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Enantioselective Total Synthesis of (−)- and (+)-Petrosin

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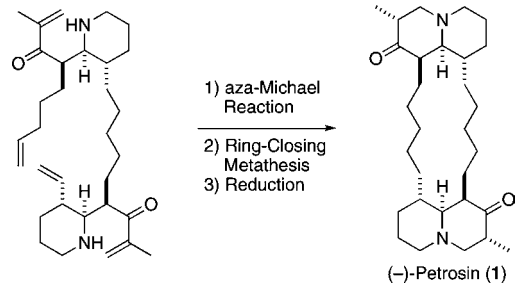
ABSTRACT



The enantioselective total synthesis of (−)- and (+)-petrosin is described. The union of two key segments was executed by Suzuki−Miyaura coupling. The quinolizidine rings were stereoselectively constructed via a diastereoselective Mannich reaction and an aza-Michael reaction. The 16-membered ring was constructed by ring-closing metathesis with the second-generation Grubbs catalyst.

The bisquinolizidine alkaloid petrosin (**1**) isolated as a racemate from the marine sponge *Petrosia seriata* by Braekman[1a] and from the *Xestospongia* sp. by Kobayashi and Kitagawa[1b] possesses activity against HIV by inhibition of reverse transcriptase and giant cell formation.[1c] In 1994, Heathcock and co-workers reported the first racemic total synthesis of (±)-**1** and other isomers.[2] They also revealed stereocenters of the quinolizidine ring epimerized via formation of bisimine derivative, retro-Mannich, and Mannich reactions by treatment with $PrNH_3OAc$ at 95 °C.[2a] Since optically active petrosin cannot be obtained either from natural sources or by chemical synthesis, the structural stability and differences of biological activity have not yet been fully investigated. In this paper, we describe the enantioselective total synthesis of (−)- and (+)-petrosin and their bioactivity.

In our retrosynthetic analysis, we set diester **2** as a precursor of (−)-**1** (Scheme 1). Formation of the 16-membered ring by ring-closing metathesis (RCM) and subsequent construction of quinolizidine rings by an intramolecular aza-Michael reaction of a dienone derivative would lead to (−)-**1**. Diester **2** could be prepared from iodide **4** and alkyl borane **5** by intermolecular Suzuki−Miyaura coupling and conversion to diene. Segments **4** and **5** would be accessible from the common piperidine intermediate **6**, which could be prepared by the Mannich reaction from **7**.

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(1) (a) Braekman, J. C.; Daloze, D.; Macedo de Abreu, P.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1982**, *23*, 4277–4280. (b) Kobayashi, M.; Kawazoe, K.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 4149–4152. (c) Goud, T. V.; Reddy, N. S.; Swamy, N. R.; Ram, T. S.; Venkateswarlu, Y. *Biol. Pharm. Bull.* **2003**, *26*, 1498–1501.
(2) (a) Scott, R. W.; Epperson, J. R.; Heathcock, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 8853–8854. (b) Scott, R. W.; Epperson, J.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 5001–5012. (c) Heathcock, C. H.; Brown, R. C. D.; Norman, T. C. *J. Org. Chem.* **1998**, *63*, 5013–5030.

