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The First Total Synthesis of (±)-Scopadulin, an Antiviral Aphidicolane Diterpene

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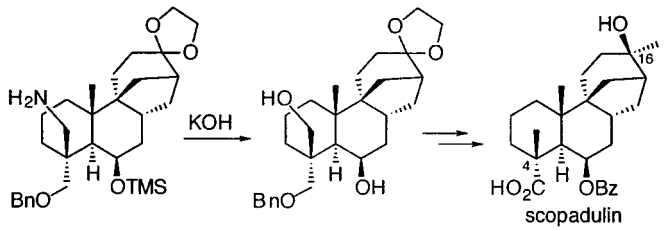
ABSTRACT



The first total synthesis of (±)-scopadulin was accomplished by a stereoselective construction of a quaternary carbon at C-4, conversion of the hindered cyano group to a methyl group via our novel reaction for conversion of primary aliphatic amines into alcohols, and a highly chemo- and stereoselective methylation at C-16.

The plant *Scoparia dulcis* (fam. Scrophulariaceae) has long been used as a folk medicine in Paraguay, India, and Taiwan for the treatment of hypertension, toothache, blennorhagia, and stomach disorders.[1] Scopadulin (**1**), a tetracyclic diterpenoid, was isolated from this plant in 1990 by Hayashi and co-workers, as the first aphidicolane diterpenoid from a higher plant.[2] The challenging structural complexity of scopadulin due to the presence of three quaternary carbons and eight stereocenters coupled with its notable antiviral and cytotoxic activities[2] makes it a worthy synthetic target to many organic chemists. Like other aphidicolane[3] and stemodane[4] diterpenes, scopadulin has the bicyclo[3.2.1]octane moiety (C/D ring system) fused with a *trans*-decalin moiety (A/B ring system). In addition, the presence of two adjacent quaternary carbon centers at C-9 and C-10 makes these diterpenes quite crowded (Figure 1).

Numerous synthetic pathways to other aphidicolane[5] and stemodane[5c,6] diterpenes and, recently, the total synthesis of scopadulcic acid A (**3**),[7] scopadulcic acid B (**4**),[7b,8] and

(1) Hostettmann, K. *Phytochemistry of Plants Used in Traditional Medicine*; Oxford University Press: New York, 1995.

(2) Hayashi, T.; Kawasaki, M.; Miwa, Y.; Taga, T.; Morita, N. *Chem. Pharm. Bull.* **1990**, *38*, 945.

(3) (a) Brundret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A. J.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1027. (b) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.

(4) (a) Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc*. **1973**, *95*, 2705. (b) Hufford, C. D.; Guerrero, R. O.; Doorenbos, N. J. *J. Pharm. Sci.* **1976**, *65*, 778. (c) Kelly, R. B.; Harley, M. L.; Alward, S. J.; Manchand, P. S. *Can. J. Chem.* **1982**, *60*, 675. (d) Chamy, M. C.; Piovano, M.; Garbariono, J. A.; Gambaro, V. *Phytochemistry* **1991**, *30*, 1719.

(5) For recent examples of the synthesis of other aphidicolanes, see: (a) Rizzo, C. J.; Smith, A. B., III. *J. Chem. Soc., Perkin Trans. 1* **1991**, 969. (b) Bélanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285. For a review on other syntheses of aphidicolanes and stemodanes up to 1996, see: (c) Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641.

(6) For the recent total and formal synthesis of stemodane diterpenes, see: (a) Hegarty, P.; Mann, J. *Tetrahedron* **1995**, *51*, 9079. (b) Tanaka, T.; Murakami, K.; Kanda, A.; Patra, D.; Yamamoto, S.; Satoh, N.; Kim, S.-W.; Ishida, T.; In, Y.; Iwata, C. *Tetrahedron Lett.* **1997**, *38*, 1801. (c) Pearson, A. J.; Fang, X. *J. Org. Chem*. **1997**, *62*, 5284.

(7) (a) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem*. **1993**, *58*, 5304. (b) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem*. **1995**, *60*, 3626. (c) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc*. **1999**, *121*, 5467.

