170.12.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.63; H, 5.51. Found: C, 61.71; H, 5.40.

# Synthesis and CuCN-Promoted Cyanation of Iodoformic Esters[1]

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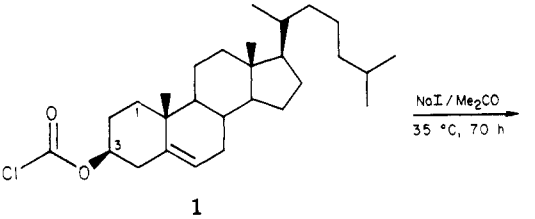
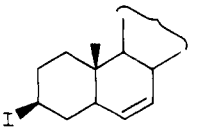
A number of iodoformic esters have been prepared, isolated, and identified for the first time. Phenyl iodoformate has been converted into phenyl cyanoformate under mild conditions. Decarboxylative iodination of iodoformates ROCOI to give RI and $CO_2$ can be slowed down by the choice of the group R.

Iodoformic esters[2] have hardly been described, although chloroformic esters[3,4] are well-known. Several years ago Kevill suggested that the "preparation of the more stable members of the iodoformate family may well be feasible".[3] Kevill and Weitl[5] had shown earlier that the reaction of cholesteryl chloroformate (**1**) and sodium iodide in acetone, at 35 °C, led to cholesteryl iodide (**2**) in 50% yield. The iodoformate of cholesterol was postulated as a reactive intermediate. Because of double bond participation, retention of configuration at C-3 is the expected steric course for the conversion of **1** into **2**. Goosen and his co-workers[6] prepared 9-triptycyl iodoformate (**4**) by irradiation of 9-triptycyl hydrogen oxalate (**3**) in the presence of mercuric oxide/iodine. Formation of 9-iodotriptycene (**5**) from iodoformate precursor **4** required extreme conditions, as expected for an ionic reaction at the triptycyl bridgehead. **4** appears to be the only iodoformate which has been described in the literature hitherto.




**1**




**2** 50%

We have recently prepared a series of iodocarbonyl compounds including acyl iodides[1d,7] and iodoglyoxalates.[1a] We now show that selected iodoformic esters **7a–d** can be prepared from chloroformic esters **6a–d** by Cl/I exchange

(1) Reactive Iodine Compounds 8. Part 7: (a) Geschwinder, P. M.; Preftitsi, S.; Hoffmann, H. M. R. *Chem. Ber.* **1984**, *117*, 408. Part 6: (b) Hoffmann, H. M. R.; Haase, K.; Ismail, Z. M.; Preftitsi, S.; Weber, A. *Chem. Ber.* **1982**, *115*, 3880. Part 5: (c) Belsner, K.; Hoffmann, H. M. R. *Synthesis* **1982**, 239. Part 4: (d) Hoffmann, H. M. R.; Haase, K.; Geschwinder, P. M. *Synthesis* **1982**, 237. Part 3: (e) Grundke, G.; Hoffmann, H. M. R. *J. Org. Chem.* **1981**, *46*, 5428. Part 2: (f) Haase, K.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 83. Part 1: ref 7.

(2) Other names: iodocarbonic acid esters (iodo carbonates) or alkoxy- or (aryloxy)carbonyl iodides.

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(4) For silver-assisted reactions of chloroformates see: Beak, P. *Acc. Chem. Res.* **1976**, *9*, 230.

(5) Kevill, D. N.; Weitl, F. L. *J. Org. Chem.* **1967**, *32*, 2633.

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