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TETRAHEDRON: *ASYMMETRY*

An expeditious formal synthesis of (–)-epibatidine

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Abstract

A short route to (–)-epibatidine is described. It includes a hetero-Diels–Alder reaction of a chiral non-racemic acyl-nitroso derivative and 2-*t*-butyldimethylsilyloxycyclohexadiene followed by chemical manipulations to furnish a known precursor of the natural product in 11% overall yield.

1. Introduction

The alkaloid epibatidine **1** (Scheme 1) has attracted a great deal of attention since its isolation from the skin of the frog *Epipedobates tricolor*.[1] Its structure was elucidated in 1992 enlightening its relative configuration.[2] Interestingly, it had a 7-azabicyclo[2.2.1]heptane frame with an original *exo* oriented 3-(6-chloropyridyl) substituent. The absolute configuration of (–)-epibatidine was reported by Fletcher et al. to be 1*R*,2*R*,4*S*.[3]

Epibatidine excited the interest of synthetic chemists because of its powerful pharmacological activity as a non-opioid analgesic. Indeed, it was shown to be a very potent nicotinic acetylcholine receptor (nAChR) agonist.[4] Therefore a large number of syntheses have emerged.[5]

We recently reported a formal synthesis of (–)-epibatidine **1**[6] based on an asymmetric hetero-Diels–Alder reaction between a chiral acyl-nitroso derivative **2** and 2-*t*-butyldimethylsilyloxy-cyclohexadiene **3** (Scheme 1).[7] This cycloaddition proceeded very efficiently to give the enone (+)-**5** in 64% overall yield as a unique diastereomer after reduction of the N–O bond of cycloadduct **4** with $Mo(CO)_6$. Enone (+)-**5** was transformed in eight steps into bicyclic ketone (–)-**6a**, a known precursor[5a,b] of natural (–)-epibatidine.

We have now explored a shorter route to ketone **6** which is described herein. Such a shorter route should involve the cleavage of the N–O bond of cycloadduct **4** to give a compound of type **7** (Scheme 1). The latter should be a precursor of the bicyclic ketone (–)-**6** after inversion of configuration and activation of the thus formed secondary alcohol.

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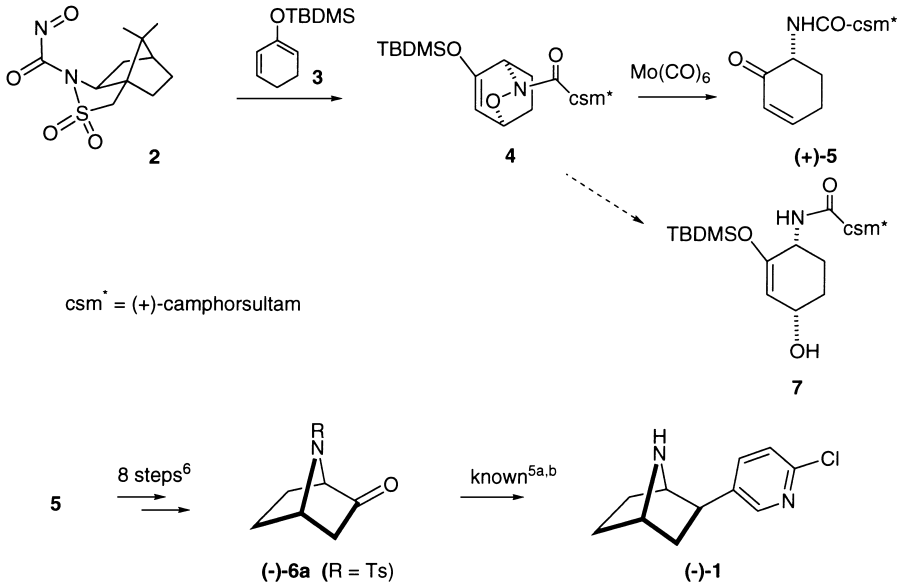


Scheme 1.

