EPC-SYNTHESIS OF (*S*)-3-HYDROXY-3-MERCAPTOMETHYL-QUINUCLIDINE, A CHIRAL BUILDING BLOCK FOR THE SYNTHESIS OF THE MUSCARINIC AGONIST AF 102B

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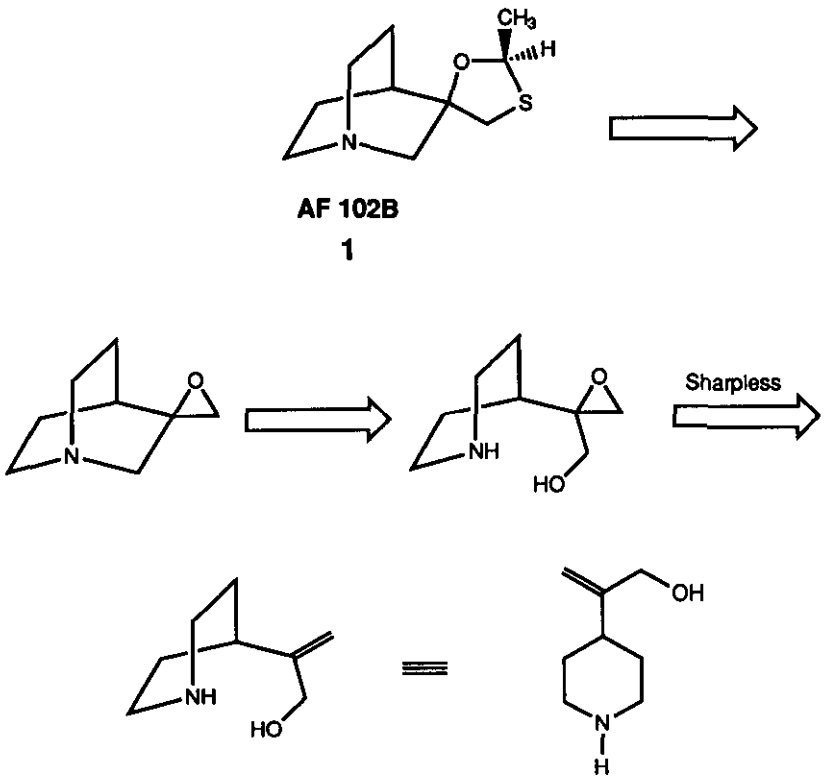
Abstract-The catalytic modification of the *Sharpless*-epoxidation reaction was employed in a short EPC-synthesis of the title compound. The asymmetric epoxidation of the allylic alcohol (**6**) proceeded in 75 % yield and 94 % enantiomeric excess. In a 4 step sequence the epoxide (**7**) was transformed to (*S*)-3-hydroxy-3-mercaptomethylquinuclidine (**11**).

Introduction

Selective muscarinic M1-type agonists, which are able to cross the blood-brain barrier, could have a therapeutic potential for the treatment of Alzheimer's disease.[1] The spiroquinuclidine AF 102B (**1**)[2] represents such an agonist and is therefore the subject of a great number of preclinical and clinical studies in this field.

Although the active enantiomer, the levorotatory isomer, has been isolated *via* the resolution of racemic **1**[3] an independent synthesis of the enantiomerically pure compound (EPC-synthesis)[4] has not been published. This report describes the EPC-synthesis of (*S*)-3-hydroxy-3-mercaptomethyl-quinuclidine (**11**), which by treatment with acetaldehyde was transformed into enantiomerically pure **1**[3] and the diastereoisomeric acetal AF 102A.

The presence of three contiguous heterosubstituted carbon atoms in **1** suggests the use of a *Sharpless*-epoxidation transform in the retrosynthetic analysis as outlined in Scheme 1. This approach allows for the synthesis of either enantiomer, since both the (*R,R*)- and (*S,S*)-tartrate esters are equally readily available, but more importantly the absolute configuration of the products is predictable. [5]



