Published in final edited form as:
J Am Chem Soc. 2011 May 25; 133(20): 7704–7707. doi:10.1021/ja2026882.

Total Synthesis of (±)-Cycloclavine and (±)-5-epi-Cycloclavine

Filip R. Petronijevic and **Peter Wipf***
Department of Chemistry and Center for Chemical Methodologies and Library Development, University of Pittsburgh, Pittsburgh PA 15260, U.S.A

Abstract

Novel routes to the naturally occurring indole alkaloid cycloclavine and its unnatural C(5)-epimer are described. Key features include the rapid construction of the heterocyclic core segments by two Diels-Alder reactions. An indole annulation was accomplished by a late-stage intramolecular Diels-Alder furan cycloaddition, and a methylenecyclopropane dienophile was used for a stereoselective intramolecular [4+2] cycloaddition to give the cyclopropa[*c*]indoline building block present in cycloclavine.

Keywords

Ergot alkaloids; cycloclavine; methylenecyclopropane Diels-Alder; IMDAF reaction; indole

Ergot alkaloids comprise a notable group of indole alkaloids, whose striking polycyclic molecular architectures and wide spectrum of physiological activities have attracted organic chemists for decades.[1] The lysergic acid and clavine subclasses of ergot alkaloids differ in the oxidation state of the substituent at C(8). Cycloclavine (**1**, Scheme 1) was first isolated in 1969 from the seeds of the African morning glory (*Ipomea hildebrandtii*) by Hoffman and coworkers.[2] In spite of its compact size ($C_{16}H_{18}N_2$, MW=238), the perimeter of this clavine alkaloid contains three contiguous stereocenters, two of which are fully substituted and part of a cyclopropane ring, thus posing a respectable synthetic challenge. In 2008, Incze et al. completed the first synthesis of (±)-cycloclavine in 14 steps and 0.2% overall yield.[3]

We have recently shown that 4-mono- and 3,4-disubstituted indoles can be synthesized through an intramolecular Diels-Alder cycloaddition of furan (IMDAF) reaction.[4] We wanted to demonstrate the utility of this methodology for the construction of indole natural products, and, furthermore, we were attracted to cycloclavine as a synthetic target due to its unusual molecular scaffold, featuring the only cyclopropane-containing ergot alkaloid. Our 1st generation retrosynthetic plan assumed that the stability of the cyclopropane moiety in the hydroindole intermediate **2** was sufficient to allow a thermal [4+2] process,[4] and that dienone **3** could be obtained by a cascade TBS-deprotection-intramolecular S_N2-displacement.[5] Indolinone **4** would be formed by *ortho*-alkylation of 3-aminophenol **5**. The selective hydrogenation of cross-conjugated dienone **3** remained a concern, but we hoped that we could effect this conversion by taking advantage of Lewis-acidic reducing agents and the electron-donating properties of the β-amino substituent.

O-TBS-protection of **5** and *N*-acylation with chloroacetyl chloride provided amide **6** (Scheme 2). Initial efforts to induce the Friedel-Crafts cyclization of **6** proved unsuccessful.

pwipf@pitt.edu.

Supporting Information Available: Experimental details, characterization data, copies of ^1H and ^{13}C NMR spectra, and crystal information files. This material is available free of charge via the Internet at http://pubs.acs.org.

However, after *N*-methylation of **6** with methyl sulfate, cyclization under $Pd(OAc)_2$ conditions[6] led to the desired indolinone **8** in 77% yield. Stepwise α-methylation and α-hydroxymethylation[7] led to the primary alcohol **4**, which was converted to the mesylate in high overall yield.

