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Synthetic studies on (−)-scabronine A

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Abstract

This Letter describes synthetic studies on (−)-scabronine A utilizing a new chiral building block successfully prepared via the catalytic asymmetric intramolecular cyclopropanation (IMCP) of an α-diazo-β-keto sulfone. The crucial transformations in this study are the coupling reaction of two fragments between the positions adjacent to a quaternary carbon center, the intramolecular aldol reaction, the C14 hydroxyl-directed hydrogenation, and the ring-expansion reaction to furnish the 5-6-7 tricyclic cyathane skeleton.

(−)-Scabronine A (**1**) (Fig. 1) was isolated from the mushroom *Sarcodon scabrosus* with some congeners[1] and recognized to be a potent stimulator of nerve growth factor (NGF) synthesis. It has attracted medicinal interest because NGF synthesis stimulators have been expected to serve as medicine for degenerative neuronal disorders such as Alzheimer's disease and to aid in peripheral nerve regeneration.[2]

The structure of **1** was elucidated by NMR techniques,[1a] and the absolute structure was unambiguously confirmed by the single X-ray crystal structure analysis of its derivative.[1b] The disclosed structure features a novel tetracyclic structure with eight stereogenic centers incorporating the cyathane skeleton. Comparing it with the other members of the cyathane family, we can note that its different structural features are a hemiacetal formed between the C14 hydoxyl and C15 aldehyde, two methoxy groups at C11 and C13, and the C17 carboxyl group, which is a methyl group in the usual cyathane system.

The promising bioactivity and fascinating structure described above prompted us and other groups to start synthetic studies of **1**,[3] and herein, we report the enantioselective synthesis of the enantiopure 5-6-7 tricyclic synthetic intermediate for the total synthesis of **1** via the convergent approach utilizing a new chiral building block developed by us.[3a,g,4,5a]

We envisioned that the two methoxy groups at C11 and C13 could be installed after the construction of the 5-6-7 tricyclic skeleton of **1**. As the alkene in the A-ring of **2** (Scheme 1) could be isomerized to the more substituted position in the later stage, our retrosynthetic analysis of **1** generated **2** as the key intermediate for the total synthesis of **1**. Then, we reasoned that **2** would be generated from **3** via the one-carbon ring-expansion, and a C5–C6 trans junction in **3** could be constructed by the C17 or C14[6] hydroxyl-directed stereoselective hydrogenation of the compound derived from **4**, which would be obtained from **5** via the installation of an isopropyl group. Ketone **5** could be prepared via the intramolecular aldol reaction of diketone **6** and subsequent dehydration, and **6** was expected to be obtained via the coupling reaction of **7** with **8**. Although a preparation of iodide **7** was previously reported

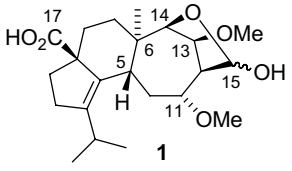

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Fig. 1. Structure of (−)-scabronine A (**1**).

