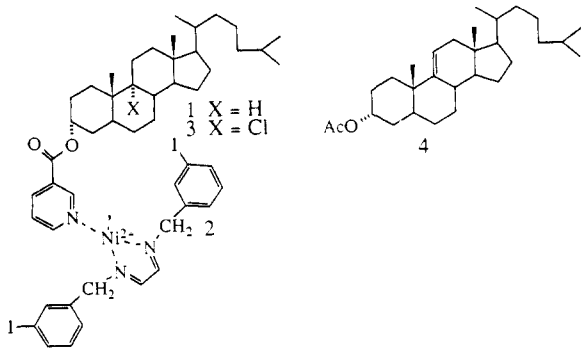

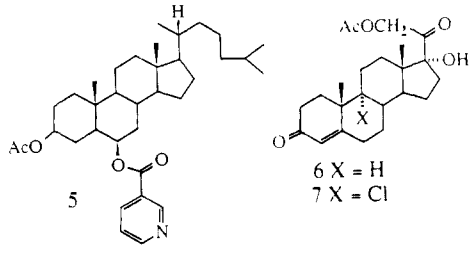

(30 mL) of substrate (**1**), of diimine **2** (trivially prepared from glyoxal and (*m*-iodobenzyl)amine), and of $Ni(ClO_4)_2$ in CH_2Cl_2/CH_3CN (14:1) with 3 equiv of $PhICl_2$ and 5 equiv of undissolved KOAc were degassed and irradiated (275 w sunlamp) at 0 °C for 10 min. After solvent removal and saponification/dehydrochlorination with KOH/MeOH the product was acetylated and analyzed[2] by NMR.

With 17 mM substrate (all experiments), the use of 17 mM Ni^{2+} and 17×10^{-3} mM **2** gave complete conversion of **1** to the product **3**, which was converted to the 9(11) olefin **4** identical with authentic material[2] and isolated in at least 95% yield. No unfunctionalized steroid was detected. When both Ni^{2+} and **2** were at 8.5×10^{-7} mM, there was again complete 9-chlorination, but with 17×10^{-7} mM **2** and 17 mM Ni^{2+} there was only 80% product and 20% unfunctionalized **1** (nonproductive complexing of Ni^{2+} to **1**). With Ni^{2+} at 17×10^{-7} mM and **2** at 17×10^{-9} mM we obtained 97% conversion to **3** and 3% **1**. Thus each template molecule **2** is performing *one billion* catalytic chlorination reactions.[6] This means that 1 g of catalyst can direct the formation of 1000 tons of steroid product.

In control reactions, with all substances at 17 mM, no functionalization occurred if Ni^{2+} or **2** were omitted. No reaction occurred with the changed complex geometry when **1** was instead the isonicotinate ester, when **2** was the diimine derived from *p*-iodoaniline, or when Zn^{2+} (tetrahedral) was substituted for Ni^{2+} (square planar). However, Cu^{2+} (square planar) could substitute for Ni^{2+} with almost equivalent results (90% functionalization in the billion-fold experiment). An HCl scavenger was needed, but KOAc could be replaced by 1,2-epoxybutane or by aqueous $NaHCO_3$.

The catalyst is eventually destroyed, apparently by the aromatic chlorination process we have seen before.[7] The very high turnover with **1** and **2** thus must reflect a particularly fast substrate chlorination in competition with this catalyst destruction. We find that the 6-β nicotinate ester **5** undergoes 20-chlorination with Ni^{2+} and **2**, and cortexolone acetate (**6**) undergoes 9-chlorination with Ni^{2+} and **2** to form **7**, apparently by coordinating its 17-OH group. However, neither of these cases shows the very high turnover of **1**. The finding that substrate **1** is not functionalized without the template, but that 1.7×10^{-11} M template allows essentially complete selective chlorination, shows how remarkably effective the radical relay mechanism is. Of course, the potential for such enormous catalytic turnovers justifies the construction of much more elaborate templates than **2**, in which additional binding interactions are used to achieve the optimal complex geometry for all substrates of interest.

