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A Highly Catalytic Asymmetric Conjugate Addition: Synthesis of the C14–C20 Fragment of Antibiotic TMC-151A, Siphonarienal and Siphonarienone

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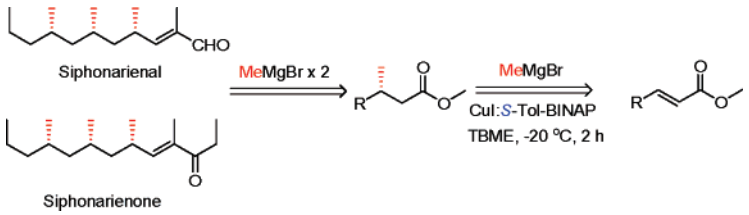
ABSTRACT



A highly selective and general method for the synthesis of enantiopure deoxypropionates via the iterative application of CuI-Tol-BINAP-catalyzed asymmetric conjugate addition is described. This method gives access to all possible stereoisomers since both *syn*- and *anti*-deoxypropionates were obtained in high diastereoselectivities. The usefulness of the method is further exemplified by the preparation of two marine organisms, siphonarienal and siphonarienone, from commercially available *trans*-2-hexenoate.

The enantiopure alternating methyl-substituted unit, or deoxypropionate, is a common recurring motif in many deoxygenated polyketide-type natural products.[1] Therefore, many methods have been developed for the synthesis of such compounds. Currently, most of the reported procedures are based on the use of chiral auxiliaries (enolate alkylations,[2] conjugate additions[3]), allylic substitutions,[4] or substrate control methods.[5] Catalytic asymmetric methods include Negishi's Zr-catalyzed carboalumination,[6] Burgess's Ir-catalyzed hydrogenation,[7] and Feringa's Josiphos-catalyzed conjugate addition (CA).[8] Conjugate addition of MeMgBr to simple and commercially available α,β-unsaturated esters is one of the most direct entries into these structural elements. In addition, not only are α,β-unsaturated esters easier to handle but also a larger scope of useful chemical transformations can be applied. In this paper, we report the iterative

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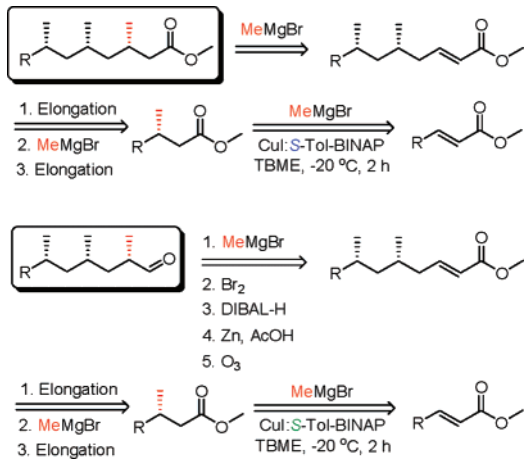
application of CuI-Tol-BINAP-catalyzed asymmetric CA of MeMgBr to commercially accessible α,β-unsaturated esters to access enantiopure deoxypropionate subunits, including the short synthesis of the C14−C20 subunit of antibiotic TMC-151A, two related marine natural products siphonarienal and siphonarienone starting from commercially available α,β-unsaturated esters.

A practical and efficient procedure for the enantioselective conjugate addition of Grignard reagents to α,β-unsaturated esters was previously developed.[9] To demonstrate the applicability and versatility of this synthetic strategy, we extended this method to an iterative sequence for the introduction of contiguous enantiopure methyl moieties into an acyclic carbon chain (Scheme 1).

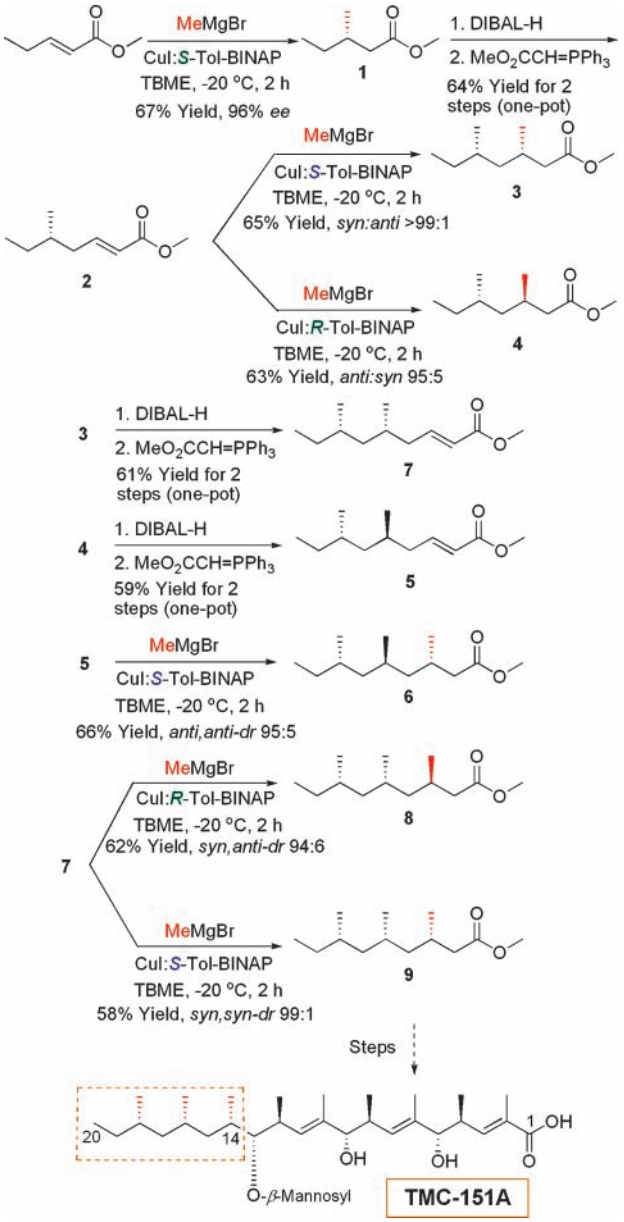
Scheme 1. General Route to Deoxypropionate Units



