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Asymmetric Total Synthesis of (−)-Scabronine G via Intramolecular Double Michael Reaction and Prins Cyclization

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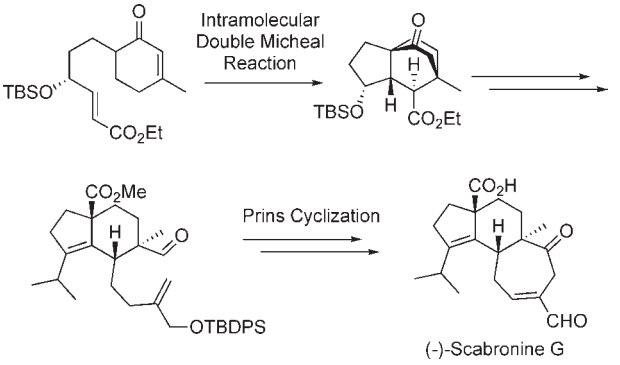
ABSTRACT



The enantioselective total synthesis of (−)-scabronine G is described. The key features of the present synthesis include the construction of a 5−6 ring system containing two quaternary carbon centers via a diastereoselective intramolecular double Michael reaction and the formation of a seven-membered ring using a Prins cyclization.

Scabronine G (**1**) is a member of the scabronine family[1] of cyathane diterpenes isolated from the fruit body of mushroom *Sarcodon scabrosus* (Figure 1). Among the related compounds, scabronine A (**3**), scabronine G (**1**), and its methyl ester (**2**) are shown to enhance the secretion of neurotrophic factors from 1321N1 human astrocytoma cells.[1c,2] Neurotrophic factors are essential for neurons to maintain and organize their own function, and therefore agents with neurotrophic activity are thought to be promising candidates for treating neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.

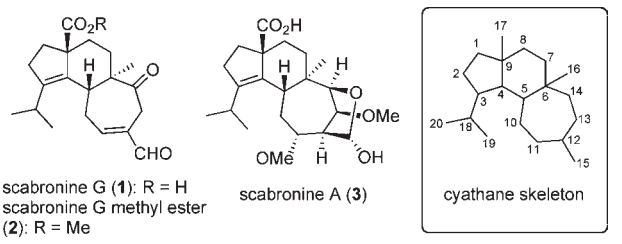


Figure 1. Scabronine G (**1**) and related molecules.

In addition to its intriguing biological activity, scabronine G (**1**) has synthetically challenging structural features, including a tricyclic 5−6−7 ring system with 1,4-*anti* quaternary carbon centers at the ring junctures, a trans-fused 6−7 ring, and especially an angular C17 carboxyl group.[3] These characteristics prompted us to embark on a program directed toward the total synthesis. To date,

(1) (a) Ohta, T.; Kita, T.; Kobayashi, N.; Obara, Y.; Nakahata, N.; Ohizumi, Y.; Takaya, Y.; Oshima, Y. *Tetrahedron Lett.* **1998**, *39*, 6229–6232. (b) Kita, T.; Takaya, Y.; Oshima, Y.; Ohta, T.; Aizawa, K.; Hirano, T.; Inakuma, T. *Tetrahedron* **1998**, *54*, 11877–11886. (c) Obara, Y.; Nakahata, N.; Kita, T.; Takaya, Y.; Kobayashi, H.; Hosoi, S.; Kiuchi, F.; Ohta, T.; Oshima, Y.; Ohizumi, Y. *Eur. J. Pharmacol.* **1999**, *370*, 79–84. (d) Ma, B. J.; Zhu, H. J.; Liu, J. K. *Helv. Chim. Acta* **2004**, *87*, 2877–2881. (e) Ma, B. J.; Ruan, Y. *J. Antibiot.* **2008**, *61*, 86–88.

