Stereoselective Dimerization of Benzylic Amines Derived from Indoline

Ireneusz Nowak* [a,b] and Clifford George[c]

[a] Drug Discovery Program, Institute for Neurology, Georgetown University Medical Center, 3900 Reservoir Road NW, Washington, DC 20007-2197, USA.
[b] Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700, USA.
E-mail: inowak@mailchem.byu.edu
[c] Naval Research Laboratory, 4555 Overlook Ave. SW, Washington, DC 20375-5341, USA.
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Treatment of benzylic amines derived from 2-(acyloxymethyl)-5-nitroindolines with sodium hexamethyldisilazide leads to dimeric products resulting from deprotonation in the benzylic position, oxidation of the resulting carbanion to radical by the nitroarene moiety of another molecule, and stereoselective radical recombination. Only those two of six possible diastereoisomers are formed in which the recombination takes place from the less hindered face in the more stable conformation of the presumably near-planar radical.

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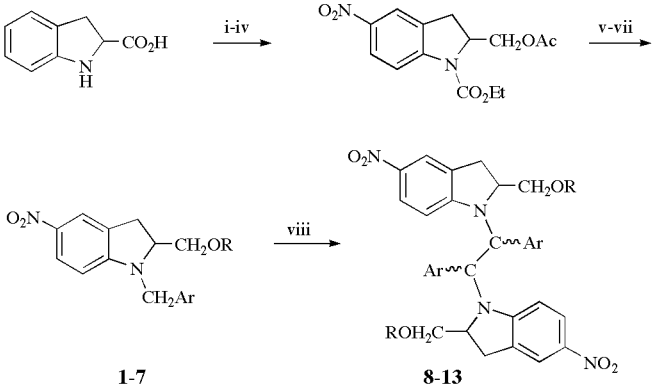
Radical recombination reactions are the subject of continuing interest and provide one possible way to form C-C bonds. More specifically, radicals generated by Kolbe electrolysis of carboxylates as well as those derived from C-H acids by deprotonation and oxidation can undergo coupling reactions [1-4]. During attempts at deprotonation of benzylic amines derived from indoline, we noticed the formation of interesting dimerization products. Exposure of compounds **1-7** at -78 to 0 °C to an excess of the sterically hindered base, sodium hexamethyldisilazide (NaHMDS, 5.0 eq), in the presence of an excess of *N*-methylmorpholine (7.0 eq) in THF resulted in low to moderate yields of the products **8-13** (Scheme 1), the structure of which was not immediately apparent. Modification of the reaction conditions was carried out in order to gain more insight into the reaction. Replacement of sodium with lithium or a change of solvent from THF to toluene suppressed the reaction as did the omission of the tertiary amine base from the reaction medium. No reaction was observed when the reaction mixture was quenched with saturated NH_4Cl at -25 °C or below, but the reaction took place upon temperature increase to above -25 °C as evidenced by the appearance of a brown precipitate which redissolved upon acidic quench.

Scheme 1



1-7 **8-13**

Reagents and conditions: (i) $NaBH_4$, I_2, THF, reflux, 18 h; (ii) $ClCO_2Et$, Na_2CO_3, rt, 2 h; (iii) Ac_2O, Et_3N, rt, 4 h; (iv) HNO_3, Ac_2O, -10 to 0 °C, 30 min; (v) Na_2CO_3, H_2O/MeOH/THF, rt, 1.5 h; (vi) NAH, $ArCH_2Br$, DMF, -20 °C, 30 min; (vii) acylating agent, Et_3N, dichloromethane, rt, 1-11 h; (viii) NaHMDS, *N*-methylmorpholine, THF, -78 to 0°C, 1-3 h.

Table 1

Results of the *Dehydrogenative* Dimerization Reaction

Amine [a]	R	Ar	Product	Yield (%) [b]	**A**/**B** [c]
1	*N*-Boc-*L*-valyl	Phenyl	**8**	51	[d]
2	MeCO	Phenyl	-	-	-
3	PhCO	Phenyl	**9**	22	20/80
4	Me_3CCO	Phenyl	**10**	67	26/74
5	Me_3CCO	4-Bromophenyl	**11**	67	27/73
6	Me_3CCO	2-Bromophenyl	**12**	60	62/38
7	Me_3CCO	2-Iodophenyl	**13**	60	74/26

[a] - starting material racemic except in the case of compound **1**, which has S-configuration in its indoline moiety; [b] - isolated yield; [c] - ratio was established by ^1H nmr of crude reaction mixture; [d] - essentially one isomer, its stereochemical structure was not established with certainty.

