Acknowledgment. We thank Dr. Brian Sweetman for the exact mass measurements and the U.S. Public Health Service for generous support of this research via project grant GM-12848 and instrumentation Grant GM-27557 for purchase of the VG 70-250 mass spectrometer.

A Fully Synthetic Route to Tunicaminyluracil

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Received April 29, 1985

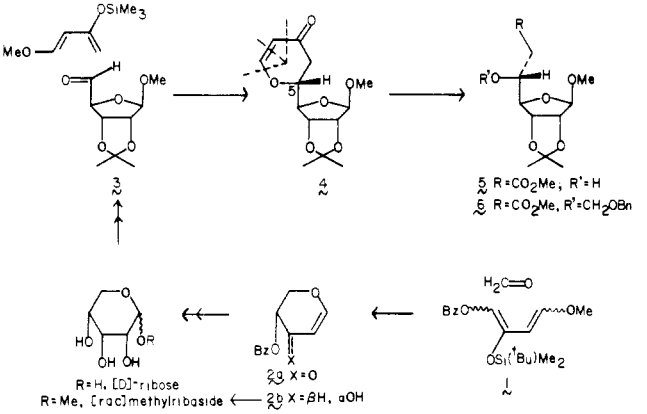
The tunicamycins form a family of closely related nucleosides of novel structure with demonstrated antibiotic and antiviral capabilities.[1] The inhibitory properties of the tunicamycins on the biosynthesis of certain polysaccharides, glycolipids, and glycoproteins render them of considerable current interest as resources for studying the finer details of the bioprocessing and utilization of complex carbohydrates.[2] The facinating though mysterious behavioral nuances manifested by seemingly closely related tunicamycin congeners (see structures **18**)[3] sharpen their value for such probing. Moreover, the reports that certain tunicamycins significantly decrease the uptake of mannose and glucosamine into the glycoproteins of L-1210 ascites leukemia cells suggest a potential anticancer role for this family, provided that host liver toxicity could be diminished.[4]

Previous synthetic work in the tunicamycin area had centered around means to couple suitably protected and matched "ribosyl" and "galactosyl" derivatives in order to arrive at the novel C_{11} (undeculose) moiety.[5a,b] Indeed, Suami[5a] has recently reported the preparation of various acylated derivatives of tunicaminyluracil (see structure **17**) through such a coupling approach. Furthermore, a closely related compound (i.e., structure **17** with NCbz instead of NAc) has been transformed by Suami[6] to several natural tunicamycins.

We have been investigating the possibility of a total synthesis wherein the relative dissymmetries in the ribosyl and galactosyl regions of tunicaminyluracil would be established *through stereochemical communication (i.e., asymmetric induction)*. Such an effort would be in contrast to that of Suami,[5a] whereby the relative relation of the two dissymmetric regions was secured through merger of naturally derived chiral subunits. Our goal has been reduced to practice in a manner that is described.

Cyclocondensation of the ribose-derived aldehyde **3**[7–9] with (*E*)-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene under catalysis by $Eu(fod)_3$[10] affords an 85% yield of the carbon-linked disaccharide **4**, mp 70–71 °C.[11] Subsequent events proved what was expected on the basis of previous precedents,[12] i.e., that the process had occurred in the sense corresponding to α-side attack of the diene on the aldehyde conformer implied in structure **3**.

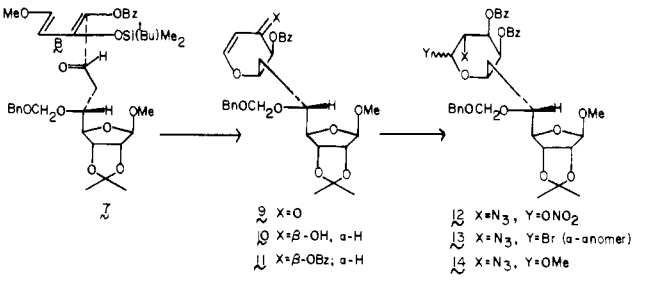
Ozonolysis of compound **4** (O_3, CH_2Cl_2, −78 °C), followed by oxidative treatment (KOH, H_2O_2) and esterification (CH_2N_2), furnished first the β-hydroxy ester **5**, mp 37–38 °C (86%) and then ($(i\text{-Pr})_2NEt$, $BnOCH_2Cl$) its BOM ether **6** in 96% yield.



