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Enantioselective Synthesis of (*R*)-Bufuralol via Dynamic Kinetic Resolution in the Key Step

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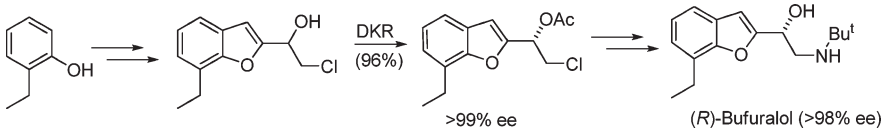

An enantioselective synthesis of (*R*)-bufuralol via a ruthenium- and enzyme-catalyzed dynamic kinetic resolution (DKR) has been achieved. The synthesis starts from readily available 2-ethylphenol and provides (*R*)-bufuralol in high ee and a good overall yield of 31%.

Introduction

Because of the chiral environment in biological systems, drug enantiomers often differ considerably in potency, pharmacological activity, and pharmacokinetics. The different physiological action has made it desirable to have access to enantiomerically pure compounds, and there is presently a requirement from the FDA that most chiral drugs are marketed as single enantiomers.[1] Therefore, the field of asymmetric synthesis is of great importance in the pharmaceutical industry.[2] Today there are a large number of methods available to prepare enantiomerically pure compounds,[2−4] and the most commonly used technique by industry is to separate racemic mixtures by resolution.[4] However, the major drawback of this technique is its limitations to give a maximum theoretical yield of 50% of the enantiomerically pure product, and furthermore, the product has to be separated from the starting material.[5] Dynamic kinetic resolution (DKR) is a solution to this problem where the nondesired enantiomer is continuously racemized during resolution. In recent years, combined enzyme- and transition-metal-catalyzed DKR of alcohols[6−8] and primary amines[6,9] has emerged as a powerful synthetic tool.

In 2004, we reported on a new efficient racemization catalyst, Ru complex **1**, which could be applied in DKR to give fast and efficient reactions at room temperature.[7] This system has successfully been applied to various secondary alcohols[10] and can be run on a large preparative scale (100 g to 1 kg).[11] In this paper, we have applied this system to DKR of a chlorohydrin

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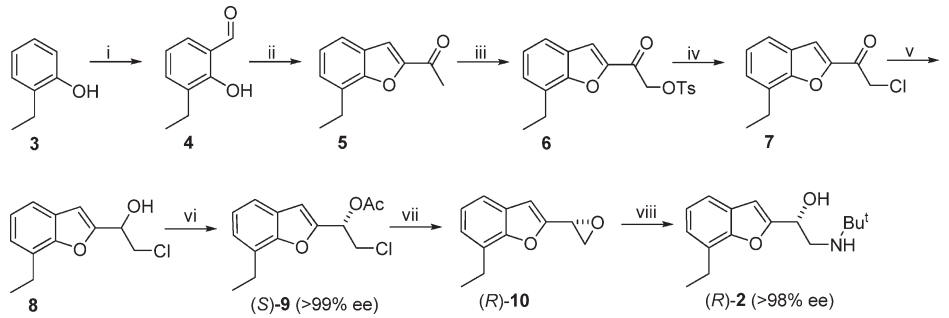
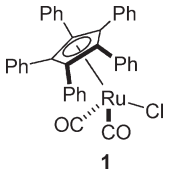
SCHEME 1[a]



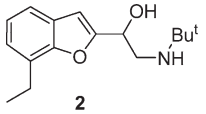
[a]Reagents and conditions: (i) HCHO, Et_3N, $MgCl_2$, MeCN, reflux for 5 h, then rt for 12 h, 77%; (ii) $ClCH_2COCH_3$, K_2CO_3, MeCN, reflux, 5 h, 80%; (iii) Koser's reagent [hydroxy(tosyloxy)iodo]benzene], MeCN, 60 °C, 1 h, 78%; (iv) $MgCl_2$, MeCN, reflux, 1 h, 94%; (v) $NaBH_4$, MeOH, rt, o/n, 94%; (vi) **1**, ^{t}BuOK, Na_2CO_3, PS-C "Amano" II, isopropenyl acetate, PhMe, 40 °C, 24 h, 96%; (vii) $LiOH \cdot H_2O$, EtOH, rt, 20 min, 93%; (viii) ^{t}BuNH$_2$, reflux, 30 h, 83%.

to give a key intermediate, which allows a total synthesis of the (*R*)-enantiomer of bufuralol (**2**, Scheme 1) in high ee from simple starting materials.



