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Convenient and highly efficient chromatographic resolution of BINOL and of 6,6′-dibromo-BINOL via *N*(α)-Boc-tryptophan esters

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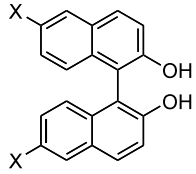
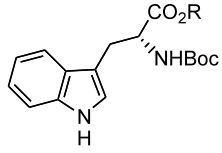
Abstract—Racemic [1,1′]binaphthalenyl-2,2′-diol (BINOL, (±)-**1**) has been esterified with various commercially available *N*-protected-L-amino acids, giving the corresponding diastereomeric esters. Their TLC separation factors were highly dependent on the amino acid pattern. Diesters of (±)-**1** and *N*(α)-Boc-tryptophan (**3a**) showed unusually large separation factors, which allowed their efficient separation by simple column chromatography. Removal of the tryptophan moieties under very mild conditions furnished each enantiomer of **1** in high overall yield and 100% ee. This procedure was also successful for the resolution of racemic 6,6′-dibromo-[1,1′]binaphthalenyl-2,2′-diol (6,6′-dibromo-BINOL, (±)-**2**).

Resolution by conversion of a racemate to a mixture of diastereomers remains of paramount importance to obtain enantiomerically pure substances. In a large majority of cases, this type of resolution is based on solubility differences of crystalline solids. The major drawbacks of this approach are that it involves necessarily crystalline materials and that, often, only one enantiomer (corresponding to the least soluble diastereomer) can be obtained in a very high optical purity. Comparatively, separations based on chromatographic separation of covalent diastereomeric pairs are much less frequent, though having, in favorable cases, some decisive advantages over crystallization methods: Mainly, there is no need to obtain crystalline materials and, in principle, both enantiomers are obtainable optically pure.[1] To be of practical use, chromatographic resolutions on covalent diastereomers have to combine the following characteristics: The resolving agent should be readily (or, even better, commercially) available at a reasonable price. Covalent bonding to the racemate should be simple, selective and high yielding. R_f differences between the diastereomeric pairs should be as large as possible. Lastly, removal of the chiral auxiliary should be easy and should allow its recovery. Herein we report a new chromatographic resolution of racemic [1,1′]binaphthalenyl-2,2′-diol (BINOL, (±)-**1**) and of racemic 6,6′-dibromo-[1,1′]binaphthalenyl-2,2′-diol (6,6′-dibromo-BINOL, (±)-**2**) that fulfils all the preceding requirements.



1 (X = H)

2 (X = Br)



3a (R = H)

3b (R = CH_3)

Various resolutions of (±)-**1** and of other atropisomeric diphenols via covalent derivatives have been described, using for example menthyl carbonates,[2] neomenthylthioacetates,[3] menthyl cyclic phosphites,[4] cyclic phosphates or thiophosphates bearing the α-methylbenzylamine moiety,[2c,f,5] camphorsulfonates,[6] and camphanates.[7,8] To our knowledge, amino acid derivatives have not yet been used for chromatographic resolution of atropisomeric diphenols via the corresponding esters, with the notable exception of Fuji's resolution of [1,1′]binaphthalenyl-8,8′-diol via monoesters of *N*-Cbz-L-proline.[7] α-Amino acids of the L series represent a natural source of optically pure compounds with an outstanding structural diversity. We have checked the resolution ability of various com-

