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Efficient resolution of *N*-Boc-7-azabicyclo[2.2.1]hept-5-en-2-one: formal syntheses of natural epibatidine and its enantiomer

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Abstract—The efficient resolution of racemic *N*-Boc-7-azabicyclo[2.2.1]hept-5-en-2-one (±)-**2** via aminal formation with (*R*,*R*)-1,2-diphenylethylenediamine **4** is reported. Acidic hydrolysis furnishes the enantiomeric ketones (+)-**2** and (−)-**2** that were transformed into 7-azabicyclo[2.2.1]heptan-2-one (−)-**3** and (+)-**3**. The process constitutes a formal synthesis of (+)- and (−)-epibatidine.

1. Introduction

For several years our research group has developed the 'naked sugar' methodology,[1] which converts furan and derivatives into enantiomerically pure monosaccharides and rare analogues, into carbopyranoses, long-chain carbohydrates, iminodeoxyalditols, *C*-linked disaccharides and into imino-*C*-disaccharides and analogues, including a new type of polyhydroxylated quinolizidines. The key intermediate to develop this methodology was the (+)- and (−)-7-oxabicyclo[2.2.1]hept-5-en-2-one (+)-**1**, (−)-**1**.[2] The aza-analog 7-azabicyclo[2.2.1]hept-5-en-2-one has been reported in 1999 by Trudell et al.[3] and its synthesis has been improved recently by Kozikowski et al.,[4a] for both groups in the racemic form (±)-**2** (Chart 1).

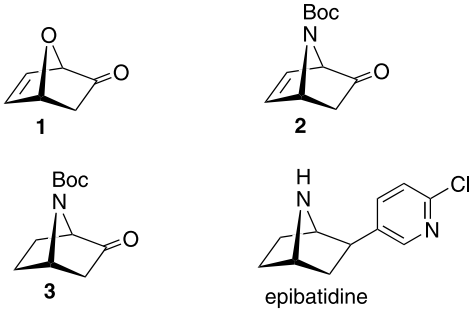

Chart 1.

The interest of this molecule is related to the synthesis of epibatidine, a natural alkaloid[5] that has been reported to be a highly potent non-opioid analgesic agent with a potency 200-fold greater than that of morphine in mice. Due to the novel structure and its remarkable analgesic activity, an unprecedent large number of syntheses of epibatidine,[6] and recently of analogs,[4] have been described. In many of these syntheses, racemic *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one (±)-**3**, that can be easily obtained from (±)-**2**, has been used as an advanced key intermediate in the synthesis.[2,6] The enantiospecific synthesis of (+)-**3** and (−)-**3** involve multiple manipulations.[6b,d–h,k]

As part of a program to develop the 'naked aza-sugar' methodology (by analogy to the 'naked sugar' methodology[1]), we report here the resolution of racemic 7-azabicyclo[2.2.1]hept-5-en-2-one (±)-**2** based on the formation of aminals derived from (*R*,*R*)-1,2-diphenylethylenediamine **4**. The same method had been successful in the case of the resolution of ketone (±)-**1**.[7] The assignment of the absolute configuration of (+)-**2** and (−)-**2** was realized by chemical correlation with known enantiomerically pure ketones (+)-**3** and (−)-**3**. Enantiomerically pure (+)-**2** and (−)-**2** have been further characterized by their circular dichroism spectra.

