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DESIGN AND SYNTHESIS OF A CHIRAL STATIONARY PHASE CONTAINING A BENZ[*de*]ISOQUINOLINONE SKELETON

I. FIRST CHROMATOGRAPHIC RESULTS

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SUMMARY

A chiral stationary phase (CSP) derived from 3-(4′-glycidyloxyphenyl)-2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-one was designed and synthesized according to the reciprocality concept. A coplanar arrangement of possible attractive sites of interaction is due to the rigid conformation of the chiral selector. It was demonstrated that this CSP exhibits a good chiral discrimination ability towards families of racemates such as 3,5-dinitrobenzoyl derivatives of α-amino esters and α-amino-amides. Significant enhancements of selectivity were observed when chloroform was used instead of ethanol as a polar modifier in hexane, emphasizing the major contribution of the nature of the mobile phase to the chiral recognition process.

INTRODUCTION

Asymmetric synthesis is now applied to a great variety of organic compounds, and requires the development of analytical methods for the determination and control of enantiomeric purity. New methods able to resolve racemates, for both analytical and preparative purposes, have been developed. Among these, chromatography on chiral stationary phases (CSPs) is an efficient and reliable method for the determination of enantiomeric purity, using either high-performance liquid chromatography (HPLC)[1] or supercritical-fluid chromatography (SFC)[2]. CSPs can also be applied on a preparative scale, which is sometimes an interesting alternative, particularly for compounds devoid of suitable functional groups and which cannot be obtained with a high enantiomeric excess by conventional techniques such as asymmetric synthesis or fractional crystallization.

An example of such a CSP, developed recently in our laboratory, is illustrated by the (*S*)-thio-DNBTyr-A (CSP 1)[3,4] (Fig. 1). CSP 1 resolves various families of racemates, such as α-methylene-γ-butyrolactam derivatives (Fig. 2A), which are potential cytotoxic agents[5].

The ability of a CSP to resolve a racemate results from a combination of

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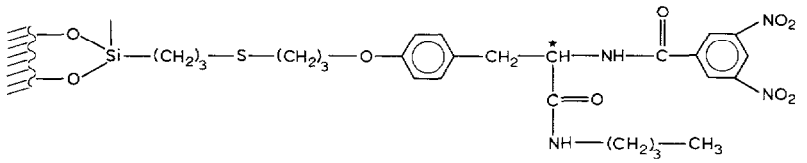


Fig. 1. Chiral stationary phase derived from (*S*)-tyrosine: (*S*)-thio-DNBTyr-A (CSP 1).

attractive interactions (such as hydrogen bonding, dipolar interactions, π–π charge-transfer overlap), and repulsive interactions such as steric hindrance effects). Several structural features of α-methylene-γ-butyrolactam are useful for chiral separation purposes: (a) the presence of a methylene group in the five membered ring, which confers a rigid quasi-planar structure to the molecule; (b) the *cis* disposition of the hydrogen atom and the carbonyl group in the amide dipole when R is a hydrogen atom (Fig. 2A); and (c) access to the chiral centre, which is limited to one side only owing to the presence of the bulky R′ moiety (Fig. 2A). A CSP whose chiral selector (CS) is structurally derived from α-methylene-γ-butyrolactam (Fig. 2A) should fulfil the requirements of an effective CSP.

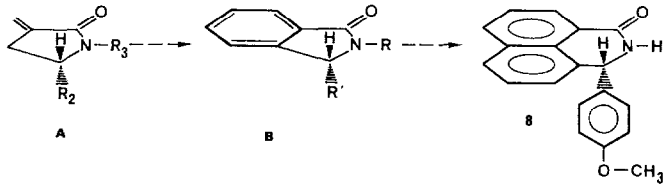


Fig. 2. Progress of the design of the chiral selector.

The synthesis of such a CSP takes into account the well known reciprocality concept[6], assuming that a resolved solute on a given CSP, such as some α-methylene-γ-butyrolactams on (*S*)-thio-DNBTyr-A, should be reciprocally operative as a chiral selector to resolve some amino acid derivatives on an α-methylene-γ-butyrolactam bonded phase. First, the optimization of the design of the CS is reported. Second, the separation of a diastereomeric mixture with respect to the carbon atom configuration in the lactam ring by preparative-scale chromatography on CSP 1 is described. Finally, the binding of one diastereomer on to LiChrosorb-NH_2, according to a previously published procedure[7], is discussed.

