Synthesis of Chiral Crown Ethers from (+)- and (−)-2-Hydronaphtoin

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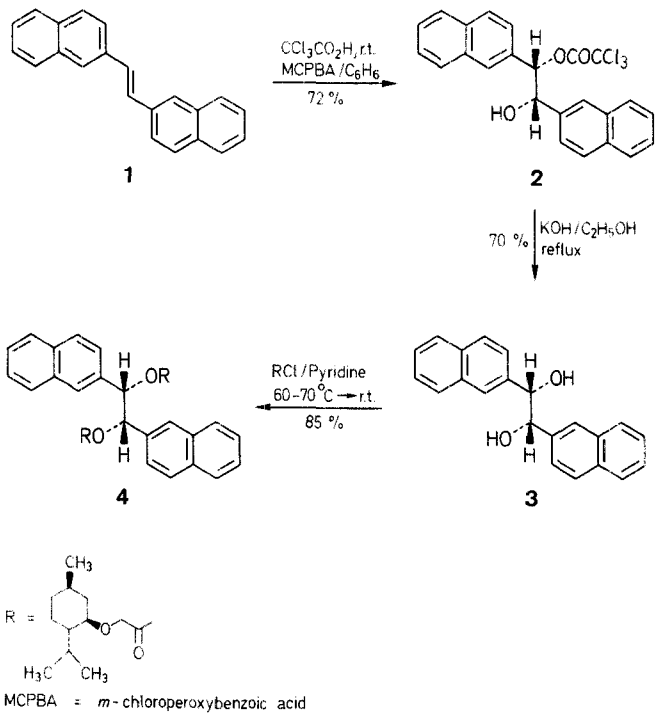
Racemic 2-hydronaphtoin has been resolved by formation of diastereoisomers with (−)-menthoxyacetyl chloride and fractional crystallization of menthoxyacetates. Enantiomers of 2,3,11,12-tetra(2-naphthyl)-18-crown-6 were obtained by condensation between (+) or (−)-2-hydronaphtoin and diethylene glycol ditosylate in the presence of potassium hydride as base and template.

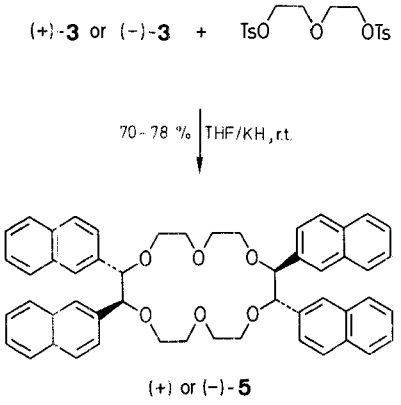
Chiral crown compounds can be used as enzyme-analog models, drug-receptor models, stereoselective catalysts and as agents for optical resolution of racemic substrates.[1-7] The number of available chiral crown ethers is limited[8,9] and some crown ethers incorporating complex moieties such as sugar derivatives are deceptive asymmetric reagents.[10,11] The fact that chiral 2,3,11,12-tetraphenyl-18-crown-6 is an effective asymmetric reagent[12] prompted us to synthesize chiral crowns from (+) and (−)-2-hydronaphtoin.

trans-1,2-Di(2-naphthyl)-ethylene **(1)** was prepared by a Wittig reaction between 2-naphthaldehyde and (2-naphthylmethyl)-triphenylphosphonium bromide according to a known procedure.[13] Reaction of *trans*-1,2-di(2-naphthyl)ethylene **(1)** with *m*-chloroperoxybenzoic acid in the presence of trichloroacetic acid[14] gave the monotrichloroacetyl derivative **2** of (±)-2-hydronaphtoin in 72% yield. Alkaline hydrolysis of the trichloroacetate **2** gave racemic 2-hydronaphtoin **3** in 70% yield. Racemic 2-hydronaphtoin **3** was resolved by formation of diastereoisomers with (−)-menthoxyacetyl chloride[15] and fractional crystallization of menthoxyacetates **4** from ethanol. Alkaline hydrolysis of each menthoxyacetate gave both enantiomers of 2-hydronaphtoin.



To the best of our knowledge, (±)-2-hydronaphtoin has been obtained as a main reaction product or as a side reaction product

in some instances[16–18] but the resolution has never been achieved.[19] Reaction of (+)- or (−)-2-hydronaphtoin with diethylene glycol ditosylate in anhydrous tetrahydrofuran with potassium hydride as base and template gave enantiomers of 2,3,11,12-tetra(2-naphthyl)-18-crown-6 (**5**) in 70–78% yield.



The crown ethers **5** have the *trans-anti-trans* configuration. The ability of the optically active crown ether **5** for chiral recognition was tested by extraction experiments monitored by ^{1}H-NMR with phenylglycine methyl ester perchlorate. Enantiodifferentiation was manifested by splitting of the signal of the ester methyl group which is sufficiently separated from the signals of the crown ether **5** as to allow the determination of the chiral recognition factor[5] directly from the integration of the splitting (3.87, 3.83 ppm) in the 200 MHz spectrum. The crown ether (+)-**5**, in deuterated chloroform, selectively extracts D-phenylglycine methyl ester perchlorate from a concentrated aqueous solution and the chiral recognition factor is 1.4. This value is similar to those reported for bis-binaphthyl-22-crown-6[20] or tetraphenyl-18-crown-6.[15] The chiral crown ethers reported here are currently being used in phase transfer asymmetric induction.

