FACILE SYNTHESIS OF OPTICALLY ACTIVE SULFONATES OF 4-*tert*-BUTOXYCARBONYL-2-HYDROXYMETHYLMORPHOLINE†

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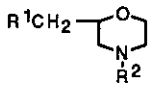
Abstract---Optically active sulfonates of 4-*tert*-butoxycarbonyl-2-hydroxymethylmorpholine were prepared from 1,2:5,6-di-*O*-D-mannitol by practical procedures. These compounds are versatile intermediates for optically active isomers of a number of neuropharmacologically or gastrokinetically active agents that have a 2-morpholinylmethyl group.

A number of compounds having a 2-morpholinylmethyl group have been reported to have neuropharmacological or gastrokinetic activities. The typical compounds are viloxazine (**1**),[1] indeloxazine (**2**),[2] teniloxazine (**3**),[3] S-11701 (**4**)[4] and AS-4370 (**5**).[5] As a part of our program of studies on cerebral-activating agents, we found that the coumarin (**6**)[6] and the dihydroquinoline (**7**)[7] had a potent antireserpine activity and suppressed the hyperviscosity of blood induced by cerebral ischemia.



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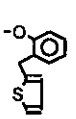
3 R^1=  , R^2=H

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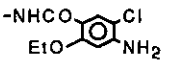
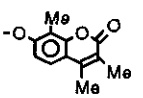
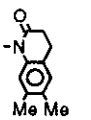
5 R^1=  , R^2=

6 R^1=  , R^2=H

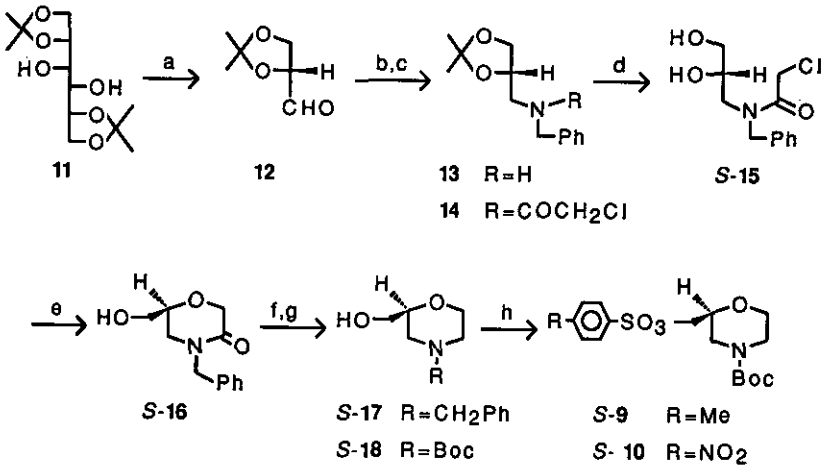
7 R^1=  , R^2=H

† Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

These compounds have an asymmetric carbon at the 2-position on the morpholine ring, and it is interesting to investigate pharmacological activities of their optical isomers, since one enantiomer often has more potent biological activity than another enantiomer. Actually the *S* isomer of **1** had at least ten times the neuropharmacological activity of the *R* isomer,[8] and the *levo*-rotatory isomer of **2** showed more antidepressive and cerebral-activating activities than the *dextro*-rotatory isomer.[2] These optical isomers were obtained by resolution of the racemates using diacylated D- and L-tartaric acids.[2,8]

In this paper we report a facile synthesis of the *R* and *S* isomers of 4-*tert*-butoxycarbonyl-2-*p*-toluene- or *p*-nitrobenzenesulfonyloxymethylmorpholines (**9**,**10**) from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11**). These sulfonates (**9**,**10**) are versatile intermediates for the synthesis of optical isomers of the 2-morpholinylmethyl derivatives.

Scheme I



(a) $NaIO_4$ (1.05 mol eq.) in H_2O, 5-10°C, 1 h, then addition of EtOH and removal of $NaIO_3$ by filtration; (b) $PhCH_2NH_2$ (1.1 mol eq.) in H_2O-EtOH, Raney Ni, H_2 atmosphere, 5-10°C, 8 h, then flash chromatography (MeOH-CH_2Cl_2 1:10) (quantitatively from **11**); (c) $ClCH_2COCl$ (1.1 mol eq.), Et_3N (1.5 mol eq.) in CH_2Cl_2, 5-10°C, 1 h, (86%); (d) 20% aqueous AcOH, 90°C, 1 h, (quantitative); (e) NaOEt (2 mol eq.) in EtOH, 20-25°C, 1 h (88%); (f) $LiAlH_4$ (1 mol eq.) in THF, 60°C, 4 h (quantitative); (g) 10% Pd-C in MeOH, H_2 atmosphere, 60°C, 8 h, then Boc_2O (1.2 mol eq.), Et_3N (1.2 mol eq.) in MeOH (79%); (h)*p*-Me-$C_6H_4SO_2Cl$ or *p*-O_2N-$C_6H_5SO_2Cl$ (1.1 mol eq.), Et_3N (1.5 mol eq.) in CH_2Cl_2, 20-25°C, 16 h (*S*-**9** 85%, *S*-**10** 94%).

