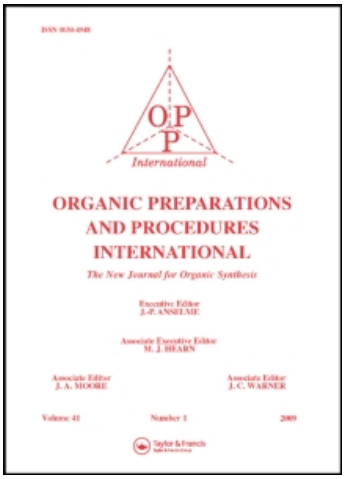

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Horacio F. Olivo[a]; Michael S. Hemenway[a]
[a] Division of Medicinal and Natural Products Chemistry, College of Pharmacy The University of Iowa, Iowa City, IA

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Horacio F. Olivo* and Michael S. Hemenway†

Division of Medicinal and Natural Products Chemistry, College of Pharmacy
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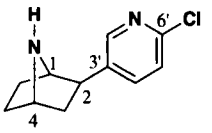
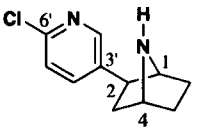
INTRODUCTION

The small molecule alkaloid and nicotinic analgesic epibatidine (**1**) has been the target of intense synthetic effort ever since its structure and initial pharmacological data were reported by Daly and co-workers in 1992.[1] Epibatidine, isolated in trace amount from the skin of the Ecuadoran poison frog *Epipedobates tricolor*, was found to be 200-400 times more



(*1R,2R,4S*)-epibatidine (**1**)
(hydrogen oxalate salt [α]= + 37.3
free base [α]= - 6.7)



(*1S,2S,4R*)-epibatidine (**1**)
(hydrogen oxalate salt [α]= - 37.4
free base [α]= + 6.5)

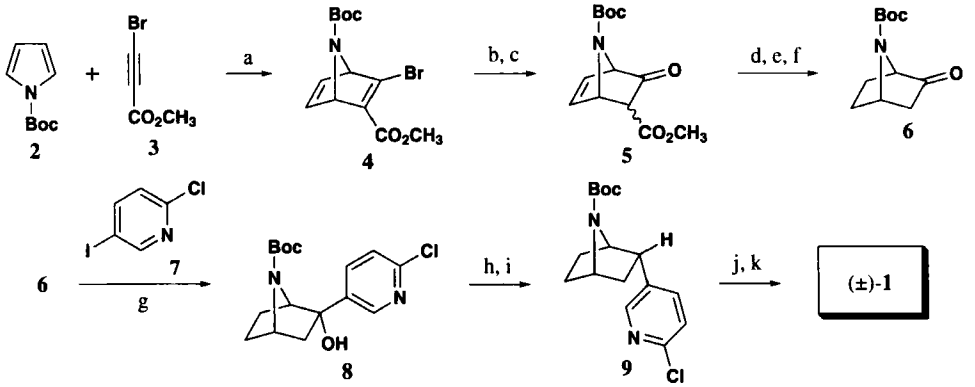
potent than morphine as an analgesic and appeared to act *via* a non-opioid mechanism since its effects are not blocked by the opiate receptor antagonist naloxone. It has been shown that epibatidine is an extremely potent agonist of the nicotinic acetylcholine receptor.[2] It was shown that the natural alkaloid possesses the *1R,2R,4S* stereochemistry (hydrogen oxalate salt: [α]= +37.3; free base: [α]= -6.7).[3] At least 60 publications concerning epibatidine syntheses have appeared, and countless more have appeared in regard to its intriguing biological properties. Not surprisingly, a number of excellent review articles about epibatidine have been written.[4-7] One of the most recent reviews comes from Bai, who synthesized epibatidine and selected analogs in 1996 and whose review was published in 1997.[7,8] Since a significant amount of synthetic work on epibatidine has appeared in the literature since Bai's review, an update on synthetic research in the epibatidine field appeared appropriate. This review only attempts to cover both total and formal synthesis research since Bai's review; a comprehensive look at all published syntheses dating back to Broka's first racemic synthesis was not deemed necessary.[9] The reader is referred to previous reviews for such information. However, reference to earlier syntheses will be made as appropriate to develop a historical perspective on a particular synthetic strategy.

Synthetic approaches to epibatidine have been categorized according to how the azabicyclic ring system is formed during the synthesis: 1) cycloaddition reactions, 2) intramolecular nucleophilic displacement reactions and 3) radical cyclizations. Since Bai covered the ring contraction of tropane-like systems *via* Favorskii rearrangement strategy in his review, this strategy will be omitted. Within each of these categories, work will be reviewed in chronological order.

CYCLOADDITION REACTIONS

1. Diels-Alder Cycloadditions

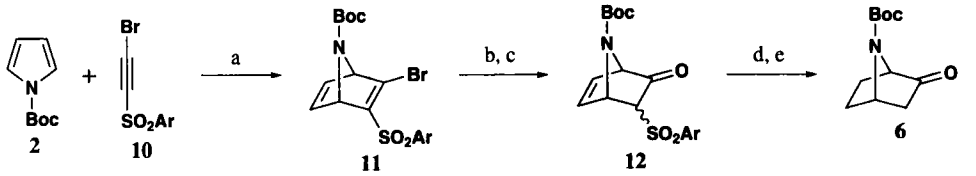
A powerful strategy to prepare the azabicyclo[2.2.1]heptane framework of epibatidine is the Diels-Alder reaction employing an *N*-protected pyrrole as the diene and a substituted acetylene as the dienophile. A novel Diels-Alder cycloaddition approach was reported by Trudell to create *N*-acyl 7-azanorbornan-2-one, a key synthetic intermediate in the total synthesis of epibatidine.[10-12] Preparation of *N*-Boc protected 7-azabicyclo[2.2.1]heptan-2-one **6** from *N*-protected pyrrole took six steps, Scheme 1.[10] *N*-Boc protecting group is preferred to other acyl groups because it is removed under milder conditions. Treatment of *N*-Boc pyrrole (**2**) with methyl 3-bromopropiolate (**3**) resulted in bromoalkenyl cycloadduct **4** as a sole product. Treatment of vinyl bromide **4** with 1.1 equiv. of diethylamine and 5 equiv of triethylamine in acetonitrile at room temperature followed by hydrolysis with 10% HCl at 100° afforded β-ketoester **5**. Decarboxylation of β-ketoester **5** was successful only after hydrogenation because of susceptibility of compound **4** to a retro Diels-Alder reaction. Addition of 5-lithio-2-chloropyridine to ketone **6** gave stereoselectively alcohol **8**. Tertiary alcohol **8** was deoxygenated by a radical reaction *via* its methyl oxalyl ester with Bu_3SnH in the presence of AIBN. Epimerization of *endo*-pyridyl compound **9** to the requisite *exo*-pyridyl compound was achieved by refluxing in the presence of potassium *tert*-butoxide. Deprotection of the *N*-Boc group gave epibatidine in racemic form (*Scheme 1*).



a) 90°C, 60%; b) Et_2NH, Et_3N; c) 10% HCl, 87%; d) H_2, Pd/C, 99%; e) 10% HCl, heat; f) $(Boc)_2O$, 77%; g) *n*-BuLi, -78°C, THF, 88%; h) $ClCOCO_2CH_3$; i) Bu_3SnH, AIBN, 88%; j) *t*-BuOK, *t*-BuOH, 60%; k) CF_3CO_2H, 99%.

Scheme 1

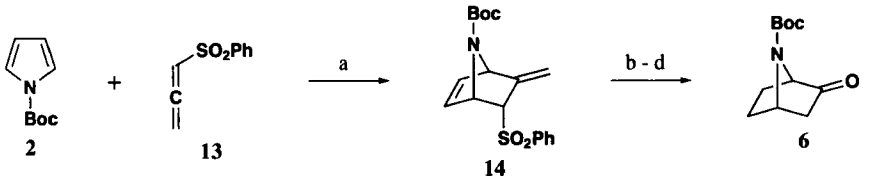
When the Diels-Alder cycloaddition was carried out with 2-bromoethynyl aryl sulfone **10** and pyrrole **2**, preparation of ketone **6** can be reduced one step (*Scheme 2*).[10] A similar chemical sequence was required to remove the vinyl bromide and hydrolyze it to ketone **12**. Hydrogenation of compound **12**, followed by metal reduction gave the desired ketone **6**.



a. 90°C, toluene, 78%; b. Et_2NH, Et_3N; c. 10% HCl, 86%; d. H_2, Pd/C, MeOH, 99%; e. Al(Hg), MeOH, 60%.

Scheme 2

A new strategy for the preparation of azabicyclic ketone **6** was based on the Diels-Alder cycloaddition of electron deficient allenes with *N*-acyl pyrroles (*Scheme 3*).[11] Treatment of *N*-Boc protected pyrrole with 1-(benzenesulfonyl)-1,2-propadiene **13** resulted in *endo*-



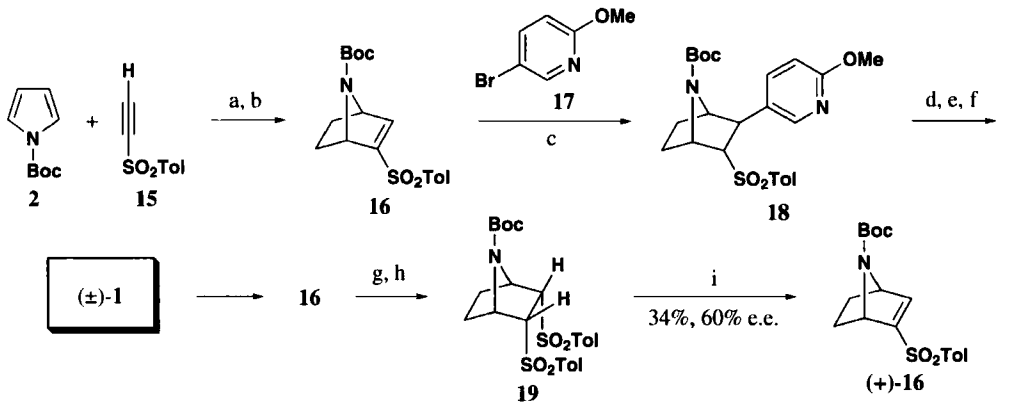
a. 85-90°C, 45%; b. H_2, Pd/C, MeOH, 90%; c. O_3, -78°C, then Me_2S, 78%; d. Al(Hg), THF-H_2O, 60%.

