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Synthesis of Polyketides via Diastereoselective Acetalization

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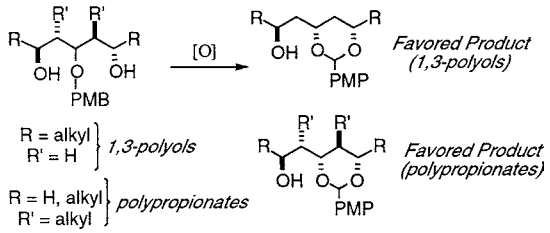
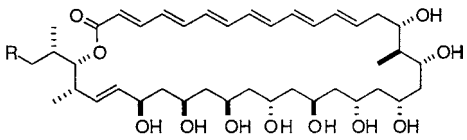
ABSTRACT

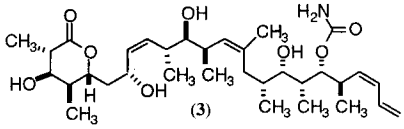


Diastereoselective acetalization of pseudo-C_2-symmetric 1,3,5-triol systems is a general strategy for the rapid generation of polyketides. The oxidative acetalization reaction shown above was studied under both kinetic and thermodynamic conditions, using synthetic 1,3,5-triol units. In addition, all possible stereochemical variants of a 1,3,5-triol system were prepared from the corresponding acetal to expand the synthetic versatility of this method.

Polyketide natural products are a structurally complex class of compounds. Many of these compounds show important biological activity. For example, the recently synthesized polyene macrolides dermostatin A (**1**) and B[1] (**2**) exhibit potent antifungal activity, while the polypropionate discodermolide[2] (**3**) exhibits potent antimitotic activity.



(**1**), R = H
(**2**), R= CH_3



(**3**)

Efficient synthetic strategies for the preparation of polyketides are necessary; however, the 1,3-polyol unit of these compounds poses a synthetic challenge. There are many reiterative strategies designed for 1,3-polyol fragment synthesis. One common theme is based on the stereoselective functionalization of allylic and homoallylic alcohols. For example, the Sharpless asymmetric epoxidation of allylic alcohols is often used for preparation of *syn*- or *anti*-1,3-polyols.[3] However, a typical sequence of this method requires about 8 linear steps. Homoallylic alcohols may be functionalized with use of cyclic iodocarbonates.[4] This strategy requires a minimum of 4 steps per iteration, but it is limited to the formation of only *syn*-1,3-diols. Other strategies include the [1,2]-Wittig rearrangement of β-alkoxyalkyl allyl ethers[5] and the selective reduction of acyclic β-hydroxy ketones.[6]

We have reported a highly general approach to the synthesis of polyacetate and polypropionate structures based

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on the oxidative acetalization of *p*-methoxybenzyl (PMB) ethers of pseudo-C_2-symmetric 1,3,5-triols (Figure 1).[7]

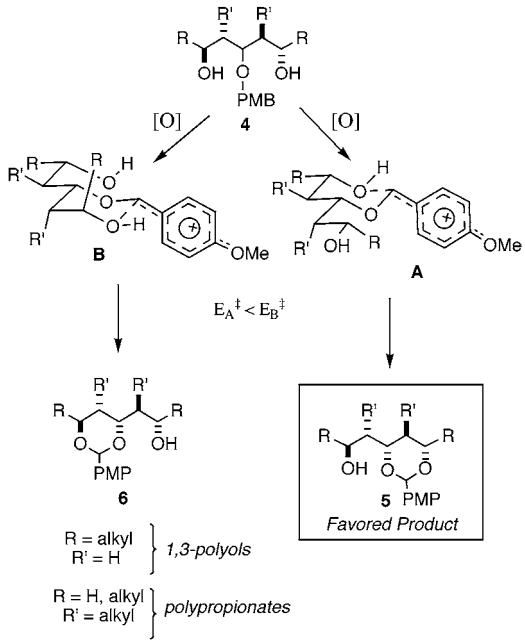


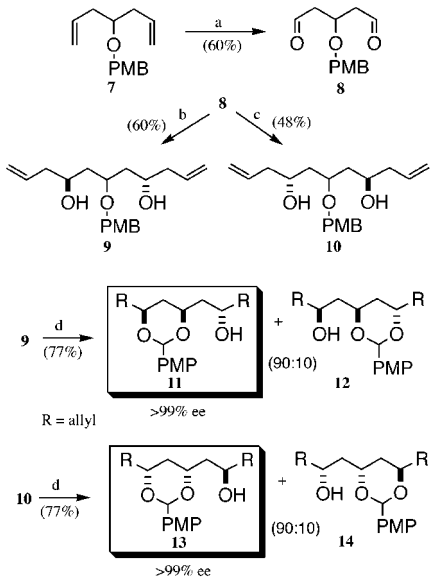
Figure 1. Oxidative acetalization.

