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Total Syntheses of Chelidonine and Norchelidonine Via an Enamide-Benzyne-[2 + 2] Cycloaddition Cascade.

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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 lab recently unveiled a de novo cascade of pericyclic ring-openings of amido-benzocyclobutanes 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 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 total syntheses of (±)- Our chelidonine and (±)- norchelidonine.

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 2 steps.²⁸

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

We proceeded in 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 conditions²⁹ for *in situ* generation of benzyne **16** from silylaryl triflate **9**, we initially explored TBAT [tetra-*n*-butyl-ammonium triphenyl-difluorosilicate].

As shown in **Table 1**, after screening through a few solvents [entries 1-3], 1,4-dioxane proves to be the optimal solvent, leading to the desired amido-benzocyclobutane **17** in 80% yield at rt, albeit 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, and CsF in CH₃CN 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 is these reactions appear to be much faster when using CH₃CN as solvent than 1,4-dioxane or THF.^{10b}

Armed with the desired amido-benzocyclobutane **17**, we removed the TIPS group using TBAF as shown in **Scheme 3**. Subsequent heating of **18** in xylene at 120 °C afforded the tetracyclic benzophenanthridine **20** through a sequence of [2 π +2 σ]-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 ($\pm$)-chelidonine, as it matched spectroscopically with Oppolzer' intermediate.^{22a-c}

Tetracycle **20** was found not to be very stable, as it was slowly converting to a new set of chemical resonances in CDCl₃ at rt. The new compound was ultimately assigned as the aromatization product **21**, which could be envisioned from *N*-acyl iminium 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 CH₃CN followed by heating at 80 °C and subsequently at 120 °C using xylene as the solvent led to **20** in 65% yield overall. Removal of CH₃CN appeared to be critical prior to the addition of xylene and further heating at elevated temperature for the Diels-Alder cycloaddition. When directly heating the mixture at 120 °C without removing CH₃CN, an indistinguishable mixture was observed by crude proton NMR. Among the mixture, the 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 base-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*-hex₂BH, and Et₂BH. 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 7-step total synthesis effort. Lastly, (±)-norchelidonine **7** was also completed through a sequence of DMP-oxidation, NaBH₄ reduction, and hydrogenation. Both synthetic samples spectroscopically matched the reported literature values.²²

We have described here total syntheses (±)-chelidonine [7 steps; 8.5% overall yield] and (±)-norchelidonine [8 steps, 8.7% overall yield], featuring an enamide-benzyne-[2 + 2] cycloaddition in a quadruple tandem cascade that also includes pericyclic ring-opening 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Feltenberger JB, Hayashi R, Tang Y, Babiash ESC, Hsung RP. *Org. Lett.* 2009; 11:3666. [PubMed: 19624104]
2. For reviews on the aryne chemistry, see: Sanz R. *Org. Prep. Proced. Int.* 2008; 40:215. Peña D, Pérez D, Guitián E. *Heterocycles*. 2007; 74:89. Peña D, Pérez D, Guitián E. *Angew. Chem. Int. Ed.* 2006; 45:3579. Guitián E, Pérez D, Peña D, Tsuji J. *Topics in Organometallic Chemistry*. 2005; 14:109–146. Springer-Verlag Weinheim. Pellissier H, Santelli M. *Tetrahedron*. 2003; 59:701. Kessar SV, Trost BM, Fleming I. *Comprehensive Organic Synthesis*. 1991; 4:83–515. Pergamon Press. New York. Heaney H. *Chem. Rev.* 1962; 62:81.
3. Also see: Sadana AK, Saini RK, Billups WE. *Chem. Rev.* 2003; 103:1539. [PubMed: 12683790] Mehtaa G, Kotha S. *Tetrahedron*. 2001; 57, 625.
4. For recent examples, see: Łaczkowski KZ, García D, Peña D, Cobas A, Pérez D, Guitián E. *Org. Lett.* 2011; 13:960. [PubMed: 21291202] Biswas K, Greaney MF. *Org. Lett.* 2011; 13:4946. [PubMed: 21859084] McAusland D, Seo S, Pintori DG, Finlayson J, Greaney MF. *Org. Lett.* 2011; 13:3667. [PubMed: 21671610] Pintori DG, Greaney MF. *Org. Lett.* 2010; 12:168. [PubMed: 19954170] Morishita T, Yoshida H, Ohshita J. *Chem. Commun.* 2010:640. Worlikar SA, Larock RC. *Org. Lett.* 2009; 11:2413. [PubMed: 19413328] Sha F, Huang X. *Angew. Chem. Int. Ed.* 2009; 38:3458. Shi F, Waldo JP, Chen Y, Larock RC. *Org. Lett.* 2008; 10:2409. [PubMed: 18476707] Allan KM, Stoltz BM. *J. Am. Chem. Soc.* 2008; 130:17270. [PubMed: 19035638] Gilmore CD, Allan KM, Stoltz BM. *J. Am. Chem. Soc.* 2008; 130:1558. [PubMed: 18193875] Bhuvaneshwari S, Jeganmohan M, Yang M-C, Cheng C-H. *Chem. Commun.* 2008:2158. Xie C, Liu L, Zhang Y, Xu P. *Org. Lett.* 2008; 10:2393. [PubMed: 18484728]