The setting for the decisive stereochemical challenge was completed by conversion ((i) LAH, Et_2O, 0 °C; (ii) PCC,[13] NaOAc) of **6** to aldehyde **7**. *For success to be achieved, it would be necessary for the asymmetry of C_5 of the* D*-ribosyl unit to dictate the emergence of the new hexose in the* D*-galactosyl sense.* An attractive scenario for fashioning the hexose in a de novo manner would be by a cyclocondensation reaction via the aldehyde conformer implied in structure **7**. Such a conformer might be favored by chelation of a Lewis acid between the aldehyde and BOM ligands.[14] Attack of the diene on the face of the aldehyde opposite to that of the proximate pentose ring would provide a pyranose in the D configuration. If the attack occurred in an overall endo sense,[15] there would be fashioned a D-galactosyl precursor.

In the event, reaction of **7** with homogeneous diene **8**[16] under catalysis by $Ce(OAc)_3$–$BF_3{\cdot}OEt_2$ ($PhCH_3$, −78 °C)[17] afforded a 45% conversion to a single isomer which subsequent events amply demonstrate to be the desired **9**. In addition, ca. 20% starting aldehyde could be recovered in homogeneous form. Reduction with sodium borohydride in the presence of $CeCl_3$[18] afforded alcohol **10** which, on benzoylation, provided dibenzoate **11** in 90% yield.

Azidonitration according to Lemieux[19] afforded the anomeric nitrates **12**, which were converted (LiBr, MeCN) to a single



bromide and then by methanolysis ($AgOTf(Me_2N)_2CO$, THF)[20]

(1) Isolation and activity: Takatsuki, A.; Arima, K.; Tamura, G. *J. Antibiot.* **1971**, *24*, 215. Takatsuki, A.; Tamura, G. *Ibid.* **1971**, *24*, 224; **1971**, *24*, 232; **1971**, *24*, 785. Structure elucidation: Ito, T.; Takatsuki, A.; Kawamura, K.; Sato, K.; Tamura, G. *Agric. Biol. Chem.* **1980**, *44*, 695 and references therein.

(2) For example, see: Elbein, A. D. *Trends Biochem. Sci.* **1981**, 219. Schwarz, R. T.; Datema, R. *Ibid.* **1980**, 65.

(3) Eckardt, K. *J. Nat. Products.* **1983**, *46*, 544.

(4) Morin, M. J.; Bernacki, R. J. *Cancer Res.* **1983**, *43*, 1669.

(5) (a) Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819. (b) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.

(6) Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N.; Fukuda, Y.; Sakanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4533.

(7) Arrick, R. E.; Baker, D. C.; Horton, D. *Carbohydr. Res.* **1973**, *26*, 441.

(8) In a parallel series of experiments, J. Y. Lee of our laboratory employed the racemic dihydropyrone **2a** to reach racemic **3**. Although the racemic material has not been carried forward at this writing, in principle this could readily be done and the claim of a fully synthetic route to the tunicaminyluracil series is amply justified.

(9) Danishefsky, S.; Webb, R. R., II *J. Org. Chem.* **1984**, *49*, 1955.

(10) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(11) All isolated compounds exhibited satisfactory ^1H NMR (250 or 490 MHz), IR, and mass spectral characteristics. Satisfactory elemental analyses were obtained for compounds **4–7**.

(12) Danishefsky, S.; Maring, C. J.; Barbachyn, M. R.; Segmuller, B. *J. Org. Chem.* **1984**, *49*, 4564.

(13) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(14) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(15) The involvement of aldol-like structures is certainly not excluded.

(16) Danishfsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.

(17) This novel catalyst system was developed by Dr. Kuo-Hua Chao. With other catalysts two of the other three possible dihydropyrones were produced to varying extents. These characterized compounds were available to us. Their absence under the conditions described herein increases our confidence as to the stereospecificity of the process.

(18) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

(19) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.

(20) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13.

