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1,12-Dioxa[12](1,4)naphthalenophane-14-carboxylic Acid: Practical Synthesis, Resolution and Absolute Configuration of the Enantiomers

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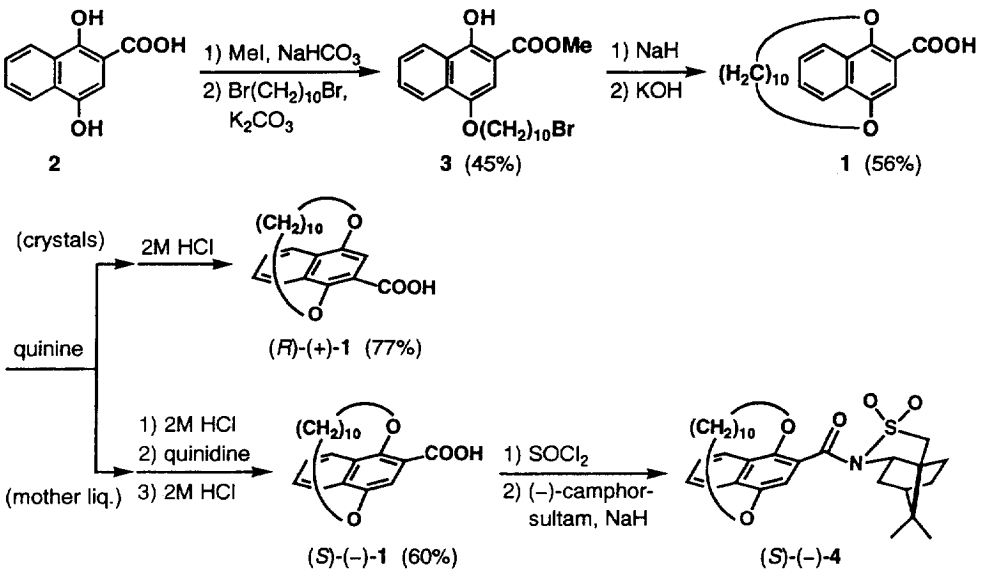
Abstract: A novel naphthalenophane, 1,12-dioxa[12](1,4)naphthalenophane-14-carboxylic acid (**1**), is conveniently prepared from 1,4-dihydroxy-2-naphthoic acid and 1,10-dibromodecane. Acid **1** is resolved by crystallization of its quinine or quinidine salt, and the absolute stereochemistry of acid (–)-**1** is determined to be *S* by the X-ray crystallographic analysis of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam amide derivative (**4**).

In the last two decades, 1,1'-binaphthyl compounds with axial chirality have been successfully utilized for chiral molecular recognition as well as in asymmetric syntheses. In a previous paper we reported that a chiral stationary phase derived from (*S*)-[10]paracyclophane-12-carboxylic acid was useful to resolve enantiomers by high-performance liquid chromatography (HPLC).[1] The results suggested that chiral cyclophanes with planar chirality would be other potential candidates for the design of chiral discriminators.[2] Herein, we report a convenient method for preparation of a chiral naphthalenophanecarboxylic acid having two ether moieties in an ansa chain (**1**) and the X-ray crystallographic determination of its absolute stereochemistry. We also report its application as a chiral derivatizing agent for discrimination of enantiomeric amines by HPLC.

Naphthalenophane **1** was prepared from 1,4-dihydroxy-2-naphthoic acid (**2**) (Scheme 1). The carboxylic function of acid **2** was initially protected as a methyl ester by treatment with 1.0 mol equiv. of $NaHCO_3$ in DMF at 50 °C and then with iodomethane at room temperature. Monoetherification of the methyl ester could be conducted by boiling the ester with 2.0 mol equiv. of 1,10-dibromodecane in the presence of 1.0 mol equiv. of K_2CO_3 in acetone to give methyl 1-hydroxy-4-(10-bromodecyloxy)-2-naphthoate (**3**) (m.p. 101 – 102 °C).[3] Monoether **3** (19.0 g) was treated with 1.0 mol equiv. of NaH in THF (150 ml) at room temperature to give a clear solution, which was added dropwise to a hot DMF (1000 ml) at 100 °C over a period of 10 h and the mixture was stirred at this temperature for further 5 h. Distillation of the crude product by use of a Kugelrohr (150 – 170 °C / 6.7 – 4.0 Pa) gave a cyclization product, which was hydrolyzed with KOH in aqueous ethanol to give acid **1** [m.p. 123 – 124 °C (ethanol)][4] in 25% overall yield based on the starting **2**. Enantiomer resolution of racemic acid **1** was easily attained by crystallization of its amine salt; treatment of acid **1** with 1.0 mol equiv. of quinine in refluxing acetone afforded the quinine salt of (+)-**1**, which was acidified with 2M HCl to generate enantiomerically pure (+)-**1** [m.p. 155 – 156 °C (acetonitrile); $[\alpha]_D^{20}$ +176 (*c* 1.02, acetone)]. The enantiomeric purity of (+)-**1** was checked by an HPLC analysis of its methyl ester on a Pirkle column [(*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine-modified column][5] with hexane – 2-propanol (0.5%) as the eluent. Similar treatment of the quinine salt in a mother liquor gave (–)-enriched **1**, which was then converted into the quinidine salt. The quinidine salt was recrystallized three times from a

