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Enantioselective Approach to 7-Azabicyclo[2.2.1]heptane Ring Systems Using D-(-)-Quinic Acid as the Chiral Educt: Application to The Formal Synthesis of (+)-Epibatidine

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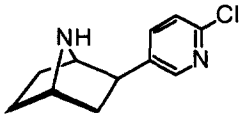
Abstract: By utilizing D-(-)-quinic acid as the chiral starting material the optically pure 7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1.]heptan-2-one **2**, an advanced intermediate already taken to (+)-epibatidine **1**, a non-opioid analgesic isolated from Ecuadorian poison frogs, was synthetized through a facile, regioselective intramolecular nucleophilic ring opening of a cyclic sulfate moiety.

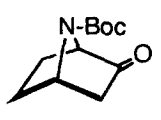
Epibatidine **1**, a simple alkaloid isolated in 1992 from the skin of the Ecuadorian poison frog *Epipedobates tricolor* [1] featuring a 7-azabicyclo[2.2.1]heptane ring system to which is attached in an *exo*-orientation a 5-(2-chloropyridinyl substituent, was reported to be a remarkable non-opiod analgesic and nicotinic acetylcholine receptor agonist.[2-4]

The unusual structure coupled with the intriguing pharmacological activity and scarcity in Nature have immediately sparked off intense synthetic interest with the publication of many different syntheses.[5-21]

Previous constructions of the 7-azabicyclo[2.2.1]heptane ring system[22] were based either on Diels-Alder reaction of N-protected pyrroles with activated dienophiles[5-8] or through intramolecular nucleophilic ring closure of aminocyclohexane derivatives.[9-18] More recently, two different approaches entailing the contraction of the tropinone skeleton via Favorskii rearrangement[19,20] and [3+2] cycloaddition of non-stabilized azomethyne ylide[21] respectively have been successfully disclosed.



1



2

Because the absolute configuration of the natural compound was not determined until 1994,[11] on three

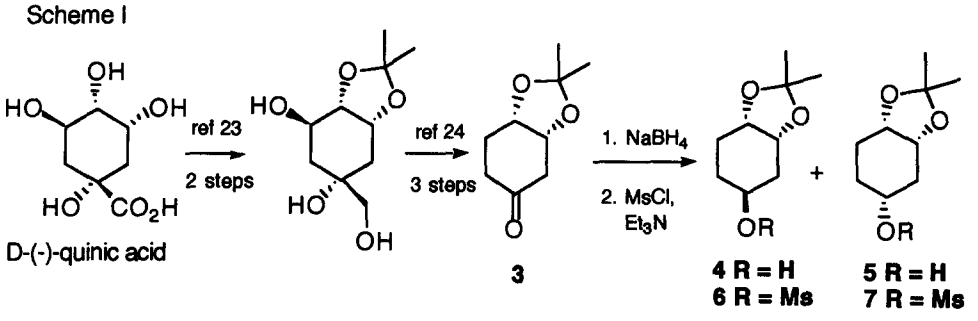
occasions the preparation of both enantiomers of epibatidine has been described, none of them being enantioselective. Thus, Huang and Shen[5] resolved (±)-epibatine via its *p*-toluoyl tartaric acid salts, while Corey et al.[12] described a stereocontrolled route to (+)- and (-)-epibatidine through HPLC separation of N-(trifluoroacetyl)epibatidines using chiral columns. Fletcher et al.[10,11] were able to establish the absolute configuration of **1** as 1R,2R,4S, separing the diastereoisomeric esters obtained by reaction between (R)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride and the secondary *exo*-alcohol corresponding to the ketone **3** subsequently utilized for the introduction of the requisite 3-pyridyl function.

The first asymmetric synthesis of (-)-epibatidine was recently disclosed by Trost and Cook[18] through a Pd catalyzed desymmetrization of *cis*-3,6-dibenzoyloxy-2-cyclohexene with trimethylsilylazide.

