Notes

Synthesis of Enantiomerically Pure 2,2′-Dihydroxy-1,1′-binaphthyl, 2,2′-Diamino-1,1′-binaphthyl, and 2-Amino-2′-hydroxy-1,1′-binaphthyl. Comparison of Processes Operating as Diastereoselective Crystallization and as Second-Order Asymmetric Transformation†

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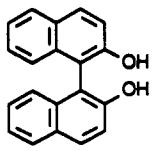
2,2′-Dihydroxy-1,1′-binaphthyl (1) is an established and highly potent chiral ligand,[1] both enantiomers of which have been utilized in a variety of synthetic reactions to induce chirality.[2] In contrast, the diamine 2 has received much less attention,[3,4] while the hydroxy amine 3 was unknown.



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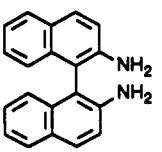

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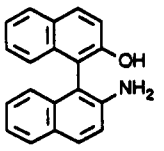

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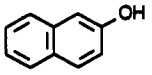

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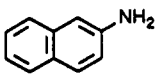

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Recently, we have described a facile method for the preparation of racemic hydroxy amine 3 by cross coupling of 2-naphthol (4) and 2-naphthylamine (5) under controlled conditions, using a $CuCl_2$–benzylamine complex in methanol.[5] Similarly, 1 and 2 have been obtained from the homo coupling of 4 or 5, respectively.[5]

Since a number of amino alcohols have proved to be highly efficient as chiral auxiliaries for asymmetric reductions[6-8] and other reactions,[8,9] it was desirable to develop a method for the preparation of optically active 3. In this paper we report on the synthesis of enantiomerically pure amino alcohol 3 and modified procedures for obtaining pure enantiomers of 1 and 2.

Brusse[10] has prepared optically active 1 by coupling of 2-naphthol with a $CuCl_2$–amphetamine complex. He has also provided evidence for the second-order transformation operating in the reaction. In view of the well-known biological activity of amphetamine, it was desirable to explore

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Table I. Preparation of Optically Active Binaphthyls 1–3

entry	product	method[a]	reagent	isolation[b]	yield,[c] %	$[\alpha]_D$, deg	ee, %
1	1	A	$CuCl_2$–sparteine[d]	P	14	−34	100[f]
2	1	A	$CuCl_2$–sparteine[d]	S	42	−7	20[f]
3	1	B	$CuCl_2$–sparteine[d]	P	36	−34	100[f]
4	1	B	$CuCl_2$–sparteine[d]	S	60	−20	59[f]
5	1	B	$CuCl_2$–sparteine[d]	PS	94	−27	80[f]
6	2	A	$CuCl_2$–sparteine[d]	P	19	−134	84[g]
7	2	A	$CuCl_2$–sparteine[d]	S	49	+50	31[g]
8	2	B	$CuCl_2$–sparteine[d]	PS	95	−1	<1[g]
9	3	A	$CuCl_2$–$PhCH(NH_2)Me$[e]	P	43	−54	46[h]
10	3	A	$CuCl_2$–$PhCH(NH_2)Me$[e]	S	42	+54	46[h]
11	3	B	$CuCl_2$–$PhCH(NH_2)Me$[e]	PS	96	+2	2[h]

[a] A = coupling experiment; B = deracemization (see the text). [b] P = from precipitate; S = from solution; PS = from a mixture of P and S. [c] For optimized method and overall yields of pure enantiomers, see the text. [d] In MeOH. [e] In *i*-PrOH. [f] Calculated from the maximum value $[\alpha]_D$ −34° (ref 1j). [g] Calculated from the maximum value $[\alpha]_D$ +159° (ref 3). [h] Calculated from the maximum value $[\alpha]_D$ −117° (this paper, see the text).

less problematical chiral amines, and (−)-sparteine and (*R*)-(+)-α-methylbenzylamine were selected as inexpensive, commercially available candidates.[11]

Results and Discussion

Coupling of 2-naphthol, using an in situ generated complex of $CuCl_2$ and (−)-sparteine, resulted in the formation of a precipitate and mother liquor. Working up the precipitate led to the isolation of (−)-binaphthol (1) (14%) whose enantiomeric purity was found to be ~100% according to the optical rotation[1] (Table I, entry 1). The mother liquor afforded, after workup, 42% of (−)-binaphthol of only 20% enantiomeric purity (entry 2).