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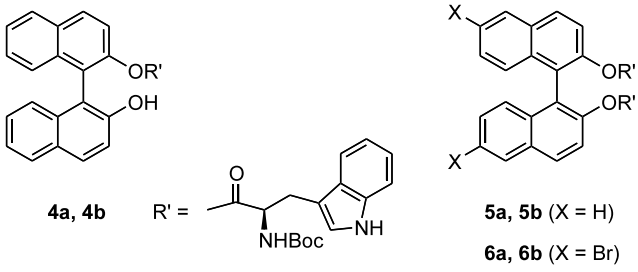
mercially available *N*-protected-L-amino acids on (±)-**1**, via the corresponding diastereomeric esters. Each reaction has been performed on an analytical scale (10 μmol). R_f values and separation factors (α) were determined by TLC analysis, in order to select the most promising candidates for efficient separations. Both conversions into mono- and into diesters have been attempted, using standard DCC/DMAP esterification method. Table 1 summarizes the TLC data for the various mono- and diesters tested. *N*-Boc- and *N*-Cbz-proline gave readily monoesters with separation factors of 1.21 and 1.15, but clean conversion into diesters failed (entries 1 and 2). Amino acids with aliphatic side chains like *N*-Boc-isoleucine and -valine gave easily mono- or diesters, but with only negligible separation factors (entries 3 and 4). *N*-Boc-asparagine and *N*(α)-Boc-histidine failed to give significant amounts of esters (entries 5 and 6). Both mono and diesterification were easily performed with *N*-Boc-phenylglycine but separation factors were very low (entry 7). *N*-Boc- and *N*-Cbz-phenylalanine gave monoesters, with separation factors in the same range as for the corresponding proline derivatives. The corresponding α factors were somewhat lower for diesters (entries 8 and 9). Fmoc nitrogen protection gave no advantage over Boc and Cbz protection (entry 10). At last, *unusually high separation factors* were observed in the tryptophan series (entries 11–13): *N*(α)-Boc-, *N*(α)-Cbz- and *N*(α)-Fmoc-tryptophan furnished monoesters with α values respectively 1.50, 1.43 and 1.31, and diesters with 2.15, 1.89 and 1.50 values. Such high TLC α values are rather uncommon and are generally indicative of easy chromatographic separations, even with the usual flash chromatography techniques.[9]

Esterifications of (±)-**1** with *N*(α)-Boc-tryptophan (**3a**) have been scaled up without difficulties. Mono esterification was performed on a 2 mmol scale of (±)-**1**, using 1 equiv. of **3a**, 1 equiv. of DCC and 10 mol% DMAP. Column chromatography on silica gel (elution CH_2Cl_2:ether, 95:5) gave 87% of monoester **4a** with $R_{f1}=0.60$ and 82% of monoester **4b** with $R_{f2}=0.40$ (Table 1, entry 11). Chromatographic separation also furnished 12% of unreacted **1**. Optical rotation of this sample was $[\alpha]_D^{18}=+5.84$ ($c=1.0$, THF), which reveals an ee of 17% in the favor of (+)-**1** and, consequently, some degree of kinetic resolution during esterification. Diesterification has next been performed on a 4 mmol scale of (±)-**1**, using 2.2 equiv. of **3a**, 2.3 equiv. of DCC and 10 mol% of DMAP. Reaction was achieved after 3 h at room temperature. The large separation factor allowed high loading of the chromatography column: complete separation was performed on 60 g silica gel, giving 1.66 g (97% yield) of diester **5a** with $R_{f1}=0.54$ and 1.70 g (99% yield) of diester **5b** with $R_{f2}=0.26$. Each diester was diastereomerically pure (HPLC control).[10]



Clean removal of the chiral auxiliaries after resolutions via covalent diastereomeric pairs remain critical for the global success of the processes. In fact, serious limitations can arise from this final step: For example camphanyl esters are best cleaved via reduction by $LiAlH_4$.[7] Not only is this procedure destructive for the chiral moiety, but it is also hard to use if sensitive functional-

Table 1. TLC data for mono- and diesters of (±)-**1** and *N*-protected-L-amino acids

Entry	Amino acid derivative	Monoesters			Diesters		
		R_{f1}[a]	R_{f2}[a]	α[b]	R_{f1}[a]	R_{f2}[a]	α[b]
1	*N*-Boc-proline	0.46	0.38	1.21	–[c]	–[c]	–
2	*N*-Cbz-proline	0.46	0.40	1.15	–[c]	–[c]	–
3	*N*-Boc-isoleucine	0.66	0.66	1	0.76	0.76	1
4	*N*-Boc-valine	0.62	0.60	1.03	0.74	0.70	1.06
5	*N*-Boc-asparagine	0.36[d]	0.36[d]	1	–[d]	–[d]	–
6	*N*(α)-Boc-histidine	–[e]	–[e]	–	–[e]	–[e]	–
7	*N*-Boc-phenylglycine	0.66	0.65	1.01	0.76	0.74	1.03
8	*N*-Boc-phenylalanine	0.62	0.52	1.19	0.78	0.70	1.11
9	*N*-Cbz-phenylalanine	0.64	0.54	1.18	0.80	0.74	1.08
10	*N*-Fmoc-phenylalanine	0.68	0.62	1.10	0.84	0.80	1.05
11	*N*(α)-Boc-tryptophan	0.60[f]	0.40[f]	1.50	0.54[f]	0.26[f]	2.15
12	*N*(α)-Cbz-tryptophan	0.60[f]	0.42[f]	1.43	0.68[f]	0.36[f]	1.89
13	*N*(α)-Fmoc-tryptophan	0.68[f]	0.52[f]	1.31	0.78[f]	0.52[f]	1.50