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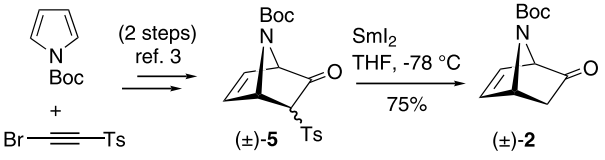
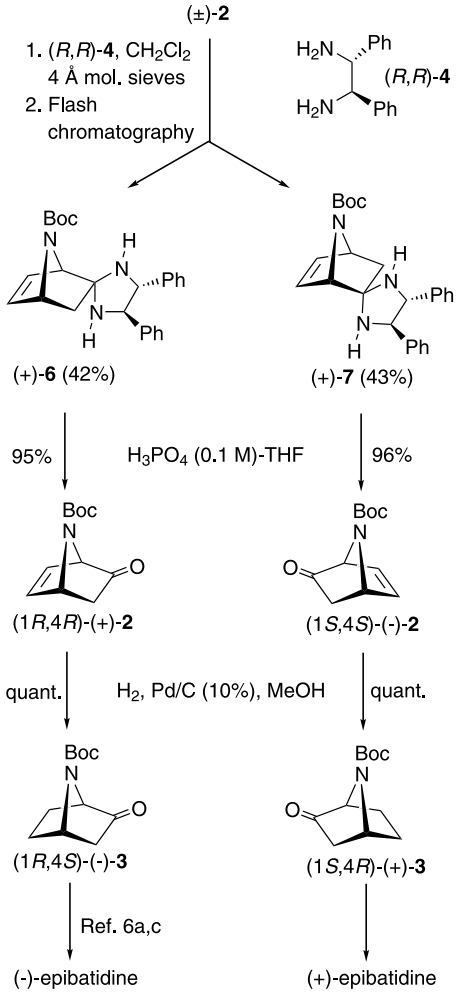


Scheme 1. Synthesis of racemic ketone (±)-**2**.



Scheme 2.

2. Results and discussion

The β-keto sulfone **5** was obtained readily from *N*-Boc-pyrrole and 2-bromoethynyl *p*-tolyl sulfone according to a literature procedure.[3] As reported by Kozikowski et al.,[4a] desulfonylation of β-keto sulfone **5** was carried out employing SmI_2[8] at −78°C. This provided ketone (±)-**2** in good yield (75%) (Scheme 1).

Recently, it was shown that (*R*,*R*)-1,2-diphenylethylenediamine **4** is an efficient reagent to determine the enantiomeric purity of the substituted cycloalkanones.[9] To our knowledge, only the resolution of ketone (±)-**1** via the formation of the corresponding aminals with diamine **4** has been reported thus far. Diphenylethylenediamine **4** is commercially available and can easily be prepared in enantiomerically pure form.[10] The diasteroisomeric aminals (+)-**6** and (+)-**7** are thus formed in nearly quantitative yield by reaction of racemic 7-azabicyclo[2.2.1]hept-5-en-2-one (±)-**2** with (*R*,*R*)-1,2-diphenylethylenediamine **4** in CH_2Cl_2 containing 4 Å molecular sieves (20°C, 24 h) (Scheme 2). The aminals (+)-**6** and (+)-**7** were not stable in solution unless 2% triethylamine was added to it. Under these conditions, it was possible to separate easily the two diasteroisomers by flash chromatography on silica gel ($\Delta R_f = 0.2$). The diastereomerically pure aminals were hydrolyzed by treatment with 0.1 M phosphoric acid–THF affording enantiomerically pure (+)-**2** and (−)-**2** nearly quantitatively. This hydrolysis is much easier that in the case of *O*-acetal analogues.[11] The chiral diamine **4** was also recovered nearly quantitatively.[7]

The hydrogenation of (+)-**2** and (−)-**2** in the presence of catalytic amounts of Pd/C (10%) afforded the known enantiomerically pure ketones (−)-**3** and (+)-**3**, respectively, in quantitative yields. The [α] values were in agreement with those reported for these compounds; [α] = +70 for (+)-**3** (lit.[6b] = +73.5) and −71 for (−)-**3** (lit.[6b] = −72.6). Ketone (−)-**3** has been converted into (−)-epibatidine.[6a,c] Therefore, the syntheses of (−)-**3** and (+)-**3** constitute formal syntheses of natural (−)-epibatidine and of its enantiomer.

