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The Enantioselective Birch–Cope Sequence for the Synthesis of Carbocyclic Quaternary Stereocenters. Application to the Synthesis of (+)-Mesembrine

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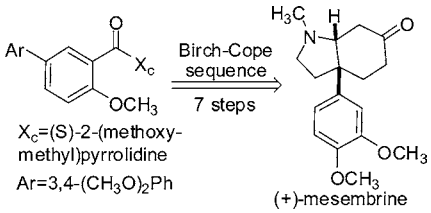
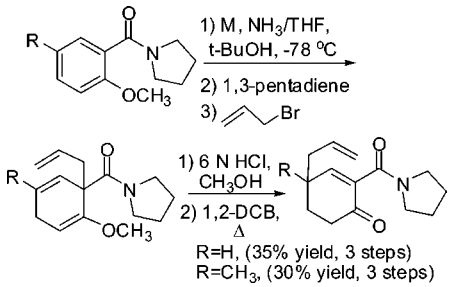
ABSTRACT



A synthetic technique for generating carbocyclic quaternary stereocenters with exceptionally high levels of enantioselectivity is described. A sequence of three reactions, enantioselective Birch reduction–allylation, enol ether hydrolysis, and Cope rearrangement, is used to stereoselectively generate chiral quaternary centers on a 2-cyclohexen-1-one ring. The products of the sequence are 4,4-disubstituted-2-carboxamide-2-cyclohexen-1-one structures which are versatile intermediates in complex natural product synthesis. An application of the sequence to the synthesis of (+)-mesembrine illustrates the utility of these intermediates.

One significant challenge in modern synthetic organic chemistry is the enantioselective synthesis of carbocyclic quaternary stereogenic centers.[1] Recently, we communicated a sequence of reactions that efficiently generates quaternary stereogenic centers.[2] The three-step sequence involves a Birch reduction−allylation, enol ether hydrolysis, and Cope rearrangement (Birch−Cope sequence, Scheme 1). Use of the elegant asymmetric Birch reduction−alkylation method of Schultz would make this process enantioselective.[3] Herein we describe our application of the asymmetric Birch reduction−alkylation method to the Birch−Cope sequence.

Scheme 1. Birch−Cope Sequence



(1) (a) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581−1587. (b) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7184. (c) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774−2775. For reviews see: (d) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Federal Republic of Germany, 2005. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (f) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (g) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (h) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (i) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(2) (a) Malachowski, W. P.; Banerji, M. *Tetrahedron Lett.* **2004**, *45*, 8183−8185. (b) Malachowski, W. P.; Banerji, M. Cope Rearrangement of Birch Reduction-Allylation Products. In *Abstract of Papers*; 228th National Meeting of the American Chemical Society, Philadelphia, August 22−26, 2004; American Chemical Society: Washington, DC, 2004.

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Furthermore, to illustrate the potential of this tool to address challenges in the asymmetric synthesis of carbocyclic quaternary stereogenic centers, the Birch−Cope sequence is applied to the enantioselective synthesis of (+)-mesembrine (Figure 1), the unnatural isomer of the bioactive alkaloid.[4,5]

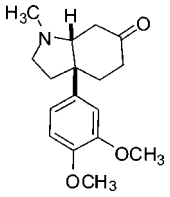
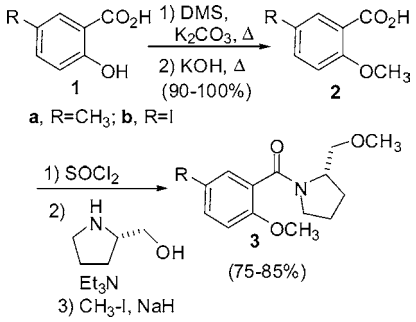


Figure 1. (+)-Mesembrine.

Mesembrine is a member of the *Sceletium* alkaloids and has demonstrated interesting bioactivity.[6] Most notably, a recent report[7] describes potent serotonin re-uptake inhibitor activity for the natural isomer, (−)-mesembrine.

The *o*-anisic acid derivatives, which were used as starting materials in the Birch−Cope sequence, were synthesized from commercially available precursors (Scheme 2).[3a]

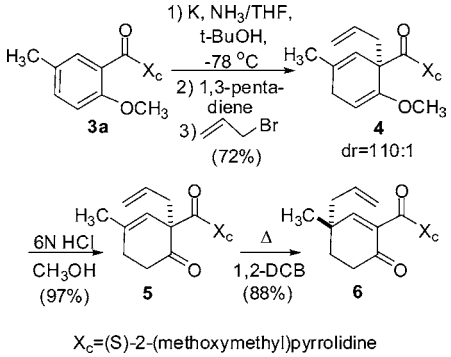
Scheme 2. Birch Reduction−Allylation Substrate Preparation



Methylation of both the phenol and the carboxylic acid was accomplished with dimethyl sulfate (DMS). After saponification, the acid was converted to the acid chloride and coupled with (L)-prolinol, the chiral auxiliary. Methylation of the alcohol of (L)-prolinol afforded the *o*-anisic acid derivatives **3**. The entire sequence affords **3** in roughly 75% yield for the five steps, with chromatographic purification only necessary for **3**.