Scheme 3

cycloadduct **14** as the sole product. Regioselective hydrogenation of the internal double bond, ozonolysis, followed by metal reduction of the β-ketosulfonyl group gave the desired bicyclic ketone **6**. This strategy required only four steps to access the key azabicyclic ketone **6**.

Simpkins used a Diels-Alder cycloaddition strategy in a racemic and also an enantioselective synthesis of epibatidine.[13-16] The synthesis involves the conjugate addition of a metallated 2-methoxypyridine derivative to *N*-Boc azabicyclic alkenyl sulfone (**16**) as the key step (*Scheme 4*). The azabicyclic alkenyl sulfone **16** was prepared by a Diels-Alder cycloaddition of ethynyl tolyl sulfone **15** with *N*-Boc protected pyrrole **2**, followed by regioselective hydrogenation. Michael addition of the metallated pyridine of **17** to alkenyl sulfone **16** gave exclusively the *exo*-4-methoxypyridyl adduct **18**. Further desulfonation, chlorination and *N*-Boc deprotection gave epibatidine. The result was a very concise six-step synthesis with an overall yield exceeding 20%. An asymmetric synthesis of *N*-Boc azabicyclic alkenyl sulfone **16** was investigated later on.[15] Desymmetrization by β-elimination of *meso-bis* sulfone **19** occurred best when adding the sodium alkoxide of (*1R, 2S*)-ephedrine to give the conjugated alkenyl sulfone (+)-**16** (34%, 60% e.e.). *bis*-Sulfone **19** was efficiently prepared by treatment of racemic alkenyl sulfone **16** with *n*-BuLi and quenching the reaction with *p*-TolSO_2F, followed

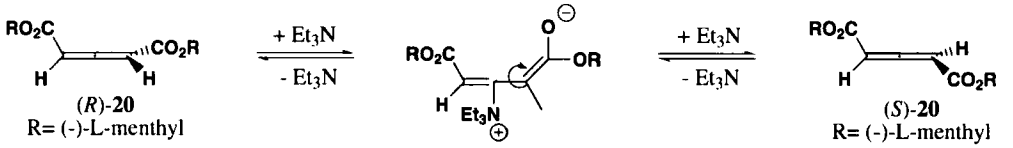
by exhaustive hydrogenation to remove the non-conjugated olefin. Simpkins' strategy, although similar to Shen's strategy in one of the first total syntheses of epibatidine,[17] allowed the development of an asymmetric synthesis.



a. 85-90°C, 82%; b. H_2, Pd/C, MeCN, 97%; c. *n*-BuLi, -78°C, THF, 85%; d. Na(Hg), THF-MeOH, 58%; e. $POCl_3$, DMF, 95°C, 78%; f. HCl, THF, 55-60°C, 79%; g. *n*-BuLi, *p*-$TolSO_2F$, 85%; h. H_2, $Pd(OH)_2/C$, 800 psi, 50%; i. (1*R*,2*S*) ephedrine, RONa, -78°C.

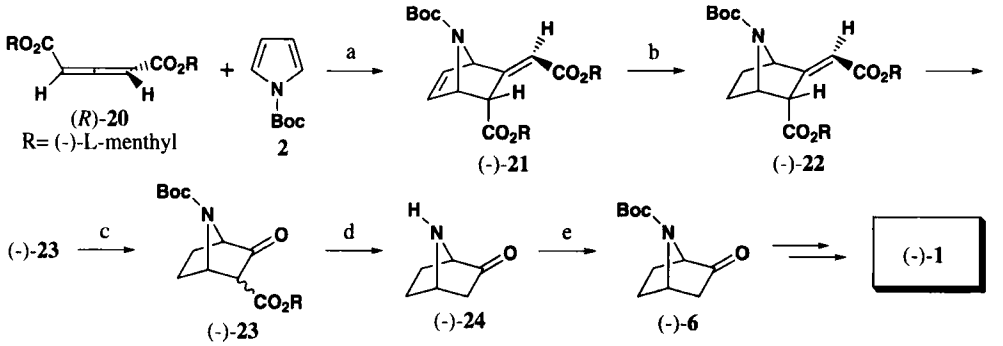
Scheme 4

Node *et al* reported an asymmetric synthesis of *N*-Boc-7-azanorbornanone (**6**), using an allene-1,3-dicarboxylate as dienophile in a Diels-Alder cycloaddition.[18] They demonstrated that a diastereomeric mixture of allenes is found in equilibrium in the presence of catalytic amount of triethylamine (*Scheme 5*). This result suggested that crystallization-induced asymmetric transformation of **20** would be possible, because the *R* diastereomer formed good crystals. Crystalline (*R*)-**20** was obtained efficiently from a diastereomeric mixture (*R*:*S* = 4:5) in 90% yield through *epimerization-crystallization*.



Scheme 5

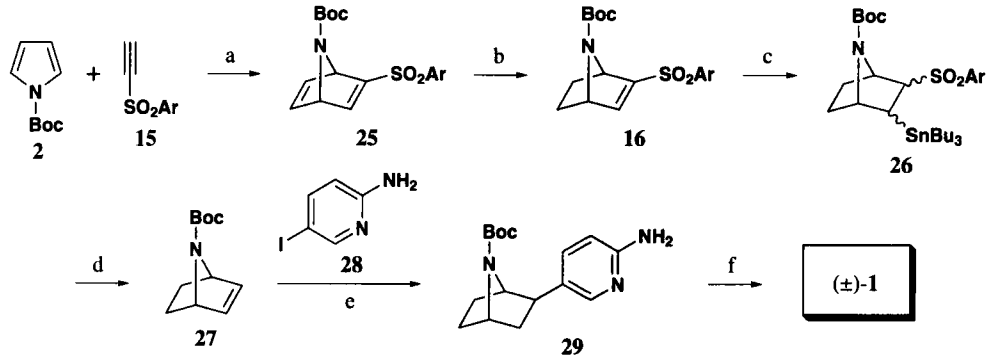
Diels-Alder reaction of allene (*R*)-**20** with *N*-Boc pyrrole **2** in CH_2Cl_2 at -78°, gave exclusively the *endo* adduct (-)-**21** as a sole product (*Scheme 6*). The *endo* stereochemistry of adduct (-)-**21** was elucidated by X-ray crystallographic analysis. Regioselective hydrogenation of the non-conjugated olefin of *endo*-adduct **21** gave the dihydro derivative (-)-**22**. Ozonolysis of the remaining double bond gave β-keto ester (-)-**23**, which was subjected to hydrolysis, decarboxylation, and *N-tert*-butoxycarbonylation to give the important key intermediate *N*-Boc-7-azanorbornanone (-)-**6**.



a. $AlCl_3$, CH_2Cl_2, -78°C, 86%; b. H_2, Pd/C, EtOAc, 99%; c. O_3, PPh_3, CH_2Cl_2, -78°C, 52%; d. 10% HCl, heat; e. Boc_2O, Et_3N, CH_2Cl_2, 55%.

Scheme 6

Carroll *et al* reported[19,20] an improved procedure to prepare *N*-Boc-7-azanorbornene (**27**), another important key synthetic intermediate, reported originally by Clayton and Regan.[21] This is one of the shortest synthesis of epibatidine described, but it had a few drawbacks in the initial versions. The least substituted double bond of cycloadduct **25** was selectively reduced using nickel boride to give vinyl sulfone **16** (*Scheme 7*). Originally, the sulfonyl group of compound **16** was removed by using large amounts of sodium amalgam. It was stated

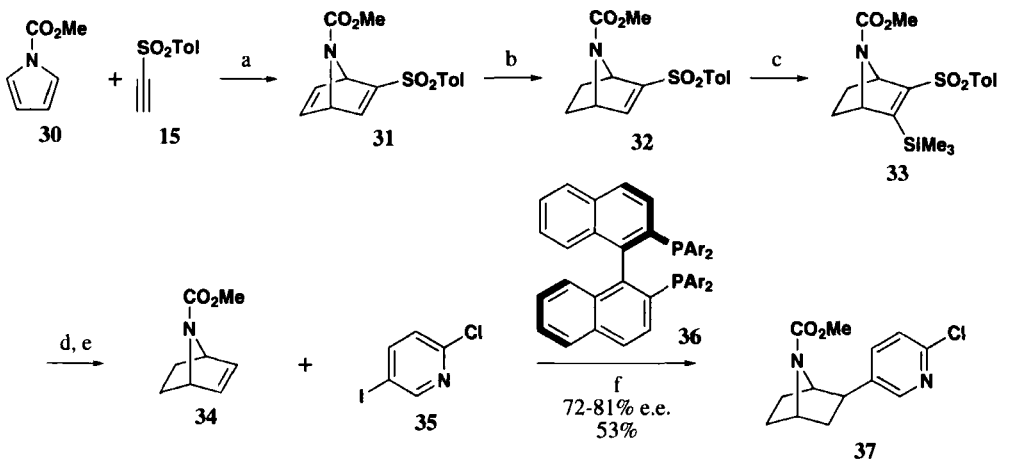


a. 80°C, 65%; b. $Ni(OAc)_4$, $NaBH_4$, MeOH, 86%; c. Bu_3SnH, AIBN, C_6H_6, 78-91%; d. Bu_4NF, THF, 93-98%; e. $Pd(OAc)_2$, *n*-Bu_4NCl, KO_2CH, DMF, 100°C, 68%; f. $NaNO_2$, HCl, CuCl, 76%.

Scheme 7

that over 2 kg of 2.5% sodium amalgam was required to synthesize 10 g of compound **27**. Carroll *et al*, found a new method for the desulfonation of sulfonyl olefins to free olefins. Addition of tributyltin hydride to vinyl sulfone **16** gave compound **26**, which was reduced upon addition of tetrabutylammonium fluoride to yield the desired 7-azanorbornene **27**. This new methodology is well suited for multigram scale synthesis. Palladium-catalyzed coupling of **27** with 2-amino-5-iodopyridine (**28**) gave exclusively *exo*-pyridinyl azabicycloalkane **29**. Diazotization and *N*-deprotection of compound **29** gave racemic epibatidine.

