Tetrahedron: Asymmetry Vol. 4, No. 12, pp. 2451-2460, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Two Enantioselective Syntheses of the Diol Precursor of the Biologically Most Active Isomer of an Insect Growth Regulator

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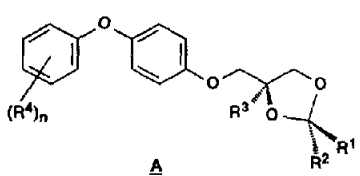
(*Received in UK* 7 *September* 1993; *accepted* 12 *October* 1993)

Abstract: The diol precursor (R)-**3** of the insect growth regulator **2** was synthesized enantioselectively by two different routes: a) via enantioselective hydrogenation of the α-hydroxy-ketone **4**, catalyzed by a Ru-BINAP-catalyst and b) via resolution of the enantiomers of glycerol using (-)-camphor-10-sulfonamide **7** as chiral auxiliary.

Introduction

1,3-dioxolane-derivatives of structure **A** show interesting activity as insect growth regulators, especially against scale insects, but also against codling moth (*Cydia*), leafrollers (*Adoxophyes spec.*) and white flies (*Trialeurodes, Bemisia*).

Figure 1



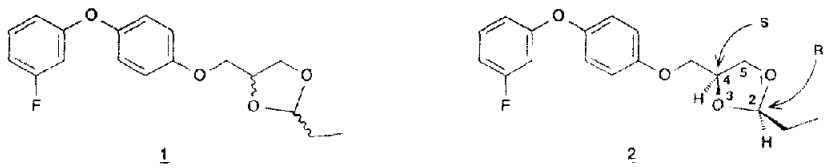
A

R^1, R^2 = H, alkyl
R^3 = H, CH_3
R^4 = H, F, Cl

n = 1 or 2

2-Ethyl-4-[(4-(3-fluorophenoxy)-phenoxy)-methyl]-dioxolane **1** is an experimental insecticide with good biological activity against scales in deciduous and citrus fruits [1]. In order to test its 4 stereoisomers individually, they were stereoselectively synthesized using the appropriate enantiomer of commercially available α,β-isopropylideneglycerol-γ-tosylate as starting material [2]. This very expensive "chiral-pool" approach quickly provided the required material for the biological tests, in which the (2R,4S)-isomer **2** proved to be clearly the most active one. At that point a less costly, technically feasible stereoselective synthesis of **2** was needed.

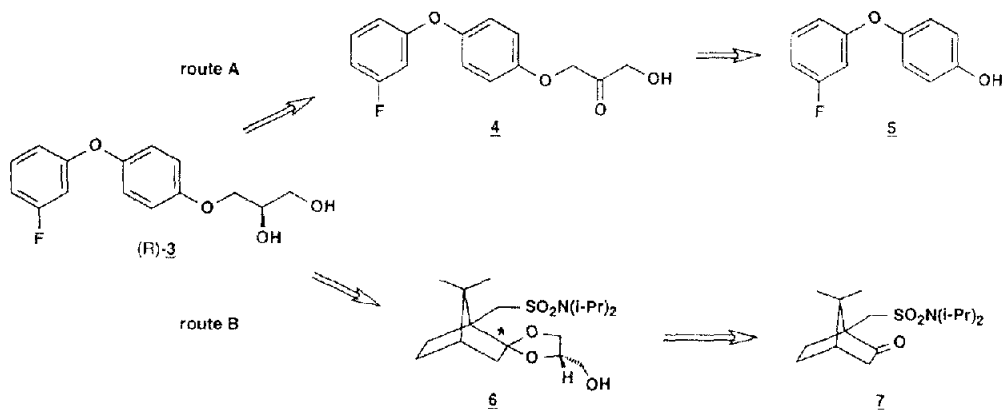
Figure 2



1 2

Central intermediate and first target molecule in the stereoselective synthesis of **2** was the (R)-enantiomer of the O-phenoxyphenyl-glycerol **3**. In this paper we will limit ourselves to reporting two conceptually different enantioselective routes to diol (R)-**3**.

