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A Practical Route to Epibatidine

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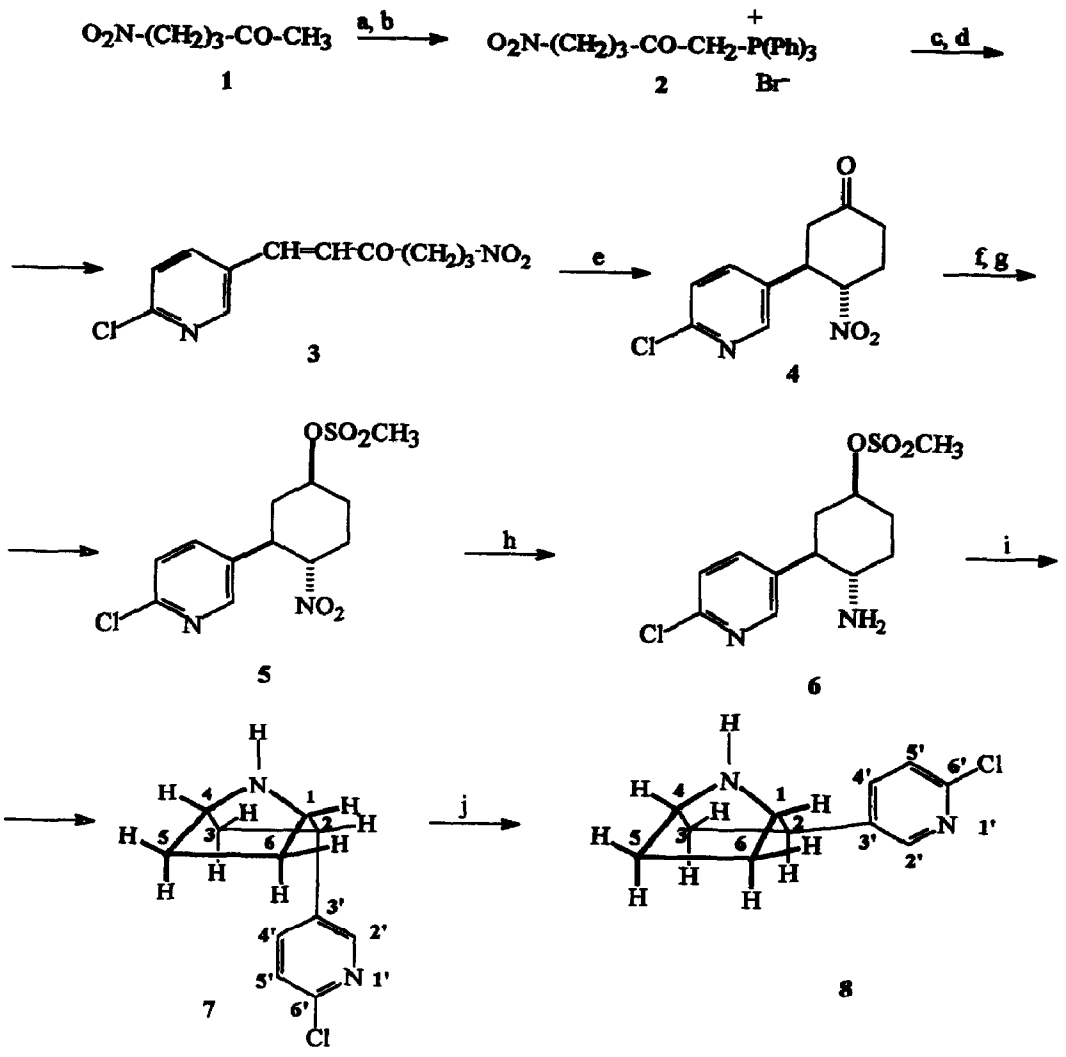
Abstract: A practical synthetic approach to the alkaloid Epibatidine has been developed. This method is convenient and easy to scale up.

The unusual biological properties of the alkaloid Epibatidine[1] (**8**) have aroused interest among organic chemists and several syntheses have recently been published[2]. This fact promted us to disclose our practical route to this unusual alkaloid. The idea of the following approach was based 1.) on molecular mechanics calculations indicating that Epibatidine (**8**) should be more stable than its endo-isomer (**7**), and 2.) the concerned stereocenter having a benzylic type hydrogen could be inverted under basic conditions without affecting the α-chloro atom in the pyridine ring.

