PREPARATION OF (*R*)-(–)-6,6′-BIS(3,5-DINITROBENZAMIDO)-BIPHENYL-2,2′-DICARBOXYLIC ACID, A POTENTIAL CHIRAL HPLC SELECTOR

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The title optically active diacid *I* has been prepared as a potential selector for chiral stationary phase in the HPLC separation of enantiomers.

In the course of our investigations of various chiral stationary phases (CSP) for liquid chromatographic separation of enantiomers we prepared and checked some CSPs based on biphenyl and bipyridyl selectors of C_2 symmetry[1,2]. Several 2,2′-dinitrobiphenyl CSPs, ionically bound to the aminopropylsilica carrier, proved to be very efficient selectors, particularly for 2-amino alcohol derivatives[1,2]. Therefore, we extended our research to biphenyls with other polar substituents. Now we report the synthesis and absolute configuration of optically active diamide *I* derived from 6,6′-diaminobiphenyl-2,2′-dicarboxylic acid. This selector combines the features of the C_2-symmetrical biphenyl skeleton with those of the polar 3,5-dinitrobenzamide moiety, the almost indispensable component of many effective CSPs, particularly of the Pirkle type[3].

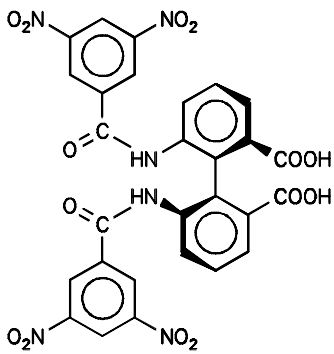
As the starting compound we used (*R*)-(+)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid (*II*). As reported[4], and also proven by us, direct reduction of the nitro groups in the free acid *II* under various conditions produced invariably the corresponding dilactam of the arising diamino diacid. Although acid *II* can be catalytically reduced as its dimethyl ester[4] *VI*, which was then converted into the diamide-diester *VII*, we did not find any suitable method for converting *VII* to the desired diacid *I*. This difficulty was circumvented by working with di-*tert*-butyl esters (Scheme 1). Catalytic reduction of the di-*tert*-butyl ester *III* (prepared from *II* via the dichloride) over Adams catalyst in methanol at low temperature gave diamino diester *IV* which was more than 98% enantiomerically pure (HPLC on triacetylcellulose) and was directly acylated with 3,5-dinitrobenzoyl chloride to give the diamide *V*. The free acid *I* was then obtained by treatment of the diester *V* with 100% formic acid at room temperature[5]. The absolute configuration of *I* is *R*, the same as of the starting diacid *II*.

The corresponding ionically bound CSP was then prepared from 3-aminopropyl silica and acid *I* in methanol using our standard method[1,2]. The content of *I* was 0.31 mmol/g CSP.

The separation properties of the synthesized CSP are being investigated and will be reported elsewhere.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were taken on a Varian Unity 200 instrument with tetramethylsilane as internal standard. Optical rotations were measured on a Perkin–Elmer 241 automatic polarimeter at 25 °C. The aminopropyl silica used was Separon SGX-NH_2 (Tessek, 7 μm, 1.48 mmol NH_2/g, determined by nitrogen analysis).



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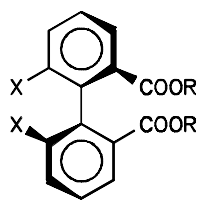
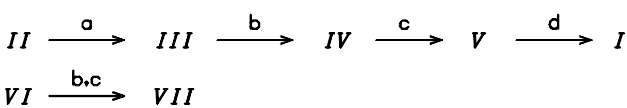


	R	X
II	H	NO_2
III	*t*-Bu	NO_2
IV	*t*-Bu	NH_2
V	*t*-Bu	3,5-dinitrobenzamido
*VI**	CH_3	NO_2
*VII**	CH_3	3,5-dinitrobenzamido

* Racemate (only one enantiomer shown)



(a) 1) $(COCl)_2$, DMF, benzene, r.t., 1 h; 2) *t*-BuOH, pyridine, r.t., 2 d;
(b) H_2/PtO_2, THF, 10 °C, 2 h; (c) 3,5-dinitrobenzoyl chloride, pyridine, r.t., overnight;
(d) 100% HCOOH, r.t., 3.5 h