Since we suspected that, as in Brusse's case,[10] the preferential formation of (−)-1 was due to the second-order asymmetric transformation rather than to asymmetric coupling, we ran a control experiment in the following way: Racemic binaphthol was treated with the $CuCl_2$–sparteine complex under the same conditions as those used for the coupling experiment. The formation of a precipitate was observed again, and both the precipitate and the mother liquor were worked up separately. The precipitate furnished 36% of enantiomerically pure (−)-1 (entry 3), while the mother liquor gave the same enantiomer of 59% ee (60% yield; entry 4). Workup of the whole mixture (i.e., without the separation) gave a crude product of 80% ee in 94% yield (entry 5). Hence, this experiment confirmed the operation of a second-order asymmetric transformation and demonstrated that the "deracemization" of racemic binaphthol is superior to the attempted asymmetric coupling.[12]

In contrast to binaphthol (1), derivatives 2 and 3 have been obtained in much higher enantiomeric purity from the coupling rather than from the "deracemization" experiment (compare entries 6 and 7 with 8, and 9 and 10 with 11).[13]

Further purification of the samples partially enriched in (−)-1 ($[\alpha]_D$ −27°; 80% ee)[14] proved difficult,[15] because repeated crystallization to a constant optical rotation afforded a product of $[\alpha]_D$ −28° (82% ee), indicating that a eutecticum had been reached.[15] However, formation of two different types of crystals was observed on the crystallization, and these were separated mechanically. Those of a large size (several cubic millimeters) turned out to be enantiomerically pure as they exhibited $[\alpha]_D$ −34°.[14] On the other hand, powder-like crystals were almost racemic ($[\alpha]_D$ −1°).[16] In a carefully run "kinetic" crystallization starting from the eutectic mixture ($[\alpha]_D$ −28°; 82% ee)[17] and substance-to-solvent (benzene) ratio 1:10, we were able to grow crystals of $[\alpha]_D$ −34° (~100% ee) in 77% yield within 6–12 h which could be isolated by filtration. When the solution had been set aside for 48 h, gradual deposition of the second-type crystals was observed.[18] Thus, the enantiomerically pure (−)-1 can be obtained by a carefully controlled "kinetic" crystallization from enantiomerically enriched material, which, in turn, is available by "deracemization" of the racemate employing a second-order asymmetric transformation.[19]

Diamine 2 proved to be more difficult to purify. After much experimentation with solvents, concentration, and temperature, we found acetic acid to be the best choice for crystallization. In one of the most successful experiments (carried out on an 8-g scale), a sample of 2[20] exhibiting $[\alpha]_D$ −68° was crystallized from a 12–15% solution in AcOH.

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(11) A few experiments were also carried out with (*S*)-(−)-α-methylbenzylamine.

(12) Less satisfactory results were obtained with $PhCH(NH_2)CH_3$.

(13) For 2, sparteine was superior to α-methylbenzylamine, whereas the opposite was found for 3.

(14) For enantiomerically pure 1, see refs 1i,j.

(15) All the binaphthyls 1–3 form racemic compounds as confirmed by IR spectroscopy in Nujol. See also: Jacques, J.; Fouquey, C.; Gabard, J.; Douglas, W. *C. R. Seances Acad. Sci. Ser. C* **1967**, *265*, 260.

(16) The ratio of these two crops was ~4:1, which corresponds to the ~80% ee of the whole mixture.

(17) The only possible way to obtain a pure enantiomer from a eutecticum by crystallization will require careful monitoring of the crystallization process and collecting the initially and spontaneously formed crystals (which may contain more of the desired enantiomer than does the eutecticum) before the eutectic or subeutectic mixture starts to crystallize. For this method of surmounting the thermodynamic obstacle posed by the existence of a eutecticum, we propose the term "kinetic crystallization".

(18) Out of 10 parallel experiments, half of them gave this result; others were less successful, indicating a partly random process, which can hamper the resolution. For review on optical resolution by direct crystallization of enantiomer mixtures, see: Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215.

(19) Seeding a solution, enriched in one enantiomer (eutectic or supereutectic mixture), with crystals of pure enantiomer (once obtained from previous experiments) also resulted in the crystallization of pure or nearly pure enantiomer.