Figure 3



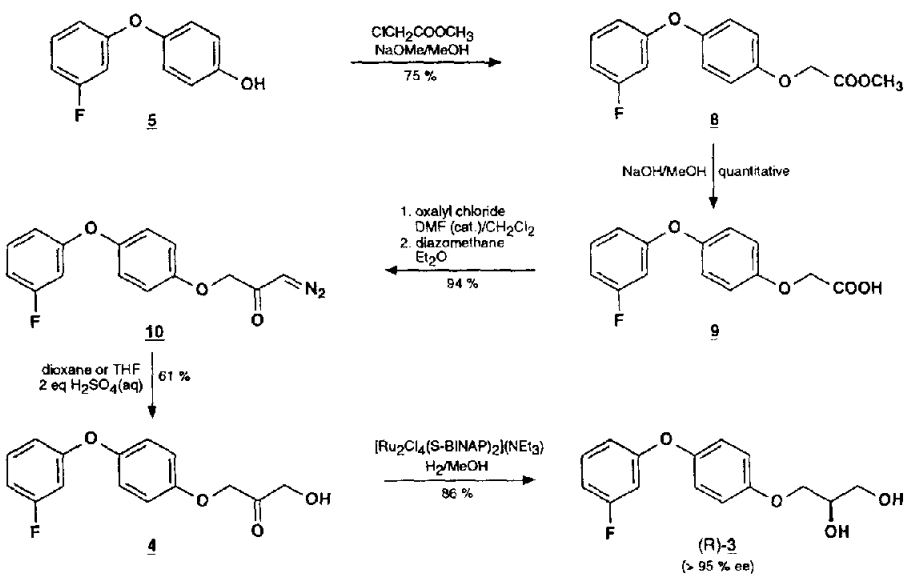
On route A the chiral information is introduced by enantioselective catalytic hydrogenation of the α-hydroxy-ketone **4**, while route B is formally based on the resolution of the enantiomers of glycerol by derivatization with (-)-camphor-10-sulfonamide **7**. The subsequent diastereoselective synthetic pathway towards **2** is discussed elsewhere [3].

Results and discussion

Asymmetric catalytic hydrogenation has become an efficient synthetic method for the enantioselective preparation of quite a variety of chemical structures [4, 5a]. In recent years, also the enantioselective hydrogenation of functionalized ketones has made impressive progress. Noyori, Takaya and coworkers as well as the Takasago group have demonstrated that the Ru-BINAP catalysts exhibit a wide scope in the hydrogenation of ketones [5]. In contrast, the use of chiral Rh-disphosphines [6], cobalt catalysts [7] or modified heterogeneous catalysts, e.g. Pt/Al_2O_3/cinchonidine, Raney-Ni/tartrate/Br [8] has lead with the same substrates only in a few cases to high optical yields.

In order to quickly answer the question, whether diol (R)-**3** was accessible via enantioselective catalytic hydrogenation, the α-hydroxy-ketone **4** was synthesized in the following straightforward fashion.