EXPERIMENTAL

Analytical chromatography

Analytical chromatography was performed with a modular liquid chromatograph (Gilson, Villiers-le-Bel, France) equipped with a Model 303 pump, a Model 802C manometric module, a Gilson 811 (1.5 ml) dynamic mixer and a Model 116 variable-wavelength UV detector (190–360 nm). All results were recorded with a Shimadzu CR3A integrator (Touzart et Matignon, Vitry-sur-Seine, France). Chiral stationary phases were packed into 150 × 4.6 mm I.D. stainless-steel columns by the usual slurry technique, at 400 bar with ethanol as pumping solvent. All chromato-

graphic determinations were carried out at room temperature with *n*-hexane–ethanol or *n*-hexane–chloroform as mobile phases (flow-rate 2 ml/min).

Preparative chromatography

Preparative chromatography was performed at room temperature with a Modulprep apparatus (Jobin-Yvon, Longjumeau, France). The (*S*)-thio-DNBTyr-A (CSP 1) (200 g, 7 μm) was packed into the column (40 mm I.D.) by axial compression at 15 bar. UV detection was carried out at 254 nm with a Model SM-25 variable-wavelength detector (195–370 nm) (Jobin-Yvon). The eluent inlet pressure was about 13 bar, which gave a flow-rate of *ca.* 30 ml/min.

Nuclear magnetic resonance spectra

^{1}H NMR spectra were recorded at 200 MHz on a Bruker-WP.200 spectrometer at 296 K, using tetramethylsilane (TMS) as internal standard and [^{2}H]chloroform or [$^2H_6$]dimethyl sulphoxide as solvent; values and constants are given in hertz.

Polarimetry

Optical rotations were measured on a Perkin-Elmer 141 micropolarimeter with a thermostated 1-dm quartz cell and using high-purity solvents (usually from Merck, Darmstadt, F.R.G.).

Physical data

The melting points were measured on a Büchi–Tottoli hot-stage apparatus and are uncorrected.

The compounds, listed with their empirical formulae, had elemental analyses consistent with their formulae to within ±0.3% (Service Central de Microanalyse du CNRS).

Materials

For analytical chromatography, *n*-hexane and ethanol were of LiChrosorb grade from Merck. Chloroform of analytical-reagent grade [stabilized with 0.6% (w/w) of ethanol] was from Prolabo (Paris, France). For preparative chromatography and packing of the columns, the solvents (*n*-hexane, ethanol) were of analytical-reagent grade, purchased from Prolabo. LiChrosorb-NH_2 γ-aminopropylsilica gel (particle diameter 5 or 7 μm) was purchased from Merck.

Classical column chromatographic purifications were carried out on Merck H-60 silica gel. Analytical thin-layer chromatography (TLC) was performed on Merck F-254 silica gel plates.

Syntheses

8-(4'-Anisoyl)-1-naphthoicacid (7). The keto acid **7** (Fig. 3) was prepared using a Grignard reaction between 1,8-naphthoic anhydride and *p*-anisylmagnesium bromide[8] instead of the procedure using aluminium chloride, which may cause several side reactions[9].

1,8-Naphthoic anhydride (Aldrich) (59.46 g, 0.3 mol) was partially dissolved in 750 ml of freshly distilled tetrahydrofuran (THF) and the Grignard reagent solution (10% excess) was slowly added through a dropping funnel, at room temperature. The

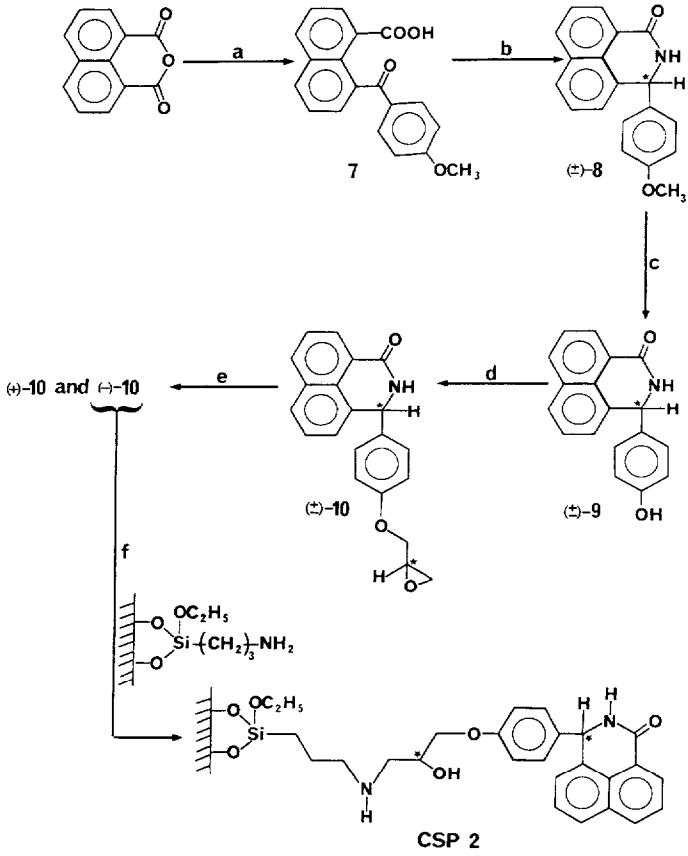


Fig. 3. Preparation of CSP 2. (a) *p*-Anisyl magnesium bromide, THF, 47% yield; (b) formamide, formic acid, reflux 2.5 h, 90% yield; (c) boron tribromide in methylene chloride, 96% yield; (d) potassium carbonate, epibromohydrin, acetonitrile, reflux 30 h, 66% yield; (e) preparative separation on CSP 1; (f) LiChrosorb-NH_2 (5 μm), triethylamine, benzene, reflux 44 h.