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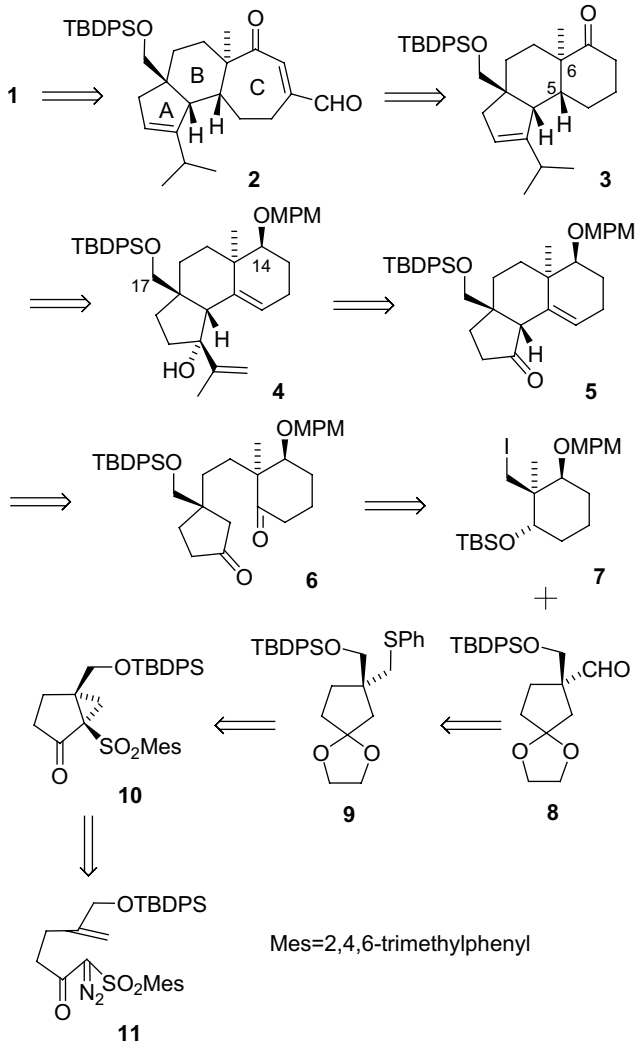
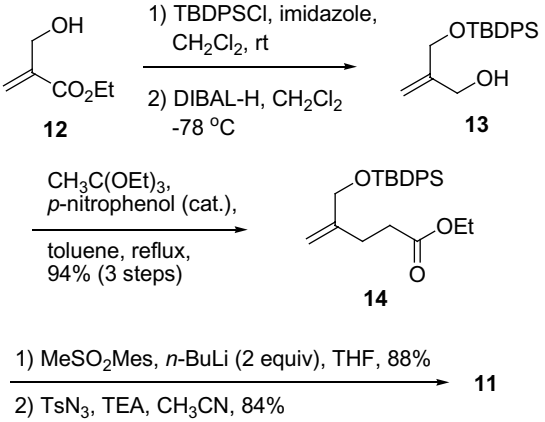


Scheme 1. Retrosynthetic analysis of (−)-scabronine A (**1**).

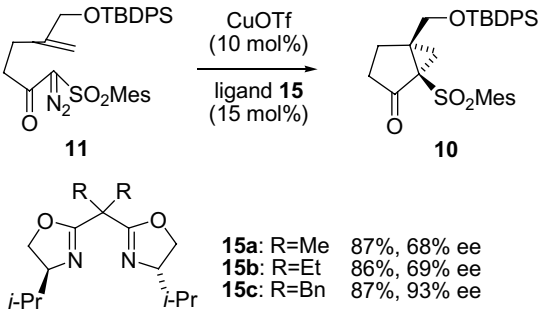
by us,[3a] **8** was a new chiral compound; hence, a new preparation method for **8** was required. We thought that chiral **8** would be obtained via Pummerer rearrangement of **9**, which could be derived from cyclopropane **10**, which in turn could be generated by the catalytic asymmetric intramolecular cyclopropanation (IMCP) of **11** developed by us.[5] As the protecting group for the hydroxyl in **11**, we selected a TBDPS group because a bulky TBDPS group could prevent the hydroxyl oxygen from forming the oxonium ylide when the metal carbene complex was generated in situ, thereby allowing cyclopropane to form in high yield.

Preparation of **11** started with forming the TBDPS ether of ethyl 2-hydroxymethylpropenoate (**12**) (Scheme 2),[7] which was reduced with DIBAL-H to provide alcohol **13**. Claisen rearrangement of **13** using a triethyl orthoacetate under acidic conditions provided **14** (94%, three steps), followed by reaction with a dianion of mesityl methyl sulfone to afford the corresponding β-keto sulfone (88%), which was subjected to the diazotransfer reaction to furnish **11** (84%).

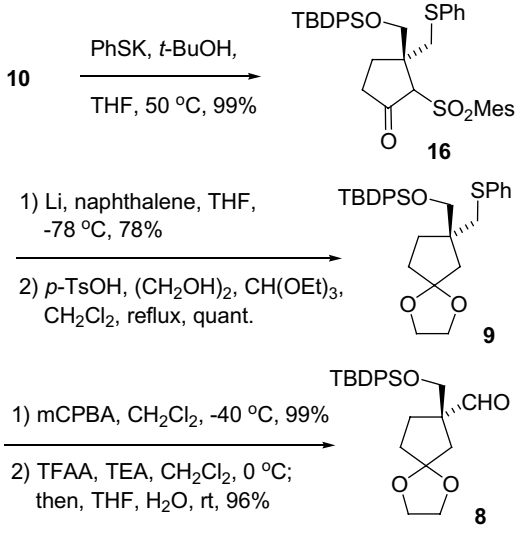


Scheme 2. Preparation of **11**.

