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Improved Synthesis of the Enantiomers of Propafenone Using Chiral Building Blocks

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Summary. A short and efficient synthesis of the enantiomers of the antiarrhythmic drug propafenone (**1**) is described using both (*R*)-isopropylideneglycerol tosylate and (*S*)-glycidyl tosylate as chiral building blocks. The key step of the high yield synthesis is the acetalization of the carbonyl group in 1-(2-hydroxyphenyl)-3-phenyl-1-propanone(**2**) which allows application of mild reaction conditions in the subsequent alkylation of the phenolic hydroxy group.

Keywords. Propafenone; Enantiomeres; Synthesis of; Chiral pool; Acetalization.

Eine verbesserte Synthese der Enantiomere von Propafenon unter Verwendung von chiralen Bausteinen

Zusammenfassung. Eine kurze und effiziente Synthese der Enantiomere des Antiarrhythmikums Propafenon (**1**) unter Verwendung von sowohl (*R*)-Isopropylidenglycerintosylat als auch von (*S*)-Glycidyltosylat als chirale Bausteine wird beschrieben. Der Schlüsselschritt der in sehr guter Ausbeute verlaufenden Synthese ist die Acetalisierung der Carbonylgruppe in 1-(2-Hydroxyphenyl)- 3-phenyl-1-propanon (**2**), welche die Anwendung milder Reaktionsbedingungen bei der anschließenden Alkylierung der phenolischen Hydroxylgruppe ermöglicht.

Introduction

We recently have described the synthesis of the enantiomers of the class 1C antiarrhythmic agent propafenone (**1**, [1]) which has prompted recent interest because of its chemosensitizing activity in multidrug resistant tumor cells [2]. The key step of that synthesis is the reaction of a racemic cyanohydrin with the enantiomerically pure reagent *MBF*-lactol [3], followed by separation of the diastereomeric acetals *via* vacuum flash chromatography. This reaction sequence allowed at the same time both assignment of the absolute configuration of the propafenone enantiomers using well established rules and ^{1}H NMR spectroscopic control of diastereomeric purity during all reaction steps. Nevertheless, it involved numerous steps and chromatographic resolution and is therefore limited to small scale synthesis. In the present paper we wish to report a "chiral pool" synthesis of the

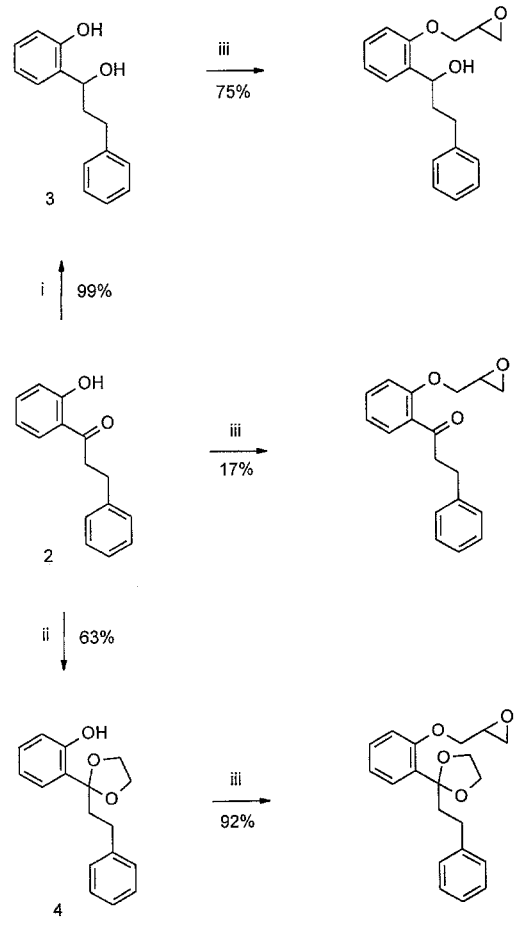
§ With our best wishes dedicated to Prof. Dr. *H. Achenbach* on the occasion of his 65th birthday

enantiomers of propafenone based on two different chiral bulding blocks, which is suitable for up-scaling.