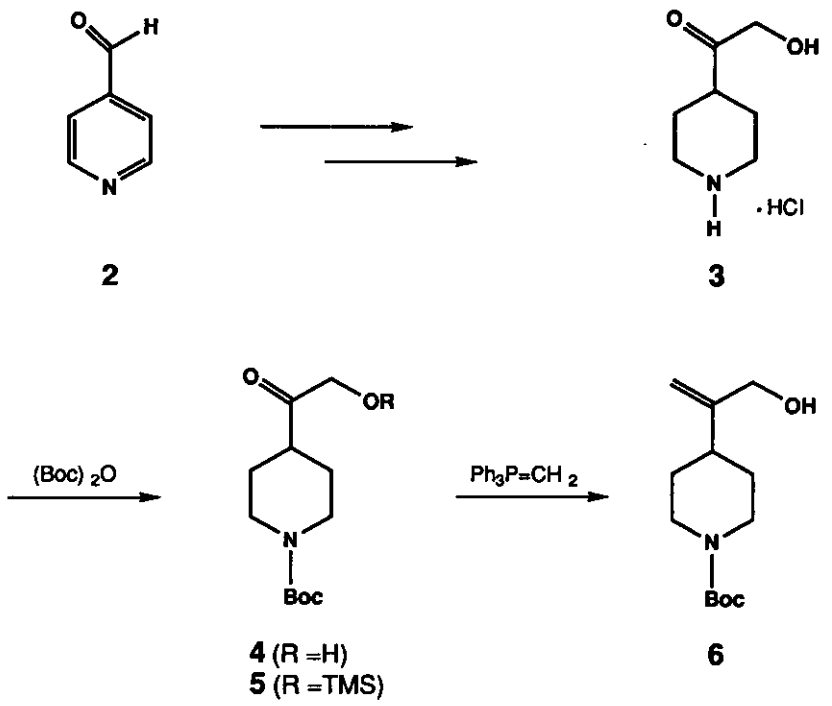
AF 102B

1

Scheme 1

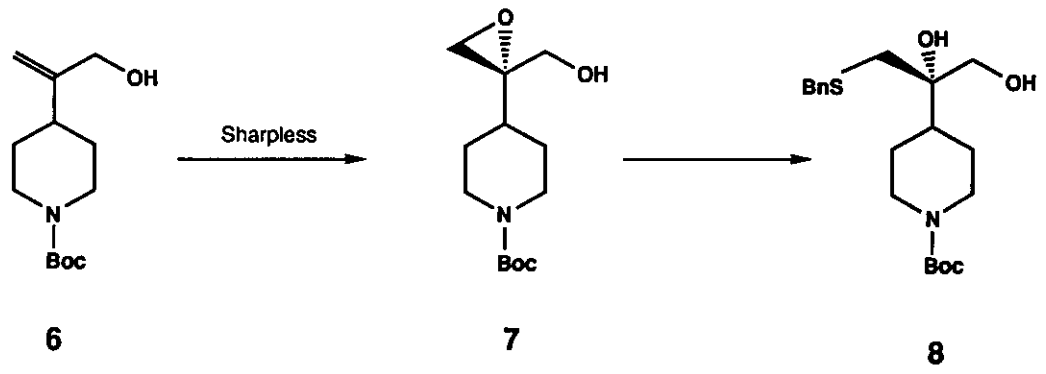
Synthetic procedure

The substrate for the *Sharpless* epoxidation, the *N*-protected allylic alcohol (**6**), was prepared in a short and efficient sequence starting from the inexpensive pyridine-4-carboxaldehyde (**2**) *via* the known 4-hydroxyacetylpiperidine hydrochloride (**3**).[6] The *N*-Boc derivative (**4**) was transformed to the allylic alcohol (**6**) by *Wittig* olefination on the silylated alcohol (**5**) (Scheme 2).