homogeneous solution was refluxed for 2.5 h then, after cooling, hydrolysed with a saturated solution of ammonium chloride. The mineral was filtered off on Celite and the filtrate partly evaporated. The crude product which appeared as a brown gum was filtered on a fine-pore sintered-glass funnel, rinsed with water and dried under vacuum. The solid residue was crystallized from methanol–benzene (5:1, v/v) to afford 43 g of a white solid (47%); m.p. 197–198.5°C. Analysis (C, H, O): $C_{19}H_{14}O_4$. ^{1}H NMR ([$^2H_6$]dimethyl sulphoxide): 3.84 (s, 3H, OCH_3), 7.02 (d, J = 10 Hz, 2H, aromatic), 7.51–7.68 (m, 4H, aromatic), 7.79 (d, J = 10 Hz, 2H, aromatic), 8.05–8.28 (m, 2H, aromatic).

*(±)-3-(4'-Anisyl)2,3-dihydro-1H-benz[de]isoquinolin-1-one (**8**)*. A solution of **7** (21.4 g, 70 mmol) in freshly distilled formamide (56 ml, 1.4 mol) and formic acid (26 ml, 0.7 mol) were refluxed for 2.5 h at 140°C[10]. The reaction mixture was allowed to cool to room temperature and water (200 ml) was added. The pale brown precipitate was filtered through a fine-pore sintered-glass funnel, rinsed abundantly with water

and triturated in hot methanol (150 ml) to afford a colorless solid (18.2 g, 90% yield); m.p. 226.5–230°C. A sample, triturated twice in hot methanol, afforded **8** as a white solid; m.p. 229–231°C. Analysis (C, H, N, O) · $C_{19}H_{15}NO_2$. ^1H NMR ([$^2H_6$]dimethyl sulphoxide): 3.70 (s, 3H, OCH_3), 6.08 (s, 1H, C*H), 6.86 (d, J = 9 Hz, 2H, aromatic), 7.20 (d, J = 9 Hz, 2H, aromatic), 7.33–8.25 (m, 6H, aromatic), 8.71 (s, 1H, NH).

3-(4'-Hydroxyphenyl)-2,3-dihydro-1H-benz[de]isoquinolin-1-one (9). A solution of **8** (15.9 g, 55 mmol) in 1 l of dichloromethane was treated dropwise with 116 ml of 1 *M* boron tribromide in dichloromethane (Aldrich) at −18°C under nitrogen[7]. During addition, the solution became homogeneously dark. The resulting mixture was allowed to come to room temperature and was stirred overnight. The reaction mixture was hydrolysed by adding water, then neutralized with sodium hydrogencarbonate solution. The solid, collected by filtration under suction, was triturated in 100 ml of a hot chloroform–methanol (50:50, v/v) solution, and finally dried under vacuum at 50°C. In this way, **9** was obtained as a pink powder (14.5 g, 96% yield); m.p. 273–275°C (decomp.). Analysis (C, H, N, O): $C_{18}H_{13}NO_2$. ^1H NMR ([$^2H_6$]dimethyl sulphoxide): 6.02 (s, 1H, C*H), 6.69 (d, J = 8 Hz, 2H, aromatic), 7.08 (d, J = 8 Hz, 2H, aromatic), 7.32–8.24 (m, 6H, aromatic), 8.67 (s, 1H, NH), 9.42 (s, 1H, OH).

