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Short Communication

Stereoselective Synthesis of (*S*)-Propranolol by the Cyclic Sulfite Route

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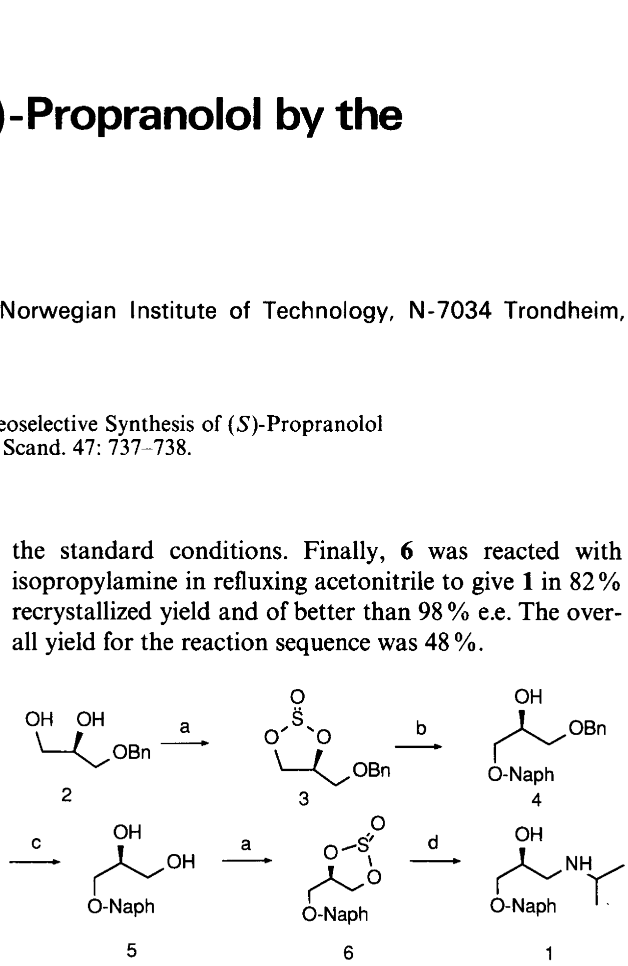
Chirality has become an important issue in pharmacological chemistry,[1] as it now has been established that, for chiral drug molecules, different enantiomers can differ considerably in their pharmacological effects. Thus, it has been shown that the β-adrenergic blocking activity for the 3-aryloxy-1-(alkylamino)-2-propanol-type drugs for the *S*-enantiomers usually has the higher binding affinity to the β receptor.

In this communication we report the synthesis of (*S*)-propranolol, (*S*)-3-isopropylamino-1-(1-naphthyloxy)-2-propanol, **1**, as a representative example utilizing the reactivity of cyclic sulfites we have reported recently.[2] Reports dealing with the same concept for 1,2-diols have only recently appeared in the literature.[3] The widely used β-blocker propranolol has long been used clinically as a racemate in the therapy of hypertensive patients. However, the *S*-enantiomer, **1**, was proved in *in vitro* experiments to be about 100 times more potent than the *R*-isomer.[4]

The readily available commercial chiral (*R*)-3-benzyloxy-1,2-propanediol, **2**, (94.8% e.e. by chiral HPLC) was transformed into the corresponding cyclic sulfite **3** by the reaction with thionyl chloride in dichloromethane at −78 °C (Scheme 1). The product was obtained essentially pure and in quantitative yield. Without further purification **3** was reacted with sodium 1-naphtholate in dry DMF at room temperature, resulting in the formation of the intermediate **4** in 74% yield. Catalytic hydrogenolysis (10% Pd–C) in ethanol gave 83% of the diol **5**, after crystallization from EtOAc–AcOH (95 : 5). It is worth noting here that the recrystallized product exhibited an increased enantiomeric excess of better than 98%, compared with the 94.8% e.e. for the starting material. Conversion of **5** into the cyclic sulfite, **6**, (96%) was again accomplished by treatment with thionyl chloride under the standard conditions. Finally, **6** was reacted with isopropylamine in refluxing acetonitrile to give **1** in 82% recrystallized yield and of better than 98% e.e. The overall yield for the reaction sequence was 48%.



Scheme 1. a: $SOCl_2$–CH_2Cl_2 (−78°C); b: 1-Naph-ONa–DMF (r.t.); c: H_2–Pd–C–EtOH; d: $(CH_3)_2CHNH_2$–CH_3CN (reflux).

Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-100 NMR spectrometer or a JEOL JM-EX400 FT NMR instrument, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. IR spectra were obtained on a Nicolet 20-SXC FT-IR spectrophotometer. Mass spectra were recorded on a AEI MS-902 spectrometer at 70 eV (IP) and 180°C inlet temperature. GLC measurements were performed on a Varian 3700 gas chromatograph equipped with a BP-a or a CPSil 5 CB capillary column (25 m). (*R*)-3-Benzyloxy-1,2-propanediol was obtained from Fluka.

Synthesis of cyclic sulfites **3** *and* **6**. *General procedure.* A solution containing 10 mmol of the 1,2-diol (**2** or **5**) in 50 ml of dichloromethane was cooled to −78°C in a dry ice–acetone bath. 1.31 g (11 mmol) of thionyl chloride were then added over a 10 min period, and the resulting

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reaction mixture was allowed to stand for another 30 min. The mixture was then warmed to room temperature and the solvent evaporated off under reduced pressure to leave a nearly quantitative yield of the desired product (**3** or **6**).

(4S)-4-(Benzyloxymethyl)-1,3-dioxa-2-thiolane 2-oxide, **3**. GLC and NMR analyses indicated two diastereomers in a 38 : 62 ratio. IR (KBr): 3064, 3031, 2903, 2867, 1734, 1497, 1453, 1209, 1105, 1052, 1028, 965, 848, 742, 699 cm^{-1}. MS [*m/z* (% rel. int.)]: 228 (M^+, 5), 164 (3), 135 (2), 134 (2), 122 (2), 107 (22), 105 (6), 92 (10), 91 (100), 77 (3), 65 (9). ^{1}H NMR (400 MHz; $CDCl_3$, TMS): (main diastereomer) δ 3.54 and 3.61 (ABX-pattern, 2 H), 4.57 (s, 2 H), 4.30 and 4.68, m, 2 H), 5.06 (m, 1 H); (minor diastereomer) δ 3.77 and 3.86 (ABX-pattern, 2 H), 4.53 (m, 2 H), 4.60 (s, 2 H), 5.06 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): (main diastereomer) δ 67.2, 69.2, 73.4, 78.6, 128.1, 128.3, 128.9, 137.4; (minor diastereomer) δ 67.8, 70.3, 73.7, 81.2, 128.1, 128.3, 128.9, 137.6.

(4R)-4-(Naphthyloxymethyl)-1,3-dioxa-2-thiolane 2-oxide, **6**. GLC and NMR analyses indicated two diastereomers in a 42 : 58 ratio. Yield 96%. The diastereomeric mixture exhibited the following spectroscopic properties: IR (KBr): 3054, 1595, 1580, 1509, 1463, 1395, 1270, 1242, 1209, 1158, 1106, 1056, 957, 836, 793, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.23 (m), 4.47 (m), 4.55 (m), 4.64 (m), 4.75 (m), 4.82 (m), 4.91 (m), 5.03 (m), 5.40 (m), 6.90 (m), 7.35 (m), 7.50 (m), 7.80 (m), 8.18 (m), 8.25 (m). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 66.7, 66.8 (minor), 68.6, 69.4 (minor), 78.0, 79.9 (minor), 104.8, 104.9 (minor), 121.4, 121.5, 121.6, 121.7, 125.2, 125.3, 125.5, 125.6, 125.7, 126.6, 126.7, 127.5, 127.6, 134.5, 153.5. MS [*m/z* (% rel. int.)]: 264 (M^+, 100), 144 (81), 127 (27), 121 (48), 115 (66).

(S)-3-Benzyloxy-1-(1-naphthyloxy)-2-propanol, **4**. To a slurry containing 0.21 g (8.8 mmol) of NaH in dry DMF (15 ml) under an atmosphere of nitrogen, was added 1-naphthol (0.70 g, 4.8 mmol) and the mixture was stirred for another 15 min. Then 1.0 g (4.4 mmol) of **3** in 5 ml of dry DMF was added and the reaction mixture was stirred at room temperature for 5 h. Ether (50 ml) was then added and the solution washed with 1 M HCl, 1 M NaOH and brine and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave the crude product, which was subjected to flash chromatography (SiO_2; 5% acetone–hexane) resulting in isolation of 1.00 g (3.3 mmol, 74%) of pure **4** (>99% by GLC). The product exhibited the following spectroscopic properties: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.78 (d, J = 6.2 Hz, 2 H), 4.22 (d, J = 5.6 Hz, 2 H), 4.36–4.43 (m, 1 H), 4.58 (s, 2 H), 6.82 (d, J = 6.3 Hz, 1 H), 7.24–7.36 (m, 9 H), 7.78–7.82 (m, 1 H), 8.18–8.21 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 63.7, 65.9, 69.0, 71.1, 73.6, 104.9, 120.7, 121.8, 125.8, 126.4, 127.5, 127.8, 128.5, 134.6, 155.8. MS [*m/z* (rel. int.)]: 308 (M^+, 34), 243 (1), 165 (2), 157 (1), 145 (9), 144 (60), 143 (2), 127 (2), 115 (3), 92 (9), 91 (100). IR (NaCl): 3500–3400, 3056, 2927, 2866, 1580, 1509, 1455, 1400, 1270, 1241, 1157, 1102, 1071, 792, 772, 737, 698 cm^{-1}.