5. For a general review on the synthesis of enamides, see: Tracey MR, Hsung RP, Antoline J, Kurtz KCM, Shen L, Slafer BW, Zhang Y. Weinreb SM. Science of Synthesis, Houben-Weyl Methods of Molecular Transformations. 2005 Georg Thieme Verlag KG Chapter 21.4
6. For reviews on Cu-mediated C-N and C-O bond formations for enamide synthesis, see: Evano G, Blanchard N, Toumi M. Chem. Rev. 2008; 108:3054. [PubMed: 18698737] Dehli JR, Legros J, Bolm C. Chem. Commun. 2005:973. Ley SV, Thomas AW. Angew. Chem. Int. Ed. 2003; 42:5400. Lindley J. Tetrahedron. 1984; 40:1433. For reviews on Pd-catalyzed *N*-arylations of amines and amides, see: Hartwig JF. Angew. Chem. Int. Ed. 1998; 37:2046. Wolfe JP, Wagaw S, Marcoux J-F, Buchwald S. Acc. Chem. Res. 1998; 31:805.
7. For a leading review on recent chemistry of enamides, see: Carbery DR. Org. Biomol. Chem. 2008; 9:3455. [PubMed: 19082143] Rappoport Z. The Chemistry of Enamines in The Chemistry of Functional Groups. 1994 John Wiley and Sons New York
8. For a leading review on thermal [2 + 2] cycloaddition reactions, see: Baldwin JE. Trost BM, Fleming I, Pattenden G. Comprehensive Organic Synthesis. 1991; 5:63. Pergamon Press New York
9. For [2 + 2] cycloadditions of arynes with enamines, see: Gingrich HL, Huang Q, Morales AL, Jones M. J. Org. Chem. 1992; 57:3803. Heaney H, Ley SV. J. Chem. Soc., Perkin Trans. 1. 1974:2693. Crews P, Beard J. J. Org. Chem. 1973; 38:522. Kametani T, Kigasawa K, Hiiragi M, Hayasaka T, Kusama O. J. Chem. Soc. (C). 1971:1051.
10. For reports on amido-benzocyclobutane formation as side products through enamide-benzynes-[2 + 2] cycloaddition, see: Castedo L, Guitian E, Saá C, Suau R, Saá JM. Tetrahedron Lett. 1983; 24:2107. Blackburn T, Ramtohul YK. 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 LW. Helv. Chim. Acta. 2001; 84:141.
12. For a recent example of such IMDA, see: Feltenberger JB, Hsung RP. Org. Lett. 2011; 13:3114. [PubMed: 21612235]
13. For reviews, see: Oppolzer W. Synthesis. 1978:793. Funk RL, Vollhardt KPC. Chem. Soc. Rev. 1980; 9:41. Kametani T, Nemoto H. Tetrahedron. 1981; 37:3.
14. For reviews on chemistry of dienamides, see: Overman LE. Acc. Chem. Res. 1980; 13:218. Petrzilka M. Synthesis. 1981:753. Campbell AL, Lenz GR. Synthesis. 1987:421.
15. For a leading review for intramolecular Diels-Alder strategies for natural product synthesis, see: Padwa A, Bur SK. Tetrahedron. 2007; 63:5341. [PubMed: 17940591]
16. For isolation of (+)-chelidonine from *Chelidonium majus* L., see: Probst JM. Ann. Pharm. 1839; 29:113.
17. For structural assignment of (+)-chelidonine, see: von Bruchhausen F, Bersch HW. Chem. Ber. 1930; 63:2520. von Bruchhausen F, Bersch HW. Chem. Ber. 1931; 64:947. Späth E, Kuffner F. Chem. Ber. 1931; 64:370. Bersch HW. Arch. Pharm. 1958; 291:491. Santavy F, Horák M, Maturová M, Brabenec J. Collect. Czech. Chem. Commun. 1960; 25:1344. 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: Slavík J, Slavíková L. Collect. Czech. Chem. Commun. 1957; 22:279. Slavík J, Slavíková L. Collect. Czech. Chem. Commun. 1959; 24:3141. The racemate of chelidonine was also isolated but was named as diphylline, see: Schlotterbeck JO, Watkins HC. Chem. Ber. 1902; 35:7. Slavík J, Slavíková L, Brabenec J. Collect. Czech. Chem. Commun. 1965; 30:3697. Slavíková L. Collect. Czech. Chem. Commun. 1968; 33:635.
19. For absolute configuration of (+)-chelidonine, see: Takao N, Bessho N, Kamiguuchi M, Iwasa K, Tomita K, Fujiwara T, Fujii S. Tetrahedron Lett. 1979; 20:495. Takao N, Morita N, Kamiguuchi M, Iwasa K, Tomita K, Fujiwara T, Fujii S. Acta Cryst. 1981; B37:2043.
20. For a biosynthetic study on chelidonine, see: Battersby AR, Staunton J, Wiltshire HR, Francis RJ, Southgate R. J. Chem. Soc., Perkin I. 1975:1147.
21. For isolation of (-)-norchelidonine, see: Slavík J. Collect. Czech. Chem. Commun. 1959; 24:3601. Slavík J, Slavíková L. Collect. Czech. Chem. Commun. 1959; 24:3141. Necas M, Dostál J, Kejnovská I, Vorlíčková M, Slavík J. J. Mol. Struct. 2005; 734:1. For isolation of (+)-norchelidonine, see: Kadan G, Gozler T, Hesse M. Planta Med. 1992; 58:477. [PubMed: 17226510]

