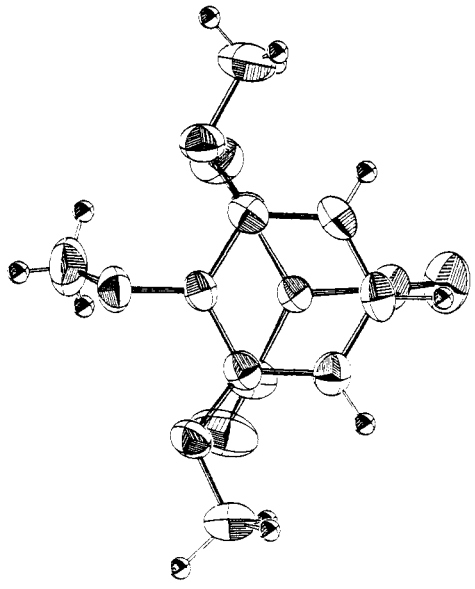

Figure 3. ORTEP view of compound 7.

these compounds exhibit strong conjugative effects of the adjacent group(s) with the arene ring; for example, in the $N(Et)_2$ case, the N–C(1) distance (1.357 (3) Å), characteristic of a partial double bond, is associated with a planar conformation of the nitrogen atom. It has been previously shown both from experimental[12] and theoretical[13] studies that the nitrogen atom of aniline is pyramidal. The structural feature of **3** and **7** (see Figures 2 and 3) may be related to the strong effect of the substituents attached to the arene. Therefore, the chromium atom displacement may follow the drift of the electron density from the barycenter of the ring.

The above data point out that, for strongly perturbing groups possessing a lone pair and situated in a position α to the arene, the structural alteration of the Cr–ring bond brings about the facile generation of the catalytic species. The previous explanations of the catalytic efficiency of monoarenes–$Cr(CO)_3$ based on the total strength of the bond must then be completed by symmetry considerations. It is clear that judiciously selected antagonist substituents might allow access to new reactive catalysts. We are now exploring the limits of this approach and looking for the extension of these ideas on new catalytic systems.[14]

Acknowledgment. We thank Professor M. Cais and Dr. D. Thompson for helpful discussions.

Registry No. 1, 12125-87-0; 2, 12116-44-8; 3, 12242-29-4; 4, 12176-27-1; 5, 12176-28-2; 6, 12176-26-0; 7, 12193-72-5; 8, 12241-72-4; 9, 12182-02-4; 10, 57629-45-5; 11, 63168-35-4; methyl sorbate, 689-89-4; methyl *cis*-3-hexenoate, 13894-62-7.

(12) D. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).
(13) W. J. Here, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 1496 (1972).
(14) Data collection and refinement of structure from the X-ray analysis are given below. **3**: monoclinic; a = 9.562 (3), b = 10.307 (3), c = 13.785 (5) Å; β = 96.34 (4)°; D_c = 1.40 mg cm^{-3}; Z = 4; space group $P2_1/n$. **7**: monoclinic; a = 7.370 (2), b = 24.731 (5), c = 6.968 (2) Å; β = 103.63 (2)°; D_c = 1.51 mg cm^{-3}; Z = 4; space group $P2_1/c$. Three-dimensional X-ray diffraction data were collected on a computer-controlled four-circle Nonius CAD 4 diffractometer using graphite-monochromated Mo Kα radiation and ω–2θ scans. Scan angle (degrees) is given by S = 1.00 + 0.35 tan θ for both compounds. Counter aperture (mm) is calculated from d = 2.0 + 0.5 tan θ for **3** and d = 2.5 + 0.4 tan θ for **7**. For both structures, atoms were located through direct method (MULTAN) and standard difference Fourier techniques and the resulting structural parameters have been refined to convergence (**3**, R = 0.064, R_w = 0.050, for 2757 independent reflections having 28° > θ > 1°; **7**, R = 0.055, R_w = 0.054, for 3301 independent reflections having 30° > θ > 1°), using unit-weighted full-matrix least-squares techniques with anisotropic thermal parameters for all nonhydrogen atoms.

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Received February 22, 1980

Synthesis of Methyl Peracetyl α-Hikosaminide, the Undecose Portion of the Nucleoside Antibiotic Hikizimycin[1]

Summary: A convergent synthesis of the fully protected derivative **2** of hikosamine, the undecose unit of the nucleoside antibiotic hikizimycin, is described.

