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Synthesis of 5-*endo*-, 5-*exo*-, 6-*endo*- and 6-*exo*-hydroxylated analogues of epibatidine

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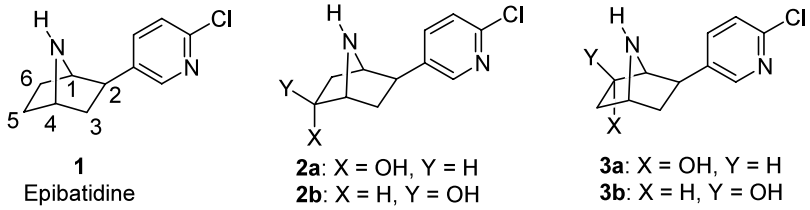
Abstract—A convenient, high-yield synthesis of *N*-Boc-7-azabicyclo[2.2.1]hept-5-en-2-one (**7**) was developed by SmI_2-mediated desulfonylation of **6**. Thus, 5-*endo*-, 5-*exo*-, 6-*endo*-, and 6-*exo*-hydroxylated epibatidine analogues **2a**,**b** and **3a**,**b** were synthesized from **7** by using a $Pd(PPh_3)_4$-catalyzed reductive Heck coupling reaction and SmI_2-mediated reduction of the carbonyl group as the key steps. Other reaction conditions for the reductive Heck procedure and the reduction step were also investigated. © 2003 Elsevier Science Ltd. All rights reserved.

The novel alkaloid epibatidine (**1**) was isolated from the skin of the Ecuadorian poisonous frog *Epipedobates tricolor* by Daly et al.,[1] and was found to have powerful analgesic activity and high binding affinity to nicotinic acetylcholine receptors (nAChRs) but not to opioid receptors.[2] Though its high toxicity limits the therapeutic potential,[3] it provides an attractive lead for the design of new ligands selective for distinct nAChR subtypes and possibly for the treatment of central nervous system disorders such as Alzheimer's disease, Parkinson's disease, dyskinesias, Tourette's syndrome, schizophrenia, attention deficit disorder, anxiety and pain.[4] However, in spite of numerous synthetic studies of this molecule, analogue synthesis has been generally limited to modification of the heteroaryl group,[3,5] alteration in position of the aliphatic ring nitrogen,[6] and expansion of the two-carbon bridge,[7] in some cases with introduction of a double bond[7c,h,j] or an additional ring nitrogen atom.[7e] However, to our knowledge, few modifications relating to the addition of heteroatom groups to the norbornane core have been made. We anticipated that introduction of an extra polar group, such as hydroxyl, to the norbornane core might alter nAChR affinity and subtype selectivity through the possibility to engage in extra H-bond donor/acceptor interactions with appropriately positioned amino acid residues present in the respective pentameric receptor subtypes. Moreover, the hydroxyl group can be manipulated chemically so as to provide access to other analogues, including ^{18}F for PET imaging purposes. Herein, we present our synthesis of the 5- and 6-hydroxyl-substituted epibatidine analogues **2a**,**b** and **3a**,**b** (Fig. 1).

Reductive Heck coupling was used as the key strategy in our synthesis. As illustrated in Scheme 1, the ketone **6** could be readily prepared from *N*-Boc-pyrrole (**4**) and 2-bromoethynyl *p*-tolyl sulfone (**5**) according to the



1 Epibatidine

2a: X = OH, Y = H
2b: X = H, Y = OH

3a: X = OH, Y = H
3b: X = H, Y = OH

Figure 1.