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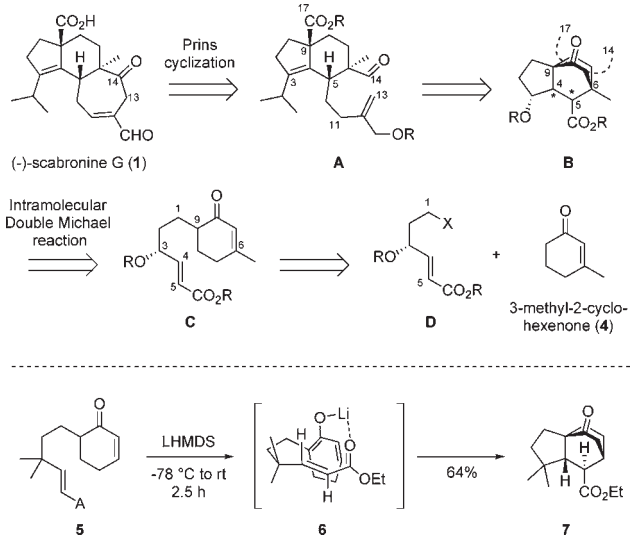
among the efforts made to synthesize the related cyathane diterpenes,[4] only one asymmetric total synthesis of scabronine G (**1**) has been reported.[5] In the present paper, we describe the total synthesis of scabronine G (**1**) by utilizing an intramolecular double Michael reaction and Prins cyclization as key steps.

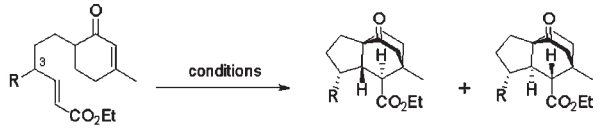
Scheme 1. Retrosynthetic Analysis of (−)-Scabronine G (**1**)



Our retrosynthetic analysis of (−)-scabronine G (**1**) is summarized in Scheme 1. The seven-membered ring (or C13−C14 bond[6]) in (−)-scabronine G (**1**) would be formed by Prins cyclization[7] of aldehyde **A**. We envisioned that the intermediate **A** having the C17 angular carboxyl functionality could be obtained by oxidative cleavage of the C14−C17 bond of tricyclic intermediate **B** and introduction of the C3-isopropyl group and C11−C13 side chain. Three stereogenic centers including two quaternary carbons (C6 and C9) in tricyclic intermediate **B** would be constructed by the intramolecular double Michael (IDM) reaction developed by Ihara et al.[8] They reported that the treatment of racemic compound **5** with a lithium base at low temperature led to the formation of only the IDM product **7**, probably through the chelated intermediate **6**.[8b] Finally, disconnection between C1 and C9 in the intermediate C generated chiral γ-alkoxy-α,β-unsaturated ester **D** and 3-methyl-2-cyclohexenone (**4**).

To ascertain the feasibility of this synthetic plan, we synthesized racemic IDM substrates **8a** and **8b** and investigated the key IDM reaction (Table 1; see Supporting Information for the synthesis of the racemic substrate **8a**). IDM reaction of substrate **8a** having no alkoxy substituent at C3 with lithium amide bases such as lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LHMDS) gave the expected IDM product **9a** as a sole product, but only in 31% yield (entry 1). Treatment of the same substrate **8a** with trimethylsilyl iodide (TMSI) and hexamethyldisilazane (HMDS)[9] resulted in an improved yield of IDM products with moderate stereoselectivity (entry 2). On the other hand, substrate **8b** having a C3 silyloxy substituent gave the expected product **9b** with good stereoselectivity (entry 3). The yield of **9b** was improved significantly by optimizing the equivalents of TMSI and HMDS (entry 4).

Table 1. Intramolecular Double Michael Reaction



entry	substrate	conditions[a]	combined yield (%)[b]	ratio (**9:10**)
1	**8a**	LHMDS (1.2), THF −78 °C to rt, 10 h	31 (60)	100:0
2	**8a**	TMSI (2), HMDS (3) CH_2Cl_2, rt, 2 h[c]	74	65:35
3	**8b**	TMSI (1.3), HMDS (2.6) CH_2Cl_2, rt, 10 h[d]	52	93:7
4	**8b**	TMSI (2), HMDS (4) CH_2Cl_2, rt, 45 min[d]	81	93:7

[a] Values in parentheses denote equivalency of reagents against the substrates. [b] Value in parentheses denote yield based on the recovered starting material. [c] Resulting enol silyl ethers were hydrolyzed with silica gel treatment. [d] Resulting enol silyl ethers were hydrolyzed with 10% aq HCl.

Although the IDM product **9b** possesses an incorrect configuration at C5, this transformation was thought to still be attractive because the two quaternary asymmetric centers at C6 and C9 were correctly introduced by the influence of the C3 asymmetric center. Therefore, we undertook an asymmetric synthesis of **9b**.

