

Synthesis of (–)-Epibatidine

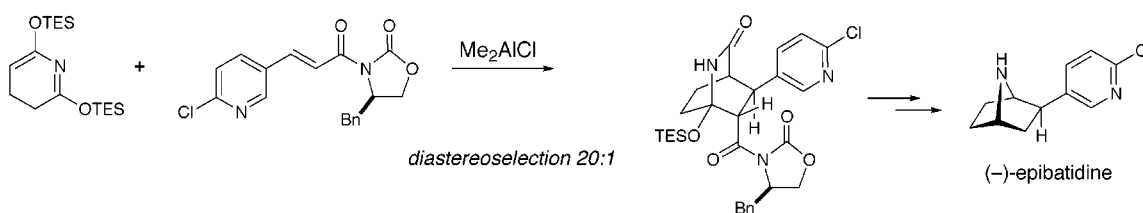
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ABSTRACT



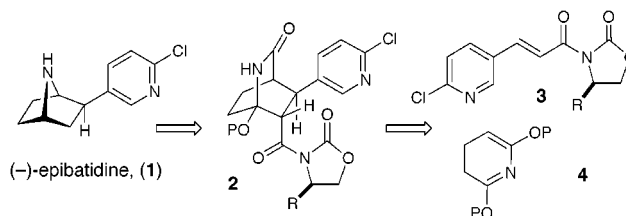
The synthesis of (–)-epibatidine has been accomplished utilizing a highly exo-selective asymmetric hetero Diels–Alder reaction. The key steps employed to transform the resulting bicycle into the natural product include a fluoride-promoted fragmentation and a Hofmann rearrangement.

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 nonopioid 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 Me₂AlCl 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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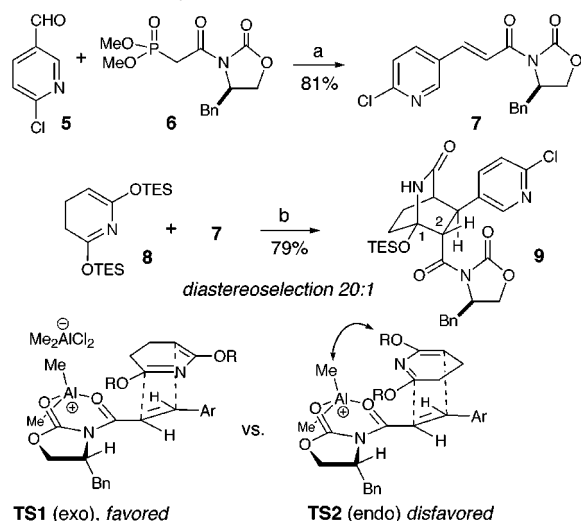
(2) (a) Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563–568. (b) Ellis, J. L.; Harman, D.; Gonzalez, J.; Spera, M. L.; Liu, R.; Shen, T. Y.; Wypij, D. M.; Zuo, F. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 1143–1150. (c) Kestingland, A. C.; Gentry, C. T.; Panesar, M. S.; Bowes, M. A.; Vernier, J. M.; Cube, R.; Walker, K.; Urban, L. *Pain* **2000**, *86*, 113–118 and references therein.

(3) For early total syntheses of epibatidine, see: (a) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251–3254. (b) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477–4480. (c) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Hobbs, S. C.; Mitchell, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1216–1218. (d) Corey, E. J.; Loh, T. P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. J. *Org. Chem.* **1993**, *58*, 5600–5602. (e) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493–7496. For reviews on the total syntheses of epibatidine, see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179–1193. For a recent synthesis, see: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166–173.

(4) For enantioselective total syntheses of epibatidine, see: (a) Hernandez, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683–2691. (b) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485–7488. (c) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major, E.; Blaskó, G. *Tetrahedron* **1996**, *52*, 11053–11062. (d) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857–1858. (e) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 4513–4516. (f) Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P. *Tetrahedron Lett.* **1998**, *39*, 1023–1024.

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*-Pr₂EtN, CH₃CN, Scheme 2).⁹ The desired α,β -

Scheme 2. Asymmetric Hetero Diels–Alder Reaction^a



^a Reaction conditions: (a) LiCl, *i*-Pr₂EtN, CH₃CN. (b) Me₂AlCl (2.2 equiv), CH₂Cl₂, –78 °C; aq. NH₄Cl.

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 Et₃N (90% yield, not shown).

The key hetero Diels–Alder reaction was performed by combining oxazolidinone **7** and bis-triethylsilyloxy azadiene **8** in the presence of 2.2 equiv of Me₂AlCl 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 Me₂AlCl with concomitant generation of a second equivalent of anionic Me₂AlCl₂.¹¹ 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).

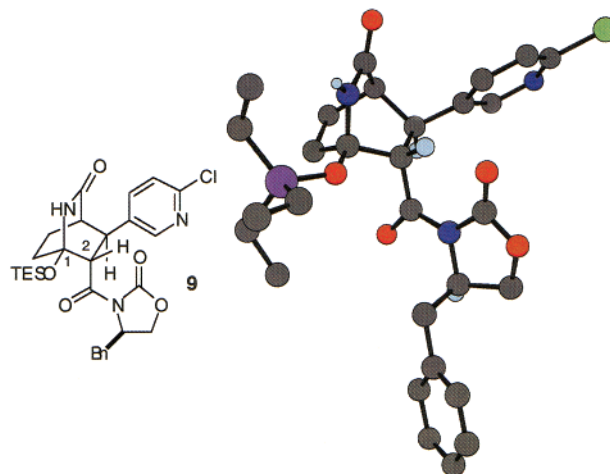


Figure 1. X-ray of Diels–Alder adduct **9**.