The first methyl stereogenic center was introduced from commercially available methyl *trans*-2-pentenoate using (*S*)-Tol-BINAP to give methyl ester **1** in 96% ee and 67% yield (Scheme 2).[9] A one-pot DIBAL-H reduction followed by Wittig olefination furnished a mixture of enoate isomers (*E*/*Z* 92:8) in 73% yield. Further chromatographic purification exclusively isolated the (*E*)-enoate **2** in 64% yield over two steps. The second methyl addition, under the same catalytic conditions, afforded the *syn*-deoxypropionate unit **3**[10] in more than 99:1 diastereoselectivity and 65% yield.

Use of the *R*-enantiomer of Tol-BINAP, under the same catalytic conditions, afforded the *anti*-deoxypropionate **4** in

Scheme 2. Synthesis of Deoxypropionate Units



95:5 diastereoselectivity and 63% yield. Thus, CA reactions of MeMgBr to α,β-unsaturated esters producing the 1,3-*syn*-stereochemistry appear to represent a "matched" case, while those producing the 1,3-*anti*-diastereoselectivity represent a "mismatched" case. It should be emphasized that even the mismatched CA reaction is highly selective, and the selectivity is governed almost exclusively by use of the appropriate enantiomer of Tol-BINAP ligand.

Further iterations of this sequence proceeded with similarly high diastereoselectivity. First, second stage elongation from methyl ester **4** via the same one-pot DIBAL-H reduction−

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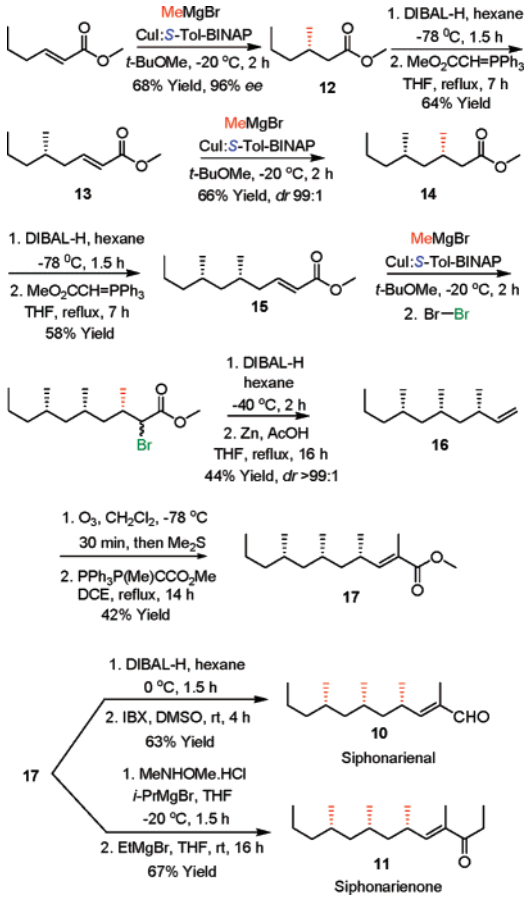
(10) (a) Assuming an analogous reaction mechanism, *syn*- and *anti*-stereochemistry were assigned on the basis of enantiomeric Tol-BINAP ligands selected in each methyl addition leading to the deoxypropionate units. (b) Diastereoselectivity was determined in ^{13}C NMR by comparing an average of carbon signals with respective diastereomeric mixtures of the deoxypropionate units. See Supporting Information for more details.

Wittig olefination protocol furnished the *anti*-enoate **5** in 59% yield. Third stage methyl addition to this *anti*-enoate **5** using (*S*)-Tol-BINAP gave the *anti*,*anti*-deoxypropionate **6** in 95:5 diastereoselectivity and 66% yield. Gratifyingly, the iterative use of appropriate CuI-Tol-BINAP catalytic systems allowed the access of *anti*,*anti*-deoxypropionate chirons in excellent stereoselectivity even though the 1,3-*anti*-stereochemistry was disfavored.