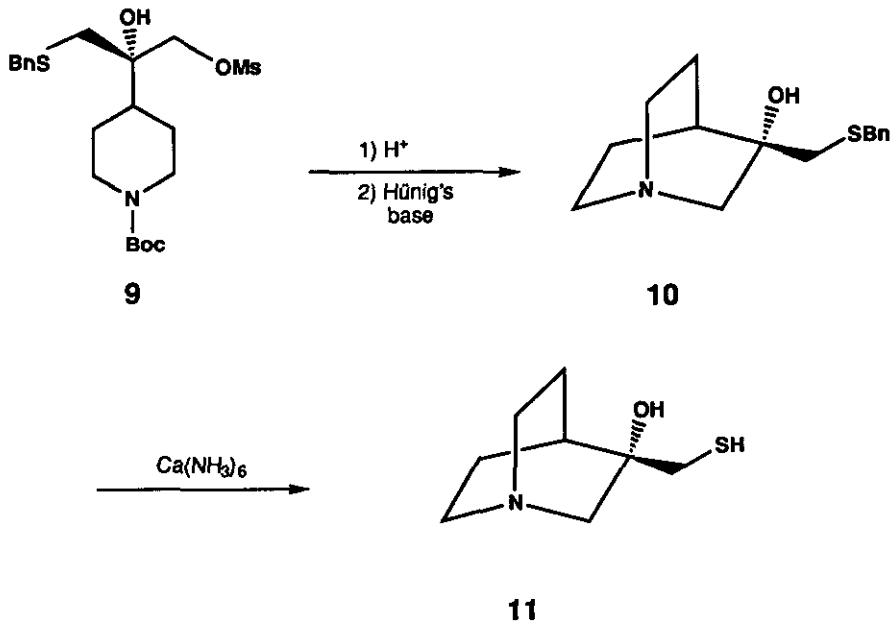
Scheme 2

The asymmetric epoxidation [7] of the allylic alcohol (**6**) yielded the chiral epoxide (**7**) (Scheme 3) in 75% chemical yield (94% ee by nmr and gc). Based upon the enantiofacial selection rule, elaborated by *Sharpless* ,[5] the L-tartrate directs the epoxidation to the bottom face of the olefin and provides the (S)-epoxide.[8]



Scheme 3

Nucleophilic ring opening with benzylmercaptan led to the sulfide (**8**), which was subsequently treated with methanesulfonyl chloride furnishing **9** (Scheme 3), the precursor to the bridged heterocycle. Conversion of **9** to the chiral quinuclidine (**10**) was accomplished with trifluoroacetic acid followed by Hünig's base [9] in acetonitrile. Finally the benzyl group was removed with $Ca(NH_3)_6$ [10] providing the free thiol (**11**) (*Scheme* 4).[11]



9 **10** **11**

Scheme 4

In summary the enantiomerically pure heterocycle (**11**) is accessible from the epoxide (**7**) in 4 steps. This exemplifies once more the wide applicability of the catalytic *Sharpless* epoxidation reaction in the field of EPC-synthesis.[5]

EXPERIMENTAL

General All laboratory glassware was flame-dried under vacuum and purged with dry Ar. THF was distilled from sodium benzophenone ketyl and was then transferred *via* a syringe. Column chromatography was carried out by using silica gel (230-400 mesh; *Merck*) and 0.3-1.0 bar pressure. Spectra were recorded with the following instruments. Ir (cm^{-1}): Digilab FTS-15E. ^{1}H-Nmr(δ values in ppm relative to internal TMS, *coupling constants J in Hz*): Varian XL-200 and Varian XL-400.MS: VG-7070HF.

4-(2-Hydroxy-1-oxoethyl)-1-piperidinecarboxylic acid (1,1-dimethylethyl) ester (4)

A solution of 4-hydroxyacetylpiperidine hydrochloride (**3**) (1.8 g, 10 mmol)[6] in 10 ml of water was cooled to 0 °C and a solution of Boc-anhydride (2.4 g, 11 mmol) in 5 ml of dioxane was added followed by 10% aqueous sodium hydroxide (5 ml). The mixture was stirred for 2 h and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil (2.35 g, 97 %) of **4**. Ir ($CHCl_3$): 3490, 1712, 1685. ^{1}H-Nmr ($CDCl_3$): 4.33 (d,J=4.7,2H); 4.13 (m,2H); 3.10 (t,J=4.7,1H); 2.79 (m,2H); 2.53 (m,1H); 1.80 (m,2H); 1.60 (m,2H); 1.45 (s,9H). HRms(M$^+$) calcd for $C_{12}H_{21}NO_4$ 243.1470. Found 243.1480.

4-[(2-Hydroxy-1-methylene)ethyl]-1-piperidinecarboxylic acid (1,1-dimethylethyl) ester (6)

A solution of **4** (3.26 g, 13.4 mmol) in 15 ml of hexamethyldisilazane was heated at 100 °C for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in 20 ml of THF and added to a solution of methyltriphenylphosphonium bromide (5.4 g, 15 mmol) and n-BuLi (15 mmol) in 18 ml of THF/hexane (2:1) at 0 °C.The reaction mixture was stirred for 2 h at room temperature, quenched with 10 ml H_2O and 5 ml 2N HCl and extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo.* The residue was subjected to column chromatography with ethyl acetate/hexane (2:3) to give 1.97 g (61 %) **6** as a colourless oil. Ir ($CHCl_3$): 3432, 2934, 1694, 1672. ^{1}H-Nmr ($CDCl_3$): 5.07 (s,1H); 4.89 (s,1H); 4.13 (m,2H); 4.08 (s,2H); 2.70 (m,2H); 2.04 (m,1H);1.70 (m,2H); 1.50-1.30 (m,3H); 1.46 (s,9H). Ms: 185 (M-C_4H_8), 168 (M-C_4H_9O).