[a] Except when otherwise stated, elution with 95:5, CH_2Cl_2:ether mixtures.
[b] α defined as: $\alpha=R_{f1}/R_{f2}$
[c] Complex mixture obtained.
[d] Low conversion.
[e] No esterification.
[f] Elution with 90:10, CH_2Cl_2:ether mixtures.

ities are present in the compound to be resolved. Similar limitations exist for the use of cyclic phosphorus derivatives[4] or of menthyl carbonates.[2] Fuji's resolution of [1,1′]binaphthalenyl-8,8′-diol via *N*-Cbz-L-proline esters allowed hydrolytic cleavage by KOH.[7] We first applied the same procedure for the saponification of diester **5a**. Reaction was completed after 18 h at room temperature, and furnished after conventional work-up, 62% (*R*)-(+)-**1** (100% ee).[11] Camphorsulfonates have been cleaved after several hours refluxing in methanolic NaOH.[6b] Gratifyingly, we found that *almost instantaneous* cleavage of diesters occurred, using a stoichiometric amount of LiOH in methanol at room temperature. In this procedure, aqueous work-up can be avoided: After completion of the cleavage, stoichiometric amount of trifluoroacetic acid was added to the reaction mixture and methanol removed at reduced pressure. For **5a**, column chromatography of the crude material gave 91% of pure (*R*)-(+)-**1** (100% ee). *N*-Boc-L-tryptophan was recovered as its methyl ester **3b** (82% recovery, 100% ee).[12] In the same way, 93% of pure (*S*)-(−)-**1** (100% ee) has been obtained, starting from diester **5b** (83% recovery of **3b**).[13]

This new method has also been applied successfully for the resolution of (±)-**2**.[14] Diesterification of (±)-**2** with **3a** furnished a mixture of diastereomeric diesters **6a** and **6b** (TLC data: $R_{f1}=0.88$, $R_{f2}=0.50$, $\alpha=1.76$, elution with 85:15 CH_2Cl_2:ether). Column chromatographic separation of the crude material gave pure **6a** (98.5% yield), followed by pure **6b** (99%) yield).[10] Hydrolysis of **6a** by LiOH in methanol gave 91% of pure (*R*)-(−)-**2** (100% ee).[11] Similarly, **6b** furnished (*S*)-(+)-**2** (100% ee).

The present procedure combines all the desirable features for efficient chromatographic resolution via covalent derivatives. It allowed the resolution of (±)-**1** and -**2** with global yields close to 90% and 100% ee′s for each of the enantiomers. Preliminary experiments indicate that it should also be applicable to other types of atropisomeric biphenols. Its scope and limitations, as well as the origin of the high separation factors are presently under investigation and will be reported in due course.

Acknowledgements

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10. Although all mono- and diesters showed single signals on HPLC analysis (performed on a μBondapack C_{18} reversed phase column, elution MeOH:H_2O, 85:15), they exist, at room temperature, as mixtures of rotamers due to restricted rotation across *N*-Boc bond, as determined by ^1H NMR spectroscopy. See Ref. 7 for similar observations.
11. Enantiomeric purity has been determined by HPLC on a Chiralpak AS column, elution hexane:*i*-PrOH, 9:1, 1 mL min^{-1}.
12. Cardillo, G.; Gentilucci, L.; Tomasini, C.; Tomasoni, L. *Tetrahedron: Asymmetry* **1995**, *8*, 1947–1955. Enantiomeric purity of **3b** has been determined by HPLC on a Chiralpak AS column, elution hexane:*i*-PrOH, 6:4, 1 mL min^{-1}. Furthermore, as variation of the enantiomeric purity of the amino acid derivatives depending on the supplier have been reported, we have also checked start-

ing **3a**, after its preliminary derivatisation into **3b** with diazomethane.