Results and Discussion

Generally, enantiomerically pure β-receptor blocking agents of the aryloxpyropanolamine type are synthesized *via* alkylation of corresponding phenols with enantiomerically pure epichlorohydrine or glycerol derivatives [4]. However, in the case of *o*-acylphenols, the reactivity of the phenolic hydroxy group is remarkably diminished due to intramolecular hydrogen bonding [5]. Thus, an excess of enantiomerically pure alkylating agent, drastic reaction conditions, and/or highly activated alkylating agents are required to achieve acceptable yields in the O-alkylation [6]. It was therefore attempted to enhance the yield of this reaction step by avoiding chelate formation.

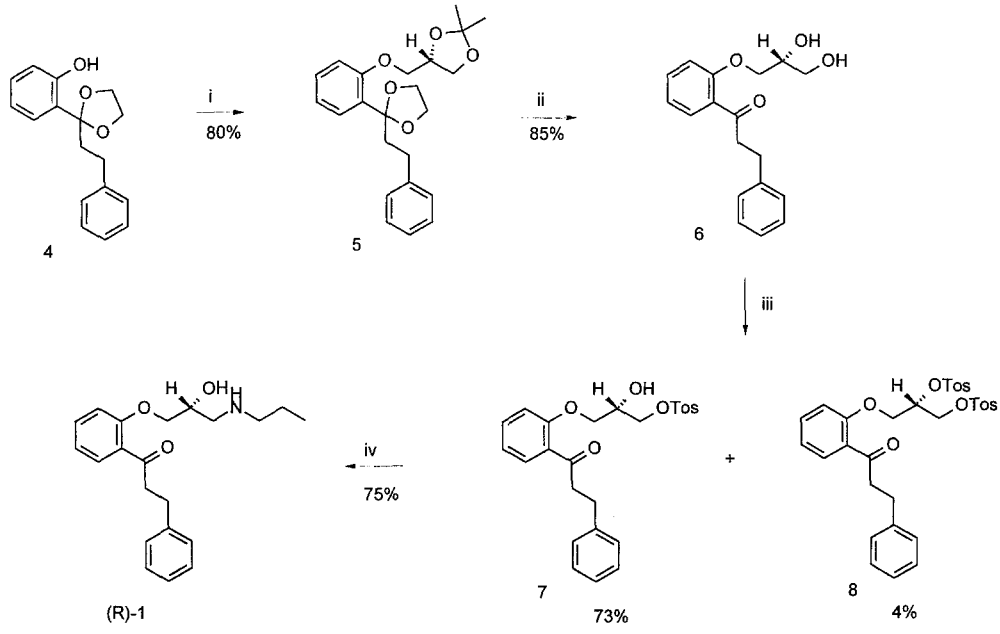
Reduction of 1-(2-hydroxyphenyl)-3-phenyl-1-propanone (**2**) with $NaBH_4$ gave alcohol **3** which could be alkylated with epichlorohydrine in excellent yields (Scheme 1). This result demonstrated that the carbonyl group in *ortho* position to the



Scheme 1. Alkylation of various phenols with epichlorohydrine; *i*: $NaBH_4$, methanol; *ii*: ethyleneglycol, *p*-toluenesulfonic acid, benzene; *iii*: NaH, epichlorohydrine (1 equiv.), *DMF*

phenolic hydroxy group was indeed responsible for the poor yields in arylether formation. However, reduction of the carbonyl group generated an additional chiral center and required a reoxidation step in the reaction sequence. Therefore, in an alternative attempt, chelate formation was excluded by acetalization of the carbonyl group with ethylene glycol. Although formation of acetal **4** proceeded only slowly, good yields (70%) were obtained after approximately 70 h of refluxing. Like compound **3**, dioxolane **4** could also be alkylated with epichlorohydrin in very good yields (Scheme 1).

