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Total Synthesis of (−)-Aspidospermine via Diastereoselective Ring-Closing Olefin Metathesis

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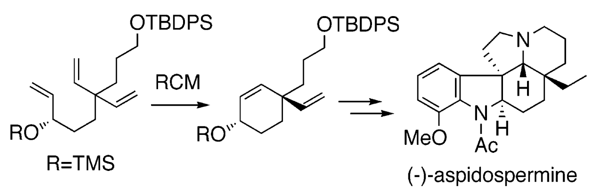
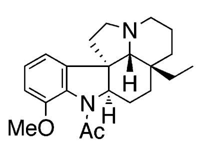
ABSTRACT



An enantiocontrolled total synthesis of (−)-aspidospermine has been achieved. The key element of the strategy is the diastereoselective construction of the quaternary stereogenic center employing 1,4-asymmetric induction during the ring-closing olefin metathesis.

Aspidospermine (**1**), an alkaloid that belongs to a family of aspidosperma indole alkaloids,[1] has generated considerable interest because of its characteristic pentacyclic structural feature and its biological profile. Consequently, for almost 40 years, intense activity has been directed toward the total synthesis of this intriguing alkaloid (Figure 1).



(-)-aspidospermine (**1**)

Figure 1.

There have been many reports on the total synthesis of this family of alkaloids in both racemic[2] and optically active forms.[3] During the course of our studies on the diastereoselective construction of a quaternary stereogenic center employing 1,4-asymmetric induction in the cyclization reaction, we developed a novel methodology based on the ring-closing metathesis (RCM) reaction[4] as shown in Scheme 1.[5]

When the trienes **2** with a tertiary stereogenic center and a prochiral quaternary carbon center were treated with

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(2) Synthesis of (±)-aspidospermine: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872−2873. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261−2268. (c) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311−1315. (d) Stevens, R. V.; Fitzpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857−858. (e) Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294−3296. (f) Pearson, A. J.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2467−2476. (g) Wu, P.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963−972. For the synthesis of (±)-aspidospermidine: (h) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599−3601. (i) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642. (j) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995−1001. (k) Urrutia, A.; Rodriguez, J. G. *Tetrahedron* **1999**, *55*, 11095−11108. (l) Quinn, J. F.; Bos, M. E.; Wulff, W. D. *Org. Lett.* **1999**, *1*, 161−164. (m) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *110*, 966−968.

(3) Formal synthesis of (+)-aspidospermine: (a) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673−4676. Asymmetric synthesis of aspidospermidine: (b) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398−13399. (c) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (d) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625−1627. (e) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855−6861. (f) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292−2303. (g) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521.

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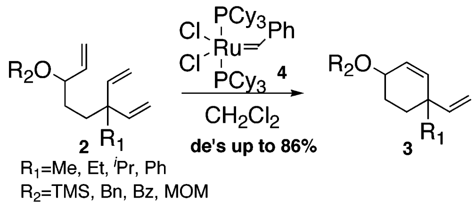
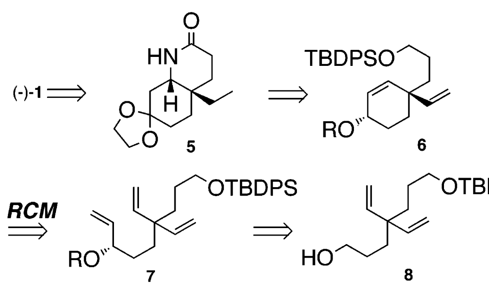
Scheme 1. Diastereoselective Ring-Closing Metathesis



Grubbs' ruthenium carbene complex **4**, the cyclohexenes **3** with a quaternary stereogenic center were obtained via 1,4-asymmetric induction in good chemical yield with up to 86% de (in the case of $R_1 = {}^iPr$, R_2 = TMS). In this communication, the application of our RCM methodology in an enantiocontrolled total synthesis of (−)-aspidospermine (**1**) is described.

