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Concise Total Synthesis of (±)-Pseudotabersonine via Double Ring-Closing Metathesis Strategy

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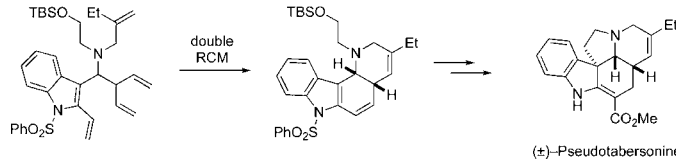
ABSTRACT



A concise synthesis of (±)-pseudotabersonine from commercially available 1-(phenylsulfonyl)-3-indolecarboxaldehyde has been accomplished. This synthesis features the convergent assembly of a key intermediate via a stepwise variant of a Mannich-type multicomponent coupling process, a double ring-closing metathesis, and a one-pot deprotection/cyclization reaction.

Members of the *Aspidosperma* family of indole alkaloids have long captured the attention of synthetic chemists owing to their complex structural frameworks and their diverse and important biological activities.[1] Most of these alkaloids comprise a pentacyclic core with an ethyl group or a functionlized ethyl group appended at the bridgehead carbon atom at C(20), as exemplified by the structure of aspidospermidine (**1**) (Figure 1). However, there is a small subfamily of *Aspidosperma* alkaloids related to pandoline (**2**) having a rearranged skeleton (Figure 1). Pseudotabersonine (**3**), a member of the pandoline alkaloids, was isolated from *Pandaca caducifolia* in 1975,[2] and two elegant syntheses of this compound were reported in the early 1990s by Kuehne[3] and Grieco.[4]

Our laboratory has had a longstanding interest in developing general strategies for the synthesis of natural products. In that context, we pioneered the application of ring-closing metathesis (RCM) to the syntheses of nitrogen heterocycles and a variety of alkaloids as well as other important natural products.[5−7] Herein, we report a concise total synthesis of (±)-pseudotabersonine that features a stepwise variant of a

(1) (a) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F. Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 199−384. (b) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 343−376. (c) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 2−197.

(2) Zeches, M.; Debray, M. M.; Ledouble, G.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1975**, *14*, 1122–1124.

(3) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752–1760.

(4) Carroll, W. A.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 1164–1165.

(5) For a general review of olefin metathesis, see: *Handbook of Metathesis*; Grubbs, R. H., Ed., Wiley-VCH: New York, 2003; Vol. 1−3.

(6) For reviews of applications of RCM to the synthesis of complex organic molecules and natural products, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.

(7) For selected examples, see: (a) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694. (b) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251–7164. (c) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781–10787. (d) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432–12433. (e) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584–8592. (f) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523–3525. (g) Neipp, C.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867–8878. (h) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301–7314. (i) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733–5735. (j) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437–11449. (k) Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342–5349. (l) Deck, J. A.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2610–2613.

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Mannich-type multicomponent reaction previously developed in our laboratory,[8] a double RCM reaction, and a one-pot deprotection/cyclization sequence.

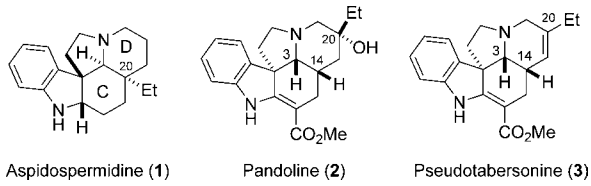
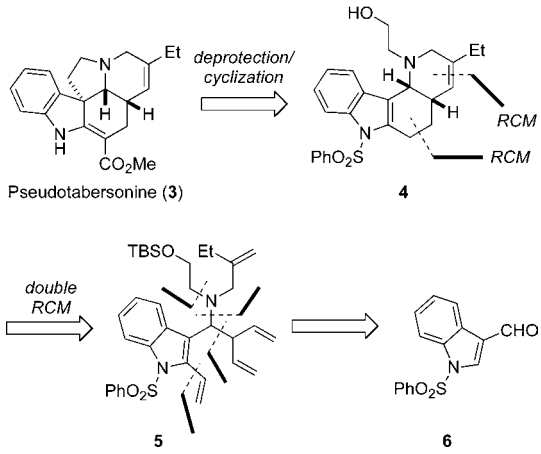


Figure 1. Examples of *Aspidosperma* alkaloids.