4-[(S)-2-Hydroxymethyl-2-oxiranyl]-1-piperidinecarboxylic acid (1,1-dimethylethyl) ester (7)

A mixture of 300 mg of 4 Å powdered, activated molecular sieves and 20 ml of dry CH_2Cl_2 was cooled to 0 °C. L-(+)-Diethyl tartrate (100 mg, 0.48 mmol) and titanium tetraisopropoxide (0.09 ml, 0.3 mmol) were added and the reaction mixture was cooled to -20 °C. A solution of *tert*-butyl hydroperoxide (4.1 ml, 12.3 mmol, 3M in isooctane) was added *via* a syringe at a moderate rate. The resulting mixture was stirred at -20 °C for 1 h. The allyl alcohol (**6**) (1.5 g, 6.2 mmol), dissolved in 5 ml of dry CH_2Cl_2, was then added dropwise while the temperature was maintained between -20 and -15 °C. The mixture was stirred over night at -20 °C. After the reaction mixture was warmed to 0 °C, the catalyst was quenched with 20 ml of water and the mixture was stirred for 1 h, while it was allowed to warm to room temperature. Hydrolysis of the tartrate was effected by adding 5 ml of a 30 % aqueous solution of NaOH saturated with NaCl and stirring vigorously. After 20 min the organic phase was separated and the suspension was extracted twice with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo.* The resulting yellow liquid was subjected to column chromatography with ethyl acetate/hexane (3:2) to give 1.2 g (75 %) of the epoxide (**7**) as a colourless oil. Ir ($CHCl_3$): 3600, 3030, 1682. ^{1}H-Nmr ($CDCl_3$): 4.17 (m,2H); 3.83 (dd,J=12.3,J=4.5,1H); 3.66 (dd,J=12.3,J=8.3,1H); 2.85 (d,J=4.5,1H); 2.70 (d,J=4.5,1H); 2.64 (m,2H);

1.85 (dd,J=8.3,J-4.5,1H); 1.80-1.60 (m,3H); 1.45 (s,9H); 1.37-1.17 (m,2H). HRms(M+) calcd for $C_{13}H_{23}NO_4$ 257.1627. Found 257.1613. $[\alpha]_D^{25}$= -8.96° (c=0.89, $CHCl_3$).

Mosher-Ester preparation and enantiomeric excess determination

A mixture of 18 mg (0.15 mmol) of 4-dimethylaminopyridine and 100 µl of triethylamine in 0.5 ml of CH_2Cl_2 was treated with 38.5 mg (1.5 mmol) of the epoxide (**7**). Immediately, 30 µl of neat (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was added. After completion, the reaction was quenched by addition of 40 µl of 3-dimethylaminopropylamine and concentrated to dryness. The residue was passed through a short plug of silica gel. Capillary GC (fused silica capillary column OV-101) and ^{1}H-nmr-analysis (in C_6D_6) indicated an ee of 94%.

4-[(S)-2-Benzylthio-1-hydroxy-1-hydroxymethylethyl]-1-piperidinecarboxylic acid (1,1-dimethylethyl) ester (8)

The epoxide (**7**) (950 mg, 3.7 mmol) was dissolved in ethanolic KOH (1.4 g in 15 ml of 80 % ethanol). Benzylmercaptane (470 mg, 3.8 mmol) was added and the solution was stirred at room temperature for 4 h. Ethanol was removed and the residue was extracted with water and ether. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography with *t*-butyl methyl ether/hexane (9:1) to give 1.25 g (88 %) of the sulfide **8** as white crystals. Recrystallization from ether. mp 89-90 °C. Ir ($CHCl_3$): 3575, 3030, 1679. ^{1}H-Nmr ($CDCl_3$): 7.28 (m,5H); 4.09 (m,2H); 3.67 (s, 2H); 3.48, 3.47 (AB,J=10,2H); 2.64 (s,2H); 2.55 (m,2H); 1.72-1.50 (m,3H); 1.41 (s,9H); 1.28-1.08 (m,2H). HRms (M^+) calcd for $C_{20}H_{31}NO_4S$ 381.1974. Found 381.1956. $[\alpha]_D^{25}$= +14.8° (c=0.15, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}NO_4S$ C 63.01, H 8.19, N 3.67. Found C 63.01, H 8.14, N 3.65.

