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Iterative Approach to Enantiopure *syn*/*anti*-1,3-Polyols via Proline-Catalyzed Sequential α-Aminoxylation and Horner−Wadsworth−Emmons Olefination of Aldehydes

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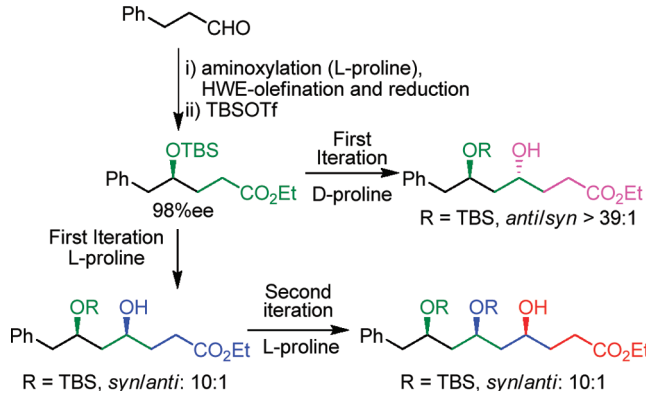
ABSTRACT



Iterative use of proline-catalyzed tandem α-aminoxylation and HWE olefination of aldehydes provided a simple access to 1,3-polyols. The feasibility of this approach is initially studied to synthesize *syn*- and *anti*-1,3-diols and is further extended to a *syn*/*syn*-1,3,5-triol at a useful level of asymmetric induction and yield. Its usage is illustrated by the short synthesis of a hydroxylactone pheromone component, (2*S*,3*S*)-2-hydroxyhexylcyclopentanone.

The 1,3-skipped polyol systems with *anti*- or *syn*-configuration are structural units of several natural products including clinically valuable polyene macrolide antibiotics. This has aroused great interest among synthetic organic chemists, resulting in an onslaught of activity directed at the development of efficient, stereoselective approaches to the assembly of 1,3-diols.[1] Despite the numerous strategies to synthesize polyols through substrate-controlled asymmetric induction, the interest in the new methods of its synthesis continues unabated.[2] We have recently developed a diastereoselective and iterative approach for the synthesis of 1,3-polyols using Jacobsen's hydrolytic kinetic resolution of racemic epoxide by which

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in principle one can prepare all the stereoisomers from easily available epoxides.[2b] However, the sequence of reaction suffers from a disadvantage due to the loss of 50% of starting compound as diol in each resolution step. Within the context of this work, the most widely used method to prepare 1,3-polyols in an iterative fashion are by allyl addition sequence utilizing stoichiometric amounts of chiral borons[3] and titanium.[4] Recently, Kirsch and co-workers have developed an efficient catalytic, iterative synthetic route to 1,3-polyols using Overmann esterification,[5a] while chromium-mediated asymmetric allylation has been reported by Kishi et al.[5b] However, the method involves a greater number of steps for each iteration[5a] (Kirsch et al.) or requires stringent reaction conditions[5b] (Kishi et al.) and uses an expensive catalyst.

In view of the above considerations, there is still need for a versatile synthetic method that addresses the following issues: mild reaction conditions, minimum steps for each iteration, cheap and readily available catalysts, and flexible construction of possible isomers. In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis.[6] As a result, the area of organocatalysis has now emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[7] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[8] Proline is among the most successful secondary amine based organocatalysts which have been widely employed in the asymmetric aldol,[9] Mannich,[10] Michael addition,[11] and α-functionalization,[12] viz. α-aminoxylation-,[12c] α-amination-,[13] and α-aminoxylation-directed tandem reactions,[14] among many others,[15] providing rapid, catalytic, and atom-economical access to enantiomerically pure products. Similarly, organocatalytic tandem processes are emerging as powerful methods for the rapid synthesis and construction of complex target molecules from simple and readily available precursors while minimizing yield, time, and energy losses.[16]

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Recently, Zhong et al. have reported an α-aminoxylation-directed tandem reaction catalyzed by proline which involves a sequential α-aminoxylation, HWE-olefination reaction at ambient temperature furnishing *O*-amino-substituted allylic alcohol from readily available achiral aldehydes.[14a] We envisioned that this reaction could give us stereocontrolled synthetic access to 1,3-polyol motifs. However, it may be pertinent to mention here that the chirality of the already established 1,3-polyol chain makes the stereoselective chain elongation a challenging process.[17] Our iterative strategy for the synthesis of polyols is outlined in Figure 1.