Figure 4

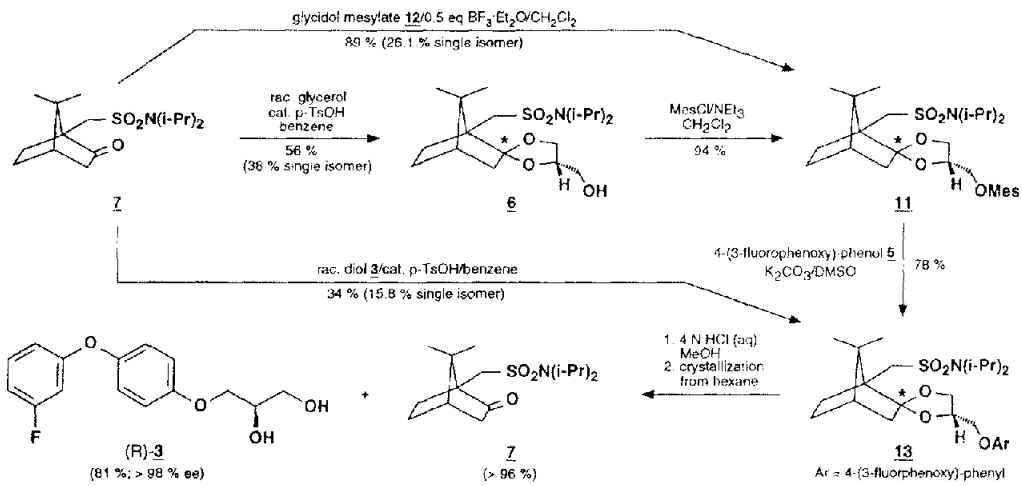


Treatment of 4-(3-fluorophenoxy)-phenol **5** [9] with methyl chloroacetate in the presence of NaOMe afforded in good yield the methyl aryloxy acetate **8** [10], which was quantitatively hydrolyzed to the acid **9** with aqueous NaOH in methanol. The corresponding acid chloride, freshly made from **9** by standard procedure (oxalyl chloride, dichloromethane, cat. DMF), reacted with diazomethane [11] in high yield to the α-diazo-ketone **10** [12]. Treatment of **10** with aqueous H_2SO_4 in dioxane or THF led to the desired α-hydroxy-ketone **4** in moderate yield [13]. The key step of this synthesis, the enantioselective hydrogenation of **4** to diol (R)-**3** proceeded smoothly in high chemical and optical yields with $[Ru_2Cl_4(S\text{-}BINAP)_2](NEt_3)$ [14] as catalyst (95 bars of H_2, MeOH, rt, 0.05 mol-% catalyst). The enantiomeric excess of >95 % in this reaction is comparable to analogous Ru-BINAP-catalyzed hydrogenations of α-hydroxy ketones [5a, 5b]. The optical purity of the received diol (R)-**3** was determined by comparison of the optical rotation with the $[\alpha]_D$-value of a sample synthesized from α,β-isopropylideneglycerol-γ-tosylate [15]. The HPLC-method applying a commercially available ®Chiralcel-OD-column (Daicel) proved, due to tailing, to be unsuited for the determination of high enantiomeric excesses of the first eluted (R)-enantiomer. For control of the accuracy of the measured ee-values, the hydrogenation experiment was repeated using the other enantiomer of the same catalyst (R-BINAP as ligand). HPLC-analysis of the formed diol (S)-**3**, which was isolated in high yield, confirmed with an ee-value of 91 % the observed high enantioselectivity of that reaction. Thus, it was shown, that optically highly enriched diol (R)-**3** was easily accessible via enantiose-

lective catalytic hydrogenation. However, for scale-up a different, technically feasible synthesis of the α-hydroxy-ketone **4** would be required.

At that time, the report of the enantioselective syntheses of two propanediol-derivatives using N,N-diisopropyl-10-camphorsulfonamide **7** as chiral auxiliary [16] prompted us, to try the synthesis of diol (R)-**3** via route B (see figure 3).

Figure 5



In order to get the required (R)-configuration in the target molecule, the (1R)-(-)-enantiomer of camphor-10-sulfonamide **7** was used as starting material. Following the described procedure (1R)-(-)-**7** [17] was ketalized with glycerol under acidic catalysis (p-TsOH·H_2O) by heating the benzene solution to reflux with azeotropic removal of water. From the reaction mixture the desired spiro-ketal **6** was isolated in 56.7 % yield along with approximately 36 % of unreacted starting material **7**. As already described, one diastereomer was formed preferentially (37.8 % yield; 59 % based on recovered starting material) and was isolated in diastereomerically pure, crystalline form [16]. In spite of extensive optimization attempts, full conversion of **7** could never be achieved. However, it could be shown that the mixture of the three minor diastereomers of **6** equilibrates under the above reaction conditions to a mixture of all four diastereomers containing again 57 % of the desired crystalline isomer. The following steps of this synthesis proceeded very smoothly in high yields. Treatment of **6** with methanesulfonyl chloride and NEt_3 in dichloromethane afforded almost quantitatively the mesylate **11**. An alternative route to mesylate **11** was also investigated, the direct Lewis-acid catalyzed ketalization of **7** with glycidol-mesylate (**12**) [18]. However, the yield of the desired diastereomerically pure mesylate **11** remained clearly lower than in the above described sequence. Reaction of **11** with 4-(3-fluorophenoxy)-phenol **5** in DMSO in the presence of anhydrous Na_2CO_3 [10] lead

to the aryl-ether **13**. Also **13** can be received in a one-step-procedure from (-)-camphor-10-sulfonamide **7**, by direct acid catalyzed ketalization with racemic diol **3**. This ketalization reaction, however, could not be brought to full conversion of starting material **7**. Therefore, the yield of diastereomerically pure **13** remained only about half of the overall yield (27.9 %) of the reaction sequence via ketalization of **7** with glycerol. Hydrolysis of **13** to the diol (R)-**3** and the (-)-camphor-10-sulfonamide **7** was carried out with 4 N aqueous HCl in methanol. From the crude mixture of the two reaction products diol (R)-**3** was isolated in high yield with an ee of >98 % by crystallization from hexane. The chiral auxiliary **7** was recovered from the mother liquors in almost quantitative yield.

Conclusion

Two new enantioselective synthetic routes to aryloxy-propanediols have been demonstrated. The first one (route A) includes as a key step the enantioselective hydrogenation of an α-hydroxy-ketone intermediate and leads in a short, straightforward sequence, well-suited for lab-scale, to the target diol (R)-**3**. The second one (route B) is based on the chemical resolution of the enantiomers of glycerol via ketalization of a recyclable chiral auxiliary, (1R)-(-)-camphor-10-sulfonamide **7**, and fulfills also the requirements for a large scale process, as long as the ketalization step can be brought to full conversion.

