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Stereoselective total synthesis of preclavulone-A methyl ester and its diastereomer

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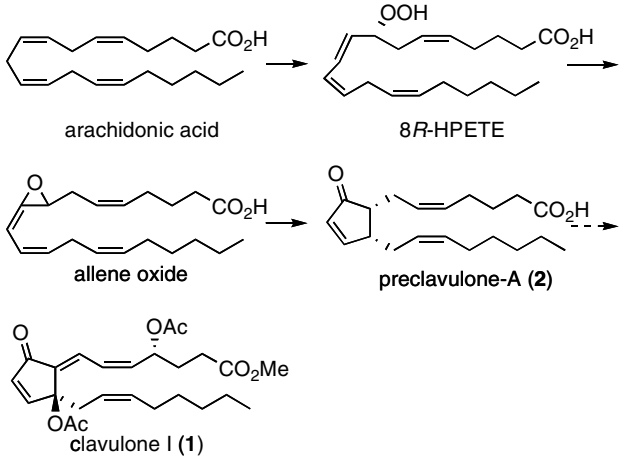
Abstract—The total synthesis of preclavulone-A methyl ester and its diastereomer was achieved from same key intermediate in diastereoselective manner. These compounds are recognized as important intermediates in a proposed biosynthesis of marine prostanoids from the Okinawan soft coral, *Clavularia viridis*, and were recently isolated from the extract of *C. viridis* by our group.

Clavulones[1] (claviridenones[2]) exemplified by clavulone I (**1**) and related marine prostanoids, isolated from the Okinawan soft coral *Clavularia viridis*, have received much attention owing to their structural features, significant biological activities, and unique biosynthesis. Corey et al. proposed a biosynthetic pathway of clavulones starting from oxidation of arachidonic acid by lipoxygenase (LOX) through (8*R*)-HPETE, allene oxide and preclavulone-A (**2**) as shown in Scheme 1.[3]



Scheme 1. Biosynthetic pathway of clavulones proposed by Corey et al.

This biosynthesis was based on experimental results showing that preclavulone-A was obtained by treating labeled arachidonic acid as well as labeled (8*R*)-HPETE with the cell-free extract or acetone powder prepared from *C. viridis*, although the absolute configuration of preclavulone-A (**2**) could not be determined due to its small amount. The *trans* diastereomer of preclavulone-A (epipreclavulone-A) was also obtained in this biosynthetic experiment, but its absolute configuration was not determined.

Very recently, the authors found small amounts of preclavulone-A and its diastereomer (epipreclavulone-A) each as a methyl ester, **4** and **3** (Fig. 1), from the methanol extract of *C. viridis*.[4] Interestingly, both compounds **4** and **3** were found to be an enantiomeric mixture (**4**: 8% ee, **3**: 46% ee) from the HPLC analysis using a chiral column. Although the preclavulone-A derivatives **3** and **4** were previously synthesized by Corey et al. (**4**: enantiomerically pure form)[5] and Traverso et al. (**3**: racemic form),[6] stereocontrolled synthesis of **3** and **4** as an enantiomerically pure form was required to

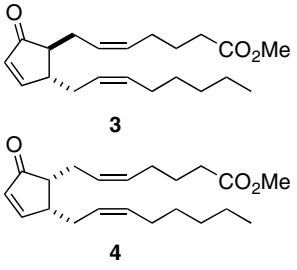


Figure 1.