1

Benzofuran derivatives have been the subject of increased interest in recent years due to their diverse biological activities.[12] For example, they act as inhibitors of 5-lipoxygenase,[13] cyclooxygenase-2,[14] and β-amyloid (Aβ) aggregations,[15] antagonists for the brain CB1 receptor,[16] the central and peripheral $GABA_B$ receptor,[17] the angiotensin II receptor,[18] and the oxytocin (OT) hormone.[19] Bufuralol (**2**) is the most studied compound of this class. It is a nonselective β-adrenoceptor blocking agent of comparable potency as propranolol[20−22] and has proved effective for treatment of hypertension.[23] Furthermore, it is a potent nonselective β-adrenergic receptor antagonist[24] and an inhibitor of testosterone 6β-hydroxylase,[25] and it has been used in studies of cytochrome P450.[26]



2
Bufuralol

Various methods have been reported for the enantioselective preparation of bufuralol, and methods that provide high enantiomeric excess include asymmetric hydroboration,[27] Rh-catalyzed transfer hydrogenation,[28] and lipase-catalyzed acylation.[29] In this paper, we present an easy and efficient synthesis of enantiopure (*R*)-bufuralol ((*R*)-**2**) using DKR in the key step (Scheme 1).

Results and Discussion

The synthesis of (*R*)-bufuralol starts from readily available 2-ethylphenol (**3**) and is summarized in Scheme 1. Reaction of **3** with formaldehyde in a modified Casiraghi formylation[27a,30] afforded **4** in 77% yield. The aldehyde **4**

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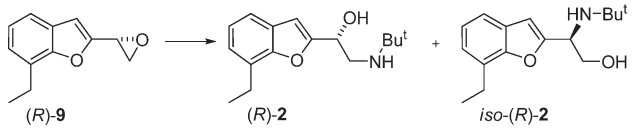
obtained was transformed into benzofuran **5** via a cyclization reaction using chloroacetone. Tosyloxylation of **5** in the α-position of the acetyl group using Koser's reagent[31] afforded **6**, and subsequent substitution of the tosylate group by a chloride using $MgCl_2$ gave chloro ketone **7** in 94% yield. The reduction of **7** with $NaBH_4$ afforded the chlorohydrin **8** in 94% yield.

PS-C "Amano" II has been shown to have an excellent enantioselectivity for the 1-phenyl-2-chloroethanol motif, and DKR has been successfully carried out on a wide range of derivatives.[10a] Racemic chlorohydrin **8** was therefore subjected to DKR using lipase PS-C "Amano" II in combination with ruthenium catalyst **1** and with isopropenyl acetate as the acyl donor. Reaction of **8** under DKR conditions in toluene at 40 °C using 2 mol % of ruthenium catalyst **1** gave full conversion after 24 h, and chlorohydrin acetate (*S*)-**9** was isolated in 96% yield in high enantioselectivity (>99% ee).

The chlorohydrin acetate (*S*)-**9** was transformed to enantiomerically pure epoxide (*R*)-**10** by treatment with 3 equiv of LiOH in 95% EtOH under ambient conditions. Attempts to purify the epoxide by column chromatography were unsuccessful and led to some decomposition. This observation is in agreement with that the epoxide has been reported to be unstable.[27] However, under basic conditions, at room temperature under oxygen atmosphere, the epoxide proved stable for extended periods of time (up to several weeks).

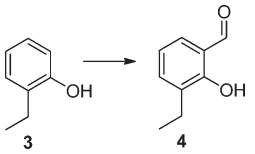


Treatment of the epoxide with *tert*-butylamine in a polar protic solvent (EtOH or $EtOH/H_2O$, 4:1) gave a fast reaction, but unfortunately with moderate regioselectivity ((*R*)-**2**/iso-(*R*)-**2** ≈ 3:1). However, carrying out the reaction in a less polar solvent (toluene) resulted in a slower reaction affording the products in an improved regioselectivity in favor of the (*R*)-**2** regioisomer. Finally, the crude epoxide was allowed to react in neat *tert*-butylamine[27a] to give a good selectivity in favor of (*R*)-**2** ((*R*)-**2**/*iso*-(*R*)-**2** ≈ 10:1), and (*R*)-**2** was isolated in a yield of 83% with >98% ee after chromatographic purification.

