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Iterative Direct Aldol Strategy for Polypropionates: Enantioselective Total Synthesis of (−)-Membrenone A and B

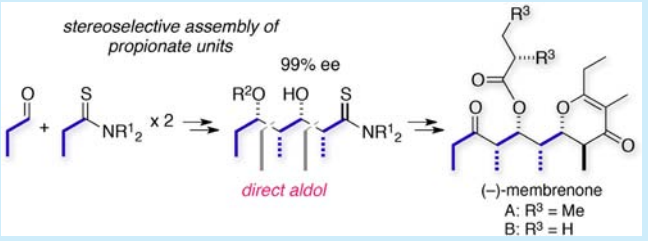
Kaliyamoorthy Alagiri,[†] Shaoquan Lin,[†] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†,‡]

[†]Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

[‡]JST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

Supporting Information

ABSTRACT: An iterative direct aldol reaction using a C3 propionate unit as an aldol donor offers expeditious access to polyketide assembly in a highly diastereo- and enantioselective manner. An all-*syn* polyketide array with four consecutive stereogenic centers was efficiently constructed by an aldol reaction of thiopropionamide via soft Lewis acid/hard Brønsted base cooperative catalysis. This iterative aldol strategy led to an enantioselective synthesis of (−)-membrenone A and B.



Membrenones A−C are marine natural products with a hexapropionate architecture with a polysubstituted γ-dihydropyrone core (Figure 1). These products were isolated

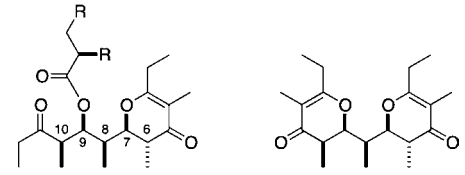
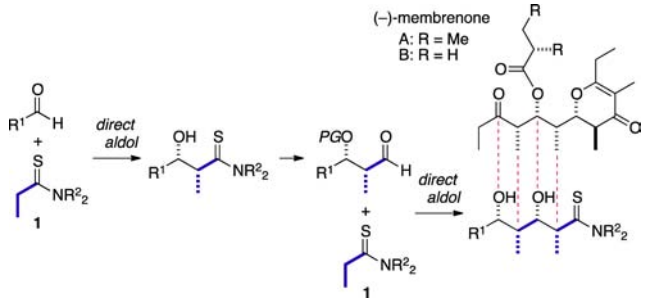


Figure 1. Structures of natural membrenones A−C with the proposed absolute configuration.

from the skin of the Mediterranean mollusc *Pleurobranchus membranaceus* by Ciavatta et al. in 1993.[1] Membrenones were considered as defense secretions to protect vulnerable soft-bodied molluscs against hostile predators. The scarcity of these products has hampered systematic biological studies. The five consecutive stereogenic centers (C6−10) initially presented an ambiguous stereochemistry, but a systematic stereoselective synthesis by Sampson and Perkins confirmed the relative configurations and revealed an inconsistency in the originally assigned optical rotation.[2] Although the absolute configuration remains unsubstantiated due to the unavailability of the natural material, the accumulated data indicate that the natural membrenones are (+)-enantiomers with the absolute stereochemistry depicted in Figure 1.[3] Ward et al. reported a stereocontrolled synthesis of (−)-membrenone B by a sequential assembly of thiopyran units through an aldol reaction, followed by desulfurization.[4,5] The stereogenic propionate array of these natural products attracted our attention as synthetic targets to showcase our direct aldol protocol.[6] Herein we report the enantioselective synthesis of (−)-membrenone A and B by an iterative use of direct catalytic asymmetric aldol reaction developed by our group. The unavailability of the natural material limits biological studies, which led us to devise a synthetic route that can be applied to the synthesis of both natural membrenones and their antipodes. A direct catalytic asymmetric aldol reaction of thiopropionamide **1** allows for efficient stereoselective construction of the *syn*-propionate unit, and both enantiomers can be produced by changing the sense of the available chiral ligands with similar cost (Scheme 1).

Scheme 1. Iterative Direct Aldol Strategy for the Construction of the Propionate Array



Thioamide bearing a longer alkyl chain can be used as an aldol donor to furnish elongated derivatives. Facile transformation of the thioamide functionality to aldehyde allowed for seamless entry into the second direct aldol reaction to furnish four consecutive stereogenic centers.

