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Review

Recent Syntheses of Frog Alkaloid Epibatidine

Ronaldo E. de Oliveira Filho and Alvaro T. Omori*

Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, 09210-580 Santo André-SP, Brazil

Many natives from Amazon use poison secreted by the skin of some colorful frogs (*Dendrobatidae*) on the tips of their arrows to hunt. This habit has generated interest in the isolation of these toxins. Among the over 500 isolated alkaloids, the most important is undoubtedly (–)-epibatidine. First isolated in 1992, by Daly from *Epipedobates tricolor,* this compound is highly toxic (LD_{50} about 0.4 μg *per* mouse). Most remarkably, its non-opioid analgesic activity was found to be about 200 times stronger than morphine. Due to its scarcity, the limited availability of natural sources, and its intriguing biological activity, more than 100 synthetic routes have been developed since the epibatidine structure was assigned. This review presents the recent formal and total syntheses of epibatidine since the excellent review published in 2002 by Olivo *et al.*[1] Mainly, this review is summarized by the method used to obtain the azabicyclic core.

Keywords: epibatidine, organic synthesis, azanorbornanes

1. Introduction

At an expedition to Western Ecuador in 1974, Daly and Myers isolated traces of an alkaloid with potential biological activity from the skin of the species *Epipedobastes tricolor*. Twenty years later, 750 frogs collected near a cocoa plantation, led to a total of 60 mg of a complex mixture of alkaloids. From this mixture, 500 μg of relatively pure (–)-epibatidine **1** was isolated. Tests with mice showed the analgesic activity of this compound to be 200 times stronger than that of morphine.[2]

The mechanism of action of epibatidine was only elucidated after the determination of the molecular structure by Daly in 1992.[3] Biological assays confirmed the analgesic activity by non-opioid mechanisms[4] through the nicotinic receptor antagonist acetylcholine (nAChR)[5] with analgesic activity at doses of 0.01 μmol kg^{-1}. Higher doses are considered highly toxic.

To date, many epibatidine analogs are synthesized and investigated as potential drugs for the treatment of diseases, such as Alzheimer's disease (AD).[4] Epiboxidine (Figure 1), for example, was shown to be more selective to ganglionic nicotinic receptors and much less toxic than epibatidine.[6]

The most recent review about epibatidine synthesis was published by Olivo *et al.*,[1] who synthesized epibatidine in a chemoenzymatic fashion.[7] Since then, fewer reports about epibatidine synthesis have appeared (Figure 2). However, the number of articles is still impressive, and therefore, an update seems appropriate.

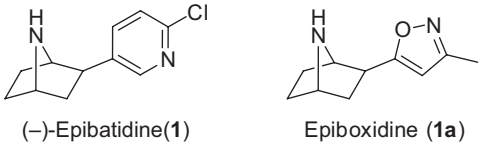


Figure 1. Structures of (–)-epibatidine and epiboxidine.

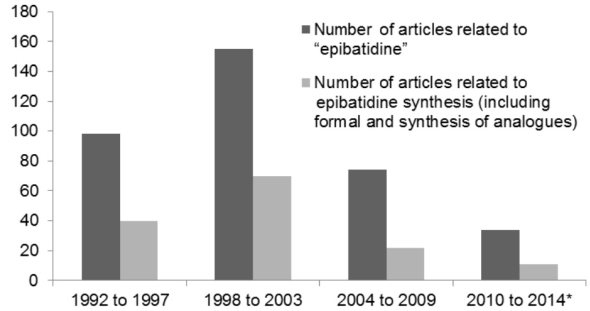


Figure 2. Number of articles about epibatidine found at Web of Science® (*until July, 2014).

This review attempts to cover epibatidine synthesis research (total and formal synthesis) since 2001. Despite the few available synthetic approaches for the construction of the azabicyclo ring (cycloaddition reactions, intramolecular nucleophilic substitution reactions, intramolecular SN, and rearrangement reaction) (Figure 3), this review presents new and modern strategies efficiently employed

*e-mail: alvaro.omori@ufabc.edu.br

to obtain the cyclohexylamine core or to incorporate the 2-chloropyridyl moiety, including ring-closing metathesis, Suzuki/Negishi coupling reactions, and rearrangements. Within each of these categories, the content in this review will be presented in chronological order.

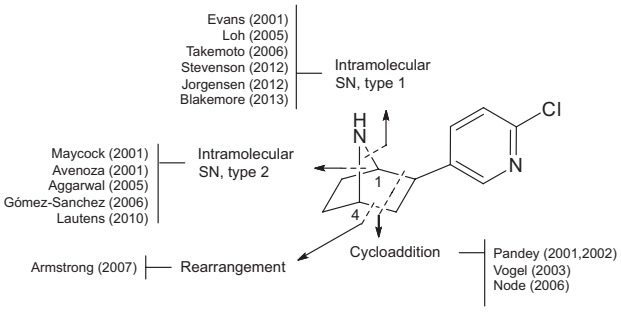
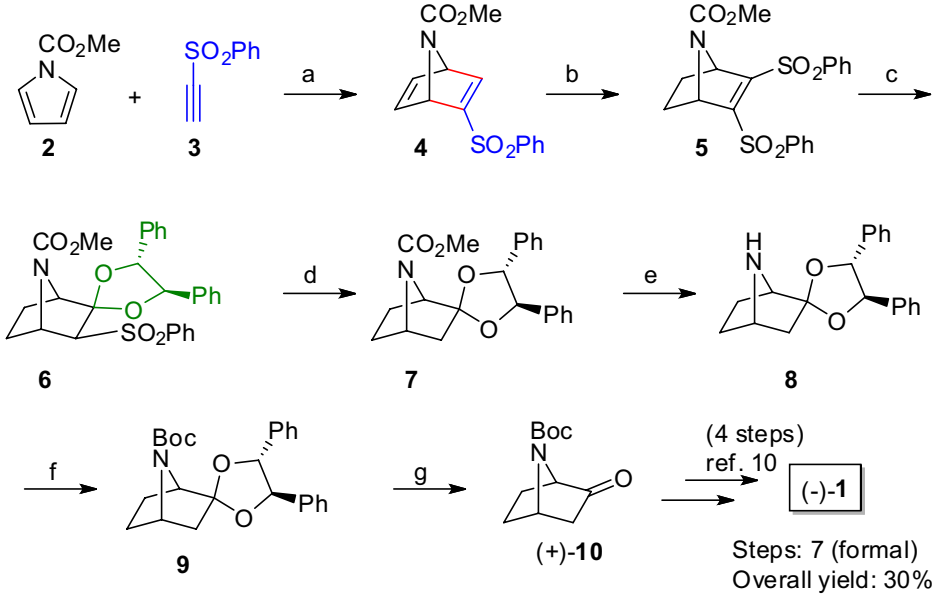


Figure 3. Recent synthetic approaches to form the azabicyclo ring during the synthesis of epibatidine.

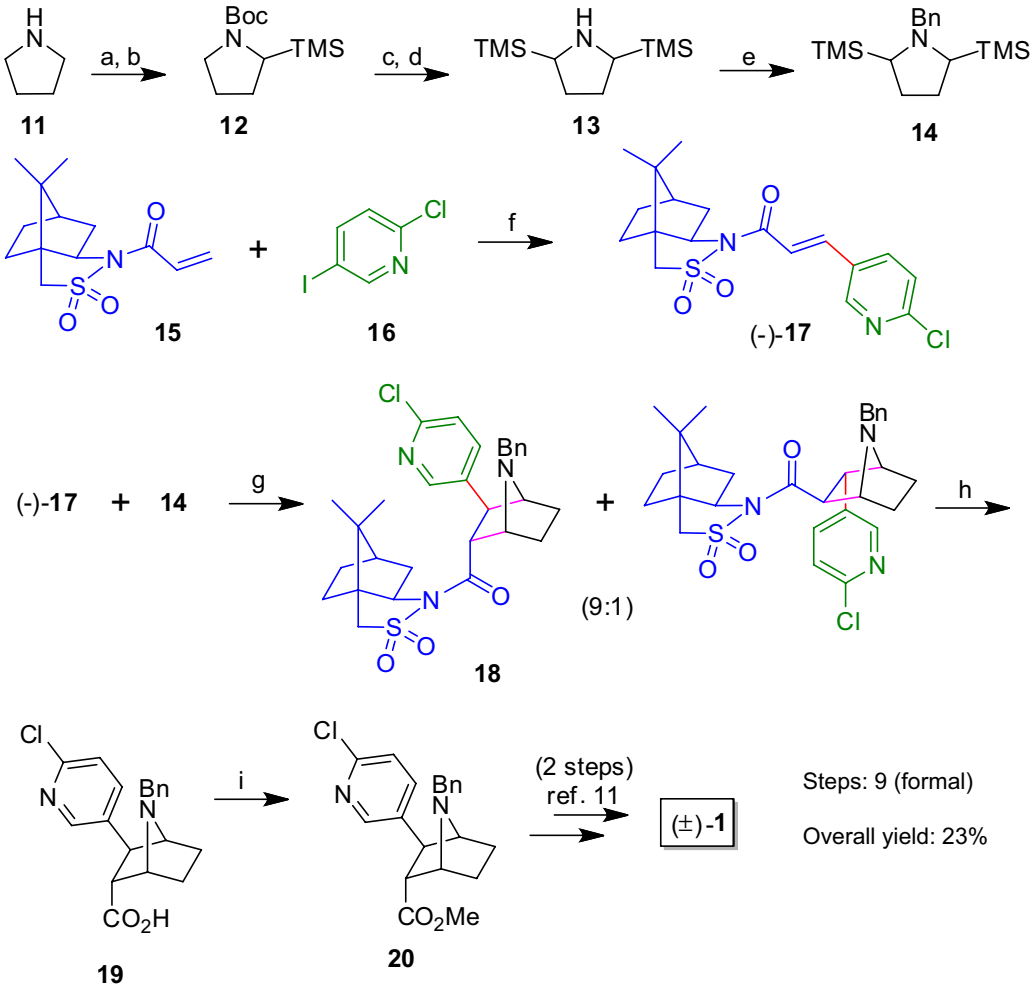
2. Cycloaddition Reactions

An efficient and short synthesis of optically pure (+)-*N*-Boc-azabicyclo[2.2.1]hept-2-one, (*tert*-butyloxycarbonyl, Boc), **10** was reported by Pandey (Scheme 1).[8] The method involves the cycloaddition of ethynyl phenyl sulfone (**3**) with *N*-methoxycarbonyl pyrrole (**2**),[9] followed by the introduction of the second phenyl sulfone group to the cycloadduct **4** by β-metalation. The desymmetrization of the bisphenylsulfonyl byciclic compound **5** was carried out by stirring with the disodium salt of *meso*-hydrobenzoin, giving **6** as a single diastereomer, indicated by nuclear magnetic resonance (NMR) and high performance liquid chromatography (HPLC) analysis. The reductive elimination of the phenyl sulfone group using Na-Hg amalgam gave the acetal **7**. Simple acetal hydrolysis would lead to the corresponding *N*-acetylazabicyclo[2.2.1] hept-2-one, but the removal of the chiral acetal moiety was possible only by changing the acetyl protecting group to the *t*-butylacetyl group. Thus, the *N*–CO_2Me bond was cleaved with trimethylsilyl chloride (TMSCl), and the amine **8** was reprotected with di-*tert*-butyl dicarbonate (Boc_2O), giving the *N*-Boc compound **9**. The ketone **10** was obtained by catalytic hydrogenation with Pd/C. The specific rotation ($[\alpha]^D$) of ketone **10** corresponds to that reported by Fletcher and Trudell[10] in their total synthesis of (–)-epibatidine.