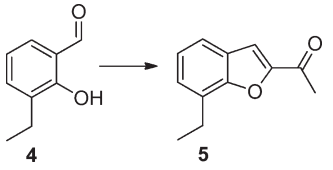
Conclusions

In summary, we have reported a highly enantioselective synthesis of (*R*)-bufuralol. The synthesis is based on the use of a simple starting material and the key step is a dynamic kinetic resolution of chlorohydrine **8** to give (*S*)-β-chloroacetate (*S*)-**9** in high ee. The latter compound was transformed into the target compound (*R*)-**2** via two further steps. The work reported herein illustrates a useful application of combined metal- and enzyme-catalyzed DKR for the synthesis of a chiral drug.

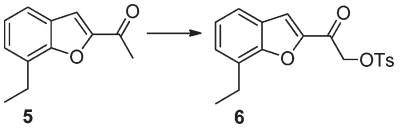
Experimental Section



Synthesis of 3-Ethyl-2-hydroxybenzaldehyde (4). Paraformaldehyde (16.21 g, 540 mmol) was added in small portions to a solution of 2-ethylphenol (**3**) (9.77 g, 80 mmol), magnesium chloride (11.42 g, 120 mmol), and triethylamine (30.36 g, 300 mmol) in acetonitrile (100 mL) at rt. The mixture was refluxed for 5 h, stirred for 12 h at rt, and acidified with a 5% hydrochloric acid (200 mL). The mixture was extracted with diethyl ether (2 × 100 mL), the extract was dried over $MgSO_4$, the solvent was removed under vacuo and the product was isolated by distillation (9.24 g, 77% yield). Spectral data were in accordance with those reported in the literature.[27a]



Synthesis of 1-(7-Ethylbenzofuran-2-yl)ethanone (5). Chloroacetone (7.32 g, 79.2 mmol) was added dropwise to a mixture of **4** (10.8 g, 72 mmol), anhydrous potassium carbonate (9.95 g, 72 mmol), and acetonitrile (60 mL) at 35 °C. The mixture was refluxed for 5 h and cooled to rt. The precipitated solid was filtered off and washed with acetonitrile (10 mL). Purification by column chromatography (pentane/ethyl acetate 95:5) afforded product **5** as a brown solid (10.9 g; 80%). Spectral data were in accordance with those reported in the literature.[27a]



Synthesis of 2-Tosyloxy-1-(7-ethylbenzofuran-2-yl)ethanone (6).[28] Kosers's reagent [hydroxy(tosyloxy)iodo]benzene][31] (2.85 g; 7.26 mmol) was added to a stirred solution of ketone **5** (1.24 g; 6.6 mmol) in MeCN (50 mL). The yellow suspension was heated to 60 °C for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). MeCN was evaporated under reduced pressure, and the remaining aqueous phase was extracted with EtOAc (4 × 50 mL). The combined organic phases were washed with brine (1 × 100), dried over Na_2SO_4, filtered, and evaporated, yielding the crude product as a brown oil. Purification by column chromatography (pentane/ethyl acetate 95:5) afforded the pure product **6** as a brown oil (1.84 g; 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.5 Hz, 3H), 2.45 (s, 3H), 2.97 (q, *J* = 7.5 Hz, 2H), 5.25 (s, 2H), 7.25−7.29 (m, 1H), 7.33−7.37 (m, 3H), 7.54 (dd, *J* = 6.6 Hz, *J* = 1.1 Hz, 1H), 7.88−7.90 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.7 (CH_3), 22.7 (CH_2), 69.6(CH_2), 115.1 (CH), 121.0 (CH), 124.6 (CH), 126.3 (C), 128.0 (CH),

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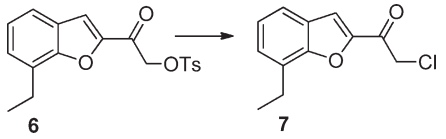
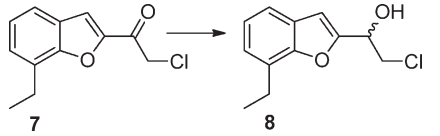
128.2 (CH), 129.0 (C), 130.0 (CH), 132.6(C), 145.4 (C), 149.5 (C), 154.5 (C) 181.5 (CO).