3-(4'-Glycidyloxyphenyl)-2,3-dihydro-1H-benz[de]isoquinolin-1-one (10). Potassium carbonate (4,5 g, 32 mmol) was added to a solution of **9** (6.88 g, 25 mmol) in 250 ml of acetonitrile. The resulting suspension was stirred magnetically for 3 h under nitrogen, then 4.11 g (30 mmol) of epibromohydrin were added and the mixture was refluxed for 30 h[7]. The solvent was evaporated and the organic material was extracted with chloroform and washed with water until neutrality, then washed with brine. The solvent was evaporated and 8.0 g of raw product resulted, which was purified by chromatography on silical gel with dichloromethane–ethyl acetate (78:22, then 75:25, v/v) as eluent. The solvent was evaporated. Trituration in hot acetonitrile (45 ml) afforded 5.5 g (66% yield) of **10** as a pale yellow powder; m.p. 177–178°C. Analysis (C, H, N, O): $C_{21}H_{17}NO_3$. ^1H NMR (C^2HCl_3): 2.74 (m) and 2.90 (t), terminal methylene, 3.33 (m, C*H glycidyloxy), 3.92 (ddd) and 4.21 (dt) for the other methylene, 6.06 (s, 1H, C*H), 6.35 (s, 1H, NH), 6.88 (d, J = 9 Hz, 2H, aromatic), 7.24 (d, J = 9 Hz, 2H, aromatic), 7.12–8.44 (m, 6H, aromatic).

The diastereomeric mixture (with regard to the glycidyloxy chirality) was separated by chiral preparative chromatography using an (*S*)-thio-DNBTyr-A (200 g) packed column (CSP 1)[3,4]. The composition of the mobile phase was determined from analytical optimization data: *n*-hexane–ethanol (65:35, v/v). UV detection was carried out at 254 nm; flow-rate, 30 ml/min; pressure, 13 bar; amount injected, 300 mg each run. The diastereomeric mixture (−)-**10**, eluted first, was obtained with 100% enantiomeric excess (e.e.), measured on analytical CSP 1 (Fig. 4); m.p. 154–156°C; $[\alpha]_D^{22} = -106.9°$ (c = 1, THF). (+)-**10** was obtained with 100% e.e.; m.p. 157–158°C; $[\alpha]_D^{22} = +113.9°$ (c = 1, THF) (Fig. 4).

Synthesis of CSP 2. Anhydrous benzene (50 ml), triethylamine (0.2 ml) and 0.66 g (2 mmol) of (−)-**10** were added to 5 g of LiChrosorb-NH_2 (5 μm). The mixture was stirred magnetically under reflux until the starting (−)-**10** has disappeared (TLC). CSP 2 was isolated by filtration on a fine-pore sintered-glass funnel and was abundantly rinsed with benzene, methanol and diethyl ether, then dried in air; 5.63 g of CSP 2 resulted. Analysis: found, C 23.20, H 3.10, N 1.21, Si 28.90%; calculated, 0.16 mmol of chiral moiety per gram of chiral phase (based on N).

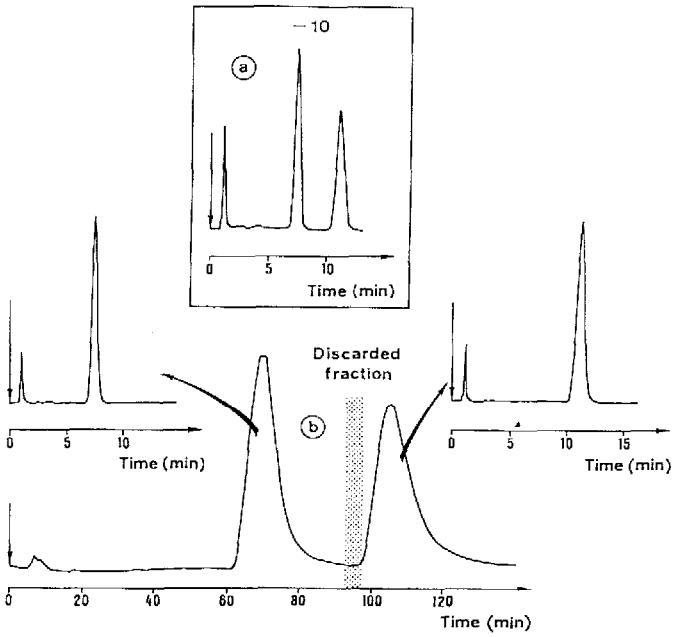


Fig. 4. (a) Analytical and (b) preparative resolution of compound **10** on CSP 1. Mobile phase: *n*-hexane–ethanol (65:35, v/v). Flow-rate: (a) 2 ml/min; (b) 30 ml/min. Amount injected, 300 mg per run; UV detection at 254 nm.

*(±)-N-(3,5-Dinitrobenzoyl)-α-aminobutylamide derivatives (**19–23**).* These compounds were prepared from the corresponding (±)-N-(3,5-dinitrobenzoyl)-α-aminomethyl ester derivatives[7], using the following procedure. The methyl ester (300 mg) was dissolved in a solution of butylamine (3 ml) in dry THF (15 ml). The reaction mixture was then stirred magnetically (about 30 days) at room temperature. Progress of the reaction was monitored by HPLC [CSP 2; mobile phase, hexane–ethanol (85:15, v/v)]. The solvent was evaporated under vacuum and the crude product obtained was purified by chromatography on silica gel with *n*-hexane–ethyl acetate as eluent. After work-up, **19** (m.p. 211.5–212.5°C), **20** (m.p. 198–199°C), **21** (m.p. 212–214°C), **22** (m.p. 130–132°C) and **23** (m.p. 174–176°C) were obtained [Table V, (70:30, v/v) except for compound 20 (75:25, v/v)].