The synthesis commenced with the known chiral alcohol (+)-**11** (Scheme 2).[10] Protection of the hydroxyl group as

(2) Obara, Y.; Kobayashi, H.; Ohta, T.; Ohizumi, Y.; Nakahata, N. *Mol. Pharmacol.* **2001**, *59*, 1287–1297.

(3) The scabronine family was originally reported to be distinct from other cyathanes by an angular C17 carboxyl group rather than a C17 methyl group. See ref 1b.

(4) (a) Wright, D. L.; Whitehead, C. R. *Org. Prep. Proced. Int.* **2000**, *32*, 307–330. (b) Enquist, J. A.; Stoltz, B. M. *Nat. Prod. Rep.* **2009**, *26*, 661–680.

(5) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514–13515.

(6) Cyathane numbering is used throughout the paper.

(7) Snider, B. B. The Prins and carbonyl ene reactions. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds. Pergamon: Oxford, 1991; Vol. 2, pp 527−561.

(8) (a) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010–1022. (b) Ihara, M.; Ishida, Y.; Abe, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1155–1163.

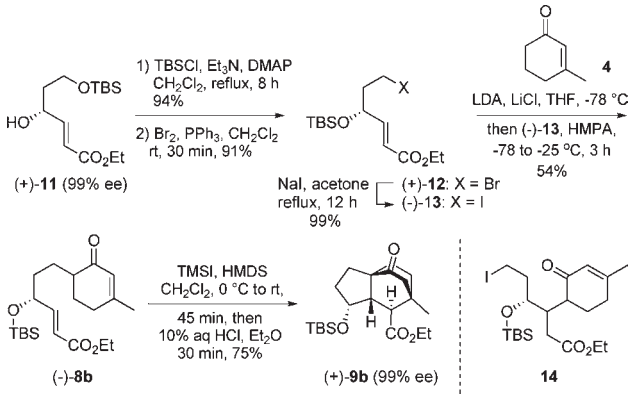
(9) Ihara, M.; Makita, K.; Fujiwara, Y.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 6416–6421.

(10) Hayashi, Y.; Shoji, M.; Ishikawa, H.; Yamaguchi, J.; Tamura, T.; Imai, H.; Nishigaya, Y.; Takabe, K.; Kakeya, H.; Osada, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6657–6660.

(11) Ashton, P. R.; Koniger, R.; Stoddart, J. F.; Alker, D.; Harding, V. D. *J. Org. Chem.* **1996**, *61*, 903–908.

TBS ether followed by selective bromination[11] and halogen exchange gave iodide (−)-**13** in 83% yield in three steps. Coupling of iodide (−)-**13** with 3-methyl-2-cyclohexenone (**4**) was accomplished as follows: a cooled (−78 °C) solution of lithium enolate, generated by mixing an LDA·LiCl complex[12] and cyclohexenone **4** at 0 °C, and hexamethylphosphoramide (HMPA) were added successively to the iodide (−)-**13** at −78 °C, and the mixture was stirred at −25 °C for 3 h to generate the coupling product (−)-**8b** as a mixture of diastereomers in 54% yield, along with the recovered iodide (−)-**13**[13] (∼10%) and the 1,4-addition product **14** (10∼20%).

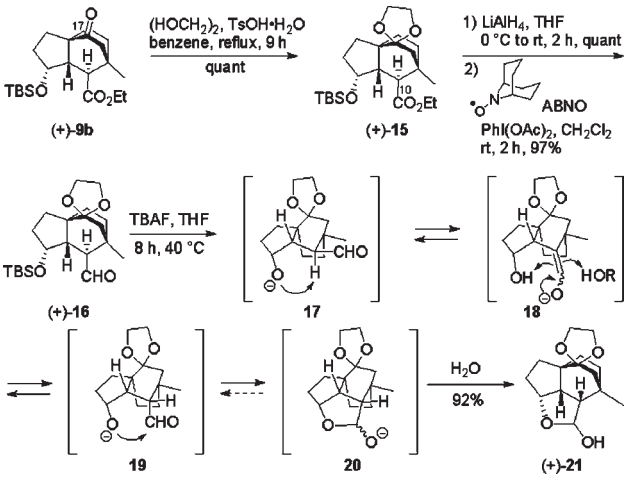
Scheme 2. Synthesis of the Key IDM Product