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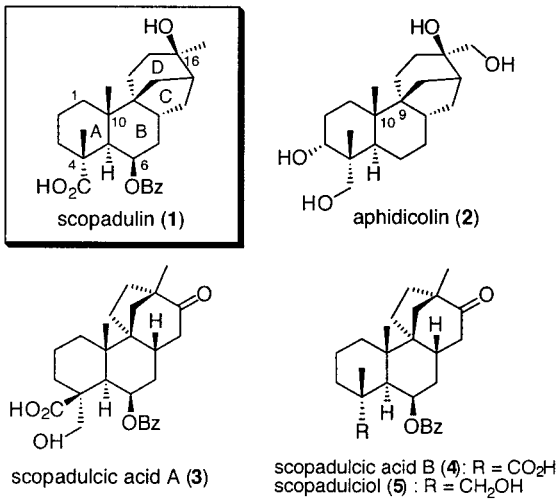


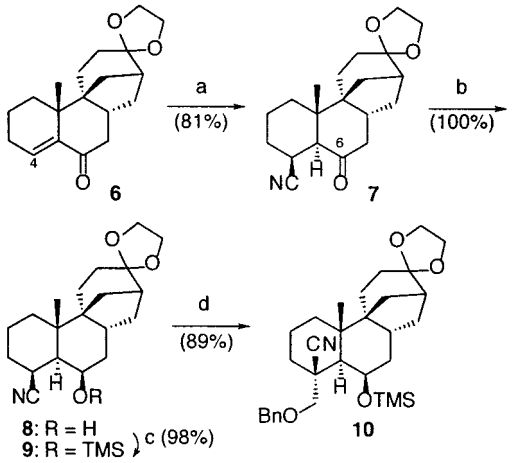
Figure 1.

scopadulciol (**5**)[7b] isolated from the same plant[9] were established; however, no synthetic route toward scopadulin (**1**) has been reported to date. After a successful synthesis of aphidicolin (**2**),[10] the synthesis of this novel diterpenoid was targeted in our laboratory. However, progress in the synthetic study was hampered due to several failed attempts for construction of the A/B ring system with the desired functionalities. Accordingly, a model study was conducted to overcome the problems associated with the synthesis.[11] In the course of the model study, we discovered a novel one-step reaction for the efficient conversion of primary aliphatic amines into alcohols.[11a] In this Letter, we wish to present the first total synthesis of (±)-scopadulin utilizing this novel reaction.

The A/B/C/D analogue **6** was synthesized according to the literature.[10] As in the model study,[11] a quaternary carbon center at C-4 with the desired stereochemistry was constructed by a sequential operation of stereocontrolled cyanation, diastereoselective reduction of C-6-ketone, and a highly stereoselective alkylation by BOMCl to afford the nitrile **10** in excellent yield (Scheme 1).

Without deprotecting the TMS group, **10** was exposed to excess $LiAlH_4$ in refluxing THF, and the resulting crude

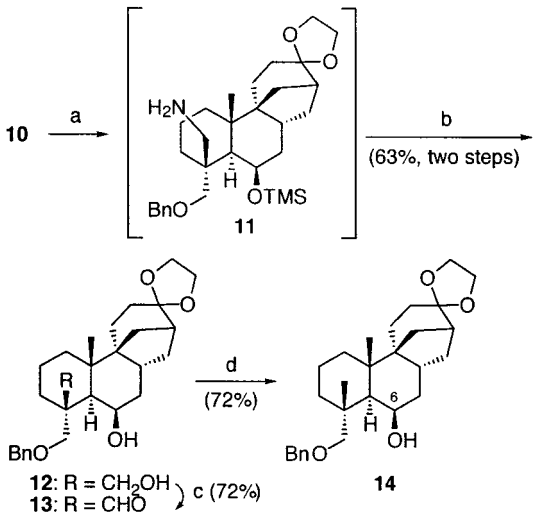
Scheme 1[a]



[a] Reaction conditions: (a) Et_2AlCN, TMSCl, C_6H_6, 0 °C; (b) $NaBH_4$, MeOH−THF (7:5), 0 °C; (c) TMSCl, Py, DMAP, CH_2Cl_2, 0 °C; (d) LDA, BOMCl, −78 to 0 °C.

