determine whether the tetrapeptide potentiation of the properties of cycloisodityrosine is conformationally or structurally based is in progress and will be reported in due course.

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Registry No. 9, 138571-36-5; 10, 138571-37-6; 11, 138605-22-8; 12, 132513-32-7; 13, 37466-41-4; 14, 138571-38-7; 15, 138571-39-8; 16, 138605-23-9; 17, 138571-40-1; 18, 138571-41-2; Cbz-Tyr(3-Ac)-OMe, 79677-60-4; Boc-NMe-Phe(I), 138571-42-3; Boc-D-Ala-Ala-NMe-Tyr(Me)-Ala, 112196-84-6.

Supplementary Material Available: Full physical and spectroscopic characterization of 14, 16, 9, and 10 and tables comparing the spectroscopic properties (^1H and ^{13}C) of 1 and 9 (6 pages). Ordering information is given on any current masthead page.

A New Iterative Route to Optically Active Polyols Using α-Alkoxy Silanes as Key Intermediates

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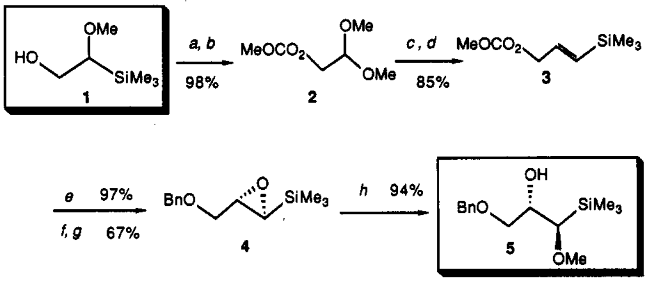
Summary: A new iterative and modular strategy which is applicable to the synthesis of any enantiomers and diastereomers of straight chain 1,*n*-polyols has been developed utilizing electrochemical oxidation of α-alkoxy silanes.

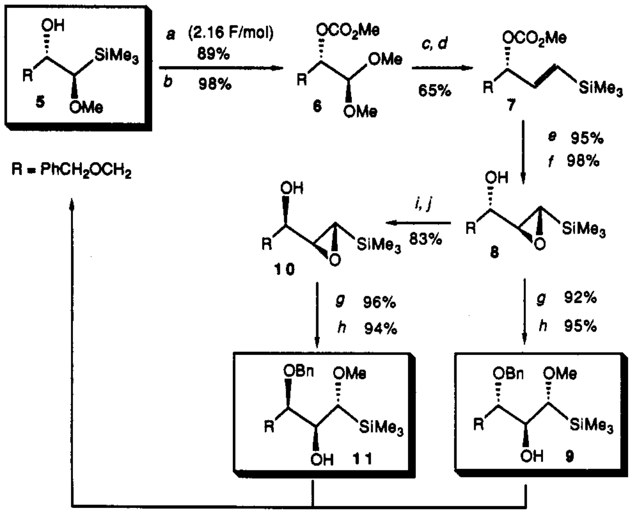
Strategies which allow synthesis of a variety of target molecules by repetition of simple procedures are needed for the development of robot synthesis.[1] As part of a program aimed at new methods for such strategies, we have developed a new iterative route[2] to optically active polyols which is applicable to the synthesis of many biologically interesting polyhydroxylated natural products.[3] Our approach is designed around a new carbonyl synthon[4] which is based upon silicon β effects in electron-transfer reactions.[5] The reaction sequences consist of several simple modules and can be applied to the synthesis of all enantiomers and diastereomers of straight-chain 1,*n*-polyols and amino polyols.[6]

Scheme I[a]



[a] Key: (a) anodic oxidation $Et_4NOTs/MeOH$; (b) $ClCO_2Me$, pyridine; (c) H^+; (d) $Br_2CHSiMe_3$, $CrCl_2$; (e) $LiAlH_4$; (f) L-(+)-DIPT, $Ti(OPr^i)_4$, TBHP; (g) NaH, $PhCH_2Br$; (h) $BF_3·OEt_2/MeOH$.