The catalytic asymmetric IMCP of **11** was examined under the reported conditions optimized for the reactions of the α-diazo-β-keto sulfones similar to **11**.[5a] Thus, the IMCP of **11** with CuOTf and ligand **15a–c** was studied (Scheme 3), and ligand **15c** was found to be most effective, providing **10** in 87% yield with excellent selectivity (93% ee).[8]



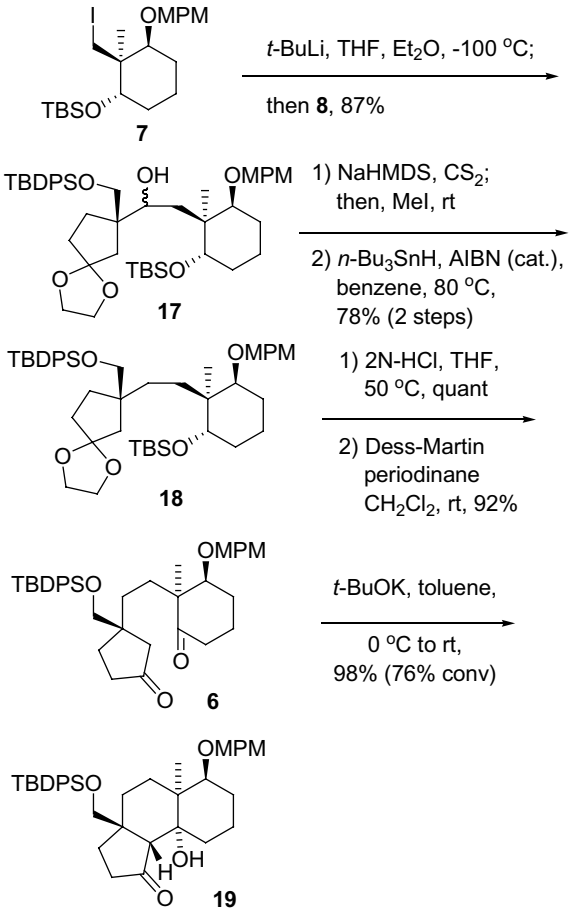
Scheme 3. Catalytic asymmetric IMCP of **11**.



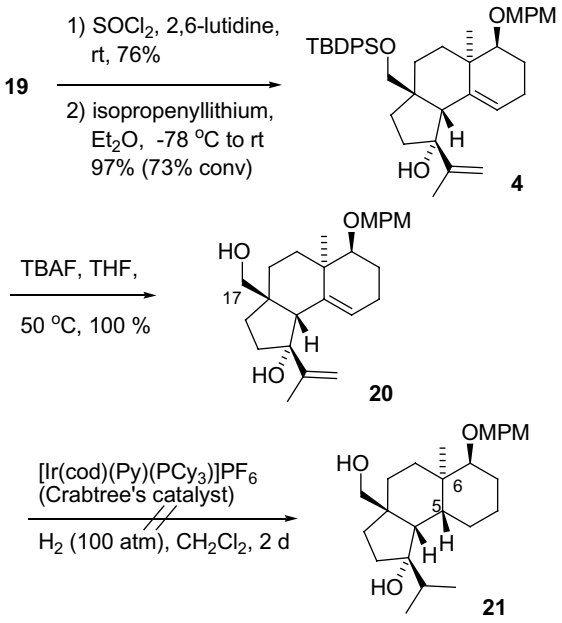
Scheme 4. Enantioselective synthesis of **8**.

This result sufficed for the study of the next step, and further elaboration of **10** to **8** was examined (Scheme 4). The ring-opening reaction of cyclopropane **10** was attained with potassium thiophenoxide to provide **16** as a mixture of diastereomers (99%), followed by desulfonation with lithium naphthalenide (78%) and ethylene ketal formation to provide **9** (quant). Oxidation of **9** with mCPBA to the corresponding sulfoxide (99%) and subsequent Pummerer rearrangement successfully provided aldehyde **8** in excellent yield (96%).

