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Expeditious Formal Synthesis of (±)-Epibatidine Using Diastereoselective Bromohydroxylation of Aminocyclohexene Derivatives

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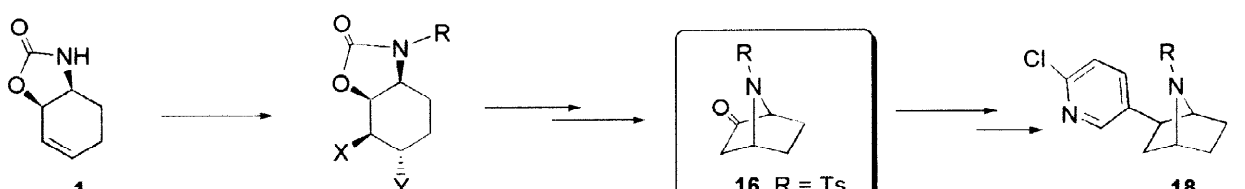
Abstract : Bromination and bromohydroxylation of oxazolidinones derived from cyclohexadiene have been studied in order to synthetize (±)-epibatidine **18**. Bromohydroxylation of compound **2** led to a polyfunctionalized halohydrin **11a** which could be further cyclized to azabicyclo[2.2.1]heptan-2-one **16** already described as a precursor of epibatidine **18**.

The increasing interest in the antinociceptive properties of epibatidine **18**, a frog skin alkaloid, has stimulated several racemic and asymmetric syntheses.[1] We have concentrated our efforts on the synthesis of a key intermediate suitable for the construction of the azabicyclo ring system of epibatidine. In designing a new approach we kept in mind the interest of a possible extension to the optically active series. Here we report an alternative synthesis of *N*-protected-7-aza-bicyclo[2.2.1]heptane-2-one **16**,[2] a key intermediate for the synthesis of epibatidine, *via* intramolecular cyclization of 1-amino-2,4-dihydro cyclohexane **11a** (Scheme 1). We first studied the reactivity of the double bond of the readily available oxazolidinone **1**[3] towards bromination and bromohydroxylation in order to obtain tetrafunctionalized cyclohexanes **5**, **6**, **11a** and **12a** which would hopefully lead to the target molecule.



Scheme 1

Oxazolidinone **1** was easily synthesized from cyclohexadiene following the literature[4] in 4 steps and 30% overall yield and was converted into tosyl derivative **2** (97% yield) and benzyl derivative **3** (65% yield). Compounds **1**, **2** and **3** were then treated with bromine (Scheme 2).[5] The choice of a removable bromine atom seemed appropriate for subsequent formation of the bicyclic system.

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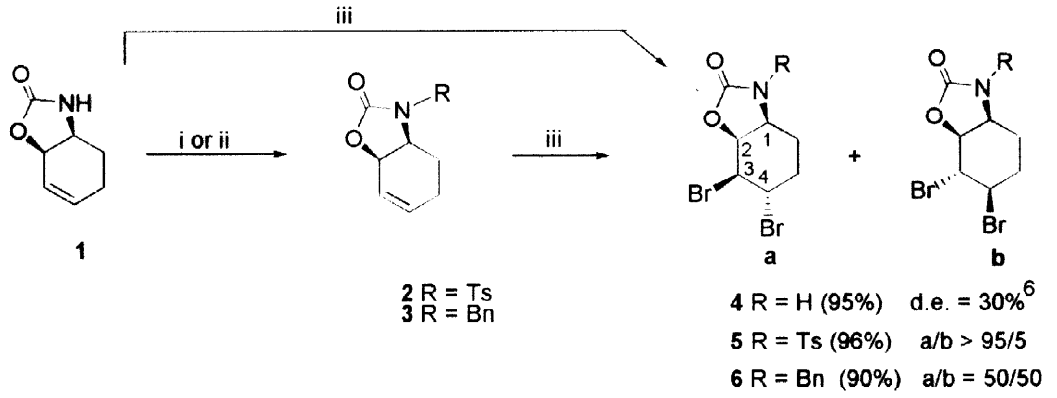
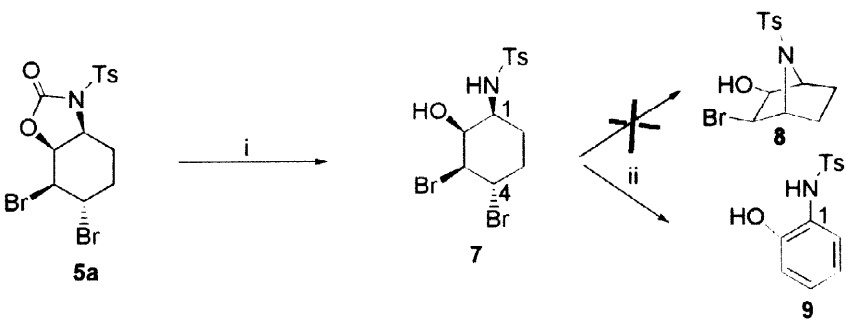


