ORGANIC LETTERS

2012
Vol. 14, No. 11
2742–2745

Total Syntheses of Chelidonine and Norchelidonine via an Enamide–Benzyne–[2 + 2] Cycloaddition Cascade

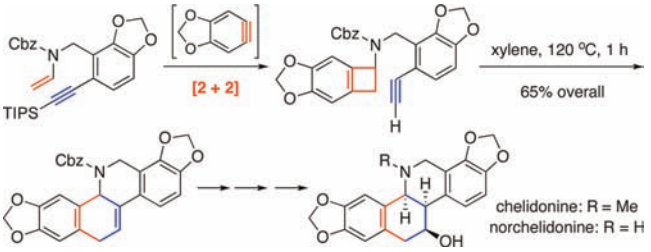
Zhi-Xiong Ma, John B. Feltenberger, and Richard P. Hsung*

Department of Chemistry and Division of Pharmaceutical Sciences, University of Wisconsin, Madison, Wisconsin 53705, United States

rhsung@wisc.edu

Received April 13, 2012

ABSTRACT



Total syntheses of chelidonine and norchelidonine featuring an enamide–benzyne–[2 + 2] cycloaddition initiated cascade is described. The cascade includes a pericyclic ring-opening and intramolecular Diels–Alder reaction.

Our laboratory recently unveiled a de novo cascade of pericyclic ring-openings of amidobenzocyclobutanes and *N*-tethered intramolecular Diels–Alder [IMDA] cycloadditions initiated through an enamide–benzyne–[2 + 2] cycloaddition (**1** → **2** → **3** → **4** in Scheme 1).[1] This tandem cascade possesses the unique feature of not only linking together the prevailing benzyne chemistry[2−4] with enamides that have become a highly versatile and accessible functional group[5−7] but also accentuating the less developed thermally driven [2 + 2] cycloaddition reaction manifold[8−10] while exploiting the powerful Oppolzer-type *N*-tethered IMDA strategy.[11−15] Accordingly, an application of this cascade in the synthesis of

(1) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666.

(2) For reviews on the aryne chemistry, see: (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (b) Peña, D.; Pérez, D.; Guitián, E. *Heterocycles* **2007**, *74*, 89. (c) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (d) Guitián, E.; Pérez, D.; Peña, D. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer-Verlag: Weinheim, 2005; Vol. 14, pp 109–146. (e) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (f) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 83–515. (g) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

(3) Also see: (a) Sadana, A. K.; Saini, R. K.; Billups., W. E. *Chem. Rev.* **2003**, *103*, 1539. (b) Mehtaa, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625.

(4) For recent examples, see: (a) Łaczkowski, K. Z.; García, D.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Org. Lett.* **2011**, *13*, 960. (b) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946. (c) McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667. (d) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (e) Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, 640. (f) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413. (g) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *38*, 3458. (h) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (i) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270. (j) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (k) Bhuvaneswari, S.; Jeganmohan, M.; Yang, M.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2158. (l) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393.

(5) For a general review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4.

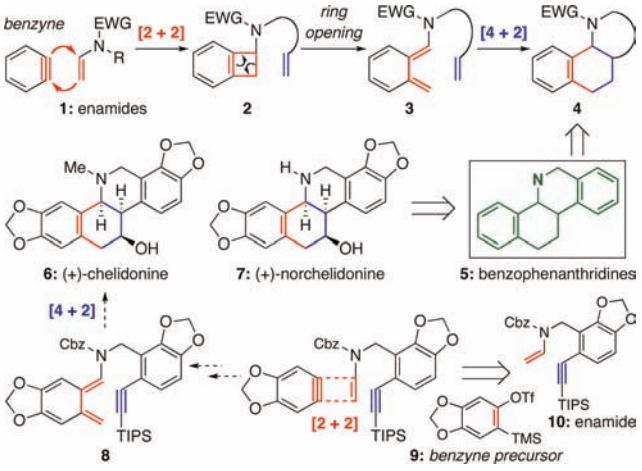
(6) For reviews on Cu-mediated C–N and C–O bond formations for enamide synthesis, see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. For reviews on Pd-catalyzed *N*-arylations of amines and amides, see: (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. *Acc. Chem. Res.* **1998**, *31*, 805.