Likewise, from the *syn*-deoxypropionate methyl ester **3**, second stage elongation proceeded similarly via the one-pot DIBAL-H reduction−Wittig olefination protocol to afford the *syn*-enoate **7** in 61% yield. Third stage methyl addition to this *syn*-enoate **7** using (*R*)-Tol-BINAP furnished the *syn*,*anti*-deoxypropionate **8** in 94:6 diastereoselectivity and 62% yield. Use of the *S*-enantiomer of Tol-BINAP afforded the *syn*,*syn*-deoxypropionate **9** in 99:1 diastereoselectivity and 58% yield, which corresponds to the C14−C20 fragment of antibiotic TMC-151A[11] without the sugar moiety.

Siphonarienal **10** and siphonarienone **11** (Scheme 3) are

Scheme 3. Synthesis of Siphonarienal and Siphonarienone



members of siphonarienes, a class of deoxypropionates produced by Gastropod mollusks of the genus *Siphonaria* found in the Mediterranean Sea.[12] Since these marine natural products possess interesting biological properties, syntheses of them have been reported. The notable synthetic procedures include iterative aldol reactions using Evan's auxiliary[12b] and alkylations with Masamune's chiral benzopyranoisoxalidine.[13] The use of a chiral ketene dimer by Calter is noteworthy,[14] while Zr-catalyzed carboalumination developed by Negishi is also another useful method.[6d] More recently, an ex-chiral pool synthesis was also reported.[15] Encouraged by the excellent selectivity achieved previously in the *syn*,*syn*-deoxypropionate **9** subunit, we proceeded to apply the iterative use of CuI-Tol-BINAP-catalyzed asymmetric CA in the synthesis of siphonarienal and siphonarienone.

Flexibility of this synthetic route is enhanced with the incorporation of bromine, as the enolate trapping reagent in the third stage methyl addition, so as to allow a one-carbon dehomologation required in subsequent steps. Other useful transformations after the bromine enolate quenching step include the conversion of the terminal bromohydrin into epoxides and olefins for further useful transformations.

Starting from commercially available methyl *trans*-2-hexenoate, the first methyl stereogenic center was installed using (*S*)-Tol-BINAP to give methyl ester **12** in 96% ee and 68% yield (Scheme 3). After the one-pot DIBAL-H reduction−Wittig olefination protocol to (*E*)-enoate **13** (64% yield), the second stage methyl addition was performed under the same catalytic conditions to afford the *syn*-deoxypropionate unit **14** in more than 99:1 diastereoselectivity and 66% yield. The same elongation protocol furnished the second (*E*)-enoate **15** in 58% yield.

The third and final stage methyl addition using (*S*)-Tol-BINAP was modified by using neat bromine as an enolate-trapping reagent to effect the following one-carbon dehomologation. Without further purification, the α-bromomethyl ester obtained was reduced to the alcohol using DIBAL-H, and this reduced alcohol was used without further isolation for the next step. Treating this alcohol in THF with zinc dust and glacial acetic acid gave the terminal olefin **16** in 44% yield over three steps from the (*E*)-enoate **15**. The diastereoselectivity for the third stage methyl addition was more than 99:1 as determined in ^{13}C NMR by comparing this to a diastereomeric mixture of the same terminal olefin.

A one-pot ozonolysis and Wittig olefination protocol gave the α,*β*-unsaturated ester **17** in 42% yield over two steps. No epimerization of the third methyl stereogenic center was observed by comparing the ^{13}C NMR to a diastereomeric mixture of the same α,*β*-unsaturated ester. From the α,*β*-unsaturated ester **17**, a two-step DIBAL-H reduction and IBX oxidation furnished siphonarienal **10** in 63% yield

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over the two-step sequence. Likewise, from α,β-unsaturated ester **17**, the application of Weinreb's ketone synthesis using MeNHOMe·HCl with *i*-PrMgCl followed by treatment of the Weinreb amide with EtMgBr in THF gave sipharienone **11** in 67% yield over two steps. Spectral data of both compounds are in good agreement with those reported.[12c,15]

In summary, we have developed a highly selective and general method for the synthesis of enantiopure deoxypropionate units via the iterative application of CuI-Tol-BINAP-catalyzed asymmetric CA to simple and commercially available α,β-unsaturated esters. These results established the excellent diastereoselectivities of all desired configurations possible with this iterative protocol since both *syn*- and *anti*-deoxypropionates were obtained in high diastereoselectivities. This method is further exemplified by the preparation of the C14−C20 subunit of antibiotic TMC-151A, two marine organisms siphonarienal and siphonarienone, from commercially available *trans*-2-hexenoate. Further investigations will be directed toward understanding the mechanism, broadening the reaction scope, and applying the catalytic system in the total synthesis of other natural products.

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

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