Journal of Inclusion Phenomena and Macrocyclic Chemistry **44:** 341–343, 2002.

A New Easy Access to Enantiomerically Pure 2,2′-Dihydroxy-1,1′-Binaphthyl

FRANCESCO TROTTA[1], LUISA COSTA[2] and GIANCARLO CRAVOTTO[2]*
[1]*Dipartimento di Chimica Inorganica, Chimica Fisica e Chimica dei Materiali (Università di Torino). Via Giuria 7, 10125 Torino, Italy;* [2]*Dipartimento di Scienza e Tecnologia del Farmaco, (Università di Torino), Via Giuria 9, 10125 Torino, Italy*

(Received: 7 May 2002; in final form: 1 October 2002)

Key words: binaphthol, racemates resolution, synthesis trihydroxyethyl cyclodextrins, tri-2-hydroxypropyl cyclodextrins

Abstract

Optically pure binaphthyl structures make up the most important family of auxiliaries, ligands and catalysts used in enantioselective reactions. Syntheses of 2,2′-disubstituted-1,1′-binaphtyl derivatives were carried out *one pot* in water by oxidative coupling with $FeCl_3$ in the presence of β- and γ-cyclodextrin (CD) derivatives. A new efficient and inexpensive preparation of trihydroxyethyl- and tri-2-hydroxypropyl- β- and γ-CD afforded these powerful solubilizing agents. The resolution of racemic 2,2′-dihydroxy-1,1′-binaphthyl was easily achieved by semipreparative HPLC separating diastereomers obtained from the reaction with (−)menthyl chloroformate. Final basic hydrolysis afforded the enantiomerically pure product.

Introduction

Binaphthylic derivatives with C_2-symmetry [1] play a very important role in asymmetric synthesis [2]. The most representative C_2-symmetric chiral compound is 1,1′-bi-2-naphthol (BINOL) [3]; many related chiral auxiliaries have been developed from this atropoisomeric structure [4, 5]. Although their outstanding efficiency in asymmetric induction would recommend their use, this is presently limited by their relatively high cost, arising from difficulties involved in obtaining them in enantiomerically pure form [6, 7, 8, 9]. Several methods are described in the literature for the asymmetric synthesis of 2,2′-dihydroxy-1,1′-binaphthyl and its derivatives; none of them however has yet proven convenient on the industrial scale, therefore in practice resolution of the racemate is usually resorted to [10, 11, 12]. BINOL can easily be made by oxidative coupling with $FeCl_3$, as is well documented in the literature [1, 13]. The remarkable solubilising effect of CDs enabled us to carry out this synthesis in water.

Experimental

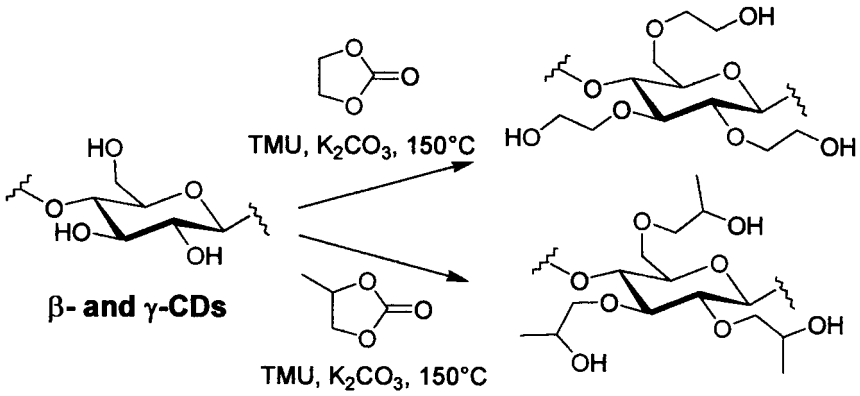
General methods. ^{1}H NMR spectra were recorded on a Bruker AC-400 spectrometer at 400 MHz; chemical shifts are expressed in parts per million downfield from TMS. ESI-MS spectra were recorded on a TSQ-700 Finnigan-Mat spectrometer (positive mode, CH_3CN); I.R. spectra with a Shimadzu FT-IR 8001 spectrometer. All solvents and chemicals were reagent grade and anhydrous conditions were achieved (when indicated) by flame-drying flasks and other critical equipment. UV measurements were performed on a LAMBDA 15 (Perkin-Elmer) UV-VIS spectrophotometer. Reactions were monitored by TLC on Alugram Sil-Macherey Nagel (F_{254}, 0.25 mm) plates; spots were detected by UV inspection or staining with 5% H_2SO_4 in EtOH and heating. Silica gel 60 (Merck) was employed for open-column chromatography and a Merck Hibar® RT 250-25 column for semipreparative HPLC with a Gilson 133 refractive index detector. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

All the reagents were used without further purification. 2-Naphthol was purchased from Carlo Erba (Italy), methyl-β-CD was kindly provided by Wacker Chemie (Germany), diethyl-β-CD [14], 2,3,6-*O*-trihydroxyethyl- β- and γ-CD, 2,3,6-*O*-tri-2-hydroxypropyl-β and γ-CD were prepared as described below.