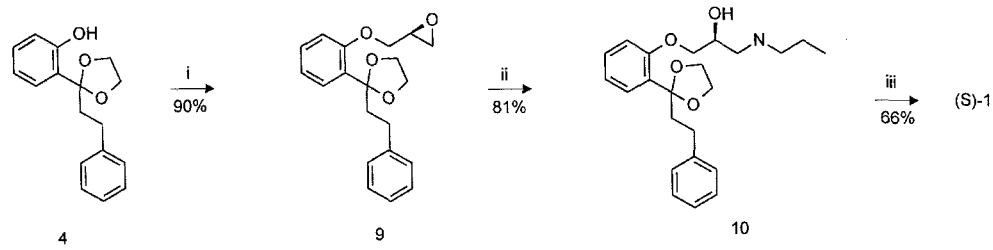
Starting from compound **4**, synthesis of the enantiomers of propafenone was achieved as follows: (*R*)-propafenone was synthesized *via* alkylation of **4** with (*R*)-isopropylideneglycerol tosylate, which, after cleavage of both acetal groups and tosylation of the primary hydroxy group, yielded the monotosylate **7**. Compound **7** was recrystallized carefully to remove small amounts of the ditosylate **8**. Reaction with 1-propanamine and subsequent formation of the hydrochloride directly afforded (*R*)-propafenone hydrochloride ((*R*)-**1**) with an overall yield of 49% and an enantiomeric purity of 97.3% (Scheme 2).



Scheme 2. Synthesis of (*R*)-**1**; *i*: NaH, (*R*)-isopropylideneglycerol tosylate, *DMF*; *ii*: acetonitrile, 2 *N* HCl; *iii*: *p*-tosylchloride, pyridine; *iv*: 1-propanamine, 2 *N* HCl

(*S*)-Propafenone was synthesized using (*S*)-glycidyl tosylate as an enantiomerically pure building block, which required perfect regioselectivity in the alkylation step to guarantee retention of configuration and to maintain high enantiomeric purity of the product. Alkylation of **4** was thus performed using *DMF*/NaH which had been shown to be superior to the system acetone/K_2CO_3 [7]. Subsequent reaction with 1-propanamine and cleavage of the acetal group by reaction with

hydrochloric acid directly afforded (*S*)-propafenone hydrochloride ((*S*)-**1**) with 65% overall yield and 95.0% enantiomeric purity (Scheme 3).



Scheme 3. Synthesis of (*S*)-**1**; *i*: NaH, (*S*)-glycidyl tosylate, *DMF*; *ii*: 1-propananmine; *iii*: 2 *N* HCl

Determination of enantiomeric purity of both enantiomers of **1** was accomplished corresponding to a previously published HPLC-procedure using (*R*)-phenylethylisocyanate [1]. Optical rotation of both enantiomers was in accordance to previously published values, thus proving in addition the assignment of the absolute configuration previously obtained *via* circular dichroism [8] and NMR measurements using *MBF*-lactol [1].

Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer. Mass spectra were measured on a Varian MAT 111A spectrometer by *A. Nikiforov* (Institute for Organic Chemistry, University of Vienna, Austria). NMR spectra were recorded on a Bruker AC 80, a Varian EM 390, or a Bruker AM 400 WB spectrometer (project P6537C), using *TMS* as internal standard. Microanalyses were done by *J. Theiner* (Institut for Physical Chemistry, University of Vienna, Austria).

2-(2-(2-Phenylethyl)-1,3-dioxolan-2-yl)phenol (**4**)

32.02 g (141.7 mmol) 1-(2-hydroxyphenyl)-3-phenyl-1-propanone (**2**) was dissolved in 250 ml benzene. 43.01 g ethylenglycol and 0.60 g *p*-toluenesulfonic acid were added, and the reaction mixture was refluxed under azeotropic removal of water for 86 h. The resulting solution was washed twice with saturated $NaHCO_3$ solution and with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness to yield 35.72 g of a mixture of 77% **4** and 23% **2** (NMR). Crystallization from methanol gave 24.04 g (62.8%) **4** as colourless needles. M.p.: 60–61 °C; ^{1}H NMR ($CDCl_3$): $\delta = 2.10$–2.93 (m, 4H, C–CH_2–CH_2–Ph), 3.85–4.25 (m, 4H, O–CH_2–CH_2–O), 6.82–7.43 (m, 9H, arom. H), 8.30 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 29.62$ (Ph–CH_2), 41.33 (C(O)–CH_2), 64.73 (O–CH_2–CH_2–O), 111.55 (O–C–O), 117.34, 120.09, 125.95, 127.13, 128.46, 130.18, 155.02 (arom. C) ppm; MS: $m/z = 270$ (M^+, 3%), 165 (100%), 121 (41.2%), 91 (19%); $C_{17}H_{18}O_3$; calcd.: C 73.06, H 6.45; found: C 73.37, H 6.46.

