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Enantioselective Synthesis of (+)-Isolysergol via Ring-Closing Metathesis

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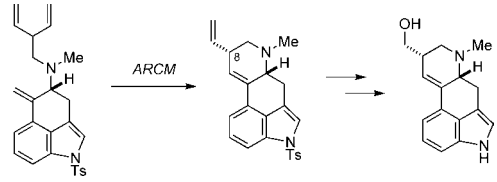
ABSTRACT



The first enantioselective synthesis of (+)-isolysergol was completed in 12 steps from commercially available materials by a novel approach that features a late stage microwave-mediated, diastereomeric ring-closing metathesis catalyzed by a chiral molybdenum catalyst to simultaneously form the D ring and set the stereocenter at C(8).

The development of new and general strategies and tactics for the efficient synthesis of biologically important natural and unnatural substances is vital to advancing the science of organic chemistry. In this context, we were attracted some years ago to the potential of using ring-closing metathesis (RCM)[1,2] as a key construction for alkaloid synthesis,[3] and we have applied such reactions to the syntheses of a number of alkaloids of varying complexity, including FR900482, manzamine A, (+)-anatoxin-a, and dihydrocorynantheol as well as other natural products.[4]

As part of an ongoing program to develop the utility and scope of RCM reactions, we became intrigued by the possibility of exploiting such a construction in the formulation of a novel synthetic approach to the tetracyclic ergot alkaloids. The ergot family of alkaloids has long attracted the interests of synthetic chemists, because of the varied and powerful biological activities of its members. Indeed, ergot alkaloids and their derivatives are widely used in the clinic, and there are numerous formulations containing natural or semisynthetic ergot alkaloids for treating a diverse array of human maladies.[5] Moreover, the challenges associated with preparing these alkaloids are legend, and despite numerous successful syntheses of lysergic acid and its derivatives,[6] there are only two reported enantioselective syntheses,[6k,n] one of which relied upon a late stage resolution.[6k] There are, however, no syntheses that exercise complete regio-

(1) For a general review of olefin metathesis and its applications, see: *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. 1−3.

(2) For a general review of applications of RCM to the synthesis of oxygen and nitrogen heterocycles, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(3) See for example: (a) Martin, S. F. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003, Vol. 2, pp 338−352. See also: (b) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694. (c) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005–6008. (d) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251–7264. (e) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867–8878. (f) Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342–5349.

(4) For selected references, see: (a) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781–10787. (b) 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. (c) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523–3525. (d) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301–7314. (e) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733–5735. (f) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547–6561. (g) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437–11449.

(5) Mukherjee, J.; Menge, M. *Adv. Biochem. Eng. Biotechnol.* **2000**, *68*, 1–20.

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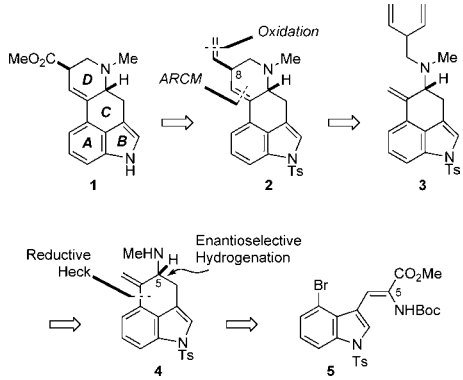
chemical control of the $\Delta^{9,10}$-double bond, the stereochemistry at C(8), and absolute stereochemistry. Thus, even though 50 years have passed since the first synthesis of lysergic acid, unsolved problems remain, despite a myriad of advances in synthetic methodology.