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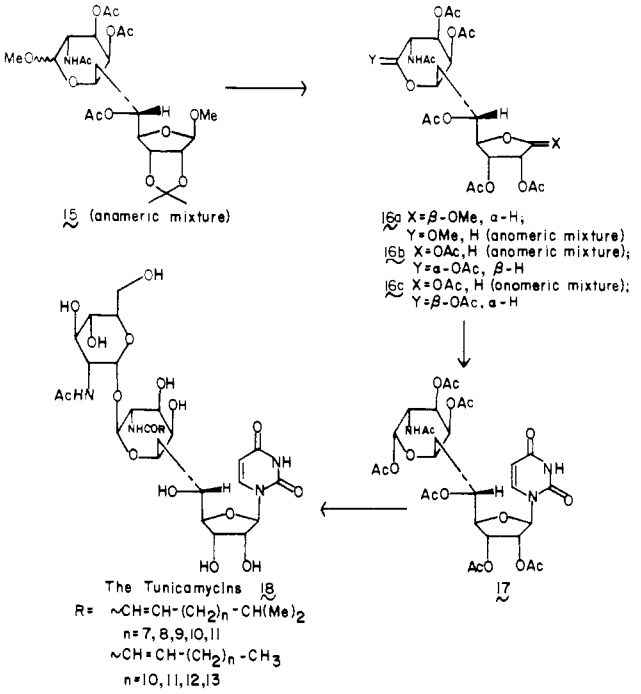
to the methyl galactoside **14** (39% overall from **11**).

A five step sequence ((i) Ph_3P, THF; (ii) Ac_2O, Py; (iii) H_2, $Pd(OH)_2/C$, MeOH; (iv) K_2CO_3, MeOH; (v) Ac_2O, Et_3N, DMAP) achieved the transformation of **14** to **15** in 77% yield. Cleavage of the acetonide was accomplished through the action of methanolic HCl. The resultant diol was acetylated to afford (76%) the tunicamine derivative **16a** as an anomeric mixture of galactosides. Acetolysis of the anomeric methoxyl functions (AcOH, Ac_2O, H_2SO_4, CH_2Cl_2) afforded (50%) a product that was ca. a 1:1 mixture of anomeric acetates in the hexose ring. Each of these components was also an anomeric mixture of ribosyl acetates with a strong preference for the desired β-ribosyl acetate. The galactosyl anomers were separated by preparative HPLC into components **16b,c**. Treatment of **16b**[21] with 2,4-bis[(trimethylsilyl)oxy]pyrimidine under the conditions of Vorbruggen (Me_3SiOTf, MeCN, room temperature)[22] afforded a 50% isolated yield of (heptaacetyltunicaminyl)uracil **17**. *The chromatographic*



properties and infrared and high-field PMR spectra of the synthetic ***17*** *were identical with those of the compound prepared from tunicamycin.*[23,24] We emphasize that in this fully synthetic route[8] to tunicaminyluracil, all nonanomeric stereochemistry is tightly controlled by taking advantage of biases within the reacting substrate molecules.

Acknowledgment. This research was supported by PHS Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. An NIH Postdoctoral Fellowship (Grant 1 F32 CA07586) to M.B. is gratefully acknowledged. In addition, we wish to acknowledge the contributions of Dr. Kuo-Hua Chao for development of the catalyst system and Ms. J. Y. Lee for providing a route to racemic **3**, thereby establishing the fully synthetic route. We also acknowledge the receipt of an authentic sample of a tunicamycin from the Eli Lilly Co. from which a reference sample of **17** was prepared.

Supplementary Material Available: High-field NMR spectra of synthetically and naturally derived compound **17** (2 pages). Ordering information is given on any current masthead page.

(21) The analogous Hilbert-Johnson reaction of **16c** afforded an adduct assigned as a pyranose nucleoside (incorporation of uracil in the galactosyl hexose).

(22) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(23) An authentic sample of (heptaacetyltunicaminyl)uracil was prepared from tunicamycin by the following sequence: (i) hydrolysis (3 N HCl, reflux, 3 h), (ii) ether wash, (iii) concentration in vacuo, (iv) acetylation (Ac_2O, Py), (v) preparative HPLC.