The absolute configuration (1*S*,4*S*) of enone (−)-**2** was confirmed by its circular dichroism spectrum (Fig. 1) which shows a negative Cotton effect at $\lambda = 304$ nm for its $n \rightarrow \pi^*_{CO}$ transition. Similar negative Cotton effect have been observed for the $n \rightarrow \pi^*_{CO}$ transitions of (1*S*,4*S*)-(−)-7-oxabicyclo[2.2.1]hept-5-en-2-one[2] and (1*S*,4*S*)-(−)-bicyclo[2.2.2]oct-5-en-2-one.[12] The CD spectra of these three latter enones show an 'extra' negative Cotton effect between λ 205 and 215 nm associated with a mixed transition resulting from through-space ($\pi(\text{alkene}) \rightarrow \pi^*_{CO}$) and through-bond ($n(CO) \rightarrow \sigma \rightarrow \pi^*(\text{alkene})$) interactions.[12] The CD spectrum of (−)-**2** also present a negative Cotton effect at 212 nm which could be assigned to a similar mixed type of transition. The surprise, nevertheless, is the observation of a third negative Cotton effect at $\lambda = 233$ nm seen only for enone (−)-**2** and not for the other analogs. This suggests that the 7-(*t*-butoxycarbonyl)aza bridge introduces further electronic interaction between the chromophores of (−)-**2**. This is also indicated by the UV absorption spectrum of (−)-**2** (Fig. 2).

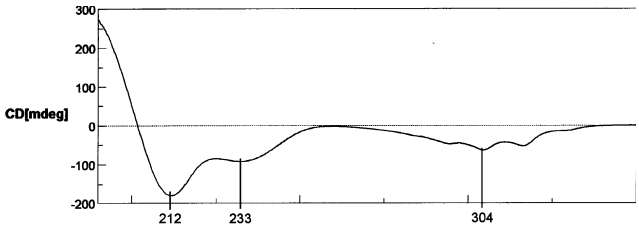


Figure 1. CD spectrum of (−)-**2** (0.0024 M^{-1} in isooctane).

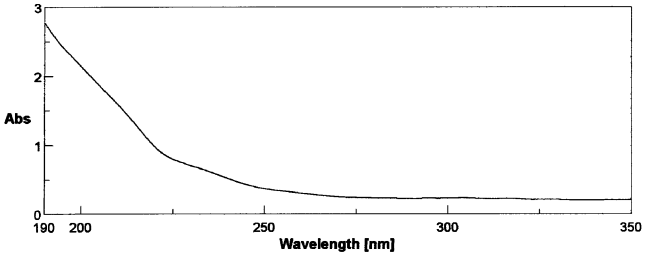


Figure 2. UV absorption spectrum of (−)-**2** (0.0024 M^{-1} isooctane).

3. Conclusions

An efficient resolution method of racemic *N*-Boc-7-azabicyclo[2.2.1]hept-2-en-5-one has been found. By analogy with the enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-ones (+)-**1** and (−)-**1** ('naked sugar'), the azaanalogs (+)-**2** and (−)-**2** are expected to open the 'naked azasugar' methodology. The use of (*R*,*R*)- and (*S*,*S*)-1,2-diphenylethylenediamine should find wider application for the resolution of chiral ketones.

4. Experimental

4.1. General

CH_2Cl_2 was distilled from CaH_2. For flash column chromatography (FC), silica gel 60 (Merck, 230–400 mesh) was used. TLC was performed on HF_{254} (Merck), with detection by UV light and charring with ninhydrin or spraying with a solution of 25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2(H_2O)_4$, 60 ml conc. H_2SO_4 and 940 ml water and subsequent heating. Mp's are not corrected. Optical rotations were measured at 25°C in a spectropolarimeter, Jasco DIP-370. ^1H and ^{13}C NMR spectra were registered in a Bruker ARX 400 apparatus. The spectra were obtained for solutions in $CDCl_3$ and chemical shifts in ^1H and ^{13}C NMR spectra are reported in parts per million (δ) relative to the peaks for $CDCl_3$ (7.27 and 77.0, respectively). ^1H and ^{13}C NMR signals assignments were confirmed by 2D COSY and HMQC when necessary. The CIMS spectra were measured with a Nermag R-10-10C mass spectrometer. The IR spectra were obtained from a Perkin–Elmer Parangon-1000 FT-IR spectrometer, the CD spectra on a JASCO J500-C dichrograph ($\Delta\varepsilon$ (λ in nm)).