mixture of acetonitrile and acetone (4:1) and treated with 2M HCl to afford enantiomerically pure (–)-**1** [m.p. 154 – 155 °C (acetonitrile); $[\alpha]_D^{20}$ –176 (*c* 1.02, acetone)].



Scheme 1

Recently we reported that (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam was very useful as a chiral auxiliary for enantiomer resolution and X-ray crystallographic determination of the absolute stereochemistry of various carboxylic acids.[6] This camphorsultam method was applied to acid **1**; acid chloride of (–)-**1** was allowed to react with anion of (1*S*,2*R*,4*R*)-(–)-2,10-camphorsultam generated with NaH in THF. The crude product of amide **4** obtained was purified by HPLC on silica gel with hexane – dichloromethane (1:1) as the eluent, and the solid material of (–)-**4** was crystallized from ethyl acetate to afford plates [m.p. 281 – 282 °C; $[\alpha]_D^{16}$ –163 (*c* 0.543, $CHCl_3$)], one of which was subjected to X-ray crystallographic analysis: crystal dimension, 0.38 × 0.36 × 0.35 mm; formula, $C_{31}H_{41}NO_5S$; formula weight, 539.74; crystal system, monoclinic; space group, $P2_1$; a = 15.721 (2) Å, b = 10.625 (1) Å, c = 8.842 (1) Å, β = 105.758 (8)°, vol = 1421.5 (3) $Å^3$; Z = 2; ρ(calcd) = 1.261 g/cm^3; ρ(obsd) = 1.261 g/cm^3 determined by flotation using a CCl_4 / hexane solution; Cu K_α (1.541 78 Å); graphite crystal monochromator; linear absorption coefficient, 12.37 cm^{-1}; temperature 20 °C; θ – 2θ scan; 2θ scan limits, 2 – 130°; no indication of standard reflection decay during data collection; independent reflections $F_o > 3.0\ \sigma(F_o)$, 2370. The crystal structure was solved by the direct method. Since the ansa chain part takes a disordered structure as illustrated in Fig. 1, only 28 hydrogens were found by the difference Fourier syntheses. Full matrix least-squares refinement of positional and thermal parameters, including anomalous scattering factors, led to the final convergence with R = 0.0608 (R_w = 0.0710) for the *S* absolute configuration, while R = 0.0628 (R_w = 0.0743) for the mirror image structure. The absolute stereochemistry of the amide (–)-**4** was thus determined as shown in Fig. 1. The *S* configuration of (–)-**4** was

also assigned by use of the (1*S*,2*R*,4*R*)-2,10-camphorsultam part as an internal reference of the absolute configuration.

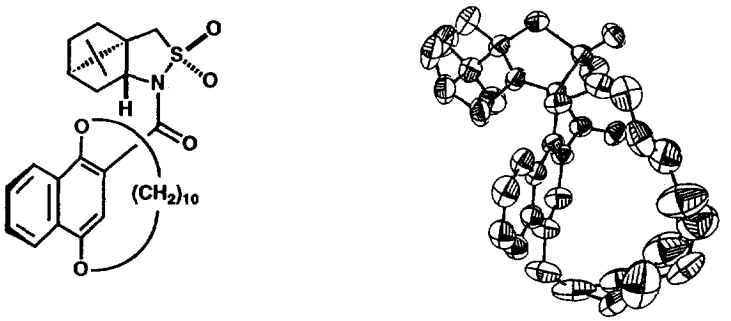
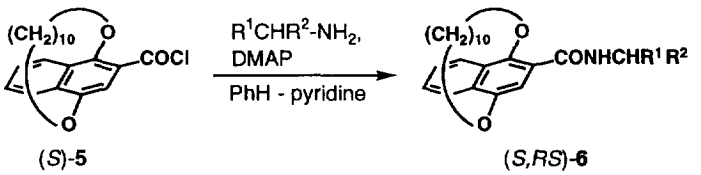


