Stereoselective Synthesis of Long-Chain Polyols by Sequential Homologation of Enals with Nonracemic γ-Silyloxy Allylic Stannanes and Directed Hydroxylation

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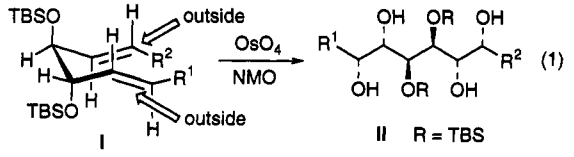
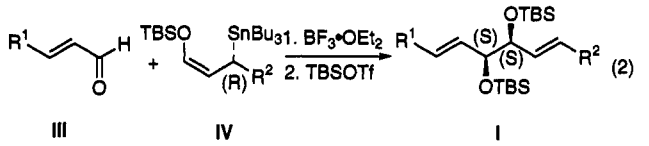
Summary: The nonracemic γ-silyloxy allylic stannanes (*S*)-8 and (*R*)-8 add to the (*R,R*)-tartrate derived enals 7 and 24 to afford the adducts 9, 14, and 25. The bis-TBS derivatives 10, 15 and 22, upon hydroxylation with catalytic OsO_4–NMO, yield the differentially protected polyols 11, 16, and 23.

An increasing awareness of the important biological role of carbohydrates has stimulated interest in the synthesis of natural and unnatural sugars. The so called "higher sugars" constitute an interesting family of monosaccharides. These relatively uncommon 7–11 carbon carbohydrates are subunits of several important antibiotics.[1] To date, most syntheses of higher sugars have employed natural hexose and pentose starting materials.[2,3] We have developed a new approach starting from readily available tartrate derivatives.

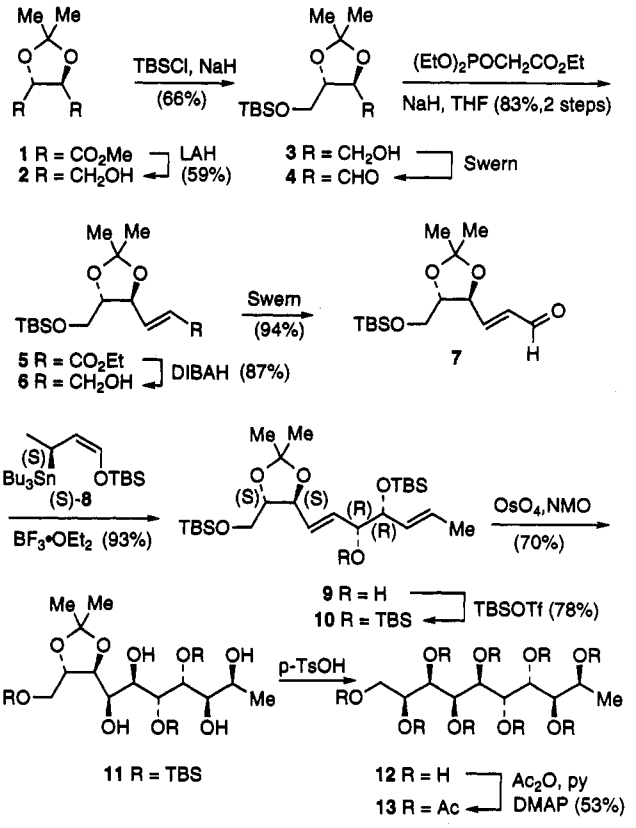
Our strategy stems from the observation that silylated *syn* diene diols such as **I** undergo highly anti selective hydroxylation (eq 1).[4] A conformational argument for this



selectivity has been advanced. Based on our recent findings, we felt that the BF_3-promoted addition of nonracemic γ-silyloxy allylic stannanes to enals would allow ready access to these valuable intermediates (eq 2).[5]



In fact, addition of allylic stannane (*S*)-8 to enal 7, derived from the acetonide 1 of (*R,R*)-dimethyl tartrate,[6a] led to the adduct 9, a single isomer, in 93% yield.[7] Hydroxylation of the bis-TBS ether 10 afforded the tetraol 11, likewise a single isomer, in 70% (unoptimized) yield. Hydrolysis followed by exhaustive acetylation gave the crystalline nonaacetate 13 whose structure was confirmed by single crystal X-ray analysis.[6b]



The diastereomeric nonaacetate 18, also a solid, was prepared analogously starting from enal 7 and stannane (*R*)-8.[7] Unfortunately, crystals of 18 were not suitable for X-ray analysis. Confirmation of stereochemistry was, therefore, achieved through conversion to the lactone 21

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(1) E.g. Lincosamine (C_8): Slomp, G.; MacKellar, F. A. *J. Am. Chem. Soc.* **1967**, *89*, 2454. Neuraminic acid (C_9): Schauer, R. *Adv. Carbohydrate Chem. Biochem.* **1982**, *40*, 132. Hikosamine (C_{11}): Vuilhorgne, M.; Ennifar, S.; Das, B.C.; Paschal, J. W.; Nagarajan, R.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289.