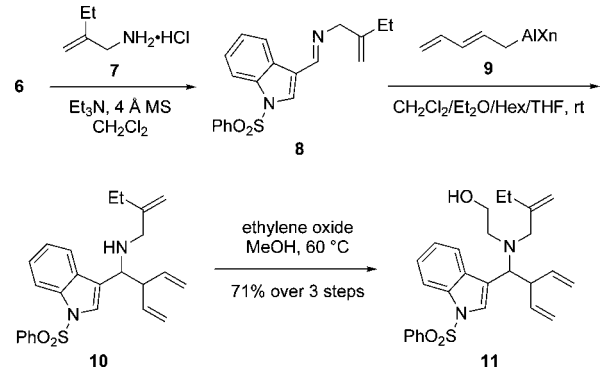
Our retrosynthetic analysis of pseudotabersonine (**3**) is shown in Scheme 1. It was envisioned that **3** could be assembled from the tetracyclic alcohol **4** via deprotection and cyclization using a protocol developed by Bosch and co-workers.[9] Access to **4** would then be achieved by a double RCM of the tetraene **5**, followed by a selective reduction of the less substituted double bond. The synthesis of **5** would involve a sequential union of aldehyde **6**, a substituted allylamine, a pentadienyl organometallic reagent, and ethylene oxide.

Scheme 1. Retrosynthetic Analysis of Pseudotabersonine (**3**)



The synthesis of pseudotabersonine commenced with the condensation of commercially available 1-(phenylsulfonyl)-3-indolecarboxaldehyde (**6**) with 2-ethylallylamine hydrochloride (**7**)[10] to provide the crude imine **8** in virtually quantitative yield (Scheme 2). The next step posed a considerable challenge as it required the selective addition of a pentadienyl organometallic reagent to the imine function to give a branched adduct. Different pentadienyl organometallic reagents (Li, Zn, In, and Al) were examined in this reaction. After considerable experimentation, we discovered that the pentadienyl aluminum reagent **9**, which was generated in situ by transmetalation of pentadienyllithium, provided the best selectivity for the branched product.[7l,11] However, it was essential to allow the reaction to warm to room temperature, because increased amounts of the linear adduct were obtained if the reaction was quenched at −78 °C. In the event, addition of **9** to a solution of crude imine **8** in CH_2Cl_2 followed by subsequent reaction of the adduct **10** with ethylene oxide in a sealed tube at 60 °C in MeOH afforded a mixure of branched and linear products (branched: linear >10:1) in 89% combined yield over two steps. After a single recrystallization, the requisite branched product **11** was obtained in 71% overall yield from **6**.

Scheme 2. Synthesis of Triene **11**



The next stage of the synthesis required the introduction of a vinyl group at C(2) of the indole ring in **11**. Toward this end, **11** was first converted to TBS ether **12** in 98% yield (Scheme 3). Deprotonation of **12** at C(2) with LDA followed by the addition of acetaldehyde generated the epimeric alcohols **13** in 78% yield (dr ≈ 2.5:1). Dehydration of **13** with Tf_2O and Hünig's base furnished the desired tetraene **5** in 92% yield.

Having the tetraene **5** in hand, we were grateful to find that the key double RCM proceeded smoothly in the presence of 5% of Hoveyda−Grubbs II (H-G II) catalyst at 100 °C (oil bath temp) to afford an inseparable mixture (∼7:10) of the C/D *cis*- and *trans*-fused tetracycles **14** and **15**, respectively (Scheme 4).[12] The crude mixture of **14** and **15** was then processed by regioselective reduction of the disubstituted olefinic moiety by catalytic hydrogenation, followed by deprotection of the TBS ether to afford a separable mixture

(8) (a) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. (b) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469.

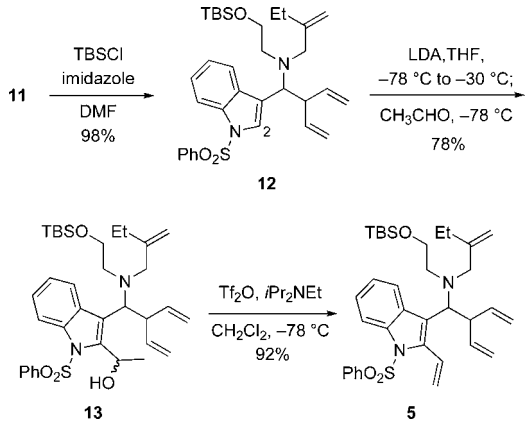
(9) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591–5597.

(10) See Supporting Information for the synthesis of **7**.