Experimental

All reagents were purchased from Fluka or Aldrich and were used without further purification. $[Ru_2Cl_4(S\text{-}BINAP)_2](NEt_3)$ was synthesized according to the published procedure [14]. The ligand (S)-BINAP was purchased from Fluka. Solvents were acquired from Fluka or Merck and stored over molecular sieves. Methanol for the hydrogenation reaction was dried over sodium methoxide and stored under argon. For flash-chromatography silicagel 60 (0.040-0.063 mm; Merck) was used; thin layer chromatography was carried out on silicagel plates 60 F-254 (Merck). HPLC was performed on commercially available chiral columns using HPLC-grade solvents. Melting points are uncorrected. NMR spectra were recorded on a Bruker AC-F-250-instrument; chemical shifts are reported in ppm relative to internal TMS standard (= 0 ppm).

Methyl (4-(3-fluorophenoxy)-phenoxy)-acetate (**8**)

Under argon, 3.48 g (62.5 mmol) of sodium methoxide were added at rt to a stirred solution of 10.2 g (50 mmol) of 4-(3-fluorophenoxy)-phenol (**5**) [9] in 250 ml of dry methanol. After the addition of 10.9 g (0.1 mol) of methyl chloroacetate, the mixture was refluxed for 5 h. Then an additional portion of 10.9 g (0.1 mol) of methyl chloroacetate was added, and the refluxing was continued for another 16 h. Since a TLC still showed some starting material, a third portion of 10.9 g (0.1 mol) of methyl chloroacetate was added, and the reaction mixture was again refluxed for 8 h. Finally, the resulting suspension was poured onto a 1:1 mixture of sat. NH_4Cl (aq) and ice and extracted twice with ether. The organic layer was washed with icecold 2N NaOH, H_2O and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography on silicagel (diethyl ether/dichloromethane/hexane 1:1:7) yielded 2.1 g (10.3 mmol; 20.6%) of unreacted starting material **5** and 10.4 g (37.6 mmol; 75.3%) of **8** as a colourless oil. R_f: (diethyl ether/dichloromethane/hexane 1:1:1) 0.49. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.83 (s, 3H, $-OCH_3$); 4.64 (s, 2H, OCH_2); 6.63 (dt, 1H, J=10 Hz and 2.5 Hz, H-C(2)); 6.68-6.79 (m, 2H, H-C(4) and H-C(6)); 6.88-7.05 (m, 4H);

7.18-7.31 (m, 1H, H-C(5)). IR ($CHCl_3$): 3030, 2955, 1760, 1600, 1500, 1485, 1442, 1307, 1272, 1194, 1122, 1084, 964, 840.

(4-(3-Fluorophenoxy)-phenoxy)-acetic acid (**9**)

To a solution of 2.76 (10 mmol) of methyl ester **8** in 20 ml of methanol 10 ml (20 mmol) of 2N NaOH (aq) were added. Immediately, in a slightly exothermic reaction a white precipitate was formed. After 10 minutes, the reaction mixture was acidified by the addition of 11 ml (22 mmol) of 2N HCl (aq) and extracted twice with ether. The organic phase was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure affording 2.74 g (quant.) of **9** as white crystals melting at 129-130° C. R_f: (ethyl acetate/toluene/glacial acetic acid 2:2:1) 0.24. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.69 (s, 2H, OCH_2COOH); 6.64 (dt, 1H, J=10 Hz and 2.5 Hz, H-C(2)); 6.68-6.81 (m, 2H, H-C(4)) and H-C(6)); 6.89-7.07 (m, 4H); 7.18-7.31 (m, 1H, H-C(5)). IR ($CHCl_3$): 3020, 2980, 2920, 1737, 1597, 1500, 1483, 1444, 1300, 1268, 1190, 1120, 1080, 963, 840.

1-Diazo-3-(4-(3-fluorophenoxy)-phenoxy)-propan-2-on (**10**)

Under argon, 4 ml (46.5 mmol) of oxalyl chloride were added at 0-5° C to a mixture of 8.07 g (30.8 mmol) of acid **9**, 100 ml of dichloromethane and a catalytic ammount of DMF (4 drops). After stirring at rt for 3 h, the gas formation stopped and all volatile components of the reaction mixture were removed under reduced pressure. The yellow oily residue (8.8 g) was dissolved in 50 ml of diethyl ether and was added at rt within 10 minutes to a solution of diazomethane (freshly made from 20 g (136 mmol) of N-methyl-N-nitroso-guanidine [11]) in 300 ml of diethyl ether. Under gas formation the initially yellow reaction solution quickly lost its colour. After stirring at rt for 30 minutes, the solvent was carefully removed under reduced pressure (no heating!), yielding 8.3 g (28.9 mmol; 93.8% from acid **9**) of the α-diazoketone **10** as yellow crystals melting at 68-70° C. R_f: (hexane/ethyl acetate 1:1) 0.46 (diethyl ether/dichloromethane/hexane 1:1:1) 0.39. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.54 (br s, 2H, OCH_2); 5.83 (br s, 1H, $COCHN_2$); 6.64 (dt, 1H, J=10 Hz and J=2.5 Hz, H-C(2)); 6.90 (dt, 2H, J=10 Hz and J=2.5 Hz); 7.02 (dt, 2H, J=10 Hz and J=2.5 Hz); 7.18-7.32 (m, 1H, H-C(5)). IR ($CHCl_3$): 3044, 2325 w, 2170, 1665, 1532, 1510, 1393, 1234, 1142, 981.