In 1998, Pandey's group reported a [3+2]-cycloaddition strategy in the racemic synthesis of epibatidine (Scheme 2).[11] Years later, the same group reported an asymmetric approach using Oppolzer's sultam as a chiral auxiliary.[12] The key step of cycloaddition involves the reaction of the *N*-alkyl-bis(trimethylsilyl) cyclic amine **14** with the dipolarophile (–)-**17** using AgF as a one-electron oxidant. The bis-silylated amine was prepared by double lithiation of pyrrolidine **11**. Heck-coupling reaction between 2-chloro-5-iodopyridine **16** and chiral camphorsultam derivative **15** gave the desired dipolarophile (–)-**17**. Surprisingly, the cycloaddition preferably gave the 2-chloropyridyl moiety in *exo*-stereochemistry, differently from the results obtained with model compounds. The authors did not mention any reasonable explanation for this favorable inversion of the *exo/endo* ratio. Careful separation of **18** followed



Scheme 1. (a) 85-90 °C; (b) *n*-BuLi, –78 °C, tetrahydrofuran (THF), $PhSO_2F$, rt (43%, 2 steps); (c) meso-hydrobenzoin, NaH, THF, 0 °C → rt (85%); (d) 6% Na/Hg, $NaH_2PO_4.H_2O$, 0 °C (95%); (e) TMSCl, NaI, CH_3CN, rt; (f) Boc_2O, Et_3N, CH_2Cl_2, rt (95%, 2 steps); (g) Pd/C, H_2, 55 psi, EtOH/EtOAc, rt (90%) (adapted from reference 8).



Scheme 2. (a) Boc-N_3, Et_3N, dioxane, rt (90%); (b) *s*-BuLi, TMSCl, TMEDA, –78 °C (90%); (c) s-BuLi, TMSCl, TMEDA, –50 → –30 °C (68%); (d) TFA, CH_2Cl_2, rt (quant.); (e) $PhCH_2Cl$, K_2CO_3, CH_3CN, rt (80%); (f) K_2CO_3, $Pd(OAc)_2$, PPh_3, CH_3CN, reflux (85%); (g) AgF, CH_2Cl_2 (58%); (h) $LiOH.H_2O$, $THF:H_2O$, 35 °C; (i) $SOCl_2$, MeOH, 0 °C → rt (90%, 2 steps) (adapted from reference 12).

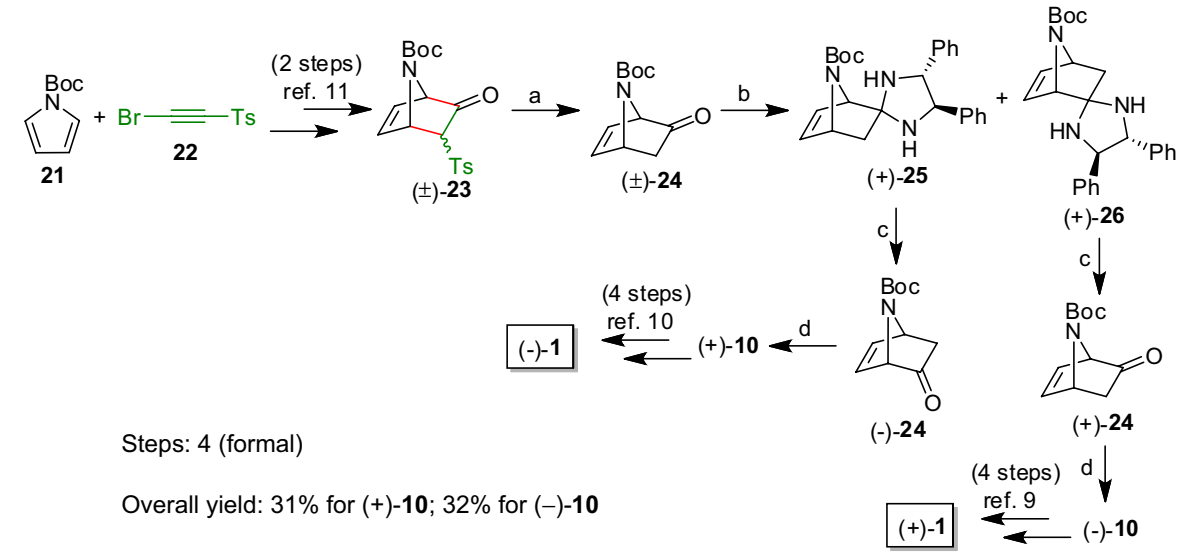
by removal of the chiral auxiliary and methylation of the acid **19** gave the compound **20**. Starting from this compound, the synthesis of (±)-epibatidine was reported.[11]

The formal synthesis of (–)-epibatidine reported by Vogel[13] uses the "naked *aza*-sugar" methodology for an efficient resolution of a racemic ketone by amination using (*R*,*R*)-1,2-diphenylethylenediamine (Scheme 3). Starting with the Diels-Alder adduct (±)-**23**,[14] the tosyl group was removed with SmI_2, giving the ketone (±)-**24**. The resolution of (±)-**24** gave a separable mixture of compounds (+)-**25** and (+)-**26**, which gives back the ketones (+)-**24** and (–)-**24** in optically active forms after acid hydrolysis. Reduction of the double bond led to (–)-**10** and (+)-**10** in quantitative yield. The total synthesis of (–)-**1** and (+)-**1** from compound **10** was reported by Fletcher and Trudell.[10]

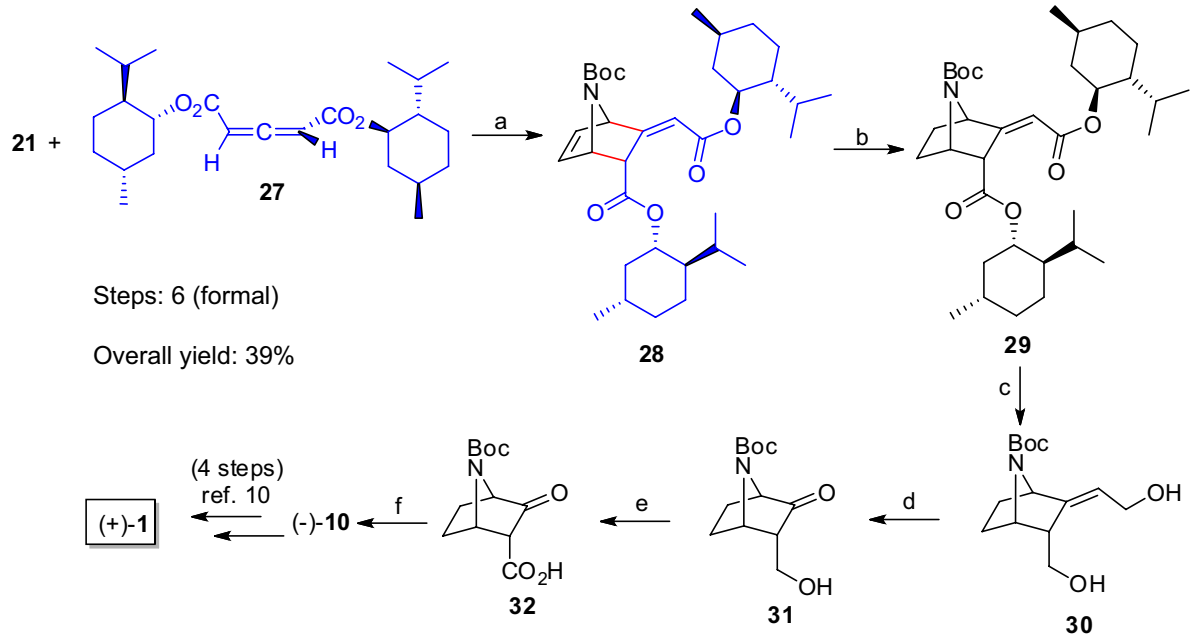
Node and co-workers[15] reported a second-generation route for the formal synthesis of (–)-epibatidine (Scheme 4). Diels-Alder reaction between the chiral dienophile di-(*l*)-menthyl (*R*)-allene-1,3-dicarboxylate **27** and the *N*-Boc-pyrrole **21** gives the *endo*-adduct **28** as the sole product. The authors mention the high *endo*/*exo* selectivity could be attributed to the steric repulsion between the Boc group of **21** and the l0-menthyl group in the dienophile **27**. Consecutive reductions of the bicyclic double bond and the menthyl diester give the diol **30**. Ozonolysis of the remaining double bond generates the β-keto alcohol **31**. The alcohol was oxidized by Jones oxidation to carboxylic acid **32**, which was decarboxylated with reflux in toluene, giving the (–)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one (**10**). Again, the total synthesis of **1** from compound **10** was already reported by Fletcher and Trudell.[10]

3. Intramolecular SN-Type 1

An asymmetric *exo*-selective hetero Diels-Alder reaction mediated by Lewis acid and an unusual ring-opening fragmentation were the key steps for the asymmetric synthesis of (–)-epibatidine reported by