(24) Optical rotations for representative structures are as follows: **4**, $[\alpha]^{25}_D$ -83.7° (*c* 1.91, $CHCl_3$); **5**, $[\alpha]^{25}_D$ -49.5° (*c* 1.10, $CHCl_3$); **6**, $[\alpha]^{25}_D$ -38.8° (*c* 1.33, $CHCl_3$); **7**, $[\alpha]^{25}_D$ -37.5° (*c* 1.27, $CHCl_3$); **9**, $[\alpha]^{25}_D$ -39.5° (*c* 1.07, $CHCl_3$); **11**, $[\alpha]^{25}_D$ -70.1° (*c* 1.01, $CHCl_3$) fully synthetic compound **17**, $[\alpha]^{25}_D$ +61.8 (*c* 0.21, $CHCl_3$); naturally derived compound **17**, $[\alpha]^{25}_D$ +60.8 (*c* 0.49, $CHCl_3$).

A Fully Synthetic Route to Hikosamine

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Received July 12, 1985

Hikizimycin (**1**, cf. anthelmycin) was isolated from a strain of *Streptomyces longissimus* and from the broth of Streptomyces A5.[1a,b] It has broad but weak antibacterial properties. More important are the anthelmintic properties which hikizimycin confers against a variety of common parasites.[2] A provocative feature of hikizimycin is the presence of an undecose with heterofunctions at every carbon atom. This component, called hikosamine, has been obtained in protected form by mild degradation of hikizimycin.[3]

Long chain (> six carbons) monosaccharide moieties are found in a variety of natural products of diverse function.[4] Accordingly, we have sought to develop new chemistry for the synthesis of such complex systems. An important contribution in the hikizimycin area had been provided by Secrist and Barnes.[5a,b] These workers coupled a hexodialdose related to 4-deoxy-4-azidoglucose with a phosphorane derived from L-arabinose. The ability to achieve an olefination reaction via a β-heterosubstituted phosphorane was a major feature of the Secrist-Barnes synthesis of methyl peracetyl-α-hikosaminide (**18**). Below we relate a totally synthetic route to compound **18**.

A key feature of the synthesis is the use of the recently developed diene-aldehyde cyclocondensation reaction[6a,b] to fashion "carbohydrate matrices" in either the *galacto* or *manno* series (cf. formation of **3a** and **10**). The interior stereochemistry in these matrices is developed by drawing upon the conformational biases of the rings (cf. **3a** → **4d** and **10** → **12**).[6] Chirality is communicated from the *galacto* ring to its side chain through a recently demonstrated adaptation of the Sakurai reaction (cf. **4d** → **5**) and further communicated via the side chain to define the sense (D rather than L) of the emerging *manno* precursor **10**. Provision is made for specific disconnection of the manno ring (cf. **12** → **13**) and for introduction of the 4-amino function in the surviving pyranose (cf. **14** → **17**).

Hexodialdose **4d**, derivable[7,8] from galactose, was synthesized starting with the Eu(fod)$_3$-mediated[6b] cyclocondensation of furfural

(1) (a) Hamill, R. L.; Hoehn, M. H. *J. Antibiot. Ser. A* **1964**, *17*, 100. (b) Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289.

(2) Uchida, K.; Wolf H. *J. Antibiot.* **1974**, *27*, 783. Gonzalez, A.; Vazquez, G. D.; Jimenez, A. *Biochem. Biophys. Acta* **1979**, *561*, 403.

(3) Uchida, K. *Agric. Biol. Chem.* **1976**, *40*, 395.

(4) For examples of such long chain monosaccharides, see: Danishefsky, S. J.; Maring, C. J.; Barbachyn, M. R.; Segmuller, B. E. *J. Org. Chem.* **1984**, *49*, 4564, ref 2-6.

(5) (a) Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526. (b) Barnes, K. D. Ph.D. Thesis, The Ohio State University, 1980.

(6) (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. (b) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(7) Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, *7*, 56.

(8) In practice, the D isomer **4c** obtained from D-galactose[7] was used in further steps. The synthesis of racemic **4c** demonstrates in principle the feasibility of synthesizing racemic hikosamine since all subsequent steps involve internal asymmetric induction.

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