Sir: The nucleoside antibiotic hikizimycin (**1**), isolated from *Streptomyces longissimus* and *Streptomyces A-5*,[2,3] is one member of a rare class of naturally occurring compounds with a long-chain complex carbohydrate as a key structural feature.[4-8] Hikizimycin (or anthelmycin) is a powerful anthelmintic agent[2] and has recently been shown to inhibit protein synthesis by preventing the peptide bond-forming reaction.[9] Other nucleoside antibiotics containing long-chain carbohydrate units are tunicamycin,[10] which is a powerful glycosylation inhibitor,[11] and sinefungin,[12,13] which has both antifungal and antiviral activity.[12-16] The undecose portion of hikizimycin is re-

(1) A portion of this research was presented at the 11th Central Regional Meeting of the American Chemical Society, Columbus, OH, May 1979; ORG-8. A systematic name for hikizimycin (anthelmycin, **1**) is 1-[6-*O*-(3-amino-3-deoxy-β-D-glucopyranosyl)-4-amino-4-deoxy-β-D-*glycero*-D-*galacto*-D-*gluco*-undecopyranosyl]cytosine. A systematic name for methyl peracetyl-α-hikosaminide (**2**) is methyl 4-acetamido-2,3,6,7,8,9,10,11-octa-*O*-acetyl-4-deoxy-α-D-*glycero*-D-*galacto*-D-*gluco*-undecopyranoside.
(2) Hamill, R. L.; Hoehn, M. M. *J. Antibiot., Ser. A* **1964**, *17*, 100–103.
(3) Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.* **1971**, *76*, 259–262.
(4) Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289–3291. Ennifar, S.; Das, B. C.; Nash, S. M.; Nagarajan, R. *J. Chem. Soc., Chem. Commun.* **1977**,41–42.
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(10) Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, J.; Ito, T.; Tamura, G. *Agric. Biol. Chem.* **1977**, *41*, 2307–2309.
(11) Mahoney, W. C.; Duksin, D. *J. Biol. Chem.* **1979**, 254, 6572–6576, and references therein.
(12) Turner, J. R.; Butler, T. F.; Fuller, R. W.; Owen, N. V. 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1977; Abstract No. 49.
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(14) Fuller, R. W.; Nagarajan, R. *Biochem. Pharmacol.* **1978**, *27*, 1981–1983.
(15) Borchardt, R. T.; Eiden, L. E.; Wu, B. S.; Rutledge, C. O. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 919–924.
(16) Nagarajan, R. U.S. Patent 4158056, 1979.

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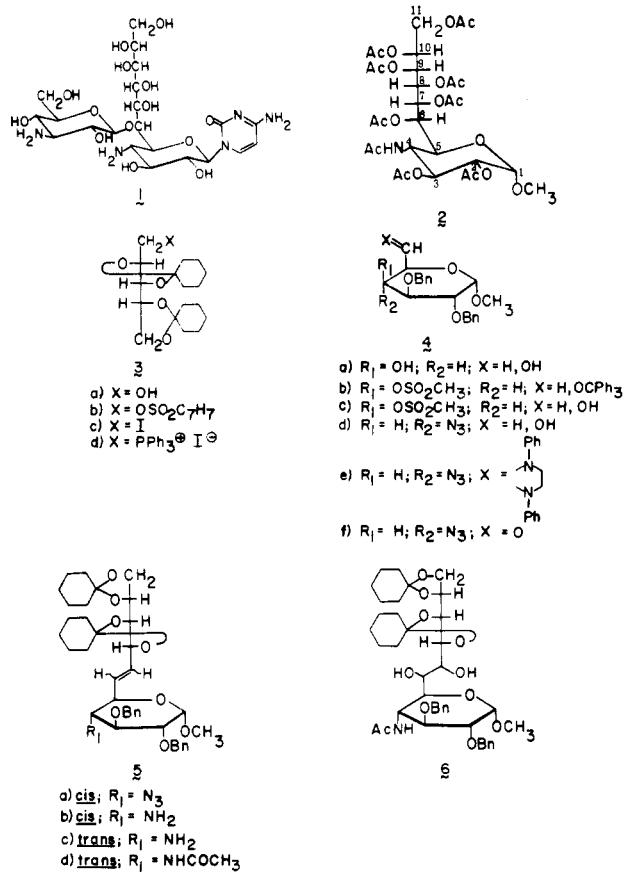
Chart I



ferred to as hikosamine, and this communication describes the synthesis of the fully protected hikosamine derivative **2** (see Chart I for structures).