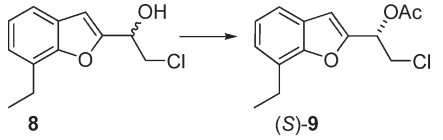
6 7

Synthesis of 2-Chloro-1-(7-ethylbenzofuran-2-yl)ethanone (7).[32] Tosylate **6** (1.84 g; 5.15 mmol) was dissolved in MeCN (50 mL). $MgCl_2$ (0.74 g; 7.73 mmol) was added, and the stirred solution was heated to reflux (90 °C). After 1 h, the reaction was quenched by dilution with water. MeCN was evaporated under reduced pressure, and the remaining aqueous phase was extracted with DCM (4 × 50 mL). The combined organic phase was washed with brine (1 × 100 mL), dried over Na_2SO_4, filtered, and evaporated, yielding 2-chloro-1-(7-ethylbenzofuran-2-yl)ethanone (**7**) as a brown solid (1.08 g; 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3H), 3.01 (q, J = 7.5 Hz, 2H), 4.75 (s, 2H, CH2Cl), 7.28−7.38 (m, 2H), 7.59 (dd, J = 6.5 Hz, J = 1.3 Hz, 1H), 7.68 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 22,7 (CH_2), 30.2 (CH_2), 115.0 (CH), 120.9 (CH), 124.4 (CH), 126.6 (C), 127.8 (CH), 129.0 (C), 149.9 (C), 154.6 (C), 182.2 (CO).



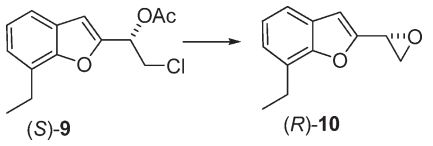
7 8

Synthesis of *rac*-2-Chloro-1-(7-ethylbenzofuran-2-yl)ethanol (8). $NaBH_4$ (63 mg, 1.65 mmol) was added portionwise to a solution of chloro ketone **7** (666 mg, 3 mmol) in MeOH (75 mL) stirred at 0 °C under argon. The stirring was continued while the mixture was allowed to warm to ambient temperature. When the reaction was complete, it was stopped and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (80 mL) and extracted with water (3 × 50 mL). The separated organic phases were washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a light yellow oil was (626 mg, 94% yield). Spectral data were in accordance with those reported in the literature.[27b]