Acknowledgment. This work was supported by the NSF.

(6) Because this result is so astonishing, it has been independently confirmed by two members of our laboratory. We wish to thank Radhika Batra and Dr. Uday Maitra for their help.

(7) Cf. footnote 5 of ref 2. By mass spectroscopy, the iodine is replaced by chlorine when the catalyst decomposes.

Total Synthesis of Octosyl Acid A: A New Departure in Organostannylene Chemistry

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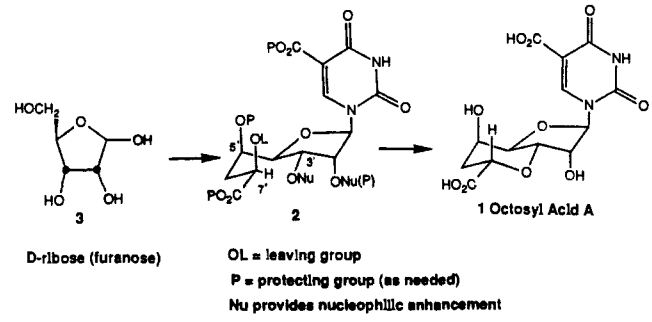
The octosyl acids were isolated from *Streptomyces cacaoi* var asensis by Isono et al.[1a,b] They are structurally related to the antifungal ezomycins.[2] While no clinically useful properties have been reported for octosyl acid A (**1**), its trans-glycosylation product, wherein the 5-carboxyuracil is replaced by an adenine base, is a powerful inhibitor of cyclic-AMP phosphodiesterases from various animal tissues.[3a,b] Indeed, the octosyl acids have been viewed as carboanalogues of 3′,5′-cyclic nucleotides.[4] This paper describes a total synthesis of octosyl acid A.[5]

The key question centered around the feasibility of establishing the provocative trans-fused furanopyran system by a Williamson-type closure of intermediate **2**. The cyclization would cojoin



a nucleophilic oxygen (cf. ONu) at $C_{3'}$ with a glycolate type carbon ($C_{7'}$ of the octose) bearing a leaving group signified as OL. Intermediate **2** was to be derived from a pentose in a fashion wherein the chirality of the furanose ring would dictate the emerging stereogenic centers on the side chain such as to give rise to an axial oxygen function at carbon 5′ and (anticipating inversion of configuration) an equatorial carboxyl group at carbon 7′. To simplify the chemical manipulations and to simplify an analogue synthesis program, a relatively late formation of the nucleoside bond was deemed to be desirable. The requirement for nucleophilic activation of the specific hydroxyl center at $C_{3'}$ in the presence of potentially conflicting functional group added to the challenge of the problem.

(1) Isono, K.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 943.

(2) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1973**, *37*, 697. Sakata, K.; Sakurai, A.; Tamura, S. *Ibid.* **1974**, *38*, 1983. Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett.* **1974**, *15*, 4327. Sakata, K.; Sakurai, A.; Tamura, S. *Ibid.* **1975**, *16*, 3191.

(3) (a) Azuma, T.; Isono, K. *Chem. Pharm. Bull.* **1977**, *25*, 3347. (b) Bloch, A. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 210.

(4) Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979; p 295.

(5) For previous synthetic works of relevance to the octosyl acid problem, see: Anzai, K.; Saita, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 169. Kim, K. S.; Szarek, W. A. *Can. J. Chem.* **1981**, *59*, 878. Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129.