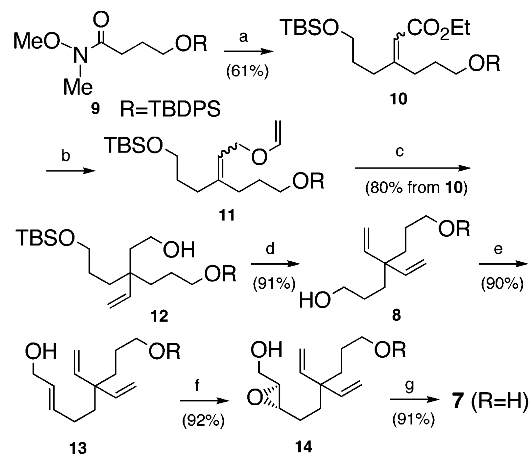
(−)-Aspidospermine (**1**) can be obtained from optically active lactam **5**, which could be prepared from **6**, according to the procedure developed by Stork.[2a] We envisaged that a pivotal construction of the quaternary carbon in **6** might be realized diastereoselectively by RCM reaction of the triene **7**, which in turn would be derived from the dienyl alcohol **8**, as shown in Scheme 2.

Scheme 2. Retrosynthetic Analysis



Preparation of the triene **7** (R = H), the substrate of diastereoselective RCM reaction, began with the reaction of the amide **9**, prepared from γ-butyrolactone,[7] with 3-(*tert*-butyldimethylsilyloxy)propyllithium[8] followed by the Horner−Emmons reaction to give the unsaturated ester **10**. Reduction with DIBAL-H followed by vinylation afforded the vinyl ether **11**, which was treated with triisobutylaluminum[9] to provide the alcohol **12** in good overall yield. Dehydration[10] followed by selective deprotection of the TBS ether afforded the hydroxy diene **8**, which was converted into the hydroxy triene **13** via sequential Wittig olefination and DIBAL-H reduction. Katsuki−Sharpless asymmetric epoxidation,[11] iodination of the resulting epoxy alcohol **14**, and treatment with zinc/AcOH produced the optically pure hydroxy triene **7** (R = H) (>99% ee by the MTPA ester). The absolute stereochemistry of the tertiary stereogenic center was confirmed to be *S* according to the modified Mosher method[12] (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) (i) $TBSO(CH_2)_3Br$, ^tBuLi, THF, −78 °C → rt; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, reflux. (b) (i) DIBAL-H, THF, 0 °C; (ii) $EtOCH{=}CH_2$, $Hg(OAc)_2$, reflux. (c) $^iBu_3Al$, CH_2Cl_2, rt. (d) (i) *o*-Nitrophenyl selenocyanate, $^nBu_3P$, THF, rt; (ii) H_2O_2, THF, rt; (iii) 1% HCl, EtOH, rt. (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux; (iii) DIBAL-H, THF, 0 °C. (f) L-(+)-DIPT, $Ti(OiPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, 25 °C. (g) (i) I_2, Ph_3P, imidazole, benzene, rt; (ii) Zn, AcOH, 50 °C.

The triene **7** (R = H) was converted by conventional means into the corresponding MOM, benzyl, and TMS ethers and the benzoate ester. These compounds were treated with 10 mol % ruthenium carbene complex **4** in CH_2Cl_2 solution (0.02 M) at room temperature for 48 h. The results are shown in Table 1. The best result was obtained in the case of R = TMS to afford the cyclohexenol **6** (R = H) quantitatively with 74% de (entry 5) after acidic hydrolysis. Fortunately, since the two diastereomers could be easily separated by chromatography, the optically pure **6** was obtained in 74% yield (Table 1). Although the absolute configuration of the newly generated quaternary stereogenic center could not be determined at this stage, it was proposed to be *R* according to our previous study. This was confirmed by its conversion into the known lactam **5**.

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(5) Fukuda, Y.; Sasaki, H.; Shindo, M.; Shishido, K. *Tetrahedon Lett.* **2002**, *43*, 2047−2049.

