Diastereoselective Acetalization of Pseudo-C_2-Symmetric 1,3,5-Triols: A New Strategy for the Synthesis of Polyacetates and Polypropionates

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In this paper, we describe a new, highly general approach to the synthesis of 1,3-polyol and polypropionate structures based on the oxidative acetalization of *p*-methoxybenzyl (PMB) ethers of pseudo-C_2-symmetric 1,3,5-triols. Polyhydroxylated carbon chains, such as those found in polyacetates (1,3...*n*-polyols) and polypropionates (2,4...*n*-polymethyl-1,3,5...*n*-polyols), are ubiquitous substructures found in many important natural products. The control of stereochemistry in the context of such structures has spawned many novel synthetic strategies often based on reiterative application of diastereoselective methodology[1] or simultaneous two-directional chain synthesis.[2] Our strategy combines elements of both of these approaches to achieve rapid access to differentially protected 1,3-polyol and polypropionate precursors with high diastereoselectivity.

The oxidative cyclization of mono-PMB ethers of 1,3-diols to afford the corresponding *p*-methoxyphenyl (PMP) acetals is well known.[3] The oxidation of the aromatic ring with DDQ under anhydrous conditions gives the benzylic cation, which undergoes cyclization via a 6-*exo-trig*[4] -like ring closure. In the case of the 1,3-diol monoethers, there is only one possible regioisomer of cyclization. In contrast, C-3 PMB ethers of pseudo C_2-symmetric 1,3,5-triols may cyclize to afford either the (1,3) or (3,5) acetal isomers. We evaluated the factors that govern which of these two isomers will predominate in the oxidative cyclization in the context of transition structures **A** and **B** (Figure 1). Cyclization via **A** places all substituents of the forming ring in pseudoequatorial locations, whereas in **B** at least one is placed in an axial location. Therefore, we expect that the energy of **A** ($\Delta G_A^{\ddagger}$) would be less than that of **B** ($\Delta G_B^{\ddagger}$), and the product mixtures obtained from the oxidative acetalization of **1** should favor acetal **2** arising from transition structure **A**.[5]

To test our hypothesis, we first examined the cyclization of polyhydroxylated PMB ether **6**, a precursor for the synthesis of 1,3-polyols (Figure 2). We prepared **6** via a short, two-directional synthesis from readily available 4-[(*p*-methoxybenzyl)oxy]-1,6-heptadiene (**4**).[6] Ozonolysis of **4**, followed by homologation with triethyl phosphonoacetate and NaH afforded the dienoate **5**. This material was then dihydroxylated under the conditions

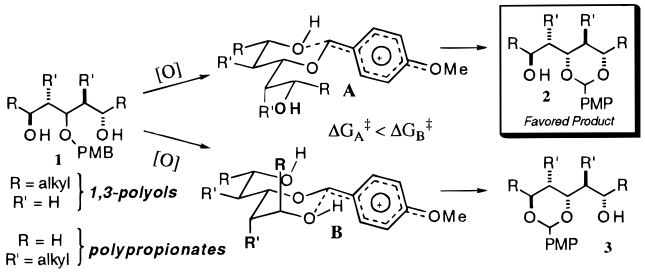

Figure 1.

described by Sharpless[7] to furnish tetrol **6**. Through this dihydroxylation, the pseudo-C_2-symmetry was established in one operation. Oxidation of the PMB ether of **6** to the corresponding acetals using DDQ afforded **7** and **8** in greater than 90% yield. Under standard conditions (DDQ, room temperature, CH_2Cl_2), we found that the oxidative acetalization gave a mixture of two acetals in a ratio of ca. 95:5. Only two acetal-containing products were observed for this cyclization. We determined the stereochemistry of the major diastereomer by examination of the NOESY spectrum of triacetate **9**, prepared by acetylation of **7** (Ac_2O, Et_3N, CH_2Cl_2, DMAP). Close contacts were observed between all axial methine protons on the newly established acetal ring. The diastereoselectivity of this cyclization shows a dramatic temperature dependence. At 25 °C, we found that the diastereomeric ratio was 95:5, at 0 °C the ratio was 98:2, and at −30 °C, the ratio of acetal isomers was >99:1.[8] Under these conditions, the oxidative acetalization is an irreversible process, and therefore, the product ratio is representative of $\Delta\Delta G^{\ddagger}$. From these ratios, we are able to estimate that the $\Delta\Delta G^{\ddagger}$ for the two cyclization pathways is 2.0 ± 0.3 kcal/mol. This value is consistant with the 2.3 kcal/mol energy difference, ΔE, between the products of cyclization as determined by MM2.[9] Having succeeded in effectively differentiating the pseudohomotopic alcohols of the starting polyol **6**, a potential precursor for the synthesis of 1,3-polyols, we next examined the cyclization of polypropionate precursors.