(7) For a leading review on recent chemistry of enamides, see: (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *9*, 3455. (b) Rappoport, Z. *The Chemistry of Enamines in The Chemistry of Functional Groups*; John Wiley and Sons: New York, 1994.

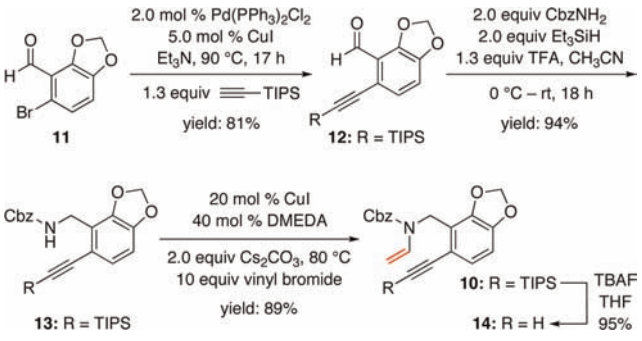
10.1021/ol300967a
Published on Web 05/10/2012

benzophenanthridine alkaloids [see **5** in the box] was pursued. In particular, we have been focusing on (+)-chelidonine **6** and (+)-norchelidonine **7**, which despite being known for well over a century,[16−21] remain an excellent proving ground for showcasing synthetic methods.[22,23] Our strategy would be based on the above cascade using benzyne precursor **9** and enamide **10**. We report here the total syntheses of (±)-chelidonine and (±)-norchelidonine.

Scheme 1. Enamide−Benzyne−[2 + 2] Cascade to Chelidonine



Scheme 2. Synthesis of Enamide **10**



Synthesis of enamide **10**[24] could be expeditiously achieved as shown in Scheme 2 from the commercially available aldehyde **11**, featuring Sonogashira coupling,[25] reductive amination,[26] and Cu(I)-catalyzed amidation of vinyl bromide.[27] For comparisons in the later benzyne−[2 + 2] cycloaddition, we also desilylated **10** to access enamide **14** with an unsubstituted alkyne. The benzyne precursor, silylaryl triflate **9**, was prepared from sesamol **15** in two steps.[28]

(8) For a leading review on thermal [2 + 2] cycloaddition reactions, see: Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 63.

(9) For [2 + 2] cycloadditions of arynes with enamines, see: (a) Gingrich, H. L.; Huang, Q.; Morales, A. L.; Jones, M. *J. Org. Chem.* **1992**, *57*, 3803. (b) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2693. (c) Crews, P.; Beard, J. *J. Org. Chem.* **1973**, *38*, 522. (d) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Hayasaka, T.; Kusama, O. *J. Chem. Soc. (C)* **1971**, 1051.

(10) For reports on amidobenzocyclobutane formation as side products through enamide−benzyne−[2 + 2] cycloaddition, see: (a) Castedo, L.; Guitian, E.; Saá, C.; Suau, R.; Saá, J. M. *Tetrahedron Lett.* **1983**, *24*, 2107. (b) Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, 1159.

(11) (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833. (b) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (c) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141.

(12) For a recent example of such IMDA, see: Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 3114.

(13) For reviews, see: (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (c) Kametuni, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3.

(14) For reviews on chemistry of dienamides, see: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Petrzilka, M. *Synthesis* **1981**, 753. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421.

(15) For a leading review for intramolecular Diels−Alder strategies for natural product synthesis, see: Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341.

(16) For isolation of (+)-chelidonine from *Chelidonium majus* L., see: Probst, J. M. *Ann. Pharm.* **1839**, *29*, 113.