SCHEME 1

(*R*)-(+)-Di-*tert*-butyl 6,6′-Dinitrobiphenyl-2,2′-dicarboxylate (*III*)

Oxalyl chloride (6.7 ml, 76 mmol) was added to a stirred suspension of (*R*)-(+)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid[6,7] (*II*) ($[\alpha]_D$ +130° (*c* 0.5, methanol), 6.0 g, 18 mmol) in benzene. Dimethylformamide (5 drops) was added and the stirring was continued for 1 h. The solution was decanted and the solvent evaporated. The residue was mixed with dry *tert*-butyl alcohol (15 ml) and pyridine (25 ml) under stirring and cooling with ice. The solution rapidly deposited a solid. After standing at room temperature for 2 days, the mixture was decomposed with water and extracted with ether. The ethereal layer was washed with water, dilute hydrochloric acid and again water, and dried over sodium sulfate. Evaporation of the solvent and crystallization from toluene afforded 7.17 g (90%) of the diester *III*, m.p. 128–129 °C, $[\alpha]_D$ +43.5° (*c* 0.5, acetone). According to chromatography on triacetylcellulose (40 × 0.8 cm column, ethanol, flow rate 0.8 ml/min), the enantiomeric purity of the ester was 98%. ^{1}H NMR ($CDCl_3$): 8.26 dd, 2 H, *J*(5,3) = 1.2, *J*(5,4) = 7.9 (H-5); 8.18 dd, 2 H, *J*(3,5) = 1.2, *J*(3,4) = 7.9 (H-3); 7.64 t, 2 H, *J*(4,3) = *J*(4,5) = 7.9 (H-4); 1.21 s, 18 H (*tert*-butyl). For $C_{22}H_{24}N_2O_8$ (444.4) calculated: 59.45% C, 5.44% H, 6.30% N; found: 59.35% C, 5.49% H, 6.60% N.

Racemic (*RS*)-di-*tert*-butyl 6,6′-dinitrobiphenyl-2,2′-dicarboxylate was prepared in the same way from (*RS*)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid (664 mg, 2 mmol) in 89% yield; m.p. 182–184 °C (toluene). ^{1}H NMR spectrum was identical with that of optically active diester *III*.

(*R*)-(+)-Di-*tert*-butyl 6,6′-Diaminobiphenyl-2,2′-dicarboxylate (*IV*)

The dinitro ester *III* (7.1 g, 16 mmol) was hydrogenated in tetrahydrofuran (120 ml) over Adams catalyst (2.0 g) at 5–15 °C and 0.6 MPa for 2 h. Filtration and evaporation of the solvent gave 6.0 g (98%) of the crude diamino diester, $[\alpha]_D$ +29.8° (*c* 0.5, THF) which was sufficiently pure (NMR) for the next reaction step. ^{1}H NMR ($CDCl_3$): 7.31 dd, 2 H, *J*(3,5) = 1.5, *J*(3,4) = 7.9 (H-3); 7.21 t, 2 H, *J*(4,3) = *J*(4,5) = 7.9 (H-4); 6.89 dd, 2 H, *J*(5,3) = 1.5, *J*(5,4) = 7.9 (H-5); 3.44 s, 4 H (NH); 1.19 s, 18 H (*tert*-butyl).

(*R*)-(–)-Di-*tert*-butyl 6,6′-Bis(3,5-dinitrobenzamido)biphenyl-2,2′-dicarboxylate (*V*)

3,5-Dinitrobenzoyl chloride (3.88 g, 16.87 mmol) was added to a vigorously stirred and ice-cooled solution of the amino ester *IV* (3.0 g, 7.81 mmol) in pyridine (15 ml). After stirring at room temperature for 5 h and standing overnight, the mixture was decomposed with water under cooling, and partitioned between water and ether. The ethereal layer was washed with dilute (1 : 10) hydrochloric acid until pyridine was completely removed. After drying over sodium sulfate the solvent was driven off and the residue was mixed with benzene. The deposited material was collected, washed with benzene and dried, yield 4.7 g (78%), m.p. 213–215 °C (decomp.), $[\alpha]_D$ –89.5° (*c* 0.5, chloroform). ^{1}H NMR ($CDCl_3$) (primed numbers refer to protons in the 3,5-dinitrobenzoyl moieties): 9.13 t, 2 H, *J*(4′,2′) = *J*(4′,6′) = 1.9 (H-4′); 8.66 d, 4 H, *J*(2′,4′) = *J*(6′,4′) = 1.9 (H-2′ + H-6′); 8.16 s, 2 H (NH); 8.15 dd, 2 H, *J*(5,3) = 1.2, *J*(5,4) = 7.9 (H-5); 7.87 dd, 2 H, *J*(3,5) = 1.2, *J*(3,4) = 7.9 (H-3); 7.94 t, 2 H, *J*(4,3) = *J*(4,5) = 7.9 (H-4); 1.29 s, 18 H (*tert*-butyl). For $C_{36}H_{32}N_6O_{14}$ (772.7) calculated: 55.96% C, 4.18% H, 10.88% N; found: 56.33% C, 4.04% H, 11.19% N.