With two fragments, **7** and **8**, in hand, their coupling reaction was executed (Scheme 5). Although this reaction was expected to be sluggish because the reacting point in both the fragments is adjacent to a quaternary carbon, the optimized conditions shown in Scheme 5 provided **17** in 87% yield. Alcohol **17** was converted to the methyl xanthate and subsequent tinhydride reduction afforded **18** (78%, two steps). The TBS and ketal groups in **18** were simultaneously removed under the acidic conditions (quant), and following Dess–Martin oxidation provided diketone **6** (92%). Various reaction conditions for the intramolecular aldol reaction of **6** were surveyed, but a substantial amount of **6** remained in most cases. However, the use of *t*-BuOK in toluene was found to provide **19** in 98% yield (76% conv), furnishing the 5-6-6 tricyclic skeleton.[3a,g]

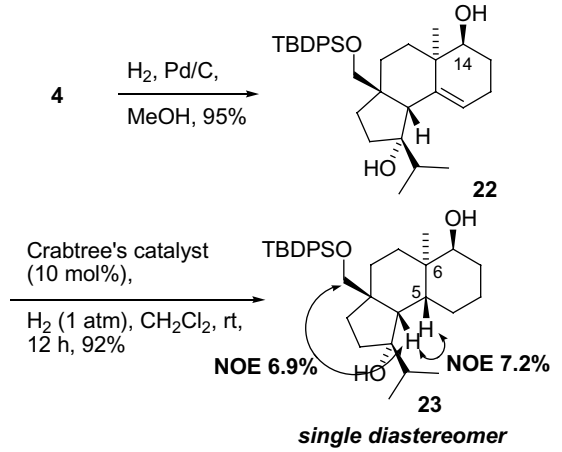


Scheme 5. Synthesis of **19** via the coupling reaction of **7** with **8** and the intramolecular aldol reaction of **6**.



Scheme 6. Installation of the isopropyl group and attempted construction of the C5–C6 trans junction via the C17 hydroxyl-directed hydrogenation of **20** by the use of Crabtree's catalyst.

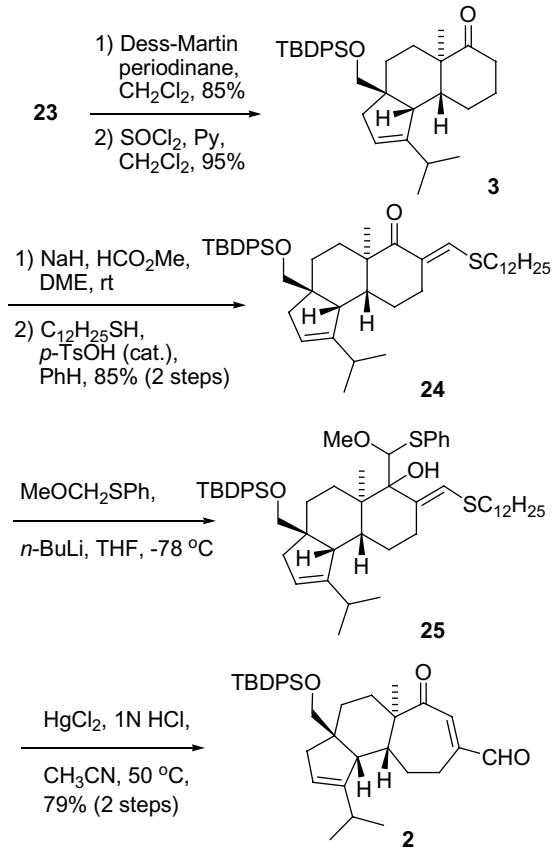
To establish the C5–C6 trans stereochemistry, we first attempted the C17 hydroxyl-directed hydrogenation of **20** (Scheme 6). To prepare **20**, **19** was dehydrated with thionyl chloride and 2,6-lutidine (76%),[9] and the resultant β,γ-unsaturated ketone **5** was reacted with isopropenyllithium to provide **4** (97%, 73% conv) because the alkenes in the product were expected to be hydrogenated at the same time. The TBDPS group in **4** was removed using TBAF to afford **20** (100%), which was subjected to the hydroxyl-directed hydrogenation by the use of Crabtree's catalyst;[10] however, although the isopropenyl group was hydrogenated, the trisubstituted alkene remained intact even under the high pressure conditions.