(20) Obtained by partial resolution of the racemate via camphorsulfonate.[3]

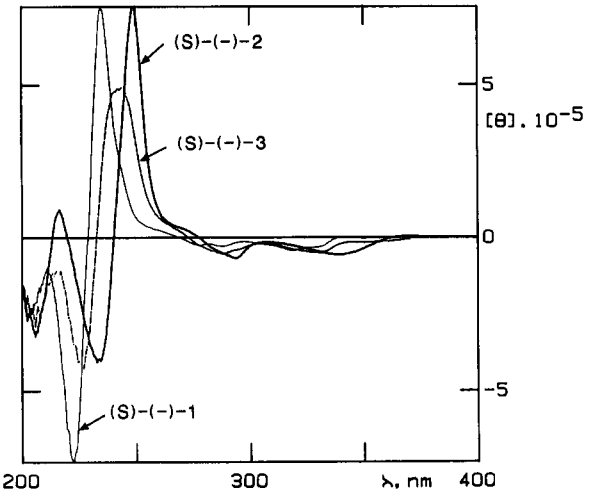

Figure 1. CD spectra of binaphthyls (*S*)-(-)-1, (*S*)-(-)-2, and (*S*)-(-)-3 in MeCN at concentration 0.14 M.

Crystals that precipitated over a period of 10 h (in 37% yield)[21] had $[\alpha]_D$ −149°. The next crop (21%), collected after 48 h, exhibited optical rotation of only −1.4°![22,23] One recrystallization of the former crop produced the enantiomerically pure (-)-2 in 86% yield.[19] Another coupling experiment giving enantiomerically pure (-)-2 and (+)-2 is described in Scheme I.

Similarly to 1, formation of two types of crystals was observed on crystallization of the enantiomerically enriched samples of hydroxy amine 3: long needles and microcrystalline clusters. Hence, as with 1, "kinetic" crystallization was attempted. Starting from a sample of $[\alpha]_D$ −54° (mp 190–202 °C)[24] dissolved in benzene,[25] we have obtained a crystalline product (26%) of $[\alpha]_D$ −3° in 20 min, while the residue, after evaporation (74%), showed $[\alpha]_D$ −72° (Scheme I). Crystallization of the latter material from benzene over 3 h afforded long needles (23% overall yield) of $[\alpha]_D$ −117°.[19] No change in $[\alpha]_D$ or mp could be observed after further crystallizations, suggesting that this sample was enantiomerically pure in analogy with the behavior of 1 and 2. Finally, the NMR spectrum (400 MHz) of the corresponding Mosher acid derivative proved the enantiomeric purity of this sample to be ~98%.[26]

The absolute configuration of 3 was determined by CD measurement (Figure 1).[28,29] The (-)-3 enantiomer exhibited the same behavior as did (-)-1 and (-)-2, whose absolute configuration is known.[1,3] An excellent overlap of the three curves (Figure 1) has been achieved, with Cotton effects for 3 being $\Delta\epsilon$ −129.2 (226 nm) and +148.5 (243 nm). Thus, in analogy with 1 and 2, the levorotatory enantiomer of 3 can be assigned the *S* configuration.

Conclusion

We have found conditions for the preparation of enantiomerically pure binaphthyls 1–3 and assigned the *S* absolute configuration to the levorotatory enantiomer of hydroxy amine 3 from its CD spectrum. While pure (-)-1 can be best obtained by a second-order asymmetric transformation from (±)-1 (Table I, entry 3) in 36% overall yield, 2 and 3 are prepared stepwise by the Cu(II)-mediated coupling (entries 6, 7, 9, and 10) followed by "kinetic" crystallization that gives enantiomerically pure compounds. Thus, pure (-)-2 and (-)-3 have been obtained in 13% and 23% overall yields (Scheme I), respectively (calculated for 4 and 5). It is pertinent to note that this method can produce both enantiomers of 2 and 3 (compare entries 6 and 7, and 9 and 10); (+)-2 and (+)-3 were thus prepared analogously in 22% and 24% overall yields, respectively. The combined yields of pure enantiomers of 2 and 3 were 35% and 47%, respectively. We are confident that this relatively inexpensive method will considerably amplify the value of 1, 2, and 3 as chiral ligands, particularly because it makes both enantiomers of each available in a simple way.[30] We also believe that our method of "kinetic" crystallization will prove useful for the preparation of other enantiomerically pure compounds.

Experimental Section

Materials and Equipment. Melting points (uncorrected) were obtained on a Boetius microapparatus. Optical rotations were measured on a Pye Unicam 143A polarimeter with an error of ≤±1°. ^{1}H NMR spectra were recorded on Varian XL-400 (FT mode) and Tesla XBS 100 instruments for acetone-d_6 solutions at 25 °C with TMS as internal reference. The high-resolution mass spectra were measured on a JEOL JMS D-100 double-focusing spectrometer (65 eV, 3 kV) using direct inlet and the lowest temperature enabling evaporation; the accuracy was ≤5 ppm. The CD spectra were measured in MeCN on a Dichrographe Mark V apparatus (Jobin-Yvon). All the solvents used for the coupling reactions or for crystallization experiments were degassed by purging with argon (20 min; 60 mL of Ar/min). Light petroleum refers to the fraction boiling in the range 40–60 °C. Yields are given in milligrams of isolated product showing one spot on a chromatographic plate and no trace of impurities detectable in the NMR spectrum.