Pseudo-C_2-symmetric models of the 1,3-polyol and polypropionate systems were previously prepared to study the oxidative acetalization process.[7] The oxidative acetalization was achieved via anhydrous DDQ in CH_2Cl_2 at room temperature. The 1,3-polyol model prepared contained R = (*S*)-CH(OH)CO_2Et and R′ = H. This compound gave a selectivity of 95:5 (**5**:**6**) in the oxidative cyclization reaction. The polypropionate model contained R = H and R′ = CH_3. A selectivity of 75:25 (**5**:**6**) was achieved in this acetalization. A low-temperature study showed increasing selectivity in the oxidative acetalization process with lower temperature. For example, the 1,3-polyol model gave a diastereoselectivity of >99:1 at −30 °C and the polypropionate model gave an improved diastereoselectivity of 82:18 at −30 °C. With use of anhydrous DDQ conditions, the oxidative acetalization process is presumed to be irreversible and therefore under kinetic control.

The irreversibility of this reaction was tested by resubmitting acetal mixtures (**5** and **6**, using both the 1,3-polyol and the polypropionate models) to the same DDQ reaction conditions. This led only to over-oxidation products. No equilibration of the diastereomers was observable. The similarity of the experimental $\Delta\Delta G^{\ddagger}$ values to the ΔE values from MM2 calculations[10] suggests that the transition state of cyclization is late. Because we have hypothesized that the DDQ-mediated oxidative acetalization of C-3 PMB ethers of pseudo-C_2-symmetric 1,3,5-triols is a kinetically controlled process, we also wanted to investigate the thermodynamic selectivity of PMP-acetal formation.

A simplified polyol model was synthesized for these thermodynamic studies. The polyol model **9** (Scheme 1) was

Scheme 1[a]



[a] Reagents and conditions: (a) (i) O_3, MeOH/CH_2Cl_2, Sudan Red III, pyr, -78 °C; (ii) DMS.(b) (i) [(+)-*i*pc]$_2$allylborane, THF, −100 °C; (ii) H_2O_2, NaOH. (c) (i) [(−)-*i*pc]$_2$allylborane, THF, −100 °C; (ii) H_2O_2, NaOH. (d) DDQ, rt, CH_2Cl_2, 4 Å molecular sieves.

prepared from the PMB-protected diene **7**. Treatment of **7** with ozone, followed by homologation with *B*-(+)-allyldiisopinocampheylborane, using conditions developed by Brown,[8] gave compound **9**. An oxidative acetalization performed on **9**, using standard kinetic conditions (DDQ, CH_2Cl_2, rt), furnished acetals **11** and **12** (90:10, 77% yield, ee >99%). MM2 calculations predicted an energy difference, ΔE = 2.6 kcal/mol, between **11** and **12**.[9] These acetals were more susceptible to over-oxidation than the previous two examples. After only 5−10 min of exposure to the acetalization conditions, 15−20% of the mass balance corresponded to a mixture of *p*-methoxybenzoate regioisomers. The enantiomeric 1,3,5-triol was also prepared with *B*-(−)-allyldiisopinocampheylborane.

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(9) Molecular modeling was carried out on a Silicon Graphics workstation using MacroModel V 5.0 (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.
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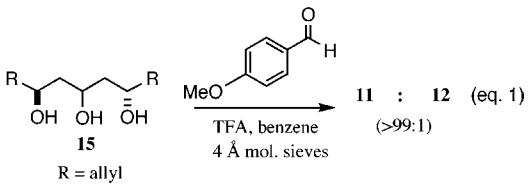
To determine if the ratio of products obtained by direct oxidation was the kinetic or thermodynamic ratio, the acetal mixture (**11**:**12**) was allowed to equilibrate for 2 h in benzene, using 20% TFA and 4 Å molecular sieves. The ratio of acetals **11** and **12** changed from 90:10 to >99:1. No further changes in the >99:1 ratio were observed after 24 h.

To investigate further the thermodynamic control in the formation of **11** and **12**, we sought to compare the product ratios from these equilibration experiments with those obtained from an acid-catalyzed acetalization of the 1,3,5-triol with PMP-aldehyde.