Treatment of this mesylate with TBAF in THF (0.1 M) resulted in a complex mixture of products. In contrast, under high dilution conditions (0.006 M), TBAF effected silylether cleavage with concomitant intramolecular alkylation to give **3**. In spite of considerable experimentation, our attempts to regioselectively reduce the trisubstituted alkene in dienone **3** remained unsuccessful. Alternatively, epoxidation of **3** with *tert*-butyl hydroperoxide (TBHP) in THF,[8] followed by selective reduction[9] of the intermediate α,β-epoxyketone, furnished β-hydroxyketone **10**, thus masking disubstituted alkene as a secondary alcohol. Another round of experiments[10] aimed at reduction of the vinylogous amide in the presence of the labile cyclopropane ring identified hydrogenation at high pressure (80 bar) using Raney-Ni as catalyst as a quantitative method to access ketone **11** after PCC oxidation.[11] While we were only able to ascertain the configuration at C(5) upon completion of the synthesis of **14** (*vide infra*), hydrogenation occurred exclusively from the α-face, and only the *cis*-fused hydroindole was accessible via this route. Exposure of **11** to a TBAF solution in THF promoted the β-elimination of the aldol product and furnished the desired α,β-unsaturated ketone in 62% yield. After lithiumtin exchange and 1,2-addition of stannane **12**, a single isomer of the tertiary alcohol **13** was obtained. Heating in *o*-dichlorobenzene at 190 °C for 1 h under microwave irradiation, followed by lactam reduction with LAH, led to 5-*epi*-cycloclavine **14**, whose analytical data did not match those of cycloclavine. An X-ray analysis of **14** confirmed the *cis*-configuration at the C(5)–C(10) ring fusion of the indoline substructure. This was surprising since not just the hydrogenation of the TBS-ether of **10**, but also the hydroxyenone **10** and the deoxygenated **10′** consistently provided a sole hydrogenation isomer, and we had hypothesized based on the Newman projection of **10′** that the cyclopropane group would shield the α-face from hydrogen delivery (Scheme 2). These substrate preferences, in addition to the difficulties in reducing the trisubstituted alkene in dienone **3**, required a complete redesign of our retrosynthetic approach.

The main feature of our 2nd generation retrosynthesis was an early introduction of the *trans*-hydroindole stereochemistry by an intramolecular methylenecyclopropane Diels-Alder reaction (Scheme 3). Triene **16** could be derived from alcohol **17** and vinylogous amide **18**.

THP-protection of β-methallyl alcohol **19** and conversion to dibromocyclopropane **20** under phase transfer conditions was accomplished in 86% combined yield (Scheme 4).[12] Exposure of **20** to *n*-BuLi (1 equiv) at −95 °C, and subsequent treatment of the monobromo-monolithiated intermediate with MeI furnished the tertiary bromide **21**.[13] Dehydrobromination under thermodynamic conditions followed by THP-deprotection gave cyclopropylmethylidene alcohol **17**. Conversion of this alcohol to the mesylate and *N*-alkylation of the anion of the vinylogous amide **18** provided the coupling product **22** in 67% yield from **17**.

Formation of the silyloxy diene from vinylogous amide **22** was achieved in quantitative yield by treatment with NaHMDS followed by TBSCl trapping of the enolate.[14] Other common bases such as LiHMDS, LDA or KHMDS gave either no reaction or very complex mixtures of products, as evidenced by ^{1}H NMR analysis.

The crude Diels-Alder precursor **16** was smoothly converted to the indoline by heating under microwave irradiation in trifluorotoluene at 195 °C for 1 h. The tricyclic ketone **23** was isolated in 85% yield after removal of the TBS group with TBAF. Gratifyingly, an X-ray crystallographic analysis of the chloroform adduct **24** confirmed the desired *trans*-

configuration at the indoline ring fusion bond as the sole product of the intramolecular Diels-Alder process. A computational analysis suggests that the energy of the *anti*-transition state **16**‡ leading to **23** is indeed 6.8 kcal/mol lower than the corresponding transition state leading to the *cis*-diastereomer.[15]

The dehydrogenation of β-aminoketone **23** to the corresponding enone **25** was problematic due to competing side reactions involving the basic amine moiety. We circumvented this problem by a dealkylative protection of the tertiary amine as a carbamate with methyl chloroformate in 71% yield.[16] Saegusa-Ito oxidation (LDA, TMSCl, −78 °C, then $Pd(OAc)_2$) served to cleanly introduce a double bond at the C(11)–C(16) position of **25**.[17]

Treatment of enone **25** with the tin-lithium exchange product of stannane **13** led to 51% of a tertiary alcohol which was subjected to the microwave-promoted IMDAF cyclization in trifluorotoluene at 190 °C to furnish indole **26** in 44% yield. Finally, reduction of the carbamate with LAH provided (±)-cycloclavine **1** in quantitative yield. The spectroscopic data for **1** were consistent with the previously reported data[2,3,18] for the natural compound.