(11) For some related references of 1,2-additions of pentadienyl organometallic agents, see: (a) Gerard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, *11* (Pt. 2), 2527–2533. (b) Courtois, G.; Mesnard, D.; Mahoungou, J. R.; Miginiac, L. *Bull. Soc. Chim. Fr.* **1986**, 449–453. (c) Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581–587. (d) Nishigaichi, Y.; Ishihara, M.; Fushitani, S.; Uenaga, K.; Takuwa, A. *Chem. Lett.* **2004**, *33*, 108–109.

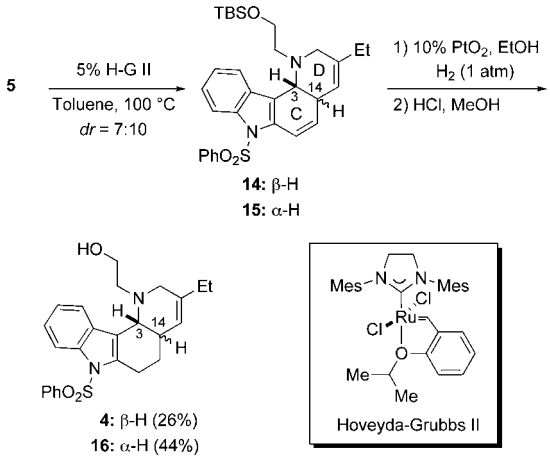
(12) The ratio of **14** and **15** was determined by integrating the signal for H(3) in the ^{1}H NMR of each in the crude double RCM reaction mixture: for **14**, H(3) (δ 4.03, d, J = 7.2 Hz); for **15**, H(3) (δ 4.10, d, J = 16.4 Hz).

Scheme 3. Synthesis of Tetraene **5**



of **4** and **16** in 26% and 44% yields, respectively, from **5** over three steps.

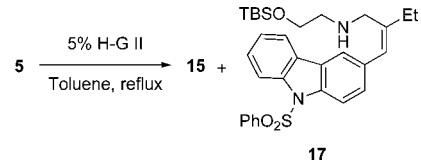
Scheme 4. Double RCM of Tetraene **5**



It is noteworthy that **14** was unstable to longer reaction times and higher temperatures, apparently fragmenting to give **17** (Scheme 5). For example, when the double RCM of **5** was conducted in toluene under reflux, a mixture (≈ 3:1) of **15** and **17**, which presumably arose from **14** via sequential 1,4-elimination and aromatization,[13] was obtained in about 65% yield. This deleterious side reaction demanded careful control of the conditions used for the RCM in order to provide optimal quantities of **14**. Although conducting the reaction at lower temperatures gave an improved ratio (∼1:1) of **14** and **15**, the overall conversions were lower. Accordingly, we decided to continue the synthesis of **3** from **14** and try to epimerize the *trans*-fused C/D ring system in **15** to the requisite *cis*-fused ring system at a later stage (vide infra).

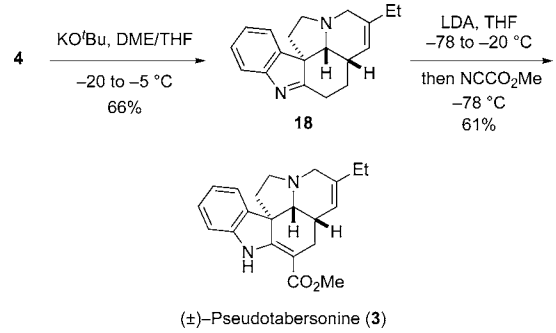
(13) For similar aromatizations, see: (a) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105–2114. (b) Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **1999**, *40*, 3343–3346. (c) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035–6041.

Scheme 5. Double RCM of Tetraene **5** at Higher Temperature



Conversion of **4** to the pentacyclic intermediate **18** was achieved by an intriguing one-pot process, which involved a sequential *N*-deprotection/*O*-sulfonylation and cyclization process, that had been reported by Bosch and co-workers (Scheme 6).[9] In the event, addition of a solution of KO^{t}Bu

Scheme 6. Completion of Total Synthesis of (±)-Pseudotabersonine (**3**)