Reagents : (i) NaH, TsCl, 1h, 97% ; (ii) NaH, THF, BnBr, 80°C, 12h, 65% ; (iii) Br_2, CH_2Cl_2, rt

Scheme 2

This reaction proved to be highly diastereoselective for *N*-tosyl derivative **2** since only one addition product **5a** was isolated in 96% yield (^{1}H NMR : $J_{2,3}$ = 3.5 Hz ; $J_{3,4}$ = 10.0 Hz).[7] We can assume that electrophilic attack occurred *syn* to the oxazolidinone group[8] followed by a nucleophilic attack at carbon C-4 for steric hindrance reasons. Compound **5a** was hydrolyzed into alcohol 7 having the required *trans* relationship for cyclization (Scheme 3). Despite numerous attempts, treatment of 7 with a variety of basic conditions[5] did not lead to bicyclic compound **8** ; only the elimination product *o*-aminophenol **9** was observed. Protection of the hydroxyl function of 7 by a thexyldimethylsilyl group[9] did not circumvent this difficulty.



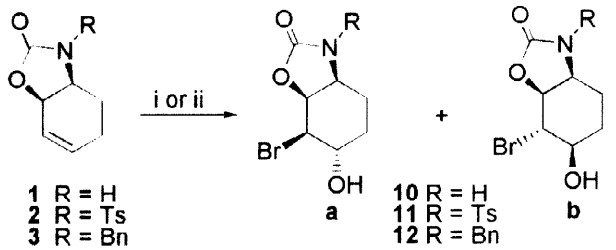
Reagents : i) LiOH, MeOH, 95% ii) NaH, THF, rt or t-BuOK, THF, -78°C or KOH, MeOH, rt to 80°C

Scheme 3

These results prompted us to the study of bromohydroxylation of **1**, **2** and **3** (Scheme 4). Some halohydroxylations have been reported in the literature as a highly regio- and diastereoselective reaction depending on the substituents.[10,11]

Two different conditions were investigated : i) NBS (2 equiv.) in DMSO/H_2O (1/1)[12,13] and ii) Br_2 (2 equiv.) in DME/H_2O (2/1). Under either conditions, and for each compound, a good regioselectivity was observed for the addition reaction, *via* a *trans* addition with hydroxyl ion adding at carbon C-4. However, the diastereoselectivity of the reaction depended on the R substituent and the experimental conditions. Using NBS as bromination agent, it appeared that the bromonium ion was formed predominantly *anti* to the oxazolidinone function, probably under steric control.[8]

Diastereomers **10b** (^{1}H NMR : $J_{2,3}$ = 8.1Hz and $J_{3,4}$ = 10.1Hz) and **12b** were isolated as the major products. The reaction of Br_2 in DME/H_2O with tosyl oxazolidinone **2** proceeds by the same mechanism as for the dibromination, *i.e.* a *syn* electrophilic attack of bromonium ion and hydroxyl addition at carbon C-4 to give compound **11a** (^{1}H NMR : $J_{2,3}$ = 3.7Hz and $J_{3,4}$ = 10.0Hz)[14] as the major product. Surprisingly, reverse diastereoselectivity was observed in these conditions for oxazolidinone **1**, which gave compound **10b** as the major product.