Kaufmann and Namyslo reported the first asymmetric version of a Heck reductive arylation process to attach the chloropyridyl ring to the 7-azanorbornene skeleton.[22-25] The Diels-Alder adduct **31** was prepared by cyclization of *N*-protected pyrrole **30** and *p*-toluenesulfonylacetylene (**15**) under high-pressure conditions, in 81% yield (*Scheme 8*).[23] Catalytic hydrogenation removed the less hindered bond of **31** to give vinyl sulfone **32**. Removal of the



a. CH_2Cl_2, 12 Kbar, 97%; b. H_2, Pd/C, MeOH, 81%; c. LDA, TMSCl, 97%; d. N_2H_2, 99%; e. TBAF, THF, 86%; f. $Pd(OAc)_2$, Et_3N, HCO_2H, 53%.

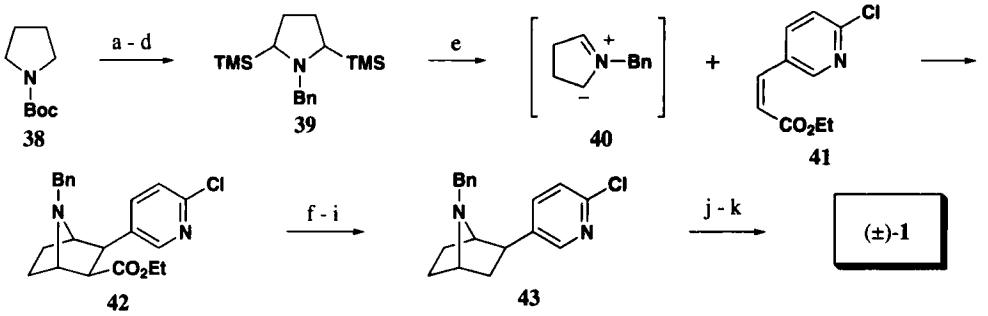
Scheme 8

tosyl group using sodium amalgam is usually a low yielding and difficult procedure. These investigators removed the tosyl group from vinyl sulfone **31** in a three step high-yielding fluoride induced desilylation/detosylation degradation procedure. Two kinds of chiral ligands were investigated in the Heck reaction of compound **34** and iodopyridine **35**: P,P ligands and P,N ligands.[25] Compared to Heck couplings with norbornene, reaction with compound **34** was very slow. The P,P ligands proved to be more effective than the P,N ligands. Noyori's BINAP ligand gave the highest enantioselectivities (72-81% e.e., 53% yield). By using either the (*R*)- or the (*S*)-BINAP ligand both enantiomers of the *N*-protected epibatidine were easily accessible with similar degree of enantioselection.

2. [3+2] Dipolar Cycloadditions

A very unique strategy to assemble the epibatidine skeleton was reported by Pandey.[26] In only one step, [3+2] cycloaddition of a nonstabilized azomethine ylide (**40**) with *cis*-ethyl-3-(6-chloro-3-pyridyl)-2-propenoate (**41**) gave the cycloadduct **42** possessing the 6-chloro-3-pyridyl ring with the desired *exo*-stereochemistry (*Scheme 9*). When the *trans*-propenoate was employed as the dipolarophile, the *endo*-chloropyridyl cycloadduct was

obtained. The generation of ylide **40** involved sequential double desilylation of compound **39** by electron-transfer initiation using Ag(I)F as a one-electron oxidant. Ester **42** was converted

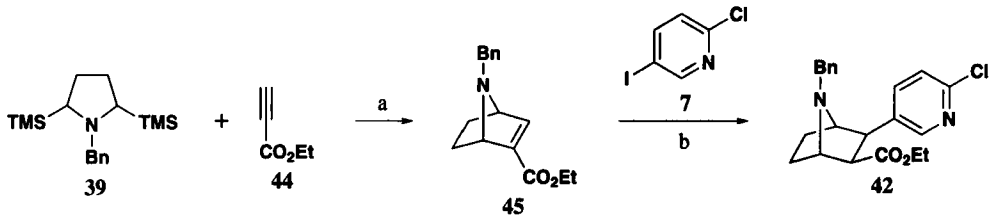


a. Et_2O, TMEDA, -78°C, *s*-BuLi, TMSCl, 90%; b. Et_2O, TMEDA, -45°C, *s*-BuLi, TMSCl, 70%; c. CH_2Cl_2, CF_3CO_2H; d. BnCl, K_2CO_3, CH_3CN, heat, 80%; e. 2 eq. Ag(I)F, CH_2Cl_2, 62%; f. LiOH; g. $(COCl)_2$; h. 2-mercaptopyridine *N*-oxide; i. *t*-BuSH, 55%; j. chloroethyl chloroformate; k. MeOH, heat, 52%.

Scheme 9

to the acyl chloride, and the acyl chloride was subjected to Barton's radical decarboxylation protocol to afford *N*-benzyl epibatidine **43**. Debenzylation of compound **43** afforded racemic epibatidine.

The same [3+2] cycloaddition strategy was also carried out with ethyl propiolate (**44**). Cycloaddition of disilylate **39** with ethyl propionate in the presence of 2 equiv. of Ag(I)F gave cycloadduct **45** in 75% yield (*Scheme 10*). Introduction of the chloropyridyl ring through reductive palladium-catalyzed coupling was not successful. However, conjugate addition of 5-lithio-2-chloropyridine afforded compound **42**, an intermediate in the previous synthesis.



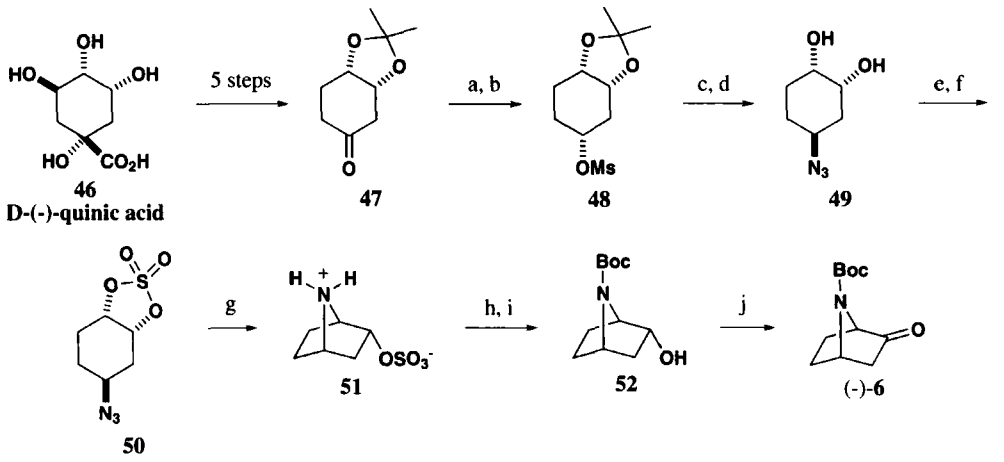
a. Ag(I)F, CH_2Cl_2, 75%; b. *n*-BuLi, Et_2O, -70°C, **7**, 60%.

Scheme 10

II. INTRAMOLECULAR NUCLEOPHILIC DISPLACEMENT REACTIONS

Another popular approach to construct the 7-azanorbornane skeleton of epibatidine is the intramolecular nucleophilic 1,4-displacement of a *trans*-substituted cyclohexane ring. Albertini and collaborators reported an asymmetric synthesis of *N*-Boc-7-azanorbornanone (**6**) starting from an inexpensive plant metabolite, D-(-)-quinine (*Scheme 11*).[27,28] This strategy

was based on the assumption that an intramolecular nucleophilic opening of the vicinal diol cyclic sulfate (**50**) would proceed with complete stereoselectivity for attack at C-4 versus C-3. Enantiopure cyclohexanone **47** was easily obtained on large scale in five steps. Reduction of ketone **47** with sodium borohydride gave an inseparable mixture of diastereo alcohols in a 1:11

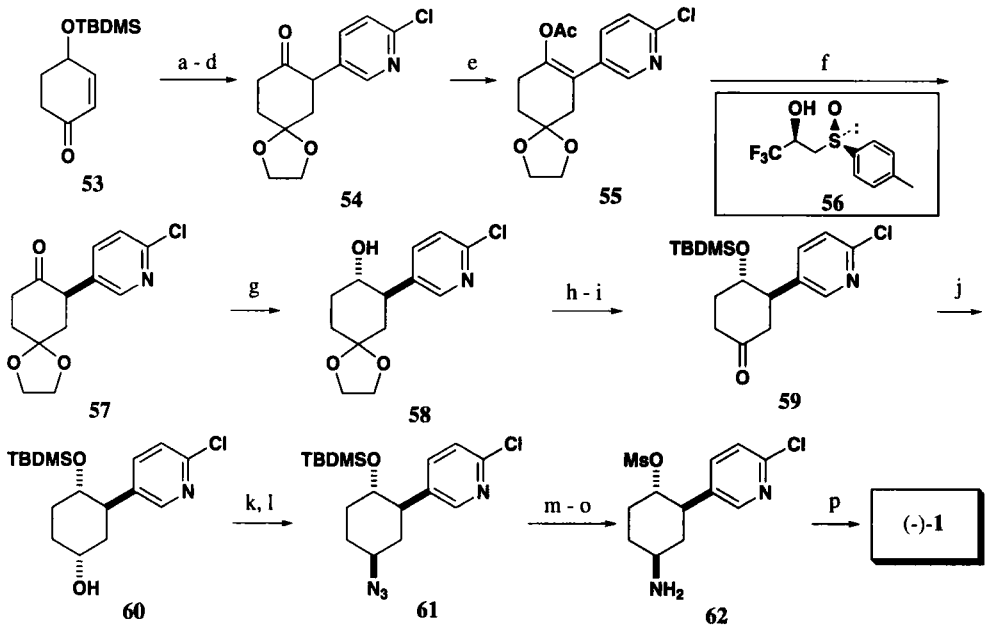


a. $NaBH_4$; b. MsCl, Et_3N, 86%; c. NaN_3, DMF, 80°C, 77%; d. HCl, 98%; e. $SOCl_2$, Et_3N; f. $NaIO_4$, $RuCl_3$, 95%; g. H_2, Pd/C, 30 psi, 95%; h. conc. H_2SO_4, H_2O-THF, 90°C, then Na_2CO_3; i. $(Boc)_2O$, CH_2Cl_2, 82%; j. $(COCl)_2$, DMSO, then Et_3N, 76%.