Scheme II[a]



[a] Key: (a) anodic oxidation $Et_4NOTs/MeOH$; (b) $ClCO_2Me$, pyridine; (c) H^+; (d) $Br_2CHSiMe_3$, $CrCl_2$; (e) $LiAlH_4$; (f) L-(+)-DIPT, $Ti(OPr^i)_4$, TBHP; (g) NaH, $PhCH_2Br$; (h) $BF_3·OEt_2/MeOH$; (i) Ph_3P, diethyl azodicarboxylate, $PhCO_2H$; (j) NaOH/MeOH.

As key intermediates for the iterative route to polyols, α-hydroxy aldehydes or their protected forms seemed attractive because the formyl group can be readily utilized for carbon extension reactions. Recently, we have found

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(1) For example: (a) Frisbee, A. R.; Nantz, M. H.; Kramer, G. W.; Fuchs, P. L. *J. Am. Chem. Soc.* **1984**, *106*, 7143–7145. (b) Takuma, Y.; Imaki, N. *J. Syn. Org. Chem. Jpn.* **1990**, *48*, 587–592.

(2) Iterative strategy. For example: (a) Watt, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 271–273. (b) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565. (c) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666. See also refs 3a,h,k,q.

(3) 1,2-Polyols. For example: (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949–951. (b) Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515–3516. (c) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373–1378. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–76. (e) Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712–3714. (f) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116–5121. (g) Solladie, G.; Hutt, J.; Frechou, C. *Tetrahedron Lett.* **1987**, *28*, 61–64. (h) Donddoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. 1,3-Polyols. For example: (i) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378–1380. (j) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292–1293. (k) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (l) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984. (m) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525–6532. (n) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383–4386. (o) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090–6093. (p) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21–22. (q) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147–1149. (r) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495–4499.

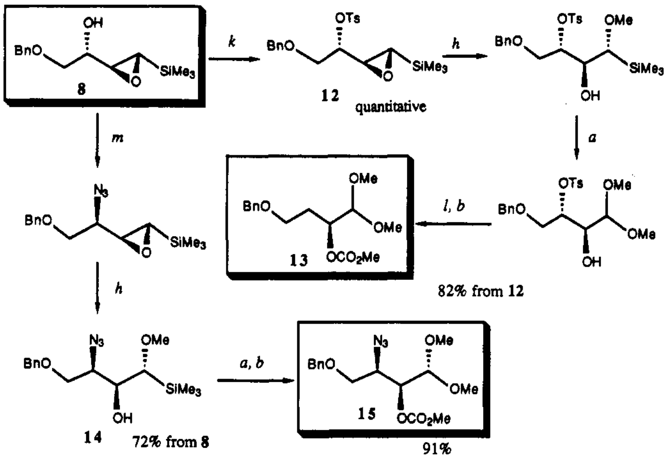
(4) (a) Yoshida, J.; Murata, T.; Isoe, S. *J. Organomet. Chem.* **1988**, *345*, C23–C27. (b) Yoshida, J.; Matsunaga, S.; Isoe, S. *Tetrahedron Lett.*, **1989**, *30*, 219–222. (c) Yoshida, J.; Matsunaga, S.; Murata, T.; Isoe, S. *Tetrahedron* **1991**, *47*, 615–624.

(5) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962–1970.

(6) For example: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217–1225.