Toward designing an enantioselective route to the lysergate group of alkaloids that addressed all of the stereo- and regiochemical control issues, we developed the plan outlined in Scheme 1. We envisioned that methyl lysergate (**1**) could be accessed from the advanced intermediate **2** by oxidative cleavage of the vinyl group at C(8) and deprotection of the indole nitrogen atom. The $\Delta^{9,10}$-double bond in **2** would be formed regioselectively via an asymmetric ring-closing metathesis (ARCM) reaction of **3**.[7] This cyclization posed a significant challenge to existing technology as it mandated that the catalyst load selectively first onto one of the two

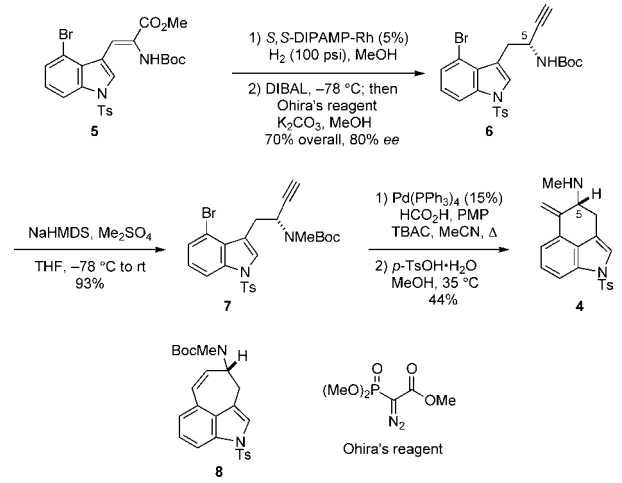
Scheme 1. Approach to Methyl Lysergate (**1**)



diastereotopic vinyl groups prior to the RCM with the disubstituted exocyclic olefin. This process is to be contrasted with the usual sequence of ARCM reactions that presumably proceed by initial loading of the chiral catalyst onto the least hindered double bond of a triene, followed by selective cyclization involving one of the two enantiotopic olefins to deliver the chiral product, often with high enantioselectivity. Whether the desired cyclization of **3** would require a chiral catalyst to optimize the diastereoselectivity could only be addressed through experimentation. Indeed, the interesting questions surrounding cyclizations of substrates like **3** via ARCM processes provided a strong impetus for our efforts. The preparation of **3** would then require the *N*-alkylation of **4**, a reaction that was by no means certain. In earlier work we had prepared racemic **4** from the dehydro tryptophan derivative **5** by a sequence that featured a reductive Heck cyclization.[8] Accordingly, access to **4** in enantiomerically pure form would require an enantioselective hydrogenation of **5**.

The known dehydroamino acid **5** was reduced with a *S*,*S*-DIPAMP modified rhodium catalyst to give a protected 4-bromotryptophan derivative in nearly quantitative yield and >90% enantioselectivity, thereby setting the absolute stereochemistry at C(5) (Scheme 2).[9] Processing of the methyl ester into an acetylene moiety was achieved in a convenient, one-pot procedure according to a process we had previously developed that involved hydride reduction followed by reaction of the intermediate aldehyde with Ohira's reagent to give **6** (80% ee).[3e,10] Despite considerable experimentation,

Scheme 2. Assembly of the Carbon Framework



we were unable to avoid some racemization during this process. Selective *N*-methylation of the carbamate moiety proceeded smoothly to give **7**. When *N*-methylation was performed on the intermediate protected amino acid ester, extensive racemization at C(5) was observed. Reductive Heck cyclization of **7** in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP), followed by acid-catalyzed removal of the Boc protecting group, gave **4** in 44% yield. This sequence was conducted without purification of the intermediate Heck product because the latter was contaminated with small quantities of the 7-membered ring

(6) For selected syntheses of and approaches to lysergic acid, see: (a) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087–3114. (b) Oppolzer, W.; Francotte, E.; Båttig, K. *Helv. Chim. Acta* **1981**, *64*, 478–481. (c) Rebek, J., Jr.; Tai, D. F.; Shue, Y.-K. *J. Am. Chem. Soc.* **1984**, *106*, 1813–1819. (d) Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 941–948. (e) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1988**, *29*, 3117–3120. (f) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487–489. (g) Özlü, Y.; Cladingboel, D. E.; Parsons, P. J. *Tetrahedron* **1994**, *50*, 2183–2206. (h) Barbey, S.; Mann, J. *Synlett* **1995**, 27–28. (i) Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704–2713. (j) Ralbovsky, J. L.; Scola, P. M.; Sugino, E.; Burgos-Garcia, C.; Weinreb, S. M.; Parvez, M. *Heterocycles* **1996**, *43*, 1497–1512. (k) Moldvai, I.; Temesvári-Major, E.; Incze, M.; Szentirmay, É.; Gács-Baitz, E.; Szántay, C. *J. Org. Chem.* **2004**, *69*, 5993–6000. (l) Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3–5. (m) Inoue, T.; Yokoshima, S.; Fukuyama, T. *Heterocycles* **2009**, *79*, 373–378. (n) Kurokawa, T.; Isomura, M.; Tokuyama, H.; Fukuyama, T. *Synlett* **2009**, 775–777.