Our strategy toward the ten consecutive chiral centers of hikosamine revolved around construction of the basic framework utilizing recently developed chemistry of carbohydrate phosphoranes.[17,18] The key step was projected to be formation of a C_6–C_7 double bond by joining a five- or six-carbon unstabilized carbohydrate phosphorane with a six- or five-carbon carbohydrate aldehyde. By appropriate selection of the precursors, all chiral centers with the exceptions of C_6 and C_7 could be properly introduced. These final two could then be elaborated from the newly formed double bond. Introduction of the amino group at C_4 posed an additional manipulative problem requiring proper selectivity at some stage of the synthesis.

Carbons 8–10 of hikosamine (in that order) have the D-*arabino* configuration, and thus, 2,3:4,5-di-*O*-cyclohexylidene-1-deoxy-1-triphenylphosphonio-D-arabinitol iodide (**3d**) was selected as one partner for the Wittig reaction. Preparation of **3d** was carried out in standard fashion from the known arabinitol derivative **3a**[19] by *p*-toluenesulfonylation (*p*-toluenesulfonyl chloride, pyridine, 16 h, room temperature), displacement with iodide (NaI, Na_2CO_3, DMF, 125 °C, 1 h), and quaternization with triphenylphosphine (sulfolane, 110 °C, 24 h, 62%).[20] The cyclohexylidene-protected compound **3d** (a pale yellow foam) proved to be more stable than the corresponding isopropylidene-protected compound, which was prepared similarly.

The second target structure selected for the key coupling reaction was the azido aldehyde **4f**, which has the α-D-*gluco* configuration. Since incorporation of the azido group at C_4 was envisioned by nucleophilic displacement of an appropriate leaving group, a D-*galacto* starting material was selected. Methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (**4a**)[21] was converted to the 4-*O*-methanesulfonyl **4c** derivative by tritylation at C_6 and mesylation at C_4 (triphenylmethyl chloride, pyridine, 75 °C, 18 h, then methanesulfonyl chloride, 0 °C to room temperature, 2 days) to produce **4b** followed by detritylation (4:1 acetic acid–water, 100 °C, 4 h). Treatment of **4c** with sodium azide in DMF (120 °C, 5 h, 92%) afforded **4d**, which was directly oxidized with dicyclohexylcarbodiimide–dimethyl sulfoxide to the aldehyde, which was conveniently isolated as the imidazolidine derivative **4e** (dianilinoethane, methanol, 24 h, room temperature, 76%).[20] Liberation of the aldehyde was accomplished by treatment with 4:1 THF–6 N HCl (0.5 h, 0 °C, then 3.5 h, room temperature) followed by chromatography. Azeotropic removal of water from the initially formed aldehyde–aldehyde hydrate mixture produced the slightly unstable aldehyde **4f** in 87% yield, which was typically utilized immediately.

Generation of the ylide derived from phosphonium salt **3d** was carried out by the addition of 1 equiv of *n*-BuLi to a solution of **3d** in 2:1 THF–HMPA at −65 °C. After 30–45 s a solution of aldehyde **4f** in THF was added, and the solution was slowly warmed to −10 °C over 1 h and then processed. Chromatographic purification produced the pure *Z* olefin **5a** (J = 10.8 Hz for the corresponding amine **5b**)[22] in 50% yield (no *E* olefin present).[20]

Proper development of the C_6 and C_7 hydroxyls of hikizimycin would require an overall trans addition across the *Z* olefin, for example, via ring opening of an epoxide by an oxygen nucleophile. Epoxidation of **5a** with *m*-chloroperoxybenzoic acid produced an unequal mixture of the two possible diastereoisomeric epoxides. Neither epoxide was successfully opened with an oxygen nucleophile, either under acidic or basic conditions, presumably due to steric constraints.[23] However, **5a** was successfully hydroxylated in a cis fashion with osmium tetroxide and potassium chlorate. Therefore, isomerization of the *Z* to the *E* olefin (thus requiring a cis addition to the double bond) was investigated. After reduction of azide **5a** to the amine **5b** with lithium aluminum hydride, irradiation of a cyclohexane solution of **5b** in the presence of diphenyl disulfide (2 equiv) for 35 min produced a mixture (ca. 3:2) of the *Z* and *E* olefins. Chromatographic separation afforded pure **5c** (J = 15.8 Hz)[22] (90% based on recovered **5b**), and the *Z* olefin was readily recycled. After N-acetylation (acetic anhydride–pyridine), **5d** was treated with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide[24] in 5:1 THF–water (5 h, room temperature, 78%) to produce *one* isomer of diol **6**, which