We prepared polypropionate precursor **11** via a short sequence from readily available 3-[(*p*-methoxybenzyl)-oxy]-2,4-dimethyl-1,4-pentadiene (**10**) (Figure 3).[10] Diastereoselective hydroboration of diene **10**[11] afforded pseudo-C_2-symmetric diol **11** as the major component of a 23:5:1 mixture of diastereomeric products. We obtained **11** in high diastereomeric purity by recrystallization of the bis(4-nitrobenzoate). As before, oxidation of the PMB ether to the corresponding acetals using DDQ afforded the expected products in greater than 90% yield. At 25 °C, we found that the oxidative acetalization gave a

(1) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.
(2) See (*inter alia*): Ho, T. L. *Tactics of Organic Synthesis* Wiley: New York, 1994; pp 33−38 and references cited therein.
(3) Oikiawa, Y.; Toshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.
(4) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(5) Hoye and co-workers have investigated structurally analogous 6-*exo-trig* cyclizations of functionalized pseudo-C_2 hydroxy diacids and esters to form valerolactones and found that the selectivity for the all-equatorially functionalized lactone was high. See: Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2748.
(6) Ether **4** was prepared from commercially available 1,6-heptadien-4-ol by benzylation (PMB-Cl, NaH, THF).
(7) (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibati, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (b) Corey , E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
(8) Diastereomeric ratios were determined by integration of the acetal proton in the ^{1}H NMR spectra.
(9) Molecular modeling was carried out on a Silicon Graphics workstation using MacroModel V5.0 (Richards, N. G. J.; Guida, W. C.; Liskamp. R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440). For compounds **7** and **8**, Monte Carlo conformational searches were carried out using Batchmin (500 MC steps, MM2, energy window = 25 kJ/mol, 2000 maximum iterations). Calculated energies are global minima.
(10) Ether **10** was prepared from methacrolein and 2-propenylmagnesium bromide followed by benzylation.
(11) Harada, T.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21.

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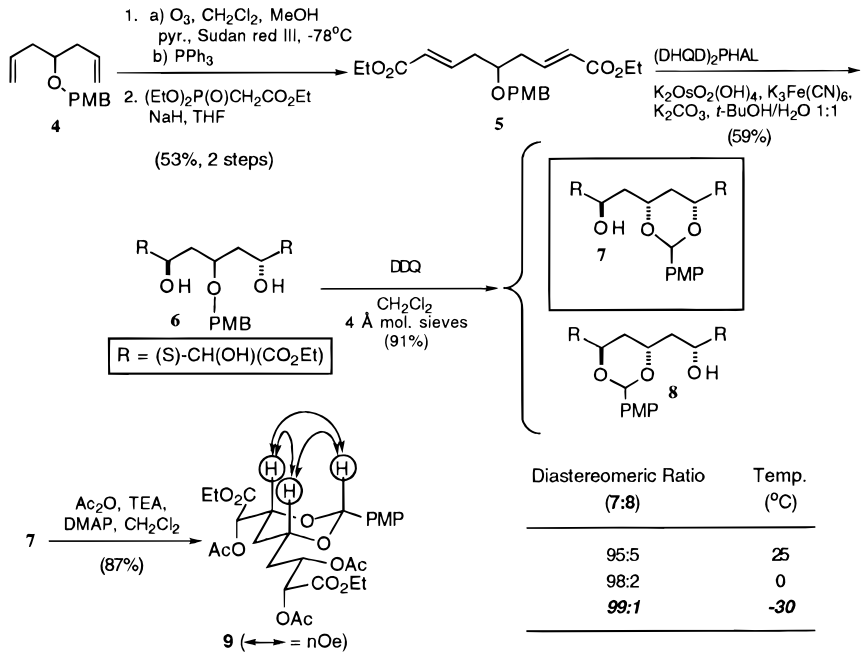

Figure 2.

