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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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

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Supporting Information

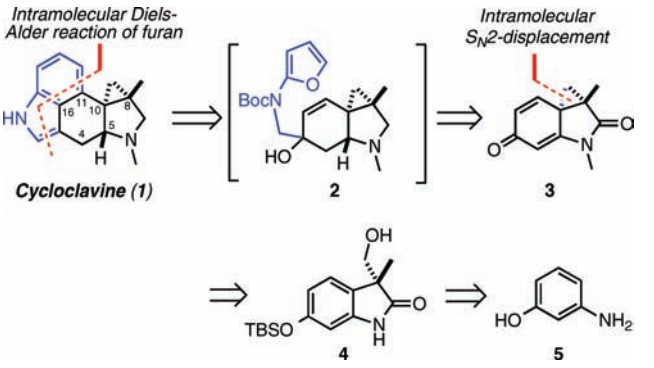
ABSTRACT: Novel routes to the naturally occurring indole alkaloid cycloclavine and its unnatural C(5)-epimer are described. Key features include the rapid construction of the heterocyclic core segments by two Diels–Alder reactions. An indole annulation was accomplished by a late-stage intramolecular 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.

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 co-workers.[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 first 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. 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]

Scheme 1. First Generation Retrosynthetic Analysis of Cycloclavine



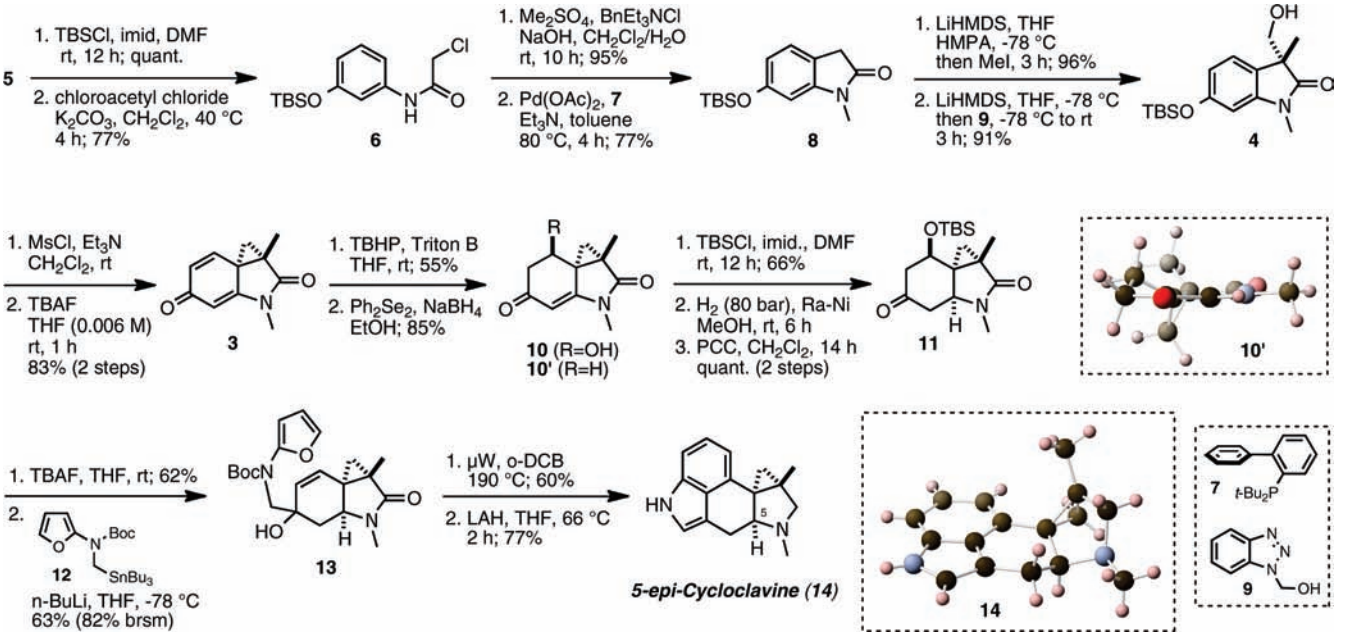
led to the primary alcohol **4**, which was converted to the mesylate in high overall yield.

