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COMMUNICATION

Stereoselective construction of the tetracyclic core of Cryptotrione†

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An efficient stereoselective approach to the tetracyclic core of Cryptotrione, involving an asymmetric Michael addition, ring-closing metathesis, and subsequent cyclopropanation, is described.

Cryptotrione (**1**) (Fig. 1), isolated by Kuo and coworkers in 2010 from the bark of *Cryptomeria japonica*, contains a unique 5-membered spirocycle fused with a cyclopropane and has been shown to possess anticancer activity against KB cells (IC_{50} = 6.44 ± 2.23 μM).[1,2] The promising biological activity and interesting structure of Cryptotrione make it an attractive synthetic target. The left-hand 6-membered fused tricyclic structures are present in a number of naturally occurring compounds, and their syntheses have been reported.[3] However, the right-hand 5-membered spirocycle fused with a cyclopropane is very rare in isolated natural products. Herein we wish to report an asymmetric approach to the right-hand tetracyclic core of Cryptotrione (**2**) (Scheme 1).

Our retrosynthetic analysis of the tetracyclic fragment is illustrated in Scheme 1. Compound **2** was envisioned to form *via* cyclopropanation of alkene **3**, which could be constructed by ring-closing metathesis of diene **4**. Compound **4** could be prepared from diester **5** *via* reduction, oxidation, and Wittig reaction. The quaternary stereocenter of diester **5** could be formed by asymmetric Michael addition of β-keto ester **6**.[4]

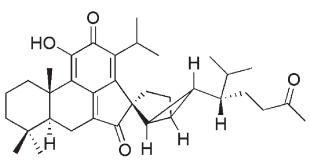

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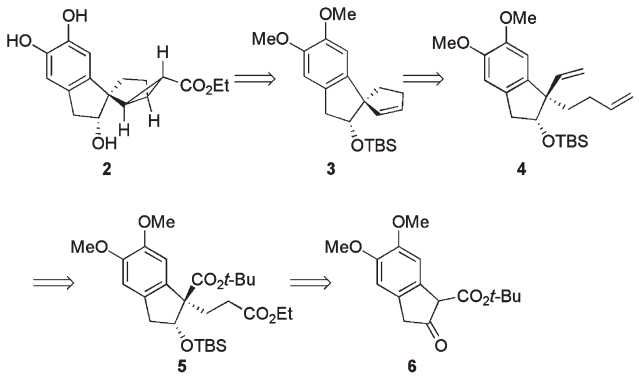
Fig. 1 Structure of Cryptotrione.



Scheme 1 Retrosynthetic analysis of Cryptotrione core.

The synthesis of 5-membered spirocycle **3** is shown in Scheme 2. The quaternary stereogenic center of compound **7** was constructed from β-keto ester **6** *via* an asymmetric Michael addition with slight modification of the reported methods.[5] After various screenings, quinine derived catalyst **8**[6] was found to be the best choice, giving compound **7** with 72% yield and 90% ee in $CHCl_3$ at 25 °C with 10 mol% catalyst.[7] The ketone in **7** was reduced with $(n\text{-Bu})_4NBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ in EtOH at −78 °C,[8] affording alcohol **9** in 72% yield and >10 : 1 dr. Addition of $CeCl_3{\cdot}7H_2O$ was found to be very important for both reactivity and diastereoselectivity of the reduction. Diol **10** was obtained from **9** *via* protection with TBSCl and DIBAL-H reduction.[9] Then compound **10** could be converted to diene **4** by Swern oxidation and Wittig olefination in 54% yield over two steps.[10] Spirocycle **3** was readily formed in 91% yield at rt *via* ring-closing metathesis with the second-generation Grubbs catalyst.[11] It is worth mentioning that the initial reduction of the ketone in **7** and TBS protection were important for the subsequent functional groups manipulations. The ketalization of the ketone was unsuccessful. When the ketone was protected as TBS enol ether, a messy mixture was obtained during the subsequent Swern oxidation step.