(17) Secrist, J. A., III; Wu, S. R. *J. Org. Chem.* **1979**, *44*, 1434–1438.
(18) Secrist, J. A., III; Wu, S. R. *J. Org. Chem.* **1977**, *42*, 4084–4088.
(19) Zinner, H.; Milbradt, J. *Carbohydr. Res.* **1966**, *2*, 470–479.
(20) Satisfactory IR, ^1H and ^{13}C NMR, elemental analysis, and exact mass data were obtained for each stable intermediate except **6**, in which difficultly removable minor impurities made a proper elemental analysis unobtainable.
(21) Kiss, J.; Burkhardt, T. *Helv. Chim. Acta* **1970**, *53*, 1000–1011.
(22) While at 60 MHz in several solvents the resonances for H_6 and H_7 fell on top of one another, at 400 MHz they were cleanly separated and the geometries were confirmed. The two olefinic resonances are the AB portion of an XABY system. However, the patterns have almost collapsed to an eight-line system, so that the chemical shifts can be calculated as an ABX system. With that approximation, the chemical shifts of the olefinic protons are: **5b**, δ 5.72 and 5.50; **5c**, δ 5.94 and 5.76.
(23) The two diastereoisomeric epoxides corresponding to **5b**, prepared by treatment of the epoxides from **5a** with triphenylphosphine followed by potassium hydroxide, likewise resisted all attempts at opening with oxygen nucleophiles under acidic or basic conditions. With both sets of epoxides, drastic conditions caused decomposition.
(24) Van Rheenan, V.; Kelly, R. C.; Cha, Y. *Tetrahedron Lett.* **1976**, 1973–1976.

was purified chromatographically.[20] Simultaneous removal of the benzyl and cyclohexylidene groups was accomplished by hydrogenation of 6 (10% palladium on carbon, ambient temperature and pressure, 24 h) in 15:4:1 methanol–water–concentrated hydrochloric acid. After filtration, neutralization with Amberlite IR-45 (OH form), and removal of solvent, the residue was directly treated with 1:1 acetic anhydride–pyridine at room temperature. Standard processing (chromatographic purification) after 24 h afforded 47% of a single product, 2, mp 177–178 °C (needles, ethanol). Synthetic 2 was indistinguishable from 2 prepared from hikizimycin in terms of melting point (lit.[6] mp 180.5–181.5 °C; mixture melting point undepressed), specific rotation [synthetic 2, $[\alpha]^{22}_D$ +90° (c 0.58, $CHCl_3$); 2 from natural sources, $[\alpha]^{29}_D$ +85° (c 1.0, $CHCl_3$)[6]], thin-layer chromatographic data, and 400-MHz ^1H NMR data,[25] where spectra of 2 from synthesis and natural sources were superimposable.

Thus, the Wittig reaction produced exclusively the *Z* olefin and the cis hydroxylation (of the *E* olefin) produced only one of the two possible diastereoisomeric diols, presumably due to steric effects, whose configuration was demonstrated by conversion exclusively to methyl peracetyl-α-hikosaminide (2). The methodology demonstrated in this synthesis opens the way for the preparation of many highly complex long-chain carbohydrates.

Acknowledgment. We thank Dr. B. C. Das of the Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, for a sample of methyl peracetyl-α-hikosaminide prepared from hikizimycin, and Dr. R. Nagarajan, Eli Lilly and Company, for a sample of hikosaminylcytosine, which we converted into 2. The 400-MHz ^1H NMR spectra were recorded by Dr. Michael Geckle of the University of Alabama in Birmingham, Comprehensive Cancer Center, supported by NCI Grant No. CA13148. We also appreciate some valuable discussions with Dr. S. R. Wu. K.D.B. received partial support from an Amoco Fellowship.

Registry No. 2, 50619-43-7; **3d**, 74844-33-0; **4a**, 29388-46-3; **4b**, 71756-39-3; **4c**, 74844-34-1; **4d**, 71756-41-7; **4e**, 74844-35-2; **4f**, 74844-36-3; **5a**, 74868-63-6; **5b**, 74868-64-7; **5c**, 74868-65-8; **5d**, 74868-66-9; **6**, 74854-29-8.

(25) Selected chemical shifts (δ) and coupling constants for 2 are as follows: H_1, 4.84 (d); H_4, 4.58 (dd); H_5, 3.83 (dd); H_7, 5.86 (dd); $J_{1,2}$ = 3.4 Hz; $J_{2,3}$ = 10.3 Hz; $J_{6,7}$ = 1.2 Hz; $J_{7,8}$ = 10.0 Hz.