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*-Bu₄NF 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 BOC₂O, 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*-Bu₄NF 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-carboxaldehyde (**5**) was prepared from 6-chloronicotinic acid. See Supporting Information for details.

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

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

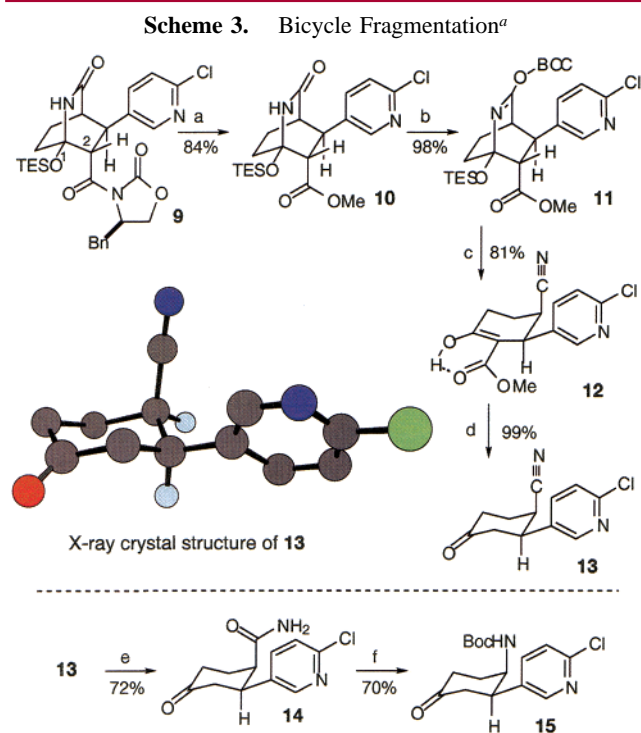
(11) This chelation activation strategy using >2.0 equiv of Me₂AlCl has also been employed for additions to carbonyls; see: (a) Evans, D. A.; Allison, B. A.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457–4460. (b) Evans, D. A.; Halstead, D. P.; Allison, B. A. *Tetrahedron Lett.* **1999**, *40*, 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, H₂O, 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.



^a Reaction conditions: (a) Sm(OTf)₃, MeOH, reflux. (b) BOC₂O, DMAP, Et₃N, CH₂Cl₂. (c) *n*-Bu₄NF, THF/H₂O. (d) DMSO, H₂O, 130 °C. (e) Me₃SiOK, toluene, 70 °C; aq. NH₄Cl; (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-Selectride¹⁹ (Table 1).²⁰ The anticipated axial alcohol (trans with respect to the protected nitrogen) could then be activated, and an intra-

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

entry	conditions ^a	solvent	<i>T</i> , °C	16:17 ^c
1	L-Selectride ^b	Et ₂ O	-78	75:25
2	<i>i</i> -Bu ₂ AlH	CH ₂ Cl 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%

molecular 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 epibatidine (**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 NaBH₄ 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.

The completion of the synthesis required inverting the equatorial alcohol **16** in order to facilitate subsequent closure to the 7-azabicyclo[2.2.1]heptane system. Accordingly, alcohols **16/17** were converted into the corresponding mesylates (MsCl, Et₃N) 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 CHCl₃ for 3 days to afford (-)-epibatidine (**1**, [α]_D²⁵ -6.7° (*c* 0.21, CH₂Cl₂))²³ in 95% yield. The structure of synthetic **1** was confirmed by comparison to reported literature data (¹H, ¹³C NMR, IR).²⁴

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(17) (a) Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747–3749. (b) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.

(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.

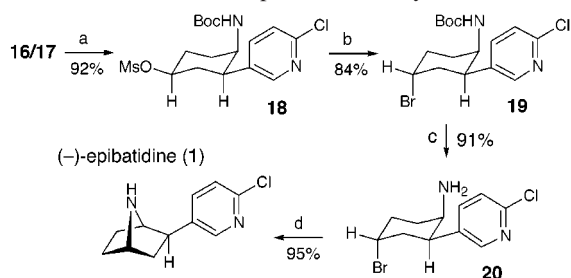
(19) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–7161.

(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 CH₂Cl₂ (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, Et₃N, CH₂Cl₂; (b) LiBr, THF, 50 °C; (c) CF₃COOH, CH₂Cl₂; (d) CHCl₃, reflux.

In summary, a highly selective asymmetric synthesis of (-)-epibatidine has been achieved in 13 steps and 13% overall yield from 6-chloropyridine-3-carboxyaldehyde. The key steps include a Lewis acid mediated exo-selective hetero Diels–Alder reaction and an unusual ring-opening fragmen-

(23) Reported literature optical rotation value for (-)-epibatidine: $[\alpha]^{25}_D$ -6.2° (c 0.42, CH₂Cl₂). Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485–7488.

tation. The route described here demonstrates the powerful utility of Me₂AlCl-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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