Heptakis-2,3,6-O-trihydroxyethyl-β-CD (HEB) and Octakis-2,3,6-O-trihydroxyethyl-γ-CD (HEG)

Both preparations were carried out in anhydrous conditions on 2.5 mmol of native CDs, using a Carius-type pyrex tube (200 mL) stoppered with a pressure-resistant screw cap. Excess ethylene carbonate (1,3-dioxolan-2-one) or propylene carbonate (4-methyl-1,3-dioxolan-2-one) (60 mmol), K_2CO_3 (5.0 mmol) and tetramethylurea (40 mL) were added. The mixture was magnetically stirred and heated at 150 °C for 5 h. The reaction was monitored by TLC with MeOH/$CHCl_3$/H_2O 20 : 10 : 1. The reacted mixture was left to cool down to room temperature, shaken with acetone (350 mL), and filtered on a sintered glass. The product was washed 4 times with acetone. Yields always exceeded 95% with a substitution degree exceeding 85% as determined by ESI-MS spectroscopy.

* Author for correspondence. E-mail: giancarlo.cravotto@unito.it



Scheme 1. Synthesis of trihydroxyethyl- and tri-2-hydroxypropyl- β- and γ-CDs.

Table 1.

Cyclodextrin (1.8%)	2-Naphthol (mg/L)	Cyclodextrin (1.8%)	2-Naphthol (mg/L)
β-CD	65	Methyl-β-CD (MB)	310
γ-CD	15	Diethyl-β-CD (DEB)	210
2,3,6-O-trihydroxyethyl-β-CD (HEB)	245	2,3,6-O-trihydroxyethyl-γ-CD (HEG)	210
2,3,6-O-tri-2-hydroxypropy-β-CD (HPB)	155	2,3,6-O-tri-2-hydroxypropyl-γ-CD (HPG)	140

General procedure for 2-Naphthol oxidative coupling

Excess 2-naphthol was stirred in water containing 10% modified CD until saturation was achieved at room temperature, then added to a freshly prepared solution of $FeCl_3$ (10%). The reaction, followed by monitoring absorbance at 273 nm, was complete in all cases after 15 min. The precipitate was recovered by filtration and the solution extracted with diethyl ether. The organic phase was washed with brine and dried over $MgSO_4$; after removal of the solvent, the product was combined with the precipitate and purification carried out by column chromatography (hexane-EtOAc 9 : 1).

2-(−)Menthyl-2′-hydroxy-1,1′-binaphthyl carbonate

In a 50 mL two-necked, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet, the following were placed: dry CH_2Cl_2 (20 mL), oven-dried powdered 5 Å-molecular sieves (0.3 g), triethylamine (1.6 mL), racemic binaphtol (2.86 g, 10 mmol), (−)menthyl chloroformate (2.31 g; 10 mmol; 0.5 eq.mol). The solution was stirred at room temperature for 30 min, washed with 10% HCl, water and brine. The organic phase was dried over $MgSO_4$ and after removal of the solvent a white crystalline solid was obtained. Diastereomers couple (**a** and **b**) was easily separated by semipreparative HPLC using hexane-ethyl acetate 9 : 1 as eluent (20 mL/min), 100 mg/injection.

Data for **a**: Mp 168 °C; $[\alpha]_D^{20}$ = −22.6 (THF); IR (KBr) 3490, 1742, 1271, 1252, 1219, 824 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.13 (1H, d, J = 8.9 Hz), 8.02 (1H, d, J = 8.2 Hz), 7.94 (1H, d, J = 8.9 Hz), 7.88 (1H, d, J = 8.4 Hz), 7.56 (1H, td, J = 9.5 Hz, J' = 1.4), 7.53 (1H, d, J = 8.9), 7.40–7.27 (5H, m), 7.09 (1H, d, J = 8.2 Hz), 5.31 (1H, brs, OH), 4.39 (1H, td, J = 15.3 Hz, J' = 4.5 Hz), 1.83–0.91 (10H, m), 0.89 (3H, d, J = 6.5 Hz) 0.70 (3H, d, J = 6.9 Hz), 0.60 (3H, d, J = 6.8 Hz); CIMS: 469 (MH^+); Rf (Hexane/EtOAc 8 : 2) 0.30; Anal. Calcd for $C_{31}H_{32}O_4$: C 79.46; H 6.88. Found: C 79.38, H 5.90.

