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A new synthetic approach to enantiomerically enriched dihydrobenzofurans: use of a hydrolytic kinetic resolution and an intramolecular epoxide ring opening protocol using 1-benzyloxy-2-oxiranylmethylbenzenes

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Abstract—A novel approach towards the preparation of racemic 1-benzyloxy-2-oxiranylmethylbenzenes using dimethyldioxirane and their hydrolytic kinetic resolution using (*R*,*R*)(Salen)Co(III)(OAc) (Jacobsen's catalyst) to afford the (*R*)-epoxides and (*S*)-1,2-diols, enantioselectively, is described. The (*R*)-1-benzyloxy-2-oxiranylmethylbenzenes were then cyclized via an intramolecular epoxide opening reaction to give (*S*)-2-hydroxymethyl-2,3-dihydrobenzofurans.

Naturally occurring 2-substituted-2,3-dihydrobenzofurans are an important class of biologically active oxygen-containing heterocycles.[1–6] Natural products possessing the dihydrobenzofuran nucleus, exhibit a wide range of biological activities. For example, arthrographol is an anti-fungal,[7] megapodiol is an anti-leukaemic,[8] 2-(3,4-dimethoxyphenyl)-3-hydroxymethyl-5-(3-hydroxypropyl)-2,3-dihydrobenzofuran-7-ol[9] and conocarpan are anti-cancer agents,[10] tremetone causes milk sickness in cattle[11] and furaquinocines are antibiotics.[12] There are only a few methods, to the best of our knowledge, established for the synthesis of enantiomerically enriched dihydrobenzofurans.[7–12]

Herein, we report a new synthesis of enantiomerically enriched dihydrobenzofuran derivatives and naphtho[1,2-*b*]furans. *o*-Allylphenols **2a**–**c**[13–15] were converted to the corresponding benzylethers **3a**–**c**,[16] in order to be able to isolate the epoxy derivatives in the subsequent step. The resulting *o*-allylbenzylethers **3a**–**c** were reacted with dimethyldioxirane[17–20] generated in situ from Oxone and acetone to furnish racemic 1-benzyloxy-2-oxiranylmethylbenzenes **4a**–**c**.[21] Next, the solvent-free hydrolytic kinetic resolution (HKR) of the racemic 1-benzyloxy-2-oxiranylmethylbenzenes **4a**–**c**, using the chiral salen cobalt complex, (*R*,*R*)(Salen)-Co(III)(OAc),[22,23] gave the optically pure (*R*)-epoxides **5a**–**c** and (*S*)-1,2-diols **6a**–**c** in 80–90% ee's and 78–85% ee's, respectively (Scheme 1).[24]

Similarly, *o*-allylnaphthol **8** was converted to benzyl ether **9** on reaction with benzyl bromide and anhydrous potassium carbonate in acetone. Benzyl ether **9** was subsequently treated with dimethyldioxirane to afford racemic epoxide **10**, which underwent solvent-free HKR using Jacobsen's catalyst to give (*R*)-epoxide **11** and (*S*)-1,2-diol **12** in 80% ee and 78% ee, respectively (Scheme 1).

The racemic epoxides **4a**–**c** and **10** and (*R*)-epoxides **5a**–**c** and **11** were debenzylated and cyclized in situ via an intramolecular epoxide opening reaction. This was accomplished using 10% Pd–C in methanol under a H_2 atmosphere and adding a catalytic amount of triethylamine and anhydrous potassium carbonate at room temperature[25] to furnish the desired products, racemates **7a**–**c** and **13** and enantiomerically enriched **1a**–**c** and **13a** in 85–92% ee's and 75% ee, respectively,[26] via a S_N2 mechanism (Schemes 2 and 3). The $[\alpha]_D^{25}$ of **1b** was +20.0 (*c* 1.5, $CHCl_3$), which compared favourably with that published, (lit. +21.0, *c* 1.0, $CHCl_3$).[27] The formation of (*S*)-5-methyl-2-hydroxymethyl-2,3-dihydrobenzofuran **1b** from (*R*)-epoxide **5b** was confirmed by