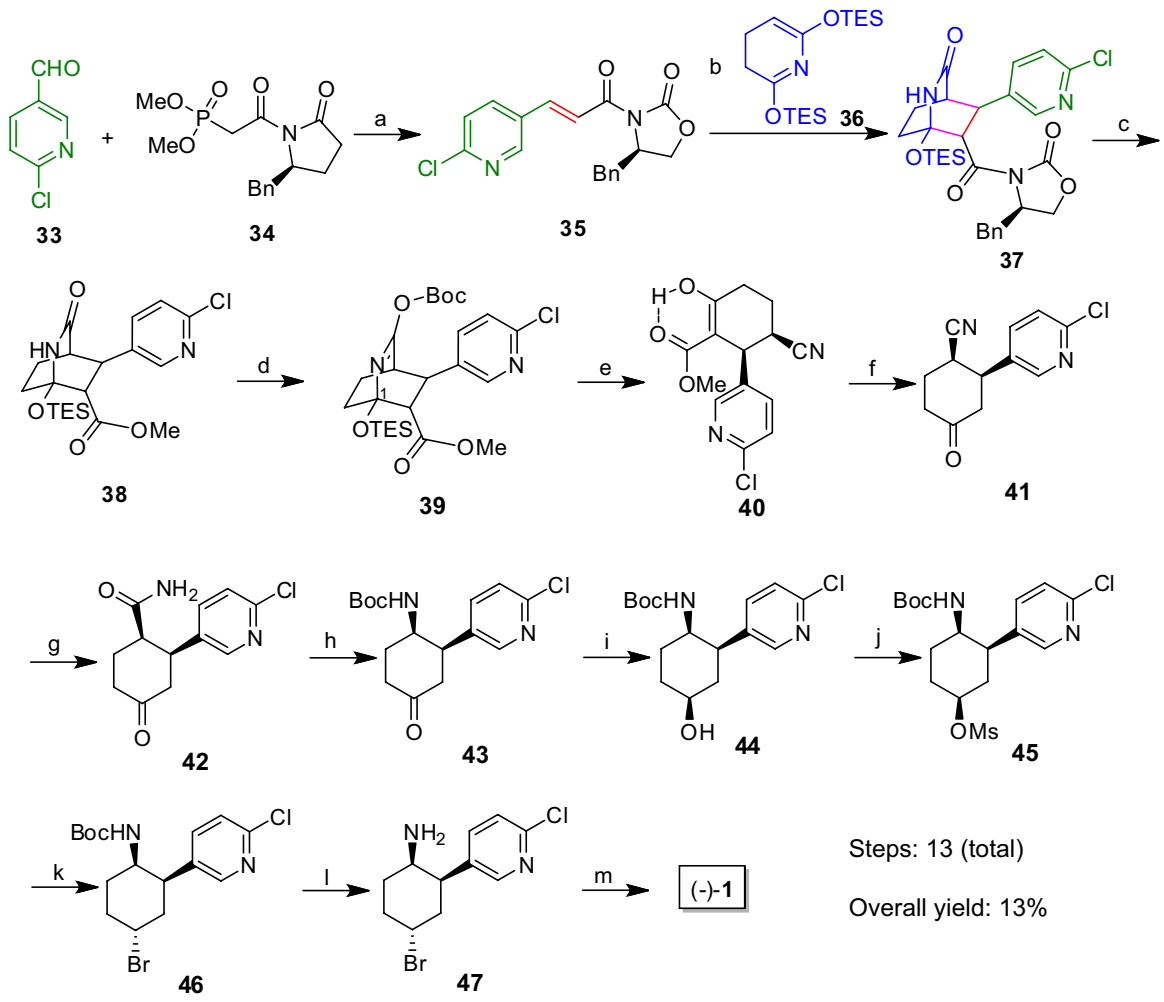


Scheme 3. (a) SmI_2, THF/MeOH, –78 °C (75%); (b) (*R*,*R*)-1,2-diphenylethylenediamine, 4Å molecular sieves, CH_2Cl_2, room temperature (rt) (42% for (+)-**25** and 43% for (+)-**26**); (c) H_3PO_4/THF, 20 °C (95% for (+)-**24** and 96% for (–)-**24**); (d) 10% Pd/C, H_2, MeOH, rt (> 99%) (adapted from reference 13).



Scheme 4. (a) $AlCl_3$, CH_2Cl_2, –78 °C (88%); (b) Pd-C, H_2, EtOAc, rt (99%); (c) $LiAlH_4$, THF, rt (90%); (d) O_3, CH_2Cl_2, –78 °C, Me_2S, rt (93%); (e) Jones reagent, acetone, 0 °C; (f) toluene, reflux (54%, 2 steps) (adapted from reference 15).

Evans (Scheme 5).[16] Dienophile **35** was formed by a Horner-Wadsworth-Emmons reaction of aldehyde **33** and phosphonate containing the chiral auxiliary **34**. The heterodiene **36** was synthesized by treatment of glutarimide with triethylsilyl triflate under basic conditions. Evidenced by NMR, the *exo* selectivity of the cycloaddition reaction was rationalized based on steric interactions between the triethylsilyloxy substituents of **36** and the Lewis acid-acyl oxazolidinone complex. Removal of the chiral auxiliary by samarium(III) trifluoromethanesulfonate [$Sm(OTf)_3$] gave the methyl ester **38**. Cleavage of the C1–N bond was accomplished by O-acylation with Boc_2O followed by treatment with tetrabutylammonium fluoride (TBAF) to produce the nitrile **40**. Krapcho decarboxylation of **40** provided the ketone **41**. The required transposition of the nitrogen atom was accomplished by the conversion of nitrile **41** to amide **42**, followed by Hofmann rearrangement to afford the amine **43**. Several reducing agents were tested for the stereoselective reduction of the ketone **43** to the desired axial alcohol for SN_2 displacement. However, all reactions gave a mixture of inseparable alcohols with equatorial alcohol as a major isomer. Therefore,

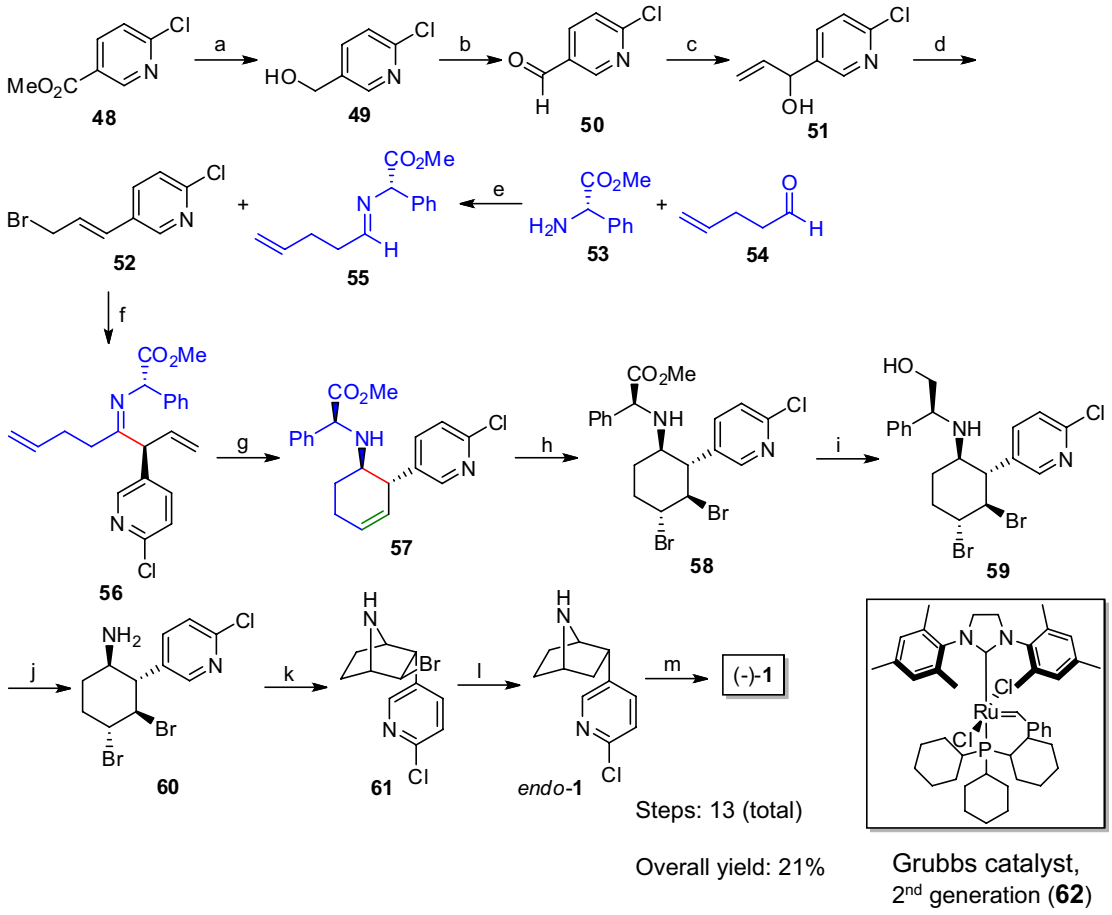


Scheme 5. (a) LiCl, *i*-Pr_2EtN, CH_3CN, rt (81%); (b) Me_2AlCl, CH_2Cl_2, –78 °C (79%); (c) $Sm(OTf)_3$, MeOH, reflux (84%); (d) Boc_2O, *p*-dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, rt (98%); (e) *n*-Bu_4NF, THF/H_2O, rt (81%); (f) dimethyl sulfoxide (DMSO), H_2O, 130 °C (99%); (g) Me_3SiOK, toluene, 70 °C (72%); (h) $Pd(OAc)_4$, *tert*-butyl alcohol, 50 °C (70%); (i) $NaBH_4$, MeOH, –40 °C, (89%, 92% enantiomeric excess (*ee*)); (j) MsCl, Et_3N, CH_2Cl_2, rt (92%); (k) LiBr, THF, 50 °C (84%); (l) TFA, CH_2Cl_2, rt (91%); (m) $CHCl_3$, reflux (95%) (adapted from reference 16).

to complete the synthesis, the alcohol **44** was converted into the corresponding mesylate **45**, and subsequent SN_2 displacement with LiBr provided the bromide **46**. Removal of the Boc group with trifluoroacetic acid (TFA) followed by reflux of amine **47** for 3 days afforded (–)-epibatidine in 13 steps and 13% overall yield.

A practical 13-step process for the synthesis of (–)-epibatidine was reported by Loh (Scheme 6).[17] The entire synthetic route is straightforward and convenient for gram-scale synthesis. The synthesis commenced from the reduction of commercially available chloro methylnicotinate **48** to the aldehyde derivative **50** in two steps, followed by Grignard addition with a vinyl group to provide the allylic alcohol **51**. Bromination of **51** provided the desired terminal bromide **52** necessary for another allylic rearrangement under Barbier conditions. The "*aza*" Barbier reaction between **52** and the imine **55** (carrying a chiral auxiliary) provided only one single isomer, the diene **56**. Using Grubbs 2nd generation catalyst of this diene provided the desired product **57**. For the intramolecular cyclization, the alkene **57** was brominated, and two isomers were obtained. Single X-ray structure confirmed that the minor isomer was the desired one, and the authors had to recycle by converting back the major isomer to the alkene **57**. Deprotection of the chiral auxiliary group provided the amine **60**, which underwent the intramolecular cyclization by heating, affording the azabicyclo compound **61**. The completion of the synthesis involved radical debromination followed by epimerization of the *endo*-epibatidine.