Scheme 11

ratio. This mixture was separated when the methanesulfonyl derivatives were prepared. Fortunately, the major diastereomer **48** was the desired compound, the stereochemistry of which was demonstrated in subsequent steps. The cyclic sulfonate was installed after mesylate displacement with azide and deprotection of the acetonide. Reduction of the azide group with concomitant internal nucleophilic displacement gave the inner salt **51**. Hydrolysis of the sulfate group, *N*-Boc protection and Swern oxidation of the hydroxyl group gave the desired 7-azanorbornanone **6**. This route provides enantiomerically pure intermediate (-)-**6**.

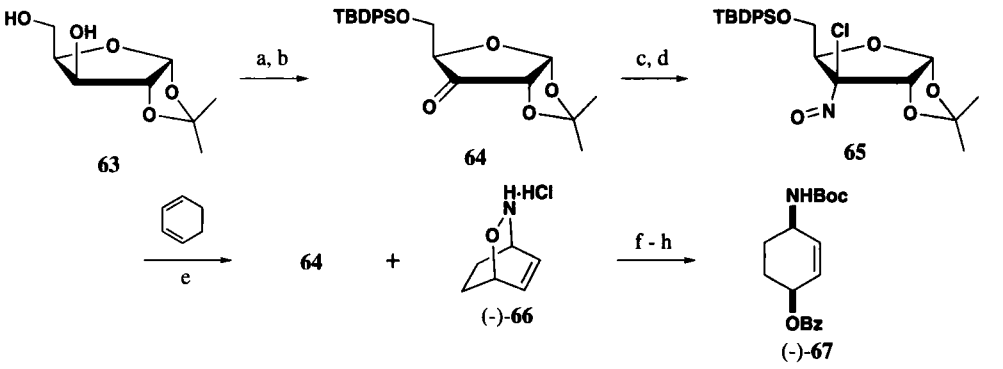
The research group of Kosugi developed a formal synthesis of (–)-epibatidine using a unique asymmetric protonation step to establish the *exo* orientation of the chloropyridyl ring.[29] The conjugate addition procedure used by Sestanj, *et al* in their total synthesis of epibatidine was used in elaborating the starting material, 4-*tert*-butyldimethylsiloxy-cyclohex-2-en-1-one (**53**), to racemic intermediate **54** (*Scheme 12*).[30] After regioselectively forming the enol acetate **55** in 99% yield, the key asymmetric protonation was accomplished by adding chiral β-hydroxy sulfoxide **56** to the achiral lithium enolate of **55** at low temperature. The product (*R*)-**57** was obtained in 63% yield and 82% ee. Converting the resulting enantiomerically enriched **57** to (–)-epibatidine was straightforward, employing a route similar to that used by Broka's original synthesis.[9]



a. 4-lithio-2-chloropyridine, lithium thienyl-cyanocuprate; b. acetalization; c. TBAF, THF; d. $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; e. *t*-BuOK, Ac_2O, THF, 99%; f. 2 eq. MeLi, Et_2O, 0°C, 15 min., then 2.5 eq. chiral β–hydroxy sulfoxide **56**, CH_2Cl_2, -90 to -60°C, 63%, 82% e.e.; g. $NaBH_4$, MeOH, 77%; h. 80% aq. AcOH; i. TBDMSCl, *i*-$PrNEt_2$, DMF, 81%; j. L-Selectride, THF, 63%; k. MsCl, Et_3N, CH_2Cl_2; l. NaN_3, DMF, 76%; m. Bu_4NF, THF; n. MsCl, Et_3N, CH_2Cl_2, 95%; o. $SnCl_2$-$2H_2O$, MeOH-THF; p. $CHCl_3$, reflux, 3 d, 69%.

Scheme 12

Wightman[31,32] claimed a formal synthesis of (+)-epibatidine by preparing a chiral intermediate previously used in the first enantioselective synthesis of (-)-epibatidine described by Trost and Cook.[33] The enantiomerically enriched *cis-N*-Boc-*O*-benzoyl-4-aminocyclohexenol **67** was prepared by addition of a chiral α-chloronitroso reagent (**65**) to 1,3-cyclohexadiene and further functionalization (*Scheme 13*). The α-chloronitroso crystalline compound **65**

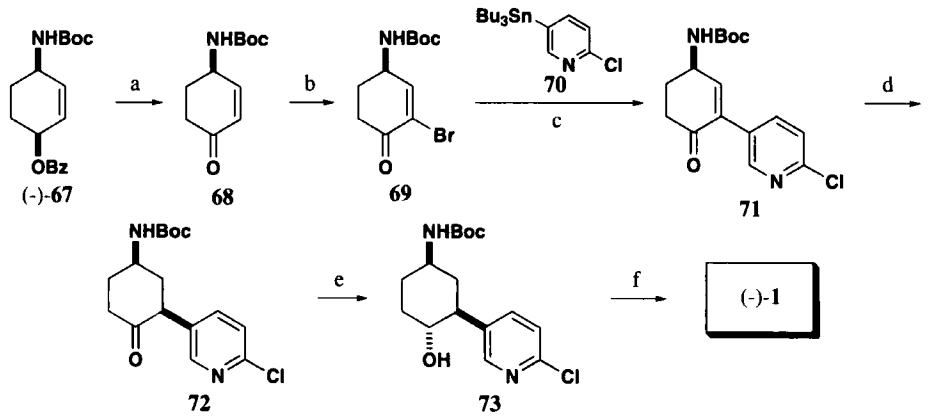


a. TBDPSCl, Et_3N, DMF, 98%; b. PCC, mol. sieves, CH_2Cl_2, 99%; c. NH_2OH•HCl, $NaHCO_3$, EtOH-H_2O, 94%; d. *t*-BuOCl, CH_2Cl_2, 91%; e. $CHCl_3$-*i*PrOH-H_2O, (100:100:1), 0°C, 94%; f. Zn, AcOH; g. Boc_2O; Na_2CO_3, acetone-MeOH, 67%; h. BzCl, DMAP, pyridine, CH_2Cl_2, 76%.

Scheme 13

was prepared in four high-yielding steps from 1,2-*O*-isopropyledene-α-D-xylofuranose (**63**). This readily available and sterically rigid nitroso compound gave recyclable ketone **64** and dihydrooxazine cycloadduct **66** with a high degree of enantioselectivity (96% e.e.). Reductive cleavage of the N-O bond, reaction with di-*tert*-butyl dicarbonate, followed by benzoylation gave intermediate **67**. The enantiomeric form of chloronitroso compound **65** was prepared from L-sorbose using similar methodology. Thus, essentially enantiomerically pure compound (+)-**67** was prepared using chiral chloronitroso compound (+)-**65**.

Chiral compound **67** was previously prepared by Trost and Cook in the first asymmetric synthesis of epibatidine (*Scheme 14*).[33] Compound **67** was functionalized to vinyl bromide **69** in a two-flask protocol. Palladium(0) catalyzed cross-coupling of aryl stannane **70**



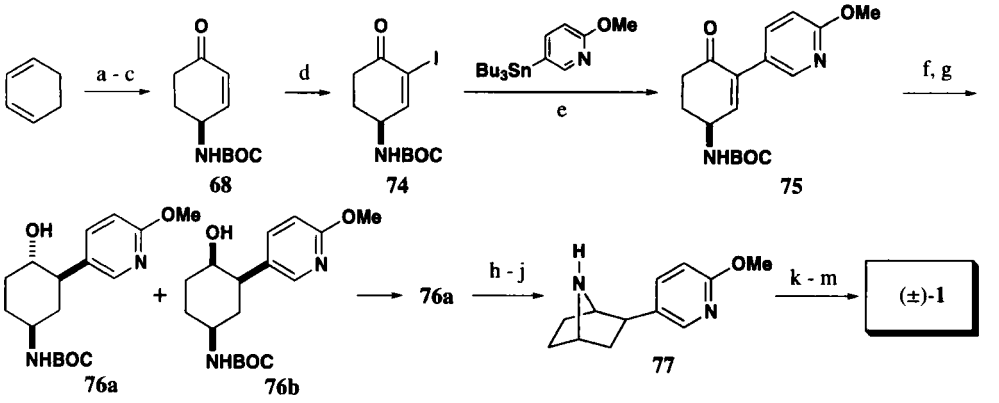
a. K_2CO_3, CH_3OH, rt then Dess-Martin periodinane, CH_2Cl_2, rt, 90%; b. Br_2, Et_3N, CH_2Cl_2, 0°C, 80%; c. 2.5 mol% $(dba)_3Pd{\bullet}CHCl_3$, 15 mol% Ph_3As, THF, 55°C; d. K-Selectride®, THF, -78 to 0°C, then cat. DBU, THF, 76%; e. $NaBH_4$, CH_3OH, 0°C, 67%; f. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; CF_3CO_2H, H_2O, rt; CH_3CN, reflux, 45%.

Scheme 14

with vinyl bromide **69** using triphenylarsine as ligand, gave enone **71**. Chemoselective reduction of the double bond with K-selectride®, followed by equilibration gave *cis*-isomer **72**. Reduction to the *trans*-amidoalcohol **73** was achieved with sodium borohydride. The final ring closure utilized a *trans*-annular cyclization. Mesylation of the alcohol, *N*-deprotection and refluxing the crude in acetonitrile yielded epibatidine.