4-[(S)-2-Benzylthio)-1-hydroxy-1-[[(methanesulfonyl)oxy]methyl]ethyl]-1-piperidinecarboxylic acid (1,1-dimethylethyl) ester (9)

A solution of the sulfide (**8**) (550 mg, 1.4 mmol) in 10 ml of dry CH_2Cl_2 and 0.5 ml of triethylamine was cooled to 0 °C and methanesulfonyl chloride (220 mg, 0.15 ml, 1.9 mmol) was added. The mixture was stirred at 0 °C for 1 h and extracted with water and dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography with ethyl acetate/hexane (6:4) to give 660 mg (99 %) of the mesylate (**9**) as colourless oil. Ir ($CHCl_3$): 3500, 3030, 1680. ^{1}H-Nmr ($CDCl_3$): 7.25 (m,5H); 4.20-4.02 (m,2H); 4.12 (s,2H); 3.72 (s,2H); 2.65 (s,2H); 2.65-2.49 (m,3H); 2.97 (s,3H); 1.75-1.55 (m,3H); 1.41 (s,9H); 1.35-1.15 (m,2H). HRms (M^++H) calcd for $C_{21}H_{33}NO_6S_2$ 460.1828. Found 460.1839. $[\alpha]_D^{25}$= +10.5° (c=0.2, $CHCl_3$).

(S)-3-Hydroxy-3-benzylthiomethylquinuclidine (10)

A solution of the mesylate (**9**) (4.78 g, 10.4 mmol) in 52 ml of CH_2Cl_2 and 4 ml of trifluoroacetic acid was stirred at room temperature for 17 h. After the removal of the solvent the residue was dissolved in of acetonitrile. The solution was added to a mixture of 18 ml of ethyldiisopropylamine and 104 ml of acetonitrile over a period of 1 h. The reaction mixture was then stirred for 120 h at room temperature and the solvent was removed. The residue was extracted with aqueous NaOH (5%) and *t*-butyl methyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was subjected to column chromatography on neutral alumina with ethyl acetate/methanol (9:1) to give colorless crystals of **10** (800 mg, 30%).^{1}H-Nmr ($CDCl_3$): 7.33-7.26 (m,5H); 3.76 (s,2H); 2.88, 2.61 (AB,J=13,2H); 2.95-2.52 (m,6H); 2.04 (m,1H); 1.82 (m,1H); 1.55-1.28 (m,3H). Ms (FAB): 264 (M^+) Ms (EI): 246 (M-OH), 205 ([M-OH]-C_3H_5), 140 (M-SC_7H_7).$[\alpha]_D^{25}$=+44° (c=0.25,$CHCl_3$).

(S)-3-Hydroxy-3-mercaptomethylquinuclidine (11)

Calcium (55 mg, 1.37 mmol) was dissolved in 4 ml of ammonia. A suspension of **10** (26 mg, 0.1 mmol) in 5 ml of ether was added dropwise. The reaction mixture was stirred for 5 h at room temperature and quenched with 10 ml of water. The pH was adjusted to 8 with conc. HCl and the mixture was extracted with ethyl acetate. The aqueous layer was subsequently extracted with chloroform. The chloroform layers were dried over sodium sulfate and evaporated to give a bright yellow solid of **11** (8 mg, 46%). ^{1}H-Nmr ($CDCl_3$): 2.88, 2,68 (AB,J=20,2H); 2.80 (m, 4H); 2.08 (m,1H);1.96 (m,1H);1.58 (m,2H); 1.40 (m,1H).

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8. A proof of the absolute stereochemistry was not pursued. The assignment is therefore tentative. The consistency of the stereochemical outcome of the *Sharpless* epoxidation, however, has, to date, never been violated (cf. ref. 5).
9. A similar cyclization has been recently reported: D. L. Flynn, D. P. Becker, R. Nosal and D. L. Zabrowski, *Tetrahedron Lett.*, 1992, , **33**, 7283.
10. J. van Schooten, J. Knoterus, H. Boer and P. M. Duinker, *Rec. Trav. Chim.*, 1958, **77**, 935.
11. Due to the instability of **11**, the crude product was reacted immediately with acetaldehyde in the presence of boron trifluoride etherate to give a diastereomeric mixture (0.8:1) of AF102A and AF102B.

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