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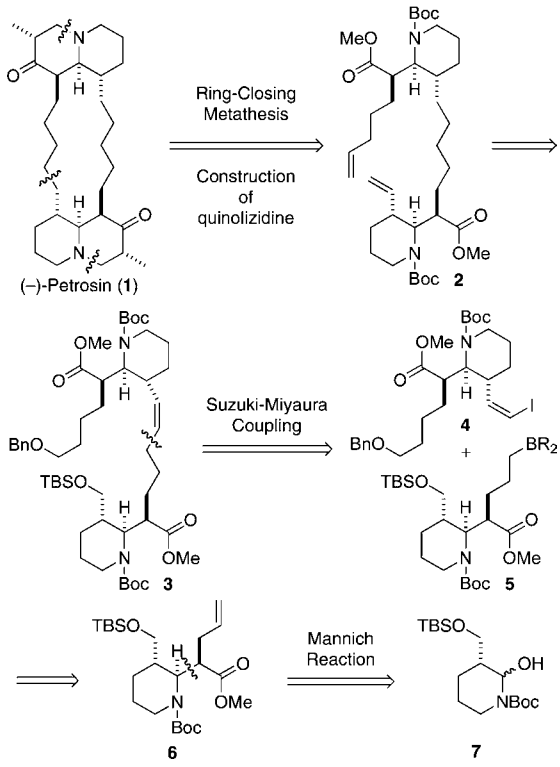
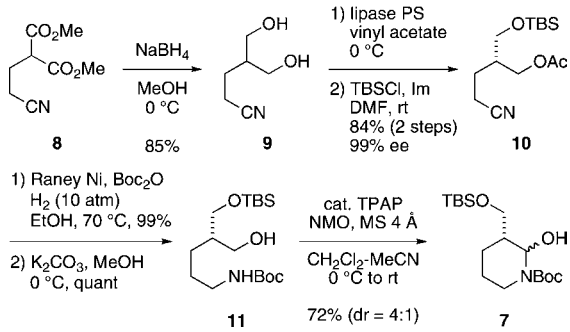
Scheme 1. Retrosynthetic Analysis of (−)-Petrosin (**1**)



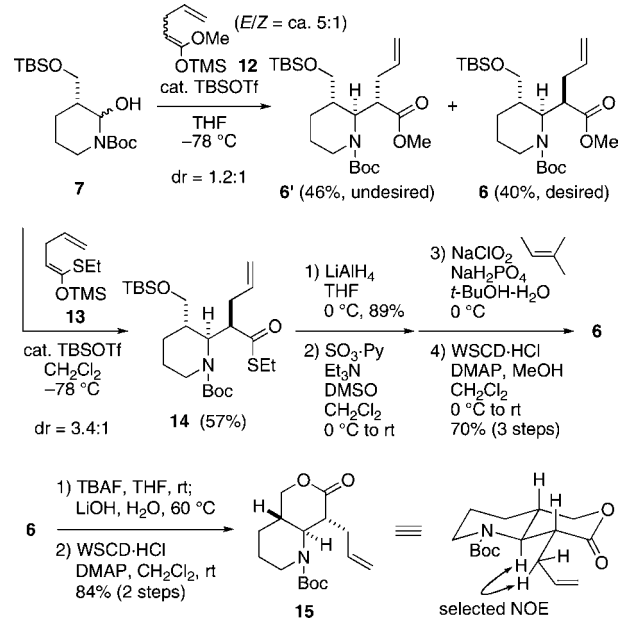
Synthesis of optically active hemiaminal **7** commenced with reduction of the known malonate **8**[3] to diol **9** (Scheme 2). Diol **9** was then subjected to lipase-mediated desymmetrization[4] followed by protection of the other hydroxy group as a TBS ether to provide acetate **10** in 99% ee.[5,6] Acetate **10** was hydrogenated with Raney nickel in the presence of Boc anhydride,[7] and the removal of the acetyl group gave alcohol **11**. When oxidation was carried out by Swern oxidation, a significant decrease in ee (69%) was observed. Among various oxidation conditions, TPAP oxidation was found to efficiently prevent racemization, and **7** was obtained as a mixture of diastereomers (4:1).

Scheme 2. Synthesis of Optically Active Hemiaminal **7**



Next, our attention was focused on introduction of the side chain to piperidine **7** (Scheme 3). Mannich reaction of ketene silyl acetal **12** (*E*/*Z* = ca. 5:1) smoothly proceeded in the presence of TBSOTf to afford a mixture of product **6′** (undesired) and **6** (desired) in a ratio of 1.2:1.[8] Stereochemistry of **6** was established based on NOE experiments after conversion to the corresponding lactone **15** by deprotection of the TBS group and lactonization. To improve diastereoselectivity, modification of nucleophile and additive effects were thoroughly investigated. To this end, we found that thioketene silyl acetal **13** improved selectivity (dr = 3.4:1). After conversion of **14** to the desired ester **6** in four steps, we obtained **6** from **7** in comparable overall yield (36%).