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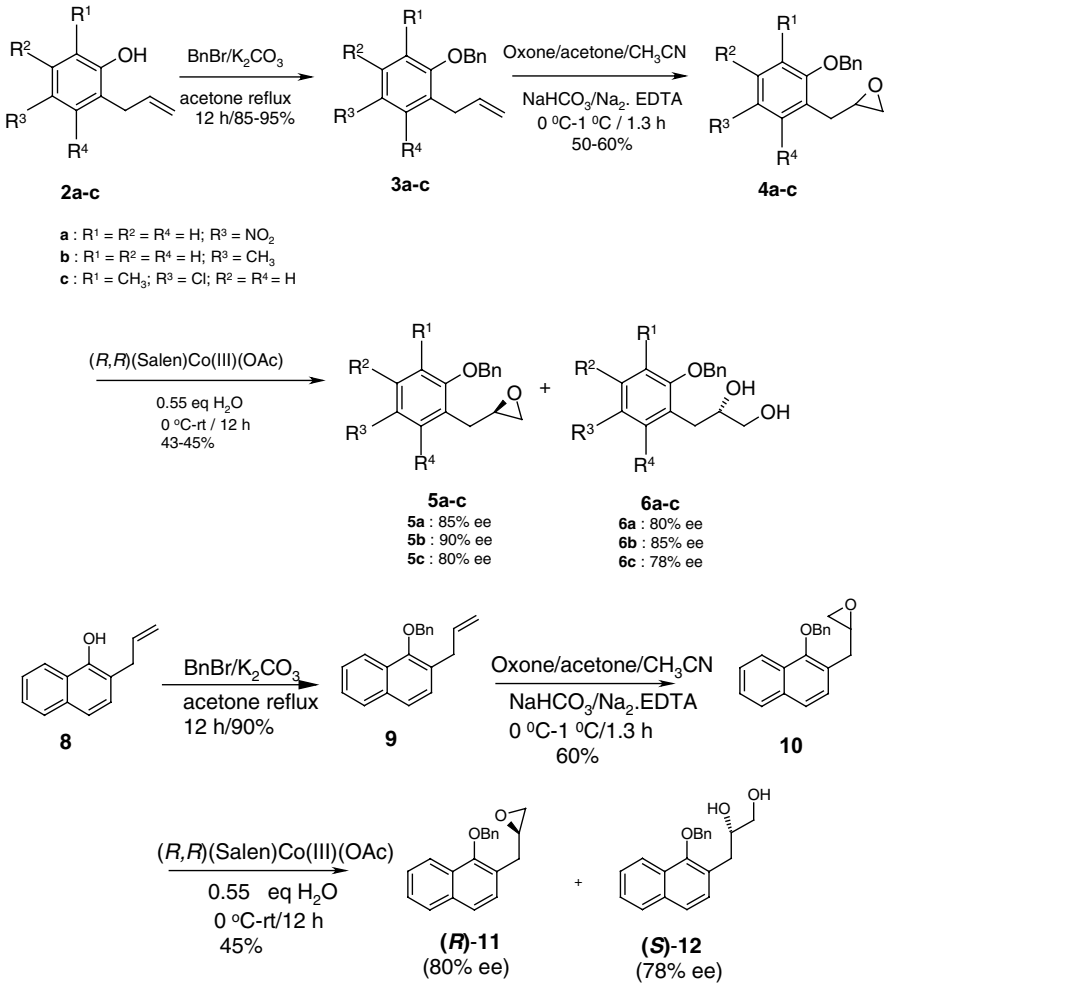
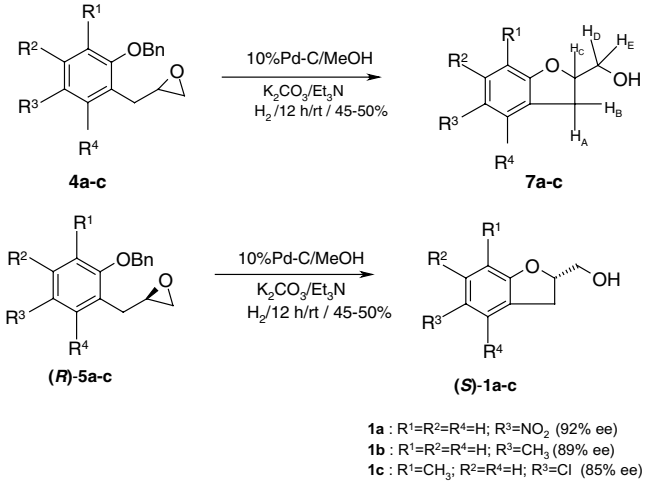
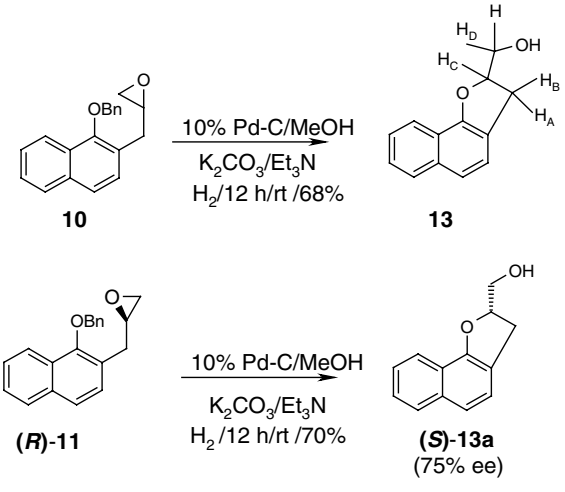


Scheme 1.



Scheme 2.



Scheme 3.

comparison with a sample prepared from enzymatic kinetic resolution by a standard procedure[27] using a lipase.

In summary, a new synthesis of optically pure 2-hydroxymethyl-2,3-dihydrobenzofurans and a naphtho[1,2-*b*]furan in 85–92% ee's and 75% ee, respectively, was accomplished by debenzylation and in situ cyclization via an intramolecular epoxide ring opening reaction of **5a**–**c** and **11**, which in turn were prepared from HKR in 80–90% ee's and 78% ee, respectively.