2. Results and discussion

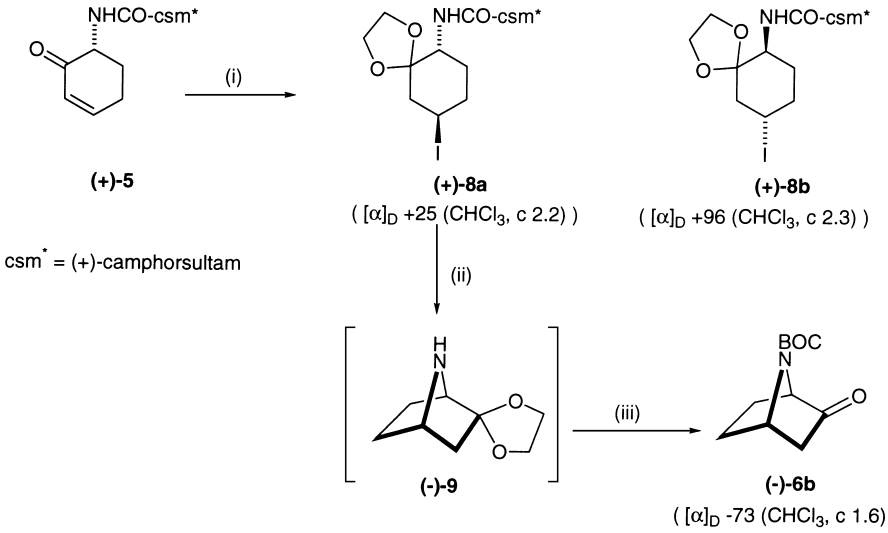
Despite numerous attempts using various conditions ($TiCl_3$, HCl, MeOH and Na/Hg, Na_2HPO_4, MeOH), we were not able to cleave the N–O bond without β-elimination which led to enone (+)-**5**. Some attempts were also made to transform the silylated enol ether function of **4** into a ketal function. These attempts were also unsuccessful due to the facile cleavage of the N–O bond with concomitant β-elimination.

Thus, enone (+)-**5** still constituted the key-intermediate in our synthesis. It was sequentially treated with TMSI in acetonitrile and then ethylene glycol[8] to give the *trans*-iodo acetal **8** in 88% yield (Scheme 2). Unfortunately, compound **8** consisted of a 65:35 mixture of diastereomers (+)-**8a** and (+)-**8b** possessing the same *trans* relative relationship and consequently were precursors of each enantiomer of epibatidine. The major diastereomer (+)-**8a** was readily separated from the mixture by column chromatography and obtained in 57% yield.

A poorly stereocontrolled iodine addition followed by an epimerization during the ketalization step could explain the formation of the mixture of isomers **8a+8b**. The epimerization gave exclusively the thermodynamically more stable *trans* (di-equatorial) iodo-amides (+)-**8a** and (+)-**8b**.

It was anticipated that the major diastereomer (+)-**8a** was the precursor of natural (–)-epibatidine and the last three steps of the synthesis were performed with this compound. Basic hydrolytic cleavage of the sultam moiety using LiOH in *t*-butanol underwent spontaneous aminocyclization to give compound **9**: The latter was not isolated and immediately subjected to acidic cleavage of the ketal, followed by protection of amine as a *N*-BOC to give known (–)-**6b** ($[\alpha]_D$ –73 ($CHCl_3$, $c=1.6$); lit.: $[\alpha]_D$ –72.6 ($CHCl_3$, $c=1.1$)[9a]; $[\alpha]_D$ –75.5 ($CHCl_3$, $c=1.0$)[9b]) in 45% yield from **8a**.

Despite the epimerization and the subsequent separation, the synthesis described herein represents a very rapid (seven steps) and efficient asymmetric synthesis (11% overall yield) of enantiopure



Scheme 2. *Reageants*: (i) (a) TMSI, NaI, (b) $HOCH_2CH_2OH$, (c) separation (chromatography); (ii) LiOH, *t*-BuOH; (iii) (a) 4N HCl, Δ, (b) BOC_2O, Et_3N

ketone (–)-**6b**, a known precursor[3,5a,b] of (–)-epibatidine and compares favorably with the other published asymmetric syntheses.

3. Experimental

IR spectra were recorded with a Genesis Matteson infrared spectrophotometer. ^1H NMR spectra were recorded on a Bruker AC 250 apparatus (250 MHz, $\delta = 0$ (TMS), in $CDCl_3$ if not specified otherwise, J in Hertz). ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AC 300 apparatus (δ in ppm relative to internal TMS). Samples were dissolved in $CDCl_3$ unless stated. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. Elemental analyses were performed by the service of microanalyse, ICSN, CNRS, Gif-sur-Yvette. Mass spectra were recorded with an AEI MS-50 (Electronic Impact 50 eV) or AEI MS-9 (Chemical Ionisation with isobutane as ionising gas). Optical rotations were measured on polarimeter Perkin–Elmer 241 MC at rt. Chromatographic solvents were distilled before use. Flash chromatographies were performed on Merck 60 silica gel (230–400 mesh). TLC were performed on Merck 60 F254 aluminum plates. All the reactions were carried out under inert atmosphere unless water was used as the solvent. Solvents were distilled prior to use (CH3CN and CH2Cl2 over CaH2, THF and Et2O over Na, benzophenone). The other solvents were used in their commercial quality grades.