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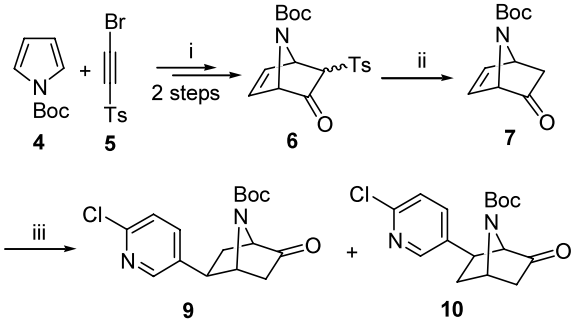


Scheme 1. *Reagents and conditions*: (i) See Ref. 8; (ii) SmI_2 (2 equiv.), THF–MeOH, −78°C to rt, 95%; (iii) Reductive Heck reaction, see Table 1.

literature procedure.[8] Removal of the α-sulfonyl group of **6** with SmI_2 provided the ketone **7** in excellent yield (95%).[9] It is noteworthy that this procedure is much superior to the reported Al–Hg method,[8] which in our case provided directly the alcohols as the major products while the desired ketone **7** was isolated in quite low yield (28%). With ketone **7** in hand, the reductive Heck coupling with 2-chloro-5-iodopyridine (**8**)[10] was investigated. Three different catalysts, $Pd(OAc)_2$, $Pd(OAc)_2(PPh_3)_2$, and $Pd(PPh_3)_4$, were examined, and the results are summarized in Table 1 (entries 1–3). All of the three coupling procedures gave a mixture of the products **9** and **10** in moderate yields, which could not be separated efficiently by flash column chromatography. The ratio of the products was determined by ^1H NMR analysis. Interestingly, different ratios of the regioisomers were obtained with different palladium catalysts. When $Pd(OAc)_2$ was used, the ratio of **9** to **10** was 5.0:1. Moving to $Pd(OAc)_2(PPh_3)_2$, **9** and **10** were isolated in a ratio of 2.5:1. When $Pd(PPh_3)_4$ was used as the coupling catalyst, almost equivalent amounts of the isomers **9** and **10** were obtained. Although the regioselectivity observed under the latter two reaction conditions are similar to that of the reductive Heck coupling of 2-azabicyclo[2.2.1]hept-5-ene,[6b,c] the higher proportion of the 2-*exo* isomer **9** obtained from the $Pd(OAc)_2$-catalyzed reductive Heck reaction of **7** may be due to subtle electronic effects involving the double bond and the carbonyl group.

The structures of the two regioisomers **9** and **10** were assigned by analysis of their ^1H NMR spectra in $CDCl_3$. The spectrum of **9** showed two doublets at

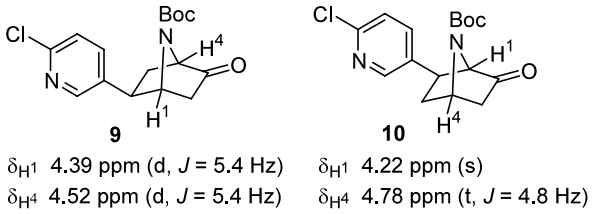


Figure 2.

$\delta = 4.39$ ppm with $J = 5.4$ Hz (H^1) and 4.52 ppm with $J = 5.4$ Hz (H^4). In contrast, the spectrum of **10** showed a singlet at $\delta = 4.22$ ppm (H^1) and a triplet at $\delta = 4.78$ ppm with $J = 4.8$ Hz (H^4) (Fig. 2).