(17) For structural assignment of (+)-chelidonine, see: (a) von Bruchhausen, F.; Bersch, H. W. *Chem. Ber.* **1930**, *63*, 2520. (b) von Bruchhausen, F.; Bersch, H. W. *Chem. Ber.* **1931**, *64*, 947. (c) Späth, E.; Kuffner, F. *Chem. Ber* **1931**, *64*, 370. (d) Bersch, H. W. *Arch. Pharm.* **1958**, *291*, 491. (e) Santavy, F.; Horák, M.; Maturová, M.; Brabenec, J. *Collect. Czech. Chem. Commun.* **1960**, *25*, 1344. (f) Soane, E. *An. Real Soc. Espan. Fis. Quim. Ser. B* **1965**, *61*, 755.

(18) Isolation of either enantiomer of chelidonine from a different plant source, see: (a) Slavík, J.; Slavíková, L. *Collect. Czech. Chem. Commun.* **1957**, *22*, 279. (b) Slavík, J.; Slavíková, L. *Collect. Czech. Chem. Commun.* **1959**, *24*, 3141. The racemate of chelidonine was also isolated but was named as diphylline, see: (c) Schlotterbeck, J. O.; Watkins, H. C. *Chem. Ber.* **1902**, *35*, 7. (d) Slavík, J.; Slavíková, L.; Brabenec, J. *Collect. Czech. Chem. Commun.* **1965**, *30*, 3697. (e) Slavíková, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 635.

(19) For absolute configuration of (+)-chelidonine, see: (a) Takao, N.; Bessho, N.; Kamiguuchi, M.; Iwasa, K.; Tomita, K.; Fujiwara, T.; Fujii, S. *Tetrahedron Lett.* **1979**, *20*, 495. (b) Takao, N.; Morita, N.; Kamiguuchi, M.; Iwasa, K.; Tomita, K.; Fujiwara, T.; Fujii, S. *Acta Crystallogr.* **1981**, *B37*, 2043.

(20) For a biosynthetic study on chelidonine, see: Battersby, A. R.; Staunton, J.; Wiltshire, H. R.; Francis, R. J.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1147.

(21) For isolation of (−)-norchelidonine, see: (a) Slavík, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 3601. (b) Slavík, J.; Slavíková, L. *Collect. Czech. Chem. Commun.* **1959**, *24*, 3141. (c) Necas, M.; Dostál, J.; Kejnovská, I.; Vorlícková, M.; Slavíik, J. *J. Mol. Struct.* **2005**, *734*, 1. For isolation of (+)-norchelidonine, see: (d) Kadan, G.; Gozler, T.; Hesse, M. *Planta Med.* **1992**, *58*, 477.

(22) For total syntheses of (±)-chelidonine and (±)-norchelidonine, see: (a) Oppolzer, W.; Kelier, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. (b) Oppolzer, W. *Heterocycles* **1980**, *14*, 1615. (c) Oppolzer, W.; Robbiani, C. *Helv. Chim. Acta* **1983**, *66*, 1119. (d) Cushman, M.; Choong, T.-C.; Valko, J. T.; Kolek, M. P. *Tetrahedron Lett.* **1980**, *21*, 3845. (e) Cushman, M.; Choong, T.-C.; Valko, J. T.; Kolek, M. P. *J. Org. Chem.* **1980**, *45*, 5067. (f) Hanaoka, M.; Yoshida, S.; Mukai, C. *Chem. Lett.* **1986**, *739*, 24. For some approaches, see: (g) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1947. (h) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron: Asymmetry* **2000**, *11*, 1227.

(23) For enantioselective total synthesis of (+)-chelidonine and (+)-norchelidonine, see: (a) Felming, M. J.; McManus, H. A.; Rudolph, A.; Chan, W. H.; Ruiz, J.; Dockendorff, C.; Lautens, M. *Chem.—Eur. J.* **2008**, *14*, 2112. Also see: (b) McManus, H. A.; Felming, M. J.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 433.

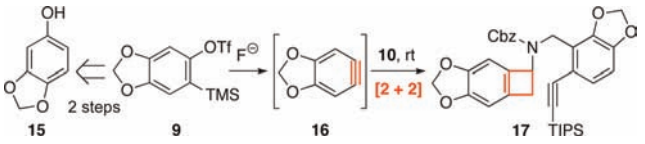
(24) See the Supporting Information.