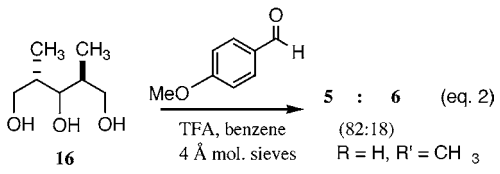
The 1,3,5-triol (**15**, eq 1) was prepared by basic hydrolysis (K_2CO_3, MeOH) of the *p*-methoxybenzoates (obtained from DDQ over-oxidation of **11** and **12**). The thermodynamically controlled acetalization (*p*-anisaldehyde, TFA, 4 Å molecular sieves in benzene)[10] of **15** gave acetals **11** and **12**, again in a >99:1 ratio.



Finally, a low-temperature experiment was performed. Compound **9** was subjected to irreversible DDQ conditions at −30 °C. A >99:1 ratio of **11**:**12** was obtained. From these results, we have concluded that the formation of the *syn*-acetal **11** is favored under both kinetic and thermodynamic conditions. However, the diastereoselectivity is the highest under thermodynamic control at room temperature or kinetic control at −30 °C.

The same two thermodynamic experiments were performed with the polypropionate model system (**4**, R = H and R′ = CH_3, Figure 1). The kinetic mixture of acetal products **5** and **6** (R = H and R′ = CH_3) was subjected to equilibration conditions. After exposure to TFA for 2 h, the acetal ratio of **5** to **6** changed from 75:25 to 82:18. No further fluctuations in this ratio were observed over 48 h.

For the second thermodynamic-based experiment, the polypropionate-derived 1,3,5-triol **16** was prepared by deprotection of **4** (CAN, CH_3CN, and H_2O).[11] Acetalization of **16** under thermodynamic conditions (*p*-anisaldehyde, TFA, 4 Å molecular sieves in benzene) gave the same 82:18 ratio of **5** and **6** as in the previous experiment (eq 2). From these

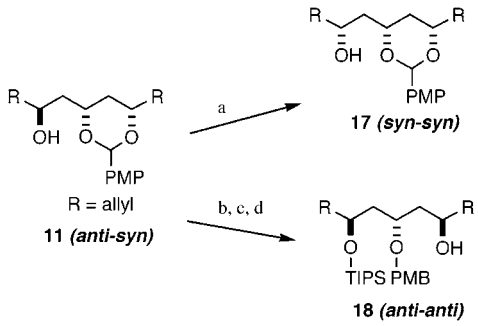


results, we propose that the polypropionate-derived acetal **5** is also favored under both kinetic and thermodynamic control. The best selectivity (82:18) can be achieved both by using reversible equilibration conditions at room temperature and by cooling to −30 °C, using the irreversible DDQ conditions.

The synthetic utility of simple polypropionate intermediates such as **5** (eq 2) is limited. However, better diastereoselectivity could perhaps be achieved with other substrates where R = alkyl instead of H. This extra substitution may stabilize the chairlike transition state **A** (see transition state model, Figure 1) and further destabilize transition state **B**. The optimization of the diastereoselective acetalization with polypropionate systems must be investigated.

The diastereoselective acetalization examples presented for 1,3-polyol synthesis gave selectively protected 1,3,5-triol units with *anti-syn* stereochemistry. To generalize our approach further, we prepared all stereochemical variants of the 1,3,5-triol unit. The *syn-syn* 1,3,5-triol **17** was prepared via a Mitsonobu inversion of the alcohol **11** (Scheme 2).[12]

Scheme 2[a]



[a] Reagents and conditions: (a) (i) DEAD, PPh_3, benzoic acid, THF; (ii) K_2CO_3, MeOH. (b) TIPSCI, NaH, TBAI, THF. (c) DIBAL-H, toluene, 0 °C. (d) (i) DEAD, PPh_3, benzoic acid, THF; (ii) K_2CO_3, MeOH.

The *anti-anti* triol **18** was prepared in a three-step sequence, also starting from **11**. First, **11** was protected with a triisopropylsilyl group. A regioselective reduction of the acetal was then achieved with DIBAL-H.[13] Finally, the *anti-anti* triol **18** was generated by a Mitsonobu inversion.

Diastereoselective acetalization of pseudo-C_2-symmetric chains is a powerful strategy for the rapid synthesis of stereochemically complex structures. The results presented here demonstrate that this strategy 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 disymmetric precursors for the preparation of complex polyoxygenated natural products. The generality of this approach makes it highly applicable for the synthesis of all stereochemical variants of the 1,3,5-triol unit. This methodology can now be utilized in the context of polyacetate and polypropionate synthesis. The development and application

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of this approach toward the synthesis of long-chain polyols will be forthcoming.

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Supporting Information Available: Experimental procedures and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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