(2) E.g. Lincosamine: Knapp, S.; Kukkola, P. J. *J. Org. Chem.* **1990**, *55*, 1632. Magerlein, B. J.; Brinkmyer, R. D.; Herr, R. R.; Kagan, F. *J. Am. Chem. Soc.* **1967**, *89*, 2549. Howarth, C. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc. C* **1970**, 2218. Undeceses: McGhie, K. E.; Paton, M. *Tetrahedron Lett.* **1993**, *34*, 2831. Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661. KDO: Haudrechy, A.; Sinay, P. *J. Org. Chem.* **1992**, *57*, 4142. Other: Jarosz, S.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 4011. Jeganathan, S.; Vogel, P. *Tetrahedron Lett.* **1990**, *31*, 1717. Dondoni, A.; Fantin, G.; Foyagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693 and refs cited therein. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1990**, *55*, 2565. For a review see: Baggett, N. Synthesis of Monosaccharides by Chain Extension. In *Carbohydrate Chemistry*; Kennedy, J. F., Ed.; Clarendon Press: Oxford, 1988; pp 397–408. Schroeder, M. *Chem. Rev.* **1980**, *80*, 187.

(3) For recent work on total synthesis, see (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524. (b) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 2193. (c) Danishefsky, S. J.; DeNinno, M. P.; Chen, S-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (d) Review: Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 15.

(4) Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424.

(5) Cf. Marshall, J. A.; Welmaker, G. S. *Synlett* **1992**, 537.

(6) (a) Saito, S.; Hamano, S.; Moriyama, H.; Okada, K.; Moriwake, T. *Tetrahedron Lett.* **1988**, *29*, 1157. (b) The authors have deposited atomic coordinates for 13 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(7) Allylstannanes of >95% ee were employed in these studies. Within limits of detection by ^1H and ^{13}C NMR analysis a single diastereomeric alcohol adduct was obtained after column chromatography on silica gel. For an overview of this chemistry see Marshall, J. A. *Chemtracts-Org. Chem.* **1992**, 75.

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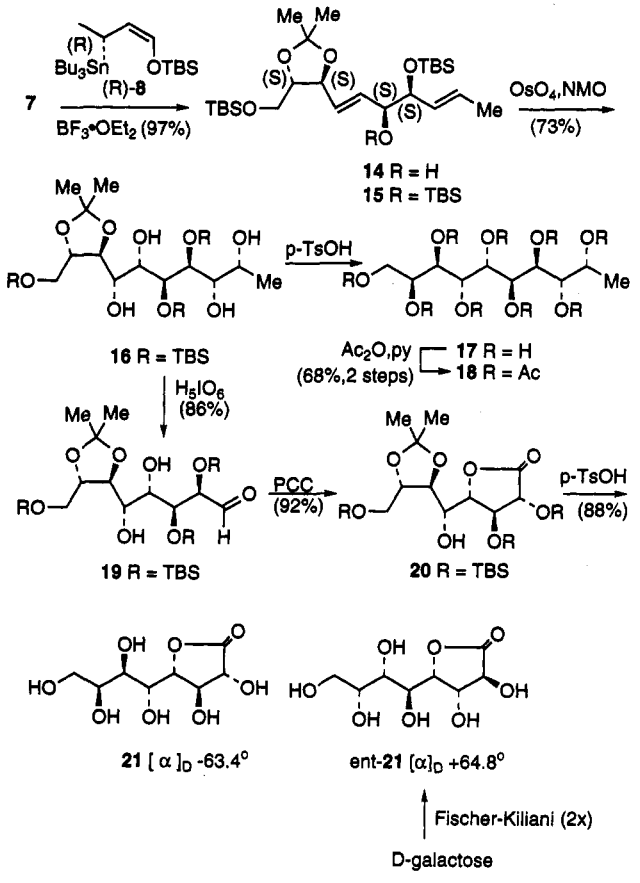
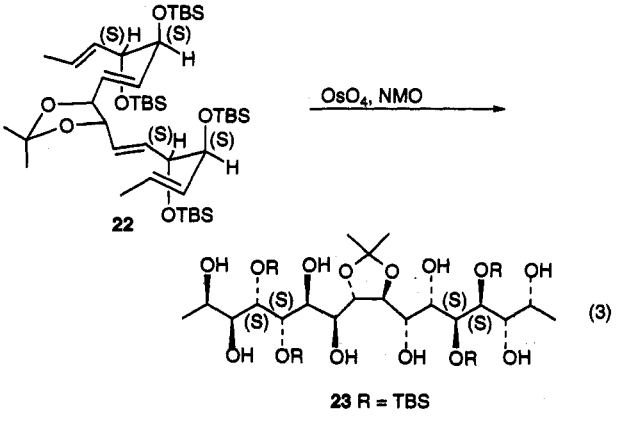
and comparison with the enantiomer *ent*-**21** prepared first by Fischer and subsequently by Hudson.[8] It is worth noting that tetraol **16** undergoes a highly selective Malaprade oxidation to aldehyde **19**, which exists primarily in the lactol form.[9]