Phthalic anhydride was a convenient precursor for the synthesis of compounds involved with the design optimization of CSP 2 (Fig. 5). Synthesis (reference) and physical data are given in Table I.

RESULTS AND DISCUSSION

Design of the chiral selector (CS)

In order to maximize the behaviour of the reciprocal CSP, we first optimized the design of the chiral moiety intended to be bound to LiChrosorb-NH_2. As compound A (Fig. 2A) is too reactive to be bound directly, the α-methylene unit was replaced with a 1,2-phenylene group combined in the 3,4 position of the lactam (Fig. 2A) to create

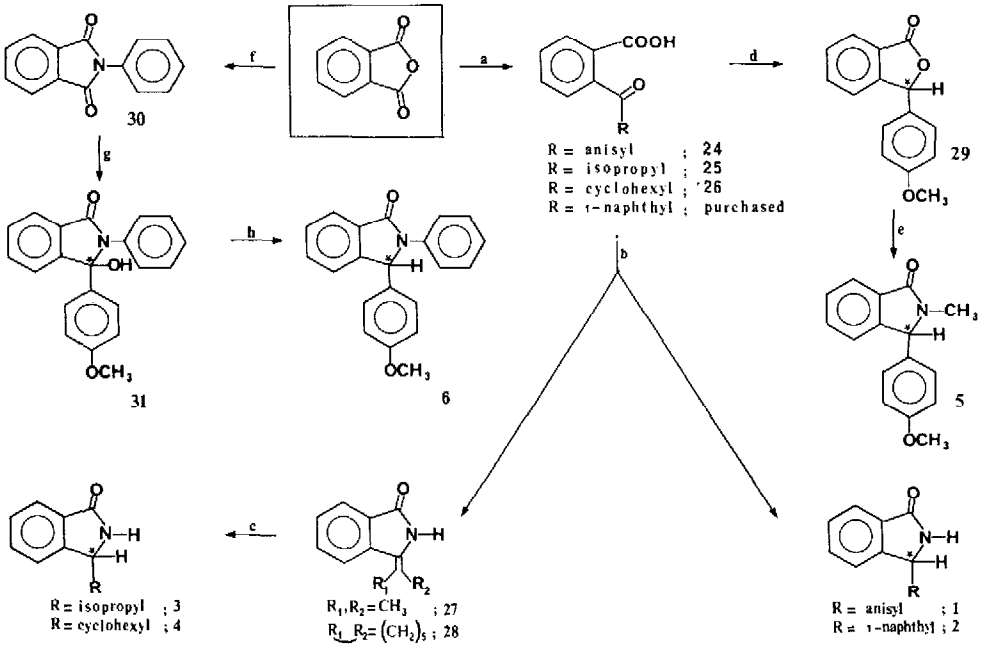


Fig. 5. Syntheses of compounds involved in the design study. (a) RMgBr, THF, reflux 2–3 h, 30–37% yield; (b) formamide, reflux 2.5 h, 52–62% yield; (c) H_2, Pd–$BaSO_4$, solvent ethyl acetate–methanol, 94–99% yield; (d) sodium borohydride, sodium hydroxide, 93% yield; (e) 40% methylamine, 190–200°C, 10 h, 9% yield [and 43% yield of demethylated product (OH)]; (f) aniline, *p*-cymene, reflux 12 h, 55% yield; (g) *p*-anisylmagnesium bromide, THF, 20% yield; (h) H_2, Pd–C, in acetic acid, 21% yield.

TABLE I

MELTING POINTS OF COMPOUNDS INVOLVED IN THE DESIGN OF THE CHIRAL SELECTOR

Compound	*m.p. (°C)*	*Ref.*[a]
1	167–168.5 (ref. 10: 165–166)	10
2	229–231.5	10
3	155.5–157	11
4	184–185.5	11
5	111–112	12
6	148–150	13
24	144–146 (ref. 9: 148)	9
25	122.5–124	9
26	Oil	9
27	220–222	10
28	218–220	10
29	115–115.5	6
30	204–207 (ref. 14: 200–210)	14
31	186–187.5	15

[a] References deal with the synthesis of analogues of the products mentioned.

the isoindolinone skeleton (Fig. 2B). Such a modification enhances the planar character of the CS candidate. With respect to the reciprocality concept, the best resolved derivative of structure B (Fig. 2) on CSP 1 will be expected to constitute the most suitable candidate to be the reciprocal CS. We studied the selectivity (α) of the separation of some B derivatives with respect to the nature of the R and R′ substituent groups (Table II).