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 the disubstituted alkene as a secondary alcohol. Another round of experiments[10] aimed at the reduction of the vinylogous amide in the presence of the labile cyclopropane ring identified hydrogenation at high pressure (80 bar) using Raney-Ni as the 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 lithium–tin 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

Received: March 24, 2011
Published: April 25, 2011

dx.doi.org/10.1021/ja2026882 | *J. Am. Chem. Soc.* 2011, 133, 7704–7707

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



substructure. This was surprising since not only 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.

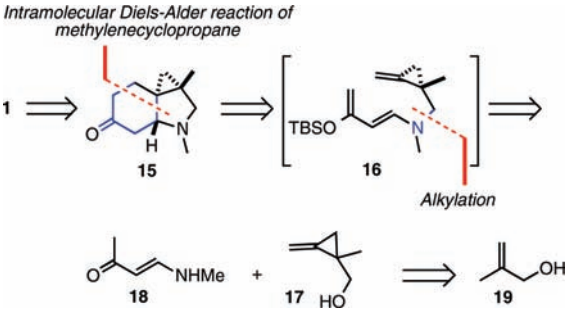
The main feature of our second generation retrosynthesis was an early introduction of the *trans*-hydroindole stereochemistry by an intramolecular methylenecyclopropane Diels–Alder reaction (Scheme 3). Triene **16** could be derived from alcohol **17** and vinylogous amide **18**.

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

Scheme 3. Second Generation Retrosynthetic Analysis



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]

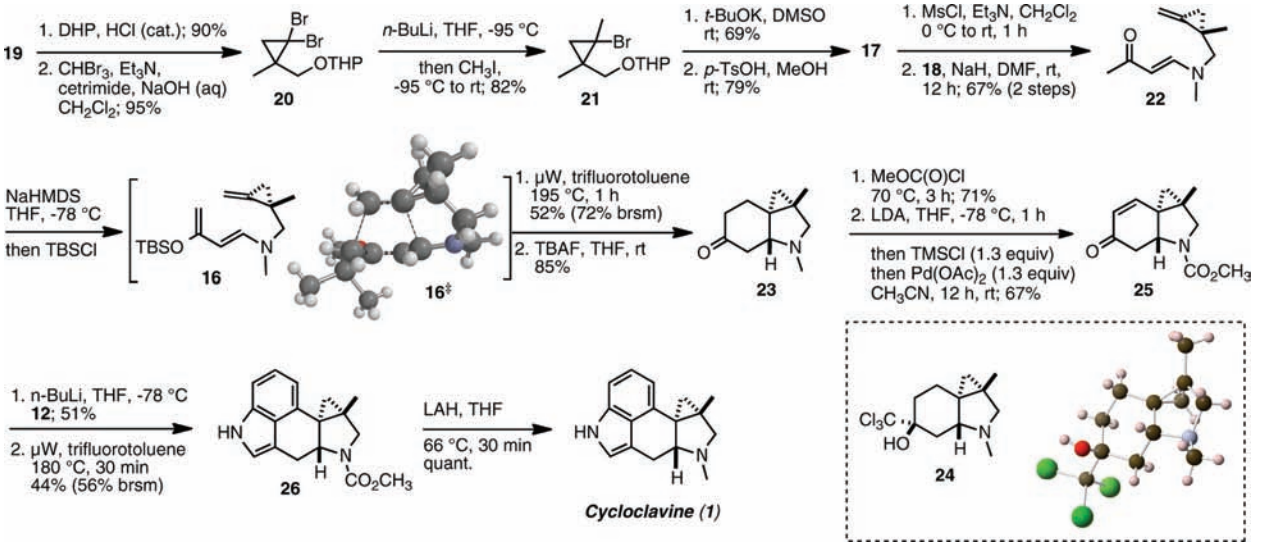
The dehydrogenation of *β*-aminoketone **23** to the corresponding enone **25** was problematic due to competing side reactions involving the basic amine moiety. We circumvented this problem by a dealkylative protection of the tertiary amine as a carbamate with methyl chloroformate in 71% yield.[16] 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 **12** 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

dx.doi.org/10.1021/ja2026882 |*J. Am. Chem. Soc.* 2011, 133, 7704–7707

Scheme 4. Synthesis of (±)-Cyclocavine



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 cyclocavine's indoline core through a novel and highly stereoselective intramolecular Diels–Alder reaction of a methylenecyclopropane.[19,20]

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

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 cyclocavine.

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(18) **1**: Mp 153.2–155.3 °C (acetone/chloroform); IR (ATR) 2921, 2798, 1591, 1590, 1441, 1150 cm^{-1}; ^{1}H 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.

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