In summary, we have developed novel synthetic routes to the ergot alkaloid cycloclavine (**1**) as well as the unnatural 5-*epi*-cycloclavine (**14**). These total syntheses proceeded in 14 steps and 1.2% overall yield for **1** and in 17 steps and 2.3% overall yield for **14.** Noteworthy features of our strategies include the formation of the indole moieties through the allylic alcohol-IMDAF reaction, as well as the rapid synthesis of cycloclavine's indoline core through a novel and highly stereoselective intramolecular Diels-Alder reaction of a methylenecyclopropane.[19,20]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

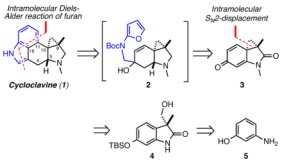
Acknowledgments

This work was supported by the NIH/NIGMS CMLD program (GM067082). We thank Dr. Steve Geib (University of Pittsburgh) for X-ray crystallographic analyses and Drs. Anthony Cuzzupe and Cody Timmons (University of Pittsburgh) for preliminary synthetic studies on the synthesis of cycloclavine.

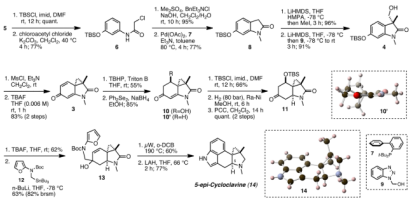
References

1. (a) Boichenko LV, Boichenko DM, Vinokurova NG, Reshetilova TA, Arinbasarov MU. Microbiology. 2001; 71:306.(b) Schiff PL. Am J Pharm Educ. 2006; 70:98. [PubMed: 17149427] (c) Wallwey C, Li SM. Nat Prod Rep. 2011; 28:496. [PubMed: 21186384]
2. Stauffacher D, Niklaus P, Tscherter H, Weber HP, Hofmann A. Tetrahedron. 1969; 25:5879. [PubMed: 5373534]
3. Incze M, Dörnyei G, Moldvai I, Temesvári-Major E, Egyed O, Szánty C. Tetrahedron. 2008; 64:2924.
4. (a) Petronijevic F, Timmons C, Cuzzupe A, Wipf P. Chem Commun. 2009; 1:104.For pioneering applications of the IMDAF cycloaddition to natural product synthesis, see: (b) Boonsompat J, Padwa A. J Org Chem. 2011 ASAP, and references cited therein.
5. Boger DL, Ishizaki T, Zarrinmayeh H, Munk SA, Kitos PA, Suntornwat O. J Am Chem Soc. 1990; 112:8961.
6. Hennessy EJ, Buchwald SL. J Am Chem Soc. 2003; 125:12084. [PubMed: 14518981]
7. (a) Katritzky AR, Manju K, Singh SK, Meher NK. Tetrahedron. 2005; 61:2555.(b) Deguest G, Bischoff L, Fruit C, Marsais F. Org Lett. 2007; 9:1165. [PubMed: 17309276]
8. Carreño MC, Merino E, Ribagorda M, Somoza Á, Urbano A. Org Lett. 2005; 7:1419. [PubMed: 15787521]