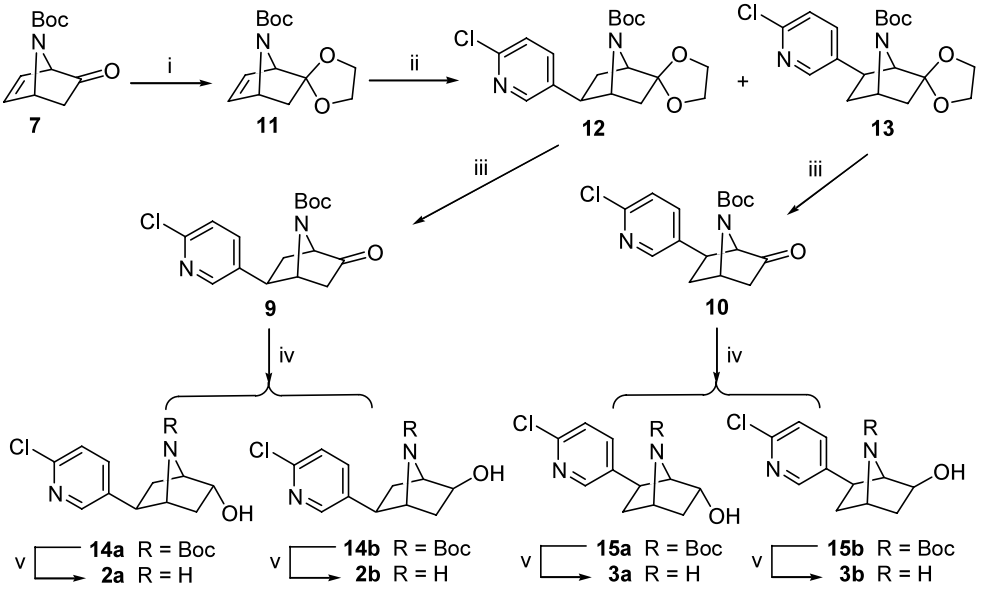
We reasoned that the moderate yields for the reductive Heck coupling of **7** with **8** might be due to the lability of the products when contaminated with the palladium catalyst. Thus, as shown in Scheme 2, the ketone **7** was protected as 1,3-dioxolane (compound **11**) with $HOCH_2CH_2OH/(EtO)_3CH/p$-TsOH.[11] Reductive Heck coupling of **11** with **8** was performed using $Pd(PPh_3)_4$ as the catalyst as we hoped to obtain both of the products **12** and **13** in good yields. Gratifyingly, **12** and **13** were isolated in a ratio of 1.2:1 in 92% combined yield (Table 1, entry 4) and were easily separated by column chromatography. Most of the signals in the ^1H and ^{13}C NMR spectra of **12** and **13** were duplicated due to the presence of two rotamers in each compound. Selective removal of the 1,3-dioxolane group in **12** and **13** was unsuccessful as the Boc group was cleaved first while the 1,3-dioxolane group persisted even in 12N HCl at room temperature. Therefore, both the 1,3-dioxolane and Boc group were removed simultaneously with 70% perchloric acid followed by reprotection of the nitrogen with Boc to provide the corresponding ketones **9** and **10** in good yields (77–83%).

With the ketones **9** and **10** in hand, reduction conditions were investigated in order to obtain both *endo*- and *exo*-alcohols in good yields. Thus, ketone **9** was subjected to different reduction conditions, and the results are summarized in Table 2. Both of the 5-*endo* and 5-*exo* alcohols **14a** and **14b** were obtained in the reduction of **9** under all conditions investigated, though 5-*endo* selectivity predominated as expected (Table 2, entries 1–6). $NaBH_4$ reduction of **9** gave the 5-*endo* alcohol **14a** in the highest selectivity (ratio of **14a**/**14b** = 10.2:1), while SmI_2 provided the best yield of the 5-*exo* alcohol **14b** (ratio of **14a**/**14b** = 3.3:1). The 6-*endo* and 6-*exo* alcohols **15a** and **15b** were obtained in a ratio of 2.2:1 by SmI_2-mediated reduction of ketone **10** (Table

Table 1. Reductive Heck reaction on **7** and **11**

Entry	Compound	Conditions	Products (ratio)[a]	Yield (%)[b]
1	**7**	**8**, $Pd(OAc)_2$, HCO_2Na, n-Bu_4NCl, DMF, 100°C	**9**:**10** (5.0:1)	56
2	**7**	**8**, $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 75°C	**9**:**10** (2.5:1)	38
3	**7**	**8**, $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75°C	**9**:**10** (0.9:1)	47
4	**11**	**8**, $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75°C	**12**:**13** (1.2:1)[c]	92

[a] Ratios were determined from the ^1H NMR spectra of the product mixtures after chromatography.
[b] Overall yields were of isolated material after chromatography.
[c] Ratio was determined from the ^1H NMR spectrum of the crude reaction products.