(7) For a review of ARCM, see: Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633.

(8) Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635–1638.

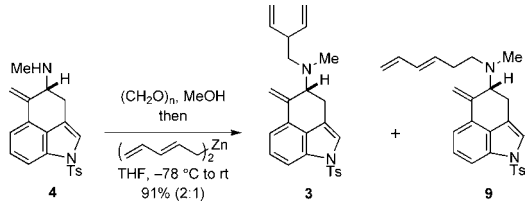
(9) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486–1487.

(10) Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597–5599.

product **8** together with other impurities that were difficult to remove.

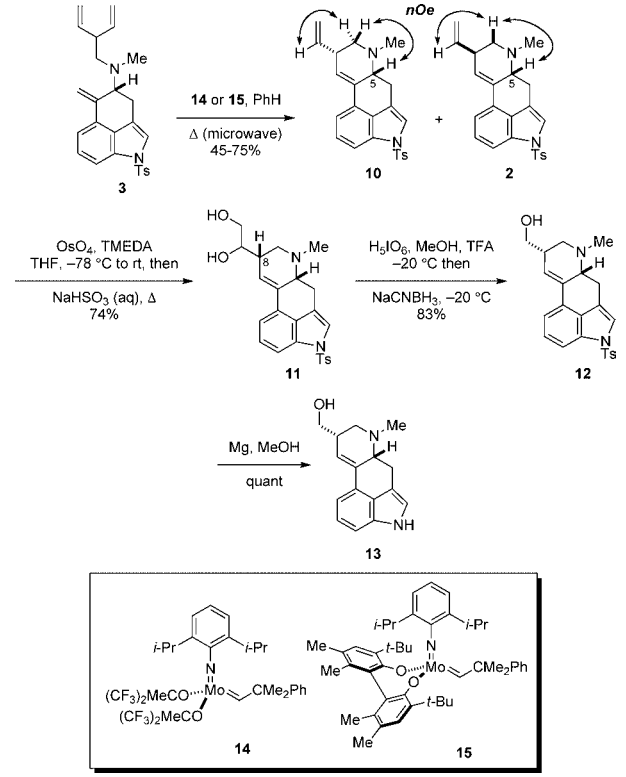
At this juncture, it was necessary to convert **4** into the triene **3**. Preliminary attempts to introduce the branched dienyl group onto **4** via alkylation with 3-bromo-1,4-pentadiene or similar amidation followed by selective reduction were unsuccessful. We eventually discovered, via extensive experimentation with reaction conditions and various pentadienyl organometallic agents, that reaction of the putative *N*,*O*-acetal derived from **4** with bispentadienylzinc provided **3** and **9** as an easily separable mixture (2:1) in 91% yield and 2:1 regioselectivity.[11]

Scheme 3. Setting up the ARCM



With triene **3** available, the key RCM was at hand. However, reaction of **3** with Grubbs I and II catalysts as well as Schrock's catalyst (**14**) either at room temperature or upon heating to 100 °C gave no isolable cyclization product. Similarly, analogues of **3** wherein the *N*-Me group had been exchanged for an *N*-Boc group or quaternized with iodomethane would not undergo metathesis. While it is well-known that microwave heating can accelerate and improve the efficiency of transition metal mediated processes,[12] we are aware of no example of the use of microwave heating with molybdenum based metathesis catalysts. We were therefore delighted to find that heating **3** in the presence of **14** using microwave irradiation (300 W, 10 min) and forced air cooling did indeed induce a diastereoselective RCM to provide **10** and **2** in about 36% and 8% yields, respectively. The relative configurations of **10** and **2** were deduced via nOe correlations of protons on the D-ring and the pendant vinyl group relative to the proton of known configuration at C(5) as shown. Because substrate-based control in the RCM led to the preferential formation of the undesired "iso" product **10**, we queried whether a chiral RCM catalyst might override this inherent diastereoselection and deliver increased amounts of **2**. Although no substrates of the complexity of **3** have been subjected to ARCM reactions, a review of the literature suggested that the Schrock−Hoveyda catalyst **15**[13] might generate **2** as the major product. However, microwave heating (50 W, 30 min) of **3** in the presence of **15** again provided a mixture of **10** and **2**, but with improved yields of 55% and 20%, respectively. The antipodal Schrock-Hoveyda ***ent*-15** catalyst did not grant favoritism of **2** versus **10** and gave instead only trace amounts of **2** and **10**, presumably as a consequence of being mismatched. We also examined several other chiral molybdenum-derived catalysts that had been more recently developed by Hoveyda, but none of these led to improved levels of diastereoselectivity for either **10** or **2**.