1-Hydroxy-3-(4-(3-fluorophenoxy)-phenoxy)-propan-2-on (**4**)

Under argon, 15 ml (7.5 mmol) of 1 N H_2SO_4 (aq) were added at 0° C to a solution of 1.055 g (3.67 mmol) of the α-diazo-ketone **10** in 15 ml of THF. After stirring the mixture at rt for 38 h, the THF was removed under reduced pressure without heating. The aqueous residue was diluted with 10 ml of H_2O and twice extracted with 25 ml of diethyl ether. The combined organic phases were washed with 10 ml of H_2O and 10 ml of brine (with brine very slow phase separation!), dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography on silicagel (diethyl ether/dichloromethane/hexane 1:1:2 (400 ml), then diethyl ether/dichloromethane/hexane 1:1:1 (450 ml)) afforded 613 mg (2.22 mmol; 60.5%) of the α-hydroxy-ketone **4** as a slightly yellowish oil. R_f: (diethyl ether/dichloromethane/hexane 1:1:1) 0.17. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.99 (t, 1H, exchanges with D_2O, J=5 Hz, OH); 3.70-4.45 (signals of some impurities, which could not be removed by chromatography); 4.625 (d, 2H, J=5 Hz, $COCH_2OH$); 4.71 (s, 3H, OCH_2CO); 6.57-6.82 (m, 3H, H-C(2), H-C(4) and H-C(6)); 6.84-7.08 (m, 4H); 7.16-7.32 (m, 1H, H-C(5)). IR ($CHCl_3$): 3580- 3510 br, 1736, 1607, 1510, 1493, 1456, 1245, 1211, 11267, 1108, 1080, 1015, 970, 844. MS m/z: 276 (M^+, 100%), 217 (67%), 204 (51%), 203 (46%), 159 (49%), 133 (29%), 109 (20%), 95 (35%).

spiro-ketal **6** [16]

Under argon, 2.45 g (approx. 26.6 mmol = 1.2 mol eq) of glycerol (containing <14% H_2O) and 844 mg (4.44 mmol; 20 mol %) of p-toluene-sulfonic acid monohydrate were added to a solution of 7.0 g (22.2 mmol) of (-)-camphor-10-sulfonamide **7** [17] in 150 ml of benzene. The mixture was heated under reflux for 22 h with azeotropic removal of water. Since TLC showed still some starting material, 1.63 g (approx. 17.8 mmol) of glycerol were added, and the refluxing was continued for another 44 h. Since conversion was still incomplete, another 2.04 g (approx. 1 eq) of glycerol an 203 mg (1.07 mmol; 4.8 mol %) of p-toluene-sulfonic acid were added and the refluxing was continued for another 4 days. During the whole reflux time, benzene was continuously removed by azeotropic distillation (totally 600 ml) and replaced by dry benzene. Even though TLC still showed some starting material, the resulting emulsion was concentrated under reduced pressure. The oily residue was immediately chromatographed on silicagel (hexane/ethyl acetate 6:1 (4.2 l), then 4:1 (2.5 l) and finally 2:1 (6.6 l)), to afford 2.55 g (8.08 mmol; 36.4 %) of the starting material **7** and 4.90 g (12.58 mmol; 56.7 %) of the spiro-ketal **6** as a mixture of diastereomers. 3.28 g (8.4 mmol; 37.8 %) of **6** were isolated in diastereomerically pure, crystalline form (mp. after recrystallization from hexane 107-108° C; $[\alpha]_D$=+13.4 (c=2.05 in chloroform)); R_f: (hexane/ethyl acetate 2:1) 0.22. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.91 (s, 3H); 0.95 (s, 3H); 1.311/1.314 (2d, 12H, J=6.8 Hz); 1.48 (d, 1H, J=12.7 Hz); 1.70-1.89 (m, 2H); 1.97-2.22 (m, 3H); 2.24-2.38 (m, 1H); 2.59 and 3.46 (AB-system, 2d, 2H, J=14.2 Hz); 3.44-3.57 (m, 1H); 3.72 (heptet, 2H, J=7 Hz); 3.80 (dd, 1H, J=11.2 Hz and 1.8 Hz); 3.91-4.16 (m, 4H). IR ($CHCl_3$): 3474, 2967, 2945, 2880, 1730 w, 1473, 1452, 1400, 1390, 1370, 1327, 1196, 1180, 1160, 1135, 1117, 1042, 1025, 978, 943 w, 924 w, 902 w, 880, 854 w, 660, 644. MS m/z: 225 (100 %), 109 (30 %), 69 (23 %), 57 (31 %), 55 (34 %), 44 (31 %).