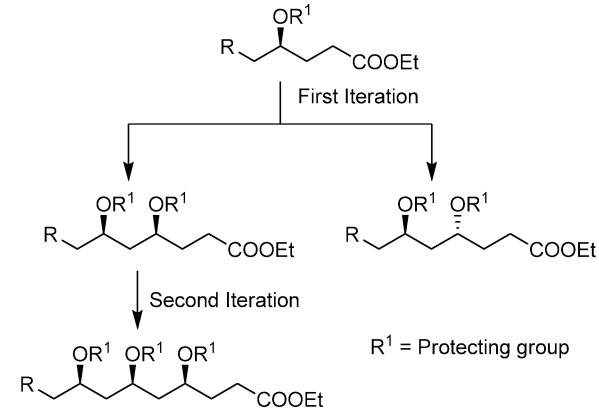
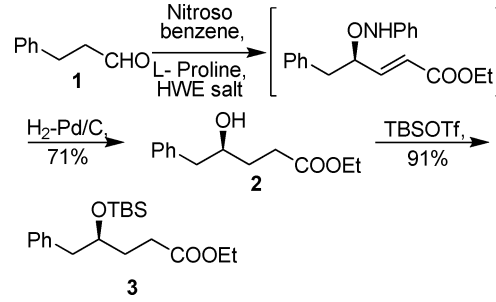


Figure 1. Iterative strategy for polyol synthesis.

Toward the synthesis of 1,3-polyols, our first goal was to synthesize γ-hydroxy ester **2** in a tandem fashion (Scheme 1). Thus, when the commercially available phenyl propanal

Scheme 1. Synthesis of γ-Hydroxy Ester

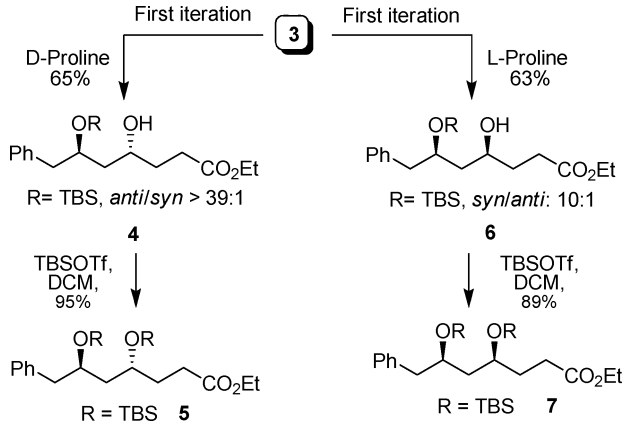


1 was subjected to sequential α-aminoxylation (L-proline as a catalyst) followed by HWE-olefination reaction, it furnished *O*-amino-substituted allylic alcohol. In an effort to minimize handling of intermediates and its time-consuming purification, the crude product obtained after workup was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the γ-hydroxy ester **2** in good yield.

Thus, in two steps and one column purification, γ-hydroxy ester **2** was obtained in 71% yield and 98% ee.[18] The free hydroxy group of γ-hydroxy ester **2** was protected as TBS

ether using TBSOTf to furnish compound **3**. With a substantial amount of the TBS ether **3** in hand, we then proceeded toward the first cycle of iteration (Scheme 2).

Scheme 2. First Iteration for Synthesis of Diol[a]

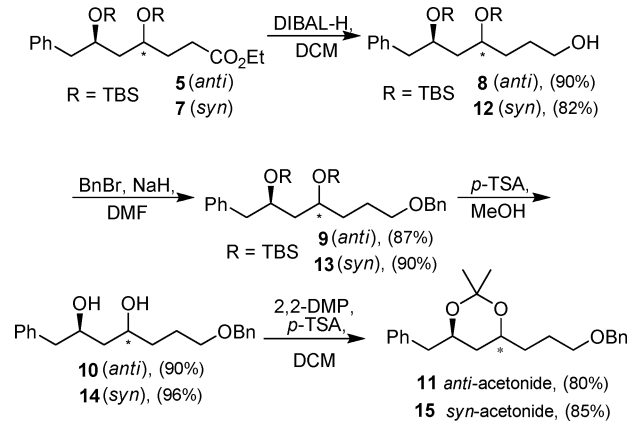


[a] One cycle of iteration is composed of a four-step sequence: (1) DIBAL-H, reduction of ester; (2) nitrosobenzene, D/L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (3) H_2/Pd−C, EtOAc; (4) TBSOTf, 2,6-lutidine, DCM.