Among the series, (±)-3-(4′-methoxyphenyl)isoindolin-1-one (**1**) appeared at this stage to be the most suitable candidate, as (a) **1** has the highest selectivity on CSP 1, which allows the isolation of enantiomers on a preparative scale by chiral chromatography and (b) as previously reported[7], the anisyl group allows easy binding of the chiral moiety to LiChrosorb-NH_2. Chromatographic results demonstrated that the driving force between CSP **1** and compounds **1–6** is governed by the dipolar interaction involving the CSP aliphatic amide dipole and the cyclic amide group (in the *Z* configuration), as no selectivity is observed for compounds **5** and **6**. It should be noted that the dipole moment of the *Z* form of an amide is lower than that of the *E* form[16].

The replacement of the *p*-anisyl moiety (R′) in **1** by an aliphatic group, such as the isopropyl group in **3** or the cyclohexyl group in **4**, leads to a decrease in selectivity. This result suggests that the mechanism for chiral recognition also involves the formation of a π–π charge-transfer complex between the anisyl group (π-electron donor) and the π-electron acceptor 3,5-dinitrobenzoyl group of CSP 1. Nevertheless, this interaction is less significant than the above-mentioned dipolar interaction, as we do not observe a complete loss of selectivity for aliphatic substitution (R′ group, Fig. 2B). More surprising is the fact that the selectivity decreases when R′ is 1-naphthyl (see compound **2**, Table II), whereas this group is considered to be more strongly π-basic than the anisyl group, and hence should be better resolved. In fact, we observed the opposite result, *i.e.*, the bulky character of 1-naphthyl group affects the dipole–dipole interaction developed by the adjacent amide bond. Chromatographic results for compound **2** (Table II) suggested that, in order to enhance the potential π-donating character of the CS candidate, an additional aromatic ring should be incorporated inside the molecule skeleton (see compound **8**, Fig. 2) rather than on the asymmetric centre. Indeed, a significant increase in selectivity is observed for compound **8** in comparison with compound **1** (Tables II and III).

Finally, the methoxy group in (±)-**8** was demethylated using boron tribromide to give the phenol (±)-**9**, then condensed with epibromohydrin to give the ether **10**, which introduces an additional asymmetric centre, thus leading to a mixture of four diastereomers. As racemate **8** is well separated on CSP 1, the separation into two peaks observed for the diastereomeric mixture **10** seems to be due to the same asymmetric centre located in the lactam ring. Therefore, the isolation of two mixtures of two diastereomers was performed by means of chiral preparative chromatography. Fig. 4 illustrates both analytical and preparative resolution of CS **10** on CSP 1. The first eluted fraction, (−)-**10**, is allowed to react with LiChrosorb-NH_2 to lead to CSP 2 (Fig. 3).

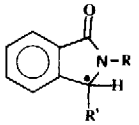
Preliminary chromatographic results

The π-basic CSP 2 provides separations of π-acid analytes such as N-(3,5-dinitrobenzoyl) derivatives of α-amino esters (Table IV) and α-aminoamides (Table

TABLE II

SEPARATION OF RACEMATES OF ISOINDOLINONE DERIVATIVES **1–6** ON CSP I

Mobile phase: *n*-hexane–ethanol (90:10, v/v).



Compound	*R*	*R'*	k'_2[a]	α[b]
1	H	*p*-Anisyl	8.15	1.36
2	H	1-Naphthyl	9.70	1.08
3	H	Isopropyl	2.40	1.07
4	H	Cyclohexyl	2.67	1.15
5	CH_3	*p*-Anisyl	4.25	1.00
6	C_6H_5	*p*-Anisyl	6.29	1.00

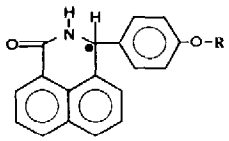
[a] k'_2 is the capacity factor of the second eluted enantiomer, $k'_2 = (t_{R2}/t_0)-1$, where t_{R2} is the retention time of the second eluted enantiomer and t_0 is the retention time of a non-retained solute.

[b] The selectivity, α, between two enantiomers is the ratio of their respective capacity factors (k'_2/k'_1).

TABLE III

SEPARATION OF RACEMATES **8–10** ON CSP I

Mobile phase: *n*-hexane–ethanol (90:10, v/v).



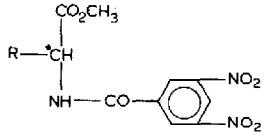
Compound	*R*	k'_2[a]	α[b]
8	CH_3	17.35	1.57
9	H	25.95	1.47
10	Glycidyloxy	48.03	1.61

[a,b] As defined in Table II.