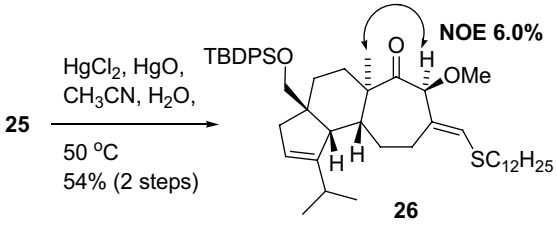
Scheme 7. Construction of the C5–C6 trans junction via the C14 hydroxyl-directed hydrogenation of **22** by use of Crabtree's catalyst.

As preparation of **21** from **20** failed, we next examined the C14 hydroxyl-directed hydrogenation (Scheme 7). Thus, **4** was subjected to the Pd-mediated catalytic hydrogenation to remove the MPM group by converting the isopropenyl group to the isopropyl group, providing **22** (95%). The hydrogenation of **22** with Crabtree's catalyst (10 mol %) under atmospheric pressure successfully provided **23** as the sole product (92%), and the C5–C6 trans stereochemistry of **23** was confirmed by NOE experiments.

It is worth noting that no reaction was observed in the hydrogenation of **22** with Pd/C, Pt_2O, or Rh/Al_2O_3 even under the high pressure conditions (80 atm) at room temperature after 12 h. These results indicated that the C14 hydroxyl group accelerated the hydrogenation of **22** with Crabtree's catalyst. Compared with the hydrogenation of **20**, the C14 secondary hydroxyl of **22** is in pseudoaxial position; hence, it would inevitably direct Crabtree's catalyst to the desired π-face of the alkene of **22**, resulting in the exclusive formation of **23**.



Scheme 8. Synthesis of the 5-6-7 tricyclic intermediate **2**.



Scheme 9. Conversion of **25** to **26** possessing a β-methoxy group at C13.

The remaining task was the one-carbon ring-expansion of a six-membered ring in **23** to generate the seven-membered C-ring in **2** (Scheme 8). To this end, we employed Guerrero's method[11] because it can convert a cyclohexanone to a β-formyl-α,β-unsaturated cycloheptenone, which is incorporated in the structure of **2**. Hence, **23** was converted to ketone **3** via Dess–Martin oxidation (85%) and subsequent dehydration (95%). Then, ketone **3** was formylated and subsequent treatment with a thiol[12] under the acidic conditions provided alkenyl sulfide **24**. Reaction of **24** with a methoxy(phenylthiomethyl)lithium provided **25** as a mixture of diastereomers, which was treated with $HgCl_2$ under the acidic conditions productively caused the ring-expansion reaction to furnish the desired ketoaldehyde **2** incorporating the 5-6-7 tricyclic cyathane skeleton.[13]

Furthermore, the reaction of **25** with $HgCl_2$ under another condition shown in Scheme 9[14] provided **26** with a methoxy group at the C13 position.[13] NOE experiments on **26** indicated that the reaction in Scheme 9 correctly constructed the stereochemistry of C13 position.

In conclusion, a new chiral building block was successfully prepared via the catalytic, asymmetric, intramolecular cyclopropanation with high ee and was effectively utilized in this synthetic study. The C5–C6 trans junction was stereoselectively constructed via the C14 hydroxyl-directed hydrogenation using the Crabtree's catalyst. The crucial one-carbon ring-expansion of the 5-6-6 tricyclic compound to the 5-6-7 tricyclic compound with a cyathane skeleton was productively achieved employing Guerrero's procedure. In addition, preparation of the more advanced intermediate possessing a methoxy group at the C13 with correct stereochemistry was achieved. Further, synthetic studies leading to the convergent total synthesis of (−)-scabronine A is now being pursued and will be reported in the future.

Acknowledgments

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