amine **11** was subjected to the novel reaction conditions for the one-step direct conversion of primary aliphatic amines into alcohols[11a] to give **12** in 63% isolated yield in two steps (Scheme 2).[12] Then **12** was transformed to the 4,10-

Scheme 2[a]



[a] Reaction conditions: (a) $LiAlH_4$, THF, 75 °C; (b) KOH, diethylene glycol, 210 °C; (c) $RuCl_2(PPh_3)_3$, C_6H_6, air, rt; (d) $NH_2-NH_2\cdot H_2O$, K_2CO_3, diethylene glycol, 170 to 210 °C.

dimethylated alcohol **14** by selective oxidation[13] and Huang-Minlon reduction.[14]

Benzoylation of the hindered secondary alcohol at C-6 of **14** having a ketal functionality at C-16 was troublesome due

(8) (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031.

(9) (a) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. *Tetrahedron Lett.* **1987**, *28*, 3693. (b) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Morita, N. *J. Nat. Prod.* **1988**, *51*, 360. (c) Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Morita, N. *J. Nat. Prod.* **1991**, *54*, 802.

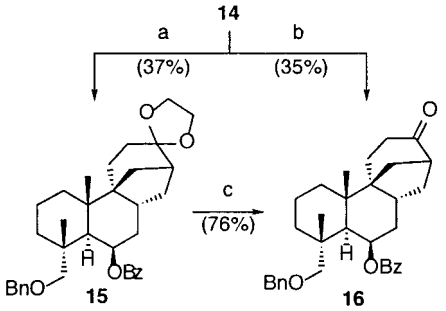
(10) (a) Tanaka, T.; Murakami, K.; Okuda, O.; Inoue, T.; Kuroda, T.; Kamei, K.; Murata, T.; Yoshino, H.; Imanishi, T.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 193. (b) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 1407.

(11) (a) Rahman, S. M. A.; Ohno, H.; Maezaki, N.; Iwata, C.; Tanaka, T. *Org. Lett.* **2000**, *2*, 2893. (b) Rahman, S. M. A.; Ohno, H.; Yoshino, H.; Satoh, N.; Tsukaguchi, M.; Murakami, K.; Iwata, C.; Maezaki, N.; Tanaka, T. *Tetrahedron.* **2001**, *57*, 127.

(12) Unlike the model study, nitrile **10** was subjected to the reaction condition without deprotection of the TMS group, which saved one step and provided a better yield.

(13) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

Scheme 3[a]



[a] Reaction conditions: (a) BzOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) BzOTf, CH_2Cl_2, −78 °C; (c) dilute HCl, MeOH, 40 °C.

to formation of undesired side products (Scheme 3). While BzOTf alone[15] furnished a number of side products[16] with the desired keto benzoate **16** (35%), very slow addition of BzOTf in the presence of 2,6-lutidine provided the benzoate **15** (37%) with only traces of the undesired products[17] and a considerable amount of the starting material was recovered which was recyclable. **15** was easily converted to the keto benzoate **16** by treatment with HCl.

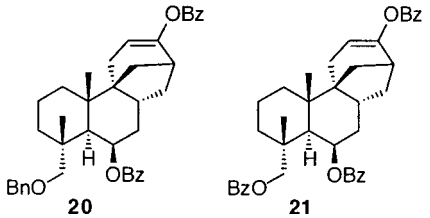
Completion of the total synthesis further required chemo- and stereoselective methylation at C-16-ketone (Scheme 4). Reaction of the ketone **16** with MeLi gave a mixture of the desired axial alcohol **17** and its isomer **18** (**17**:**18** = 54:46)[18] with traces of a debenzoylated product. MeLi−$LiClO_4$[19] was not selective, and the reaction became sluggish. However, we were pleased to find that when **16** was allowed to react with an excess of $MeTi(OPr^i)_3$[20] at room temperature, **17** was obtained exclusively (>99:1).[21] This exclusive equatorial addition occurred due to the steric repulsion of the bulky reagent with the axial hydrogens at both C-11 and C-14.