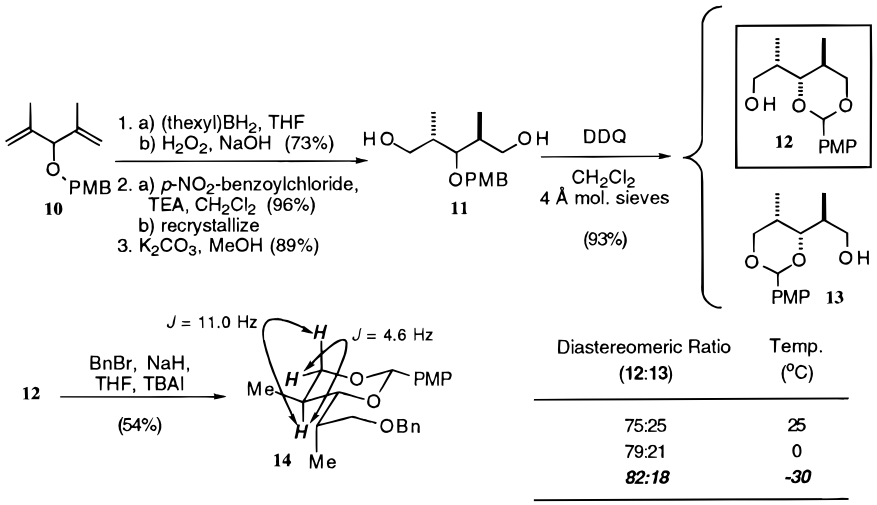

Figure 3.

mixture of acetals **12** and **13** in a ratio of *ca.* 75:25. Only two acetal-containing products were observed for this cyclization. We determined the stereochemistry of the major diastereomer by examination of the indicated $^1H-^1H$ coupling constants of benzyl ether **14**, prepared by benzylation of **12** with benzyl bromide and sodium hydride in THF (Figure 2). Like the previously described cyclization, the diastereoselectivity of this cyclization also shows a temperature dependence. At 25 °C, we found that the diastereomeric ratio was 75:25, at 0 °C the ratio was 79:21, and at −30 °C the ratio of acetal isomers was 82:18. From these ratios, we are able to estimate that the $\Delta\Delta G^{\ddagger}$ for the cyclization pathways leading to **12** and **13** is 0.7 ± 0.1 kcal/mol. Computational analysis (MM2) of the energies of **12** and **13** gave a ΔE for these compounds of 0.7 kcal/mol.

End differentiation of pseudo-C_2-symmetric chains is a powerful strategy for the rapid synthesis of stereochemically complex structures. The results presented in Figures 2 and 3 demonstrate that oxidative acetalization can be used to differentiate the end groups in 1,3,5-triol systems having pseudo-C_2-symmetry. These reactions can be used to synthesize highly dissymmetric precursors for the preparation of complex polyoxygenated natural products. The similarity of the calculated ΔE of the products and the experimentally determined $\Delta\Delta G^{\ddagger}$ suggests that the transition state is late. Furthermore, the similarity of these energy values suggests that computational analysis of potential substrates to predict product ratios should be useful in the optimization of this reaction for use in synthesis. We are currently developing this methodology in the context of 1,3-polyol and polypropionate synthesis.

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Supporting Information Available: Experimental procedures and analytical data for compounds **4**−**14** and copies of ^1H and ^{13}C NMR spectra and depictions of minimized structures of **7**, **8**, **12**, and **13** (32 pages).

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