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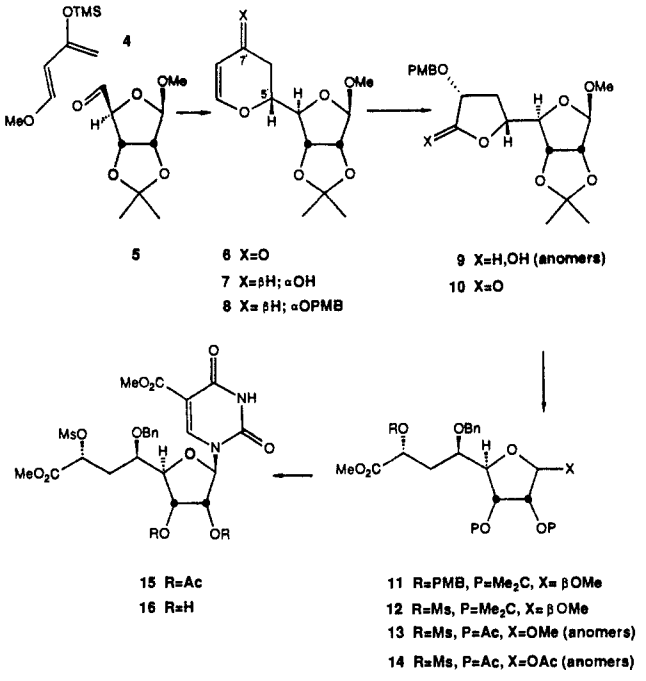
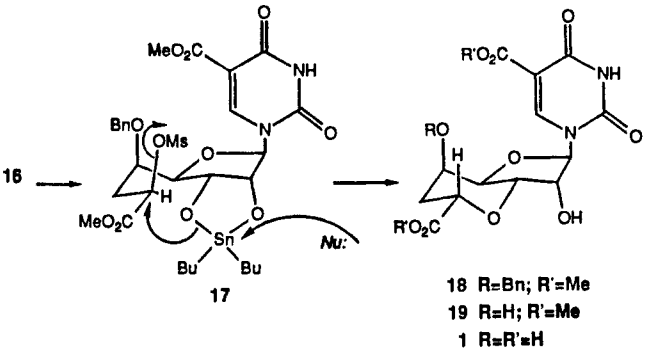
The nonose **6** was obtained by a cycloaddition reaction of **4** with aldehyde **5** (85%).[6] The configuration at carbon 5′ served to control the stereochemistry at $C_{7'}$. Thus, reduction of **6** with $NaBH_4$–$CeCl_3$ in methanol[7] afforded alcohol **7**,[8,9] which was converted (NaH; *p*-methoxybenzyl chloride; 90% yield for the two steps) to its *p*-methoxybenzyl (PMB) derivative. Compound **8**, was subjected to degradation with osmium tetroxide (catalytic) and sodium metaperiodate.[10] Upon cleavage of the resulting formate (K_2CO_3–methanol room temperature), the lactol anomers **9**[8] emerged (93% yield). Oxidation (Ag_2CO_3–Celite–xylene, reflux) of **9** afforded an 86% yield of lactone **10**.[8]

A three-step sequence [(i) $LiOH{\cdot}H_2O$/THF, (ii) NaH, BnBr/DMF, and (iii) diazomethane/ether] served to produce **11**[8] (53%). Deprotection of the $C_{7'}$ alcohol (DDQ)[11] followed by



mesylation (MsCl, TEA/CH_2Cl_2) afforded a 52% overall yield of **12**.[8] As seen below, the α-mesyl ester exhibited remarkable durability to a range of experimental conditions. Cleavage of the isopropylidene group of **12** (HCl/MeOH) followed by acetylation provided **13** (78%).[8,12a] This, upon reaction with Ac_2O, AcOH, CH_2Cl_2, and H_2SO_4,[13] afforded the anomeric acetates **14** (75%).[8,12b] The base was installed by a Vorbrüggen-type reaction of **14** with 2,4-bis[(trimethylsilyl)oxy]-5-carbomethoxypyrimidine in the presence of TMSOTf (91%).[14] Deacylation of the acetates (NaOMe–MeOH) provided **16** (81%), setting the stage for the decisive challenge, i.e., the intramolecular Williamson reaction.