Scheme 4. ARCM and Completion of the Synthesis of (+)-Isolysergol (**13**)



Conversion of either **2** or **10** into methyl lysergate (**1**) or methyl isolysergate via oxidative cleavage of the vinyl group at C(8) proved to be an insurmountable challenge, a difficulty we attributed to the apparent instability of the intermediate aldehyde.[14] After considerable experimentation, we discovered that the vinyl group in **10** could be cleaved by selective dihydroxylation of the terminal olefin, using a protocol reported by Donohoe, to give diols **11** as an inconsequential mixture (6.5:1) of diastereomers.[15] Attempted oxidation of an analogue of **11** having a protected primary alcohol to give

(11) For related additions, see: (a) Courtois, G.; Harama, M.; Miginiac, P. *J. Organomet. Chem.* **1981**, *218*, 275–298. (b) Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581–587.

(12) For some recent leading references, see: (a) Michaut, A.; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2007**, 2867–2871. (b) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125–1132. (c) Nicks, F.; Borguet, Y.; Delfosse, S.; Bicchielli, D.; Delaude, L.; Sauvage, X.; Demonceau, A. *Aust. J. Chem.* **2009**, *62*, 184–207.

(13) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.

(14) Lysergaldehyde has not been characterized, and the few reports dealing with it or derivatives thereof describe only difficulties in formation of the aldehyde. For examples, see: (a) Lin, C.-C. L.; Blair, G. E.; Cassady, J. M.; Gröger, D.; Maier, W.; Floss, H. G. *J. Org. Chem.* **1973**, *38*, 2249–2251. (b) Choong, T. C.; Thompson, B. L.; Shough, H. R. *J. Pharm. Sci.* **1977**, *66*, 1340–1341.

(15) Donohoe, T. J.; Moore, P. R.; Waring, M. J. *Tetrahedron Lett.* **1997**, *38*, 5027–5030.

the corresponding ketone led to an intractable mixture, further supporting the unstable nature of such compounds having an aldehyde or a ketone at C(8) rather than the more commonly observed carboxylic acid derivatives. Subsequent reaction of **11** with periodic acid in the presence of TFA, followed by immediate reduction of the unstable aldehyde thus produced with $NaBH_3CN$, then furnished **12** in 83% yield. Removal of the tosyl protecting group from the indole nitrogen atom delivered (+)-isolysergol (**13**). Synthetic **13** displayed spectral characteristics (^1H NMR, ^{13}C NMR, TLC, HPLC) identical with those in the literature and with an authentic sample of racemic **13** provided by Professor Ohno.[16] The ee of **13** thus obtained was determined to be 85% using chiral HPLC in comparison with racemic **13**.

In summary, we have completed the first enantioselective synthesis of isolysergol. The synthesis features a novel RCM, which was promoted by the chiral catalyst **15** using microwave heating, of the complex triene **3** bearing diastereotopic vinyl groups to give preferentially **10**, a cyclization that is enhanced through the agency of the chiral catalyst **15**. The synthesis requires a total of only 12 steps from commercially available 4-bromoindole. Other applications of olefin metathesis to solving problems in the total synthesis of complex natural products are under active investigation, and the results of these studies will be disclosed in due course.

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

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(16) (a) Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T.; Barton, D. H. R.; Lusinchi, X.; Milliet, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 707–713. (b) Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 5239–5242.