(*R*)-(–)-6,6′-Bis(3,5-dinitrobenzamido)biphenyl-2,2′-dicarboxylic Acid (*I*)

A slurry of the ester-amide *V* (3.4 g, 4.4 mmol) in 100% formic acid (25 ml) was stirred at room temperature. The compound gradually dissolved and after 3.5 h the mixture was diluted slowly with water, the precipitate was collected, washed thoroughly with water and dried at 40 °C to constant weight. Yield 2.5 g (86%), not melting up to 360 °C, $[\alpha]_D$ –23.9° (*c* 0.5, 0.1 M NaOH). ^{1}H NMR (hexadeuteriodimethyl sulfoxide) (primed numbers refer to protons in the 3,5-dinitrobenzoyl

moieties): 12.43 s, 2 H (CO_2H); 9.82 s, 2 H (NH); 8.91 t, 2 H, *J*(4′,2′) = *J*(4′,6′) = 2.1 (H-4′); 8.64 d, 4 H, *J*(6′,4′) = *J*(6′,2′) = 2.1 (H-6′and H-2′); 7.95 dd, 2 H, *J*(5,3) = 0.9, *J*(5,4) = 7.9 (H-5); 7.81 dd, 2 H, *J*(3,5) = 0.9, *J*(3,4) = 7.9; 7.54 t, 2 H, *J*(4,3) = *J*(4,5) = 7.9.

(*RS*)-Dimethyl 6,6′-Bis(3,5-dinitrobenzamido)biphenyl-2,2′-dicarboxylate (*VII*)

3,5-Dinitrobenzoyl chloride (500 mg, 2.16 mmol) was added to a stirred ice-cold solution of dimethyl 6,6′-diaminobiphenyl-2,2′-dicarboxylate[4] (300 mg, 1 mmol) in pyridine (2 ml). After stirring overnight the mixture was decomposed with much ice-cold water and the product was collected and dried. Yield 625 mg (91%). After crystallization from ethyl acetate it melted at 229–231 °C with change in modification at 150–160 °C. For $C_{30}H_{18}N_6O_{14}$ (688.5) calculated: 52.33% C, 2.93% H, 12.21% N; found: 51.99% C, 2.88% H, 12.32% N. ^{1}H NMR ($CDCl_3$) (primed numbers refer to protons in the 3,5-dinitrobenzoyl moieties): 9.14 t, 2 H, *J*(2′,4′) = 2.1 (H-2′); 8.70 d, 2 H, *J*(4′,2′) = 2.1 (H-2′); 8.35, 2 H (NH); 8.07 ddd, 2 H, *J*(5,3) = 1.8, *J*(5,NH) = 2.8, *J*(5,4) = 8.2 (H-5); 7.97 dd, 2 H, *J*(3,5) = 1.8, *J*(3,4) = 8.2 (H-3); 7.67 td, 2 H, *J*(4,NH) = 1.0, *J*(4,5) = *J*(4,3) = 8.2 (H-4); 3.70 s, 6 H ($2 \times CH_3$).

Preparation of CSP

A solution of (*R*)-(–)-diacid *I* (1.462 g, 2.21 mmol) in methanol (15 ml) was added to a suspension of Separon SGX-NH_2 (3.00 g) in methanol (10 ml). After standing for 24 h with intermittant gentle stirring, the mixture was filtered, the adsorbent washed with methanol and acetone (50 ml each) and dried in vacuo; weight 3.80 g. Evaporation of the filtrate recovered 671 mg of the acid; thus 791 mg of the acid was anchored and the modifier content was 0.31 mmol/g phase.

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