V). Two different mobile phases were studied: *n*-hexane–ethanol and *n*-hexane–chloroform. The sensitive difference in selectivity observed with these two mobile phases clearly indicates how important for chiral recognition is the relative ability of a solvent to act as a proton acceptor (as defined by Snyder[17]), such as ethanol, or as a proton donor[17], such as chloroform. As selectivity is a direct consequence of various interactions between the CSP and each enantiomer, it is not surprising that any competing interaction occurring between the mobile phase and the CSP may alter or enhance chiral separations[18]. The results in Tables IV and V indicate that, regarding selectivity, chloroform is more suitable than ethanol in the mobile phase for the resolution of ester and amide derivatives (Fig. 6).

TABLE IV

SEPARATION OF RACEMATES OF N-(3,5-DINITROBENZOYL) DERIVATIVES OF α-AMINO ESTERS **11–18** ON CSP 2



Compound	*R*	*n-Hexane–ethanol (85:15)*			*n-Hexane–chloroform (50:50)*		
		k'_2 [a]	α [b]	*Elution order* [c]	k'_2 [a]	α [b]	*Elution order* [c]
11	$CH_2C_6H_5$	7.44	1.10	*S*	6.23	1.19	*S*
12	C_6H_5	8.10	1.17	*S*	6.30	1.26	*S*
13	$CH_2CH(CH_3)_2$	4.09	1.15	*S*	8.11	1.32	*S*
14	$CH(CH_3)_2$	4.15	1.08	*S*	3.95	1.21	*S*
15	$CH_2CH_2SCH_3$	8.92	1.15	*S*	10.38	1.30	*S*
16	CH_3	6.39	1.15	*S*	10.57	1.31	*S*
17	p-$CH_2C_6H_4OCH_2CH=CH_2$	9.33	1.08	*S*	5.93	1.16	*S*
18	$CH_2CH_2CO_2CH_3$	9.80	1.13	*S*	6.80	1.26	*S*

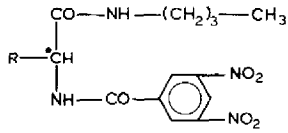
[a,b] As defined in Table II.

[c] Absolute configuration of the first-eluted enantiomer.

The most important phenomenon is a reversal of elution order of enantiomers between α-amino esters **11–18** (*S,R* elution order, Table IV) and α-aminoamides **19–23** (*R,S* elution order, Table V). This indicates that the two families of racemates are resolved according to two different chiral recognition mechanisms. The presence of

TABLE V

SEPARATION OF RACEMATES OF N-(3,5-DINITROBENZOYL) DERIVATIVES OF α-AMINOBUTYLAMIDES **19–23** ON CSP 2



Compound	*R*	*n-Hexane–ethanol (90:10)*			*n-Hexane–chloroform (30:70)*		
		k'_2 [a]	α [b]	*Elution order* [c]	k'_2 [a]	α [b]	*Elution order* [c]
19	$CH_2C_6H_5$	9.71	1.13	*R*	9.37	1.48	*R*
20	C_6H_5	9.25	1.08	*R*	5.30	1.32	*R*
21	$CH_2CH(CH_3)_2$	5.12	1.33	*R*	8.4	1.92	*R*
22	$CH_2CH_2SCH_3$	10.06	1.08	*R*	8.79	1.49	*R*
23	p-$CH_2C_6H_4OCH_2CH=CH_2$	12.36	1.18	*R*	8.88	1.79	*R*

[a,b] As defined in Table II.

[c] Absolute configuration of the first-eluted enantiomer.

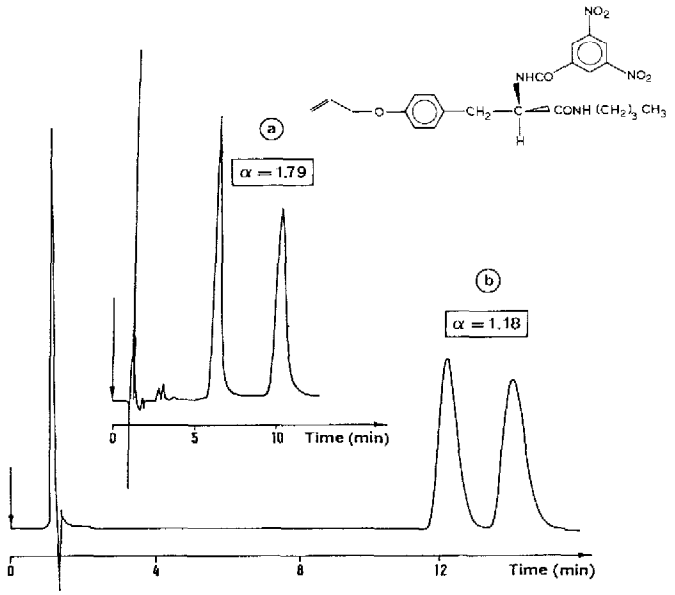


Fig. 6. Resolution of (±)-N-(3,5-dinitrobenzoyl)-O-allyltyrosine *n*-butylamide, (±)-**23**, on CSP 2. Mobile phase: (a) *n*-hexane–chloroform (30:70, v/v); (b) *n*-hexane–ethanol (90:10, v/v). Flow-rate, 2 ml/min; UV detection at 254 nm.

a second aliphatic amide dipole for solutes **19–23** influences the nature and/or the strength of interaction prevailing in the chiral recognition mechanism.