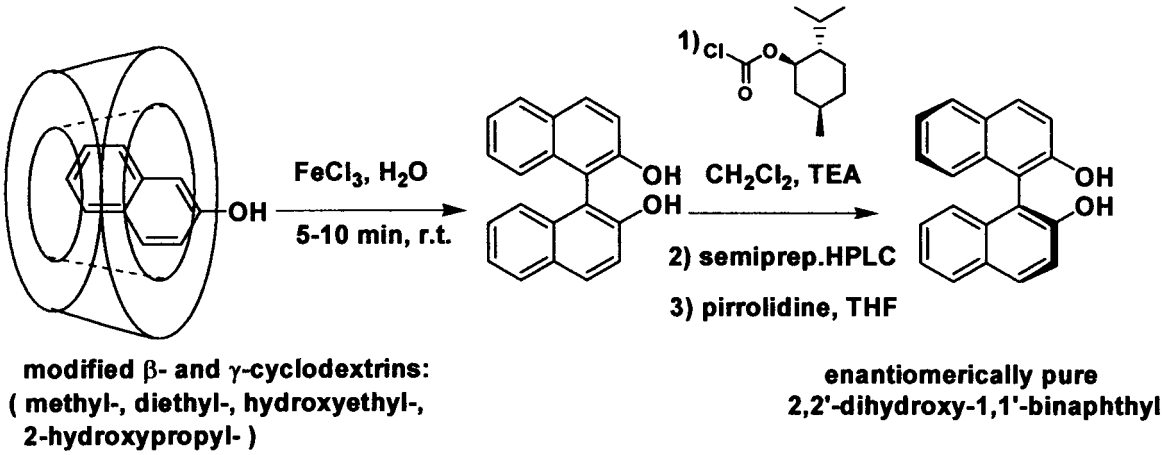
Data for **b**: Mp 199–200 °C; $[\alpha]_D^{20}$ = −33.4 (THF); IR (KBr) 3490, 1742, 1270, 1250, 1218, 824 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.13 (1H, d, J = 8.8 Hz), 8.02 (1H, d, J = 8.1 Hz), 7.95 (1H, d, J = 8.8 Hz), 7.88 (1H, d, J = 7.5 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.39–7.28 (5H, m), 7.07 (1H, dd, J = 8.8 Hz, J' = 0.5 Hz), 5.28 (1H, s, OH), 4.37 (1H, td, J = 10.9 Hz, J' = 4.5 Hz), 1.73–1.58 (6H, m), 1.40–1.21 (4H, m), 0.91 (3H, d, J = 6.6 Hz) 0.77 (3H, d, J = 6.9 Hz), 0.57 (3H, d, J = 6.9 Hz); CIMS: 469 (MH^+); Rf (Hexane/EtOAc 8 : 2) 0,23.

Results and discussion

Trihydroxyethyl- and tri-2-hydroxypropyl- β- and γ-CD derivatives were synthesized in very good yields by treatment of the native CDs with ethylene or propylene carbonate and K_2CO_3 in tetramethylurea at 150 °C in anhydrous conditions (Scheme 1).

As shown in Scheme 2, 2-naphthol was dissolved in water containing the appropriate CD until saturation was achieved at room temperature [15]. The table shows the solubilizing effect on 2-naphthol of modified CDs compared with native β-CD. The concentration of 1.8% was chosen because it is the solubility of β-CD in water at 20 °C [16, 17].

All these modified CDs are much more soluble in water than β-CD (300–550 mg/ml compared to 18 mg/ml at room temperature) and form soluble complexes with 2-naphthol, so that guest concentration increases linearly as the concentration of the CD increases [18, 19]. HE- and



Scheme 2. Preparation procedure of enantiomerically pure 2,2′-dihydroxy-1,1′-binaphthyl.

HP- β- and γ-CD do not change the surface tension of water so much as other CDs such as MB and DEB, which exert a detergent-like effect. The largest 2,2′-dihydroxy-1,1′-binaphthyl crops were obtained using HEB and HEG that permit to carry out the coupling reaction on a 10-gram scale in 700 mL of water; yields were always over 90%. This procedure was also tested with 2-naphthylamine, 2-thionaphtol and its methyl thioether. 2,2′-Diamino-1,1′-binaphthyl and 2,2′-dimethylmercapto-1,1′-binaphthyl were isolated in low yields (4% and 9% respectively). 2-Thionaphtol gave only the corresponding disulfide (80%).

The resolution of racemates was easily achieved by chromatographic separation of diastereomers obtained from their reaction with (−)menthyl chloroformate in CH_2Cl_2 and TEA at room temperature. The reaction was over in 20 min (yield about 95%). The diastereomers were easily separated by semipreparative HPLC using hexane-ethyl acetate 9 : 1 as eluent (20 mL/min). Final basic hydrolysis was carried out with pirrolidine in THF. Optical rotation and chiral HPLC analysis (Chiralpak AD®, Daicel) confirmed the stereochemical purity of both enantiomers.

Conclusion

We have described a simpler access to enantiomerically pure 2,2′-dihydroxy-1,1′-binaphthyl. The racemic form was obtained by a *one pot* efficient synthesis carried out in water and was resolved, after reaction with (−)menthyl chloroformiate, by chromatographic separation of the diastereomeric carbonates. The oxidative coupling of 2-naphtol with $FeCl_3$ could be carried out in water thanks to the solubilizing effect of appropriately modified cyclodextrins. We have presented a straightforward synthesis for trihydroxyethyl- and tri-2-hydroxypropyl β- and γ-CDs, the derivatives that proved most efficient in the complexation of 2-naphtol.

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