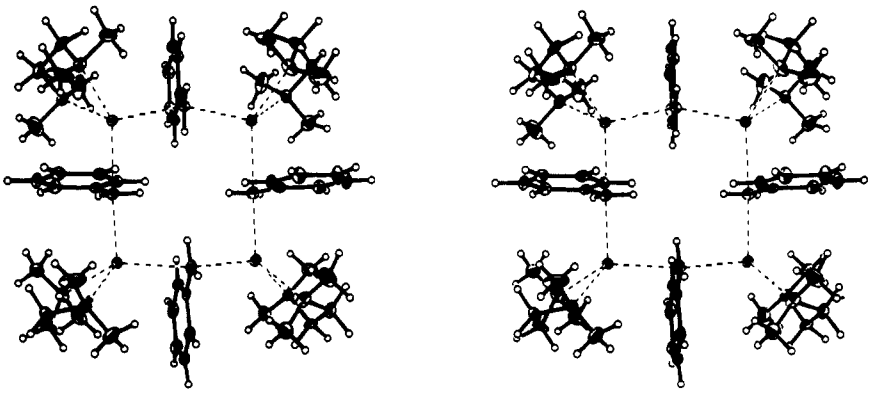

Figure 1. Stereoview of the $[C_6H_5CH_2Na\cdot TMEDA]_4$ crystal structure (30% probability elipsoids). The four sodium atoms form a nearly perfect square ($\angle NaNaNa(av) = 90.0\ (6)°$ and Na···Na lengths 5.05 (6) Å). The average benzyl CC bond lengths: C(2)–Cl(IPSO), 1.404 (8); C(ipso)–C(ortho), 1.431 (5); C(ortho)–C(meta) 1.375 (7); C(meta)–C(para), 1.381 (6) Å. The benzyl groups are planar (rmsd's average 0.0041 Å for the ring atoms). The disorder in the TMEDA ligands is not shown; alternative positions with populations less than 50% have been omitted. Other details are given in the text.

pseudomonomeric benzyllithium–bis(quinuclidine), lithium prefers an asymmetric $^3\eta$-allylic site,[8] but the distances to the α-carbon and ipso-carbon are shorter than to the ortho position. Like $(benzylsodium–TMEDA)_4$, $(benzyllithium–Et_2O)_n$ also shows trigonal-bipyramidal coordination of α-methylene groups but is a linear polymer.[7c] Model MNDO calculations on $C_6H_5CH_2Li_2^+$ confirm the preference for an essentially linear LiCLi configuration at the α-carbon.[9] Ring formation of $C_6H_5CH_2Li$ may be sterically prohibited because of greater crowding due to the shorter C–Li than C–Na distances. A magnesium-lithium complex, $[Li(TMEDA)_2][Li(TMEDA)Mg(CH_2C_6H_5)_4]$, exhibits magnesate–Li(TMEDA) ion pairing involving benzylic α-carbons, but with front-side coordination to carbon.[10]

Tetrahedral arrangements generally are favored over planar ring structures for tetrameric alkali-metal compounds.[1,2,11] However, lithium amides prefer cyclic structures due to the lone pair orientations.[11,12] Similar carbanion orbital–ion triplet interactions[11] (as depicted in **1**) are responsible for the nontetrahedral benzylsodium–TMEDA and polymeric benzyllithium–Et_2O structures. Other examples of stable eight-membered ring structures are found in some coinage metal as well as lithium–coinage metal complexes.[13]

Prochiral α-CH_2 groups in aggregated alkyllithium compounds are known to stereomutate intramolecularly.[14] We have suggested that this may occur by unfolding of the tetrahedral tetramer into an eight-membered ring, followed by planarization of a RCH_2 moiety (as in **2**).[15] Calculations are consistent with this proposed mechanism.[15b] The $(benzylsodium–TMEDA)_4$ ring structure now provides a nice experimental analogy.

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Supplementary Material Available: Tables of atomic positions and isotropic and anisotropic thermal parameters for $(C_6H_3CH_2Na–TMEDA)_4$ (3 pages). Ordering information is given on any current masthead page.

(9) Kos, A., unpublished calculations.
(10) Schubert, B.; Weiss, E. *Chem. Ber.* **1984**, *117*, 366.
(11) Sapse, A. M.; Raghavachari, K.; Kaufmann, E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1985**, *107*, 6483–6486.
(12) Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. *J. Am. Chem. Soc.* **1983**, *105*, 302–304.
(13) Jarvis, J. A. J.; Kilbourn, B. T.; Pearce, R.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1973**, 475. Van Koten, G.; Jastrzebski, J. T. B. H.; Muller, F.; Stam, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 697–698 and referenced cited. Gambarotta, S.; Floriani, C.; Chiesa-Villa, A.; Guastini, C. *J. Chem. Soc. Chem. Commun.* **1983**, 1087–1089, 1156–1158, and references cited. Stewart, K. R.; Jever, J. R.; Whangbo, M.-H. *J. Org. Chem.* **1982**, *47*, 1472–1474. Bandy, J. A.; Berry, J. A.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1462.
(14) (a) Witanowski, M.; Roberts, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 736–741. (b) Fraenkel, G.; Beckenbaugh, W. E.; Yang, P. P. *Ibid.* **1976**, *98*, 6878. (c) Fraenkel, G.; Hsu, H.; Su, B. M. In *Lithium: Current Application in Science, Medicine, and Technology*; Bach, R. O., Ed., Wiley: New York, 1985; Chapter 19, p 273 ff.
(15) (a) Clark, T.; Schleyer, P. v. R.; Pople, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 137–138. (b) Raghavachari, K.; Kaufmann, E.; Schleyer, P. v. R., unpublished results. See: Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151–162.