(S)-3-(1-Naphthyloxy)-1,2-propanediol, **5**. A solution containing 0.50 g (1.6 mmol) of **4** in 50 ml of 96% ethanol was treated with 0.1 g of 10% Pd–C and hydrogenated at 5 atm hydrogen pressure for 2 h. The reaction was worked up by filtration and evaporation of the solvent under reduced pressure. The crude product was recrystallized from ethyl acetate containing 5% acetic acid, to yield 0.30 g (1.3 mmol, 83%) of the pure product, **5** m.p. 110–112°C. $[\alpha]_D$ = +7.6° (c = 1.0, MeOH), lit.[5] $[\alpha]_D$ = + 7.7° and 6.7° (MeOH). The product exhibited the following spectroscopic properties: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 3.92 (d, J = 6.4 Hz, 2 H), 4.18–4.36 (m, 3 H), 6.82 (d, J = 7.2 Hz, 1 H), 7.24–7.44 (m, 4 H), 7.78 (m, 1 H), 8.21 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 63.8, 69.2, 70.6, 105.0, 121.0, 121.6, 125.4, 125.8, 126.5, 127.7, 134.5, 154.0. MS [*m/z* (rel. int.)]: 218 (M^+, 34), 187 (2), 169 (1), 157 (1), 145 (15), 144 (10), 129 (2), 128 (2), 127 (9), 116 (10), 115 (20), 89 (2). IR(KBr): 3500–3400, 3055, 2928, 2865, 1580, 1453, 1397, 1349, 1271, 1240, 1104, 1073, 1017, 891, 792, 770 cm^{-1}.

(S)-3-Isopropylamino-1-(1-naphthyloxy)-2-propanol, (S)-propranolol, **1**. A solution containing 0.20 g (0.68 mmol) of **6** and 0.22 g (3.9 mmol) of isopropylamine in 5 ml of acetonitrile was refluxed overnight. 10 ml of 1 M NaOH solution was then added, and the mixture was extracted with ethyl acetate. Drying over anhydrous magnesium sulfate, filtration and evaporation of the solvent gave 0.15 g, (0.55 mmol, 82%) of (*S*)-propanolol, **1**, m.p. 72°C (lit.[6] 73°C). $[\alpha]_D$ = −9.8° (c = 1.0, EtOH), lit.[7] $[\alpha]_D$ = −9.7° (c = 1.5, EtOH). The spectroscopic properties were in agreement with those of an authentic sample.

References

1. Stinson, S. C. *Chem. Eng. News* (1992) Sept. 28, 46; FDA announcement, *Chirality 4* (1992) 338; DeCamp, W. H. *Chirality 1* (1989) 2.
2. Carlsen, P. H. J. and Aase, K. *Acta Chem. Scand. 47* (1993). *In press.*
3. Lohray, B. B. and Ahuja, J. R. *J. Chem. Soc., Chem. Commun.* (1991) 95; Rebiere, F., Samuel, O., Ricard, L. and Kagan, H. B. *J. Org. Chem. 56* (1991) 5991.
4. Barett, A. and Cullum, C. *J. Pharmacol. 334* (1968) 43; Rahn, K., Hawlina, A., Kersting, F. and Planz, G. *Naunyn-Schmiedeberg Arch. Pharmacol. 286* (1974) 319; Hoyer, D., Engel, G. and Berthold, R. *Naunyn-Schmiedeberg Arch. Pharmacol. 318* (1982) 319.
5. Iruchijima, S. and Kojima, N. *Agric. Biol. Chem. 46* (1982) 1153; Ogg, G. D., Nelson, D. G., Stevenson, I. H. and Lyles, G. A. *J. Pharm. Pharmacol 39* (1987) 378.
6. Howe, R. and Shanks, R. G. *Nature (London) 210* (1966) 1336.
7. Bevinakatti, H. S. and Banerji, A. A. *J. Org. Chem. 56* (1991) 5372.

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