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Synthesis of (−)-Epibatidine

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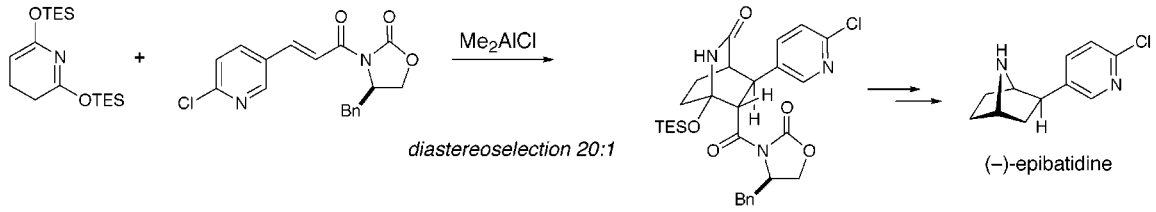
ABSTRACT

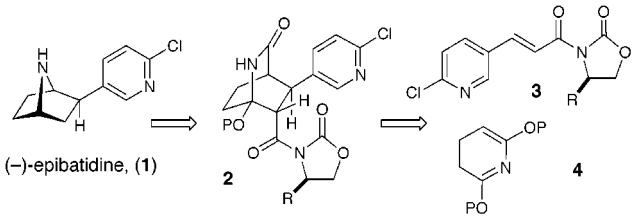


The synthesis of (−)-epibatidine has been accomplished utilizing a highly exo-selective asymmetric hetero Diels−Alder reaction. The key steps employed to transform the resulting bicycle into the natural product include a fluoride-promoted fragmentation and a Hofmann rearrangement.

In 1992, Daly and co-workers disclosed the structure of epibatidine (**1**), an alkaloid isolated from the skin of the Ecuadorian frog *Epibatidores tricolor*.[1] Because of its scarcity and unprecedented biological activity as a nonopiate analgesic approximately 200 times more potent than morphine,[2] widespread efforts have culminated in numerous total and formal syntheses.[3] Surprisingly, while approximately 50 syntheses have been reported, few full syntheses are enantioselective.[4] In this Letter, we wish to report a highly stereoselective synthesis of (−)-epibatidine by a route that is readily amenable to analogue production.

Our approach to **1** relies on a selective hetero Diels−Alder reaction between bis-silyloxy azadiene **4**[5] and an unsaturated acyl oxazolidinone (**3**) appended to the requisite chloropyridine ring (Scheme 1). We anticipated that this Diels−Alder reaction promoted by Me_2AlCl would exhibit high levels of facial selectivity due to the rigid chelate of the activated acyl oxazolidinone.[6] Furthermore, previous contributions by Ghosez and co-workers have established that Diels−Alder reactions utilizing 2-azadienes such as **4** are highly exo-selective.[5] The union of these two control elements would afford an appropriately functionalized 2-azabicyclo[2.2.2]octanone **2**.

Scheme 1. Epibatidine Retrosynthesis



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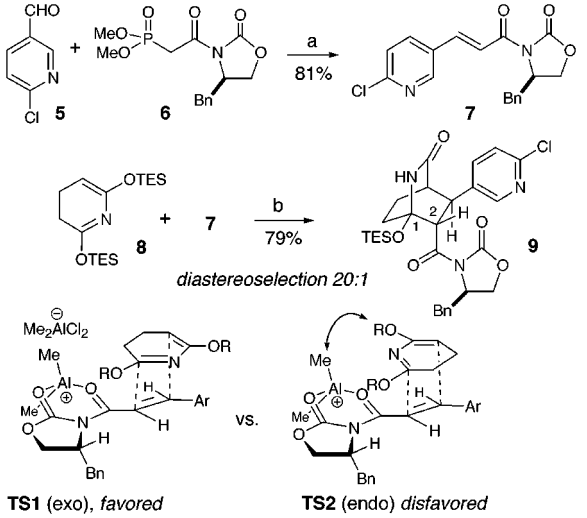
The synthesis of acyl oxazolidinone dienophile **7** began with a Horner−Wadsworth−Emmons reaction of aldehyde **5**[7] and phosphonate **6**[8] using Masamune−Roush conditions (LiCl, *i*-Pr_2EtN, CH_3CN, Scheme 2).[9] The desired α,β-unsaturated acyl oxazolidinone **7** was isolated in 81% yield (*E*/*Z* selectivity >20:1). Azadiene **8** was synthesized by the addition of 2.2 equiv of triethylsilyl triflate to an ethereal suspension of glutarimide in the presence of Et_3N (90% yield, not shown).