Nitromethane was allowed to react with methyl vinyl ketone to give compound **1**[3]. After bromination[4] and subsequent quaternarization with triphenylphosphine the salt **2**[5] was obtained. Wittig reaction of the appropiate phosphorane[6] with chloropyridine aldehyde[7] gave rise to **3**[8]. Treatment of compound **3** with potassium fluoride/alumina furnished the cyclohexane derivative **4**[9]. Reduction of the keto group[10] followed by mesylation (**5**)[11] and subsequent reduction of the nitro group gave amine **6**[12], which on heating resulted in the epimer of Epibatidine, i.e. **7**[13]. On boiling the latter compound in *tert.*-butanol in the presence of potassium *tert.*-butoxide epimerization occurred, and racemic Epibatidine (**8**)[14] was obtained. The resolution of its N-BOC derivative has already been described[2c]. Epimerization of the N-BOC derivative of **8** is also known[2c].

The above described procedure is convenient and easy to scale up.



a) Br_2 (1 equiv.), MeOH, rt, 4 h, 55 %; b) Ph_3P (1.2 equiv.), bz, rt, 24 h, 89 %; c) CH_2Cl_2, 1 % NaOH, rt, 0.5 h, 72 %; d) 6-chloropyridine-3-carboxaldehyde (0.6 equiv.), CH_2Cl_2, reflux, 8 h, 84 % (based on the aldehyde); e) KF/alumina (14 equiv.), THF, rt, overnight, 59 %; f) $NaBH_4$ (3 equiv.), EtOH, 0 °C, 1.5 h, (67 %); g) CH_3SO_2Cl (1.2 equiv.), CH_2Cl_2, pyridine, rt, overnight, 91 %; h) $SnCl_2.2H_2O$ (14 equiv.), EtOH, reflux, 24 h, 80 %; i) toluene, reflux, 24 h, 46 %; j) $KOBu^t$ (10 equiv.), Bu^tOH, reflux, 30 h 50 %.

The NMR spectra for compounds **7** and **8** corresponded with those reported earlier[2a,b]. However, we note that the previous assignments[2b] of H-$3_{\alpha(eq)}$ and H-$3_{\beta(ax)}$ in Epibatidine (**8**), as well as those of C-5' and C-4' in **7** and **8** should be reversed. For completeness below we list our experimental NMR data for both **8** and **7**. The present assignments were confirmed by 2D homo- (COSY) and hetero-correlation (HETCOR) as well as detailed $^1H\{^1H\}$ NOE experiments using various solvents to circumvent some overlap difficulties. In **7** a relatively large (ca. 3 Hz) 'W' coupling is observed between H-3_β and H-5_β, which can be used to identify these protons; this was pointed out before in connection with the pertinent N-acyl analogues[2a]. Due to the aromatic ring anisotropic effect the relative spectral positions of H-3_α and H-3_β in **7** are reversed compared to **8**. In **7** C-6 and C-3 show characteristic upfield shifts due to steric interaction with the pyridyl ring.

Table. ^1H and ^{13}C NMR Data for Compounds **7** and **8** [^1H: 300 MHz, $CDCl_3$, δ_{TMS}=0.00 ppm, J (Hz)]