(25) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299.

(26) Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295.

(27) (a) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (b) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (c) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (e) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.

Table 1. Enamide−Benzyne−[2 + 2] Cycloaddition



entry	9 (equiv)	F^- source (equiv)	solvent	time (h)	yield[a] (%)
1	3.0	TBAT[b] (5.0)	CH_2CI_2	48	trace
2	3.0	TBAT (5.0)	THF	72	43
3	3.0	TBAT (5.0)	1,4-dioxane	96	80
4	3.0	KF (5.0)	THF[c]	96	11
5	2.0	CsF (4.0)	CH_3CN	15	79
6	3.0	CsF (5.0)	1,4-dioxane	48	trace

[a] Isolated yields. [b] TBAT: tetra-*n*-butylammonium triphenyldifluorosilicate. [c] 18-Crown-6 (6.0 equiv) was used.

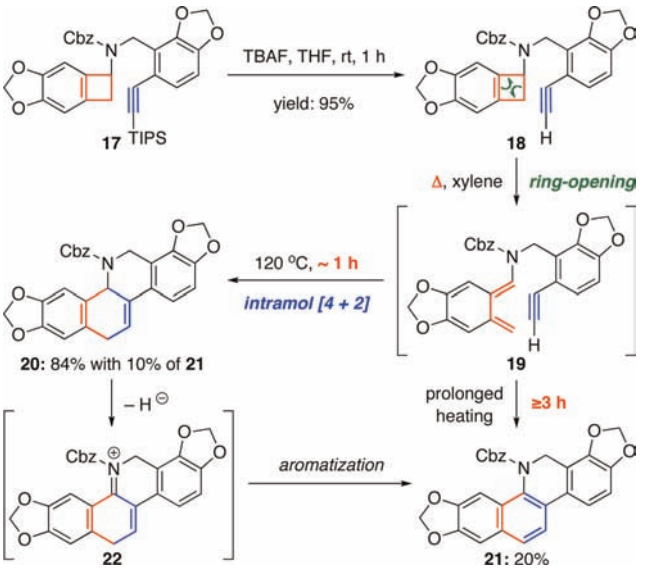
We proceeded with the key enamide−benzyne−[2 + 2] cycloaddition with some trepidation because we had failed related cycloadditions using enamide tethered to an alkyne motif such as **10** during our method development.[1] Following Kobayashi's fluoride-based conditions[29] for in situ generation of benzyne **16** from silylaryl triflate **9**, we initially explored TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate).

As shown in Table 1, after screening a few solvents (entries 1−3), 1,4-dioxane proved to be the optimal solvent, leading to the desired amidobenzocyclobutane **17** in 80% yield at rt, although it took 96 h (entry 3). It is noteworthy that the benzyne−[2 + 2] cycloaddition is completely chemoselective in favor of the enamide motif as long as the alkyne is substituted with TIPS. On the other hand, when using enamide **14** with terminally unsubstituted alkyne, the cycloaddition was not clean. The crude NMR suggests that the acetylene had likely attacked the benzyne.

However, the reaction time was clearly too long using TBAT−dioxane conditions. Thus, inorganic fluorides (entries 4−6) were also examined; CsF in CH_3CN at rt turned out to be equally effective in providing **17**, and more importantly, the reaction time was reduced to 15 h (entry 5). It should be noted here that to avoid the competing removal of the TIPS group, we focused on low temperature reaction conditions instead of 110 °C adopted in our earlier communication.[1] As a result, an intriguing observation was made that these reactions appear to be much faster when CH_3CN is used as solvent than 1,4-dioxane or THF.[10b]

Armed with the desired amidobenzocyclobutane **17**, we removed the TIPS group using TBAF as shown in Scheme 3. Subsequent heating of **18** in xylene at 120 °C afforded the