Diethylene glycol and methoxyacetic acid are available from Aldrich Chem. Co. Diethylene glycol ditosylate,[21,22] phenylglycine methyl ester perchlorate,[23] menthoxyacetyl chloride,[24] and *trans*-1,2-di(naphthyl)ethylene[13] are obtained according to known procedures. Apparatus: Carlo Erba Strumentazione-1106 element analyser. Hewlett-Packard 5992-GC–MS (70 eV) and quadrupolar VG-micromass 1212 (DCI, isobutane) MS spectrometers; Beckmann-4250 IR spectrometer; Varian XL-200 NMR spectrometer.

(±)-*threo*-1,2-Di(2-naphthyl)-2-trichloroacetoxyethanol (2):
trans-1,2-Di(2-naphthyl)ethylene (**1**; 2.900 g, 10.3 mmol) is dissolved in warm benzene (2.5 L). The solution is cooled to room temperature and trichloroacetic acid (2.075 g, 12.7 mmol) is added, followed by addition of *m*-chloroperbenzoic acid (2.187 g, 12.7 mmol). The solution is stirred at room temperature for 2 days. Another portion of *m*-chloroperbenzoic acid (2.187 g, 12.7 mmol) is added and the solution is stirred for three more days. The solution is concentrated to 200 mL and washed successively with a saturated K_2CO_3 solution (30 mL) and with water (30 mL). The organic layer is dried ($MgSO_4$) and evaporated to dryness. The crude product is recrystallized from benzene and petroleum ether; yield: 3.41 g (72%); m.p. 157–158°C.

$C_{24}H_{17}Cl_3O_3$	calc.	C 62.72	H 3.69
(459.6)	found	62.60	3.70

MS (70 eV): *m/e* = 460 (M^+, very weak).

IR (KBr): ν = 3540, 3460, 3050, 2980, 2900, 1750, 1600, 1510, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.58 (m, 1H, OH); 5.38 (d, 1H, CHOH, *J* = 8 Hz); 6.18 (d, 1H, CH–$OCOCl_3$, *J* = 8 Hz); 7.2–7.9 (m, 14 H_{arom}).

(±)-1,2-Di(2-naphthyl)-1,2-ethanediol (3) [(±)-2-Hydronaphtoin]:
Compound **2** (2.400 g, 5.2 mmol) is dissolved in EtOH (200 mL) and a 0.2 molar solution of KOH in EtOH (26 mL) is added. The solution is stirred under reflux for 2 h. The solvent is concentrated to 10 mL and H_2O (30 mL) is added. The crude product is filtered off and recrystallized from benzene; yield: 1.15 g (70%); m.p. 218–219°C (hydrate; Lit. m.p. 220–222°C,[17] 218–219°C[18]).

MS (70 eV): *m/e* = 314 (M^+, 1.5%).

IR (KBr): ν = 3570, 3540, 3400, 3040, 3005, 2900, 1590, 1500 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 3.33 (s, 2H, OH); 5.11 (s, 2H, H_2O); 5.66 (s, 2H, CHOH); 7.3–7.9 (m, 14 H_{arom}).

1,2-Dimenthoxyacetoxy-1,2-di(2-naphthyl)ethane (4):
A solution of the racemate **3** (1.143 g, 3.6 mmol) is anhydrous pyridine (30 mL) is stirred under nitrogen at room temperature. (−)-Menthoxyacetyl chloride (3.349 g, 14.4 mmol) is added dropwise, the solution is heated at 60–70°C for 30 min, then stirred at room temperature for 2 days. The solution, is poured onto ice water (300 mL), acidified with 10% hydrochloric acid, and extracted with $CHCl_3$ (3 × 150 mL). The organic layer is washed with H_2O (100 mL), with saturated K_2CO_3 solution (60 mL), and again with water (100 mL), dried ($MgSO_4$), and evaporated. EtOH (30 mL) is added to the crude product and the suspension is filtered to yield a mixture of diastereoisomers **4a** + **4b** (2.16 g, 85%) which is separated by fractional crystallization from EtOH.

Isomer **4a**; yield: 793 mg (31%); m.p. 158.5–159.5°C; $[\alpha]_D^{22}$: −54° (*c* = 1.08, $CHCl_3$).

$C_{46}H_{58}O_6$	calc.	C 78.20	H 8.21
(706.5)	found	77.97	8.30

IR (KBr): ν = 3060, 3020, 2950, 2920, 2900, 2870, 2850, 1760, 1600, 1510, 1185, 1135 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.72 [d, 6H, $CH(CH_3)_2$, *J* = 7.0 Hz]; 0.85 (d, 6H, 2 CH_3, *J* = 6.3 Hz); 0.86 [d, 6H, $CH(CH_3)_2$, *J* = 7.0 Hz]; 1.0–2.0 (m, 16H, other H of menthoxy ring); 2.24 [hd, 2H, 2 $CH(CH_3)_2$ *J* = 7.0, 2.0 Hz]; 3.05 (td, 2H, 2 CH–O, *J* = 10.5, 4.1 Hz); 4.14 (AB system, 4H, 2 $COCH_2$–O, *J* = 16 Hz); 6.46 (s, 2H, 2 CH–OCO); 7.2–7.8 (m, 14 $H_{naphthyl}$).