(*S*)-(-)-2,2′-Dihydroxy-1,1′-binaphthyl (1). (A) By Coupling. To a solution of copper(II) chloride tetrahydrate (400 mg; 2 mmol) in degassed methanol (20 mL) was added (-)-sparteine (936 mg; 4 mmol) in degassed methanol (20 mL), and after purging with argon for 10 min, a solution of 2-naphthol (288 mg; 2 mmol)[31] in degassed methanol (20 mL) was added. The mixture was stirred

(21) Calculated from the mass balance: 3.04 g of the product was obtained by crystallization of 8.25 g. Calculation on the enantiomeric enrichment would give the rather different figure of 87%.

(22) Solvents considerably influence the composition of a eutecticum. Thus in other solvents, such as C_6H_6, dioxane, EtOH, and DMSO, the eutecticum is presumably closer to the racemate, so that the attempted enhancement of ee was unsuccessful with samples at this level of ee. For general discussion, see: Jacques, J.; Collet, A.; Willen, S. H. *Enantiomers, Racemates, and Resolutions*; J. Wiley: New York, 1981.

(23) Starting from a sample of $[\alpha]_D$ +95°, we were able to get a 42% yield of an enantiomerically pure[3] product ($[\alpha]_D$ +158°) by single crystallization.

(24) Obtained from a coupling experiment (Table I, entry 9).

(25) The compound to solvent ratio was 1:15.

(26) The chloride (2.2 equiv), prepared from (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) of 99%+ ee[27] (purchased from Aldrich), was reacted with a sample of (-)-3 (1 equiv) to afford the corresponding ester amide. For comparison, an analogous experiment was carried out with (±)-3. The ^{1}H NMR spectrum of the MTPA derivative of (-)-3 showed two peaks at 2.606 and 2.874 ppm corresponding to amide MeO and ester MeO, respectively. In contrast, two additional peaks at 2.756 and 3.049 ppm appeared in the spectrum of the MTPA derivative of (±)-3. Those were very low in the spectrum of the (-)-3 derivative, indicating 98% ee, according to integration.[28]

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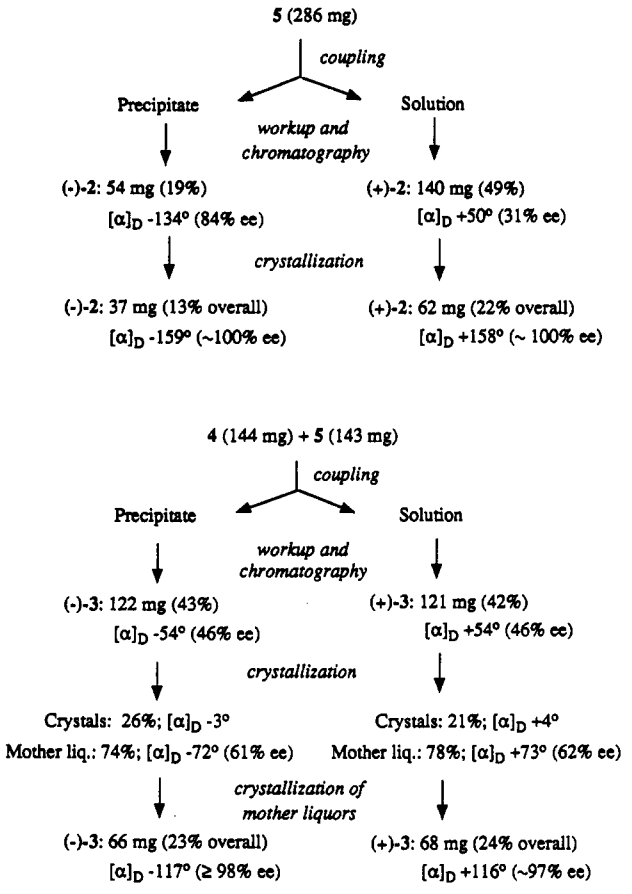
(29) For determination of absolute configuration of biaryl systems by CD and for quantum chemical calculations, see: Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671.