Scheme 3. Ring-Opening and [4 + 2] Cycloaddition Cascade



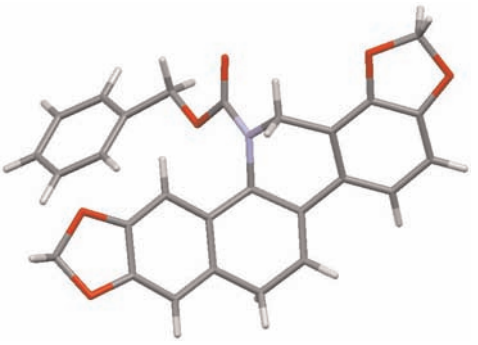


Figure 1. X-ray structure of tetracycle **20**.

tetracyclic benzophenanthridine **20** through a sequence of [2π + 2σ]-pericyclic ring-opening and intramolecular Diels−Alder cycloaddition. An X-ray structure of **20** was attained to ascertain the integrity of this sequence (Figure 1), although **20** constitutes a formal synthesis of (±)-chelidonine, as it matched spectroscopically with Oppolzer's intermediate.[22a−c]

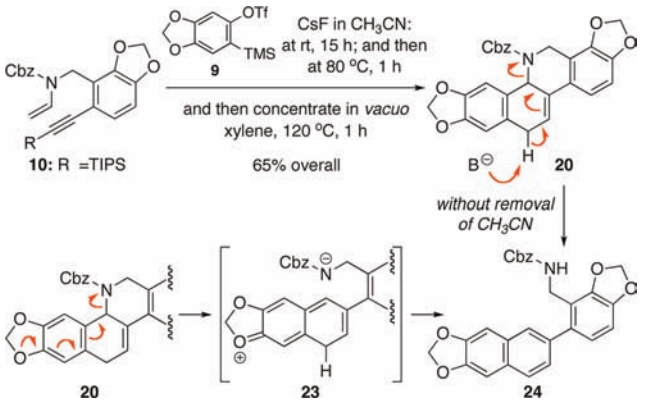
Tetracycle **20** was found to be unstable, as it slowly converted to a new set of chemical resonances in $CDCl_3$ at rt. The new compound was ultimately assigned as the aromatization product **21**, which could be envisioned from *N*-acyliminium ion **22**. It was later confirmed that **21** was a minor but persistent byproduct during the heating in xylene and that an increasing amount of **21** was present when prolonged heating took place.

Most critically, we succeeded in a tandem process or one-pot formation of tetracycle **20**. As shown in Scheme 4, treatment of enamide **10** with CsF at rt in CH_3CN followed by heating at 80 °C and subsequently at 120 °C using

(28) Synthesis of aryl triflate **9**, see: (a) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436. (b) Alexander, B. H.; Oda, T. A.; Brown, R. T.; Gertler, S. I. *J. Org. Chem.* **1958**, *23*, 1969.

(29) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

Scheme 4. Tandem Enamide–Benzyne–[2 + 2]–[4 + 2]



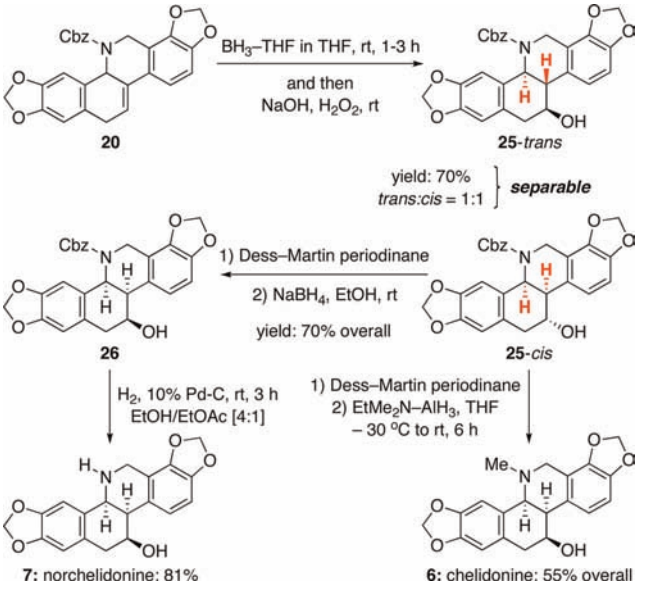
xylene as the solvent led to **20** in 65% yield overall. Removal of CH_3CN appeared to be critical prior to the addition of xylene and further heating at elevated temperature for the Diels–Alder cycloaddition. When the mixture was directly heated at 120 °C without removing CH_3CN, an indistinguishable mixture was observed by crude proton NMR. In the mixture, a ring-opened product such as **24** is likely present, presumably derived from the ring-opened zwitterionic intermediate **23** or directly from tetracycle **20** via a based-promoted elimination.