mesylate **11** [16]

from spiro ketal 6: Under argon, 5.0 g (12.8 mmol) of spiro-ketal **6** were dissolved in 50 ml of dichloromethane. At 0° C 2.24 ml (16.1 mmol) of NEt_3 and 1 ml (12.9 mmol) of methanesulfonyl chloride were added and the solution was stirred at rt for 2 h. Afterwards, the reaction mixture was diluted with 50 ml dichloromethane and extracted 3 times with 50 ml of 1N HCl (aq). The aqueous layers were reextracted twice with 50 ml of dichloromethane. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford 5.65 g (12.1 mmol; 94.4%) of mesylate **11** as a slightly yellow solid. Recrystallization from cyclohexane lead to diastereomerically pure white crystals melting at 116-117° C ($[\alpha]_D$=+12.7 (c=2.16 in chloroform). R_f: (hexane/ethyl acetate 2:1) 0.22. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.90 (s, 3H); 0.99 (s, 3H); 1.23-1.39 (m, including d at 1.31, 12H, J=6.8 Hz, and underneath 1H); 1.47 (d, 1H, J=13 Hz); 1.70-2.10 (m, 4H); 2.19-2.33 (m, 1H); 3.15 (s, 3H); 2.61 and 3.26 (AB-system, 2d, 2H, J=14 Hz); 3.63-3.82 (m, 3H); 4.05 (t, 1H, J=7 Hz); 4.21-4.36 (m, 2H); 4.5-4.62 (m, 1H). IR ($CHCl_3$): 2965, 2950, 2890, 1472, 1450, 1400, 1390, 1355, 1330, 1195, 1175, 1137, 1120, 1025, 977, 878, 850, 830, 657. MS (FD) m/z: 468 (M^++1, 100 %).

from glycidol-mesylate 12: Under argon, a solution of 157.7 mg (0.5 mmol) of (-)-camphor-10-sulfonamide **7** and 152.2 mg (1 mmol) of glycidol-mesylate **12** (synthesized from glycidol by standard procedure [19]) in 4 ml of dichloromethane was added at 0° C to a solution of 35.5 mg (0.25 mmol) of $BF_3{\cdot}Et_2O$ in 2 ml of dichloromethane. After stirring the reaction mixture at 0° C for 2 h and at rt for 2 1/2 h, it was diluted with 10 ml of dichloromethane. The organic layers were washed with 10 ml of H_2O, combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The colourless, oily residue (290 mg) was chromatographed on silicagel (hexane/ethyl acetate 4:1 (200 ml) then hexane/ethyl acetate 3:1 (300 ml)), to

yield 209 mg (0.45 mmol; 89.4%) of the mesylate **11** as a mixture of diastereomers. 61 mg (0.13 mmol; 26.1%) of **11** were isolated in diastereomerically pure and crystalline form. Analytical data as above.

aryl ether **13**

From mesylate 11: To a solution of 1.5 g (3.2 mmol) of mesylate **11** and 720 mg (3.52 mmol) of 4-(3-fluorophenoxy)-phenol **5** [9] in 10 ml of DMSO were added 970 mg (7.04 mmol) of anhydrous K_2CO_3. After stirring at 100° C for 19 h, the brown reaction mixture was poured onto 50 ml of H_2O and extracted 3 times with ether. The organic layers were washed with 50 ml of H_2O and 50 ml of brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The oily residue was chromatographed on silicagel (hexane/ethyl acetate 8:1) to afford 1.44 g (2.5 mmol; 78.2%) of the aryl ether **13** as a colourless oil ($[\alpha]_D$=+7.78 (c=1.92 in chloroform; sample still contained traces of solvent)). R_f: (hexane/ethyl acetate 2:1) 0.46. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.96 (s, 3H); 1.02 (s, 3H); 1.20-1.38 (m including d at 1.30, 12Hz, J=6.8 Hz, and underneath 1H); 1.51 (d, 1H, J=13 Hz); 1.72-1.87 (m, 2H); 1.99-2.14 (m, 2H); 2.21-2.38 (m, 1H); 2.72 and 3.24 (AB-system, 2d, 2H, J=14 Hz); 3.72 (heptet, 2H, J=7 Hz); 3.81-3.90 (m, 1H); 3.98-4.19 (m, 2H); 4.22-4.39 (m, 2H); 6.62 (dt, 1H, J=10.5 Hz and J=2.5 Hz, arom. H-C(2)); 6.66-6.79 (m, 2H, arom. H-C(4) and H-C(6)); 6.90-7.03 (m, 4H); 7.16-7.29 (m, 1H, arom. H-C(5)). IR (CH_2Cl_2): 2975, 2950, 2885, 1733, 1616, 1598, 1504, 1485, 1450, 1373, 1333, 1242, 1205, 1160, 1138, 1122, 1043, 1027, 979, 965. MS (FD) m/z: 576 (M^++1, 45 %), 575 (M^+, 100 %).