22. For total syntheses of ($\pm$)-chelidonine and ($\pm$)-norchelidonine, see: Oppolzer W, Kelier K. J. Am. Chem. Soc. 1971; 93:3836. Oppolzer W. Heterocycles. 1980; 14:1615. Oppolzer W, Robbiani C. Helv. Chim. Acta. 1983; 66:1119. Cushman M, Choong T-C, Valko JT, Kolek MP. Tetrahedron Lett. 1980; 21:3845. Cushman M, Choong T-C, Valko JT, Kolek MP. J. Org. Chem. 1980; 45:5067. Hanaoka M, Yoshida S, Mukai C. Chem. Lett. 1986; 739:24. For some approaches, see: Vicario JL, Badía D, Domínguez E, Crespo A, Carrillo L. Tetrahedron: Asym. 1999; 10:1947. Vicario JL, Badía D, Domínguez E, Carrillo L. Tetrahedron: Asymmetry. 2000; 11:1227.
23. For enantioselective total synthesis of (+)-chelidonine and (+)-norchelidonine, see: Felming MJ, McManus HA, Rudolph A, Chan WH, Ruiz J, Dockendorff C, Lautens M. Chem. Eur. J. 2008; 14:2112. [PubMed: 18200643] Also see: McManus HA, Felming MJ, Lautens M. Angew. Chem. Int. Ed. 2007; 46:433.
24. See Supporting Information.
25. Ohta Y, Kubota Y, Watabe T, Chiba H, Oishi S, Fujii N, Ohno H. J. Org. Chem. 2009; 74:6299. [PubMed: 19572599]
26. Dubé D, Scholte AA. Tetrahedron Letters. 1999; 40:2295.
27. a Han C, Shen R, Su S, Porco JA Jr. Org. Lett. 2004; 6:27. [PubMed: 14703342] b Pan X, Cai Q, Ma D. Org. Lett. 2004; 6:1809. [PubMed: 15151420] c Langner M, Bolm C. Angew. Chem. Int. Ed. 2004; 43:5984. d Jiang L, Job GE, Klapars A, Buchwald SL. Org. Lett. 2003; 5:3667. [PubMed: 14507200] e Shen R, Lin CT, Porco JA Jr. J. Am. Chem. Soc. 2002; 124:5650. [PubMed: 12010033]
28. Synthesis of aryl triflate **9**, see: Sato Y, Tamura T, Mori M. Angew. Chem. Int. Ed. 2004; 43:2436. Alexander BH, Oda TA, Brown RT, Gertler SI. J. Org. Chem. 1969; 1958:23.
29. Himeshima Y, Sonoda T, Kobayashi H. Chem. Lett. 1983:1211.

Scheme 1.

An Enamide-Benzyne-[2 + 2] Cascade to Chelidonine.

Scheme 2.
Synthesis of Enamide **10**.

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Figure 1.
X-Ray Structure of Tetracycline **20**.

Scheme 4.
A Tandem Enamide-Benzyne-[2 + 2]-[4 + 2].

Scheme 5.
Completion of the Total Syntheses.

Figure 2.
X-Ray Structure of **25'-cis** [C11-*ep*morchelidonine].

Table 1

The Enamide-Benzzyne-[2 + 2] Cycloaddition.

entry	9; equiv	F ⁺ source [equiv]	solvent	time [h]	yield [%] ^a
1	3.0	TBAT ^b [5.0]	CH ₂ Cl 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 ₃ CN	15	79
6	3.0	CsF [5.0]	1,4-Dioxane	48	trace

^a Isolated yields.

^b TBAT: Tetra-*n*-butyl-ammonium triphenyl-difluoro-silicate.

^c 18-Crown-6 [6.0 equiv] was used.