(30) The synthetic utility of 3 is now being intensively studied in our laboratories.

(31) Brusse[10] had optimized the ratios of naphthol:Cu(II):amine as 1:2:8. We have reduced this ratio to the present one, which still gave acceptable results, in order to save the optically active amine.

(32) Samples crystallized from benzene originally showed maximum $[\alpha]_D$ −97° as a result of inclusion of benzene molecules (as revealed by mass spectrometry). Drying of samples in vacuo at 35 °C for 24 h afforded benzene-free material of the same mp and $[\alpha]_D$ −117°. Identical mp and $[\alpha]_D$ were obtained by recrystallization of the former samples from toluene.

Scheme I. Optimized Procedures for Obtaining Pure Enantiomers of 2 and 3



at rt for 20 h under an argon atmosphere. Then concd HCl (5 mL) was added, followed by water (100 mL). The precipitate was filtered off, suspended in acetone with silica gel (20 g), and chromatographed on a silica gel column (40 g) using a light petroleum–ether mixture (1:1) as eluent. The eluate was evaporated to afford 1 (43 mg; 14%): mp 205–207 °C (no depression was observed for a mixture with an authentic sample of enantiomerically pure 1); $[\alpha]_D$ −34° (c 5.0, THF; 100% ee) (lit.[1i,j] mp 207–209 °C and $[\alpha]_D$ −35.5° or −33.4°, respectively, for optically pure compound and $[\alpha]_D$ +34.3° for the enantiomer.) Analogous workup of the solution furnished 1 (121 mg; 42%): mp 210–214 °C; $[\alpha]_D$ −6.8° (c 5.0, THF; 20% ee).

(B) By Deracemization of (±)-1. To a degassed solution of $CuCl_2 \cdot 4H_2O$ (200 mg; 1 mmol) in methanol (10 mL) was added a solution of (−)-sparteine (468; 2 mmol) in methanol (10 mL), and the mixture was stirred at rt for 10 min under argon. A solution of (±)-1 (286 mg; 1 mmol) in degassed methanol (10 mL) was added, and the mixture was stirred under argon at rt for 20 h. The mixture was then worked up as above to give 1 (267 mg; 94%): mp 212–214 °C; $[\alpha]_D$ −27.2° (c 5.0, THF; 80% ee). For further resolution, see the text.

(*R*)-(+)- and (*S*)-(−)-2,2′-Diamino-1,1′-binaphthyl (2). (A) By Coupling. A mixture of (−)-sparteine (702 mg; 3 mmol) and 2-naphthylamine (286 mg; 2 mmol) in degassed methanol (15 mL) was added to a solution of $CuCl_2 \cdot 4H_2O$ (400 mg; 2 mmol) in degassed methanol (15 mL), and the mixture was stirred under argon at rt for 4 h. The precipitate was filtered off, washed with methanol (5 mL), decomposed with concd HCl (3 mL), and then neutralized by concd aqueous ammonia (15 mL) and water (100 mL). The crude solid product (67 mg; 24%) was chromatographed as described for the first experiment to yield enriched (−)-2 (54 mg; 19%): mp 235–239 °C; $[\alpha]_D$ −134° (c 2.0, pyridine; 84% ee). On single crystallization from acetic acid, this crop gave enantiomerically pure (−)-2 (27 mg; 13% overall). The mother liquor from the reaction was worked up separately in the same way and furnished enriched (+)-2 (140 mg; 49%): mp 184–216 °C; $[\alpha]_D$ +50° (c 5.0, pyridine; 31% ee). Further resolution furnished enantiomerically pure (+)-2 (62 mg; 22% overall): mp 245–246 °C; $[\alpha]_D$ +158° (c 2.0, pyridine)[23] (lit.[3] mp 245–246 °C and $[\alpha]_D$ +159° for enantiomerically pure product).

(B) By Diastereoselective Crystallization of (±)-2. A hot solution of (±)-2 (284 mg; 1 mmol) in degassed methanol (30 mL; minimal amount) was added to a mixture of $CuCl_2 \cdot 4H_2O$ (200 mg; 1 mmol) and (−)-sparteine (234 mg; 1 mmol) in degassed methanol (5 mL), and the resulting mixture was stirred under argon at rt for 40 h and then worked up as described for the previous experiment. The precipitate and mother liquor were worked up separately, and the crude products were purified by chromatography as above. The precipitate afforded (−)-2 (51 mg; 18%): mp 231–239 °C; $[\alpha]_D$ −134° (c 2.0, pyridine; 84% ee). The mother liquor furnished (+)-2 (132 mg; 46%): mp 190–218 °C; $[\alpha]_D$ +72° (c 5.0, pyridine; 45% ee).