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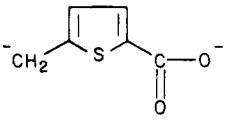
Received June 10, 1980

Dianions of Methylated Thiophene-2-carboxylic Acids: Their Formation and Reactivity

Summary: Methylated thiophene-2-carboxylic acids can be readily homologated by treatment with LDA (2 equiv) followed by the addition of carbon-containing electrophiles.

Sir: The use of the thiophene nucleus as a template for the construction of a wide variety of compounds (e.g., hydrocarbons, fatty acids, and amino acids) has been well documented.[1] The general utility of this procedure could be improved markedly if a simple method was available for the preparation of a variety of substituted thiophene derivatives. Recently, we examined the dilithiation of methylated thiophene-2-carboxylic acids and the reactivities of the resultant dianions toward several electrophiles. Our initial findings from studies using acids 1–4[2] are summarized in Table I.[3]

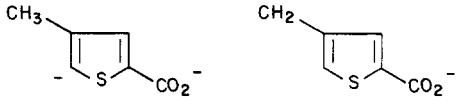
The reactions of 5-methylthiophene-2-carboxylic acid (entries 1–3) clearly support the intermediacy of dianion 6. The ease of generation of this dianion is attributable



6

to resonance stabilization. In contrast, when 2,5-dimethylthiophene was treated under more stringent conditions with *n*-BuLi–TMEDA, rather limited metalation was observed.[4] Direct homologation of acid 1 as shown here represents a route which is apparently superior to the classical Wynberg approach[5] for the synthesis of 2,5-disubstituted thiophenes.

In the case of 4-methylthiophene-2-carboxylic acid, the result recorded in entry 4 indicates that dianion 7 instead of 8 is the reactive intermediate. This result is not surprising, since in 7 the sulfur atom, owing to its polarizability,[6,7] presumably helps stabilize the adjacent negative charge, whereas in 8, significant inductive and resonance stabilization is lacking.



7 8

To our surprise, the reactions of 3-methylthiophene-2-carboxylic acid were more complex. The reaction of entry 5 gave the single ester 9,[8] whereas, that of entry 6 led to a mixture of products 11 and 12 (38:62). Azeotropic reflux of this mixture in toluene in the presence of a trace of PTSA gave a mixture of acid 13 and lactone 14. The identities of both 11 and 13 were confirmed by inde-

(1) For a comprehensive review, see Meyer, A. I. "Heterocycles in Organic Synthesis"; Wiley: New York, 1974.

(2) Acid 1 was purchased from Aldrich Chemical Co. Treatment of 3-methylthiophene in ether with *t*-BuLi at −70 °C followed by carbonation gave a mixture of 2 and 3 in a ratio of 88:12. Pure 2 was obtained after two recrystallizations from acetonitrile, mp 118–120 °C [lit. 116–117 °C (Goyte, V. N.; Tilak, D. B.; Gadekarand, K. N.; Sahasrabudhe, M. B. *Tetrahedron* **1967**, *23*, 2443)]. Acid 3 was prepared from 3-methylthiophene-2-carboxaldehyde (supplied by Aldrich) by Jones' oxidation. Compound 4, mp 169–170 °C [lit. 171–172 °C (Gatterman, L. *Justus Liebigs Ann. Chem.* **1888**, *244*, 29)] was synthesized from 3-methylthiophene by sequential treatment with *t*-BuLi and iodomethane in ether at −70 °C and then lithiation with *n*-BuLi in ether at room temperature followed by carbonation.

(3) A typical procedure, exemplified by the preparation of 5, is described in the supplementary material.

(4) Clarke, A. I.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 2373.

(5) Wynberg, H.; Logothetis, A. *J. Am. Chem. Soc.* **1956**, *78*, 1958.

(6) Streitwieser, A., Jr.; Ewig, S. P. *J. Am. Chem. Soc.* **1975**, *97*, 190.

(7) Bernardi, F.; Csizmadia, J. G.; Mangini, A.; Schlegel, H. B.; Whangbo, M.-H.; Wolfe, S. *J. Am. Chem. Soc.* **1975**, *97*, 2209.

(8) The GC analysis (1% OV-210 on Chromosorb Q, 100 °C) of the predistillation material indicated the presence of <2% of ester 10.[9]

(9) The authentic sample of this product was conveniently provided from the reaction of entry 9.

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