On the other hand, further purifying the crude desilylated benzocyclobutane **18** even through a short bed silica gel filtration proved to be unnecessary and provided no better yield. It is noteworthy that the overall process constitutes a four-bond and two-ring formation, thereby further accentuating the synthetic imminence of an enamide-benzyne-[2 + 2] cycloaddition manifold.

To complete our total syntheses, tetracycle **20** was subjected to BH_3-hydroboration–oxidation conditions to give a 1:1 separable isomeric mixture of alcohol **25**-*trans* and **25**-*cis* [Scheme 5]. Relative stereochemistry of the three contiguous stereocenters in **25**-*cis* was unambiguously assigned through X-ray structure of **25′**-*cis*, which has the Cbz protecting group removed and is essentially the C11-*epimer* of norchelidonine (Figure 2). Unfortunately, we could not improve the diastereomeric ratio via other boranes such as 9-BBN, *c*-hex$_2$BH, and Et$_2$BH. Nevertheless, (±)-chelidonine **6** could be rapidly and efficiently synthesized from **25**-*cis* through DMP-oxidation and alane reduction of both ketone and Cbz-urethane motifs. This would complete a facile seven-step total synthesis effort. Lastly, (±)-norchelidonine **7** was also completed through a sequence of DMP-oxidation, $NaBH_4$ reduction, and hydrogenation. Both synthetic samples spectroscopically matched the reported literature values.[22]

We have described here total syntheses of (±)-chelidonine (seven steps; 8.5% overall yield) and (±)-norchelidonine (eight steps, 8.7% overall yield), featuring an enamide–benzyne–[2 + 2] cycloaddition in a quadruple tandem cascade that also includes pericyclic ring-opening

Scheme 5. Completion of the Total Syntheses



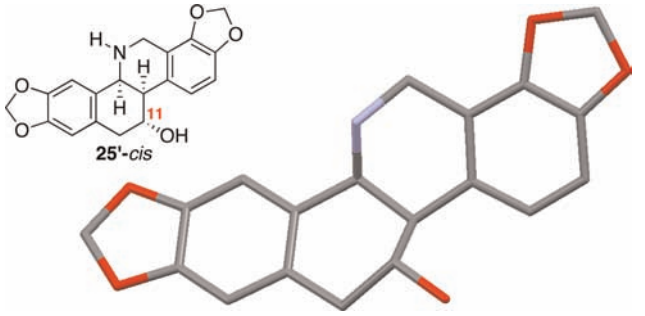


Figure 2. X-ray structure of **25′**-*cis* [C11-*epi*-norchelidonine].

and intramolecular Diels–Alder cycloaddition. While Oppolzer's 1971 seminal total synthesis[22a] inspired our efforts, the current total syntheses underscore both the power of enamides as synthetic building blocks and the significance of benzyne chemistry, in particular, the benzyne–[2 + 2] cycloaddition in the efficient assembly of complex targets.

Acknowledgment. We thank the NIH (GM066055) for funding. We thank Dr. Victor G. Young and Mr. Gregory T. Rohde of the University of Minnesota for providing X-ray structural analysis.

Supporting Information Available. Experimental procedures as well as NMR spectra, characterizations, and X-ray data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.