As outlined in Scheme 3, the cyclopropanation of spirocycle **3** was achieved with ethyl diazoacetate, 2.5 mol% $(CuOTf)_2{\cdot}PhH$, and 5.5 mol% ligand **12** in CH_2Cl_2 at 25 °C, giving compound **11** in 93% yield with >10 : 1 dr.[12] It was found that slow addition of ethyl diazoacetate *via* syringe pump was important for the high yield. Compound **11** was finally converted to compound **2** by deprotection of the TBS group with TBAF (88% yield) and methyl groups with BBr_3 (79% yield).[13]

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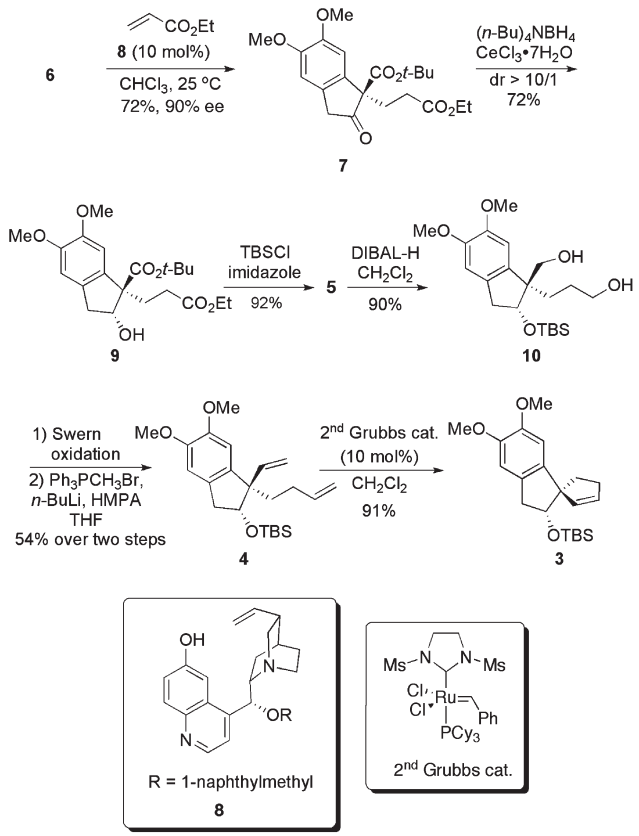
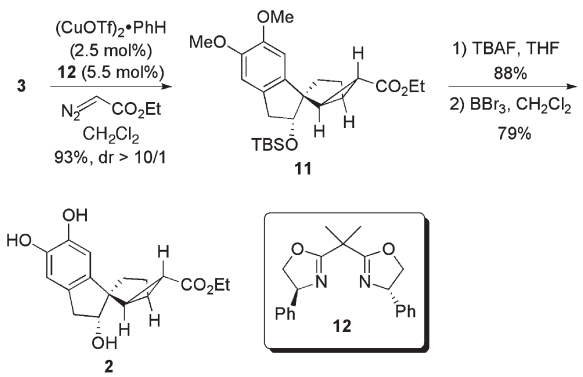
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and X-ray structure of **15** along with NMR spectra. CCDC 881889. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25923k



Scheme 2 Synthesis of compound **3**.

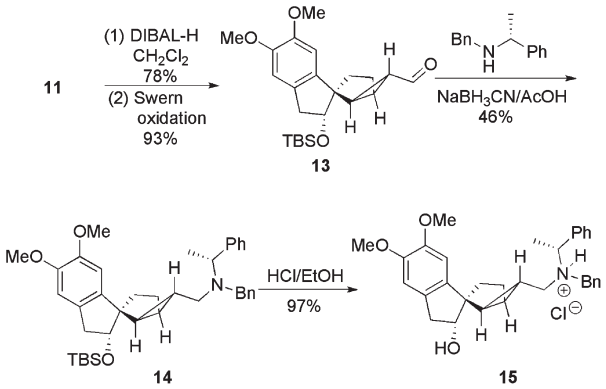


Scheme 3 Synthesis of compound **2**.

After many attempts, the X-ray structure was finally obtained for ammonium salt **15**, derived from compound **11** and (*R*)-(+)-*N*-benzyl-1-phenylethylamine (Scheme 4), which allows the determination of the absolute configuration of the synthesized spiro tetracyclic structure (Fig. 2).

Conclusion

In summary, we have developed a stereoselective strategy to construct the right-hand tetracyclic core of Cryptotrione. The key steps involve an asymmetric Michael addition to form the quaternary stereocenter, ring-closing metathesis to achieve the spirocycle, and copper-catalyzed stereoselective cyclopropanation to construct the fused cyclopropane. The absolute configuration of the core was determined by X-ray structure. The application of this strategy to the total synthesis of Cryptotrione and its derivatives as well as biological activity studies are currently under way.



Scheme 4 Synthesis of compound **15**.

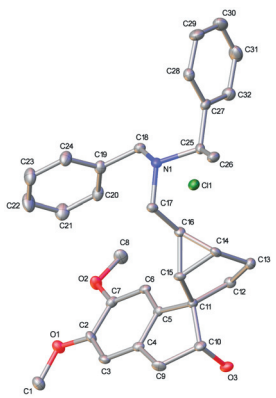


Fig. 2 The X-ray structure of compound **15**.

Acknowledgements

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