Each cycle of iteration consists of four steps, viz. DIBAL-H reduction of ester to aldehyde, sequential α-aminoxylation, HWE olefination, and H_2−Pd/C reduction, followed by TBS protection of the hydroxy group to eventually furnish the TBS protected γ-hydroxy ester. As illustrated in Scheme 2, the DIBAL-H reduction of ester **3** furnished the corresponding aldehyde which on α-aminoxylation using D-proline as a catalyst followed by HWE olefination and subsequent Pd/C reduction gave the *anti*-diol **4** in 65% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of the reaction to be >95%. Further TBS protection of free hydroxy group afforded TBS ether **5** in 95% yield. Following similar iteration with L-proline-catalyzed sequence of reactions provided the *syn*-diol **6** as a 10:1 unseparable mixture of diastereomers in 63% yield. Nevertheless, after protection of the hydroxyl group of **6** with TBS, we were able to separate the major diastereomer **7** in 89% yield in diastereomerically pure form as determined from ^{1}H NMR. These findings could probably be attributed to match/mismatch effect of the TBS group, without any appreciable change in yield of the reaction[19] (Scheme 2).

The relative stereochemistry of 1,3-diols **4** and **6** was determined by using Rychnovsky's acetonide method[20] (Scheme 3). Thus, DIBAL-H reduction of esters **5** and **7**

Scheme 3. Relative Stereochemistry Determination



afforded alcohols **8** and **12**, respectively, which on benzyl protection gave compounds **9** and **13**. Subsequent TBS deprotection furnished the diols **10** and **14**, which on treatment with 2,2-DMP gave the *anti*-acetonide **11** and *syn*-acetonide **15**, respectively. The appearance of methyl resonance peaks at δ 19.8 and 30.2 ppm and acetal carbon resonating at δ 98.5 ppm confirmed the presence of *syn*-acetonide **15**. Similarly, *anti*-acetonide **11** was confirmed by the appearance of the methyl carbons resonance at δ 24.8 ppm and the acetal carbon at δ 100.3 ppm (Scheme 3).

This iterative sequence is particularly attractive because of mild reaction conditions, use of proline as a cheap and commercially available catalyst,[21] and the overall short reaction sequence involving four steps and two column purifications per iteration. Since the stereochemical outcome of the reaction can be predicted on the basis of the catalyst used, this method gives an easy access to 1,3 *syn*/*anti*-diols with predictable and useful stereocontrol in good yield.

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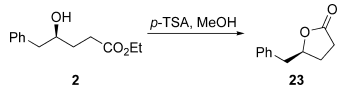
(18) In order to determine the chiral purity of (*S*)-ethyl 4-hydroxy-5-phenylpentanoate **2** formed, it was converted into known lactone by treatment with *p*-TSA in methanol.

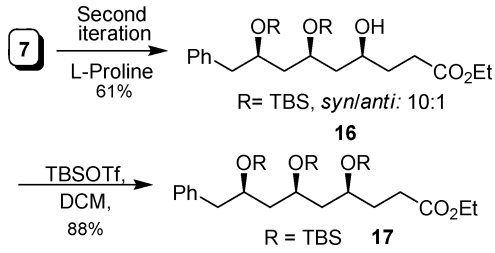


HPLC: Chiracel OD-H column (2-propanol/petroleum ether = 10:90, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 17.17 (major) and 20.67 (minor). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 98%.

(19) Overall yield per iteration cycle can be slightly improved by following the two-step process for aldehyde formation that is reduction of ester to alcohol followed by IBX oxidation.

To illustrate the feasibility of this approach for preparing 1,3,5-polyols, we further attempted the synthesis of a *syn*/*syn*-1,3,5-triol as a representative example (Scheme 4).