A variety of attempts to achieve the closure of **16** by using conventional metal alkoxide combinations resulted in either recovery of starting material or in extensive decomposition. *It was reasoned that a cyclic stannylene derivative engaging the two hydroxyl groups of* **16** *might be advantageous for the purpose at hand in that it would activate the* $C_{3'}$ *hydroxyl group under essentially neutral conditions, while the* $C_{2'}$ *hydroxyl is, in effect, protected.* In the event, compound **16** reacted with Bu_2SnO in methanol. Treatment of the presumed but uncharacterized **17** with CsF in DMF at 60 °C afforded a 77% yield of **18**.[8] Cleavage of the benzyl group ($Pd(OH)_2$)[15] afforded compound **19**, the dimethyl ester of octosyl acid A.[8] The NMR, infrared, and chromatographic mobility of compound **19** derived by total synthesis were identical with those obtained from a sample prepared by esterification (MeOH/HCl) of authentic octosyl acid A[16] supplied by Professor Isono. Finally, hydrolysis of **19** ($LiOH{\cdot}H_2O/H_2O$/THF) followed by acidification, afforded octosyl acid A (**1**), darkening at approximately 260 °C, $[\alpha]^{23}_D$ +9.1° (*c* 0.8, *N* NaOH) [lit. mp 290–295 °C dec, $[\alpha]^{20}_D$ +13.3° (c 0.425, *N* NaOH],[17] whose NMR spectrum (250 MHz) is identical with that of an authentic sample. The total synthesis of **1** is thus accomplished.



The concept of using organostannylene derivatives, ordinarily employed for purposes of protection,[16] to achieve synthetically useful cyclization reactions has many implications which await assessment at the experimental level.

Acknowledgment. This research was supported by PHS Grant HL25848. 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. Postdoctoral Fellowships from NIH (Grant 1F32 CA07583-01A1) and ACS (Grant PF-2514) to R.H. are gratefully acknowledged. in addition, we thank Professor K. Isono of the Institute of Physical and Chemical Research in Saitama, Japan, for providing us with an authentic sample of octosyl acid A and J. Y. Lee of Yale University for carrying out the synthesis of racemic **5** (from formaldehyde and 4), thereby achieving a formal total synthesis of **1**.

Supplementary Material Available: Characterization data for compounds **8**, **10**, **11**, **15**, and **19** as well as comparison NMR spectra of natural and synthetic dimethyl ester **19** (3 pages). Ordering information is given on any current masthead page.

(6) Jones, G. H.; Moffatt, J. G. *Methods Carbohydr. Chem.* **1979**, *7*, 315. This material has also been prepared in racemic form from diene **4** and formaldehyde, unpublished results from J. Y. Lee, Yale University.

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

(8) All new compounds exhibited satisfactory MS, IR, and NMR spectra; representative spectral values are included as supplementary material.

(9) NMR analysis of the crude reduction product suggested a 9:1 ratio of α- and β-alcohols. The pure α-isomer could be obtained via careful chromatography (Flash or MPLC) of **8** or more conveniently, on large scale, at the lactone (**10**) stage.

(10) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(12) (a) The exact ratio of anomers varied from 3:1 to 7:1 (β/α), depending on the precise reaction conditions employed. Generally, ratios of 3:1 were encountered and the mixture was used in subsequent operations without separation. (b) It was possible to separate this mixture (4:1), although this was not necessary since both anomers react to give a single compound in the Vorbrüggen-type reaction.

(13) An earlier example for the conversion of methyl ribosides to their 1-O-acetyl derivatives can be found in the work of: Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, *42*, 1171.

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

(15) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *10*, 1663. In this system debenzylation is also accompanied by hydrolysis of the heterocyclic ring. This can be minimized by employing a large percentage of catalyst (300% by weight) and keeping reaction times short (5–10 min).

(16) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643 and references therein. See, particularly: Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24.

(17) Although we have no explanation for the discrepancies in these values, the degree of hydration in the final product may be responsible for the irregularities. It should be noted that the value for $[\alpha]_D$ reported herein agrees very closely with that obtained by Professor Hanessian on his fully synthetic material (private communication).