4.2. (1*RS*,4*RS*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo-[2.2.1]hept-5-en-2-one (±)-2

To a solution of SmI_2 (0.1 M) in THF (70 ml) cooled to −78°C, a solution of keto sulfone **5** (1 g, 2.75 mmoles) in THF–MeOH (3:1, 8 ml) cooled at −78°C was added. The resultant brown mixture was stirred for 10 min at −78°C, warmed to room temperature, and then poured into saturated aqueous solution of K_2CO_3. The aqueous phase was extracted with Et_2O, the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was purified by flash chromatography (ether:petroleum ether, 1:2) affording **2** (431 mg, 75%) as a colorless oil. IR ν_{max} 2978, 2933, 1767, 1709, 1369, 1170, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 6.73 (dd, 1H, $J_{5,6}=5.4$, $J_{1,6}=1.7$, H-5), 6.43 (br. d, 1H, H-6), 5.10 (br. s, 1H, H-4), 4.53 (br. s, 1H, H-1), 2.41 (dd, 1H, $J_{3a,3b}=15.7$, $J_{3a,4}=0.8$, H-3a), 2.02 (d, 1H, H-3b), 1.56 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100.5 MHz, $CDCl_3$, δ ppm) δ 205.7 (CO of ketone), 155.4 (CO of carbamate), 143.4 (C-5), 130.8 (C-6), 81.8 ($(CH_3)_3C$), 68.6 (C-1), 60.4 (C-4), 36.2 (C-3), 28.5 ($(CH_3)_3C$); CIMS: *m*/*z* 210 (100%, $[M+H]^+$), *m*/*z* 227 (100%, $[M+NH_4]^+$). Anal. calcd for $C_{11}H_{15}NO_3$ (209.24): C, 63.14;H, 7.22; N, 6.69. Found: C, 63.23;H, 7.29; N, 6.65.

4.3. (1*R*,4*R*,4′*R*,5′*R*)- and (1*S*,4*S*,4′*R*,5′*R*)-4′,5′-Diphenylspiro[7-(*tert*-butoxycarbonyl)-7-azabicyclo-[2.2.1]hept-5-en-2,2′-imidazolidine] (+)-6 and (+)-7

(*R*,*R*)-Diphenylethylenediamine **4** (200 mg, 0.94 mmol) was added under N_2 to a solution of ketone (±)-**2** (188 mg, 0.90 mmol) in dry CH_2Cl_2 (3 ml) containing 4 Å molecular sieves. The reaction mixture was stirred for 24 h, Et_3N (0.5 ml) was added and the molecular sieves then eliminated by filtration. The filtrate was concentrated and the resultant residue purified by flash chromatography (ether:petroleum ether:Et_3N, 10:15:1→15:10:1) affording first (1*S*,4*S*)-(+)-**6** (156 mg, 43%) and then (+)-**7** (154 mg, 42%), both as white solids. Data for (+)-**6**: mp 133–135°C; $[\alpha]_D=+19$ (*c* 0.5, $CHCl_3$); IR ν_{max} 3361, 3027, 2975, 1704, 1367, 1168, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.28–7.18 (m, 10H, H-aromat.), 6.63 (br. d, 1H, H-5), 6.50 (br. d, 1H, H-6), 4.72 (br. s, 1H, H-4), 4.50 (br. s, 1H, H-1), 4.24, 4.18 (2d, 1H each, $J_{4',5'}=8.5$, H-4′ and H-5′), 2.42 (br. s, 2H, N*H*), 2.41 (dd, 1H, $J_{3a,3b}=11.8$, $J_{3a,4}=4.4$, H-3a), 1.61 (d, 1H, H-3b), 1.43 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100.5 MHz, $CDCl_3$, δ ppm) δ 155.9 (CO), 141.8, 140.2 (2 C-1 aromat.), 137.7, 135.1 (br., C-5 and C-6), 128.0, 127.4, 127.2, 127.0 (10 C-aromat.), 83.9 (br., C-2), 80.0 ($(CH_3)_3C$), 70.1, 69.5 (C-4′, C-5′), 68.5 (C-1), 60.5 (C-4), 46.9 (C-3), 28.2 ($(CH_3)_3C$); CIMS: *m*/*z* 404 (90%, $[M+H]^+$). Anal. calcd for $C_{25}H_{29}N_3O_2$ (403.52): C, 74.41;H, 7.24; N, 10.41. Found: C, 74.43;H, 7.22; N, 10.30. Data for (+)-**7**: mp 110–112°C; $[\alpha]_D=+60$ (*c* 1.5, $CHCl_3$); IR ν_{max} 3346, 3028, 2976, 1698, 1455, 1367, 1171, 760, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.32–7.47 (m, 10H, H-aromat.), 6.53–6.49 (m, 1H, H-5 and H-6), 4.80 (br. s, 1H, H-4), 4.64 (br. s, 1H, H-1), 4.36, 4.17 (2d, 1H each, $J_{4',5'}=8.4$, H-4′ and H-5′), 2.44 (br. s, 2H, N*H*), 2.33 (dd, 1H, $J_{3a,3b}=11.6$, $J_{3a,4}=4.3$, H-3a), 1.65 (d, 1H, H-3b), 1.49 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100.5 MHz, $CDCl_3$, δ ppm) δ 155.4 (CO), 140.4 (2 C-1 aromat.), 138.8, 134.1 (br., C-5 and C-6), 128.4, 128.2, 127.6, 127.2, 126.9, 126.4 (10 C-aromat.), 84.5 (br., C-2), 80.0 ($(CH_3)_3C$), 70.6, 69.8 (C-4′, C-5′), 69.0, 68.9 (C-1, rotamers), 60.5 (C-4), 45.6 (C-3), 28.3 ($(CH_3)_3C$); CIMS: *m*/*z* 404 (45%, $[M+H]^+$). Anal. calcd for $C_{25}H_{29}N_3O_2$ (403.52): C, 74.41;H, 7.24; N, 10.41. Found: C, 74.37;H, 7.24; N, 10.40.