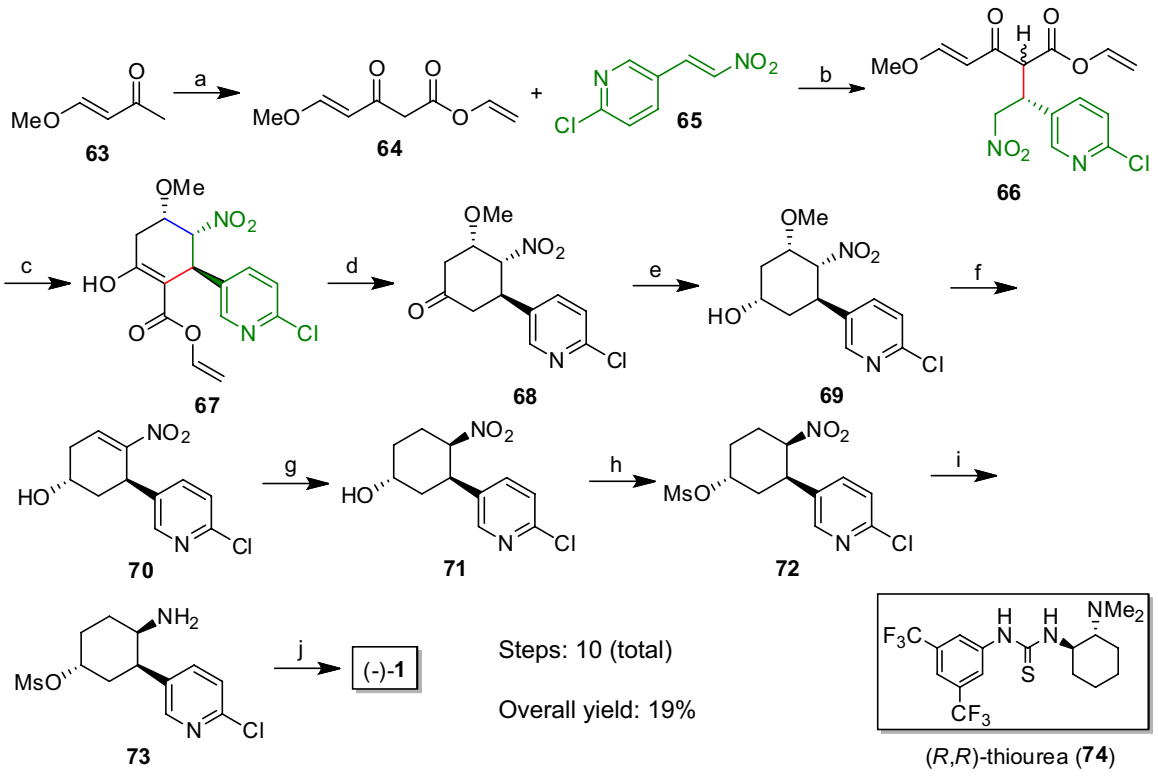
Takemoto's research group developed a protocol to synthesize chiral 4-nitrocyclohexanones through an enantioselective tandem Michael addition between nitroalkenes and γ,δ-unsaturated β-ketoesters catalyzed by chiral thiourea **74**.[18] This protocol was applied to synthesize (–)-epibatidine in 10 steps at 19% overall



Scheme 6. (a) $NaBH_4$, THF:MeOH (3:1), 0 °C (99%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C (99%); (c) vinyl magnesium bromide, THF, 0 °C (96%); (d) PBr_3, Et_2O, 0 °C (98%); (e) $NaSO_4$, CH_2Cl_2, 0 °C (99%); (f) Zn, THF, 0 °C (93%);. (g) 10% **62**, CH_2Cl_2, 25 °C (94%); (h) Br_2, $Et_4N^+Br^-$, CH_2Cl_2, –78 °C (92%, dr 66:34); (i) diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, 0 °C (88%); (j) $Pb(OAc)_4$, CH_2Cl_2:MeOH (2:1), 0 °C (65%); (k) CH_3CN, 82 °C (85%); (l) Bu_3SnH, azobisisobutyronitrile (AIBN), benzene, reflux (99%); (m) *t*-BuOK, *t*-BuOH, reflux (58%) (adapted from reference 17).

yield (Scheme 7). The route commenced by treatment of enone **63** with lithium bis(trimethylsilyl)amide (LHMDS), followed by the addition of allylcyanoformate to obtain **64**. The Michael addition between **64** and **65** in the presence of chiral thiourea **74** gave **66** in lower enantioselectivity (75% *ee*) compared to the model compounds. The second Michael addition occurred with KOH in ethanol and provided the cyclic ketoester **67**. Decarboxylation of **67** under Tsuji conditions gave **68** in quantitative yield. The remaining tasks were the stereoselective reduction of carbonyl group and the configuration inversion of the nitro group. For this purpose, the axial methoxy group assisted the stereoselective reduction of the ketone **68** by lithium tri-sec-butylborohydride (*L*-selectride), and the alcohol **69** was giving. After several attempts, the authors found that the best result to remove the OMe group was the treatment of **69** with NaOMe in *t*-butanol. At this stage, the *ee* was improved by recrystallization of compound **70**. Finally, 1,4-hydride reduction of **70** with $NaBH_3CN$ followed by mesylation of the remaining alcohol afforded the axial nitroalkane **72** as the major product. Successive treatment of **72** with zinc dust and refluxing in $CHCl_3$ gave (–)-epibatidine.

Stevenson and co-workers[19] described an excellent route for the total synthesis of (–)-epibatidine through enzymatic *cis*-dihydroxylation of bromobenzene using the microorganism *Pseudomonas putida* UV (Scheme 8).[19,20] The *cis*-dihydrodiol (+)-**76** was giving with > 98% *ee,* and its chemoselective hydrogenation produced the tetrahydrodiol (–)-**77** with 90% yield. The hydroxyl group in C-2 prefers to occupy a pseudo-axial position to minimize allylic 1,2-strain with the substituent on the alkene, while the hydroxyl group in C-1 is equatorial. The silylation of (–)-**77** was chemoselective with the hydroxyl group in the equatorial position with 86% yield. The alcohol (–)-**78** was converted to urethane **79** using Ichikawa's conditions, with 90% yield. The urethane **80** was dehydrated, providing the intermediate cyanate **80**, which underwent a rapid [3,3]-sigmatropic rearrangement under the reaction conditions to furnish the intermediate isocyanate **81**. This intermediate was protected with



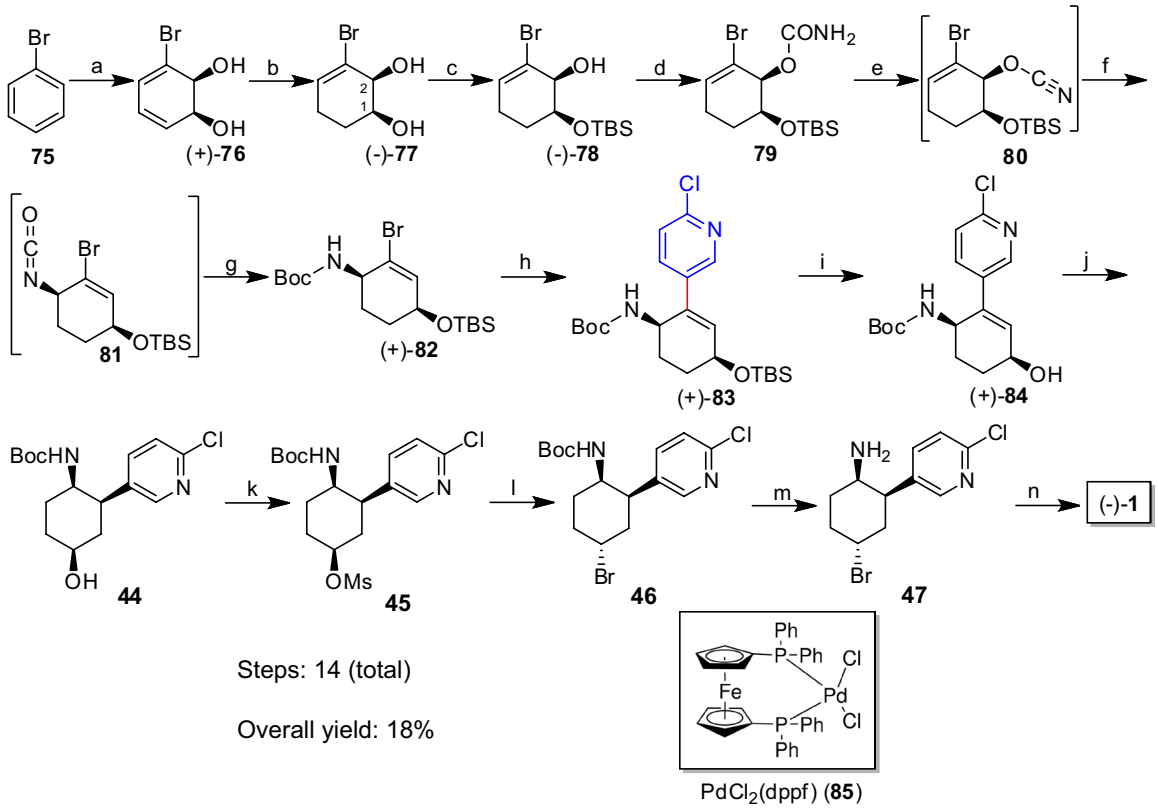
Scheme 7. (a) $LiN(SiMe_3)_2$, THF, –78 °C, vinyl 2-cyanoacetate, hexamethylphosphoramide, THF, rt (73%); (b) 10% (*R*,*R*)-**74**, toluene, 0 °C (90%, 75% *ee*); (c) KOH, EtOH, 0 °C (85%, 75% *ee*); (d) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N, THF, rt (99%); (e) *L*-selectride®, THF, –78 °C → 0 °C (71%); (f) NaOMe, *t*-BuOH, rt (71%); (g) $NaBH_3CN$, CH_3CO_2H, MeOH, –20 °C (87%, 90% dr); (h) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (91%); (i) CH_3CO_2H, Zn, THF, rt; (j) $CHCl_3$, 60 °C (85%, 2 steps) (adapted from reference 18).

N-protective group Boc by the Bruckner protocol with 76% yield for three steps in a one pot reaction.