Scheme 4. Second Iteration for Synthesis of Triol[a]

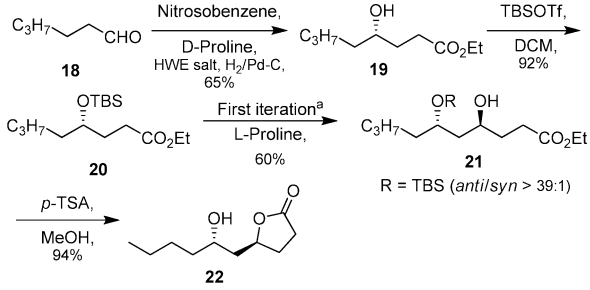


[a] One cycle of iteration is composed of a four-step sequence: (1) DIBAL-H, reduction of ester; (2) nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (3) H_2/Pd−C, EtOAc; (4) TBSOTf, 2,6-lutidine, DCM.

Thus, by subjecting *syn*-diol **7** to a second cycle of iteration using the L-proline-catalyzed sequence of reactions, triol **16** was obtained as a 10:1 unseparable mixture of diastereomers in 61% yield as determined from ^{1}H NMR. However, the diastereomerically pure triol was obtained as the TBS ether **17** in 88% yield after TBS protection of the hydroxyl group of **16** and separation by flash chromatography.

As an outgrowth from these efforts, we became interested in the application of this approach for the expedient total synthesis of (2*S*,3*S*)-2-hydroxyhexylcyclopentanone **22**, representative of 6-hydroxyalkan-4-olides, hydroxy lactones with chain lengths between 10 and 13 carbon atoms, which are part of the complex mixture of compounds that giant white butterfly *Idea leuconoe* hairpencils release as a pheromone (Scheme 5). They seem to act synergistically with

Scheme 5. Synthesis of (2*S*,5*S*)-2-Hydroxyhexylcyclopentanone



[a] One cycle of iteration here is composed of a three-step sequence: (1) DIBAL-H, reduction of ester; (2) nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (3) H_2/Pd−C, EtOAc.

the other pheromone components and are probably involved in male−male interactions.[22] To this end, commercially available hexanal **18** was subjected to sequential α-aminoxylation (D-proline as a catalyst), HWE olefination, and reductive hydrogenation to furnish the γ-hydroxy ester **19** in 65% yield and 94% ee.[23] This on TBS protection (**19** → **20**) followed by a first cycle of iteration using L-proline-catalyzed reaction conditions afforded the *anti*-diol **21**, with de >95% as determined from ^{1}H NMR. Subsequent acid treatment with *p*-TSA in methanol resulted in deprotection of TBS group and concomitant lactonization to furnish the required lactone **22**.

In conclusion, a practical and efficient iterative approach to the stereocontrolled synthesis of 1,3-polyols from commercially available and inexpensive starting materials has been developed. The advantages of using this process are as follows: (a) the reaction uses mild reaction conditions (at room temperature, air and moisture are tolerated), (b) the *O*-amino-substituted allylic alcohol that is formed after sequential α- aminoxylation and HWE olefination can be isolated in good yield and is converted to γ-hydroxy ester without requiring a separate column purification step, and (c) both enantiopure forms of proline are commercially available, and thus, in principle, all possible combinations of 1,3,5-polyols can be accessed. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of a pheromone component, (2*S*,3*S*)-2-hydroxyhexylcyclopentanone. This synthetic strategy, which is amenable to both *syn*- and *anti*-1,3-polyols, has significant potential for its further extension to the synthesis of variety of biologically important natural products. Currently, studies are in progress toward this goal.

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

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(21) Cost of L-proline in Aldrich catalogue 2009−2010 for 100 g is INR 4404 (USD $60.40).

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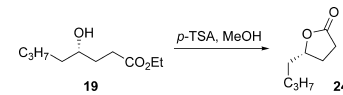
(23) In order to determine the chiral purity of (*S*)-ethyl 4-hydroxyoctanoate **19** formed it was converted into known lactone on treatment with *p*-TSA in methnol.



Chiral GC using cyclodextrin TA column (70 kPa pressure, 140 °C isotherm for 30 min, minor enantiomer 17 min, major enantiomer 15 min). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 94%.