(*R*)-(+)- and (*S*)-(−)-2-Amino-2′-hydroxy-1,1′-binaphthyl (3). A solution of (*R*)-(+)-α-methylbenzylamine (1.21 g; 10 mmol) in degassed 2-propanol (10 mL) was added to a solution of $CuCl_2 \cdot 4H_2O$ (500 mg; 2.5 mmol) in degassed propanol (10 mL), the mixture was stirred for 10 min under argon, and then a solution of a mixture of 2-naphthylamine (143 mg; 1 mmol) and 2-naphthol (144 mg; 1 mmol) in degassed propanol (10 mL) was added. The mixture was stirred under argon at rt for 20 h. Both the precipitate and the mother liquor were worked up and chromatographed separately as above. The precipitate afforded (−)-3 (122 mg; 43%): mp 212–228 °C; $[\alpha]_D$ −54° (c 1.0, THF). The mother liquor yielded (+)-3 (121 mg; 42%); mp 212–230 °C; $[\alpha]_D$ +54° (c 1.0, THF). Further resolution by "kinetic" crystallization of the former product from benzene (see the text and Scheme I) afforded (−)-3 (66 mg; 23% overall): mp 171–173 °C; $[\alpha]_D$ −117° (ref 32); ^1H NMR 6.78 (1 H, *J* = 6.8, 1.4, 0.9, and 0.6 Hz), 6.96 (1 H, *J* = 6.8, 1.3, 1.1, and 0.5 Hz), 6.99 (1 H, *J* = 6.8, 6.8, and 1.7 Hz), 7.02 (1 H, *J* = 6.8, 6.8, and 1.4 Hz), 7.10 (1 H, *J* = 6.8, 6.8, and 1.4 Hz), 7.12 (1 H, *J* = 8.8 Hz), 7.17 (1 H, *J* = 8.0, 6.8, and 1.3 Hz), 7.26 (1 H, *J* = 8.8 Hz), 7.64 (1 H, *J* = 6.8, 1.7, 0.6, and 0.5 Hz), 7.65 (1 H, *J* = 8.8 and 0.5 Hz), 7.77 (1 H, *J* = 8.0, 1.4, 0.5, and 0.5 Hz), 7.81 (1 H, *J* = 8.8 and 0.5 Hz); ^{13}C NMR 110.71 (s), 115.87 (s), 119.33 (d), 119.45 (d), 122.20 (d), 123.79 (d), 124.43 (d), 125.34 (d), 126.93 (d), 127.13 (d), 128.80 (s), 128.80 (d), 128.97 (d), 130.06 (d), 130.18 (s), 130.46 (d), 134.80 (s), 135.55 (s), 145.55 (s) 154.04 (s); HRMS (EI 70 eV) *m/z* (relative intensity) 286 (27.5), 285 (100, $M^{\bullet+}$, $C_{20}H_{15}NO$), 284 (10.4), 268 (20, $C_{20}H_{13}N$), 267 (11.3, $C_{20}H_{12}O$), 256 (13), 239 (12.2), 143.5 (12.2), 142.5 (9.6 M^{2+}), 129.5 (15.6), metastable transitions $285^{\bullet+} \rightarrow 268^{\bullet+} + 17$, $285^{\bullet+} \rightarrow 267^{\bullet+} + 18$.

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Registry No. (*S*)-(−)-1, 18531-99-2; (*R*)-(+)-1, 18531-94-7; (*R*)-(+)-2, 18741-85-0; (*S*)-(−)-2, 18531-95-8; (*R*)-(+)-3, 137848-28-3; (*S*)-(−)-3, 137848-29-4; 4, 135-19-3; 5, 91-59-8; (−)-sparteine, 90-39-1; (*R*)-(+)-α-methylbenzylamine, 3886-69-9.

Supplementary Material Available: NMR spectra of the Mosher acid derivatives of (±)- and (−)-3 and IR spectra of (−)- and (±)-1, (−)- and (±)-2, and (−)- and (±)-3 (8 pages). Ordering information is given on any current masthead page.

Aldol Reactions of Pyroglutamates: Chiral Synthesis of 4α(*S*)- and 4β(*R*)-(Arylmethyl)pyroglutamates[1]

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Nonproteinogenic prolines are important because of their use in the synthesis of conformationally rigid

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