Scheme 3. Mannich Reaction with Ketene Silyl Acetal



With the common intermediate **6** in hand, we continued with the elaboration to vinyl iodide **4**, one of two key segments for Suzuki−Miyaura coupling (Scheme 4). The terminal olefin in **6** was elongated by cross metathesis with (*Z*)-1,4-bis(benzyloxy)but-2-ene[9] under Grubbs' modification with *p*-quinone to prevent isomerization of the C−C double

(3) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44–48.

(4) (a) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200–7205. (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354.

(5) Enantiomeric excess was determined by HPLC as a TBDPS ether.

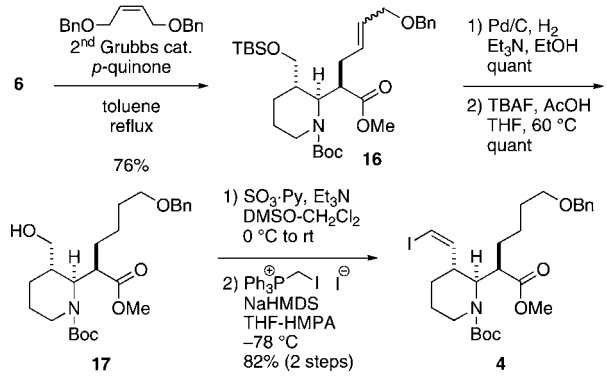
(6) The absolute configuration was determined by conversion of **10** to the previously reported product, (+)-(3*S*)-*N*-*tert*-butoxycarbonyl-3-hydroxymethyl-piperidine. See Supporting Information for details.

(7) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097–2099.

(8) (a) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825–2828. (b) Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335–5337.

(9) Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E. *Org. Lett.* **2006**, *8*, 705–708.

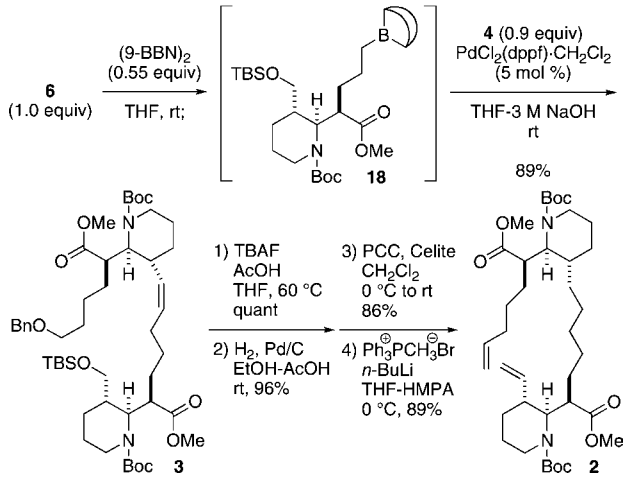
Scheme 4. Synthesis of **4** for Suzuki−Miyaura Coupling



bond.[10] The resulting internal double bond was selectively hydrogenated in the presence of Et_3N without debenzylation.[11] Finally, removal of the TBS group followed by iodovinylation by Parrikh−Doering oxidation to aldehyde and Wittig reaction provided the vinyl iodide **4**.

The coupling partner **18** was prepared by hydroboration of **6** with $(9\text{-BBN})_2$. Without separation, alkyl borane **18** was coupled with vinyl iodide **4** to afford the desired product **3** in excellent yield (Scheme 5).[12] After desilylation, one-pot

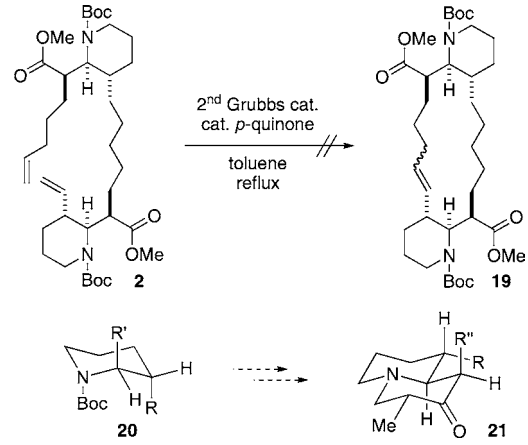
Scheme 5. Key Intermolecular Suzuki−Miyaura Coupling



reduction of the double bond and debenzylation, PCC oxidation of the resultant diol to dialdehyde, and finally Wittig methylenation yielded diene **2**, a precursor of (−)-petrosin (**1**).