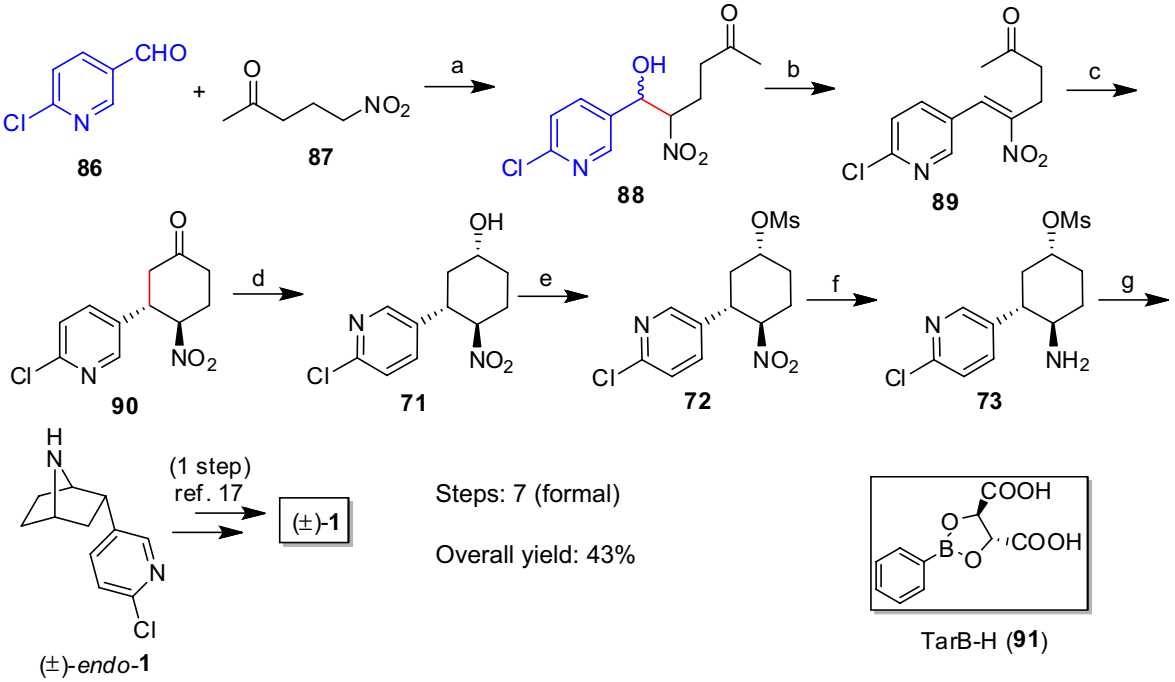
The alkenyl bromide (+)-**82** was subjected to Suzuki cross coupling with commercially available 6-chloropyridin-3-yl boronic acid, giving the compound (+)-**83** with 93% yield. Deprotection of O-silyl was induced by fluoride, giving the alcohol (+)-**84** with 95% yield. The next step involved a stereoselective catalytic reduction with the addition of the hydrogens in *anti* in relation to the hydroxyl and the amine, giving the compound (–)-**44** with 60% yield. The alcohol (μ)-**44** was made by Evan's protocol, giving the bromide (–)-**46** with 91% yield for mesylation and 78% yield for bromination. The compound (–)-**46** was deprotected with TFA, giving the amine (–)-**47** with 94% yield, which was then cyclized (95% yield), giving the (–)-epibatidine with an overall yield of 18% and 14 steps.

Huang *et al.*[21] described a fast and practical synthetic route involving seven steps for diastereoselective synthesis for (±)-endo-**1**, leaving the 6-choro-3-pyridinecarboxaldeide **86** (Scheme 9). Henry's reaction catalyzed by KF generates a β-nitro alcohol, which was treated with DMAP and acetic anhydride, giving the precursor **88** by means of desidratation with 76% yield for two steps. The next step was using the intramolecular Michael's reactions between the ketone and the pyridinylnitroolefin catalyzed with *L*-proline, giving the key intermediated **90** with 81% yield and dr ≥ 97%. The compound **90** was asymmetrically reduced by (4R,5R)-2-phenyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid - **91** (TarB-H) and $NaBH_4$, building three chiral centers with 95% yield for compound **71**. The alcohol giving was mesylated with 94% yield. The group nitro was reduced to amine with Zn/H^+. The compound was refluxed with chloroform, giving (±)-*endo*-**1** with 78% yield for two steps. The conversion of compound (±)-*endo*-**1** to (±)-epibatidine was reported using *t*-BuOK/*t*-BuOH under reflux.[17,22]

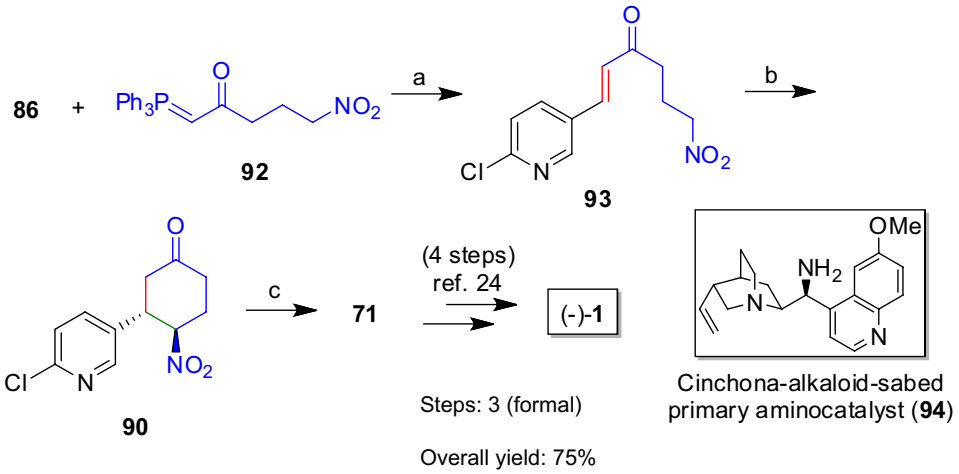
Jorgensen and co-workers[23] developed a diastereoisomeric and enantioselective intramolecular Michael addition using a chiral organocatalyst for formal synthesis of (–)-epibatidine (Scheme 10). The Wittig reaction of ylide **92** and aldehyde **86** gave the γ-nitroenone **93** with 98% yield. The intramolecular cyclization by Michael addition using 10 mol% catalyst and hindered protic solvent gave the trans-4-nitrocyclohexanone **90** with 80% yield (96% *ee*, 14:1 dr). The compound **90** has been reduced with $NaBH_4$ to the 4-nitrocyclohexanone **71** with 87% yield (10:1 dr). The total synthesis of (–)-epibatidine from compound **71** was reported by Szántay,[24] involving over 4 steps with 22% yield.



Scheme 8. (a) *Pseudomonas putida* UV4 (> 98% *ee*); (b) H_2 (1,5 bar), 5% Rh-graphite catalyst, MeOH, rt (90%); (c) TBSCl, Py, rt (86%); (d) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C, Na_2CO_3, Et_2O:MeOH:H_2O (4:4:1:), rt (90%); (e) Ph_3P, Et_3N, CBr_4, CH_2Cl_2, –10 °C; (f) [3,3] sigmatropic rearrangement; (g) 1% $MoCl_2O_2$, CH_2Cl_2, *t*-BuOH, rt (76%, 3 steps); (h) 6-chloropyridin-3-ylboronic acid, 2% **85**, PhMe:EtOH:H_2O (1:1:1), Na_2CO_3, 100 °C (93%); (i) TBAF, THF (95%); (j) PtO_2, H_2 (1 bar), EtOH, rt (60%); (k) Et_3N, MsCl, CH_2Cl_2, 0 °C (91%); (l) LiBr, THF, 60 °C (78%); (m) TFA, CH_2Cl_2, rt (94%); (n) $CHCl_3$, 55 °C (95%) (adapted from reference 19).



Scheme 9. (a) KF.H_2O, *i*-PrOH/THF, rt; (b) DMAP, Ac_2O, CH_2Cl_2, rt (76%, 2 steps); (c) *L*-proline, 2,5-dimethoxybenzoic acid, DMSO, rt (81%, dr > 97%); (d) **91**, NaBH4, THF, 0 °C (95%); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C (94%); (f) Zn, CH_3CO_2H/THF, rt; (g) $CHCl_3$, reflux (78%, 2 steps) (adapted from reference 21).



Scheme 10. (a) 1,2-dicloroethane, 50 °C (98%); (b) **94** (2×(*S*)-*N*-BocPhGly), *t*-BuOH, 75 °C (88%, 14:1 dr, 96% *ee*); (c) $NaBH_4$, MeOH, 0 °C (87%, 10:1 dr) (adapted from reference 23).

Blakemore and co-workers[25] investigated the functionalizing of α-chloroalkylllithiums, generating *in situ* the sulfoxide-lithium for stereospecific reagent-controlled homologation with available 6-chloropyridin-3-yl boronic acid for the formal synthesis of (–)-epibatidine, **1** (Scheme 11). The reaction of *p*-thiocresol (**95**) with acrolein generates the aldehyde **96** with 95% yield, which was treated with ethylene glycol, generating the thioether **99**. The two enantiomers of *syn*-chlorosulfoxide **99** were prepared by Ellamn-Bolm enantioselective oxidation using the appropriate enantiomer of Jackson's *tert*-leucinol derived ligand **109**, giving 80% yield (> 98% *ee*) for the sulfoxidation and non-racemizung chlorination with 86% yield (95:5 dr).

The epimerization of *syn*-chlorosulfoxide was conducted by sodium bis(trimethylsilyl)amide (NaHMDS) and [D_4]methanol, giving the *anti*-D-chlorosulfoxide **100** with 85% yield and 86% dr. There was a double one-pot reaction between the 6-chloropyridin-3-yl boronic acid and sulfoxide-lithium (generated from the *anti*-D-**100** *in situ*), which led to two reactional cycles, the first using the enantiomer *(S)-anti*-D-**100** and the second using *(R)-anti*-D-**100**. The alcohol (*R,S*)-D,D-**101** was obtained with 49% yield (97% *ee* and 79% dr).