(S)-2,2-Dimethyl-4-(2-(2-(2-phenylethyl)-1,3-dioxolan-2-yl)phenoxymethyl)-1,3-dioxolan (**5**)

8.51 g (31.5 mmol) **4** were dissolved in 80 ml of dry *DMF*, and 1.17 g NaH (80% in paraffinum) were added. The reaction mixture was heated to 60 °C for 2 h; then, a solution of 9.12 g (31.8 mmol) (*R*)-isopropylideneglycerol tosylate in 30 ml dry *DMF* was added dropwise. After addition of 0.12 g KI, the solution was heated at 60 °C for 20 h. The reaction mixture was diluted with diethyl ether and

washed twice with 2 *N* NaOH and with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give 11.47 g (95%) **5** as a yellowish oil which was used for the next reaction step without further purification. Column chromatography of 0.50 g (silica gel; petrolether/diethyl ether = 1/1) gave 0.42 g **5** (80%) as colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.33–2.82 (m, 4H, C–CH_2–CH_2–Ph), 3.83–4.25 (m, 8H, O–CH_2–CH_2–O, Ar–O–CH_2, CH_2–O), 4.5 (qui, 1H, CH), 6.93–7.65 (m, 9H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.28$, 26.72 (2 CH_3), 30.00 (Ph–CH_2), 39.53 (CH_2–C), 64.57 (O–CH_2–CH_2–O), 67.13, 69.49 (Ar–CH_2, CH_2–O), 73.85 (CH), 109.29, 109.84 (O–C–O, O–$C(CH_3)_2$–O), 113.50, 120.54, 125.36, 127.46, 128.02, 128.20, 129.28, 130.16, 142.32, 156.11 (arom. C) ppm; MS: $m/z = 384$ (M^+, 0.7%), 279 (100%), 165 (15%), 91 (20%); $[\alpha]_{364} = +32.5°$ ($c = 0.827$ in methanol); $C_{23}H_{28}O_5$; calcd.: C 71.85, H 7.34; found: C 71.89, H 7.40.

(R)-1-(2-(2,3-Dihydroxypropoxy)phenyl)-3-phenyl-1-propanone (**6**)

9.90 g (25.7 mmol) **5** were dissolved in 80 ml acetonitrile, and 80 ml 2 *N* HCl were added. The resulting mixture was stirred for 1 h at 50 °C, diluted with water, and extracted twice with diethyl ether. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness to yield 7.72 g (99.8%) **6** as a yellowish oil which was used for the next reaction step without further purification. Column chromatography of 0.40 g (silica gel; petrolether/diethyl ether = 1/1) gave 0.36 g (85%) **6** as colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 2.93$–3.42 (m, 5H, CO–CH_2–CH_2, OH), 3.61–3.93 (m, 3H, –CH_2–OH, OH), 3.98–4.17 (m, 3H, O–CH_2–CH(O)), 6.92–7.68 (m, 9H,arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 29.95$ (Ph–CH_2), 44.13 (CO–CH_2), 63.28 (CH_2–OH), 69.92 (CH(OH)), 70.12 (O–CH_2), 113.05, 120.69, 125.71, 128.08, 129.77, 133.24, 140.95, 157.19 (arom. C), 201.93 (CO) ppm; IR: $\nu = 1680$ (CO) cm^{-1}; MS: $m/z = 300$ (M^+, 63%), 208 (201%), 135 (46%), 121 (100%), 91 (76%), 77 (22%); $[\alpha]_{364} = -36.3°$ ($c = 1.039$ in methanol); $C_{18}H_{20}O_4$; calcd.: C 71.98, H 6.71; found: C 71.68, H 6.69.