Fig. 1 Absolute stereostructure and ORTEP drawing of amide (*S*)-(–)-**4**

To examine the ability of acid **1** as a chiral discriminating auxiliary in HPLC separation, the enantiopure (*S*)-**1** was allowed to react with several scalemic (partially optically active) amines of known absolute configurations. A mixture of amine, acid chloride (*S*)-**5** (1.2 mol equiv.), and 4-dimethylaminopyridine (DMAP, 1.0 mol equiv.) in benzene – pyridine (15:1) was refluxed for 3 h to give a diastereomeric mixture of amides (*S,RS*)-**6** in a quantitative yield (Scheme 2). The diastereomeric mixture was subjected to HPLC



Scheme 2

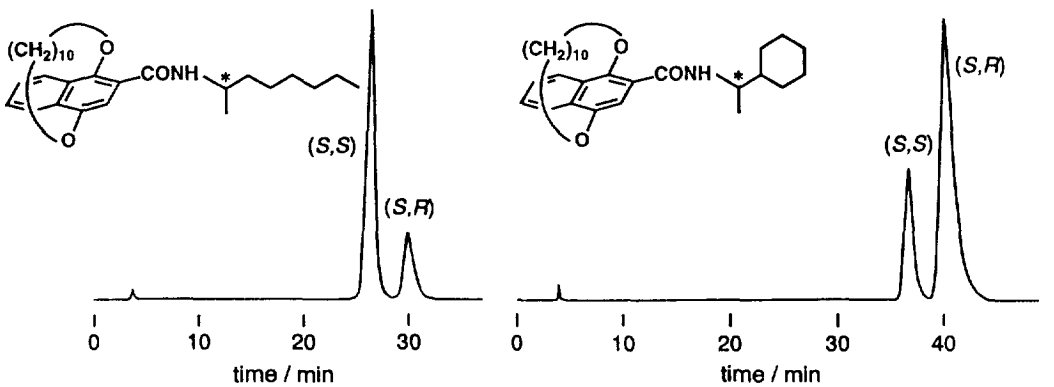


Fig. 2 Chromatograms of diastereomeric amides derived from partially active amines and (*S*)-**5**

analysis on a silica-gel column (4.6 mm i.d. × 250 mm) with hexane – ethyl acetate (24:1) as the eluent. The separation results are listed in Table 1, and Fig. 2 shows typical chromatograms. Good to fair separation was attained except the case of 1-phenylethylamine. It should be noted that the (*S,S*)-diastereomers eluted faster than the (*S,R*)-counterparts. Further studies on chiral discrimination mechanisms are in progress.

Table 1 HPLC separation of diastereomeric amides (*S,RS*)-**6**

R^1	R^2	$k_1'^{a)}$	$\alpha^{b)}$
CH_3	n-C_5H_{11}	7.43 (*S,S*)	1.13
CH_3	n-C_6H_{13}	6.84 (*S,S*)	1.16
CH_3	iso-C_3H_7	9.90 (*S,S*)	1.02
CH_3	cy-C_6H_{11}	9.62 (*S,S*)	1.10
CH_3	Ph	12.55	1.00
CH_3	1-Naphthyl	9.58 (*S,S*)	1.06
H	$PhCH(CH_3)$	20.97 (*S,S*)	1.19

a) Capacity factor of first eluting diastereomer. b) Separation factor.

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3. **3**: IR (KBr) ν 3455 and 1656 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 1.34 – 1.94 (16H, m, CH_2), 3.41 (2H, t, *J* 6.8, CH_2Br), 4.00 (3H, s, CH_3), 4.09 (2H, t, *J* 6.4, OCH_2), 7.02 (1H, s, ArH), 7.53 – 7.67 (2H, m, ArH), 8.21 – 8.40 (2H, m, ArH), and 11.60 (1H, s, OH). Found: C, 60.57; H, 6.71; Br, 18.54%. Calcd for $C_{22}H_{29}BrO_4$: C, 60.42; H, 6.68; Br, 18.27%.
4. (±)-**1**: IR (KBr) ν 2600 – 3300 and 1669 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 0.45 – 2.00 (16H, m, CH_2), 4.37 – 4.76 (4H, m, OCH_2), 7.57 (1H, s, ArH), 7.59 – 7.67 (2H, m, ArH), 8.09 – 8.35 (2H, m, ArH), and 11.7 (1H, br, OH). Found: C, 73.72; H, 7.72%. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65%.
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