Scheme 2. Asymmetric Hetero Diels−Alder Reaction[a]



[a] Reaction conditions: (a) LiCl, *i*-Pr_2EtN, CH_3CN. (b) Me_2AlCl (2.2 equiv), CH_2Cl_2, −78 °C; aq. NH_4Cl.

The key hetero Diels−Alder reaction was performed by combining oxazolidinone **7** and bistriethylsilyloxy azadiene **8** in the presence of 2.2 equiv of Me_2AlCl at −78 °C. The crystalline bicyclic adduct **9**, as the desired exo diastereomer, was isolated in 79% yield from a 20:1 diastereomeric mixture.[10] Scheme 2 depicts two possible transition states for this reaction (**TS1** and **TS2**) in which the oxazolidinone−Lewis acid complex is highly organized as a result of chelation of both carbonyl units of the acyl oxazolidinone to the cationic aluminum. Presumably, this complexation promotes ionization of the first equivalent of Me_2AlCl with concomitant generation of a second equivalent of anionic Me_2AlCl_2.[11] In this fixed conformation, the benzyl substituent of the oxazolidinone effectively shields the bottom face of the dienophile. The azadiene's preference for an exo approach (**TS1**) over an endo approach (**TS2**) is likely attributable to steric interactions between one of the triethylsilyloxy substituents of **8** and the aluminum Lewis acid. The stereochemistry of **9** was unambiguously established by X-ray crystallography (Figure 1).

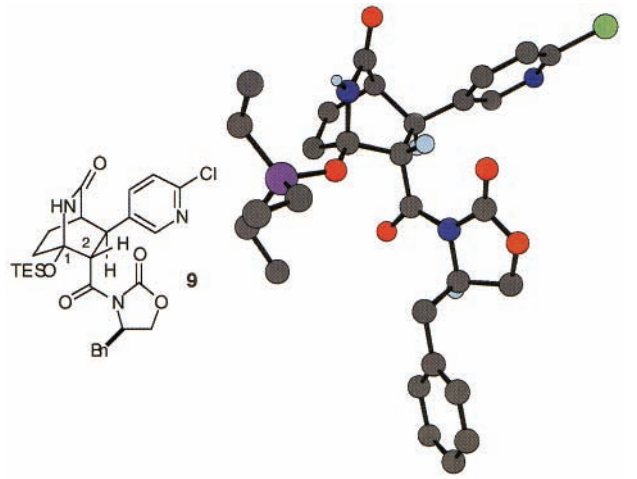


Figure 1. X-ray of Diels−Alder adduct **9**.

With the appropriately functionalized bicycle in hand, our investigations focused on the cleavage of the C1−N bond to reveal the desired substituted cyclohexanone core. It was found that treatment of **9** with *n*-Bu_4NF preferentially induced a retro-aldol scission of the C1−C2 bond.[12] It was postulated that removal of the oxazolidinone auxiliary might prevent the undesired fragmentation (C1−C2). However, standard methods to replace the auxiliary failed. Nucleophiles such as LiSEt, LiOOH, and LiOMe preferentially added to the urethane carbonyl of the acyl oxazolidinone, presumably as a result of steric congestion around the imide carbonyl. Fortunately, it was found that **9** could be converted to methyl ester **10** using $Sm(OTf)_3$ in refluxing MeOH. The success of this reaction may be due to activation of the imide by chelation of the Sm(III) cation with both carbonyl oxygens.[13]

To facilitate the desired C1−N bond scission, amide **10** was converted to the *tert*-butyl carbonate **11** using BOC_2O, DMAP conditions.[14] The preference for *O*- over *N*-acylation may be rationalized on the basis of steric effects. Subsequent exposure of **11** to *n*-Bu_4NF resulted in fragmentation to nitrile

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(6) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

(7) 6-Chloropyridine-3-carboxyaldehdye (**5**) was prepared from from 6-chloronicotinc acid. See Supporting Information for details.

(8) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. Supporting Information.

(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(10) Determined by ^1H NMR analysis (500 MHz) of the unpurified reaction mixture.

(11) This chelation activation strategy using >2.0 equiv of Me_2AlCl has also been employed for additions to carbonyls; see: (a) Evans, D. A.; Allison, B. A.; Yang, M. G. *Tetrahedron Lett.* **1999**, 40, 4457−4460. (b) Evans, D. A.; Halstead, D. P.; Allison, B. A. *Tetrahedron Lett.* **1999**, 40, 4461−4462.