I. Preparation of *S*-**9** and *S*-**10** (Scheme I)

Cleavage of **11** with sodium metaperiodate, followed by reductive amination of the aldehyde (**12**) with benzylamine in the presence of Raney nickel, gave the benzylamine (**13**) quantitatively. Acylation of **13** with chloroacetyl chloride gave the chloroacetamide (**14**) as a syrup in 86% yield. Removal of the isopropylidene group of **14** with 20% aqueous acetic acid gave the diol (*S*-**15**) which was then treated with sodium ethoxide to afford the lactam (*S*-**16**) as a syrup. Reduction of *S*-**16** with lithium aluminum hydride gave the *N*-benzylmorpholine (*S*-**17**). Reductive removal of the benzyl group of *S*-**17** with palladium on carbon and subsequent *tert*-butoxycarbonylation with di-*tert*-butyl dicarbonate (Boc_2O) gave the *N*-*tert*-butoxycarbonylmorpholine (*S*-**18**). Sulfonylation of *S*-**18** with *p*-toluenesulfonyl chloride or *p*-nitrobenzenesulfonyl chloride gave the crystalline sulfonates (*S*-**9**,*S*-**10**). Hplc analysis[11] of these products on a chiral column showed no contamination of the *R* isomers.

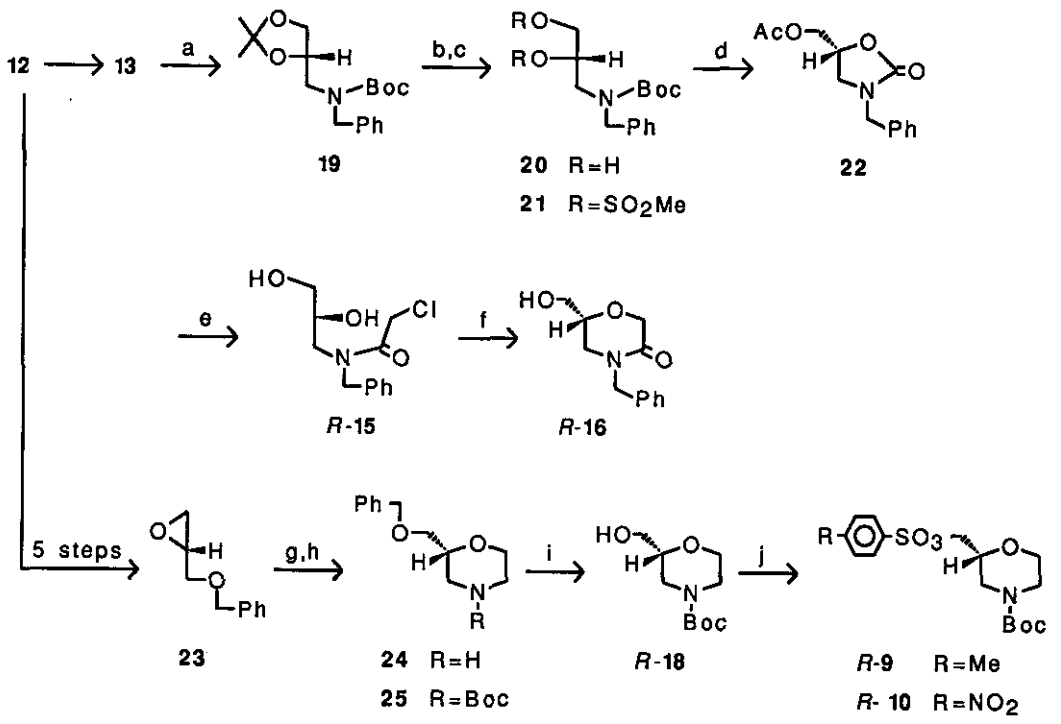
II. Preparation of *R*-**9** and *R*-**10** (Scheme II)

At first, in order to obtain the *R* enantiomer, we planned epimerization of the asymmetric carbon of **13**. Treatment of **13** with Boc_2O, followed by removal of the isopropylidene group and mesylation, afforded the dimesylate (**21**). Heating of **21** with potassium acetate in 2-butanone afforded the oxazolidone (**22**) in 90% yield. Acid hydrolysis of **22**, followed by acylation with chloroacetyl chloride, gave the diol (*R*-**15**) in 52% yield. Ring closure of *R*-**15** with sodium ethoxide gave the lactam (*R*-**16**). The optical rotations $[\alpha]_D$ of 1% solutions of *R*-**15** and *R*-**16** in dimethyl formamide (DMF) were +2.6° and +40.0°, respectively, while the optical rotations of *S*-**15** and *S*-**16**, prepared by the procedure illustrated in Scheme *I*, were -4.7° and -64.1°, respectively. These results mean that **15** and **16**, prepared from the oxazolidone (**22**), contain about 20% of the *S* isomers. The undesired contaminations of the *S* enantiomers would be caused by incomplete inversion on the asymmetric carbon of **21** with sodium acetate. Therefore, we decided to prepare the *R* enantiomer without utilizing inversion.