Scheme 2. *Reagents and conditions:* (i) $HOCH_2CH_2OH$, $(EtO)_3CH$, *p*-TsOH (cat.), THF, 64%; (ii) **8**, $Pd(PPh_3)_4$ (cat.), piperidine, HCO_2H, DMF, 75°C, 92%; (iii) 1. $HClO_4$, 2. Boc_2O, Et_3N, THF, 77–83% for two steps; (iv) see Table 2; (v) CF_3COOH, CH_2Cl_2, 93–97%.

Table 2. Results from ketone reductions of **9** and **10** under different reaction conditions

Entry	Compound	Conditions	Products (ratio)[a]	Yield (%)[b]
1	**9**	$NaBH_4$, THF, H_2O, rt	**14a**/**14b** (10.2:1)	82
2	**9**	$LiBH_4$, THF, −78°C to rt	**14a**/**14b** (5.5:1)	93
3	**9**	BH_3, THF, −78°C to rt	**14a**/**14b** (7.0:1)	41
4	**9**	L-Selectride, THF, −78°C to rt	**14a**/**14b** (3.4:1)	97
5	**9**	$LiAlH(O\text{-}t\text{-}Bu)_3$, THF, 0°C	**14a**/**14b** (6.1:1)	95
6	**9**	SmI_2, THF, H_2O, rt	**14a**/**14b** (3.3:1)	86
7	**10**	SmI_2, THF, H_2O, rt	**15a**/**15b** (2.2:1)	91

[a] Ratios were determined from the ^1H NMR spectra of the crude reaction products.
[b] Combined yields are of isolated material after chromatography.

2, entry 7). Removal of the Boc protecting groups from **14a**,**b**, **15a**, and **15b** afforded the products **2a**,**b**, **3a**, and **3b**, respectively (Scheme 2).

The stereochemistry of **2a**,**b** and **3a**,**b** could be inferred from their ^1H NMR spectra[12] and was confirmed for compound **2a** by X-ray crystallographic analysis (Fig. 3).[13]

In summary, we have described a practical route to the 5-*endo*-, 5-*exo*-, 6-*endo*-, and 6-*exo*-hydroxylated epibatidine analogues **2a**,**b** and **3a**,**b** using a reductive Heck procedure and SmI_2-mediated reduction as the key steps. Further functionalization on the alicyclic part based on the parent skeleton of epibatidine and the evaluation of their biological activity are now underway.

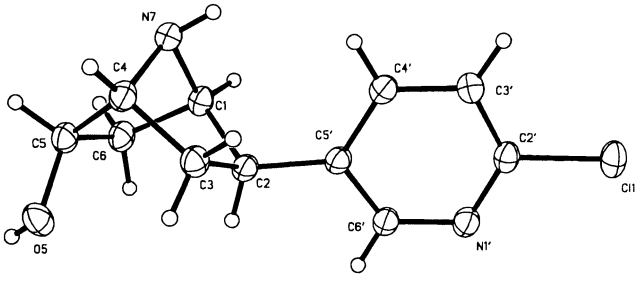


Figure 3. X-Ray crystal structure of **2a**.