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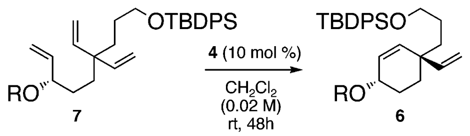
(12) Ohtani, I.; Kusumi, T.; Kashmann, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

Table 1. RCM Reaction of Triene **7** Leading to **6**



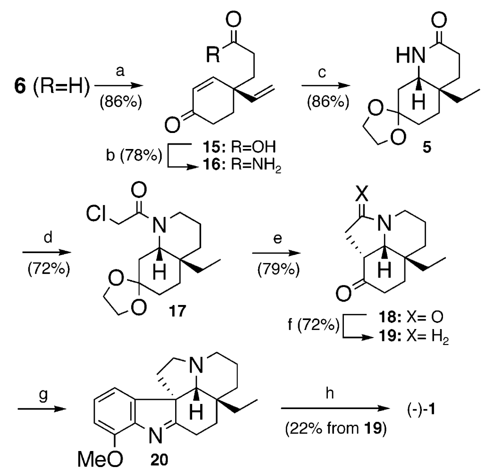
entry	R	yield [%] of **6** (recovered **7** [%])	diastereomeric ratio
1	H	7 (81)	59:41
2	Bz	95 (5)	72:28[b]
3	MOM	92 (5)	85:15
4	Bn	94 (6)	88:12
5	TMS	quantitative[a] (0)	87:13[b]

[a] Isolated as alcohol **6** (R = H) after hydrolysis. [b] Diastereomers can be separated by chromatography.

The optically pure **6** (R = H) thus prepared was desilylated and oxidized to give the keto acid **15**, which was converted into the amide **16** via the acid chloride. Treatment of the amide **16** with *p*-TsOH in refluxing benzene afforded the corresponding keto lactam, which was ketalized and whose double bond was reduced to give the keto lactam **5**. The enantiomer of compound **5** is identical to an intermediate synthesized by Meyers.[3a] With the key intermediate in hand, we converted **5** into **1** using a slightly modified procedure of Stork.[2a] Reduction of the lactam carbonyl followed by acylation with chloroacetyl chloride afforded **17**. After hydrolysis of the ketal moiety, treatment with base produced the tricyclic keto lactam **18**. For the selective reduction of the lactam carbonyl, the ketone was reprotected as a ketal, reduced with borane, and hydrolyzed to give **19**. It was then converted into the *o*-methoxyphenylhydrazone, which was heated in acetic acid to afford the pentacyclic compound **20**. Finally, sequential treatment with $LiAlH_4$ and acetic anhydride/pyridine produced (−)-aspidospermine (**1**), whose spectral properties and optical rotations are identical to those reported[13] (Scheme 4).

(13) Campbell, W. E.; Jackson, G. E.; Ravenscroft, N. *Spectrosc. Lett.* **1993**, *26*, 707−719.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) TBAF, THF, rt; (ii) Jones oxidation, acetone, rt. (b) (i) $(COCl)_2$, CH_2Cl_2, rt; (ii) NH_3, THF, rt. (c) (i) *p*-TsOH·H_2O, benzene, reflux, then $HO(CH_2)_2OH$, reflux; (ii) H_2, PtO_2, EtOH, rt. (d) (i) $LiAlH_4$, THF, reflux; (ii) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2, rt. (e) (i) 1 N HCl, THF, reflux; (ii) KO*t*Bu, benzene, reflux. (f) (i) $HO(CH_2)_2OH$, *p*-TsOH·H_2O, benzene, reflux; (ii) BH_3·THF, reflux; (iii) 1 N HCl, THF, reflux. (g) (i) *o*-Methoxyphenylhydrazine·HCl, Na_2CO_3, EtOH, reflux; (ii) AcOH, 95 °C. (h) (i) $LiAlH_4$, THF, rt; (ii) Ac_2O, pyridine, rt.

In summary, we have completed an enantiocontrolled total synthesis of (−)-aspidospermine using a methodology for assembling the quaternary stereogenic center via a diastereoselective RCM reaction developed in our laboratory. The optically active cyclohexenol derivative **6** produced by the RCM reaction is suitably functionalized and could be a versatile chiral building block not only for aspidosperma indole alkaloids but also for other biologically important natural products.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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