Herein we describe the preliminary results of our own efforts in the field, leading to the enantioselective synthesis of the advanced intermediate **2** already taken to the same target.

We embarked upon the optically active synthesis of **2** selecting the enantiopure cyclohexanone **3** as the convenient starting material, being easily available on a large scale in five steps[23,24] from D-(-)-quinic acid, an inexpensive plant metabolite. (Scheme I).

Scheme I



It was envisaged to construct the desired ring system through internal displacement, as in Fraser's efficient synthesis of 7-azabicyclo[2.2.1]heptane itself from *trans*-4-*p*-toluensulfonyloxycyclohexylamine.[25] Therefore, the synthetic problem was limited to the elaboration of the keto group of **3** into a required *trans*-amino substituent, the electrophilic counterpart being easily created simply converting the deprotected vicinal hydroxyl groups of **3** into the corresponding cyclic sulfate moiety.

We were confident that the nucleophilic opening of the vicinal diol cyclic sulfate moiety could proceed with complete selectivity for attack at C-4 versus C-3, its electrophilic reactivity assuring a fast and clean internal displacement under milder conditions than those required by other leaving groups previously utilized in similar schemes.

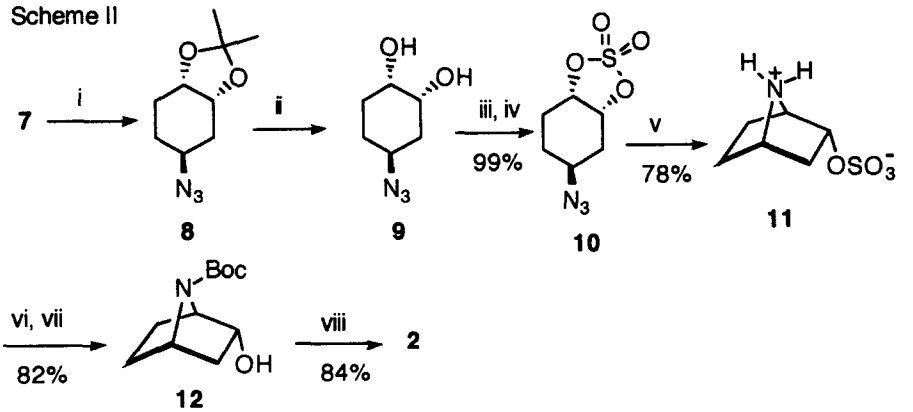
Thus, hydride reduction of the keto group in **3** with $NaBH_4$ furnished an unseparable 1:11 mixture of cyclohexanols **4** and **5**, which could be separed by chromatography as the corresponding methansulfonyl derivatives **6** and **7**.* Attempts to differentiate unequivocally between these isomers by chemical and spectroscopic means were unsuccessful; however, this was achieved indirectly in the sequel.

The predominant diastereomer **7** was submitted to azide displacement to produce a 77% yield of **8**, the acetonide of which was then hydrolyzed with aqueous acid to give **9** as a white solid, mp 51°C, $[\alpha]_D^{25}$ +17.5 (c, 1.12, $CHCl_3$). The transformation of the diol moiety of **9** into the corresponding cyclic sulfate was easily

accomplished through the standard two-step methodology introduced by Sharpless and Gao[26] allowing to obtain **10** as an oil, in practically quantitative yield, $[\alpha]_D^{25}$ +49.7 (c, 1.25, $CHCl_3$).

When **10** was submitted to hydrogenation over 10% palladium on carbon in THF : H_2O in order to convert the azido group into the corresponding amino group, a concomitant internal displacement took place spontaneously forming the inner salt **11**. Removal of the catalyst by filtration and elimination of the solvents and crystallization (dioxane : H_2O) gave a 78% yield of **11** as white solid, mp.> 300°C, $[\alpha]_D^{25}$ +25.8, (c, 1.07, H_2O).