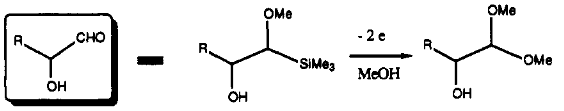
0022-3263/92/1957-1321$03.00/0

Scheme III[a]



[a] Key: (a) anodic oxidation Et_4NOTs/MeOH; (b) $ClCO_2Me$, pyridine; (h) BF_3·OEt_2; (k) LDA/TsCl; (l) NaI, Bu_3SnH/AIBN; (m) $(PhO)_2P(O)N_3$, Ph_3P, DEAD.

that α-alkoxy silanes are efficient precursors of aldehydes by electrochemical oxidation.[3] The silyl group promotes electron transfer from the oxygen atom at the β position, and thus the electrochemical oxidation of α-alkoxy silanes takes place at reasonably low oxidation potentials ($E_{1/2}$ = 1.4–1.6 V vs Ag/AgCl) effecting selective cleavage of the carbon–silicon bond and the introduction of a methoxy group onto the carbon. The resulting acetal is readily hydrolyzed to the corresponding aldehyde. The compatibility of the α-alkoxy silanes with various reagents and conditions is also advantageous. Thus, we chose β-hydroxy-α-alkoxy silanes as key intermediates.



The first cycle of the iterative scheme for polyol synthesis begins with a single fundamental building block, 2-methoxy-2-(trimethylsilyl)ethanol (1) (Scheme I). Electrochemical oxidation in methanol followed by protection of the hydroxyl group afforded the dimethyl acetal **2**. Acidic hydrolysis followed by $CrCl_2$-promoted olefination with $Br_2CHSiMe_3$[7,8] provided vinylsilane **3**. The sequence consisting of deprotection of the hydroxyl group, Sharpless epoxidation using L-(+)-DIPT,[9-11] hydroxyl reprotection, and Lewis acid-catalyzed ring opening in methanol[12] gave optically pure homologated β-hydroxy-α-methoxy silane **5**[13] (8 steps, 51% from **1**).

A double application of this basic cycle provided the 2,3-*anti*-3,4-bis(benzyloxy)-1-methoxy-1-(trimethylsilyl)butan-2-ol (**9**) (8 steps, 46% from **5**) which is a protected form of 2,3,4-trihydroxybutyraldehyde (Scheme II). Compound **9** is extendable to higher homologues by simple repetition of the cycle. The corresponding syn form **11** (10 steps, 40% from **5**) can also be readily synthesized by the inversion of the stereochemistry at C3 at the stage of epoxy alcohol **8** by the Mitsunobu reaction.[15] Thus, the present method provides access to both *anti*- and *syn*-1,2-polyols of any chain length in optically pure form.

The conversion of the hydroxyl group of the epoxy alcohol **8** to the tosylate followed by ring opening, anodic oxidation, and tin hydride reduction under radical conditions[16] provided 3-deoxy acetal **13** (5 steps, 82% from **8**) (Scheme III) opening a new route to 1,3-polyols. A double application of the reductive scheme can afford 1,4-polyols. The combination of Schemes I and II provides access to any type of 1,*n*-polyols and their linear combinations. Thus, our strategy has proved to be generally applicable and efficient in the stereoselective construction of acyclic polyhydroxylated carbon frameworks in optically pure form.

It should be noted that the hydroxyl group of **8** can be replaced by azide using the Mitsunobu reaction to give azide acetal **15** (4 steps, 66% from **8**) (Scheme III).[17] Since the azide group is readily converted into an amino group, this approach also provides an efficient route to optically pure amino polyols.[6]

The present strategy for the synthesis of polyols combines a limited number of simple, reliable, and potentially automatable procedures. The modular nature of this scheme also seems to be suitable for robot synthesis because various types of compounds can be synthesized by simply changing or adding appropriate modules in the synthetic scheme. Possibilities of other iterative schemes for the synthesis of polyoxygenated compounds are currently being evaluated.

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Supplementary Material Available: Experimental details including preparations and analysis data (32 pages). Ordering information is given on any current masthead page.

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(13) Alcohol **5** was converted to 2,3-bis(benzyloxy)propanal which was found to be essentially optically pure $[\alpha]_{546}$ = −58° (*c* = 2.00, benzene). Reference 14 $[\alpha]_{546}$ = +58° (*c* = 2.00, benzene).

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(17) Lai, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.