(S)-1-(2-(2-Hydroxy-3-tosyloxy-propoxy)phenyl)-3-phenyl-1-propanone (**7**) and
(S)-1-(2-(2,3-Bistosyloxy-propoxy)phenyl)-3-phenyl-1-propanone (**8**)

2.15 g (7.2 mmol) **6** were dissolved in 23 ml pyridine; 1.40 g *p*-tosylchloride were added at 5 °C, and the reaction vessel was stored in a refrigerator for 16 h (5–8 °C). The resulting suspension was diluted with diethyl ether and extracted with 1 *N* HCl till the aqueous phase showed acidic *pH*. The organic layer was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated to dryness. Crystallization from diethyl ether and subsequent column chromatography (silica gel, petrolether/diethyl ether = 2/1) gave 2.38 g (73%) **7** as colourless needles and 0.17 g (4%) ditosylate **8** as colourless oil which solidifies slowly.

7: M.p.: 81–83 °C; ^{1}H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 2.82–3.28 (m, 4H, CO–CH_2–CH_2), 3.40 (m, 1H, OH), 4.02–4.18 (m, 5H, O–CH_2–CH(O)–CH_2–O), 6.82–7.79 (m, 13H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.53$ (CH_3), 30.06 (Ph–CH_2), 44.49 (CO–CH_2), 67.69 (CH(O)), 69.06, 69.97 (O–CH_2, CH_2–O *Tos*), 113.50, 121.27, 126.00, 127.86, 128.35, 128.42, 129.92, 132.40, 133.46, 141.26, 145.11, 157.13 (arom. C), 201.55 (CO) ppm; IR: $\nu = 1680$ (CO) cm^{-1}; MS: $m/z = 454$ (M^+, 5.4%), 436 (21%), 224 (25%), 147 (23%), 120 (52%), 91 (100%), 77 (18%); $[\alpha]_{364} = +6.3°$ ($c = 1.324$ in methanol); $C_{25}H_{26}SO_6$; calcd.: C 66.06, H 5.77; found: C 65.99, H 5.73.

8: ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.83–3.18 (m, 4H, CO–CH_2–CH_2–Ph), 4.15 (t, 4H, $J = 6.5$ Hz, O–CH_2, –CH_2–O*Tos*), 4.86 (qui, 1H, $J = 6.5$ Hz, CH(O*Tos*)), 6.73–7.81 (m, 17H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.59$ (2 CH_3), 30.00 (Ph–CH_2), 45.03 (CO–CH_2), 65.89, 66.65 (2 CH_2), 75.28 (CH), 112.44, 121.66, 125.95, 127.83, 127.88, 128.43, 128.71, 129.99, 130.24, 132.00, 132.85, 133.21, 141.41, 145.39, 145.51, 156.18 (arom. C), 200.63 (CO) ppm; MS: $m/z = 608$ (M^+, 6%), 436 (11%), 224 (16%), 155 (34%), 120 (27%), 91 (100%); $C_{32}H_{32}S_2O_8$; calcd.: C 63.14, H 5.30; found: C 63.16, H 5.38.

*(R)-1-(2-(2-Hydroxy-3-propylamino-propoxy)phenyl)-3-phenyl-1-propanone hydrochloride ((R)-propafenone hydrochloride, (R)-**1**)*

4.30 g (9.5 mmol) **7** were dissolved in 6.20 g 1-propanamine and heated under reflux for 2 h. The reaction mixture was diluted with diethyl ether and washed with water, 2 *N* NaOH, and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The resulting yellow oil (3.41 g) was suspended in 50 ml 2 *N* HCl, heated to 80 °C for 1 h, and diluted with water. The white precipitate was filtered off and recrystallized from acetone/methanol (80/20) to give 2.45 g (75%) (*R*)-**1** as colourless needles. M.p.: 176–177 °C; $[\alpha]_{364} = +23.7°$ ($c = 1.026$ in methanol); *ee* (HPL C) = 94.6%.