(12) Ghosez has observed a strong dependence of C−N vs C−C bond scission on the electron withdrawing group at C2 in related 2-azabicyclo-[2.2.2]octanones systems, see: Rivera, M.; Lamy-Schelkens, H.; Sainte, F.; Mbiya, K.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 4573−4576.

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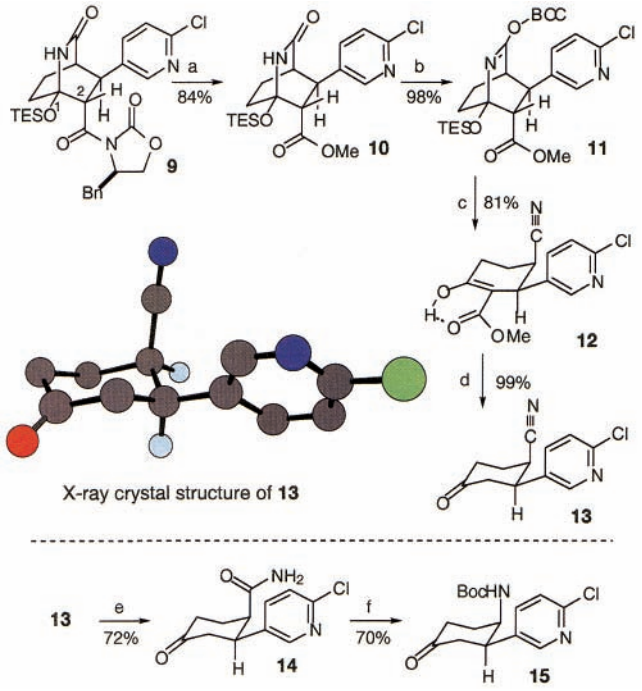
(14) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *38*, 2424−2426.

12, isolated exclusively as the enol tautomer, in 81% yield.[15] Enol **12** was subjected to a Krapcho decarboxylation (DMSO, H_2O, 130 °C) to provide ketone **13** in 99% yield.[16] A single-crystal X-ray structure of **13** confirmed that the nitrile was disposed in the axial position, cis to the chloropyridine ring.

Scheme 3. Bicycle Fragmentation[a]

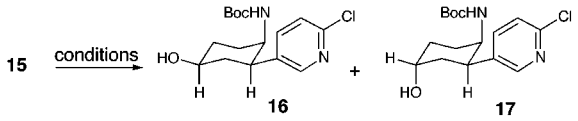


[a] Reaction conditions: (a) $Sm(OTf)_3$, MeOH, reflux. (b) BOC_2O, DMAP, Et_3N, CH_2Cl_2. (c) *n*-Bu_4NF, THF/H_2O. (d) DMSO, H_2O, 130 °C. (e) Me_3SiOK, toluene, 70 °C; aq. NH_4Cl; (f) $Pb(OAc)_4$, *tert*-butyl alcohol, 50 °C.

The synthesis now required the transposition of nitrogen from the nitrile to a protected amine, as well as a stereoselective ketone reduction. The conversion of nitrile **13** to the derived primary amide **14** was accomplished in 72% yield with potassium trimethylsilanolate in toluene at 70 °C.[17] Amide **14** was then subjected to lead(IV) acetate in *tert*-butyl alcohol, which induced a Hofmann rearrangement to afford the BOC-protected amine **15** in 70% yield.[18]

Initial attempts to reduce ketone **15** utilized sterically demanding hydride reagents such as L-Selectride[19] (Table 1).[20] The anticipated axial alcohol (trans with respect to the protected nitrogen) could then be activated, and an intramolecular S_N2 displacement by nitrogen would follow. Although the reduction proceeded without affecting the chloropyridine ring,[21] a 75:25 mixture of inseparable alcohols was obtained. The structural assignment of the major diastereomer was complicated as a result of slowly interconverting conformations as observed by ^1H NMR spectroscopy, even at elevated temperatures. Ultimately, the major isomer was determined to be equatorial alcohol **16** by the straightforward conversion of *minor* isomer **17** to epibatadine (**1**) by a three-step sequence.[22] Although hindered hydride reagents did not produce the desired axial alcohol, relatively smaller reducing agents afforded the equatorial alcohol with good selectivity (Table 1). Whereas lithium borohydride was modestly selective for alcohol **16** (86:14; entry 3), the treatment of ketone **15** with $NaBH_4$ in MeOH at −40 °C (entry 4) afforded an 89% yield of alcohols **16**/**17** as a 92:8 mixture favoring **16**. These experiments seem to indicate that conformational effects play an important role in the stereochemical outcome of this reduction.