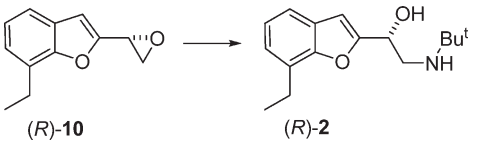
8 (*S*)-**9**

DKR of 2-Chloro-1-(7-ethylbenzofuran-2-yl)ethanol ((*S*)-9).[29] A 10 mL Schlenk flask was charged with $RuCl(CO)_2(\eta^5\text{-}C_5Ph_5)$[7b] (38.4 mg, 0.06 mmol), PS-C "Amano" II (100 mg), and Na_2CO_3 (318 mg, 3 mmol). Toluene was added, and the flask was evacuated and backfilled with argon three times. To this mixture was added a solution of ^{t}BuOK (0.5 M in THF; 120 μL, 0.06 mmol) and the mixture stirred for 5 min. Chlorohydrin **8** (672 mg, 3 mmol) was added, and after 5 min of stirring, isopropenyl acetate (450 mg, 4.5 mmol) was injected. After being stirred for 24 h at 40 °C, the reaction mixture was filtered through a short Celite plug and concentrated. Purification by column chromatography (silica gel; pentane/EtOAc 9:1) afforded (*R*)-1-acetoxy-2-chloro-1-(7-ethylbenzofuran-2-yl)ethane ((*S*)-**9**) as a light yellow oil (766 mg, 96% yield, >99% ee): $[\alpha]^{23}_D$ = +139.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.5 Hz, 3H), 2.16 (s, 3H), 2.93 (dq, J = 1.3 Hz, J = 7.5 Hz, J = 14.6 Hz, 2H), 3.99 (dd, J = 0.4 Hz, J = 6.2 Hz, 2H), 6.18 (dt, J = 0.5 Hz, J = 6.2 Hz, 1H), 7.12−7.15 (m, 1H), 7.16 (q, J = 6.3 Hz, J = 14.6 Hz, 1H), 7.39 (dd, J = 1.6 Hz, J = 7.3 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.9 (CH_3), 22.8 (CH_2), 43.2 (CH_2), 68.8 (CH), 106.6 (CH), 118.9 (CH), 123.3 (CH), 124.1 (CH), 127.1 (C), 127.9 (C), 151.2 (C), 153.5 (C), 169.8 (CO).



(*S*)-**9** (*R*)-**10**

Synthesis of (*R*)-7-Ethyl-2-oxiranylbenzofuran ((*R*)-10). Chloroacetate (*S*)-**9** (464 mg, 1.74 mmol) was dissolved in 95% EtOH (20 mL) under ambient conditions. $LiOH \cdot H_2O$ (219 mg, 5.22 mmol) was added, and the mixture was stirred at room temperature. The reaction was followed by TLC (silica plate, pentane/EtOAc 95:5), and after 20 min no starting material was left. The reaction was quenched with $NaHCO_3$ (877 mg, 10.44 mmol), and the EtOH was removed on a rota-vap. To the residue was added brine (10 mL), and the mixture was extracted with Et_2O (5 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give (*R*)-**10** as a light yellow oil (305 mg, 93% yield): $[\alpha]^{23}_D$ = +36.6 (*c* 1, $CHCl_3$). Spectral data were in accordance with those reported in the literature.[27a]



(*R*)-**10** (*R*)-**2**

Synthesis of (*R*)-(+)-2-*tert*-Butylamino-1-(7-ethylbenzofuran-2-yl)ethanol ((*R*)-2).[27b] A mixture of epoxide (*R*)-**10** (200 mg, 1.06 mmol) and *tert*-butylamine (20 mL) was placed in a 50 mL round-bottomed flask and refluxed for 30 h. After the mixture was cooled to rt, the excess of *tert*-butylamine was removed under reduced pressure. Chromatographic purification (silica gel, dichloromethane/methanol/triethylamine 9:1:0.1) afforded (*R*)-**2** as a light yellow oil (231 mg, 83%, >98% ee): $[\alpha]^{25}_D$ = +53.2 (*c* 0.25, $CHCl_3$) [lit.[28] (for (*S*)-**2**) $[\alpha]^{20}_D$ = −54.5 (*c* 0.37, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.33 (t, J = 7.5 Hz, 3H), 2.92 (q, J = 7.2 Hz, J = 7.5 H, 2H), 3.06 (dd, J = 7.9 Hz, J = 12.1 Hz, 1H), 3.12 (dd, J = 4.1 Hz, J = 11.9 Hz, 1H), 4.94 (dd, J = 4.2 Hz, J = 6.4 Hz, 1H), 6.68 (d, J = 0.9 Hz, 1H), 7.07−7.16 (m, 2H),7.37 (dd, J = 1.3 Hz, J = 7.6 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.8 (CH_2), 29.1 ($3CH_3$), 46.2 (C), 50.3 (CH_2), 66.5 (CH), 103.1 (CH), 118.4 (CH), 122.8 (CH), 123.0 (CH), 127.6 (C), 127.8 (C), 153.4 (C), 158.3 (C).

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Supporting Information Available: General methods. Copies of ^{1}H and ^{13}C NMR spectra of **6**, **7**, **8**, (*S*)-**9**, and (*R*)-**10**. This material is available free of charge via the Internet http://pubs.acs.org.

(32) Jordan, S.; Markwell, R. E.; Woolcott, B. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 928–933.