The 5-methyl derivative **3a** was chosen as the first test of the enantioselective Birch−Cope sequence. *o*-Anisic acid **3a** was subjected to Birch reduction−allylation to afford cyclohexadiene **4** (Scheme 3). Compound **4** was obtained in 72% isolated yield and shown to be a 110:1 mixture of diastereomers by GC analysis and comparison with an independently synthesized 1:1 diastereomeric mixture.[8] The other major product (~15%) was the result of γ-allylation at the C-3 position.[9] The absolute sense of the new quaternary center in **4** and all subsequent Birch products is based on the preferences reported by Schultz.[3] Hydrolysis of the methyl enol ether afforded the 1,5-diene Cope substrate **5**, which was heated at reflux in 1,2-dichlorobenzene (1,2-DCB) for 10 h to effect the stereospecific Cope rearrangement,[10] leading to the thermodynamically more stable isomer **6**. The entire process can be conducted on gram scale in ~60% overall yield.

Scheme 3. Enantioselective Birch−Cope Sequence



Variation of the C-5 group of the *o*-anisic acid derivatives was pursued through a divergent strategy that utilized **3b** as a substrate in cross-coupling reactions (Scheme 4). Previous reports have described biaryl Birch substrate synthesis via

(3) (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828−7841. For reviews of the asymmetric Birch reduction−alkylation, see: (b) Schultz, A. G. *Chem. Commun.* **1999**, 1263−1271. (c) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207−213.

(4) For the isolation and structural determination of the natural isomer (−)-mesembrine, see: (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind.* **1961**, 402−403.

(5) For leading references to previous enantioselective syntheses of (−)-mesembrine, see: (a) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711−7714. (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143−147. (c) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747−7750. (d) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979−8982. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675−1686. (f) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263−3270. (g) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135−139. (h) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785−6790. (i) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239−1242. (j) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479−4482. For leading references to previous enantioselective syntheses of (+)-mesembrine, see: (k) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1409−1412. (l) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776−7778.

(6) Smith, M. T.; Crouch, N.; Gericke, N.; Hirst, M. *J. Ethnopharmacol.* **1996**, *50*, 119−130.

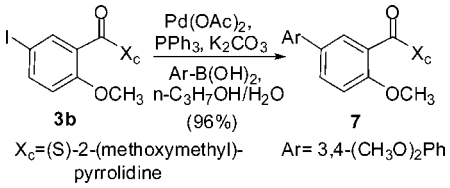
(7) Gericke, N. P.; VanWyk, B.-E. PCT Int. Appl., WO 9746234 CAN 128:80030, 1997.

(8) A diastereomeric mixture of **4** was synthesized as described in ref 3a. A diastereomeric mixture of **8** was generated by modifying the Birch reduction conditions, i.e., removal of NH_3, as described in ref 3a.

(9) γ-Alkylation of amide enolates derived from Birch reduction has previously been reported, see ref 3a and references therein.

(10) (a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441−444. For reviews of the Cope rearrangement, see: (b) Nubbemeyer, U. *Synthesis* **2003**, *7*, 961−1008. (c) Hill, R. K. Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon Press: Oxford, UK, 1991; Vol. 5, Chapter 7.1. (d) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1−252.

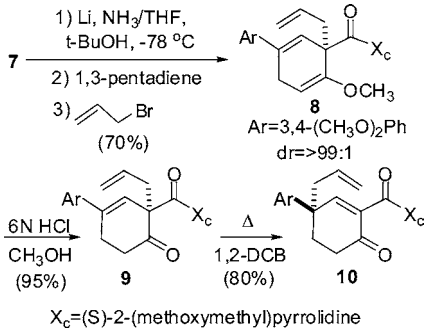
Scheme 4. Biaryl Birch Substrate Preparation



Suzuki−Miyaura reactions prior to the addition of the chiral auxiliary.[11] However, (L)-proline is inexpensive and the divergent strategy was more efficient to synthesize a selection of biaryl compounds. For the present study, a cross-coupling reaction between **3b** and 3,4-dimethoxyphenylboronic acid generated **7**.