The results for the enantiomerically pure starting material **1** and the racemic starting materials **2-7** are summarized in Table 1. Amine **1** gave a single dimer **8** in 51% yield. In the case of amines **3-7**, mixtures of two isomers (**9-13A** and **B**) were formed, the ratio of which depends on the position of the aromatic substituent. Satisfactory yields (60-67%) were obtained only for the pivalic acid esters, while the benzoate **3** gave a low (22%) yield of product, and the acetate **2** failed to provide any product at all, probably because its acetyl group is far more acidic than its benzylic methylene group. Analytical data are consistent with a dehydrodimer structure of the products; however, the highest masses observed in their mass spectra are $(M/2)^+$ ions. The only significant and consistent difference in the ^1H NMR spectra of the **A** and **B** type isomers is the relative chemical shift of their geminal benzylic protons.

In type **A** isomers, the lower field resonance of one of these protons appears as a doublet of doublets, and the higher field signal of the second one as a doublet. This pattern is reversed for **B** type isomers.

As the information gathered from the spectroscopic properties of the products was insufficient to firmly establish their structure, we sought to obtain crystals for X-ray structure analysis. Compound **8** failed to crystallize, possibly as a consequence of the conformational flexibility of its protected valyl substituent. Three of the pivalic acid esters, however, could be crystallized, and one example each for both types of isomers (compounds **11B** and **12A**, respectively) was selected for X-ray crystallography. Both compounds have "dimeric" structures but they differ in the relative stereochemistry at their four stereocenters (Figures 1, 2). In the **A** series, both the pair of stereocenters residing in the indoline moieties and that residing on the bibenzyl moieties are each of opposite configuration, and so are pairs of adjacent stereocenters belonging to non-identical moieties. In the **B** series, stereocenters within pairs of identical moieties are of the same configuration, and those within the indoline moieties are of the opposite configuration compared to those within the bibenzyl moieties. In both structures, both of the indoline moieties adopt orientations in which the bulky pivaloyloxymethyl substituents point away from the crowded central C-C bond of the bibenzyl partial structure. Additional diastereoisomers that could theoretically be formed were not observed.

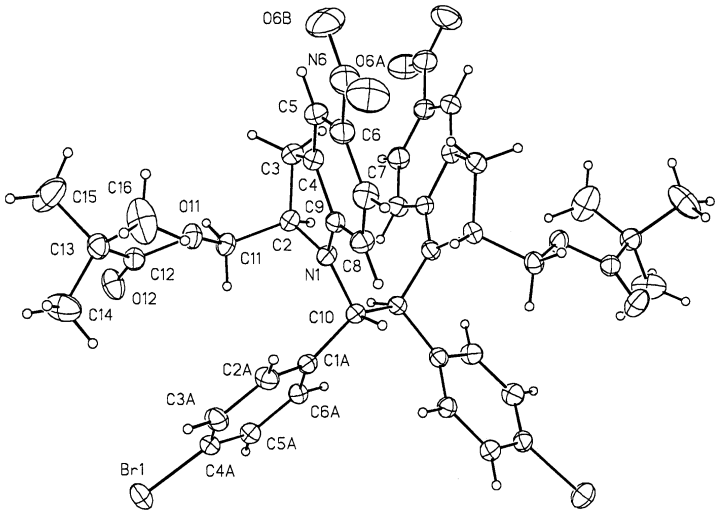


Figure 1. ORTEP plot and labeling for dimer **11B**.

The formation of "dimeric" products can be accounted for by assuming deprotonation at the benzylic site and subsequent oxidative coupling. The deprotonation of simple tertiary benzylic amines, for example *N*,*N*-dimethylbenzylamine, is known to require organolithium bases and

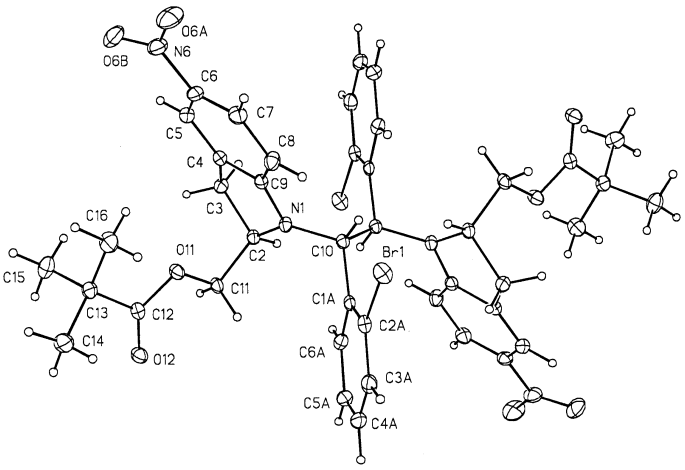


Figure 2. ORTEP plot and labeling for dimer **12A**.

then takes place exclusively in *ortho* position, [5-7] with the amine nitrogen providing stabilization of the resulting aryllithium species through chelation. In the present case, acidification of the benzylic position is achieved by a combination of resonance (phenyl ring), a weak dipole contribution [8] of the *p*-nitro substituent, and chelation by one of the ester oxygen atoms. Usually, nitrogen-substituted benzylic carbanions require stronger organolithium bases for their formation; [9-14] in the present case, the electron-withdrawing effect of the nitro group and chelation of the sodium cation acidify the benzylic methylene group sufficiently that a weaker amide base can be used. The role of the tertiary amine may include additional stabilization of the organosodium intermediate as a consequence of its better donor properties compared to THF.