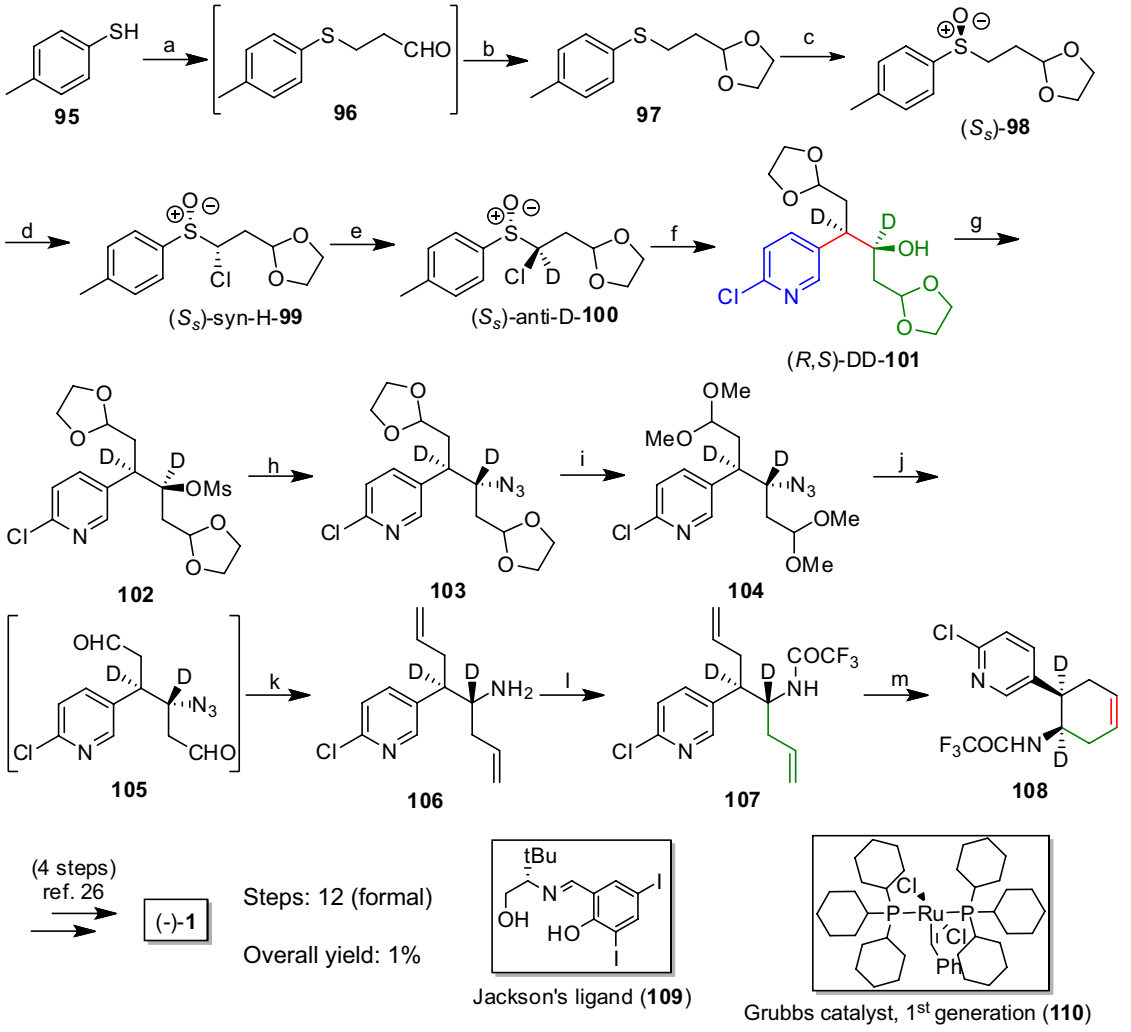
The alcohol **101** was mesylated and substituted by azide group, and acetal was hydrolysed, generating the compound **104** with 52% yield for three steps. The compound **104** was converted to dialdehyde **105**, which was used without purification and converted to dienyl amide **107** by exposure to methylenetriphenylphosphorane (generated *in situ* with *n*-BuLi and PPh_3CH_3I), giving 12% yield for two steps. The compound **107** was cyclized by Grubbs' first-generation catalyst, giving the compound **108** with 85% yield. The total synthesis of (–)-epibatidine from compound **108** was reported by Corey.[26]

4. Intramolecular SN-Type 2

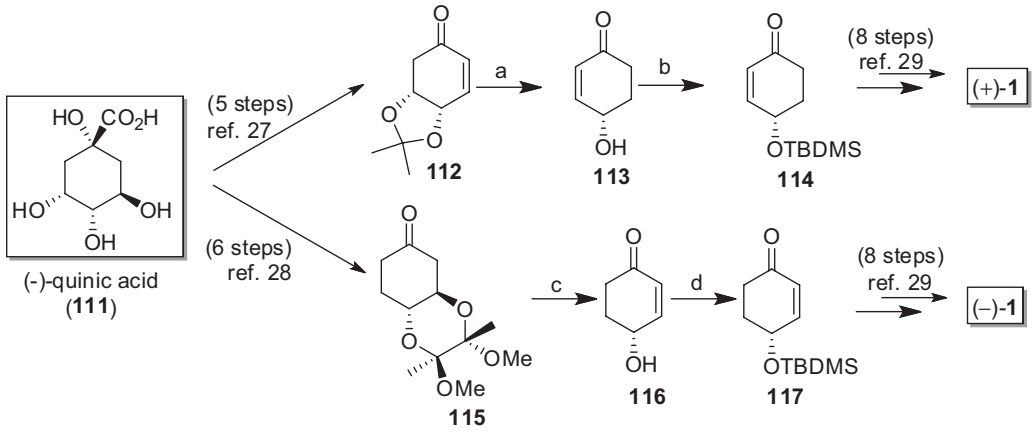
In 1999, Maycock and co-workers[27] reported a formal synthesis of (+)-epibatidine starting from (–)-quinic acid (Scheme 12).[27,28] Analogously, the same authors revealed years later that the same precursor (quinic acid) can be used for the formal synthesis of the corresponding levorotary epibatidine by the synthesis of the enantiopure *R*-4-hydroxy-2-cyclohexen-1-one (**116**).[29]

Avenoza *et al.*[30,31] described a synthetic route to 7-azabicyclo[2.2.1]heptane containing a carboxylic acid group at the bridgehead carbon atom (Scheme 13). The synthesis begins with preparation of the dienophile **120** from racemic serine through esterification followed by double benzoylation in the presence of base. Diels-Alder reaction between **120** and Danishefsky's diene gave a mixture of cycloadducts, which was treated under dilute HCl and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the enone **125**. Hydrogenation of this product followed by reduction with *L*-selectride and mesylation gave the compound **127**. Internal nucleophilic displacement with *t*-BuOK gave the desired compound **128** with the 7-azabicyclo[2.2.1]heptane core. Selective hydrolysis of the ester gave **129**, which was used to prepare the Barton ester derivative **130**. Simple decarboxylation of the Barton ester was achieved using tin hydride as a source of hydrogen radical, yielding the *N*-benzoyl-7-azabicyclo[2.2.1]heptane **131**, the precursor for Olivo's synthesis of epibatidine.[32]

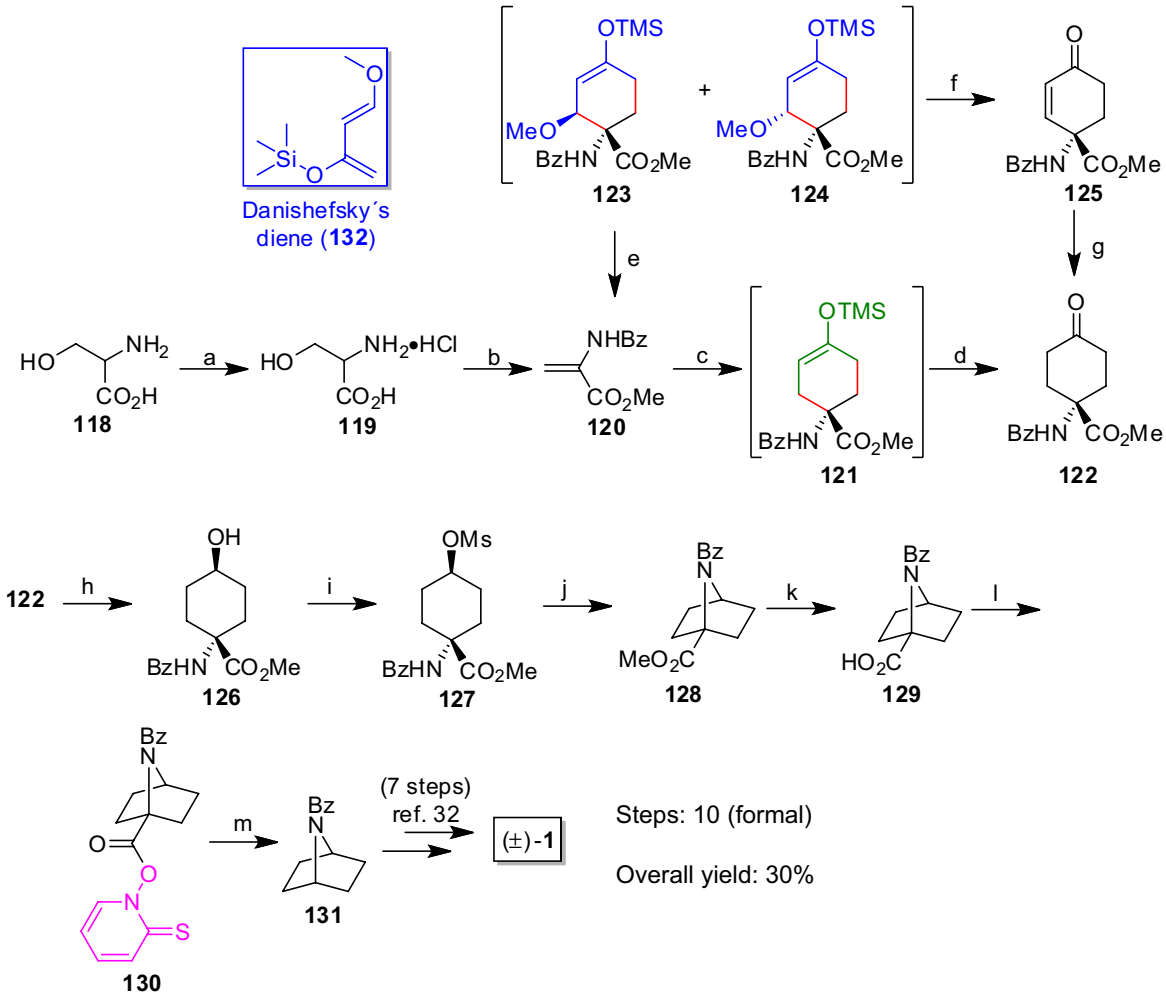
Aggarwal and Olofsson[33] described a good methodology of direct asymmetric arylation for the cicloexanone **139**, applying it for the total synthesis of (–)-epibatidine (Scheme 14). The electrophile pyridyl iodonium salt (**135**) was synthetized in two steps: obtaining the compound **134** from acetylene gas with 21% yield, which was reacted with



Scheme 11. (a) Acrolein, Et_3N, CH_2Cl_2, 0 °C; (b) ethylene glycol, *p*-TsOH·H_2O, benzene, reflux (95%); (c) **109**, [VO(acac)$_2$], aq. H_2O_2, $CHCl_3$, 0 °C (80%, > 98% *ee*); (d) NCS, K_2CO_3, CH_2Cl_2, 0 °C (86%, 95:5 dr); (e) NaHMDS, CD_3OD, THF, −78 °C (85%, 86% dr); (f) (*i*) 6-chloro-3-pyridineboronic acid pinacol ester, (*S*)-anti-D-**100**, PhLi, THF, −78 °C → rt; (*ii*) (*R*)-anti-D-**100**, PhLi, THF, −78 °C → rt, then KOOH (49%, 97% *ee*, 79% dr); (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaN_3, DMF, 80 °C; (i) TsOH, MeOH, reflux (52%, 3 steps); (j) aq. TFA, $CHCl_3$, rt; (k) Ph_3PCH_3I, *n*-BuLi, THF, −10 °C → reflux; (l) $(CF_3CO_2)_2O$, Et_3N, rt (12%, 3 steps); (m) 10% **110**, CH_2Cl_2, reflux (85%) (adapted from reference 25).



