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Total Synthesis of (+)-Chinensiolide B via Tandem Allylboration/Lactonization

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α-Methylene γ-lactones are privileged structures present in a large number of natural products displaying a wide scope of biological activities.[1] The chinensiolides constitute a family of guaiane type α-methylene γ-lactone natural products with a tricyclic 5,7,5-ring system (Figure 1). The various members of the chinensiolide family were recently isolated from *Ixeris chinensis Nakai*,[2,3] a plant used in Chinese folk medicine. Chinensiolide B (**1**) has been shown to display cytotoxic behavior against human primary liver cancer (HepG2) and human lung fibroblast (WI-38 and VA-13) cell lines.[4] The activity of **1** against HepG2 is comparable to that of paclitaxel; however, its selectivity remains to be explored.

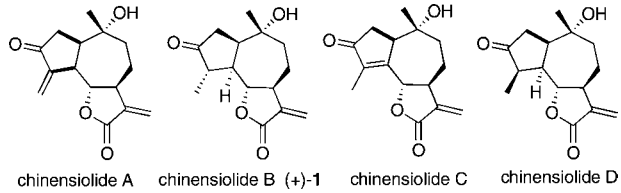


Figure 1. Structures of chinensiolides A−D.

No total synthesis of any of the chinensiolides has been reported to date. The challenge of chinensiolide B is alluring. It contains six contiguous stereocenters, including five along a flexible seven-membered ring,[2] and the sixth stereocenter may be subject to epimerization due to a neighboring ketone. The α-methylene γ-lactone itself is a reactive center, and reactions carried out after its installation must be carefully optimized to avoid possible side reactions. Keeping these potential pitfalls in mind, a retrosynthetic analysis suggested that (+)-**1** could be accessed via regioselective reductive opening of epoxide **2** (Figure 2). The latter intermediate would arise from a desilylation/elimination followed by a chemoselective ring-closing metathesis and diastereoselective epoxidation of **3**. Precursor **3** would be produced directly from the key tandem allylboration/lactonization reaction between carvone-derived aldehyde **4** and allylboronate **5**, which would be made in three steps from 4-pentyn-1-ol.

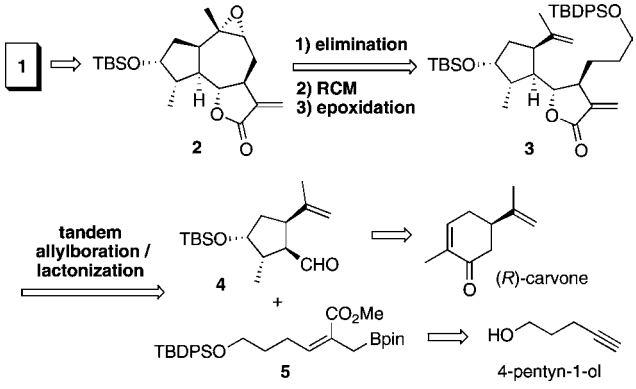
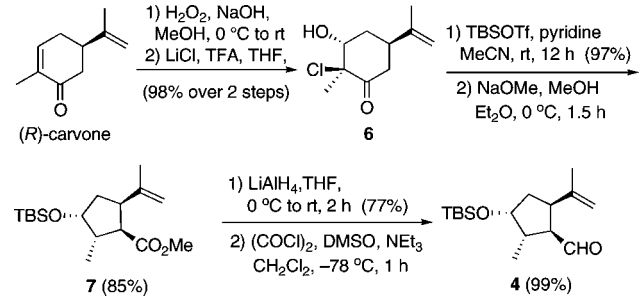


Figure 2. Retrosynthetic analysis of chinensiolide B (+)-**1**.

Substituted α-methylene γ-lactones can be assembled in one step via a thermal, Lewis, or Brønsted acid catalyzed addition of 2-alkoxycarbonyl allylboronates to aldehydes in tandem with lactonization.[5] This attractive process has never been applied to substrates as densely functionalized as **4** and **5**, and the critical issue of diastereofacial selectivity is unclear. Moreover, early introduction of the reactive α-methylene γ-lactone is risky due to potential chemoselectivity issues later on in the sequence. Regardless, it was expected that aldehyde **4** would arise from (*R*)-carvone via a Favorskii rearrangement. This enantioselective route would provide an opportunity to confirm the absolute configuration of natural chinensiolide B.

The synthesis began with a two-step protocol reported by Ley and co-workers to convert carvone into ketone **6**[6] (Scheme 1). Using ketone **6**, protection of the secondary alcohol was followed by a Favorskii rearrangement[6] to provide the desired tetrasubstituted cyclopentane **7** in an excellent yield of 85%. The ester was fully reduced and then reoxidized under Swern conditions[7] to provide aldehyde **4**. Converting 4-pentyn-1-ol into allylboronate **5** was achieved by standard literature protocols.[8−10] Unfortunately, **5** could only be prepared as a mixture of alkene isomers (*Z*/*E* ratio of ∼3.5:1) and these isomers could not be separated on a gram scale. As a result, the isomeric mixture was employed in the allylboration of aldehyde **4**.

Scheme 1



With the two key fragments **4** and **5** in hands, the key tandem allylboration/lactonization step was attempted. After much experimentation with thermal and catalytic methods, it was found that using 2.5 mol % of $BF_3 \cdot OEt_2$ at 0 °C for 48 h provided *trans* γ-lactone product **3** in a remarkable yield of 87% (based on the amount of *Z*-**5**) (Scheme 2). The observed diastereoselectivity (>95% dr) was surprising since four isomers could be expected from this reaction. Indeed, the reaction was *E*/*Z*-selective as allylboronate *E*-**5** proved to be essentially inert to the reaction conditions. The *trans* diastereoselectivity in the allylboration step can be explained with the usual six-membered chairlike transition state of this reaction. The remarkable diastereofacial selectivity on aldehyde **4** can be rationalized according to the Felkin model shown in Scheme 2, with the large vinyl-bearing carbon placed opposite to the approach of reagent **5**.

