Concise Synthesis of Reduced Propionates by Stereoselective Reductions Combined with the Kobayashi Reaction

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A concise and straightforward synthesis of 2,4,6-trimethyloctanoates was established by using the sequence of the vinylogous Mukaiyama aldol reaction and regio- and stereoselective reduction reactions. All isomers were obtained selectively in a few steps. The short step synthesis of septoriamycin A, an antimalarial and antileishmanial agent, has been achieved by this methodology.

Reduced polypropionates are frequently seen in natural products. A variety of synthetic methods have been developed to achieve the structures.¹ Some of them include

Scheme 1. Synthetic Plan to Reduced Propionates Using the Kobayashi Reaction

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iterative methods² while others involve multiple reactions in one pot by transition metal catalysts.³ The methods to realize the short step synthesis of the reduced polypropionates should be powerful tools to obtain bioactive

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compounds. In the search for efficient routes to the polypropionates, we have developed the vinylogous Mukaiyama aldol reactions using the chiral dienol ether 1^4 (the Kobayashi reaction, Scheme 1) and applied it to the syntheses of natural products.^{5,6} Since the vinylogous Mukaiyama aldol reaction gave the polypropionate skeleton **3** directly, the sequential regio- and stereoselective reductions of olefins would provide an efficient method to synthesize reduced polypropionate **4** (Scheme 1). This method is also applicable to the synthesis of deoxypropionate she because we have already succeeded in deoxygenation at the C5 position in the total synthesis of lagunamycin. Herein, we present the concise and stereochemically flexible synthesis of 2,4,6-trimethyloctanoates.

In the course of the total synthesis of actinopyrone A, we performed the vinylogous Mukaiyama aldol reaction with

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(7) Crystallographic data (excluding structure factor(s) for the structures of TBS ether 7) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 602830. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. [fax: +44(0)-1223-336033 or E-mail: deposit@ccdc.cam.ac.uk]. tiglic aldehyde **5** to give adduct **6** as a single isomer, which was determined by the absolute configuration by X-ray crystallography of TBS ether **7** (Scheme 2).^{5c,g} The ORTEP drawing in Figure 1^7 shows that the TBS group covers the one face of the olefins. Thus, hydrogenation of compound **7** would proceed from the face opposite to the TBS group to give 4,6-*anti* product **8** (Scheme 3). On the other hand, a cationic catalyst might promote hydrogenation directed by the hydroxyl group of the adduct **6**,⁸ which would produce 4,6-*syn* product **9** having another stereochemistry.







Figure 1. ORTEP drawing of the TBS ether 7.

Scheme 3. Suggested Stereochemical Courses toward 8 and 9



According to the hypothesis, we achieved the stereoselective synthesis of 2,4,6-trimethyloctanoates (Scheme 4).

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Scheme 4. Stereoselective Synthesis of 2,4,6-Trimethyloctanoates



Compound ent-6, the product of the vinylogous Mukaiyama aldol reaction using dienolate 1 and tiglic aldehyde 5, was submitted to hydrogenation using the Schrock-Osborn catalyst to give ent-9 selectively. After protection of the hydroxyl group as methoxymethyl ether, Birch reduction afforded the 2,4,6-syn compound 10 in high yield and stereoselectivity. On the other hand, ent-9 was submitted to hydrogenation using palladium on alumina, which proceeded in quantitative yield in a ratio of 1:6.7. The major product was 2,4-anti-4,6-syn product 11, which was isolated by column chromatography on silica gel in 87% yield. The stereoselectivity of these reductions is explained by using the models in Figure 2. In the Birch reduction, the intermediate enolate should be A including chelation of the alkali ion, of which the isopropyl group interfered with the protonation from the upper face to give all syn product 10. On the other hand, in the major conformation of *ent*-9, the carbonyl groups of the oxazolidone and imide would direct the opposite sides due to the dipole moment, which would make the isopropyl group of the chiral auxiliary covering the lower face of the double bond as **B**. Thus, the catalyst would approach from the opposite face of the isopropyl group to give 2,4-anti product 11 as a major product.

Next, TBS ether *ent-***7** was submitted to hydrogenation with a platinum catalyst, which proceeded regio- and stereo-selectively to give 4,6-*anti* product *ent-***8** as expected. Unsaturated imide *ent-***8** was submitted to Birch reduction to give 2,4-*syn* product **12**. The best result was obtained in the presence of bis(methoxyethyl)amine to give **12** in 71% isolated yield. Finally, hydrogenation of *ent-***8** proceeded to give reduced products in a ratio of 1:5.2, from which 2,4,6-*anti* product **13** was isolated in 81% yield. Therefore, all stereoisomers of 2,4,6-trimethyloctanoate were obtained stereoselectively in a short sequence consisting of the Kobayashi reaction and regio- and stereoselective reductions.



Figure 2. Proposed intermediate of the Birch reduction (A) and the conformation of the α , β -unsaturated imide moiety (B).

Upon establishing efficient methodology to construct 2,4,6-trimethyloctanoates, we applied it to the natural product synthesis (Scheme 5). Septoriamycin A has been isolated from the culture broth of plant pathogen Septoria pistaciarum as an antiplasmodial agent by Nanayakkara's group in 2010.9 Septoriamycin A was also reported to have potent antileishmanial activity in 2012.¹⁰ Herein, we present the first and efficient synthesis of septoriamycin A. As shown in Scheme 5, ent-9 was directly reduced by the Birch reduction, which was followed by lactonization under the acidic conditions to give δ -lactone 14 in good yield. Lactone 14 was obtained as crystals which allowed the X-ray crystallography to determine the configuration. DIBAL reduction afforded the corresponding lactol, which was submitted to the Knoevenagel condensation with pyridone 16^{11} in the presence of amine 15. The Knoevenagel condensation was followed by oxa-Michael addition in one pot, and this sequence directly gave

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Scheme 5. Synthesis of Septoriamycin A



septoriamycin A as a major compound of the separable mixture of C2 epimers in a ratio of 8:1. The synthetic septoriamycin A was identical in all respects with the natural product including the optical rotation (synthetic: $[\alpha]_D^{29} + 201^\circ$ (*c* 0.55, MeOH), natural: $[\alpha]_D^{26} + 201^\circ$ (*c* 0.4, MeOH)). Thus, septoriamycin A was synthesized in 35% over six steps from silyl dienol ether **1**.

In conclusion, we established the concise and straightforward synthesis of 2,4,6-trimethyloctanoates by a sequence that includes the vinylogous Mukaiyama aldol reaction and regio- and stereoselective reduction reactions. All isomers were obtained selectively in a few steps. Allylic olefin underwent catalytic hydrogenation in a stereoselective manner. Additionally, we achieved the synthesis of septoriamycin A using this methodology with minimal steps. The present method is effective to synthesize polypropionates. Natural product syntheses using this methodology are in progress in our laboratory.

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Supporting Information Available. The experimental procedure and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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