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Enantioselective Total Synthesis of (+)-Tricycloclavulone

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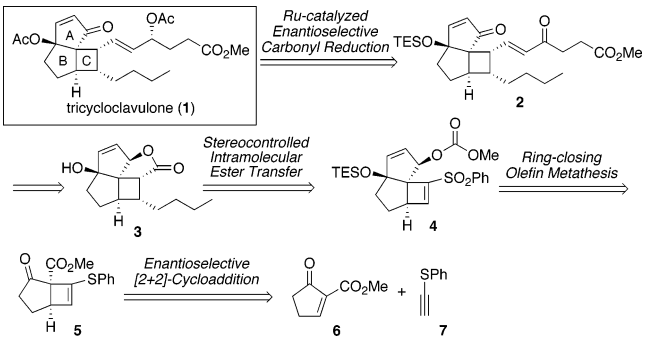
Marine natural products have received much attention for their attractive structural features and biological activities.[1] Since the isolation of clavulone I, about 40 related marine prostanoids were isolated from Okinawan soft coral *Clavularia viridis*.[2] Many of these compounds have antiproliferative activities in human cancer cell lines. Tricycloclavulone (**1**), which has a tricyclo[5.3.0.0^{1,4}]-decane skeleton, was recently isolated as an abnormal marine prostanoid from *C. viridis* by our group.[3] Although its planar structure and the relative stereochemistry of the chiral centers on the tricyclic core in **1** were determined by spectroscopic analysis, the stereochemistry of the carbon bearing the acetoxy group on the α-chain as well as the absolute stereochemistry have not yet been examined. In addition, tricycloclavulone (**1**), possessing a highly functionalized and strictly fixed 5,5,4-ring system, is a quite attractive synthetic target for organic chemists. The diverse structural features of **1** in conjunction with its potential for biological activity have stimulated our considerable interest. We report herein the first enantioselective total synthesis of (+)-tricycloclavulone (**1**).[4]

Our strategy for the total synthesis of tricycloclavulone (**1**) as an optically active form focused on the use of an enantioselective [2+2]-cycloaddition reaction catalyzed by a novel catalyst and sequential addition of an *ω*-chain and an α-chain to establish the stereogenic centers on the C-ring with complete control of the stereochemistry through an intramolecular ester transfer reaction (Scheme 1). The strictly fixed tricyclic system would efficiently work to shield the concave face of the C-ring. Therefore, the introduction of both side chains could be carried out on the convex face in a highly diastereoselective manner. From a retrosynthetic perspective, we envisioned the construction of the tricyclic ring system at an early stage for the total synthesis.

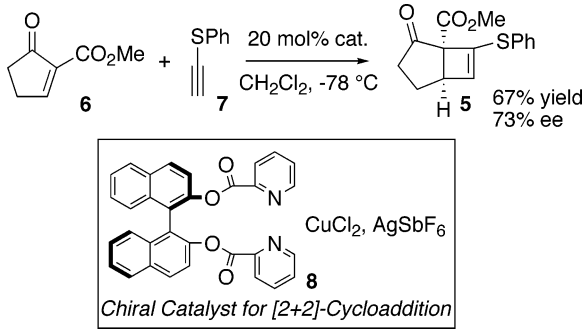
An efficient synthesis of the tricyclic system[4] was developed by starting from 2-methoxycarbonyl-2-cyclopenten-1-one (**6**)[5] and phenylthioacetylene (**7**)[6] via a chiral Lewis acid-catalyzed enantioselective [2+2]-cycloaddition reaction (Scheme 2).[7] Our initial effort for developing an enantioselective [2+2]-cycloaddition by using known chiral catalysts (Ti-TADDOL,[8] Cu-BOX[9]) gave unsatisfactory results. Therefore, we examined the development of an efficient catalytic system for the reaction of **6** with **7**. As shown in Scheme 2, a novel catalyst prepared from simple chiral bis-pyridine ligand **8** and copper salt accelerated the reaction of **6** with **7** and gave bicyclic intermediate **5**[10] with 73% ee in 67% yield.

The synthesis of the tricyclic core was improved over that of our reported procedure[4] by the use of second generation Grubbs catalyst (Scheme 3). The bicyclic compound **5** was converted to **9** by five steps. The construction of the tricyclic ring system from **9** using first generation Grubbs catalyst[11] was examined under several conditions, but the desired compound was not obtained because of the steric hindrance around both vinyl groups on compound **9**. Thus, the ring-closing metathesis of desilylated compound of **9** proceeded

Scheme 1. Synthetic Plan of Tricycloclavulone (**1**)



Scheme 2. Enantioselective [2+2]-Cycloaddition Reaction



to give a tricyclic compound in 94% yield.[4] On the other hand, second generation Grubbs catalyst[11] was employed, and the reaction of **9** proceeded to give a tricyclic compound in satisfactory yield.