Application of the Birch−Cope sequence to **7** began with the asymmetric Birch reduction−allylation to yield **8** (Scheme 5). The Birch reduction demonstrates excellent chemoselectivity for the more electron deficient aromatic ring.[12] Decomposition of **8** under GC conditions necessitated the use of HPLC analysis to determine the stereoselectivity of the process. HPLC analysis of **8** revealed maximum stereoselectivity with more dilute reactions. Therefore a diastereomeric ratio (dr) of 60:1 was seen when **7** was reduced at 8 mM, but that stereoselectivity increased to >99:1 when **7** was reduced at a more dilute 4 mM. Completion of the Birch−Cope sequence entailed hydrolysis of **8** to provide a 3-cyclohexen-2-one **9** that efficiently rearranged to **10**.

Scheme 5. Birch−Cope Sequence with Biaryl Substrate



Despite the presence of phenyl conjugation in **9**, the equilibrium favors **10** to a significant extent, albeit slightly less than the equilibrium for **5**/**6**. The Cope rearrangement of **5**/**6** provides complete conversion to **6**. However, under the same thermal equilibration conditions, 15% of **9** is recovered after chromatographic purification. To the best of our knowledge, this represents the first case of a Cope equilibrium that balances the stabilization of phenyl group conjugation versus conjugation with a ketone. Amide conjugation is expected to be weak based on literature reports of related structures[13] and computational studies[14] (Figure 2) that show the amide to be orthogonal to the enone system due to steric hindrance.

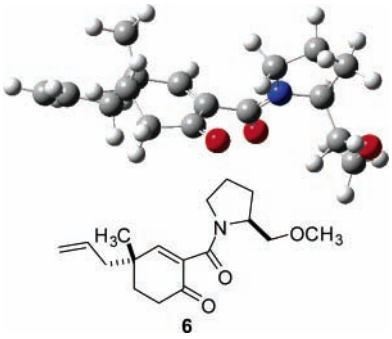
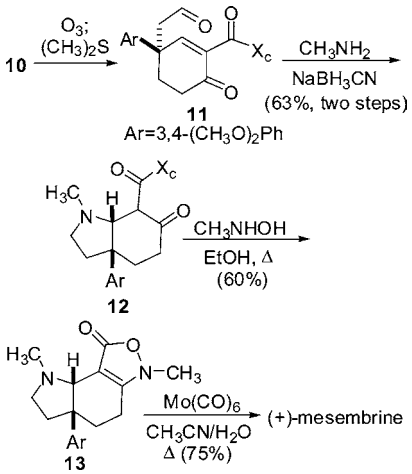


Figure 2. Semiempirical minimization of **6**.

With both **5** and **7**, the Cope rearrangement generated a versatile 4-allyl-2-cyclohexen-1-one system. To demonstrate the potential of these structures as important intermediates in complex natural product synthesis, **10** was elaborated into (+)-mesembrine (Scheme 6). Ozonolysis of the terminal alkene afforded aldehyde **11**. This was unstable, so it was immediately subjected to reductive amination. The resulting secondary amine spontaneously underwent conjugate addition to afford **12**. Cleavage of the chiral auxiliary with *N*-methylhydroxylamine afforded **13**, which was reduced, hydrolyzed, and decarboxylated in one step to afford (+)-

Scheme 6. (+)-Mesembrine Synthesis



(11) Khim, S.-K.; Dai, M.; Zhang, X.; Chen, L.; Pettus, L.; Thakkar, K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7728−7733.

(12) For other examples of chemoselective biaryl Birch reduction−alkylations, see ref 11 and: (a) Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919−921. (b) Guo, Z.; Schultz, A. G.; Antoulinakis, E. *Org. Lett.* **2001**, *3*, 1177−1180. (c) Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931−4936. (d) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 2456−2464.

(13) Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926−4931.

mesembrine, identical with authentic material (see the Supporting Information). The one-step N−O reduction, hydrolysis, and concomitant decarboxylation was a fortuitous event and, to our knowledge, represents the first report of such a tandem process caused by $Mo(CO)_6$.[15]

In conclusion, an enantioselective Birch−Cope sequence has been developed and shown to be effective in the synthesis of carbocyclic quaternary stereocenters. To demonstrate the application of this synthetic tool, (+)-mesembrine has been synthesized in a concise sequence of eight steps from **3b**. Further studies are being undertaken to explore the breadth of applications possible for this exciting new sequence.

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Supporting Information Available: General experimental details, copies of ^1H and ^{13}C NMR spectra, and chromatographs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Minimization of compound **6** was accomplished with semiempirical calculations (AM1), using the Gaussian 03 suite of programs. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.05; Gaussian, Inc.: Wallingford, CT, 2004.

(15) Molybdenum hexacarbonyl deallylation and decarboxylation of a β-ketoester has been described: Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1984**, *10*, 1721−1724.