(S)-2-(2-Oxiranylmethyloxy)phenyl)-2-(2-phenylethyl)-1,3-dioxolan (**9**)

5.02 g (18.6 mmol) **4** was dissolved in 40 ml dry *DMF*, and 0.67 g NaH (80% suspension in paraffinum) was added. After stirring for 1 h at 50 °C, a solution of 5.00 g (21.9 mmol) (*S*)-glycidyltosylate in 25 ml dry *DMF* was added dropwise, and the reaction mixture was stirred at 50 °C for 3 h. The resulting mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$ solution and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give 5.87 g (97%) **9** as a colourless oil which was used for the next reaction step without further purification. Column chromatography of 0.52 g (silica gel, petrolether/diethyl ether = 1/1) gave 0.48 g (90%) **9** as colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 2.41–2.68$ (m, 4H, C–CH_2–CH_2–Ph), 2.90 (d, 2H, $J = 3.6$ Hz, epoxide CH_2), 3.35–3.47 (m, 1H, CH(O)), 3.85–4.15 (m, 4H, –O–CH_2–CH_2–O), 4.15–4.23 (m, 2H, O–CH_2), 6.93–7.58 (m, 9H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 30.01$ (Ph–CH_2), 39.43 (C–CH_2), 44.41 (epoxide CH_2), 50.03 (CH), 64.60 (O–CH_2–CH_2–O), 68.93 (O–CH_2), 109.78 (O–C–O), 113.69, 120.63, 125.32, 127.41, 128.01, 128.19, 129.28, 130.17, 142.27, 156.05 (arom. C) ppm; MS: $m/z = 221$ (100%), 91 (17%); $[\alpha]_{364} = +19.6°$ ($c = 1.042$ in CH_2Cl_2); $C_{20}H_{22}O_4$; calcd.: C 73.60, H 6.79; found: C 73.71, H 6.73.

(S)-1-(2-(2-(2-Phenylethyl)-1,3-dioxolan-2-yl)phenoxy)-3-propylamino-2-propanole (**10**)

5.85 g (17.9 mmol) **9** were dissolved in 12 g 1-propanamine and heated under reflux for 2 h. The propylamine was removed under reduced pressure, and the resulting yellowish oil (6.90 g; 99.9%) was used for the next reaction step without further purification. Column chromatography of 0.57 g (silica gel; CH_2Cl_2/methanol/conc.NH_3 = 200/10/1) gave 0.46 g (81%) **10** as colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.53 (sext, 2H, CH_2), 2.32–2.94 (m, 8H, C–CH_2–CH_2–Ph, CH_2–N–CH_2), 3.25 (s, 2H, OH, NH), 3.78–4.23 (m, 7H, O–CH_2–CH_2–O, O–CH_2–CH(O)), 6.78–7.63 (m, 9H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.73$ (CH_3), 23.04 (CH_2), 29.98 (Ph–CH_2), 39.98 (C–CH_2), 51.94 52.02 (CH_2–N–CH_2), 64.74 64.82 (O–CH_2–CH_2–O), 68.93 (CH), 72.76 (O–CH_2), 110.35 (O–C–O), 114.41, 120.89, 125.60, 127.14, 128.25, 128.33, 129.63, 130.11, 142.18, 156.70 (arom. C) ppm; MS: $m/z = 385$ (M^+, 9%), 165 (40%), 121 (13%), 91 (15%), 73 (100%); $[\alpha]_{364} = +3.8°$ ($c = 1.102$ in methanol); $C_{23}H_{31}NO_4$; calcd.: C 71.66, H 8.11, N 3.63; found: C 71.79, H 8.10, N 3.68.

*(S)-1-(2-(2-Hydroxy-3-propylamino-propoxy)phenyl)-3-phenyl-1-propanone hydrochloride ((S)-propafenone hydrochloride; (S)-**1**)*

2.31 g (6.0 mmol) **10** were suspended in 60 ml 2 *N* HCl and stirred at 80 °C for 1 h. The white precipitate was filtered off and recrystallized twice from acetone/methanol = 80/20 to give 1.53 g (66%) (*S*)-**1** as colourless crystals. M.p.: 176–177 °C; $[\alpha]_{364} = -22.1°$ ($c = 1.003$ in methanol); *ee* (HPLC) = 90.0%.

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