Johnson and Sirisoma reported a total synthesis of epibatidine achieved in 13 steps using a modified Stille coupling reaction on an α-iodocyclohexenone.[34] Cyclohexenone **68** was prepared in three steps from 1,3-cyclohexadiene using a hetero Diels-Alder cycloaddition approach (*Scheme 15*). The requisite α-iodo enone **74** was obtained from cyclohexenone **68** by addition of iodine in the presence of pyridine. Because hydrogenation of chloropyridyl derivatives usually cleaves the chlorine atom, installation of the chlorine substituent on the pyridine ring was left at a later stage. Modified Stille coupling of α-iodo enone **74** and 2-methoxy-5(tri-*n*-butyl)stannylpyridine gave the desired adduct **75** in excellent yield. Compound **75** was

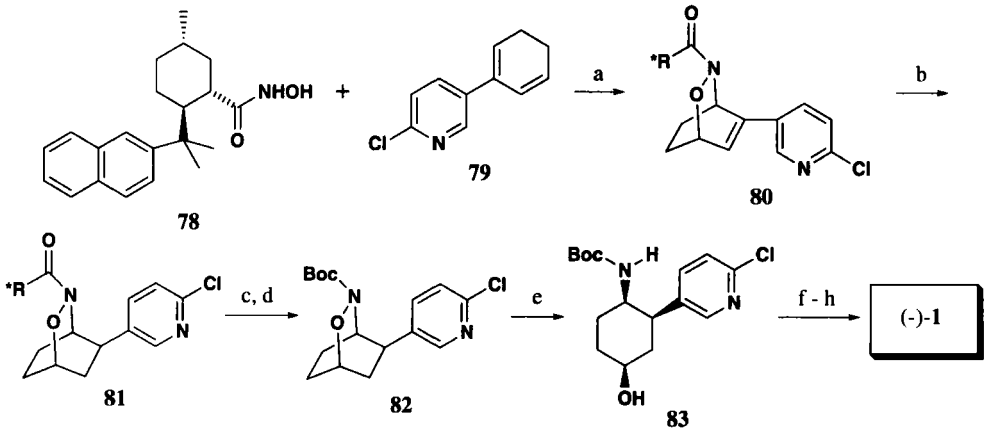
reduced in two steps to a 1:2 mixture of separable diastereomeric alcohols **76a** and **76b**. The minor isomer **76a** was mesylated and deprotected to set the stage for intramolecular cyclization. Cyclized compound **77** was converted to epibatidine after three more steps.



a. *t*-BuOCONHOH, $(n\text{-Bu})_4NIO_4$, CH_2Cl_2, MeOH, -25°C, 89%; b. $Mo(CO)_6$, MeCN, H_2O, 91%; c. MnO_2, 88%; d. I_2, pyridine, 88%; e. $Pd[(o\text{-tolyl})_3P]_2Cl_2$ 5%, $ZnBr_2$, DMF, 65°C, 95%; f. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78°C, 96%; g. 5% Pd/C, EtOH, 1 atm, H_2, 98%; h. MsCl, Et_3N, CH_2Cl_2, 98%; i. trifluoroacetic acid then 10% NaOH, 0°C; j. $CHCl_3$, 55°C, 4 days, 90%; k. $(CF_3CO)_2O$, CH_2Cl_2, pyridine, 0°C, 100%; l. $POCl_3$, DMF, 0 - 100°C, 70%; m. NaOMe, MeOH, 97%.

Scheme 15

An asymmetric hetero-Diels-Alder cycloaddition involving a novel chiral auxiliary derived from (*S*)-pulegone was reported by Kibayashi and co-workers.[35,36] The acyl nitroso dienophile bearing (*1S*)-8-(2-naphthyl)menthol was formed *in situ* from the hydroxamic acid **78** using a Swern oxidation (*Scheme 16*). Facial selectivity of the Diels-Alder reaction was theorized to occur *via* π–π stacking interactions between the naphthyl and nitrosocarbonyl

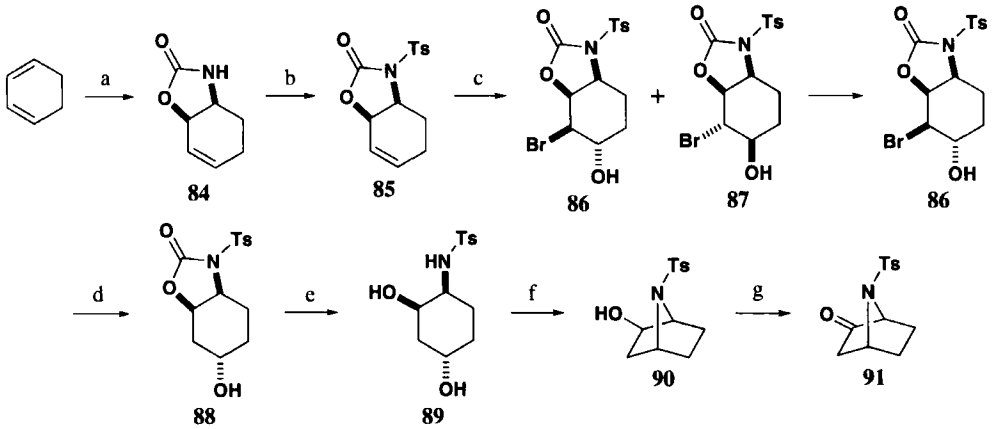


a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 42%; b. H_2, PtO_2, dioxane, 81%; c. $LiNH_2BH_3$, THF; d. $(Boc)_2O$, Na_2CO_3, 58%; e. $Mo(CO)_6$, CH_3CN-H_2O, 85%; f. PPh_3, CBr_4; g. CF_3CO_2H, 40%; h. $CHCl_3$, reflux, 97%.

Scheme 16

groups of the chiral auxiliary. The cycloaddition occurred under Swern reaction conditions to give the desired *meta-aza* regioisomer **80** in 42% yield as the major product. Hydrogenation and reductive cleavage of the chiral auxiliary was followed by *N*-Boc protection. Intramolecular displacement of a bromide was achieved after N-O reductive cleavage with molybdenum hexacarbonyl, bromination, and *N*-Boc removal. Intramolecular cyclization delivered levo-epibatidine.

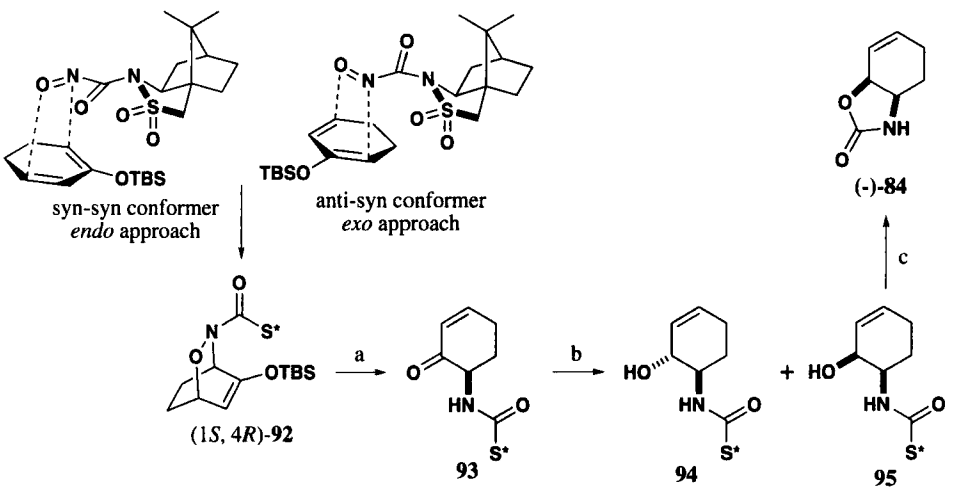
An oxazolidinone derived from cyclohexadiene was employed to prepare *N*-tosyl-7-azanorbonanone **91** (*Scheme 17*).[37] Treatment of *N*-tosyl protected oxazolidinone **85** with aqueous bromine regioselectively yielded diastereomers **86** and **87**, which were easily separated by column chromatography. Reductive removal of the bromine atom followed by hydrolysis of the oxazolidinone ring gave diol **89**. Cyclization under Mitsunobu conditions yielded bicyclic alcohol **90**, which was oxidized to ketone **91** using Swern conditions. Okabe and Natsume have previously reported the conversion of *N*-tosyl-7-azanorbonanone **91** into epibatidine.[38]



a. 4 steps; b. NaH, TsCl, 1h, 97%; c. 2. Eq. Br_2, DME-H_2O (2:1), 75%; d. AIBN, Bu_3SnH, 70°C, 1h, 80%; e. LiOH, MeOH, rt, 80%; f. PPh_3, DEAD, THF, rt, 90%; g. $(COCl)_2$, DMSO, Et_3N, 88%.

Scheme 17

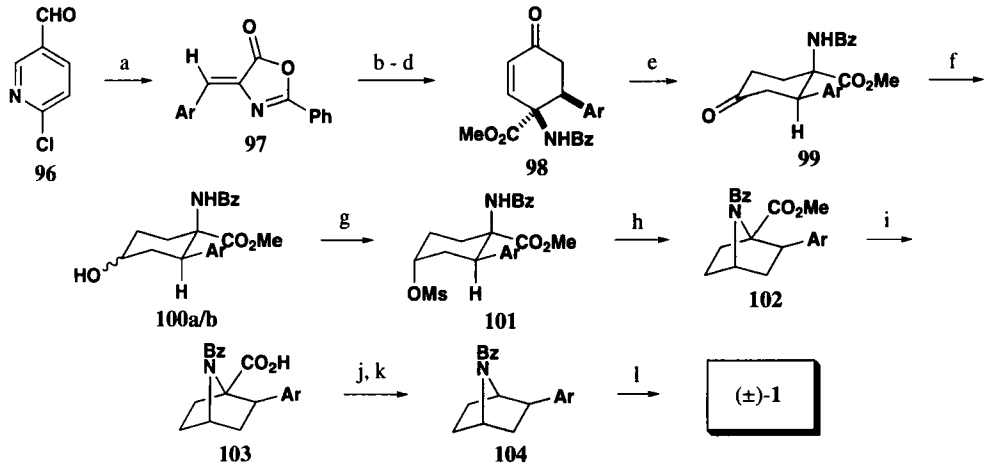
An asymmetric version of oxazolidinone **84** was reported employing an asymmetric hetero Diels-Alder cycloaddition of silyloxycyclohexadiene with an acylnitroso reagent derived from (+)-camphorsultam.[39,40] This cycloaddition was rationalized on the basis of two transition states, shown in *Scheme 18*, involving (a) an *endo*-approach of the diene from the less hindered face of the dienophile in a *syn-syn* conformation or (b) an *exo*-approach of the diene from the less-hindered face of the dienophile in an *anti-syn* conformation. Cycloaddition gave exclusively adduct **92**, evidenced by extensive NMR studies of the crude mixture, which was immediately converted to enone **93**. Reduction of the carbonyl following Luche's protocol, gave a 1:9 mixture of diastereomers **94** and **95**. *cis*-Diastereomer **95** was easily purified by chromatography, and treated with base to give oxazolidinone (-)-**84**. Levo-oxazolidinone **84** was converted into 7-azanorbonanone (-)-**91**, using the protocol discussed above.



a. $Mo(CO)_6$, CH_3CN, H_2O, heat, 3.5 h, 63%; b. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 95%; c. KOH, MeOH, rt, 95%.