The "direct" catalytic asymmetric aldol reaction is characterized by the direct use of an aldol donor substrate without preformation of an active enolate species, allowing for a truly

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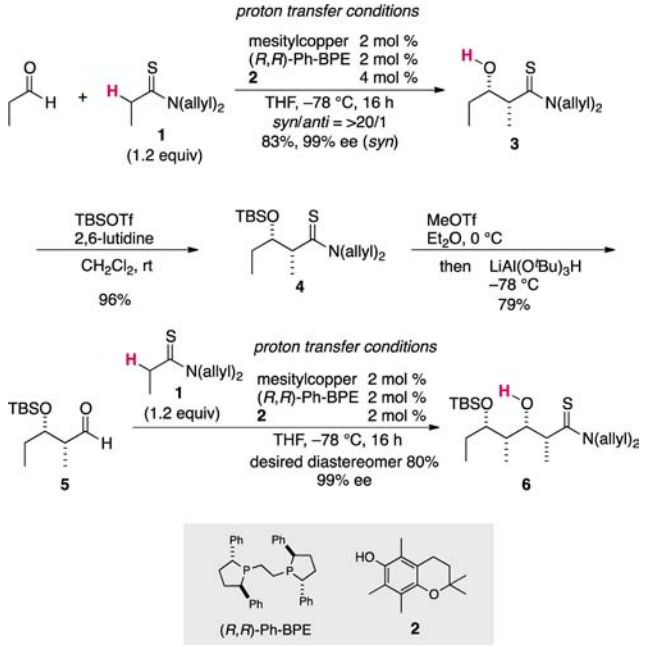
catalytic protocol to afford enantioenriched aldol products with perfect atom economy.[7,8] Chemoselective and catalytic enolization of aldol donors in the presence of fairly enolizable aldehydes (as an aldol acceptor) is indispensable to initiate the reaction, which severely limits the scope of compatible aldol donors. As part of our continuing studies of the direct aldol reaction, we reported that soft Lewis acid/hard Brønsted base cooperative catalysis is a viable strategy to enable chemoselective enolization of soft Lewis basic aldol donors.[9] Thiopropionamide **1** serve as an efficient aldol donor to undergo chemoselective enolization, and a subsequent aldol reaction with propanal by a cooperative catalyst comprising mesitylcopper, (*R*,*R*)-Ph-BPE, and 2,2,5,7,8-pentamethylchromanol (**2**), exclusively producing the *syn*-aldol adduct **3** among four possible isomers (Scheme 2).[6,10,11] The thioamide functionality of **3** was transformed into

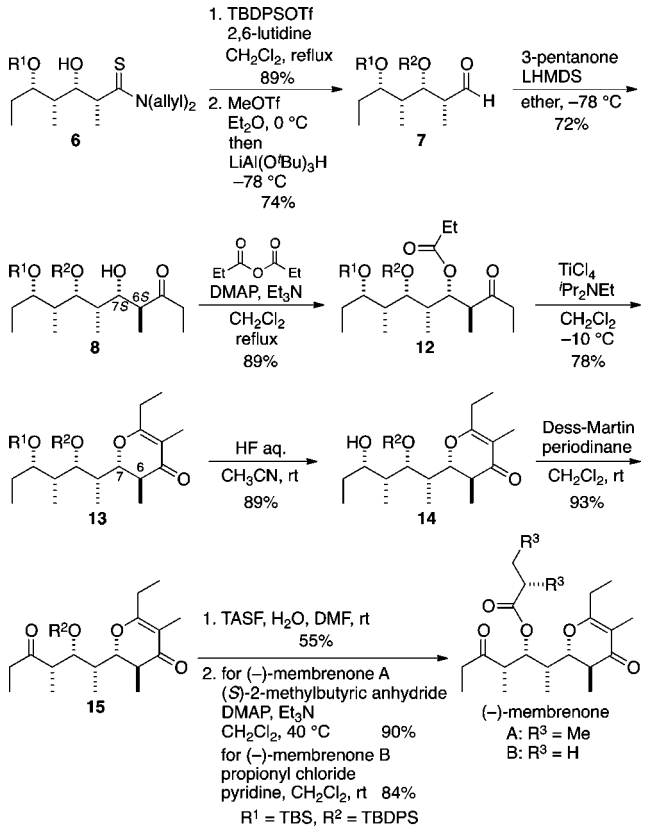
Scheme 2. Iterative Direct Catalytic Asymmetric Aldol Reaction To Construct Tripropionate Unit 6 Bearing Consecutive Four Stereogenic Centers



an aldehyde for the second aldol reaction. After protecting the secondary alcohol by TBS under conventional conditions, thioamide was activated by *S*-methylation with MeOTf.[12] The intermediary iminium thioether was highly electrophilic, and subsequent treatment with $LiAl(O^tBu)_3H$ afforded the aldehyde **5**.[13] The second aldol reaction using sterically congested aldehyde **5** proceeded smoothly with a 2 mol % catalyst loading, affording the desired tripropionate unit **6** bearing four consecutive stereogenic centers in 80% yield with 99% ee.[14] Minor diastereomers were observed in ca. 10% and readily separated by chromatography.