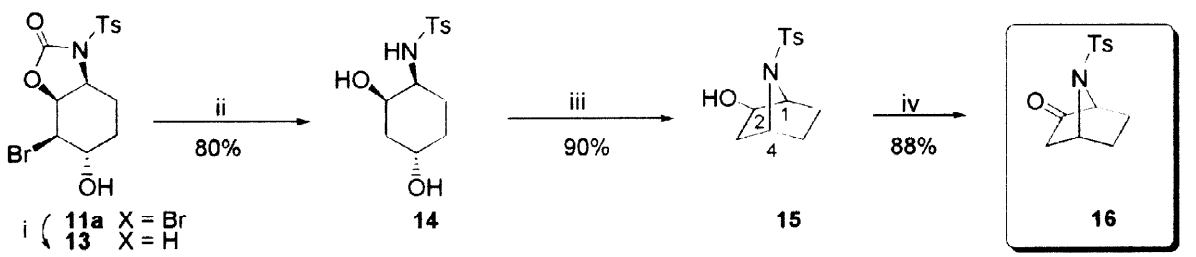
St. material	Conditions	Product (Y %)	a/b
1	i	10 (50%)	<5/95
2	i	11 (0%)	=
3	i	12 (72%)	20/80
1	ii	10 (70%)	35/65
2	ii	11 (75%)	80/20

Reagents : (i) NBS (2 equiv.) DMSO/H_2O (1/1), rt ; (ii) Br_2 (2 equiv.) DME/H_2O, rt

Scheme 4

Better results for cyclization were expected with bromhydrin **11a**, obtained in 60% yield, since bromine in this case could be selectively removed before cyclization.

The diol **14** was isolated in 80% yield after radical reductive removal of bromine[15] from **11a**, followed by hydrolysis of the oxazolidinone function (Scheme 5). Cyclization under Mitsunobu's conditions[16] gave the bicyclic compound **15** in 90% yield. Oxidation of the hydroxyl function of compound **15** following the Swern procedure[17] afforded the ketone **16**[2] in 88% yield. Intermediate **16**, whose spectral data are in full agreement with those reported,[18] has been previously converted to epibatidine.



Reagents : (i) AIBN, Bu_3SnH, 70°C ; (ii) LiOH, MeOH, rt ; (iii) PPh_3, DEAD, THF, rt ; (iv) $(COCl)_2$, DMSO, Et_3N

Scheme 5

In conclusion we have prepared the azabicyclo[2.2.1]heptane-2-one **16** in 5 steps and 37% overall yield starting from oxazolidinone **1**.

These results compare favorably with previous approaches and it is also expected that this strategy could be adapted for optically active syntheses.

References and notes

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6. Compounds **4a** et **4b** showing some instability, and could not be isolated separately by chromatography on silica gel. The product ratio was determined as 65/35 by NMR analysis but the major product could not be identified.
7. Compound **5a** : ^{1}H NMR δ(ppm) : 7.9 (2H, d, J = 8.0 Hz) ; 7.3 (2H, d, J = 8.0 Hz) ; 4.8 (1H, dd, J = 3.3 Hz, J = 6.0 Hz) ; 4.6 (1H, td, Jt = 6.0, Jd = 8.0) ; 4.25 (1H, dd, J = 3.5, J = 10.0) ; 3.45 (1H, dd, J = 4.4, J = 10.0) ; 2.55 (3H, s) ; 2.2-1.4 (4H, m). IR (cm^{-1}) : 1785 (ν CO) ; 1363 ; 1162 (ν SO_2). MS : 456/454/452 (MH^+).
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14. Compound **11a** : ^{1}H NMR δ(ppm) : 7.95 (2H, d, J = 8.3) ; 7.45 (2H, d, J = 8.3) ; 5.6 (1H, d , J = 5.5) ; 5.15 (1H, dd, J = 3.7, J = 5.8) ; 4.75 (1H, td, Jt = 5.9, Jd = 6.0) ; 4.35 (1H, dd, J = 3.7, J = 10.0) ; 3.7 (1H, ddt, Jd = 5.3, Jd = 5.0, Jt = 10.1) ; 2.5 (3H, s) ; 2.4-2.3 (1H, m) ; 1.9 (1H, m) ; 1.60-1.45 (1H ; m) ; 1.45-1.30 (1H, m). IR (cm^{-1}) : 3300 (ν OH) ; 1785 (ν CO) ; 1370 ; 1173 (ν SO_2). MS : 395/390 (MH^+) ; 238/236.
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18. Compound **16** : ^{1}H NMR δ(ppm) : 7.8 (2H, d, J = 8.0) ; 7.3 (2H, d, J = 8.0) ; 4.25 (1H, t, J = 4.3) ; 4.0 (1H, d, J = 4.1) ; 3.85 (1H, ddd, J = 2.5, J = 7.5, J = 10.1) ; 2.6 (1H, d, J = 10.4) ; 2.0-1.4 (6H, m). IR (cm^{-1}) : 3400 (ν OH) ; 1317 ; 1151 (ν SO_2). MS : 268 (MH^+) ; 157; 155.