4.4. (1*S*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo-[2.2.1]hept-5-en-2-one (−)-2

A solution of (+)-**6** (112 mg, 0.28 mmol) in 0.1 M H_3PO_4–THF (2:1, 15 ml) was stirred for 30 min at 20°C. Then, the mixture was diluted with H_2O and extracted with ether. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The resultant residue was purified by flash chromatography (ether:petroleum ether, 1:1) affording (−)-**2** (54 mg, 95%), as a colorless oil. $[\alpha]_D = -360$ (*c* 0.25, $CHCl_3$). CD (isooctane): molar ellipticity $[\theta](212\ nm) = -75000$, $[\theta](233\ nm) = -40000$, $[\theta](304\ nm) = -25000$ (see Fig. 1). Other spectral data are identical to those of (±)-**2**.

4.5. (1*R*,4*R*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo-[2.2.1]hept-5-en-2-one (+)-2

Compound **2** was prepared according to the procedure described for (−)-**2**, starting from (+)-**7** (120 mg, 0.3 mmol): (+)-**2** (60 mg, 96%), a colorless oil. $[\alpha]_D = +384$ (*c* 0.9, $CHCl_3$).

4.6. (1*S*,4*R*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo-[2.2.1]heptan-2-one (+)-3

A mixture of (−)-**2** (30 mg, 0.14 mmol) in MeOH (2 ml) and Pd/C (10%, 7 mg) was hydrogenated under atmospheric pressure for 1 h. The Pd/C was removed by filtration, washed with MeOH and the filtrate concentrated to dryness affording pure (+)-**3** (30 mg, 100%) as a colorless oil. $[\alpha]_D = +70$ (*c* 1.5, $CHCl_3$); lit.[6b] +74 (*c* 1.0, $CHCl_3$).

4.7. (1*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo-[2.2.1]heptan-2-one (−)-3

Compound **3** was prepared according to the procedure described for (+)-**3**, starting from (+)-**2** (25 mg, 0.12 mmol): (−)-**3** (25 mg, 100%) as a colorless oil. $[\alpha]_D = -71$ (*c* 1.25, $CHCl_3$); lit.[6b] −73 (*c* 1.0, $CHCl_3$).

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