Treatment of the epoxide (**23**), which was prepared from **12** through 5 steps by the known procedure,[12] with aminoethyl hydrogen sulfate gave the morpholine (**24**). *N*-*tert*-Butoxycarbonylation of **24**, followed by reductive removal of the benzyl group, gave the crystalline morpholinylmethanol (*R*-**18**). Sulfonylations of *R*-**18** afforded the sulfonates (*R*-**9**,*R*-**10**). Hplc analysis[11] of these products showed that they contained about 5% of the *S* enantiomers. Although the *p*-nitrobenzenesulfonate (*R*-**10**) could not be completely separated from *S*-**10** by recrystallization, the pure tosylate (*R*-**9**) was easily obtained by recrystallization from ethanol.

In summary, the optically pure tosylates (*R*-**9**,*S*-**9**) and *p*-nitrobenzenesulfonate (*S*-**10**), which are versatile intermediates of optically active 2-morpholinylmethyl derivatives, were prepared from **11**, though the *p*-nitrobenzenesulfonate (*R*-**10**) could not be obtained in a pure form.

Scheme II



(a) Boc_2O (1.2 mol eq.), Et_3N (1.5 mol eq.) in CH_2Cl_2, room temperature, 4 h (78%); (b) 20% aq. AcOH, 70°C, 50 min (quantitative); (c) $MeSO_2Cl$ (2.8 mol eq.), pyridine (5.6 mol eq.) in CH_2Cl_2, 0°C, 1 h, then 20-25°C, 16 h (97%); (d) KOAc (8 mol eq.) in MeCOEt, reflux, 40 h (90%); (e) 6N HCl, reflux, 40 h, then $ClCH_2COCl$ (1.2 mol eq.), Et_3N (5 mol eq.), 20-25°C, 1 h (52%); (f) NaOEt (2 mol eq.) in EtOH, 20-25°C, 1 h (84%); (g) $H_2NCH_2CH_2OSO_3H$ (4 mol eq.), NaOH (4 mol eq.) in H_2O, 50°C, 1 h, then addition of NaOH (8 mol eq.) in H_2O, 55°C, 20 h (62%); (h) Boc_2O (1.05 mol eq.), Et_3N (1.05 mol eq.) in CH_2Cl_2, 20-25°C, 2 h (88%); (i) 5% Pd-C in EtOH, H_2 atmosphere, 70°C, 9 h (quantitative); (j) *p*-Me-$C_6H_4SO_2Cl$ or *p*-O_2N-$C_6H_4SO_2Cl$ (1.1 mol eq.), Et_3N (1.5 mol eq.) in CH_2Cl_2, 20-25°C, 16 h (*R*-**9** 82%, *R*-**10** 85%).

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9. mp 105-107°C (EtOH); ir (KBr) 1685 cm^{-1}; ^{1}H-nmr (270 MHz, $CDCl_3$) δ 1.46(9H, s), 2.45(3H, s), 2.60-2.74(1H, m), 2.82-2.97(1H, m), 3.46(1H, dd, J=12, 3 Hz), 3.55-3.67(1H, m), 3.75-3.95(3H, m), 4.03(2H, d, 5.5 Hz), 7.35(2H, d, J=8 Hz), 7.80(2H, d, J=8 Hz); $[\alpha]_D$ +22.8° (c 1, DMF).
10. mp 107°C (EtOH); ir (KBr) 1685, 1525 cm^{-1}; ^{1}H-nmr (270 MHz, $CDCl_3$) δ 1.45(9H, s), 2.60-2.76(1H, m), 2.80-2.94(1H, m), 3.43(1H, dd, J=12, 3 Hz), 3.57-3.67(1H, m), 3.73-3.93(3H, m), 4.15(2H, d, J=5.5 Hz), 8.13(2H, d, J=9 Hz), 8.41(2H, d, J=9 Hz); $[\alpha]_D$ +23.1° (c 1, DMF).
11. The chiral column, CHIRALCEL OJ (Daicel Chemical Industries, Ltd.) and the solvent system of isopropanol-hexane (1:1) were used for analysis of the sulfonates (**9**,**10**).
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