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Novel Approach to the Lundurine Alkaloids: Synthesis of the Tetracyclic Core

Suvi T. M. Orr, Jianhua Tian, Meike Niggemann, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712, United States

sfmartin@mail.utexas.edu

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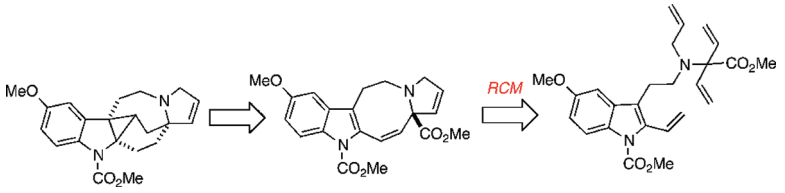
ABSTRACT

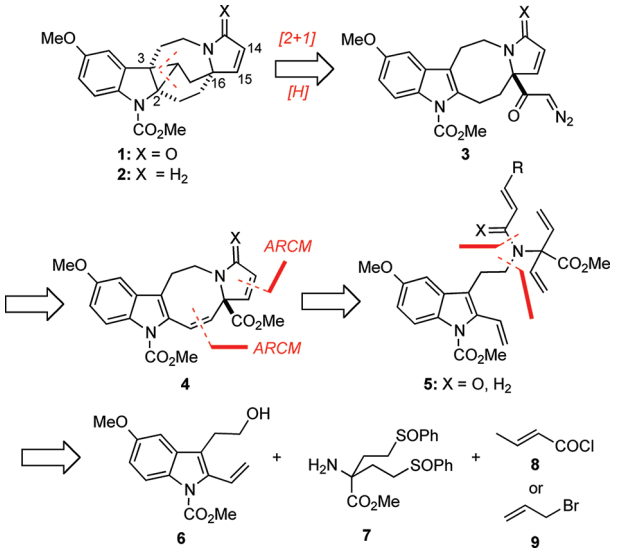


The tetracyclic core of the lundurine family of alkaloids has been synthesized by a novel approach that features a double ring-closing olefin metathesis to form the five-and eight-membered rings.

Lundurine A (**1**) and lundurine B (**2**) belong to a small but important family of hexacyclic alkaloids that was first isolated in 1995 from *Kopsia K. tenuis*.[1] These alkaloids are characterized by a unique propellane structure that comprises a dihydroindole ring fused with eight- and three-membered rings. Because of its limited availability, it was not until 2004 that lundurine B was found to exhibit potent in vitro activity toward B16 melanoma cells (IC_{50} of 2.8 μg/mL); it is also effective in circumventing multidrug resistance in vincristine-resistant KB cells.[2] Lundurine B is thus important as a potential anticancer agent. There are no reported syntheses of any of the lundurines to date, although a few approaches to the skeleton have been reported.[3]

Our retrosynthetic analysis of lundurine B is depicted in Scheme 1. We envisioned that the cyclopropane ring could be constructed via a copper(I)-catalyzed, intramolecular cyclopropanation of an intermediate as **3** followed by a selective deoxygenation using a modified Wolff–Kishner procedure.[4] High facial selectivity in this cyclization would be anticipated in this step owing to the stereochemistry at the preformed quaternary center at C(16). Similar

Scheme 1. Retrosynthetic Analysis



(1) Kam, T.; Yoganathan, K.; Chuah, C. *Tetrahedron Lett*. **1995**, *36*, 759–762.

(2) Kam, T.; Lim, K.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745.

(3) (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358–1373. (b) Donets, P. A.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Org. Lett*. **2009**, *11*, 3618–3621. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020.

(4) (a) Miller, V. P.; Yang, D.; Weigel, T. M.; Han, O.; Liu, H. *J. Org. Chem*. **1989**, *54*, 4175–4188. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc*. **1973**, *95*, 3662–3668.

(5) (a) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett*. **2006**, *8*, 2187–2190. (b) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed*. **2008**, *47*, 3618–3621. (c) Gagnon, D.; Spino, C. *J. Org. Chem*. **2009**, *74*, 6035–6041.