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16. General procedure for the synthesis of 1-benzyloxy-2-allyl-4-nitrobenzene **3a**. A mixture of 2-allyl-4-nitrophenol (350 mg, 1.95 mmol) and anhydrous K_2CO_3 (540 mg, 4 mmol) in dry acetone (10 mL) was allowed to stir for 30 min at room temperature. To this was added benzyl bromide (334 mg, 1.95 mmol) dropwise and the resulting mixture refluxed for 12 h at 60 °C. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure to afford a residue, which was extracted with dichloromethane (5 × 10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography over silica gel using pet. ether as eluent to furnish **3a** as a semi-solid (490 mg, 94%), (**3b**,**c** and **9** were prepared similarly). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.41 (m, 2H) 5.20 (m, 4H), 5.99 (m, 1H), 6.89 (m, 1H), 7.40 (m, 5H), 8.00 (m, 2H); MS (EI): *m/z* 269 (M^+, 100%).
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21. Typical procedure for the synthesis of (±)-1-benzyloxy-2-oxiranylmethyl-4-nitrobenzene **4a**. To an acetonitrile solution (54 mL) of olefin **3a** (1.74 g, 7.3 mmol) was added Na_2. EDTA solution (36.3 mL, 4×10^{-4} M) and the resulting homogeneous solution was cooled to 0 °C. To this was added precooled acetone (7.3 mL) using a precooled syringe. After 10 min, a mixture of $NaHCO_3$ (4.75 g, 56 mmol) and Oxone (22.5 g, 36 mmol) was added in portions over a period of 1 h while maintaining a pH of 7. The reaction was complete in 1.3 h by TLC. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (250 mL). The combined extracts were washed with brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography using pet. ether to afford **4a** as an oil (50%). Similarly, **4b**,**c** and **10** were prepared in 50–60% yields, respectively. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (m, 1H), 2.69 (m, 1H), 2.99 (m, 2H), 3.20 (m, 1H), 5.20 (s, 2H), 6.99 (d, J = 10.0 Hz, 1H), 7.40 (m, 5H), 8.20 (m, 2H); MS (EI): *m/z* (M^+, 285, 100%).
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(a) (*R*)-1-Benzyloxy-2-oxiranylmethyl-4-nitrobenzene **5a**. Yield: 45%, $[\alpha]_D^{25}$ +12.2 (*c* 1.0, $CHCl_3$), HPLC {column chiracel OD, 0.5:9.5 ^{i}PrOH/*n*-hexane, flow rate: 1 mL/min, ee: 85%}.
(b) (*S*)-1-Benzyloxy-2-(2′,3′-dihydroxy)propanyl-4-nitrobenzene **6a**. Yield: 43%, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (br s, 1H), 2.82 (m, 2H), 3.30 (m, 3H), 4.10 (m, 1H), 5.20 (s, 2H), 6.90 (d, J = 10.0 Hz, 1H), 7.40 (m, 5H), 8.10 (m, 2H); $[\alpha]_D^{25}$ +10.1 (*c* 1.0, $CHCl_3$), HPLC {column chiracel OD, 0.5:9.5 ^{i}PrOH/*n*-hexane, flow rate: 1 mL/min, ee: 80%}.
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(a) (*S*)-5-Nitro-2-hydroxymethyl-2,3-dihydrobenzofuran **1a**. Yield: 50%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80 (s, 1H, OH), 3.20 (m, 1H, H_A), 3.40 (m, 1H, H_B), 3.80 (m, 1H, H_D), 3.95 (m, 1H, H_E), 5.10 (m, 1H, H_C), 6.80 (d, J = 10.0 Hz, 1H), 8.10 (m, 2H); MS (EI): *m*/*z* 195 (M^+, 100%), 149 (M^+-NO_2, 80%), 164 (55), 141 (34), 118 (25), 89 (10); $[\alpha]_D^{25}$ +14.00 (*c* 1.5, $CHCl_3$); HPLC {column chiracel OD, 0.5:9.5 ^{i}PrOH/*n*-hexane, flow rate: 1 mL/min, ee: 92%}.
(b) (*S*)-2-Hydroxymethyl-2,3-dihydronaphtho[1,2-*b*]furan **13a**. Yield: 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (br s, 1H, OH), 3.25 (m, 1H, H_A), 3.50 (m, 1H, H_B), 3.80 (m, 1H, H_D), 3.90 (m, 1H, H_E), 5.10 (m, 1H, H_C), 7.00 (m, 1H), 7.30 (m, 1H), 7.45 (m, 1H), 7.52 (m, 1H), 7.65 (m, 1H), 7.80 (m, 1H); MS (EI): *m*/*z* 200 (M^+, 100%); $[\alpha]_D^{25}$ +38.0 (*c* 1.0, $CHCl_3$); HPLC {column chiracel OD, 0.5:9.5 ^{i}PrOH/*n*-hexane, flow rate: 1 mL/min, ee: 75%}.

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