From racemic 3-[4-(3-fluorophenoxy)-phenoxy]-1,2-propanediol (3): Under argon, a solution of 410.1 mg (1.3 mmol) of (-)-camphor-10-sulfonamide **7**, 362.5 mg (1.3 mmol) of rac. diol **3** and 26.5 mg (0.14 mmol; 10.7 mol %) of p-toluene-sulfonic acid monohydrate in 20 ml of benzene was heated under reflux for 19 h with azeotropic removal of water. After removing the solvent under reduced pressure, the brownish, oily residue (910 mg) was flash-chromatographed (hexane/ethyl acetate 10:1 (660 ml), then 8:1 (450 ml), then 4:1 (500 ml)), to yield 257.2 mg (0.45 mmol; 34.4 %) of aryl ether **13** as a mixture of diastereomers. 118.2 mg (0.21 mmol; 15.8 %) of **13** were isolated in diastereomerically pure form as colourless oil. Analytical data see above.

(2R)-(-)-3-[4-(3-fluorophenoxy)-phenoxy]-1,2-propanediol ((R)-**3**)

Route A: Under argon, a solution of 0.609 g (2.2 mmol) of α-hydroxy-ketone **4** in 10 ml of methanol and a solution of 18.8 mg ($2.3 \cdot 10^{-3}$ mmol) of $[Ru_2Cl_4(S\text{-BINAP})_2](NEt_3)$ in 10 ml of methanol were successively transfered via a steel capillary into a 50-ml-autoclave. The inert gas in the autoclave was replaced by hydrogen in three cycles (20 bar/normal pressure). Finally, the autoclave was pressurized to 95 bar with hydrogen. After completion of the reaction (12 hours at 25° C), TLC-analysis showed complete conversion of **4**. The reaction mixture was concentrated under reduced pressure and the orange-brown, oily residue (640 mg) was flash-chromatographed (dichloromethane/diethyl ether 1:1), to afford 530 mg (1.90 mmol; 86.4 %; 95 % ee) of the diol (R)-**3** as white crystals ($[\alpha]_D$=-6.2 (c=0.93 % in ethanol) [15]). R_f: (dichloromethane/diethyl ether 1:1) 0.14. HPLC: hexane/2-propanol 90:10; flow=1ml/min; detection: 230 nm; Chiralcel-OD (Daicel; 4.6x250 mm): 22.7 min (major enantiomer), 28.3 min (minor enantiomer). ^{1}H-NMR (250 MHz, $CDCl_3$): 2.08 (br t, 1H, J=5.9 Hz, exchanges with D_2O); 2.66 (br d, J=4.3, 1H, exchanges with D_2O); 3.72-3.92 (m, 2H); 4.04 (d, 1H, J=2.2 Hz), 4.06 (br s, 1H); 4.06-4.18 (m, 1H); 6.63 (dt, 1H, J=10.4 Hz and 2.4 Hz, arom. H-C(2)); 6.67-6.79 (m, 2H, arom. H-C(4) and H-C(6)); 6.92 and 7.01 (2 dt, 4H, J=9.3 Hz and 2.6 Hz); 7.18-7.29 (m, 1H, arom. H-C(5)). IR (CH_2Cl_2): 3580, 2935, 1610, 2595, 1500, 1483, 1457, 1448, 1240, 1205, 1120, 1042, 1009, 963, 840. MS m/z: 278 (M^+, 100 %).