Table 1. Diastereoselective Reductions of Ketone **15**



entry	conditions[a]	solvent	*T*, °C	**16**:**17**[c]
1	L-Selectride[b]	Et_2O	−78	75:25
2	*i*-Bu_2AlH	CH_2Cl_2	−78	65:35
3	$LiBH_4$	THF	−78	86:14
4	$NaBH_4$	MeOH	−40	92:8[d]

[a] All reactions were 0.1 M in substrate and proceeded to ≥95% conversion. [b] L-Selectride = lithium tri-*sec*-butylborohydride. [c] Product ratios were determined by ^1H NMR (500 MHz, 60 °C). [d] Isolated yield of **16**/**17** = 89%

The completion of the synthesis required inverting the equatorial alcohol **16** in order to facilitate subsequent closure to the 7-azabicylco[2.2.1]heptane system. Accordingly, alcohols **16**/**17** were converted into the corresponding mesylates (MsCl, Et_3N) from which **18** was isolated in high yield (92%). Subsequent S_N2 displacement (LiBr, THF, 50 °C) furnished bromide **19** in 84% yield (Scheme 4). Treatment of bromide **19** with trifluoroacetic acid provided the primary amine **20** in 91% yield. Finally, penultimate amine **20** was heated at reflux in $CHCl_3$ for 3 days to afford (−)-epibatidine (**1**, $[\alpha]^{25}_D$ −6.7° (*c* 0.21, CH_2Cl_2))[23] in 95% yield. The structure of synthetic **1** was confirmed by comparison to reported literature data (^1H, ^{13}C NMR, IR).[24]

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(18) (a) Baumgarten, H. E.; Staklis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141−1142. (b) Wallis, E. S.; Lane, J. F. *The Hofmann Reaction*; John Wiley: New York, 1946; Vol. 3, pp 267−306.

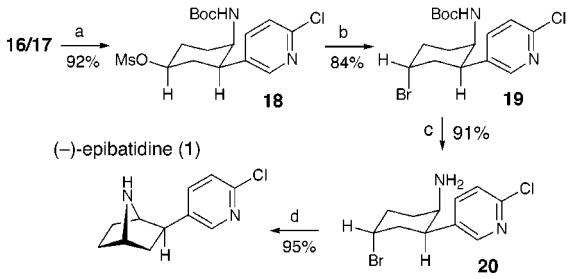
(19) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159−7161.

(20) For a review on the origin of stereoselectivity of metal hydride additions to cyclohexanones, see: Gung, B. W. *Tetrahedron* **1996**, *52*, 5263−5301.

(21) Undesired reduction of the chloropyridine ring has complicated previous syntheses; see: (a) Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059−2062. (b) Palmgren, A.; Larsson, A. L. E.; Bäckvall, J.-E.; Helquist, P. *J. Org. Chem.* **1999**, *64*, 836−842.

(22) The mixture of alcohols **16** and **17** were converted to the mesylates (MsCl, Et3N, 92%), the BOC protecting groups were removed with 10% trifluoroacetic acid in CH_2Cl_2 (95%), and the amines were heated in refluxing chloroform to afford a separable 3:1 mixture of mesylate and (−)-epibatidine.

Scheme 4. Completion of the Synthesis[a]



[a] Reaction conditions: (a) MsCl, Et_3N, CH_2Cl_2; (b) LiBr, THF, 50 °C; (c) CF_3COOH, CH_2Cl_2; (d) $CHCl_3$, reflux.

In summary, a highly selective asymmetric synthesis of (−)-epibatidine has been achieved in 13 steps and 13% overall yield from 6-chloropyridine-3-carboxyaldehdye. The key steps include a Lewis acid mediated exo-selective hetero Diels−Alder reaction and an unusual ring-opening fragmentation. The route described here demonstrates the powerful utility of Me_2AlCl-promoted Diels−Alder reactions of 2-azadienes and α,β-unsaturated imides for the synthesis of alkaloids.

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Supporting Information Available: Experimental procedures for all new compounds and X-ray crystallographic data for **9** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Reported literature optical rotation value for (−)-epibatidine: $[\alpha]^{25}_D$ −6.2° (*c* 0.42, CH_2Cl_2). Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485−7488.

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