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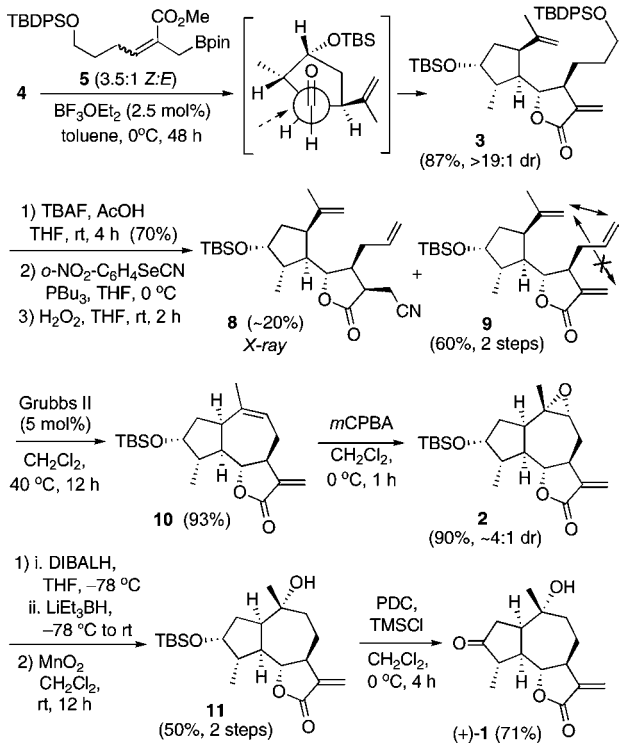
Scheme 2



Selective deprotection of the primary TBDPS group[11] on **3** was followed by a Grieco elimination[12] of the primary alcohol to afford desired triene **9**, albeit with only a moderate yield of 60% for the two steps. Careful control of the stoichiometry of both reagents was important to minimize formation of byproduct **8** where the cyanide anion had undergone conjugate addition to the enoate.[10] Fortuitously, byproduct **8** proved to be crystalline and allowed for X-ray crystal structure[13] confirmation of the allylboration's stereoselectivity. Formation of medium rings by RCM can be problematic when the final alkene is tri- or tetrasubstituted.[14] In spite of our apprehension, a chemoselective RCM of triene **9** using 5 mol % of Grubbs II catalyst provided the desired tricycle **10** in high yield. Most likely, steric bulk around the lactone's α-methylene unit and formation of a bridgehead olefin helped suppress closure to the possible tetrasubstituted six-membered enoate, allowing the desired RCM pathway to proceed uncontested. The final stage of the synthesis involves the diastereoselective epoxidation of this newly formed alkene in **10**. Nucleophilic epoxidation reagents could not be used due to the electrophilic nature of the α-methylene γ-lactone. Satisfactorily, treatment of **10** with *m*CPBA gave epoxide **2** as an unseparable 4:1 mixture of diastereomers favoring the desired one. Regioselective opening of epoxides to give Markovnikov products is typically achieved through the use of nucleophilic hydride reagents.[15] However, with **2**, over-reduction of the γ-lactone occurred with $LiAlH_4$ to give the fully saturated triol and conjugate reduction of the α-methylene group took place preferentially to epoxide opening with $LiEt_3BH$. What proved ultimately successful was a one-pot double reduction protocol whereby the γ-lactone moiety of **2** was first reduced to the diol with DIBALH, and then $LiEt_3BH$ was added to regio- and chemoselectively open the epoxide. This unusual protocol allowed for protection of the α-methylene γ-lactone group from undergoing conjugate addition with the highly reactive $LiEt_3BH$. Simple treatment of the crude triol with MnO_2 easily reformed the α-methylene γ-lactone. The two diastereomers originating from the epoxidation could now be separated to provide the desired γ-lactone **11**. Finally, oxidative cleavage of the secondary TBS protecting group[16] was achieved in one step to reveal the ketone, thus completing the total synthesis.[17]

This first enantioselective total synthesis of (+)-chinensiolide B (**1**) was achieved in 15 steps for the longest linear sequence with an overall yield of 6.7% starting from inexpensive and readily available (*R*)-carvone. The absolute configuration of the chinensiolides is thus confirmed. A highly stereoselective and *E*/*Z*-selective tandem allylboration/lactonization reaction between two highly functionalized partners was exploited as a key step. The synthesis also highlights several solutions to chemoselectivity issues arising from the reactive α-methylene γ-lactone. For instance, ring-closing metathesis formed the requisite seven-membered ring chemoselectively while avoiding the reactivity of the conjugated α-methylene unit.

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Supporting Information Available: Full experimentals and NMR spectral reproductions for all compounds, and complete ref 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystallographic data (excluding structure factors) for the structure of **9** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-756958. Copies of the data can be obtained in the SI. (cif file) or via www.ccdc.cam.ac.uk/data_request/cif.
(14) For example, see: (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784. (b) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6571–6758.
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(17) The NMR spectral data and the optical rotation of synthetic **1** were in full agreement with that of natural chinensiolide B (+)-**1**.[3,9] We thank Prof. M. Ando for supplying a copy of the ^{1}H NMR spectrum of isolated (+)-**1**. As it has been shown that (+)-**1** obtained from the natural source can be converted into chinensiolide C in three steps, this total synthesis of **1** also constitutes a formal total synthesis of chinensiolide C in 18 steps for the longest linear sequence.

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