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# One- and two-directional iterative 1,2-asymmetric induction in acyclic systems — easy access to *anti,anti* and *anti,syn* dipropionate and diphenylacetate stereotriads

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**Abstract**

Stereocontrolled addition of organocuprate reagents to γ-alkoxy-α,β-unsaturated esters can be done in one- and two-directional modes with excellent 1,2-induction. Enolate hydroxylations proceed with high diastereoselectivity affording acyclic chains with three to five contiguous stereogenic centers of the propionate and phenylpropionate triad types. 

*Keywords:* conjugate addition; enolate hydroxylation; iterative 1,2-induction; propionate; phenylpropionate triads.

The stereocontrolled introduction of alkyl and aryl groups on alternating carbon atoms in acyclic chains presents a great challenge in organic synthesis.[1] The task is rendered more difficult when multiple stereocenters are involved such as propionate triads related to natural products.[2] There are a number of elegant methods for the stereocontrolled synthesis[2] of such motifs harboring hydroxy–methyl–hydroxy triads which are biosynthetically assembled via the so-called propionate pathway.[3] Of these, the *anti,anti* dipropionate stereotriad appears to be the most arduously accessible[4] (Fig. 1). To the best of our knowledge, the analogous phenyl–hydroxy–phenyl triads are not known, and they could constitute interesting phenylacetate counterparts of the ubiquitous propionate assembly protocol.

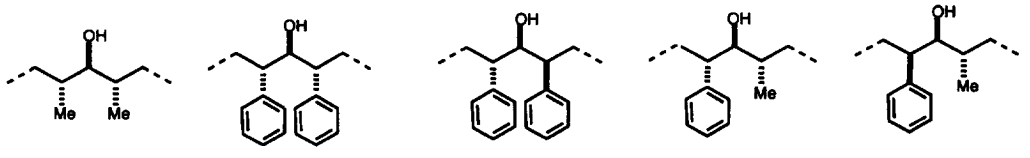


Figure 1.

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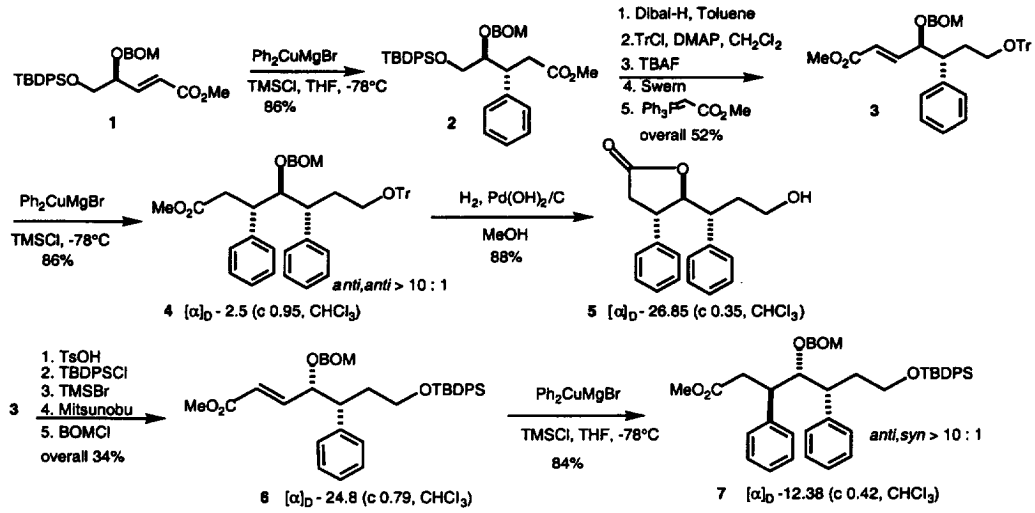
We report herein synthetic routes that exploit 1,2-asymmetric induction in conjugate additions[5] of alkyl, and phenyl units to acyclic γ-alkoxy-α,β-unsaturated esters. The power of this method is validated further by the demonstration that excellent stereoselectivity can be maintained in an iterative and a two-directional protocol[6] as well.