*3.1. 10,10-Dimethyl-3,3-dioxo-3λ⁶-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-4-carboxylic acid-(9-iodo-1,4-dioxa-spiro[4,5]dec-6-yl)-amide (+)-**8a** and (+)-**8b***

In a 10 ml flask were introduced enone (+)-**5**[6] (341 mg, 0.96 mmol), NaI (654 mg, 4.5 equiv.) and 5 mL of dry CH_3CN. The temperature was cooled to 0°C to give a white slurry solution. Then TMSCl (0.553 mL, 4.5 equiv.) was added dropwise and stirring was maintained for 15 min. Ethyleneglycol (0.065 mL, 1.2 equiv.) was added and the cooling bath was removed. After 30 min

stirring at room temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and 10 mL of pentane were added. The aqueous phase was removed and the organic layer was washed successively with 10 mL of a 5% aqueous solution of $Na_2S_2O_3$, 10 mL of a saturated solution of NaCl and three times with 10 mL H_2O. The aqueous layers were joined and extracted twice with 15 mL CH_2Cl_2. The organic layers were gathered, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The crude product was purified by flash chromatography to give iodoacetals **8a** (263 mg, 57%) and **8b** (142 mg, 31%) as white solids.

(1*R*, *R*) (+)-**8a**: $[\alpha]_D$ +25.1 ($c=2.2$; $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 0.95 (s, 3H), 1.1 (s, 3H), 1.2–2.6 (m, 13H), 3.35 (s, 2H), 3.6–4.2 (m, 7H), 6.0 (d, 1H, $J=9.2$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.8, 20.1, 21.5, 26.6, 31.6, 31.9, 32.1, 37.4, 37.8, 44.0, 47.8, 47.9, 48.5, 51.6, 52.5, 64.0, 65.2, 107.8, 150.5; IR (KBr, cm^{-1}): 3020, 1686; m/z (C.I.): 525 (MH^+). Anal. calcd for $C_{19}H_{29}N_2O_5IS$: C, 43.51; H, 5.53; N, 5.34. Found: C, 43.55; H, 5.75; N, 5.24.

(1*S*,9*S*) (+)-**8b**: $[\alpha]_D$ +96.0 ($c=2.3$; $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 0.95 (s, 3H), 1.1 (s, 3H), 1.2–2.6 (m, 13H), 3.35 (s, 2H), 3.6–4.2 (m, 7H), 6.0 (d, 1H, $J=8.9$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.8, 20.0, 21.2, 26.5, 31.7, 31.9, 37.6, 37.7, 44.0, 47.8, 48.7, 51.7, 52.7, 64.1, 65.1, 65.5, 108.2, 150.4; IR (KBr, cm^{-1}) 3020 (NH), 1686 (CO); m/z (C.I.): 525 (MH^+).

3.2. (1R,4S)-N-(tert-Butyloxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (–)-6b

In a 10 mL flask were introduced the iodoacetal (+)-**8a** (600 mg, 1.14 mmol, 1 equiv.), LiOH 56% (171 mg, 2 equiv.) and 10 mL of *t*BuOH. After heating for 20 h at 90°C under vigorous stirring, the reaction mixture was cooled to room temperature and a 5% aqueous solution of HCl was added to pH 2–3. The solvents were removed under reduced pressure. The residue was suspended in 20 mL of 1N HCl solution and extracted twice with 20 mL Et_2O. The organic layer was washed four times with a 5% aqueous solution of HCl, dried over Na_2SO_4 and the solvent evaporated under reduced pressure to give (+)-camphorsultam (220 mg, 89%) in good purity. The aqueous layers were joined, and the water removed under reduced pressure. The resulting green–white crude salt was then heated in 15 mL of a 12% aqueous solution of HCl to 90°C for 5 h. The aqueous phase was removed under pressure and 20 mL portions of ethanol were successively added and evaporated under reduced pressure for azeotropic removal of water (three times). To the crude amine hydrochloride were added 30 mL of CH_2Cl_2, $(BOC)_2O$ (500 mg, 2 equiv.) and Et_3N (2.37 mL, 15 equiv.). The solution was stirred at 35°C for 12 h and treated with 10 mL of a saturated aqueous solution of K_2CO_3. After stirring for 2 h, the organic layer was decanted and the aqueous phase extracted twice with 20 mL of CH_2Cl_2. The organic layers were joined, dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude carbamate was purified by flash chromatography (hexane:ethyl acetate, 9:1) to give bicycle (–)-**6** (110 mg, 45% overall) as a standing-solidifying colorless oil. $[\alpha]_D$ –72.8 ($c=1.6$; $CHCl_3$); lit.: $[\alpha]_D$ –72.6 ($c=1.1$; $CHCl_3$)[9a]; $[\alpha]_D$ –75.5 (c = 1.0; $CHCl_3$);[9b] ^1H NMR ($CDCl_3$) δ (ppm): 1.7 (s, 9H), 1.8–2.0 (m, 5H), 2.25 (ddd, 1H, $J=1.1$, 5.2, 17.5 Hz), 4.1 (d, 1H, $J=4.9$ Hz), 4.3 (t, 1H, $J=4.4$ Hz).

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