Scheme 12. (a) (*i*) *K*-Slectride®, THF, −78 °C; (*ii*) aq. 0.5 mol L^{-1} NaOH, THF, 0 °C; (b) *tert*-butyldimethylsilyl chloride (TBDMSCl), (*i*-Pr)$_2$NEt, DMAP, CH_2Cl_2, 0 °C → rt (51%, 3 steps); (c) TFA, H_2O, CH_2Cl_2, reflux (85%); (d) TBDMSCl, (*i*-Pr)$_2$NEt, DMAP, CH_2Cl_2, 0 °C → rt (98%) (adapted from reference 29).



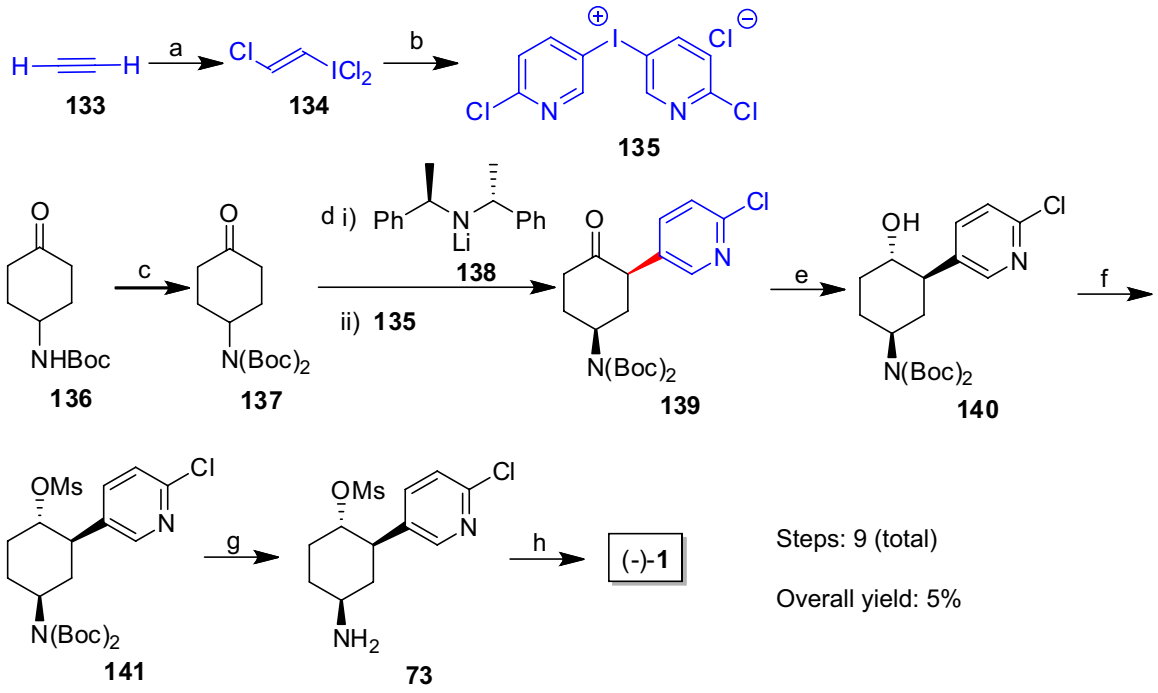
Scheme 13. (a) HCl, MeOH, 0 °C → reflux (> 99%); (b) BzCl, Et_3N, CH_2Cl, rt, DBU, MeOH, rt (94%); (c) 2-trimethylsiloxy-1,3-butadiene, ZnI_2, CH_2Cl_2, reflux; (d) aq. HCl, THF, rt (94%, 2 steps); (e) **132**, toluene, reflux; (f) aq. HCl, THF, rt, DBU, MeOH, 5 °C (55%, 2 steps); (g) H_2, Pd/C, CH_2Cl_2, rt (95%); (h) *L*-selectride®, THF, –78 °C; (i) MsCl, *N*,*N*-diisopropylethylamine (DIPEA), CH_2Cl_2, rt (68%, 2 steps); (j) *t*-BuOK, THF, rt (81%); (k) LiOH. H_2O, MeOH:H_2O, rt (99%); (l) (*i*) $(COCl)_2$, DMF, $CH_3CH_2Cl_2$; (*ii*) *N*-hydroxypyridine-2-thione, Et_3N, THF, 0 °C; (m) Bu_3SnH, THF, light, rt (61%, 3 steps) (adapted from reference 31).

2-chloro-5-bromopyridine, generating the electrophile **135** with approximately 70% yield.

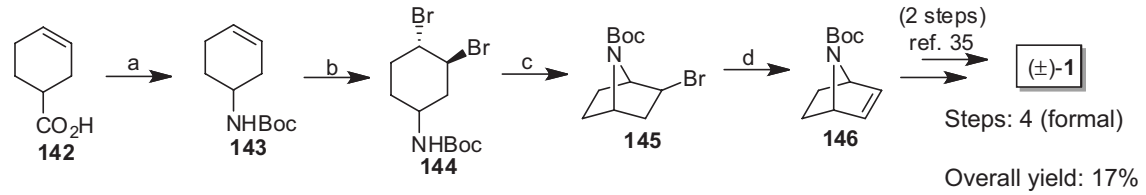
The carbamate **136** was protected with 100% yield. The ketone **137** was transformed in 2-pyridyl ketone **139** with 41% yield (> 20:1 dr). The base **138** was used to generate the enolate, favoring the coupling between **137** and **135**. The 2-pyridyl ketone was reduced to alcohol **140** with 83% yield (10:1 dr). The alcohol was mesylated, giving the compound **141**. This was deprotected, giving the amine **73**, which was cyclized, giving the (–)-epibatidine with 90% yield for three steps.

Gómez-Sánchez and Marco-Contelles[34] reported a direct base-catalyzed heterocyclization of *N*-Boc protected 3,4-dibromocyclohex-1-yl amine (**144**) as a key-step for the synthesis of the azabicycloheptane core (Scheme 15). Starting from cyclohex-3-enecarboxylic acid **142**, the *N*-Boc cyclohexene derivative **143** was obtained by Curtius rearrangement by diphenylphosphoryl azide (DPPA) under reflux of toluene. Bromination of the alkene gave the dibromo compound **144** in *cis* configuration as a major product. The authors found that NaH in dimethylformamide (DMF) is the best condition for the intramolecular cyclization of **144**, affording the known compound **145**, which gave the azabicycloheptene **146** after reaction with potassium *t*-butoxide. This azanorbornene is a known intermediate for the synthesis of epibatidine.[35]

Lautens and Bexrud[36] developed a highly selective catalyst for the asymmetric hydroarylation of azabicycles and applied it to the synthesis of epibatidine (Scheme 16). Initially, the reaction of *N*-Boc-7-azanorbornene **146** with 2-chloropyridine-5-boronic acid **147** generated less than 12% of protected epibatidine **149**. To circumvent the low reactivity of boronic acid, the authors used the potassium trifluoroborate **148** to produce the desired compound **149**



Scheme 14. (a) ICl_3, HCl, H_2O, 0 °C → rt (21%); (b) 2-chloro-5-bromopyridine, BuLi, Et_2O, −78 °C → rt (ca. 70%); (c) Boc_2O, DMAP, THF, reflux (> 99%); (d) (*i*) THF, −118 °C; (*ii*) DMF, −45 °C (41%, > 20:1 dr, 94% *ee*, 2 steps); (e) $NaBH_4$, MeOH, −98 °C (83%, 10:1 dr); (f) MsCl, Et_3N, CH_2Cl_2, rt; (g) TFA, CH_2Cl_2, rt; (h) $CHCl_3$, reflux (90%, 3 steps) (adapted from reference 33).



Scheme 15. (a) DPPA, Et_3N, toluene, reflux, *t*-BuOH, reflux (85%); (b) Br_2, Et_4NBr, CH_2Cl_2, −78 °C (50%); (c) NaH, DMF, rt (52%); (d) *t*-BuOK, THF, rt (78%) (adapted from reference 34).

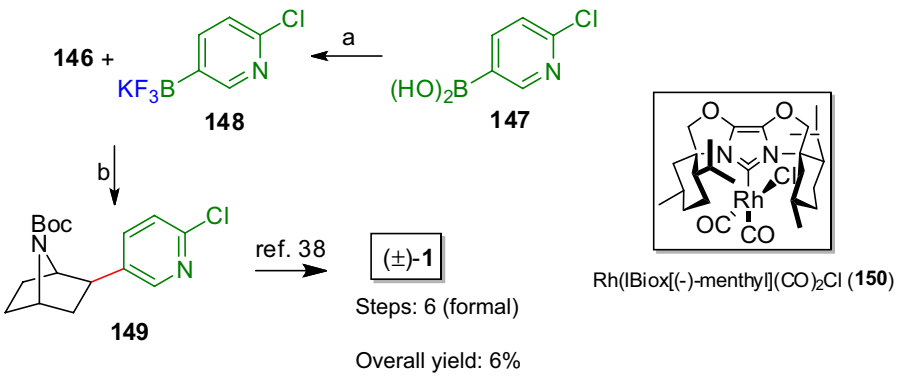
in moderate yield, but with high enantiomeric excess. The steps a to d were reported by Gomez-Sanchez.[37] The deprotection of *N*-Boc was reported by Armstrong.[38]