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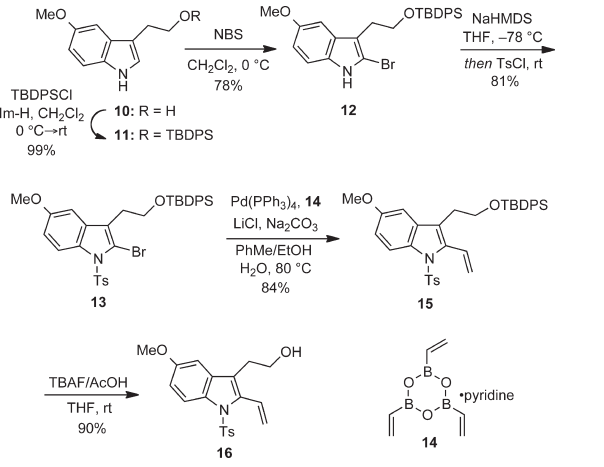
intramolecular cyclopropanations of the C(2)−C(3) double bond of indoles with diazo ester in the presence of transition-metal catalysts are known.[5] The diazoketone moiety of **3** would then arise from the corresponding ester group in **4** via hydrolysis followed by diazomethylation. The tetracycle **4**, a key intermediate in our plan, would be accessed via an enantioselective, double ring-closing metathesis (RCM) reaction involving the tetraene **5**.[6−8] Indeed, the inspiration for utilizing an RCM for the synthesis of the lundurines owes its origin to our long-standing interest in using RCM as a key construction for alkaloid synthesis.[9] Assembly of compound **5** would require coupling of the 2-vinyl indolylethanol derivative **6**, the amine **7**, and a suitable electrophile such as **8** or **9**.

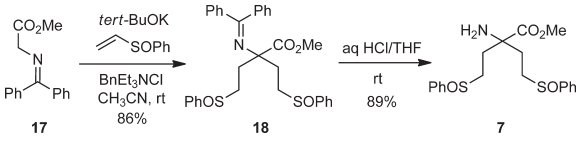
Lundurine B possesses an *N*-carbomethoxy group, but we had some concerns regarding the stability of this moiety during some transformations that we anticipated might be involved as we worked out the synthetic details. We thus decided to conduct our exploratory studies with an *N*-tosyl group that could be easily removed at a later stage. Accordingly, we initiated our investigations by protecting the primary hydroxyl group in **10**, which was prepared according to a known procedure, to give **11** (Scheme 2).[10] Bromination of the protected indolyl ethanol with *N*-bromosuccinimide (NBS) selectively afforded the 2-bromoindole derivative **12** in 78% yield. It should be noted that dibromination of the indole ring, which is the major side reaction in this step, could be suppressed by slow addition of NBS to a solution of **11**. Treatment of **12** with NaHMDS followed by *p*-toluenesulfonyl chloride cleanly provided the tosyl-protected indolyl bromide **13** in 81% yield. Subsequent Suzuki-type cross coupling of **13** with trivinylboroxane (**14**) delivered the 2-vinylindole **15**, which underwent facile fluoride-induced deprotection of the TBDPS group to furnish **16** in 90% yield.

Scheme 2



The next step of the synthesis required preparation of the amine **7** (Scheme 3). Bisalkylations of the imine anion derived from **17** have been reported to provide geminally dialkylated glycine derivatives.[11] Accordingly, the commercially available glycine Schiff base **17**, which can be easily prepared,[12] was subjected to reaction with 2 equiv of phenylvinyl sulfoxide and a stoichiometric amount of K_2CO_3 according to a literature procedure.[9] However, the monoalkylated compound was obtained as the only product in 80% yield. Because this compound could not be further transformed to **18** by resubjection to these reaction conditions, a modified protocol was developed. We eventually discovered that when a stoichiometric amount of *t*-BuOK was employed as the base under phase-transfer conditions, the desired bisalkylated product **18** could be isolated in 86% yield. Hydrolysis of the diphenylimine moiety was achieved by stirring **18** in THF in the presence of aqueous HCl at room temperature for 1 h to give the requisite amine **7** in 89% yield.

Scheme 3



With the alcohol **16** and amine **7** in hand, the secondary amine **19** was readily prepared in 89% yield over two steps by sequential oxidation of **16** to the corresponding aldehyde with 2-iodoxybenzoic acid (IBX) and reductive amination with **7** in the presence of $NaBH(OAc)_3$ (Scheme 4). Amine **19** was then heated in a microwave reactor to induce

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(7) For an example of a RCM of a tetraene, see: Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027–2029.

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(9) (a) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694. (b) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781–10787. (c) 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. (d) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523–3525. (e) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867–8878. (f) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301–7314. (g) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733–5735. (h) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547–6561. (i) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437–11449. (j) Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342–5349. (k) Deck, J. A.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2610–2613.