Scheme 18

During the synthetic studies of conformationally restricted α-aminoacids, the Avenoza group reported the use of (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone as a dienophile with several dienes, allowing the synthesis of interesting compounds.[41] Using this methodology, the key Diels-Alder cycloaddition of oxazolone **97** with Danishefsky's diene was employed in the preparation of a cycloadduct that was used to synthesize epibatidine (*Scheme 19*). The oxazolone **97** was prepared from 6-chloropyridine-3-carboxaldehyde (**96**)

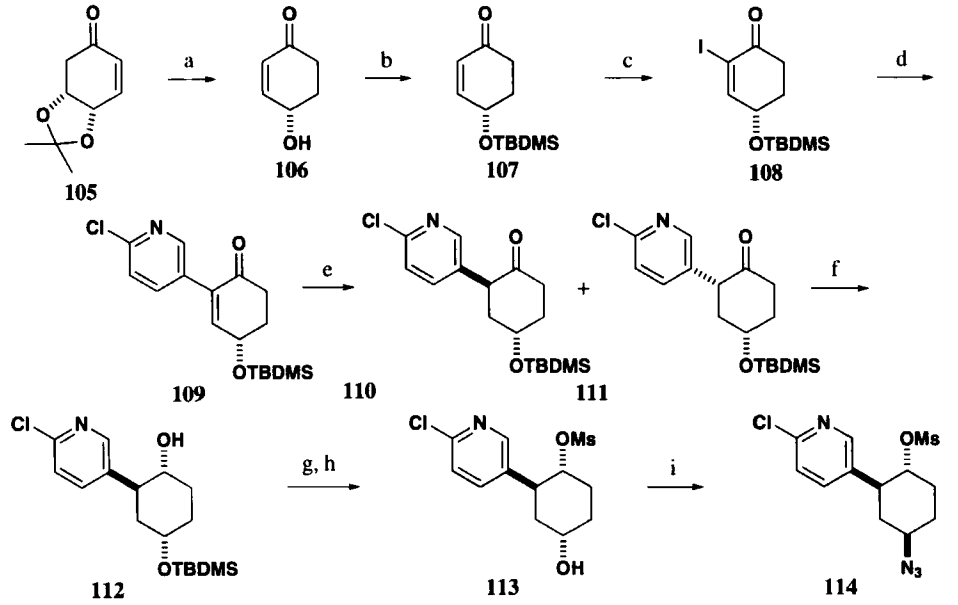


a. $BzNHCH_2CO_2H$, AcONa, Ac_2O, reflux, 60%; b. Danishefsky's diene, toluene, reflux; c. 0.005N HCl-THF (1:4), rt; d. DBU, MeOH, 0°C, 71%; d. DBU, MeOH, 0°C, 71%; e. H_2, Pt-C, EtOH, rt, 87%; f. L-Selectride®, THF, -78°C; g. MsCl, Et_3N, CH_2Cl_2, 0°C, 55%; h. *t*BuOK, THF, -78°C, 90%; i. LiOH, MeOH-H_2O (3:2), reflux, 99%; j. 2-chloro-N-methylpyridinium iodide, Et_3N, N-hydroxy-2-thiopyridone, CH_2Cl_2, reflux; k. Bu_3Sn, CH_2Cl_2, *hv*, rt, 49%; l. 6N HCl, reflux, then pH= 7, extraction with CH_2Cl_2, 77%.

Scheme 19

and hippuric acid using the Erlenmeyer-Plöchl method. Diels-Alder cycloaddition, followed by treatment with very dilute HCl/THF gave a mixture of both *cis*- and *trans*-2-methoxy-1-spiro-oxazolone cycloadducts, which are both converted into the sole enone product **98** by elimination of their methoxy groups. Hydrogenation of the enone **98** followed by L-Selectride® reduction of the carbonyl group gave a mixture of axial and equatorial alcohols **100a/b** in a 70:30 ratio. After obtaining the mesylates in excellent yield, the desired axial mesylate **101** was isolated by column chromatography. Cyclization of the mesylate **101** using potassium *tert*-butoxide proceeded in 90% yield to give azabicyclic intermediate **102**. Decarboxylation was successful after some experimentation using a reductive radical method. Debenzoylation of *N*-benzoyl epibatidine **104** was accomplished using acid hydrolysis.

Barros and co-workers reported a formal synthesis of (+)-epibatidine starting from (-)-quinic acid.[42] They found that the presence of DMSO increased the stereoselectivity of a key borohydride reduction step. Enone **105** was prepared in three steps from (-)-quinic acid using a known procedure (*Scheme 20*). Chiral enone **106** was obtained by saturation with K-Selectride® followed by base catalyzed elimination of acetone. After protecting the resulting



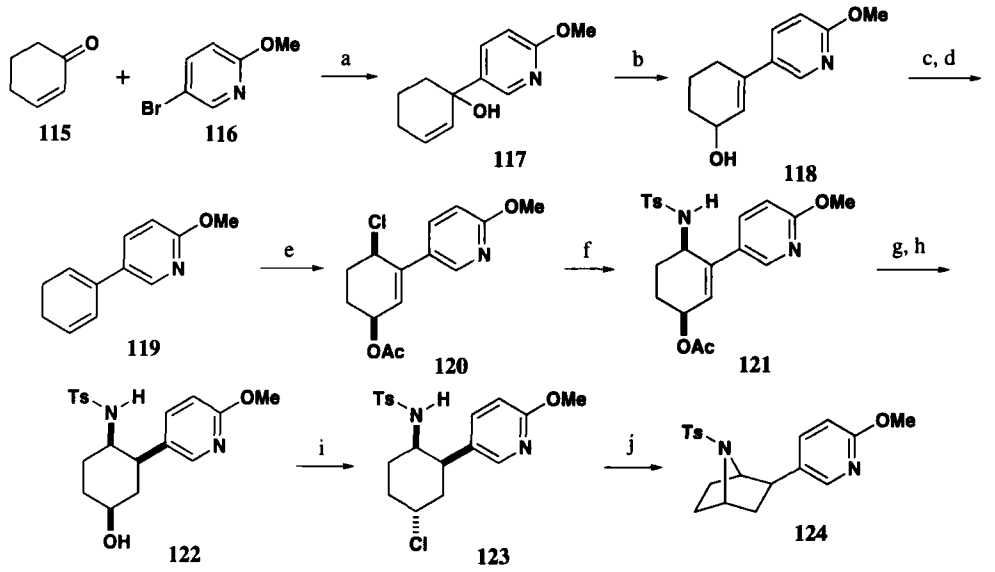
a. K- Selectride®, THF, -78°C; 0.5 N NaOH, THF, 0°C; b. TBDMSCl, (i-Pr)$_2$Net, DMAP, CH_2Cl_2, 0°C, rt, 51%; c. I_2, DMAP, pyridine/CCl_4 (1/1), 0°C, rt, 82%; d. $Bu_3SnC_5H_3NCl$, Pd_2(dba) 3•$CHCl_3$, $AsPh_3$, CuI, THF, rt, to 60°C, 90%; e. K- Selectride®, THF, -78°C, 88%; f. $NaBH_4$, DMSO (2 eq), MeOH, -20°C, 62%; g. MsCl, Et_3N, CH_2Cl_2, 0°C, 99%; h. Bu_4NF, THF, rt, 88%; i. PPh_3, HN_3, DEAD, THF, 0°C, 95%.

Scheme 20

alcohol **106** as the TBDMS ether **107**, Johnson's direct α-iodination method was used to obtain iodo enone **108**. Installation of the chloropyridyl ring occurred in excellent yield *via* a modified Stille coupling using triphenylarsine as the palladium ligand and co-catalytic Cu(I) and Pd(0) species. K-Selectride® reduction of **109** gave a 1:1 mixture of inseparable ketonic

epimers **110** and **111** in 88% yield. After much experimentation with a variety of reduction conditions, this mixture of epimers was reduced stereoselectively to the desired diastereomeric alcohol **112** in 62% yield using $NaBH_4$ in MeOH at -20° with two equivalents of DMSO. This high yield of the required diastereomer **112**, was explained by suggesting that ketone **110** was reduced more rapidly than ketone **111**, and that the two epimeric ketones are in equilibrium *via* an enol under the reaction conditions. Mesylation, desilylation and azide modification of the Mitsunobu reaction produced azide **114**, which has been previously elaborated to epibatidine by both Broka[9] and Albertini.[27,28]

An approach to racemic epibatidine was reported by Bäckvall and Helquist, which highlights a highly regio- and stereoselective palladium(II)-catalyzed 1,4-chloroacetoxylation of 2-aryl-1,3-cyclohexadienes.[43] The synthesis begins with 1,2-addition of the lithium anion of 5-bromo-3-methoxypyridine (**116**) to cyclohexenone **115** to give tertiary alcohol **117**, which was rearranged to allylic alcohol **118** with *p*-toluenesulfonic acid (*Scheme 21*). Regioselective elimination of **118** occurred upon treatment with methyl chloroformate, followed by $Pd(PPh_3)_4$