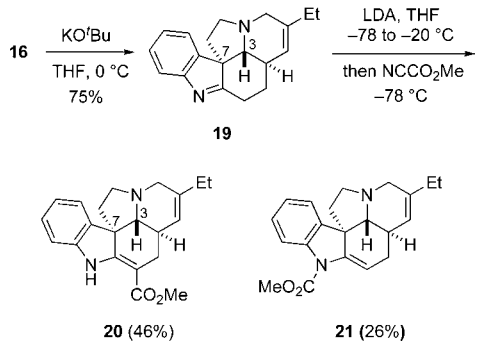
in THF to a solution of **4** in DME afforded **18** in 66% yield. Finally, following a procedure developed by Rawal and co-workers,[14] **18** was deprotonated with LDA, and the intermediate metallo enamine was selectively acylated on carbon using Mander's reagent to furnish (±)-pseudotabersonine (**3**) in 61% yield with only trace amounts of the corresponding *N*-acylated product being detected. The synthetic pseudotabersonine thus obtained gave ^{1}H and ^{13}C NMR spectra that are consistent with the assigned structure of **3** and with those reported and provided by Kuehne.[3,15]

The tetracycle **16** was then transformed to (±)-14-*epi*-pseudotabersonine (**20**) by a series of reactions analogous to those used to convert **4** into **3** (Scheme 7). Namely, treatment of **16** with KO^{t}Bu afforded the C/D *trans* pentacycle **19** in 75% yield. Deprotonation of **19** followed by trapping with Mander's reagent afforded **20** in 46% yield together with the *N*-acylation product **21** in 26% yield. The significant difference in the regioselectivity in the acylations

(14) Kozmin, S.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

(15) Kuehne reported a multiplet for three protons in the range δ 2.01−2.20 and a peak for one proton at δ 1.61 in the ^{1}H NMR spectrum of **3**. Examination of our spectra, including 2D spectra, shows that there are four protons in the range of δ 2.03−2.20, and although there is sometimes a proton at δ 1.60, that has been shown to be water. Given the difference in field strength of our spectra and those of Kuehne, the spectra appear consistent, although there are no integrations on the spectrum of the authentic sample. There are no significant differences in the ^{13}C NMR spectra.

Scheme 7. Synthesis of (±)-14-*epi*-Pseudotabersonine (**20**)



of **18** and **19** using Mander's reagent is both noteworthy and unexpected.

We briefly examined the possibility of epimerizing at C(3) and C(7) of both **19** and **20** via a reversible retro-Mannich/Mannich process, which is precedented for related compounds having a *cis*-fused C/D ring system.[16] Stork has also observed the *trans*- to *cis*-isomerization of the C/D ring subunit of an intermediate during the synthesis of aspidospermine.[17] However, all efforts to convert either **19** or **20** into either **18** or **3** under a variety of acidic conditions (TsOH, AcOH, TFA, TMSOTf, BF_3•Et_2O, HCl, and $Cu(OTf)_2$) led only to recovery of starting material or decomposition. Our failure to effect this equilibration was disappointing but not wholly unexpected as Kuehne was also unable to epimerize a similar C/D *trans*-fused pentacycle.[18] There is thus a significant and heretofore underappreciated difference in the propensity of *cis*- and *trans*-fused C/D ring derivatives having the *Aspidosperma* skeleton to undergo reversible retro-Mannich/Mannich reactions.

In conclusion, we have developed a concise entry to the pentacyclic core of *Aspidosperma* alkaloids via a sequence that featured a stepwise variant of a Mannich-type coupling process to generate a highly functionalized intermediate that was elaborated by a double ring-closing metathesis and a one-pot deprotection/cyclization reaction. This strategy was applied to a total synthesis of (±)-pseudotabersonine that required a total of 14 steps in which the longest linear sequence starting from commercially available **6** was 11 steps. The application of this strategy to the syntheses of other *Aspidosperma* alkaloids having an ethyl group at the C/D bridgehead are currently under investigation in our laboratory.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For examples, see: (a) Smith, G. F.; Wróbel, J. T. *J. Chem. Soc.* **1960**, 792–795. (b) Kutney, J. P.; Piers, E.; Brown, R. T. *J. Am. Chem. Soc.* **1970**, *92*, 1700–1704. (c) Lewin, G.; Poisson, J. *Tetrahedron Lett.* **1984**, *23*, 3813–3814. (d) Pilarèík, T.; Havlíèek, J.; Hájíèek, J. *Tetrahedron Lett.* **2005**, *46*, 7909–7911. (e) Tóth, F.; Oláh, J.; Kalaus, G.; Greiner, I.; Szõllõsy, Á.; Gömöry, Á.; Hazai, L.; Szántay, C. *Tetrahedron* **2008**, *64*, 7949–7955.

(17) Stork, G. *Pure Appl. Chem.* **1964**, *9*, 131–144.

(18) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331–4339.