The readily available enoate **1**[5a] was treated with the reagent resulting from the addition of CuI to phenylmagnesium bromide in the presence of TMSiCl in THF at −78°C to afford a single adduct **2** (Scheme 1). In order to differentiate the end groups in the intended seven-carbon acyclic motifs, we converted the ester group into a protected alcohol, then proceeded to extend the chain to create another γ-alkoxy-α,β-unsaturated ester as in **3**. Conjugate addition was equally stereoselective in this case to afford the end-group differentiated symmetrical (3*S*,5*R*)-diphenyl-(4*S*)-ol motif **4**. Stereochemical purity was ascertained by removal of the BOM group, conversion to the corresponding lactone, and detailed NMR analysis of the resulting (3*S*)-phenyl substituted branched butyrolactone **5**.

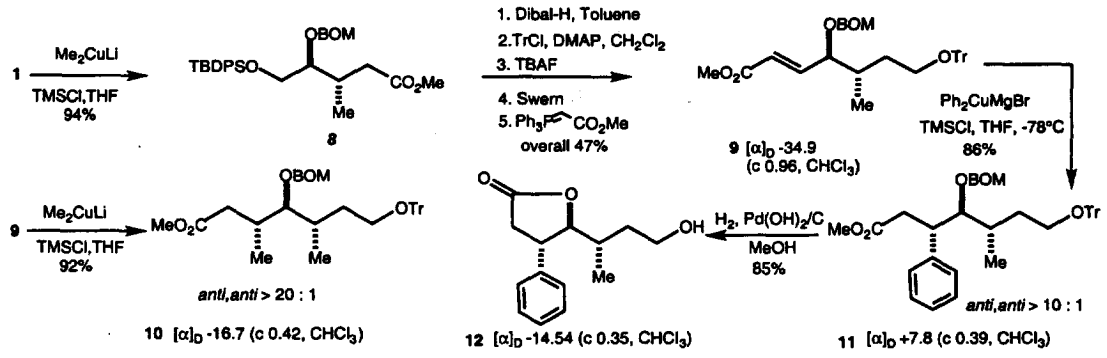



Scheme 1.

In an effort to fully exploit the symmetry elements offered by this methodology, we proceeded with an inversion of configuration of the alkoxy group in **3** adopting a classical Mitsunobu reaction[7] to give **6** as shown in Scheme 1. Conjugate addition with the mixed phenyl cuprate reagent led to the end-group differentiated $C_2$-symmetrical (3*R*,5*R*)-diphenyl-(4*R*)-ol motif **7** in excellent yield and diastereoselectivity. Enantiopure material was obtained after chromatography, and transformation to the corresponding (3*R*)-phenyl butyrolactone derivative allowed definitive stereochemical assignment. Addition of lithium dimethylcuprate to **6** led to the corresponding *anti,syn*-*C*-methyl analog in 92% yield and >20:1 selectivity.

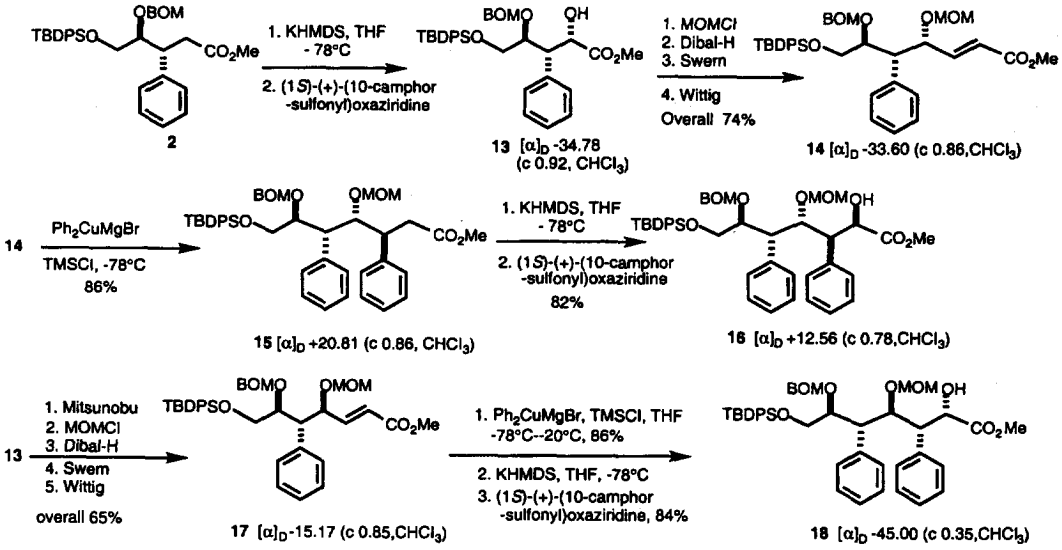
The prospects for generating propionate units in a two-directional strategy was also successfully realized by using lithium dimethylcuprate as shown in Scheme 2. Thus, extension of the acyclic motif **8**[5a] to the enoate **9**, followed by cuprate addition led to essentially a single isomer **10** having the expected *anti,anti* orientation. Addition of the mixed phenyl cuprate reagent led to the corresponding adduct **11** in excellent yield and high diastereoselectivity (10:1, separable by chromatography). Stereochemical assignments were corroborated by transformation into the corresponding lactone **12** and NMR analysis or by independent synthesis.