	8	**7**
H-1:	3.57 d *$J(1,6_\beta) \approx 1.7$; $J(1,6_\alpha) \approx J(1,2_\alpha) < 1$*	3.78 t *$J(1,6_\beta) \approx J(1,2_\beta) \approx 4.4$; $J(1,6_\alpha) < 1$*
H-2:	2.77 dd *$J(2_\alpha,3_\alpha) = 9.0$; $J(2_\alpha,3_\beta) = 5.1$; $J(1,2_\alpha) < 1$*	3.32 ddd *$J(2_\beta,3_\alpha) = 5.6$; $J(1,2_\beta) \approx 4.4$; $J(2_\beta,3_\beta) \approx 12.0$; $J(2_\beta,6_\beta) < 1$*
H-3_α:	1.92 dd *$J(2_\alpha,3_\alpha) = 9.0$; $J(3_\alpha,3_\beta) = 12.2$; $J(3_\alpha,4) < 1$*	1.52 dd *$J(2_\beta,3_\alpha) = 5.6$; $J(3_\alpha,3_\beta) = 12.5$; $J(3_\alpha,4) < 1$*
H-3_β:	1.48-1.70 m (overlapping)	2.13 dddd *$J(2_\beta,3_\beta) \approx 12.0$; $J(3_\alpha,3_\beta) = 12.5$; $J(4,3_\beta) \approx 4.0$; $J(3_\beta,5_\beta) \approx 3$*
H-4:	3.81 t *$J(4,3_\beta) \approx J(4,5_\beta) \approx 4.0$; $J(4,3_\alpha) \approx J(4,5_\alpha) < 1$*	3.79 t *$J(4,3_\alpha) \approx J(4,5_\alpha) < 1$; $J(4,3_\alpha) \approx J(4,5_\alpha) < 1$*
H-5_α:	1.48-1.70 m (overlapping)	1.31-1.48 m (overlapping)
H-5_β:	1.48-1.70 m (overlapping)	1.66 m
H-6_α:	1.48-1.70 m (overlapping)	1.31-1.48 m (overlapping)
H-6_β:	1.48-1.70 m (overlapping)	1.31-1.48 m (overlapping)
NH:	2.01 brs	1.88 brs
H-2':	8.28 d; H-4': 7.78 dd; H-5': 7.23 d	H-2': 8.25 d; H-4': 7.48 dd; H-5': 7.28 d
C-1:	62.6 *$J_{C\text{-}1,H\text{-}1} = 151$; $J_{C\text{-}1,H\text{-}4} = 9.5$*	61.1 *$J_{C\text{-}1,H\text{-}1} = 150$*
C-2:	44.4 *$J_{C\text{-}2,H\text{-}2} = 132$*	44.9 *$J_{C\text{-}2,H\text{-}2} = 132$*
C-3:	40.2	34.8
C-4:	56.4 *$J_{C\text{-}4,H\text{-}4} = 151$; $J_{C\text{-}4,H\text{-}1} = 9.5$*	57.5 *$J_{C\text{-}4,H\text{-}4} = 150$*
C-5:	31.2*	31.0
C-6:	30.0* (interchangeable)	24.1
C-2':	148.7; C-3': 140.9; C-4': 137.6;	C-2': 149.6; C-3': 135.8; C-4': 138.3;
C-5':	123.8; C-6': 148.8	C-5': 123.7; C-6': 149.5

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4. 1-Bromo-nitro-pentane-2-one, yellow oil, $IR_{(neat)}$: 2950, 1720, 640 cm^{-1}.
5. (5-Nitro-pentane-2-one)-triphenyl-phosphonium bromide (**2**), mp: 70-72 °C.
6. (5-Nitro-pentane-2-one)-triphenyl-phosphorane, mp: 94-97 °C.
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8. 1-[3-(6-Chloro-pyridyl)]-3-oxo-6-nitro-hexa-1-ene (**3**), mp: 97-100 °C, $IR_{(KBr)}$: 1700, 1680, 1620, 1580, 1550, 1100 cm^{-1}.
9. (±)-1α-Nitro-2ß-[3-(6-chloro-pyridyl)]-cyclohexane-4-one (**4**), mp: 118-121 °C, $IR_{(KBr)}$: 1710, 1585, 1550, 1100 cm^{-1}.
10. (±)-1α-Nitro-2ß-[3-(6-chloro-pyridyl)]-cyclohexane-4ß-ol, mp: 149-153 °C, $IR_{(neat)}$: 3380, 1580, 1570, 1550, 1100, 1080 cm^{-1}.
11. (±)-1α-Nitro-2ß-[3-(6-chloro-pyridyl)]-4ß-mesyloxy-cyclohexane (**5**), mp: 120-122 °C, $IR_{(KBr)}$: 1590, 1570, 1540, 1450, 1350, 1180, 1090 cm^{-1}.
12. (±)-1α-Amino-2ß-[3-(6-chloro-pyridyl)]-4ß-mesyloxy-cyclohexane (**6**), yellow oil.
13. epi-Epibatidine (**7**), yellow oil, $IR_{(neat)}$: 3260, 3220, 1580, 1560, 1200, 1100 cm^{-1}.
14. Epibatidine (**8**), colourless crystals, mp: 57-59 °C.

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