Acknowledgements

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12. Compound **2a**: ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, $J=2.4$ Hz), 7.72 (dd, 1H, $J=8.4$, 2.4 Hz), 7.25 (d, 1H, $J=8.4$ Hz), 4.35 (dtd, 1H, $J=10.2$, 4.8, 1.2 Hz), 3.68 (t, 1H, $J=4.5$ Hz), 3.48 (d, 1H, $J=5.1$ Hz), 2.97 (dd, 1H, $J=9.0$, 4.5 Hz), 2.70 (dd, 1H, $J=12.6$, 9.0 Hz), 2.13 (ddd, 1H, $J=12.9$, 9.9, 5.4 Hz), 1.80 (br s, 2H), 1.55 (dtd, 1H, $J=12.6$, 4.8, 1.2 Hz), 1.24 (dd, 1H, $J=12.9$, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 149.12, 148.74, 140.82, 137.67, 123.98, 72.27, 63.52, 60.48, 44.81, 41.00, 31.51. Compound **2b**: ^{1}H NMR ($CDCl_3$) δ 8.28 (d, 1H, $J=2.4$ Hz), 7.81 (dd, 1H, $J=8.4$, 2.4 Hz), 7.25 (d, 1H, $J=8.4$ Hz), 4.07 (dd, 1H, $J=6.3$, 1.5 Hz), 3.58–3.53 (m, 2H), 2.64 (dd, 1H, $J=9.0$, 4.2 Hz), 1.98 (dd, 1H, $J=13.5$, 6.3 Hz), 1.84 (br s, 2H), 1.75 (dd, 1H, $J=13.2$, 9.0 Hz), 1.61 (dt, 1H, $J=13.2$, 4.8 Hz), 1.42 (dd, 1H, $J=13.5$, 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 149.23, 148.89, 140.31, 137.83, 123.96, 74.11, 63.40, 61.59, 43.38, 33.91. Compound **3a**: ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 1H, $J=2.7$ Hz), 7.74 (dd, 1H, $J=8.4$, 2.7 Hz), 7.25 (d, 1H, $J=8.4$ Hz), 4.34 (dt, 1H, $J=10.2$, 4.5 Hz), 3.71 (t, 1H, $J=5.4$ Hz), 3.69 (dd, 1H, $J=9.3$, 5.4 Hz), 3.44 (d, 1H, $J=4.8$ Hz), 2.11 (m, 1H), 2.10 (dd, 1H, $J=12.6$, 9.3 Hz), 1.83 (br s, 2H), 1.72 (m, 1H), 1.16 (dd, 1H, $J=12.6$, 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 149.29, 149.00, 140.76, 138.07, 123.98, 72.59, 66.82, 57.67, 40.77, 39.18, 35.10. Compound **3b**: ^{1}H NMR ($CDCl_3$) δ 8.28 (d, 1H, $J=2.4$ Hz), 7.78 (dd, 1H, $J=8.4$, 2.4 Hz), 7.25 (d, 1H, $J=8.4$ Hz), 4.08 (d, 1H, $J=5.7$ Hz), 3.79 (t, 1H, $J=4.5$ Hz), 3.35 (s, 1H), 2.57 (dd, 1H, $J=8.7$, 5.7 Hz), 1.92 (dd, 1H, $J=13.2$, 6.3 Hz), 1.79 (dd, 1H, $J=12.0$, 8.7 Hz), 1.72 (br s, 2H), 1.58–1.49 (m, 1H), 1.45–1.36 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 149.25, 148.72, 137.75, 124.12, 74.33, 69.78, 55.33, 42.43, 39.77, 39.09.
13. Crystal data of **2a**: triclinic crystal ($0.41\times0.23\times0.11$ mm^3) in space group $P1$; $a=9.069(1)$ Å, $b=9.604(1)$ Å, $c=12.200(1)$ Å, $\alpha=91.430(1)°$, $\beta=96.301(1)°$, $\gamma=93.072(1)°$, $V=1054.27(4)$ Å^3; $Z=4$; $D_{calcd}=1.416$ Mg/m^3; $F(000)=472$; absorption coefficient $=2.993$ mm^{-1}; reflections collected $=4422$, independent reflections $=2771$ ($R_{int}=0.0221$); parameters $=284$; goodness-of-fit $=0.953$; final R indices [$I>2\sigma(I)$]: $R=0.0506$, $Rw=0.1867$.