Now the stage was set for implementation of the crucial RCM to construct the 16-membered ring. However, despite extensive efforts, the planned RCM did not proceed at all (Scheme 6). A careful conformation analysis suggested that

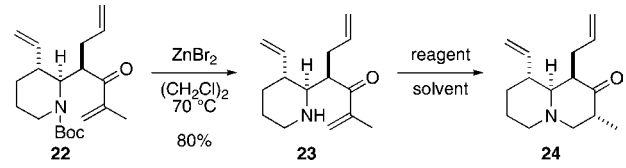
Scheme 6. Unsuccessful Ring-Closing Metathesis



the each Boc-protected piperidine in **2** has two side chains located in the trans diaxial position like **20**, which might hamper the reaction of two terminal alkenes. On the other hand, the two side chains should become axial−equatorial after construction of quinolizidine rings like **21**. On the basis of these considerations, we decided to examine the RCM after formation of quinolizidine rings, expecting that the more closely located two terminal alkenes would promote the RCM.

Another critical issue, which had to be solved before the RCM, was stereochemistry in quinolizidine formation. Thus, we executed a model study on the aza-Michael reaction using a simple substrate **22**[13,14] (Table 1). The Boc group was

Table 1. Construction of the Quinolizidine Skeleton



entry	reagent	solvent	temp	time	yield (%)
1	$NaHCO_3$ aq	CH_2Cl_2	rt	48 h	-
2	NH_3 aq	MeOH	60 °C	12 h	64
3	wet SiO_2	$(CH_2Cl)_2$	reflux	20 min	64

removed with zinc bromide to give **23**, which was subjected to basic conditions (entry 1).[14a] However, the reaction

(10) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(11) Locardi, E.; Boer, J.; Modlinger, A.; Schuster, A.; Holzmann, B.; Kessler, H. *J. Med. Chem.* **2003**, *46*, 5752–5762.

(12) (a) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743–8744. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

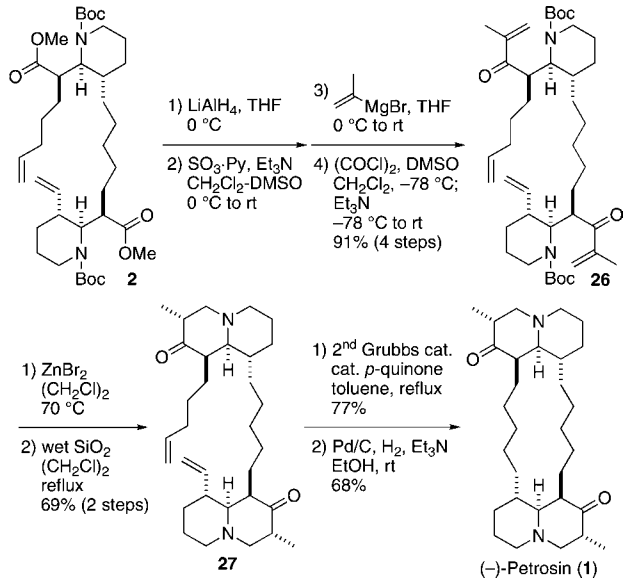
(13) We synthesized **22** from racemic **6** in 7 steps in a similar manner. See Supporting Information for details.