Isomer **4b**; yield: 865 mg (34%); m.p. 129–129.5°C; $[\alpha]_D^{22}$: −73° (*c* = 1.13, $CHCl_3$).

$C_{46}H_{58}O_6$	calc.	C 78.20	H 8.21
(706.5)	found	78.32	8.07

IR (KBr): ν = 3065, 3030, 2965, 2925, 2875, 2860, 1770, 1608, 1515, 1180, 1125 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.75 [d, 6H, $CH(CH_3)_2$, *J* = 7 Hz]; 0.88 (d, 6H, $CH(CH_3)_2$, *J* = 7.0 Hz); 0.86 (d, 6H, 2 CH_3, *J* = 6.3 Hz); 1.0–2.0 (m, 16H, other H of the menthoxy cycle); 2.26 [hd, 2H, 2 $CH(CH_3)_2$, *J* = 7.0 Hz, 2.0 Hz]; 3.10 (td, 2H, 2 CH–O, *J* = 10.5, 4.1 Hz); 4.15 (AB system, 4H, 2 $COCH_2$–O, *J* = 16.0 Hz); 6.46 (s, 2H, CH–OCO); 7.2–7.8 (m, 14 $H_{naphthyl}$).

(+) and (−)-Hydronaphtoin (3):
Alkaline hydrolysis of diastereoisomer **4a** and **4b** according to the procedure described above for the hydrolysis of compound **2** affords the enantiomers of 2-hydronaphtoin.

Compound **4a** gives (+)-2-Hydronaphtoin; yield: 90%; m.p. 237–238°C (hydrate); $[\alpha]_D^{23}$: +212° (c = 1.04, THF).

Compound **4b** gives (−)-2-Hydronaphtoin; yield: 85%, m.p. 237–237.5°C; $[\alpha]_D^{22}$: −210° (c = 0.97, THF).

The spectrometric data of both isomers are identical to those reported above for the racemate.

(+) and (−)-2,3,11,12-Tetra(2-naphthyl)-18-crown-6 (5):
A solution of potassium hydride (0.176 g, 4.4 mmol) in dry THF (100 mL) is stirred under nitrogen at room temperature. A solution of (+) or (−)-2-hydronaphtoin (700 mg, 2.2 mmol) in dry THF (100 mL) is added dropwise and the mixture is heated at 60°C until formation of an insoluble salt is noticed. Diethylene glycol ditosylate (912 mg, 2.2 mmol) in dry THF (150 mL) is added dropwise and the mixture is stirred at room temperature for 4 days. Water (75 mL) is then added and THF is evaporated. The aqueous phase is extracted with $CHCl_3$ (3 × 100 mL) and the organic phase is dried ($MgSO_4$) and evaporated. The crude product is purified by column chromatography (alumina, neutral, grade I) with first benzene and then $CHCl_3$ as eluents.

The reaction of (+)-2-Hydronaphtoin gives crown ether (+)-**5** as an oil; yield: 659 mg (78%); $[\alpha]_D^{22}$: +22° (c = 1.05, $CHCl_3$)

$C_{52}H_{48}O_6$ (768.6) calc. C 81.26 H 6.25
found 81.40 6.21

MS (DCI): m/e = 769 (M + 1).

IR (neat): ν = 3050, 3000, 2920, 2900, 2860, 1600, 1505, 1120, 1090 cm^{-1}

^1H-NMR ($CDCl_3$): δ = 3.4–3.9 (m, 16 H, 4 OCH_2CH_2O); 4.5–5.1 (m, 4 H, 4 CH–O); 7.2–7.8 (m, 28 H_{arom}).

The reaction of (−)-2-hydronaphtoin gives crown ether (−)-**5** as an oil; yield: 592 mg (70%); $[\alpha]_D^{21}$: −23° (c = 1.00, $CHCl_3$).

$C_{52}H_{48}O_6$ (768.6) calc. C 81.26 H 6.25
found 81.13 6.38

Determination of the Chiral Recognition Factor:

A solution of D,L-phenylglycine methyl ester perchlorate (3.0 mmol) in deuterium oxide (6 mL) is added to a solution of crown ether (+)-**5** (1.0 mmol) in NMR grade $CDCl_3$ (5.0 mL) in a 25 mL centrifuge tube, which is kept at 0°C for 1 h. The mixture is vortexed for 30 s and centrifuged in a cold room for 15 min. The organic phase is decanted and submitted to NMR spectrometry. The procedure is repeated with pure D-phenylglycine methyl ester perchlorate to determine which enantiomer is extracted preferentially.

We thank the Natural Sciences and Engineering Research Council of Canada and the Ministère de l'éducation du Québec for financial support.

Received: 4 February 1987

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