5. Rearrangement

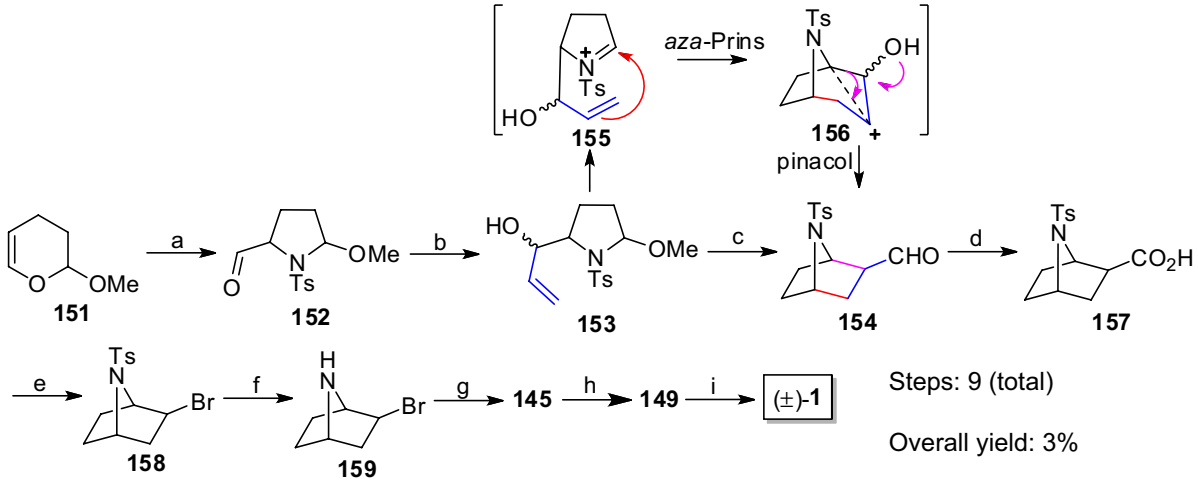
Armstrong *et al.*[38] accomplished the racemic synthesis of epibatidine from commercial 2-methoxy-3,4-dihydro-2*H*-pyran. The key step consisted of the construction of the 7-azabicyclo[2.2.1]heptane (**154**) through an elegant and *exo*-selective aza-Prins-pinacol rearrangement (Scheme 17). The bicyclic was obtained in only three steps from the pyran (**151**) (sulfonamidation using cheap chloramine-*T*),[39] the addition of vinyl Grignard reagent, and treatment with $SnCl_4$.[40] Attempts for a *de novo* synthesis of the chloropyridine group using the aldehyde moiety through a [4+2] cycloaddition approach failed, and the authors had to convert the aldehyde into a bromine group with aims at a cross-coupling approach. Thus, Jones oxidation of compound **154** followed by Barton bromodecarboxylation under sunlight gave the desired bromide **158**. Changing the protecting group was necessary, with the authors commenting that the tosyl group interferes with the desired Suzuki coupling, and an unexpected intramolecular cyclization through a radical mechanism was observed. Deprotection of tosylate **158** with HBr and protection with Boc_2O led to the bromide **145**. Suzuki coupling using bis(1,5-cyclooctadiene)nickel ($Ni(COD)_2$) in combination with bathophenanthroline yielded the *N*-Boc protected racemic (±)-epibatidine.

6. Conclusions

The number of articles published from 2001 to 2014 about the synthesis of epibatidine is still significant. However, strategies for building azabicyclic systems are still limited due to its relatively low structural complexity. Therefore, the syntheses presented in this review focused



Scheme 16. (a) KHF_2, MeOH, H_2O (71%); (b) Cs_2CO_3, 10% **150**, THF/H_2O, 80 °C (45%) (adapted from reference 36).



Scheme 17. (a) NBS, TsNClNa, CH_3CN, rt (79%); (b) vinyl magnesium bromide, Et_2O, –30 °C → rt (56%); (c) $SnCl_4$, CH_2Cl_2, 0 °C → rt (32%); (d) Jones reagent, acetone, 0 °C → rt (92%); (e) $(COCl)_2$, CH_2Cl_2, reflux, 2-mercaptopyridine-1-oxide, $BrCCl_3$, 90 °C, sunlight (61%); (f) aq. HBr, phenol, reflux; (g) $NaHCO_3$, Boc_2O/THF, H_2O (67%, 2 steps); (h) $Ni(COD)_2$, bathophenanthroline, KO'Bu, BuOH, rt, 6-chloropyridin-3-yl boronic acid, 60 °C (56%); (i) TFA, CH_2Cl_2 (89%) (adapted from reference 38).

on modern methods to obtain the cyclohexylamine ring or to incorporate the 4-chloropyridyl ring, including Pd catalyzed reactions and metathesis reactions.

Among the syntheses covered in this review, the synthesis reported by Jorgensen[23] seems to be the most attractive in terms of the number of steps. However, if the overall yield is evaluated, the Huang's route cannot be tolerated.

Concomitantly, advances in synthesis and biological activity studies of epibatidine analogs such as epiboxidine are ongoing.

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Álvaro Takeo Omori *is Bachelor in Chemistry at São Paulo University (2000) and PhD in Organic Chemistry under guidance of Prof João Valdir Comasseto at the Chemistry Institute of São Paulo Univeristy (2005). He was supervised by Prof Tomas Hudlicky in his post-doctoral at Brock University (Canada, 2006). He has experience in Organic Chemistry, acting on the following topics: biocatalysis, total synthesis (morphinanes), palladium chemistry and selenium/tellurium chemistry. Currently, he is associate professor at Universidade Federal do ABC, working with total syntheses of epibatidine and oseltamivir phosphate.*

Ronaldo Epifanio de Oliveira Filho *is Bachelor of Industrial Chemistry at Universidade São Francisco (2012)*

and Master of Science and Technology/ Chemistry at Universidade Federal do ABC (2015). He has experience in Organic Chemistry, acting on the following topics: organic synthesis (alkaloids), biocatalysis and polymers.

References

1. Olivo, H. F.; Hemenway, M. S.; *Org. Prep. Proced. Int.* **2002**, *34*, 1 and references therein.
2. Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Decker, M. W.; Sullivan, J. P.; Williams, M.; *Nat. Prod. Rep.* **2000**, *17*, 131.
3. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Lewis, P. U.; Daly, J. W.; *J. Am. Chem. Soc.* **1992**, *114*, 3415.
4. Garraffo, H. M.; Spande, T. F.; Williams, M.; *Heterocycles* **2009**, *79*, 207.
5. Falkenberg, M. B.; Pereira, P. A.; *Lat. Am. J. Pharm.* **2007**, *26*, 614.
6. Badio, B.; Garraffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W.; *Eur. J. Pharmacol.* **1997**, *321*, 189.
7. Olivo, H. F.; Colby, D. A.; Hemenway, M. S.; *J. Org. Chem.* **1999**, *64*, 4966.
8. Pandey, G.; Tiwari, S. K.; Singh, R. S.; Mali, R. S.; *Tetrahedron Lett.* **2001**, *42*, 3947.
9. Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P.; *Tetrahedron Lett.* **1998**, *39*, 1021.
10. Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G.; *J. Org. Chem*. **1994**, *59*, 1771; Zhang, C.; Trudell, M. L.; *J. Org. Chem.* **1996**, *61*, 7189.
11. Pandey, G.; Bagul, T. D.; Sahoo, A. K.; *J. Org. Chem*. **1998**, *63*, 760.
12. Pandey, G.; Laha, J. K.; Lakshmaiah, G.; *Tetrahedron* **2002**, *58*, 3525.
13. Moreno-Vargas, A. J.; Vogel, P.; *Tetrahedron Asym.* **2003**, *14*, 3173.
14. Zhang, C.; Ballay II, C. J.; Trudell, M. L.; *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 675.
15. Kimura, H.; Fujiwara, T.; Katoh, T.; Nishide, K.; Kajimoto, T.; Node, M.; *Chem. Pharm. Bull.* **2006**, *54*, 399.
16. Evans, D. A.; Scheidt, K. A.; Downey, W.; *Org. Lett.* **2001**, *3*, 3009.
17. Lee, C-L. K.; Loh, T-P.; *Org. Lett.*, **2005**, *7*, 2965.
18. Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y.; *Tetrahedron* **2006**, *62*, 365.
19. Boyd, D. R.; Sharma, N. D.; Kaik, M.; McIntyre, P. B. A.; Stevenson, P. J.; Allen, C. C. R.; *Org. Biomol. Chem.* **2012**, *10*, 2774.
20. Boyd, D. R.; Dorrity, M. R. J.; Malone, J. F.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P.; *J. Chem. Soc., Perkin Trans. 1* **1990**, *1*, 489.
21. Huang, X.; Shi, H.; Ren, J.; Liu, G.; Tang, Y.; Zeng, B.; *Chin. J. Chem.* **2012**, *30*, 1305.
22. Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay Jr., C.; Temesvári-Major, E.; Blaskó, G.; *Tetrahedron Lett*. **1994**, *35*, 3171.
23. Jensen, K. L.; Weise, C. F.; Dickmeiss, G.; Morana, F.; Davis, R. L.; Jorgensen, K. A.; *Chem. - Eur. J.* **2012**, *18*, 11913.
24. Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay Jr., C.; Temesvári-Major, E.; Blaskó, G.; *Tetrahedron* **1996**, *52*, 11053.
25. Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R.; *Chem. - Eur. J.* **2013**, *19*, 16342.
26. Corey, E. J.; Loh, T-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S.; *J. Org. Chem*. **1993**, *58*, 5600.
27. Barros, M. T.; Maycock, C. D.; Ventura, M. R.; *Tetrahedron Lett*. **1999**, *40*, 557.
28. Barros, M. T.; Maycock, C. D.; Ventura, M. R.; *J. Org. Chem.* **1997**, *62*, 3984.
29. Barros, M. T.; Maycock, C. D.; Ventura, M. R.; *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 166.
30. Avenoza, A.; Cativiela, C.; Busto, J. H.; Fernández-Recio, M. A.; Peregrina, J. M.; Rodríguez, F.; *Tetrahedron* **2001**, *57*, 545.
31. Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; *Tetrahedron* **2002**, *58*, 1193.
32. Olivo, H. F.; Hemenway, M. S.; *J. Org. Chem*. **1999**, *64*, 8968.
33. Aggarwal, V. K.; Olofsson, B.; *Angew. Chem., Int. Ed.* **2005**, *44*, 5516.
34. Gómez-Sánches, E.; Marco-Contelles, J.; *Lett. Org. Chem.* **2006**, *3*, 827.
35. Che, C.; Petit, G.; Kotzyba-Hibert, F.; Bertrand, S.; Bertrand, D.; Grutter, T.; Goeldner, M.; *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1001.
36. Bexrud, J.; Lautens, M.; *Org. Lett.* **2010**, *12*, 3160.
37. Gómez-Sánchez, E.; Soriano, E.; Marco-Contelles, J.; *J. Org. Chem*. **2007**, *72*, 8656.
38. Armstrong, A.; Bhonoah, Y.; Shanahan, S. E.; *J. Org. Chem*. **2007**, *72*, 8019.
39. Armstrong, A.; Cumming, G. R.; Pike, K.; *Chem. Commun.* **2004**, 812.
40. Armstrong, A.; Shanahan, S. E.; *Org. Lett*. **2005**, *7*, 1335.

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