The synthesis of propionate triads in an iterative manner starting with **1** was recently demonstrated in our laboratory.[8] The basic reaction sequence involved cuprate addition to **1** to afford **8**, and hydroxylation




Scheme 2.

of the K enolate with the Davis oxaziridine reagent[9] to afford a single isomer with an *anti,syn* γ-hydroxy–methyl–hydroxy unit on the five-carbon chain. It was of interest to explore the stereoselectivity of hydroxylation of the 3-phenyl analog **2** (Scheme 3). Surprisingly, no selectivity was observed with the achiral Davis oxaziridine.[9] High stereoselectivity was found with the matched (*S*)-10-camphorsulfonyl oxaziridine[10] (>20:1) which afforded the (2*S*)-hydroxy ester derivative **13** (Scheme 3). Selectivity with the (1*R*)-oxaziridine was >12:1.




Scheme 3.

The prospect of generating phenylacetate triads by iterative cuprate addition and hydroxylation in acyclic motifs such as **2** was successfully realized as shown in Scheme 3. Thus, chain extension of **13** to the γ-alkoxy enoate **14**, followed by conjugate addition proceeded with high selectivity to afford a single adduct **15** with the *syn,anti* triad combination. Treatment of the corresponding K enolate with the (*S*)-10-camphorsulfonyl oxaziridine reagent gave a single hydroxylation product **16** in excellent yield. To extend the stereochemical versatility of this protocol, the α-hydroxy function in **13** was inverted and the product was chain-extended to give **17** as shown in Scheme 3. Conjugate addition gave the corresponding *anti,anti* phenylacetate triad as a single isomer, which was α-hydroxylated as before affording the seven-carbon motif **18** in excellent yield and diastereoselectivity. The enantiopurity of the compounds **16** and **18** was

ascertained by conversion to their Mosher esters and NMR analysis. The origin of these stereocontrolled conjugate additions and enolate hydroxylations have been discussed previously.[5a,11]

In conclusion, we have demonstrated that the stereocontrolled conjugate addition of organocuprates to γ-alkoxy-α,β-unsaturated esters proceeds in high diastereoselectivity in a two-directional strategy. This protocol affords acyclic chains that contain three contiguous substituents of the *anti,anti* dipropionate triad type and its diphenylacetate equivalent. Enolate hydroxylation and cuprate additions can be done in an iterative manner in this series to generate seven carbon acyclic motifs harboring five contiguous stereocenters consisting of alternating hydroxy and phenyl substituents with complete stereocontrol. A series of 1,2-asymmetric inductions start with a resident γ-alkoxy group and propagate with excellent stereoselectivity through two successive conjugate additions and two enolate hydroxylations.

The enantiopure symmetry-related acyclic motifs described in this work will find applications as chirons in synthesis and in biosynthesis, as functionalized ligands in catalysis, as well as in the design of scaffolds with hydrophobic appendages for chemical and molecular diversity in medicinal chemistry.[12]

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12. New compounds were characterized by standard analytical techniques. $^{1}H$, $^{13}C$ NMR spectra are available upon request.