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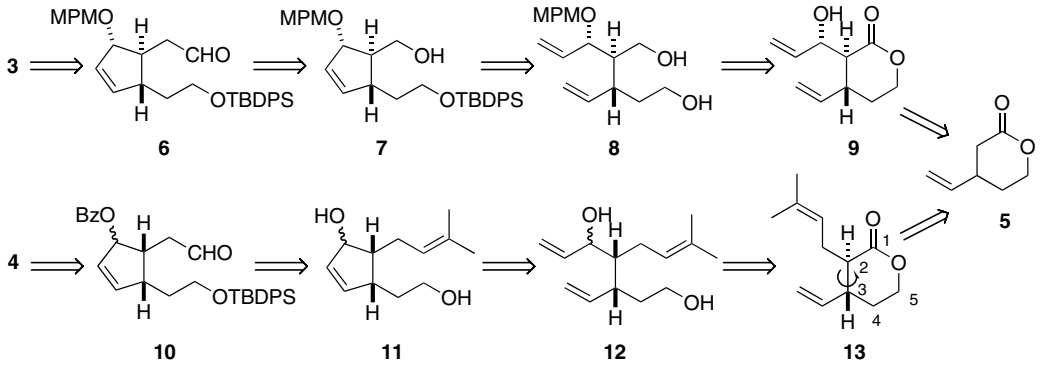
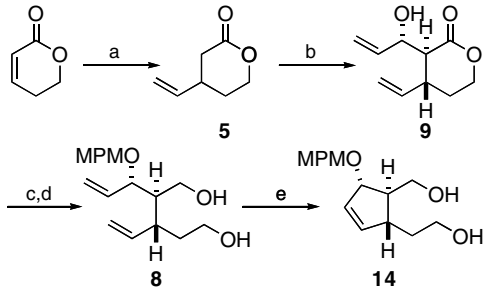


Scheme 2. Retrosynthetic pathway of compounds **3** and **4**.

establish the stereochemistry of natural compounds and to clarify the detailed stereochemical course of the biosynthesis of clavulones. We have developed a new efficient method for the synthesis of (±)-**3** and (±)-**4** in a highly stereoselective manner via the common intermediate **5**.

Our retrosynthetic pathway for compounds **3** and **4** is outlined in Scheme 2. The α- and ω-chains of compounds **3** and **4** could be constructed from the corresponding aldehyde by Wittig reaction with high *Z*-selectivity. So, it is important to prepare the compounds **6** and **10** in a highly diastereoselective manner. For the synthesis of the cyclopentene ring of *trans*-isomer **6**, ring-closing olefin metathesis was employed. The precursor **8** was synthesized from compound **9**, which has a *trans* relationship between the vinyl group at the β-position and the 1-hydroxyallyl group at the α-position of the lactone, prepared from **5** through diastereoselective Mukaiyama aldol reaction. On the other hand, compound **10** could be prepared from **12** through ring-closing olefin metathesis of two terminal vinyl groups and selective oxidative cleavage of the tri-substituted carbon–carbon double bond of **11**. Compound **12** could be prepared from compound **13**, which has a *trans* relationship between the vinyl group and the α-substituent. Therefore, another vinyl group for ring-closing metathesis was introduced to the C-1 position on the lactone **13**, and the rotation of the C2–C3 bond of the reduction product from **13** gave compound **12**, which has the desired stereochemistry for the preparation of compound **10**. The prenyl group having tri-substituted carbon–carbon double bond was employed as a precursor of the α-chain because it was useful for the site-selective ring-closing metathesis and following oxidative cleavage by using *m*CPBA and periodic acid for the preparation of compound **10**.