Next, the key IDM reaction of (−)-**8b** was carried out. To our delight, we observed no racemization at the C3 asymmetric center under the TMSI−HMDS conditions and the IDM product (+)-**9b** was obtained in 75% and in an enantiomerically pure form (99%ee).[14]

We then focused on epimerization of the C5 stereocenter (Scheme 3). Before this, the C17 ketone in (+)-**9b** was protected as a cyclic acetal and the C10 ester was converted to the corresponding aldehyde by $LiAlH_4$ reduction followed by 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO)-catalyzed oxidation[15] to give aldehyde (+)-**16** in 97% yield in three steps. Initially, we treated aldehyde (+)-**16** or ester (+)-**15** with various bases (KHMDS, KH, *tert*-BuOK, etc.), but no epimerization was observed in these cases. However, when the aldehyde (+)-**16** was treated with tetra-*n*-butylammonium fluoride (TBAF) at 40 °C, epimerization and lactol formation were concomitant with deprotection of the TBS group to give lactol (+)-**21** in 92% yield, probably through the intramolecular proton abstraction (**17**→**18**) followed by intermolecular protonation (**18**→**19**) and irreversible lactol formation (**19**→**20**).

Scheme 3. Epimerization of the C5 Stereocenter



With the lactol (+)-**21** in hand, we next pursued the synthesis of the key Prins cyclization substrate (Scheme 4). Reduction of lactol followed by selective protection and 2-azaadamantane *N*-oxyl (AZADO)-catalyzed oxidation[16] yielded ketone (+)-**23**. Regioselective enol triflate formation was accomplished by using KHMDS and *N*-phenylbis(trifluoromethanesulonamide) ($PhNTf_2$) to give enol triflate (+)-**24** in good yield. A Kumada coupling reaction[17] followed by removal of the TBS group afforded primary alcohol (−)-**25** in 69% yield in two steps.

Introduction of the C11−C13 alkenyl side chain **26**, prepared from ethyl phosphonoacetate in four steps[18] (see Supporting Information), was achieved by a Nozaki−Hiyama coupling reaction. Thus, alcohol (−)-**25** was oxidized with *o*-iodoxybenzoic acid (IBX) to the corresponding aldehyde, which was then treated with allyl iodide **26** and $CrCl_2$ to afford a ca. 1:1 mixture of coupling products (−)-**27a** and (−)-**27b** quantitatively. The mixture of (−)-**27a** and (−)-**27b** was converted to ketal (−)-**28** using a standard Barton−McCombie procedure in 71% yield. Finally, deprotection of ketal and oxidation of ketone (−)-**29** using Davis oxaziridine **30**[19] afforded the corresponding acyloin, which was oxidized further with $Pb(OAc)_4$ to give the Prins cyclization precursor aldehyde (−)-**31** in 66% yield in three steps.

Now the stage was set for construction of the seven-membered ring. After several preliminary experiments, we were pleased to find that the treatment of aldehyde (−)-**31** with Me_2AlCl[20] at low temperature afforded the desired

(12) Galianoroth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053–5055.

(13) The recovered (+)-**13** is contaminated with the corresponding chloride.

(14) An enantiomeric excess was determined by chiral HPLC analysis of its benzoylated derivative. See the Supporting Information.

(15) Shibuya, M.; Tomizawa, M.; Sasano, Y.; Iwabuchi, Y. *J. Org. Chem.* **2009**, *74*, 4619–4622.

(16) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

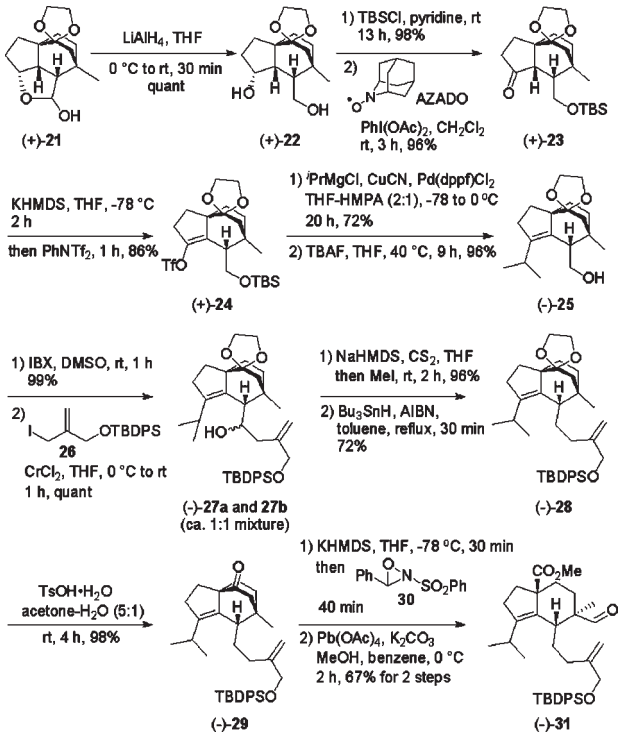
(17) Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