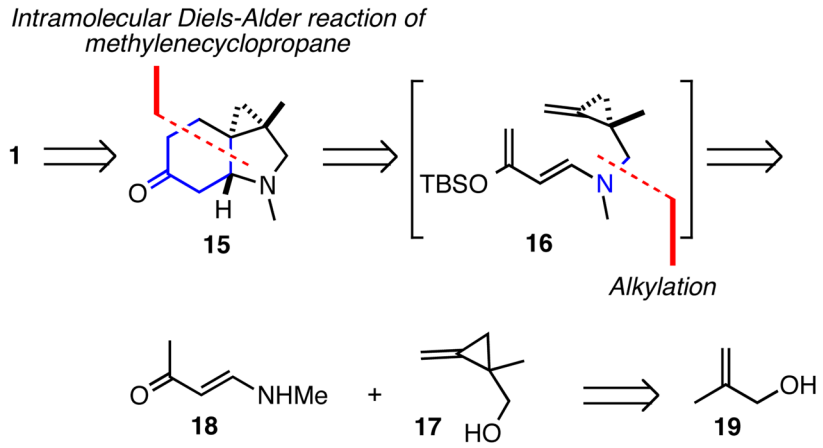
9. Miyashita M, Suzuki T, Hoshino M, Yoshikoshi A. Tetrahedron. 1997; 53:12469.
10. Hydrogenation conditions using Pd, PtO_2, or Rh/Al_2O_3 as catalysts, hydride reduction ($NaBH_4$, $LiAlH_4$, or $NaBH_3CN$) or single-electron reduction conditions (SmI_2) failed to provide the desired product, instead favoring cyclopropane ring opening.
11. Koelsch CF, Ostercamp DL. J Org Chem. 1961; 26:1104.
12. Baird MS, Boitsov VM, Stepakov AV, Molchanov AP, Kopf J, Rajaratnam M, Kostikov RR. Tetrahedron. 2007; 63:7717.
13. Kitatani K, Hiyama T, Nozaki H. Bull Chem Soc Jpn. 1977; 50:3288.
14. For the formation and use in Diels-Alder reactions of amino dienes, see: (a) Oppolzer W, Fröstl W. Helv Chim Acta. 1975; 58:590.(b) Overman LE, Taylor GF, Jessup PJ. Tetrahedron Lett. 1976; 36:3089.(c) Kozmin SA, Rawal VH. J Org Chem. 1997; 62:5252.(d) Wipf P, Wang X. Tetrahedron Lett. 2000; 41:8747.(e) Kozmin SA, He S, Rawal VH. Org Synth. 2002; 78:152.ibid. 160.
15. Transition states were identified using a RHF/6-311G* transition state search in Spartan 10 (Wavefunction, Inc., Irvine, CA).
16. Bonjoch J, Solé D, García-Rubio S, Bosch J. J Am Chem Soc. 1997; 119:7230.
17. Ito Y, Toshikazu H, Saegusa T. J Org Chem. 1978; 43:1011.
18. **1**: Mp 153.2–155.3 °C (acetone/chloroform); IR (ATR) 2921, 2798, 1591, 1590, 1441, 1150 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.92 (bs, 1 H), 7.15 (d, 1 H, *J* = 8.4 Hz), 7.10 (app t, 1 H, *J* = 7.7 Hz), 7.91 (s, 1 H), 6.84 (d, 1 H, *J* = 7.0 Hz), 3.17 (d, 1 H, *J* = 9.1 Hz), 3.15 (dd, 1 H, *J* = 14.0, 4.2 Hz), 2.79 (dd, 1 H, *J* = 11.2, 3.5 Hz), 2.61 (t, 1 H, *J* = 12.6 Hz), 2.42 (d, 1 H, *J* = 8.4 Hz), 2.37 (s, 3 H), 1.70 (s, 3 H), 1.61 (d, 1 H, *J* = 2.8 Hz), 0.46 (d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 133.5, 128.7, 122.9, 118.1, 113.2, 110.3, 107.9, 69.6, 65.6, 39.9, 34.3, 27.8, 24.9, 24.2, 16.5; HRMS (API+) *m/z* calcd for $C_{16}H_{19}N_2$ 239.1548, found 239.1572.
19. In a few cases, unsubstituted methylenecyclopropane and a other simple derivatives such as perfluoromethylenecyclopropane, 2,2-difluoromethylenecyclopropane and methyl 2-chloro-2-cyclopropylidene acetate, have been used in intermolecular [4+2]-cycloadditions,[19] but to the best of our knowledge there is only one prior report of an intramolecular, high pressure Diels-Alder variant with this strain-activated dienophile: Heiner T, Kozhushkov SI, Noltemeyer M, Haumann T, Boese R, De Meijere A. Tetrahedron. 1996; 52:12185.
20. (a) Adam W, Doerr M, Hill K, Peters EM, Peters K, Von Schnering HG. J Org Chem. 1985; 50:587.(b) Smart BE. J Amer Chem Soc. 1974; 96:929.(c) Dolbier WR Jr, Seabury M, Daly D, Smart BE. J Org Chem. 1986; 51:974.(d) Meyer FE, Ang KH, Steinig AG, De Meijere A. Synlett. 1994:191.



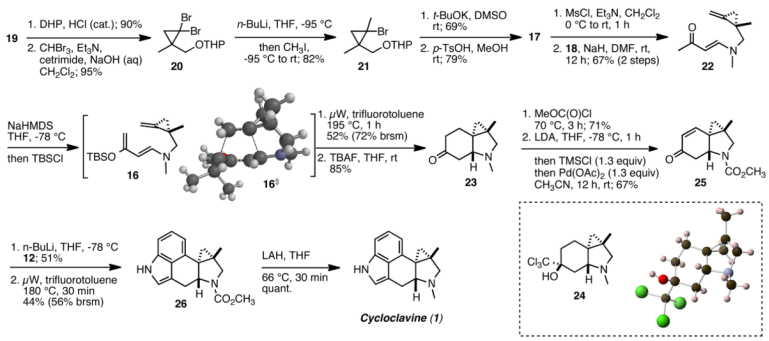
Scheme 1.
1st Generation Retrosynthetic Analysis of Cycloclavine



Scheme 2.
Synthesis of (±)-5-*epi*-Cycloclavine



Scheme 3.
2nd Generation Retrosynthetic Analysis



Scheme 4.
Synthesis of (±)-Cycloclavine