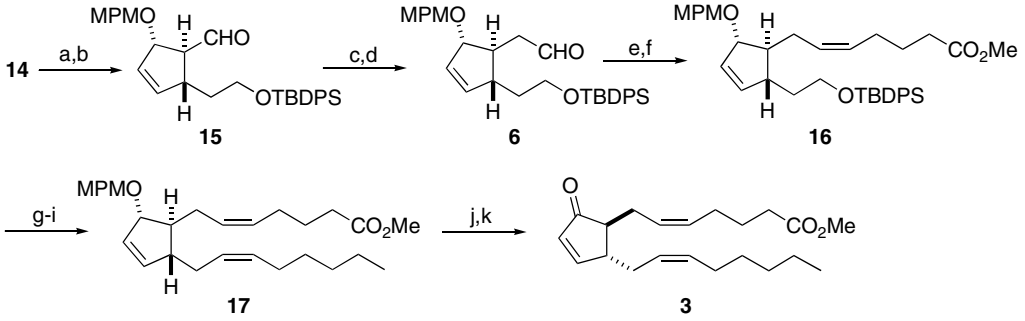
The synthesis of compound **3** was carried out as follows. Vinyl lactone **5**, which was prepared by the copper(I) iodide-catalyzed 1,4-addition of vinylmagnesium chloride to 5,6-dihydro-2*H*-pyran-2-one, was subjected to diastereoselective Mukaiyama aldol reaction using dibutylboron triflate[7] with acrolein to give compound **9** as a single diastereomer (Scheme 3). In the transition state for the aldol reaction of boron enolate, the electrophile would come from another site of the vinyl



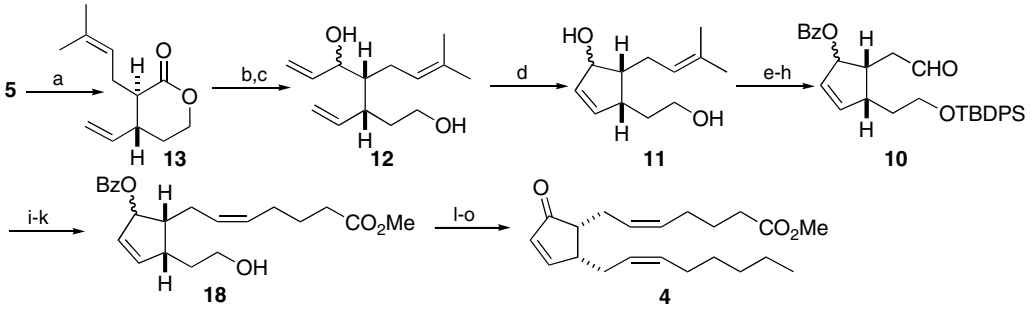
Scheme 3. Reaction conditions: (a) vinylMgCl, CuI, THF, −78 °C, 69%; (b) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, then acrolein, −78 to 0 °C, 61%; (c) *p*-methoxybenzyl trichloroacetimidate, camphorsulfonic acid, CH_2Cl_2, 0 °C–rt; (d) $LiAlH_4$, ether, rt, 2 steps 49%; (e) first Grubbs catalyst, toluene, 50 °C, 76%.

group on the β-position of the carbonyl group and the *trans* isomer could be obtained with high diastereoselectivity.[8] For the construction of the cyclopentene ring, ring-closing metathesis of **9** using first generation Grubbs catalyst[9] was examined, but the desired product could not be obtained. Therefore, after the protection of the allylic hydroxyl group by the *p*-methoxybenzyl group, the lactone was reduced with $LiAlH_4$ to give **8**. The ring-closing olefin metathesis of compound **8** gave cyclopentene derivative **14** having two hydroxyalkyl groups in good yield.

For the synthesis of the *trans* isomer, one-carbon elongation of the hydroxymethyl group was crucial (Scheme 4). After selective protection of the hydroxyl group on the ω-chain of **14** by TBDPSCl, the hydroxyl group on the α-chain was oxidized to the aldehyde by Dess–Martin periodinane. Wittig reaction of **15** by the use of (methoxymethyl)triphenylphosphonium chloride with *n*-BuLi and following hydrolysis of the resulting enol ether gave compound **6**. Wittig reaction of **6** with the ylide prepared from (4-carboxybutyl)triphenylphosphonium bromide with NaHMDS proceeded in a *Z*-selective manner exclusively followed by methylation to afford **16** (the minor isomer could not be detected). After the construction of the ω-chain by using *Z*-selective Wittig reaction (hexyltriphenylphosphonium bromide with NaHMDS, the minor isomer could not be detected), the following deprotection and oxidation of