13. Overall procedure for the resolution of **1**: A solution of racemic **1** (1.145 g, 4 mmol), **3a** (2.618 g, 8.8 mmol) (100% ee, supplied by ACRÔS Organics),[12] DCC (1.898 g, 9.2 mmol) and DMAP (0.048 g, 0.4 mmol) in anhydrous dichloromethane (80 mL) was stirred at room temperature for 3 h. After filtration of dicyclohexylurea, the solvent was removed at reduced pressure. The residue was chromatographed over silica gel (60 g). Elution with dichloromethane: ether (95:5) gave pure **5a** (1.663 g, 97% yield) as an amorphous solid: $[\alpha]_D^{25}$ −68.3 ($c=1.0$, THF). ^{1}H NMR (DMSO d_6) δ 1.19 and 1.27 (2br s in a 0.22:1 ratio, 18H), 1.85–2.20 (m, 4H), 4.00–4.20 (m, 2H), 6.90–7.59 (m, 20H), 8.04–8.17 (m, 4H), 10.74 (br s, 2H). ^{13}C NMR (DMSO d_6) δ 24.90, 28.05, 54.47, 78.26, 109.58, 111.37, 117.77, 118.42, 120.90, 121.83, 122.86, 123.61, 125.44, 125.89, 126.65, 126.95, 128.22, 129.98, 131.33, 132.64, 135.96, 146.51, 155.42, 171.01. IR (KBr pellet) ν 3412, 3053, 2980, 2931, 1763, 1706, 1502, 1371, 1159. MS (DCI, NH_3+isobutane) m/z 875, 858, 759, 659, 473. Anal. calcd for $C_{52}H_{48}N_4O_8$: C, 72.88; H, 5.64; N, 6.53. Found: C, 72.28; H, 5.82; N, 6.57. Further elution gave pure **5b** (1.697 g, 99% yield) as an amorphous solid: $[\alpha]_D^{25}$ −44.5 ($c=1.0$, THF). ^{1}H NMR (DMSO d_6) δ 1.15 and 1.29 (2 br s in a 0.27:1 ratio, 18H), 2.00–2.60 (m, 4H), 3.70–3.90 (m, 2H), 6.30–6.40 (m, 2H), 6.70–6.80 (m, 2H), 6.95–7.05 (m, 6H), 7.20–7.35 (m, 4H), 7.40–7.65 (m, 6H), 8.00–8.20 (m, 4H), 10.69 (br s, 2H). ^{13}C NMR (DMSO d_6) δ 25.58, 28.33, 55.03, 78.68, 109.83, 111.45, 117.67, 118.56, 121.05, 121.96, 122.78, 124.10, 127.48, 126.25, 126.71, 127.48, 128.71, 130.12, 131.58, 132.96, 136.13, 146.51, 155.68, 170.99. IR (KBr pellet) ν 3412, 3331, 3061, 2971, 2931, 1763, 1714, 1502, 1363, 1159. MS (DCI, NH_3+isobutane) m/z 875, 858, 759, 659, 473. Anal. calcd for $C_{52}H_{48}N_4O_8$: C, 72.88; H, 5.64; N, 6.53. Found: C, 72.10; H, 5.87; N, 6.65. To a solution of diester **5a** (1.663 g, 1.940 mmol) in methanol (5 mL) was added a 1 M solution of $LiOH\cdot H_2O$ in methanol (3.88 mL, 3.88 mmol). After 5 min stirring at room temperature, trifluoroacetic acid (0.29 mL, 3.88 mmol) was added. Removal of the solvent in vacuo gave a solid residue, which was subjected to column chromatography on silica gel (15 g). Elution with CH_2Cl_2 gave *R*-(+)-**1** (0.504 g, 91% yield): mp 206–207°C. $[\alpha]_D^{25}$ +34 ($c=1.0$, THF), ee = 100%.[11] Further elution with CH_2Cl_2 gave **3b** (1.009 g, 3.169 mmol, 82% yield): mp 142–144°C (lit.[12]: 142–144°C). In the same way, **5b** (1.697 g, 1.979 mmol) gave *S*-(−)-**1** (0.530 g, 93% yield): mp 209–210°C; $[\alpha]_D^{25}$ −34.0 ($c=1.0$, THF), ee = 100%.[11] Further elution of the column gave **3b** (1.049 g, 3.293 mmol, 83% yield) identical to the sample obtained from **5a**.
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