Route B: To a solution of 2.04 g (3.54 mmol) of aryl ether **13** in 25 ml of methanol 10 ml (40 mmol) 4N of HCl (aq) were added at rt. The white suspension was stirred at rt for 16 h and was then diluted with methanol containing 10% H_2O. The resulting mixture was extracted 3 times with cyclohexane. The cyclohexane-phases were washed twice with methanol containing 10% H_2O, dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 920 mg of a colourless oil. The polar phases ($MeOH/H_2O$) were combined and the methanol was removed under reduced pressure. The residue was diluted with H_2O and extracted 3 times with diethyl ether. The organic phases were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The colourless, oily residue (2.1 g) was crystallized from hexane to afford 797 mg (2.86 mmol; 80.9%; >98% ee) of the diol (R)-**3** as white crystals melting at 57-59° C ($[\alpha]_D$=-6.53 (c=1.32 % in ethanol) [15]). The mother liquor was combined with the residue of the cyclohexane-phases and the solvent was removed under reduced pressure. The residue was chromatographed on silicagel (hexane (300 ml), then hexane/ethyl acetate 10:1 (500 ml)), to afford 1.077 g (3.41 mmol; 96.4%) of (-)-camphor-10-sulfonamide **7** as a colourless oil. In an analogous experiment it could be shown, that diol (R)-**3** and (-)-camphor-10-sulfonamide **7** can be easily separated by direct crystallization from hexane. In that procedure the reaction mixture was diluted with water, and the methanol was removed under reduced pressure. Extraction with dichloromethane afforded a crude mixture of the two reaction products. Crystallization from hexane yielded the diol (R)-**3** as white crystals, while the (-)-camphor-10-sulfonamide **7** was isolated from the mother liquor. Analytical data see above.

Acknowledgements

The authors thank Mrs. Gabrielle Lecis, Mrs. Nadia Vostenka, Mr. Beat Eng and Mr. Christoph Handschin for their skillful assistance and Mrs. Maja Schwarb for helping to prepare the manuscript.

References

[1] Karrer, F. *EP-A-0 276 196* (Ciba-Geigy AG, Basel, Switzerland), 1988.

[2] Nelson,W. L.; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006.

[3] Karrer, F.; Kayser, H.; Buser, H.P.; Ramos Tombo, G.M. to be submitted to *Chimia* **1993**.
see also: Karrer, F.; Buser, H.P.; Ramos, G.; Rindlisbacher, A.; Venanzi, L.M.; Ward, T. R. *EP 501912-A1*, (Ciba-Geigy AG, Basel, Switzerland), 1991.

[4] Koenig, K. E. in Morrison, J. D. (Ed.) *Asymmetric Synthesis, Vol 5*; Academic Press, New York, 1985, chapter 3.

[5] a) Noyori, R.; Takaya, H. *Acc. Chem Res.* **1990**, *23*, 345.
b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.
c) Sayo, N.; Akutagawa, S.; Noyori, R.; Takaya, H. *EP-A-0 295 890* (Takasago Int. Corp., Tokyo, Japan), 1988.
d) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5658.
e) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509

[6] a) Spindler, F.; Pittelkow, U.; Blaser, H.U. *Chirality* **1991**, *3*, 370.
b) Yoshikawa, K.; Yamamoto, N.; Murata, H.; Awano, K.; Morimoto, T.; Achiwa, K. Tetrahedron *Asymmetry* **1992**, *3*, 13.

[7] a) Ohjo, Y.; Natori, Y.; Takeuchi; S.; Yoshimura, J. *Chem. Lett.* **1974**, *33*, 709.
b) ibid, 1327.

[8] a) Blaser, H.U.; Müller, M. *Studies in Surface Science and Catalysis. (Heterogeneous Catalysis and Fine Chemicals II)* **1991**, *59*, 73.
b) Blaser, H.U. *Tetrahedron:Asymmetry* **1991**, *2*, 843, and references cited therein.
[9] a) Zurflüh, R.; Urech, P. *EP-A-0 072 475* (Hoffmann-LaRoche & Co, Basel, Switzerland), 1983.
b) *Methoden der Organischen Chemie (Houben-Weyl) Vol. VI/3*, 85, 145.
[10] Shivarama Holla, B.; Kalluraya, B.; Nath, S. C. *J. prakt. Chemie* **1988**, *330*, 549.
[11] Fales, H. M.; Jaouni, T. M.; Babashak, J. F. *Anal. Chem.* **1973**, *45*, 2302.
[12] a) Long Jr., L.; Burger, A. *J. Org. Chem.* **1941**, *6*, 852.
b) Eistert, B. *Ang. Chem.* **1949**, *61*, 185.
[13] Burckhalter, J. H.; Sam, J. *J. Am. Chem. Soc.* **1952**, *74*, 187.
[14] a) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.
b) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans 1*, **1989**, 1571.
c) Taber, D.; Silverberg, L. *Tetrahedron Lett.* **1991**, *32*, 4227.
[15] G. Ramos, Ciba-Geigy AG, Basel; unpublished results: diol (R)-**3**, synthesized from α,β-isopropylidene-γ-tosylate (Fluka): $[\alpha]_D$=-6.5 (c = 1 % in ethanol).
[16] Hsu, C.-Y.; Lin, Y.-S.; Uang, B.-J. *Tetrahedron: Asymmetry* **1990**, *1*, 219.
[17] Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885.
[18] Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.
[19] Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. A.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.