Scheme II



Reagents: i, NaN_3, DMF; ii, 5% HCl; iii, $SOCl_2$, Et_3N, CH_2Cl_2, 10min, 0°C; iv, $NaIO_4$, $RuCl_3$ (cat.), CCl_4, MeCN, H_2O, 1h, 20°C; ; v, H_2, Pd/C, THF/H_2O,30psi, 2h; vi, conc. H_2SO_4 (cat.), H_2O (1equiv.), THF, 1h, 90°C, then Na_2CO_3; vii, $(Boc)_2O$, CH_2Cl_2, 1h, 25°C; viii, $(COCl)_2$, DMSO, Et_3N, -70°C to 25°C, 30min.

Hydrolysis of the sulfate group was effected by heating a THF solution of **11** at 90°C for 1 h using a catalytic amount of concentrated sulfuric acid in the presence of 1 equivalent of H_2O. Solid sodium carbonate was then added to the cooled mixture which was stirred for 30min, filtered and concentrated in vacuo. The crude residue was dissolved in CH_2Cl_2 and directly converted to **12** (mp 70-71°C, $[\alpha]_D^{25}$ -3.8 (c, 0.79, $CHCl_3$) by treatment with di tertbutyldicarbonte. Its subsequent Swern oxidation gave rise to the formation of **2** as a white solid, mp 41-42°C, $[\alpha]_D^{25}$ -78, c, 1.18, $CHCl_3$), [lit[27] $[\alpha]_D^{20}$ -75.5, c, 1, $CHCl_3$], already taken to (+)-epibatidine by Fletcher et al.[10,11]

The chemistry described here establishes that D-(-)-quinic acid, already widely utilized as the chiral educt for the synthesis of a variety of cyclohexane and cyclopentane derivatives as well as of linear homochiral natural products, can serve as suitable precursor to optically pure 7-aza-bicyclo[2.2.1]heptane ring system derivatives. The intermediate **2** serves as a platform for introducing the requisite 3-pyridyl function found in epibatidine, as well as for preparing analogues.

Moreover, our findings underline once more the versatility of vicinal diol cyclic sulfates as reactive synthetic intermediates in organic synthesis and further applications of this strategy are underway in our laboratories.

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* Satisfactory spectral and analytical data were obtained for all new compounds. Selected ^{1}H NMR data (200 MHz): **6** ($CDCl_3$): δ 1.33 (s, 3H, CH_3C-), 1.48 (s, 3H, CH_3C-), 1.7-2.3 (m, 6H, 3-CH_2-), 3.01 (s, 3H, CH_3S-), 4.2 (m, 1H, -CHOC-), 4.3 (m, 1H, -CHOC-), 5.0 (m, 1H, -CHOS-); **7**, ($CDCl_3$): δ 1.47 (s, 3H, CH_3C-), 1.65 (s, 3H, CH_3C-), 1.8-2.1 (m, 4H, 2-CH_2-), 2.2-2.5 (m, 2H, -CH_2-), 3.16 (s, 3H, CH_3S-), 4.2-4.4 (m, 2H, 2-CHOC-), 4.8 (m, 1H, -CHOS-); **8**, ($CDCl_3$): δ 1.34 (s, 3H, CH_3C-), 1.49 (s, 3H, CH_3C-), 1.7-2.3 (m, 6H, 3-CH_2-), 3.76 (m, 1H, -CHN_3), 4.13 (m, 1H, CHOC-), 4.13 (m, 1H, -CHOC-), 4.26 (m, 1H, -CHOC-); **10**, ($CDCl_3$): δ 1.7 (m, 1H, -CH_2-), 1.9-2.1 (m, 1H, -CH_2-), 2.1-2.5 (m, 4H, 2CH_2-), 4.0 (m, 1H, -CHN_3), 5.07 (m, 2H, 2-CHOS-); ^{13}C NMR ($CDCl_3$): 22.91, 24.10; 31.25; 55.07; 80.65; 80.89; **11**, ^{13}C NMR (D_2O): 21.80, 29.07; 36.92; 61.97; 62.99; 76.39.

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