(18) (a) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857–3859. (b) Watanabe, H.; Nakada, M. *Tetrahedron Lett.* **2008**, *49*, 1518–1522.

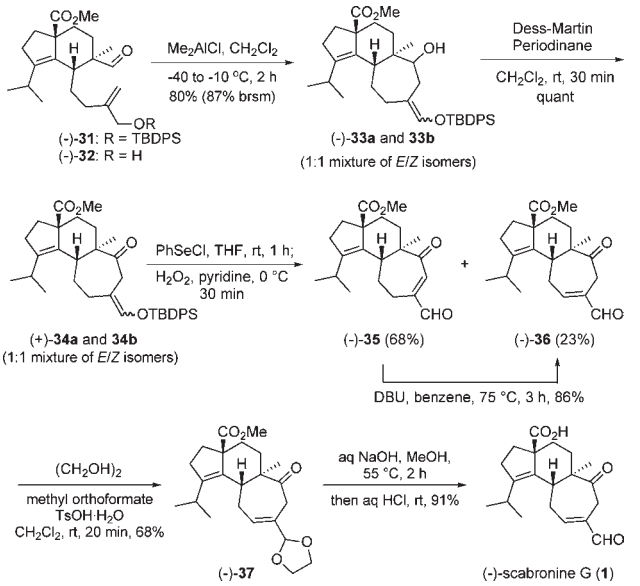
(19) Davis, F. A.; Nadir, U. K.; Kluger, E. W. *J. Chem. Soc., Chem. Commun.* **1977**, 25–26.

(20) Snider, B. B.; Vo, N. H.; ONeil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644–7645.

Scheme 4. Synthesis of the Prins Precursor (−)-**31**



Scheme 5. Completion of the Total Synthesis



cyclic alcohols (−)-**33a** and **33b** as a 1:1 separable mixture of *E*/*Z* isomers (Scheme 5). It should be noted that protection on the C15 hydroxyl group was needed for a successful cyclization reaction. Alcohol (−)-**32** did not give any cyclized product under these conditions.

The remaining tasks for the total synthesis were the removal of the TBDPS group and oxidation state adjustment. First, the mixture of alcohols (−)-**33a** and **33b** was oxidized using Dess−Martin periodinane to ketones (+)-**34a** and **34b**. Then, upon treatment of the mixture of ketones with phenylselenenyl chloride (PhSeCl) and H_2O_2,[21] the enol silyl ether moiety in both compounds was oxidatively converted to conjugated enal (−)-**35** and scabronine G methyl ester (−)-**36**. Finally, the four-step procedure (isomerization, protection of aldehyde, hydrolysis of methyl ester, and deprotection of 1,3-dioxolane) developed by Danishefsky et al.[5] afforded (−)-scabronine G (**1**), which proved identical to those derived from the natural sample.

In conclusion, we have accomplished an enantioselective total synthesis of scabronine G (**1**) using a diastereoselective intramolecular double Michael reaction and Prins cyclization as key steps. The current strategy would be useful for the synthesis of congeners and derivatives of scabronine-type diterpenes, especially those having a C5−C10 double bond such as scabronines E and F,[1b] and SAR studies thereof. Efforts along these lines are now in progress.

Acknowledgment. We thank Professor Tomihisa Ohta (Kanazawa University) for providing the NMR data of scabronine G and other useful information. This paper is dedicated to Professor Norimichi Nakahata (Graduate School of Pharmaceutical Sciences, Tohoku University), who passed away on October 27, 2010.

Supporting Information Available. Full experimental and characterization details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359–362.