(14) To the best of our knowledge, there is no example of quinolizidine synthesis by aza-Michael reaction using α-substituted enone as a substrate. For an example of quinolizidine synthesis in a similar system, see: (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717–722. (b) Maldaner, A. O.; Pilli, R. A. *Synlett* **2004**, 1343–1346.

resulted in recovery of only the starting material. The desired quinolizidine **24** was obtained as a single isomer when using NH_3 in methanol (entry 2).[14b] Furthermore, wet SiO_2 in refluxing 1,2-dichloroethane was found to give quinolizidine **24** effectively as a single isomer (entry 3).[15,16] The stereochemistry of **24** was tentatively assigned by good agreement of ^1H NMR for the reduced compound **25**[17] with that of natural petrosin.

With the stage set for the endgame, diester **2** was converted to dienone **26** by a four-step sequence (Scheme 7). After

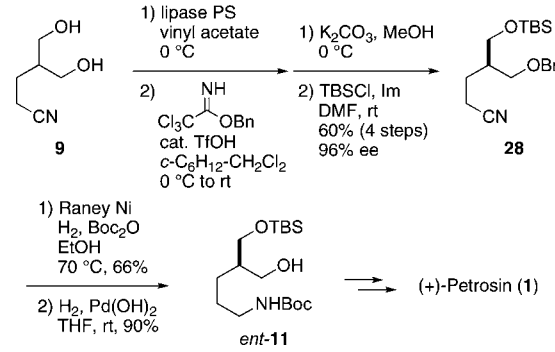
Scheme 7. Synthesis of (−)-Petrosin (**1**)



removal of the Boc group, two quinolizidine rings were constructed by aza-Michael reaction under the established conditions to give **27** as a sole product. To our delight, the expected RCM of diene **27** proceeded nicely with a combination of the second-generation Grubbs catalyst and *p*-quinone[18] to afford the 16-membered compound. Finally, reduction of the double bond in the presence of Et_3N[19] completed the total synthesis of (−)-petrosin (**1**).[20]

(+)-Petrosin was also synthesized by modification of the synthetic route (Scheme 8). The optically active nitrile **28** was prepared via lipase-mediated desymmetrization of diol **9**. Reduction

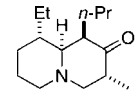
Scheme 8. Synthesis of (+)-Petrosin (**1**)



of the cyano group and debenzylation gave *ent*-**11**. (+)-Petrosin was synthesized from *ent*-**11** in the same manner as described above.

Both enantiomers of petrosin and monomer unit **25** were evaluated for inhibitory activity against syncytium formation (Table 2).[21] While a significant difference was not observed between each enantiomer, monomer unit **25** exhibited no

Table 2. Inhibition of Syncytium Formation



(±)-**25**

sample	IC_{50} (μM)
(−)-petrosin	100.2
(+)-petrosin	102.3
(±)-**25**	>400

inhibitory activity against giant cell formation, indicating that the dimeric structure would be essential for bioactivity.

In conclusion, we have accomplished an enantioselective total synthesis of (−)- and (+)-petrosin featuring construction of quinolizidine rings by an aza-Michael reaction and formation of the 16-membered ring by ring-closing metathesis. We found that the dimeric structure was essential for anti-HIV activity. Further SAR studies are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures including biological evaluations and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Basu, B.; Das, P.; Hossain, I. *Synlett* **2004**, 2630–2632.

(16) The product **24** is presumably a thermodynamic product since this isomer was obtained as a single isomer under the basic conditions with heating (Table 1, entry 2), in which the analogous compound underwent epimerization (ref 14b).

(17) We synthesized the partial structure **25** from **24** by hydrogenation with Pd/C in the presence of Et_3N. See Supporting Information for details.

(18) When the reaction was performed without *p*-quinone, a significant decrease in yield (45%) was observed, likely due to isomerization of the terminal C−C double bonds (ref 10).

(19) When the reaction was carried out without Et_3N, a decrease in yield (<60%) was observed.

(20) The optical purity of the synthetic petrosin (>99% ee) was confirmed by Mosher's method for a diol derived from **1**, which was prepared by reduction of two carbonyl groups, indicating that epimerization of optically active petrosin did not proceed at all in our case.

(21) Chiba, H.; Asanuma, S.; Okamoto, M.; Inokoshi, J.; Tanaka, H.; Fujita, K.; Omura, S. *J. Antibiot.* **2001**, *54*, 818–826.