(14) (a) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487. (b) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301.

(15) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875.

(16) Due to the Lewis acidic nature of BzOTf, a number of undesired side products formed rapidly by a combination of deketalization and debenzylation and no starting material was detected.

(17) Addition of BzOTf to a mixture of the alcohol **14** and 2,6-lutidine afforded undesired enolates **20** and **21** with the desired benzoate **15**. However, very slow addition substantially decreased the side product formation due to low concentration of free BzOTf (as the rate of complexation between BzOTf and 2,6-lutidine is faster than the Lewis acidic behavior to the ketal functionality).[15]



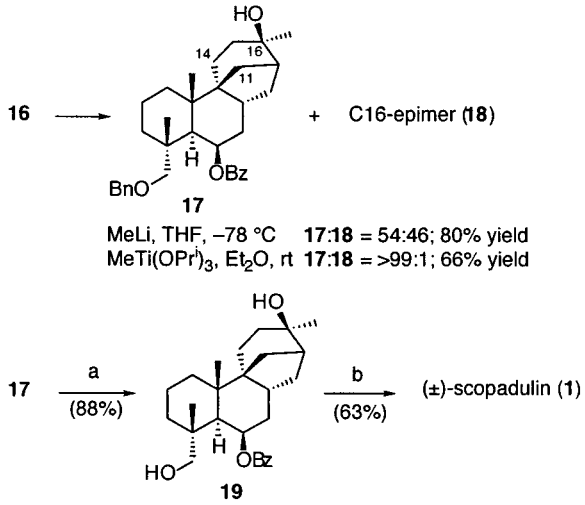
(18) The reaction was conducted initially with MeLi to recognize the two isomers. The desired and the undesired isomers were identified by converting both the isomers to scopadulin and 16-*epi*-scopadulin.

(19) Ashby, E. C.; Nodling, S. A. *J. Org. Chem.* **1979**, *44*, 4371.

(20) (a) Reetz, M. T.; Weatermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (b) Reetz, M. T.; Steinbach, R.; Weatermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441.

(21) Only the less polar desired isomer was detected by TLC and ^1H NMR spectra.

Scheme 4[a]



[a] Reaction conditions: (a) Pd/C, H_2, MeOH, rt; (b) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt.

Finally, debenzylation of **17** by the usual method provided **19**, whose primary hydroxyl group was oxidized by RuO_4,[22,23] affording (±)-scopadulin (**1**) in 63% yield (Scheme 4). This synthetic scopadulin was in all respects (500 MHz ^1H NMR pyridine-d_5, 125 MHz ^{13}C NMR pyridine-d_5, IR spectra, and TLC mobility in three solvent systems) indistinguishable from an authentic sample of scopadulin supplied by Professor Hayashi.[24]

In conclusion, we have developed an efficient synthetic route to (±)-scopadulin. The first total synthesis of (±)-scopadulin was accomplished by stereoselective construction of a quaternary carbon at C-4, conversion of the hindered cyano group to a methyl group via the novel reaction,[11a] highly stereocontrolled and chemoselective methylation at C-16, and subsequent functional group modification. In addition, the synthetic usefulness of our novel reaction for conversion of primary amines to alcohols was clarified by this total synthesis.

Acknowledgment. The authors are indebted to Professor T. Hayashi, Toyama Medical and Pharmaceutical University, Japan, for his generous supply of authentic natural scopadulin as well as its spectra. Special thanks go to the Ministry of Education, Science, Sports and Culture of Japan for providing a scholarship to S. M. A. Rahman.

Supporting Information Available: Experimental procedures for synthesis of compounds **7**, **12**, **13**, and scopadulin (**1**) as well as ^1H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(23) We preferred RuO_4 instead of the Jones reagent which was used in the model study[11] because we surmised that the highly acidic nature of the Jones reagent might cause elimination of the tertiary alcohol at C-16.

(24) The C16-epimer of scopadulin was also synthesized from the undesired methyl adduct **18**. This isomer showed marked differences in ^1H NMR and ^{13}C NMR spectra from those of natural and synthetic scopadulin.