Scheme 4. Reaction conditions: (a) TBDPSCl, imidazole, DMF, rt, 40%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (c) $Ph_3P^+Cl^-CH_2OMe$, *n*-BuLi, THF, rt; (d) TsOH, acetone, rt, 2 steps 50%; (e) $Ph_3P^+Br^-(CH_2)_4CO_2H$, NaHMDS, THF, rt, 76%; (f) CH_2N_2, ether, 0 °C, 90%; (g) TBAF, THF, rt, 99%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 89%; (i) $Ph_3P^+Br^-(CH_2)_5CH_3$, NaHMDS, THF, rt, 87%; (j) DDQ, CH_2Cl_2–H_2O, rt, 95%; (k) Dess–Martin periodinane, CH_2Cl_2, rt, 98%.



Scheme 5. Reaction conditions: (a) lithium bis(trimethylsilyl)amide, 1-bromo-3-methyl-2-butene, THF, −78 °C, 94%; (b) DIBAL-H, ether, −78 to 20 °C, 94%; (c) vinylMgCl, THF, 0 °C–rt, 91%; (d) second generation Grubbs catalyst, CH_2Cl_2, rt, 64%; (e) TBDPSCl, triethylamine, DMAP, CH_2Cl_2, 0 °C, 90%; (f) benzoyl chloride, pyridine, DMAP, CH_2Cl_2, 0 °C, 65%; (g) *m*CPBA, CH_2Cl_2, 0 °C, 80%; (h) HIO_4, H_2O, *t*-BuOH, rt, 99%; (i) $Ph_3P^+Br^-(CH_2)_4CO_2H$, NaHMDS, THF, 0 °C–rt, 76%; (j) CH_2N_2, ether, 0 °C, 90%; (k) TBAF, THF, 0 °C–rt, 98%; (1) Dess–Martin periodinane, CH_2Cl_2, rt, 99%; (m) $Ph_3P^+Br(CH_2)_5CH_3$, NaHMDS, THF, −78 °C–rt, 98%; (n) KCN, MeOH, rt, 88%; (o) MnO_2, CH_2Cl_2, rt, 95%.

the hydroxyl group on the cyclopentene ring gave the desired *trans* isomer **3** (Scheme 5).

The examination of the stereoselective synthesis of *cis* isomer **4** (preclavulone-A methyl ester) was as follows. Two chiral centers of **4** were constructed diastereoselectively through the α-alkylation of compound **5** by employing 1-bromo-3-methyl-2-butene. The reaction proceeded to give compound **13** as a single diastereomer in 94% yield.[10] After conversion of the compound **13** to **12**, the ring-closing metathesis of **12** was examined by the use of first generation Grubbs catalyst. The reaction, however, proceeded for one diastereomer and the other one was recovered. So, we employed second generation Grubbs catalyst[11] and compound **11** was obtained as a diastereomeric mixture in 64% yield. After selective protection of two hydroxyl groups with TBDPSCl and benzoyl chloride, the site-selective oxidative cleavage of the tri-substituted carbon–carbon double bond was achieved to give compound **10**. Stereoselective construction of both side chains was achieved in the same manner as mentioned for the synthesis of the *trans* isomer through the Wittig reaction. At the final stage, the use of Dess–Martin periodinane for the oxidation of the cyclopentenol moiety to the enone caused epimerization and gave the *trans* isomer as a major product. This step was successful by the use of manganese and the compound **4** was obtained as a single stereoisomer. The NMR data and the chiral HPLC behavior (CHIRALCEL OD) for both isomers of synthetic racemic preclavulone-A methyl esters were in good accordance with those of natural products.[4]

In conclusion, total synthesis of (±)-preclavulone-A methyl ester and its diastereomer [(±)-epipreclavulone-A methyl ester] was achieved in a stereoselective manner from the common intermediate **5**. The preparation of compound **5** as an enantiomerically pure form for the enantioselective total synthesis of **3** and **4** will be reported in due course.

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