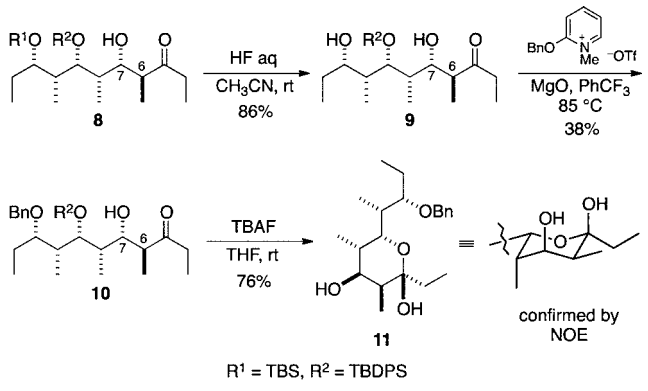
With **6** in hand via the iterative aldol protocol, further elongation was pursued to construct the requisite γ-pyrone unit for the total synthesis of (−)-membrenone A and B (Scheme 3). Aldehyde **7** bearing a TBDPS protecting group at the β-hydroxyl group was selected because the analogous bis-TBS-protected aldehyde is prone to β-elimination under the basic conditions of the aldol reaction to give α,β-unsaturated aldehyde. TBDPS-protected **7** was more resistant to elimination and worked well under the screening of aldol reaction conditions with 3-

Scheme 3. Synthesis of (−)-Membrenone A and B



pentanone as an aldol donor. Various attempts of Lewis acid mediated aldol reactions featuring stereoinduction resulted in particularly little conversion, presumably due to the steric hindrance of the TBDPS group. Employment of organocatalysts barely led to scarce production of aldol adducts. The Felkin−Anh model suggested that the aldol addition preferentially delivered the desired 7*S* stereochemistry.[15] Therefore, simple Li enolate conditions were attempted with various solvents. Although the reaction using LHMDS in THF produced mixtures of diastereomers, less coordinative solvents gave the preferred formation of the diastereomer **8**, and ether solvent was optimal to obtain **8** in 72% yield. The absolute configurations of the newly formed stereogenic centers of **8** were determined to be the desired 6*S*,7*S* after derivatization, as outlined in Scheme 4.[16] Treatment with aqueous HF in acetonitrile allowed for selective removal of the TBS group, and subsequent protection

Scheme 4. Stereochemical Determination of 8



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by a benzyl group with Dudley's reagent gave **10**.[17] Deprotection of the TBDPS group of **10** by TBAF led to the spontaneous formation of cyclic ketal **11** as a single diastereomer, which allowed us to confirm the desired stereochemistry at C6 and C7 by NOE experiments.[18] Given the unequivocal stereochemistry of the six consecutive stereogenic centers of **8**, further transformation toward (−)-membrenone B was pursued. A propionyl group was installed to a free hydroxyl group to give the cyclization precursor **12**, which gave rise to γ-pyrone **13** by following the reported procedure.[3a,19] Treatment with aqueous HF removed the TBS group, leaving the TBDPS group untouched, and subsequent oxidation by Dess-Martin periodinane gave **15**.[20] Replacement of the TBDPS group with the requisite acyl group was performed with TASF-mediated deprotection and acylation, affording (−)-membrenone A and B with spectroscopic data identical to those previously reported.[2c,4]

In conclusion, we demonstrated that iterative use of the direct aldol reaction of a thiopropionamide is a powerful strategy for furnishing the polyketide array in a highly stereocontrolled manner. The requisite catalyst was readily prepared from commercial sources, and facile reduction of the thioamide functionality of the aldol adduct delivered the corresponding aldehyde to engage the subsequent aldol reaction. Biological studies of the synthetic (−)-membrenone A and B, and further application of the iterative aldol reaction in enantioselective polyketide synthesis, will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nkumagai@bikaken.or.jp.
*E-mail: mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

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(13) While **5** tended to partly epimerize under chromatographic conditions with silica gel, applying the sample on SiO_2 with cooling prevented epimerization. See Supporting Information for details.

(14) Standard conditions included the use of equimolar amounts of mesitylcopper, (*R*,*R*)-Ph-BPE, and **2**. Using a 2-fold excess of **2** led to a marginal increase in stereoselectivity in the first aldol reaction.

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