Catalytic Directed Steroid Chlorination with Billionfold Turnovers

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We have developed methods to direct chlorination to various tertiary positions on steroids by the use of attached templates.[1] With iodophenyl groups,[2] diphenyl sulfide groups,[3] or thiophene rings[4] an incoming chlorinating species puts the chlorine on the heteroatom of the template, and this is then relayed to a geometrically accessible hydrogen. Since the template is recovered unchanged it is formally catalytic but used in stoichiometric amounts. A move toward true turnover catalysis was seen with templates attached to (and halogenating) three steroids,[4] thus showing three turnovers. We now wish to describe true turnover catalysis, in which a template species moves from substrate to substrate. In the best cases, one template catalyst functionalizes 10^9 substrate molecules.

We had examined the use of ion-pairing forces in nonpolar media to cause oppositely charged templates and substrates to associate. Poor selectivities and low conversions were seen.[5] Thus we went to metal coordination as a force that would promote well-defined but temporary binding of catalyst to substrate. The nicotinate ester of 3-α-cholestanol (**1**) was used as a substrate, while the catalyst was a metal complex of diimine **2**. Solutions

(1) Breslow, R.; Corcoran, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791.
(2) Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.
(3) Breslow, R.; Wife, R. L.; Prezant, D. *Tetrahedron Lett.* **1976**, 1925.
(4) Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045.
(5) Breslow, R.; Heyer, D. *Tetrahedron Lett.* **1983**, *24*, 5039–5042.

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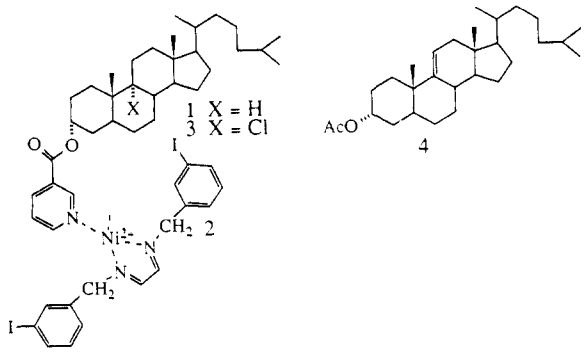

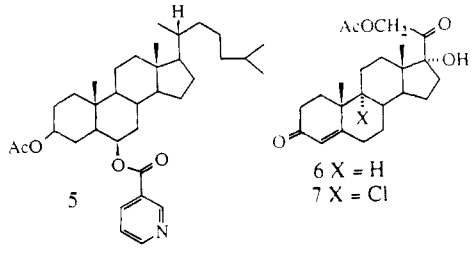

(30 mL) of substrate (**1**), of diimine **2** (trivially prepared from glyoxal and (*m*-iodobenzyl)amine), and of $Ni(ClO_4)_2$ in CH_2Cl_2/CH_3CN (14:1) with 3 equiv of $PhICl_2$ and 5 equiv of undissolved KOAc were degassed and irradiated (275 w sunlamp) at 0 °C for 10 min. After solvent removal and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

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(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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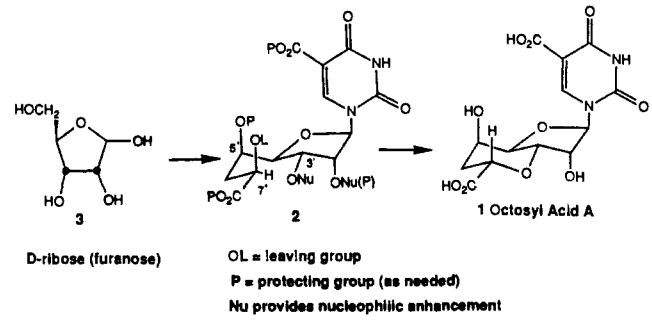
The octosyl acids were isolated from *Streptomyces cacaoi* var asensis by Isono et al.[1a,b] They are structurally related to the antifungal ezomycins.[2] While no clinically useful properties have been reported for octosyl acid A (**1**), its trans-glycosylation product, wherein the 5-carboxyuracil 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.

0002-7863/86/1508-2486$01.50/0