To achieve the total synthesis of **1**, the development of an efficient constructive method for the side chains was very important. Our efforts for the stereoselective introduction of both side chains to the tricyclic core are shown in Scheme 3. For the protection of the α,*β*-unsaturated ketone moiety on the A-ring, the carbonyl group on the A-ring was stereoselectively converted to a hydroxyl group with DIBAL-H[12] to give **12** (diastereomeric ratio was 3.8:1). Although other reducing agents were also examined, undesired 1,4-reduction on the A-ring and/or the reduction of the vinyl sulfone moiety proceeded. Stereoselective introduction of the *ω*-chain was easily achieved by treatment of **12** with *n*-butyllithium in 92% yield. This result encouraged us to construct both side chains in a one-pot reaction. Therefore, the capture of the anion on the carbon bearing the sulfone, which was generated after the 1,4-addition of *n*-butyllithium, was examined. When the capture of the anion intermolecularly by using some electrophilic reagents (aldehydes or acid halides) was examined, only hydroxymethylation by using formaldehyde proceeded, albeit in unsatisfactory yield. So, we planned to incorporate a carbon electrophile into the hydroxyl group on the A-ring for the introduction of the α-chain by an intramolecular ester transfer reaction.[13] Methoxycarbonylation of the

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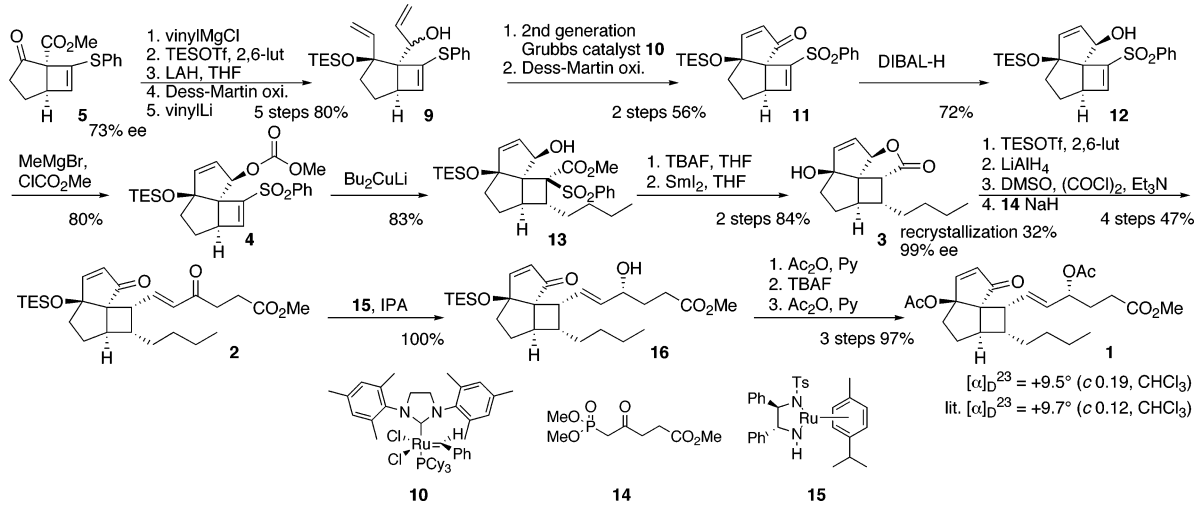
Scheme 3. Total Synthesis of (+)-Tricycloclavulone



sterically hindered hydroxyl group was achieved by employing methylmagnesium bromide as a base followed by addition of methyl chloroformate to afford **4** in 80% yield. The stereoselective 1,4-addition of the ω-chain by dibutylcopper lithium followed by the intramolecular ester transfer reaction succeeded to give compound **13** as a single stereoisomer in 83% yield. Stereoselective preparation of **3** was achieved through deprotection of the TES group and subsequent intramolecular lactonization followed by treatment of SmI_2 for the reductive desulfonylation.[14] Recrystallization of compound **3** was examined to increase the optical purity, and twice recrystallization gave compound **3** as an almost optically pure form (99% ee). Elongation of the α-chain was achieved as follows. The lactone was reduced with $LiAlH_4$ to give a diol. Oxidation of the diol was successful by employing Swern oxidation to afford a keto aldehyde in 74% yield. The Wittig−Horner−Emmons reaction of keto aldehyde with 5-(dimethoxyphosphoryl)-4-oxopentanoic acid methyl ester (**14**)[15] gave compound **2** in 72% yield. Enantioselective reduction of the carbonyl group on the α-chain of **2** with chiral ruthenium catalyst **15** developed by Noyori et al.[16] proceeded to give **16** in a highly diastereoselective manner (11:1, major isomer had the same stereochemistry as natural product **1**). The absolute configuration of the hydroxyl group on the α-chain was determined by the Kusumi−Kakisawa method.[17] Acetylation of **16**, desilylation, followed by acetylation completed the enantioselective total synthesis of (+)-tricycloclavulone (**1**). The spectral data (^1H, ^{13}C, and Ms) and $[\alpha]_D$ value of synthetic tricycloclavulone were identical to those of natural **1**.[3]

In conclusion, the first enantioselective total synthesis and determination of the complete stereochemistry of (+)-tricycloclavulone were achieved through an enantioselective [2+2]-cycloaddition reaction with a novel catalyst, ring-closing olefin metathesis, sequential addition of an α- and an ω-chain through a stereocontrolled intramolecular ester transfer reaction, and enantioselective reduction of the carbonyl group with a chiral ruthenium catalyst. The results of the biological assay of **1** and the details of the catalytic enantioselective [2+2]-cycloaddition reaction will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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