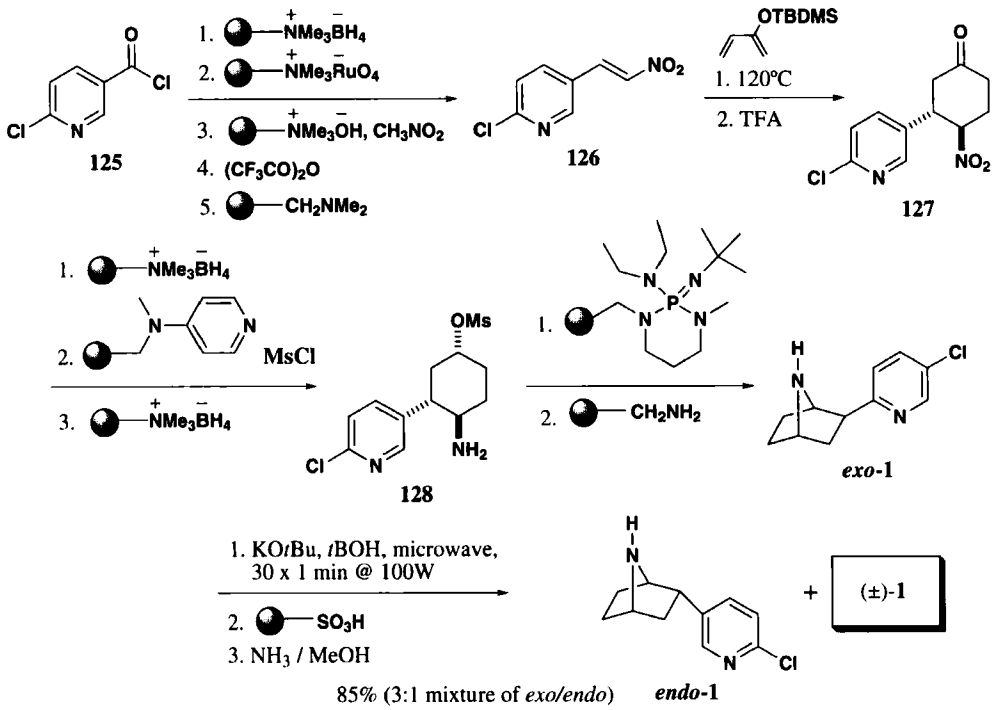
a. *n*-BuLi, Et_2O, -78°C; b. *p*-TsOH, 1,4-dioxane-H_2O, 91%; c. methyl chloroformate, pyridine, CH_2Cl_2, 72%; d. $Pd(PPh_3)_4$, THF, rt, 90%; e. $Pd(OAc)_2$, *p*-benzoquinone, LiCl, LiOAc, AcOH, acetone, 30%; f. $Pd(PPh_3)_4$, NaNHTs, CH_3CN, 71%; g. K_2CO_3, MeOH; h. H_2, PtO_2, EtOH, 94%; i. $SOCl_2$, $CHCl_3$, 65%; j. K_2CO_3, MeOH, rt, 63%.

Scheme 21

to give diene **119**. The *cis*-chloroacetoxylation reaction employs $Pd(OAc)_2$, *p*-benzoquinone, LiCl and LiOAc in acetone-acetic acid, but proceeded in only 30% yield when the relevant methoxypyridyl diene **119** was used. The chlorine of **120** is converted to sulfonamido acetate **121** by palladium-catalyzed allylic substitution with NaNHTs in 71% yield. After hydrolyzing the acetyl group of **121**, the double bond was hydrogenated with Adam's catalyst in a highly stereoselective manner to afford **122** in 93% yield with the pyridyl ring in the correct orienta-

tion. Chlorination of the alcohol **122** with inversion of stereochemistry and subsequent cyclization using potassium carbonate in methanol both proceeded in moderate yield to give *N*-tosyl protected epibatidine **124**, which has been deprotected to epibatidine by Okabe and Natsume.[38]

Ley reported a ten-step synthesis of racemic epibatidine using an array of polymer supported reagents and sequestering reagents in a successive manner (*Scheme 22*).[44] No chromatographic work was necessary and the product was obtained in > 90% purity. After

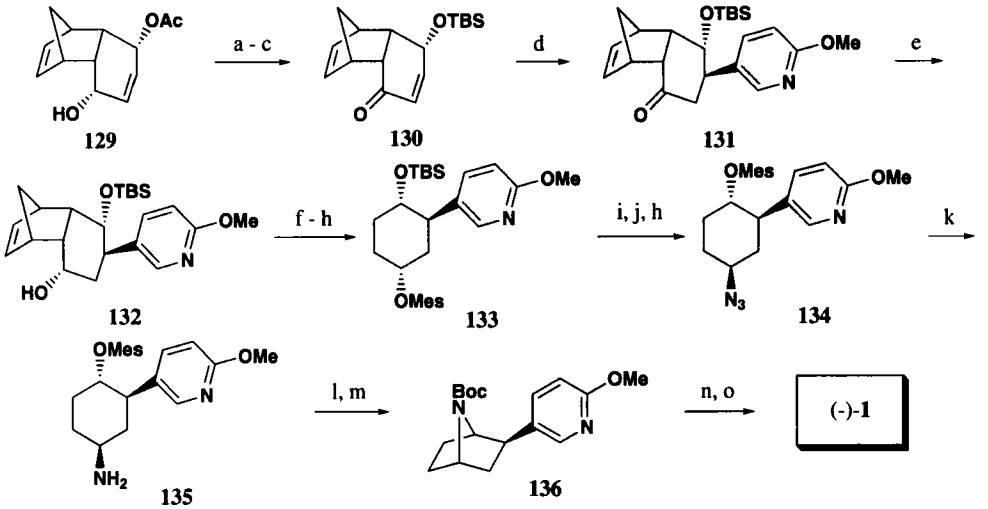


Scheme 22

reducing commercially available acid chloride **125** in 95% yield with polymer supported borohydride, the corresponding alcohol was oxidized to the aldehyde also in 95% yield using polymer supported perruthenate, with no over oxidation to the acid. A basic Amberlite resin in the presence of nitromethane was sufficient for the Henry reaction to produce unstable nitro alcohol, which was quickly derivatized with trifluoroacetic anhydride and then eliminated with dimethylaminomethyl polystyrene resin in CH_2Cl_2 to give exclusively the *trans* alkene **126** in 87% overall yield. Thermal Diels-Alder cycloaddition of alkene **126** and TBDMS protected 2-oxadiene in an undried, sealed vial gave quantitative, reproducible yields of the cycloadduct **127**. After desilylation, polymer supported borohydride reduced the carbonyl group of **127** in 89% to give a 7:1 diastereomeric ratio in favor of the desired equatorial cyclohexanol. After mesylation of the alcohol in 90% yield, numerous conditions were investigated for reducing the nitro group, without dechlorination. Polymer supported borohydride in $NiCl_2$ hexahydrate

proved to be the best method and was superior to $NaBH_4$ and $NiCl_2$ under the usual conditions. Commercially available polymer supported phosphazene base was used to cyclize the *trans*-aminomesylate **128** in 71% yield. The notoriously problematic epimerization of *endo*-epibatidine ***endo*-1** to the corresponding *exo*-isomer ***exo*-1** was dramatically improved upon by simply using microwave irradiation in the presence of potassium *tert*-butoxide in *tert*-butanol. A 3:1 ratio of epimers in favor of the thermodynamically more stable *exo*-isomer provided (±)-epibatidine in 85% yield and a short reaction time.

An enantio-controlled construction of (-)-epibatidine was reported by Ogasawara using a synthetic equivalent of *cis*-cyclohexadiene-1,4-diol.[45] The synthesis of (-)-epibatidine was accomplished in 16 steps from the enantiopure tricyclic acetate (+)-**129** (*Scheme 23*). To introduce the pyridyl functionality tricyclic acetate **129** was transformed into the keto-silyl



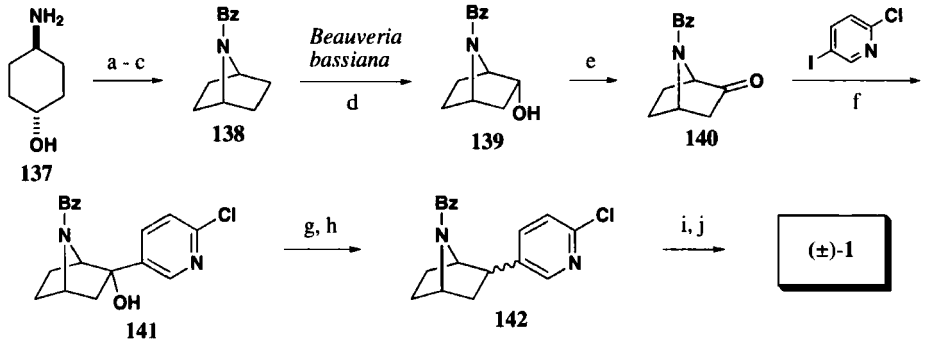
a. PDC, CH_2Cl_2, 95%; b. lipase PS, phosphate buffer, rt, 93%; c. TBSCl, imidazole, DMF, 98%; d. 5-bromo-2-methoxypyridine, lithium 2-thienylcyanocuprate, BF_3•Et_2O, Et_2O-THF, 64%; e. $NaBH_4$, MeOH, 83%; f. $NaHCO_3$, reflux in Ph_2O, 73%; g. H_2, PtO_2, AcOEt, 77%; h. MesCl, pyridine, DMAP, CH_2Cl_2, 90%; i. NaN_3, DMF, rt, 84%; j. TBAF, THF, 90%; k. H_2, 10% Pd-C, EtOH; l. MeCN, reflux; m. (*t*-Boc) 2O, 1N NaOH-dioxane, 83%; n. $POCl_3$, DMF, 95°C, 49%; o. 2N HCl-THF, 60°C, 60%.