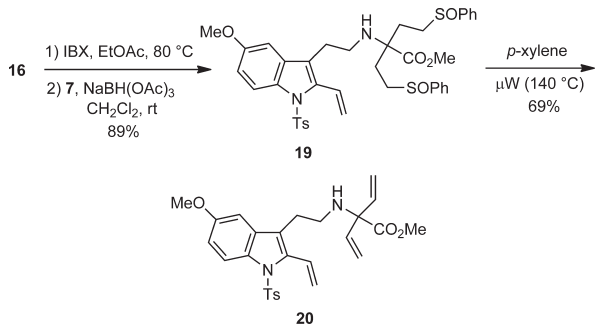
(10) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82.

(11) Opio, J. O.; Labidalle, S.; Galons, H; Micoque, M. *Synth. Commun.* **1991**, *21*, 1743–1754.

(12) (a) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666. (b) Danner, P.; Bauer, M.; Phukan, P.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 317–325.

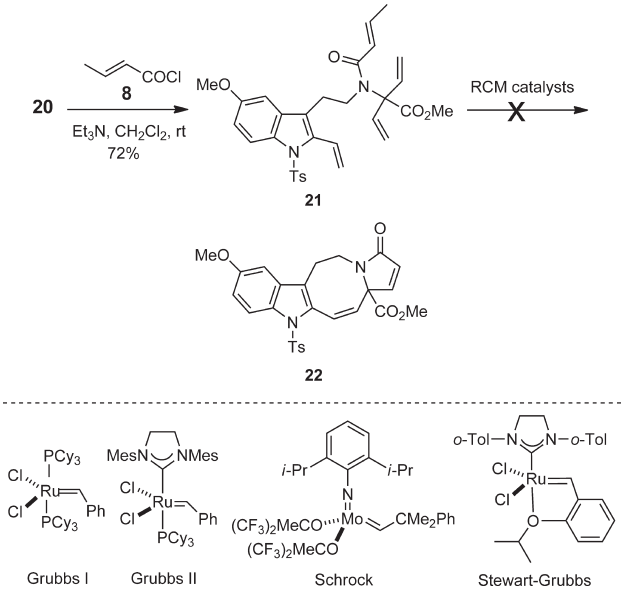
pyrolytic elimination and afford the key intermediate triene **20** in 69% yield.

Scheme 4



With a view toward preparing lundurine A (**1**), which has an unsaturated lactam moiety in the five-membered ring, triene **20** was treated with crotonyl chloride in CH_2Cl_2 in the presence of Et_3N to deliver the tetraene **21** in 72% yield (Scheme 5). Unfortunately, when **21** was heated with Grubbs I catalyst in refluxing CH_2Cl_2 or benzene or at various temperatures with microwave heating, none of the desired tetracyclic compound **22** was isolated. Grubbs II catalyst was also examined as a catalyst as were other RCM catalysts, including the Schrock catalyst and the Stewart–Grubbs catalyst,[13] but none of these afforded detectable amounts of **22**. Use of Grubbs II catalyst in refluxing benzene provided small amounts of a tricyclic compound having an eight-membered ring, perhaps arising from initial loading of the catalyst onto the vinylindole moiety, but further experiments were not pursued because of the low yields. We hypothesized that an unreactive metal–carbene chelate involving the amide oxygen atom

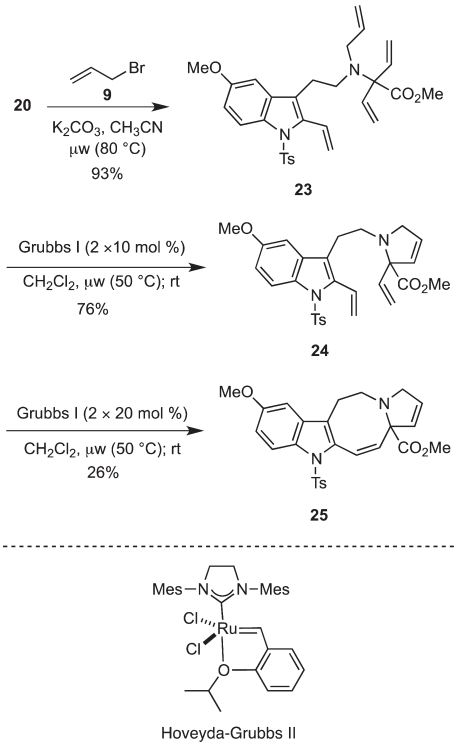
Scheme 5



was formed that shut down the catalytic cycle and precluded an RCM.[14] Toward obviating this potential problem, we conducted the RCM in the presence of $Ti(O-i\text{-}Pr)_4$ (30 mol %),[14b] albeit to no avail.