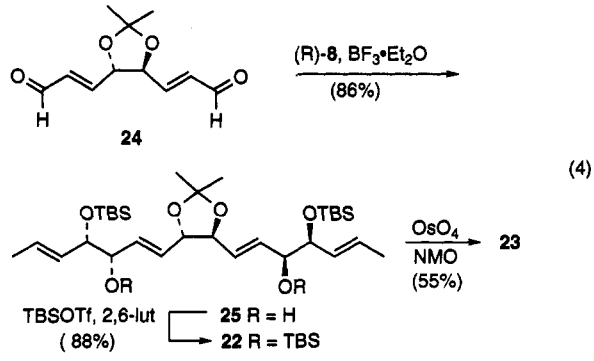
It was of interest to explore the possible bidirectional assemblage of higher sugars by this methodology as exemplified in eq 3.[10] To that end, we prepared the diene



(3)

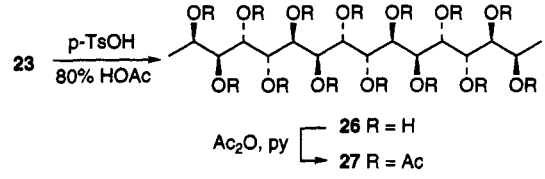
dial **24** from tartrate **1**.[6] This derivative was selected not only because of its close structural similarity to enal **7**, but also because the acetonide ring separates the diene side chains in the silylated bis-adduct **22**, thus enabling each to act more or less independently of the other (see eq 3).

Bis-homologation of dial **24** with stannane (*R*)-**8** followed by silylation afforded the tetraene **22** in high yield. Hydroxylation, as before, led to the octaol in 66% yield as a separable 5:1 mixture of **23** and other diastereomers (eq 4).



(4)

Octaol **23** was converted to the corresponding polyacetate **27** upon hydrolysis and *in situ* acetylation (eq 5).



(5)

The foregoing examples illustrate the applicability of this methodology to fairly complex polyols. Through variations in hydroxylation protocols[11] and alcohol protecting groups, other isomeric polyols could possibly be prepared. Further work along these lines is in progress.

Acknowledgment. This work was supported by Research Grant 5R01 AI31422 from the NIH. Preliminary studies on the addition of γ-silyloxy allylstannanes to achiral enals and subsequent hydroxylation of the TBS ethers were carried out by George P. Luke.

Supplementary Material Available: ^{1}H and selected ^{13}C NMR spectra and experimental procedures for all compounds (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Fischer, E. *Liebigs Ann. Chem.* **1895**, *288*, 150. Maclay, W. D.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1938**, *60*, 1035. Fischer reports mp 225–228 °C and $[\alpha]_D$ +64°. Hudson reports mp 219–220 °C dec and $[\alpha]_D$ +64.8° (c, 0.8) in water.

(9) Malaprade, L. *Bull. Soc. Chim. Fr.* **1928**, *43*, 638.

(10) For a related application, see ref 3a and citations therein.

(11) For example, epoxidation–hydration (after TBS cleavage) or asymmetric dihydroxylation after TBS cleavage. Johnson, R. A.; Sharpless, K. B. in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.