Scheme 23

ether **130**. Enzymatic hydrolysis of the ester group was necessary to avoid decomposition. 1,4-Addition of a higher order cyanocuprate reagent from the convex face of the enone **130**, gave compound **131** as a single isomer. Reduction of the carbonyl group also occurred stereoselectively on the convex face, regardless of the presence of the *exo*-pyridine ring, giving the *endo*-alcohol **132** as a single product. Retro-Diels-Alder cycloaddition of tricyclic **132** was accomplished in refluxing diphenyl ether in the presence of sodium hydrogen carbonate. Introduction of the azide group was carried out by displacement of mesylated alcohol. Silyl ether **133** was transformed into mesylate **134** and displaced after reduction of the azide group to the amine functionality. Intramolecular cyclization of amino-mesylate **135** was accomplished in

refluxing acetonitrile, and the product was isolated as the carbamate **136**. Conversion of intermediate **136** into epibatidine was carried out using established protocols.

Our group investigated the microbial functionalization of unactivated carbons on the 7-azanorbornane system to prepare epibatidine and analogs with other ring sizes.[46,47] *N*-Substituted 7-azanorbornanes were easily prepared from commercially available *trans*-aminocyclohexanol **137** (*Scheme 24*). We found that the fungus *Beaveria bassiana* contains an oxidative enzyme capable to hydroxylate the unactivated methylene of *N*-benzoyl-7-azanorbornane



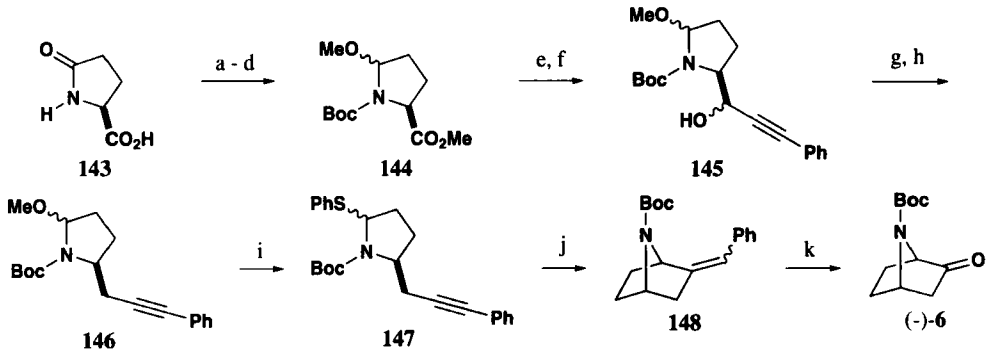
a. Benzoyl chloride, K_2CO_3, THF-H_2O, 100%; b. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 90%; c. KO-*t*-Bu, DMF-C_6H_6, 88%; d. *B. bassiana*, Iowa medium, 56%; e. cat. TPAP, NMO, CH_2Cl_2, 89%; f. 2-chloro5-iodopyridine, *n*-BuLi, THF, -78°C, 78%; g. $CH_3O(CO)_2Cl$, 2,6-lutidine, DMAP, CH_2Cl_2, 100%; h. *n*-Bu_3SnH, cat. AIBN, 98%; i. *t*-BuOK, *t*-BuOH, 100°C, 33%; j. 6N HCl, 100°C, 94%.

Scheme 24

(**138**) in good yield and excellent stereocontrol but low enantioselectivity (22% e.e.). Better enantioselectivities were achieved when using other *N*-substituents.[48,49] This strategy using a biocatalytic step is a short and efficient route to prepare *N*-substituted 7-azanorbornan-2-one. Current research in our group involves the use of chiral/docking groups in biocatalytic transformations to prepare optically pure products. The hydroxylated metabolite **139** was oxidized to ketone **140**, and this intermediate was used to complete the synthesis of epibatidine employing similar methodology previously employed by Trudell[10] and Fletcher.[50] Tertiary alcohol **141** was deoxygenated *via* free radical cleavage of a mixed oxalyl anhydride to give a mixture of *endo/exo*-chloropyridinyl isomers **142**, which could be separated. The undesired *endo*-pyridinyl isomer was isomerized using potassium *tert*-butoxide in *tert*-butanol, and *N*-benzoyl deprotection was achieved in acidic medium.

III. RADICAL CYCLIZATION STRATEGIES

Clive and Yeh prepared *N*-Boc-7-azanorbornanone (**6**) based on the idea that this bicyclic ring should be accessible by sequential *5-exo-dig* radical cyclization and double bond cleavage.[51] The known ester **144** was prepared in four steps from (*S*)-pyroglutamic acid (**143**) (*Scheme 25*). Introduction of the acetylene side chain that would serve as the radical acceptor was achieved by converting the ester to an aldehyde and addition of lithium phenylacetylide.

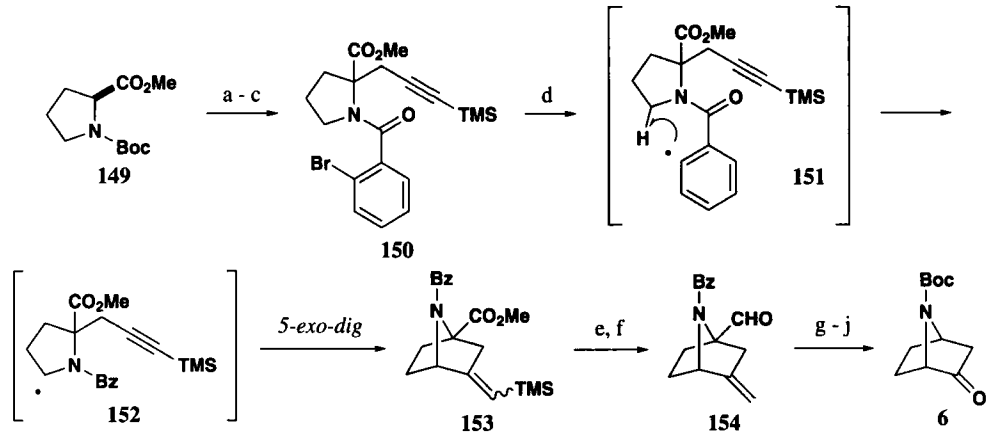


a. CH_2N_2, Et_2O, 100%; b. $(Boc)_2O$, DMAP, CH_2Cl_2, 90%; c. DIBAL-H, CH_2Cl_2-THF, -78°C, 89%; d. MeOH, $TsOH•H_2O$, 81%; e. DIBAL-H, CH_2Cl_2, -78°C, 73%; f. PhCCLi, THF, -78°C, 90%; g. $Im_2C(S)$, DMAP, CH_2Cl_2, 77%; h. Bu_3SnH, AIBN, PhMe, 80°C, 76%; i. PhSH, CH_2Cl_2, $TsOH•H_2O$, 80%; j. Bu_3SnH, AIBN, PhMe, 110°C, 76%; k. O_3, CH_2Cl_2-MeOH, Sudan III, -78°C, then, Me_2S, 95%.

Scheme 25

Removal of the hydroxyl group was achieved using Barton's radical deoxygenation. Replacement of the methoxy group with a phenylthio group followed by radical cyclization *via* addition of tributyltin hydride gave the required 7-azanorbornane **148**. Ozonolysis of the double bond of compound **148** gave the desired 7-azanorbornanone (-)-**6**. Ketone (-)-**6** has been used previously to prepare (-)-epibatidine.[28]

Ikeda examined the Bu_3SnH-mediated radical translocation/cycloaddition of 2-alkenyl and 2-alkynyl-1-(*o*-iodobenzoyl)pyrrolidine carboxylates.[52] Treatment of compound **150** with tributyltin hydride gave the functionalized 7-azanorbornene **153** (*Scheme 26*). A mechanistic rationalization of this transformation would involve a 1,5-hydrogen transfer of the



a. $(TMS)_2NLi$, THF, -78°C, and then $TMSCCCH_2I$, 62%; b. TMSI; c. *o*-Iodobenzoyl chloride, Et_2NHPh, DMAP, 77%; d. Bu_3SnH, AIBN, toluene, reflux; e. TsOH, CH_3CN; f. DIBAL-H, Et_2O, -50°C; g. $Rh(PPh_3)$ 3Cl, xylene, 49%; h. OsO_4-$NaIO_4$; i. 5% HCl, dioxane, reflux; j. (Boc) 2O, CH_2Cl_2, 54%.

Scheme 26

initially formed aryl radical **151** to form the α-acylamino radical **152**, followed by a *5-exo-dig* cyclization to give 7-azanorbornene **153**. Ester **153** was reduced with Dibal-H to aldehyde **154**. Decarbonylation of aldehyde **154** was accomplished with Wilkinson's catalyst. Oxidation of the remaining olefin with OsO_4 and $NaIO_4$ yielded *N*-benzoyl ketone which was converted into *N*-Boc-7-azanorborn-3-one **6** by acid hydrolysis and protection with di-*tert*-butyl dicarbonate.

IV. CONCLUSIONS

For nearly a decade now, chemical research groups all over the world have been captivated by a small molecule alkaloid whose molecular weight is barely 208 and whose structural architecture is only modestly complex. Epibatidine's intriguing biological activity as one of the most potent nicotinic acetylcholine receptor ligands is largely responsible for such worldwide excitement. Much has been learned about how to efficiently assemble the unique 7-azanorbornyl moiety of epibatidine, including Diels-Alder cycloaddition, dipolar cycloaddition, radical cyclization, ring contraction and transannular nucleophilic displacement. The most desirable method for an epibatidine synthesis depends on how efficient subsequent steps are. Nearly every retrosynthetically viable strategy for constructing this natural product has been successfully conceived and executed experimentally. With the epibatidine total synthesis field fully mature, the future likely involves creating structural analogs which may impart lower toxicity without reducing this alkaloid's remarkable affinity for cholinergic receptors. Current and future efforts might also result in highly useful medical diagnostics, such as epibatidine analogs for imaging nicotinic acetylcholine receptors in the central nervous system, and high affinity ligands for studying the electrophysiological characteristics of the same receptors.

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† Current Address: Albany Molecular Research, Inc., Biocatalysis Division, 2501 Crosspark Road, Suite C-150, Iowa City, IA 52242.

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