Two chiral recognition models can be proposed (Fig. 7) to account for possible interactions between CSP 2 (arbitrary *R* configuration) and amide or ester solutes. From steric considerations, the preferred approach of the solute towards the CSP

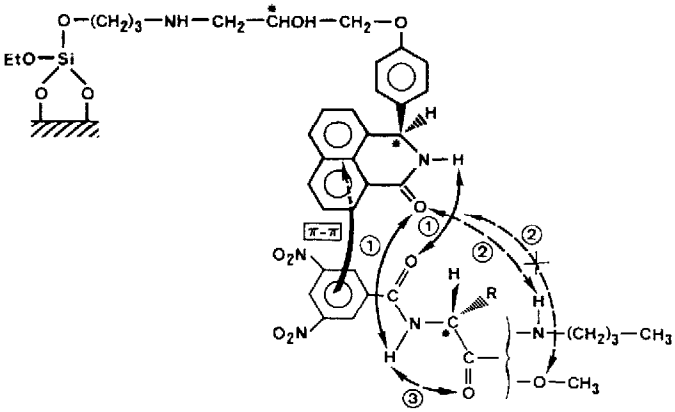


Fig. 7. Proposed chiral recognition model, showing the relative coplanar arrangement which provides several simultaneous interactions between CSP 2 (of arbitrary *R* configuration) and (*R*)-N-(3,5-dinitrobenzoyl) derivatives of α-amino methyl esters and *n*-butylamides. Interactions depicted are π–π charge-transfer complex; (1) dipole stacking between the two aromatic amide functional groups; (2) hydrogen bonding for *n*-butylamide only; (3) intramolecular hydrogen bonding.

occurs preferably on the side of the hydrogen atom, rather than on the side of the aromatic substituent.

Both mechanisms involve the formation of a π–π charge-transfer complex between the 1,8-naphthylene group of CSP 2 and the 3,5-dinitrophenyl group of α-amino ester or α-aminoamide derivatives. In mechanism (1), a stacking dipole interaction [Fig. 7, see (1)] is expected between the solute aromatic amide dipole and the CSP 2 amide group. In mechanism (2), a hydrogen-bonding interaction [Fig. 7, see (2)] is established between the aliphatic NH group of the solute and the carbonyl group of the CSP 2. α-Amino esters **11–18** can only be resolved according to mechanism (1), whereas α-aminoamides **19–23** can be resolved according to both mechanisms. From the examination of CPK models, these two mechanisms act in opposite stereochemical senses. As a reversal of elution order is observed between esters and amides, mechanism (2) seems to prevail for the resolution of α-aminoamides **19–23**. The study of the influence of the nature of the mobile phase on selectivity further confirms this assumption. In fact, owing to its acidic character, chloroform interacts with carbonyl groups of either ester or aliphatic amide groups. This competing interaction may lead to a decrease in the intramolecular hydrogen bonding [Fig. 7, see (3)] and may reinforce the acidic character of the hydrogen atom of the solute aliphatic amide. This may create stronger hydrogen bonding [Fig. 7, see (2)], thus leading to a noticeable increase in selectivity for amides **19–23**. Such a phenomenon cannot occur for esters **11–18**: the increase in the selectivity for the resolution of these solutes was observed to be of lesser importance when chloroform was used instead of ethanol as organic modifier (Table IV).

CONCLUSION

In this paper, the step-by-step optimization of the design of a new π-basic CSP derived from the benz[*de*]isoquinolinone skeleton has been presented. The choice of a chiral selector based on the reciprocality concept was described. This chiral selector was easily prepared with high optical purity by means of preparative-scale chromatography, and was easily bound to LiChrosorb-NH_2. First chromatographic results were presented. Once again, the nature of the polar modifier in the mobile phase (as defined by Snyder[17]) was found to be of great importance for the chiral recognition process[18,19]. *n*-Hexane–chloroform was shown to be more suitable than *n*-hexane–ethanol for the resolution of series of N-(3,5-dinitrobenzoyl) derivatives of α-aminoamides and α-amino esters. Two chiral recognition processes were finally proposed, depending on the chemical nature of the solute.

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