Reasoning that the tertiary amine derived from **20** might not suffer the same fate, we turned our attention to a synthesis of lundurine B, which lacks a lactam function in the five-membered ring. Accordingly, the tetraene **23** was prepared in excellent yield by allylation of **20** with allyl bromide (Scheme 6). Grubbs I, Grubbs II, Hoveyda–Grubbs II, and Schrock catalysts all promoted the RCM cyclization of **23**, but the yields of **24** were best using the less reactive Grubbs I catalyst. Grubbs I, Grubbs II, and Schrock catalysts promoted the cyclization of **24** to **25**, but the cyclization with the former gave the best yield. Increasing the catalyst loading or using the hydrochloride salt of either **23** or **24**, a tactic that sometimes proves advantageous for cyclizations of bis-olefinic, tertiary amines,[8b] did not improve the yield. Although **25** could also be obtained in a one-pot procedure using Grubbs I catalyst, the overall yield was not as high.

Scheme 6



With the tetracycle **25** in hand, we turned our attention to its conversion to lundurine B (**2**). Catalytic hydrogenation of **25** (Pd/C, 1 atm H_2) gave **26** by

(13) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.

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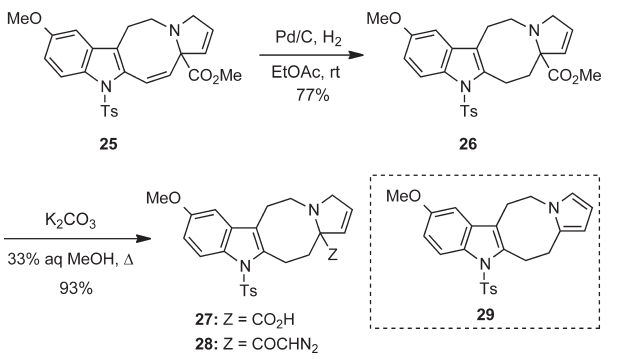
highly selective reduction of the double bond in the eight-membered ring (Scheme 7); no reduction of the olefin in the five-membered ring was observed under these conditions. Subsequent saponification of **26** with K_2CO_3 in $MeOH/H_2O$ (2:1) at 80 °C provided acid **27** in 93% yield.

Preliminary experiments to convert the acid **27** into diazoketone **28** have been unsuccessful. For example, sequential treatment of **27** with isobutyl chloroformate at −20 °C and then diazomethane at 0 °C according to Wardrop's protocol[15] did not provide **28**. Attempts to activate the carboxyl function using thionyl chloride or oxalyl chloride under mild conditions followed by reaction with diazomethane were also unsuccessful. Mixtures of starting material, unidentifiable products, and small amounts of a side product that appeared to be the pyrrole **29** were typically isolated. The pyrrole **29** is presumably formed by decarbonylation of the activated carboxylic acid moiety, giving an iminium intermediate that tautomerizes to give the pyrrole. It has been shown that activation of tertiary amino acids may lead to the formation of iminium ions via decarbonylation, but reported conditions that result in such fragmentations are typically more forcing.[16,17]

In summary, we have developed a novel route to the tetracyclic framework of lundurine B (**2**). Notable features of the approach are a high-yielding reductive amination of a 2-vinylindole-3-acetaldehyde derived from alcohol **16** with a geminally substituted glycine derivative **7**, followed by a thermal elimination of phenylsulfoxide groups to access a prochiral divinyl moiety in **20** and a two-step RCM procedure to form the five-and eight-membered rings of the lundurine skeleton. We are currently exploring several other approaches to the lundurines that will enable the RCM with a chiral catalyst and that will avoid the problematic steps to generate a diazoketone. The results of those investigations will be disclosed in due course.

Scheme 7



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

(15) Wardrop, D. J.; Forslund, R. E. *Tetrahedron Lett.* **2002**, *43*, 737–739.

(16) For example, see: (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448–7449. (b) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990–6997.

(17) For example, see: (a) van Tamelen, E. E.; Oliver, L. K. *Bioorg. Chem.* **1976**, *5*, 309–326. (b) Ambra, T. E. D.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M.; Beglin, N. C.; Chippari, S. M.; Grego, J. D.; Kullnig, R. K.; Daley, G. T. *J. Med. Chem.* **1992**, *35*, 124–135.