Single-electron transfer from carbanions to aromatic nitro compounds is well established and gives as a side product the radical anion of the nitro compound [3]. The fate of the carbanion-derived radical depends on its redox potential and structure: it can, for example, be further oxidized or deprotonated, react with the radical anion of the nitro compound, disproportionate, or dimerize. No defined products derived from reduction of the nitro group were isolated in the present investigation. Alternatively, nitro compounds may participate in non-electron-transfer processes when treated with bases and nucleophiles. In the present case, this type of reaction does not intervene because of the low nucleophilicity of NaHMDS and the aprotic reaction medium.

The stereochemical outcome is readily understood by inspecting a list of all possible six diastereoisomers (Figure 3) generated from conformational formulas derived from the ORTEP plots (Figures 1, 2) by keeping the indolinyl substituents in place while permutating the configurations at the two central carbon atoms. No attempt was made to

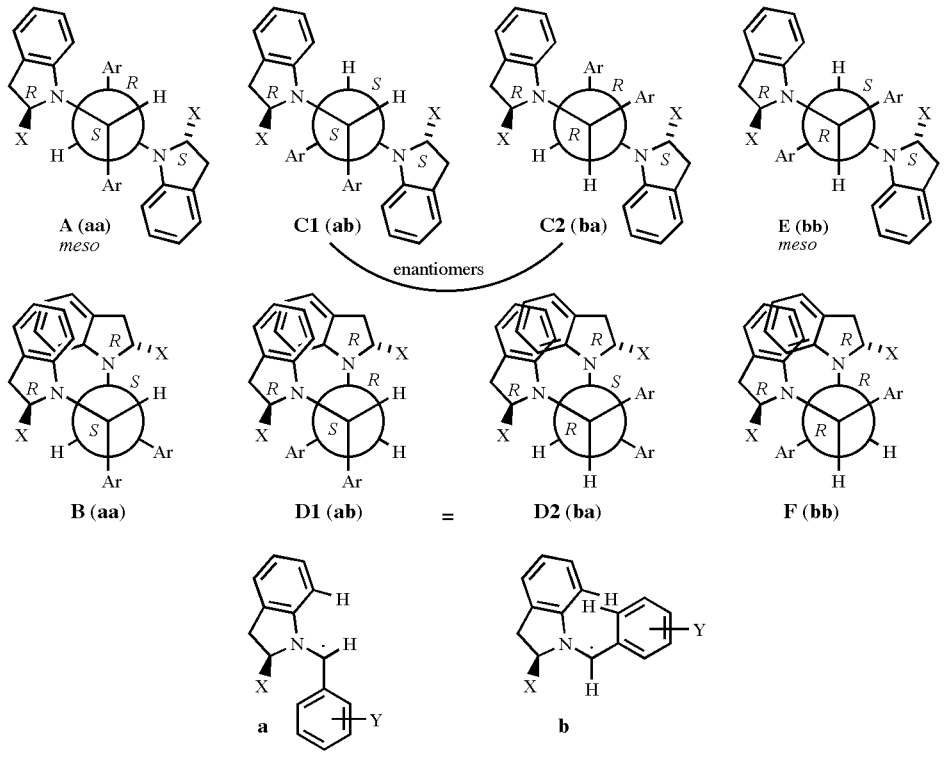


Figure 3. The six theoretically possible diastereoisomers **A**-**F** of compounds **9**-**13**, and the two near-planar conformations **a** and **b** of their precursor radical. Nitro groups on the indoline moieties have been omitted for clarity. X = $CH_2OCOCMe_3$ or $CH_2OCOC_6H_5$.

adjust the NCCN dihedral angle, which may differ in the isomers **C**-**F** from those observed for **A** and **B**. Note that structures **D1** and **D2** are identical, and structures **C1** and **C2** are enantiomers (and therefore need not to be considered separately as long as the compounds are racemic). Only those two product diastereoisomers are formed that result from recombination of two benzyl radicals adopting both the conformation designated as conformation **a**. In contrast, the non-observed diastereoisomers would require one or both radicals to adopt conformation **b**. In both of these conformations, the aryl ring attached to the radical center may be assumed to be essentially coplanar with this carbon atom to maximize resonance stabilization. The indolinyl group, while not necessarily truly planar, comes nevertheless reasonably close to this description, with the exception of the pivaloyloxymethyl subsituent which projects out of the approximate plane. We assume that, to maximize radical stabilization by the nitrogen lone pair and to render the approach of a second radical to the radical center sterically possible, the indolinyl group, too, will be approximately coplanar with the radical carbon atom. In conformation **b**, one *ortho* hydrogen atom of the aryl group suffers a severe steric interaction with H-7 of the indoline moiety. There is no similar interaction with the groups attached to C-2 in conformation **a** as these groups are oriented out-of-plane. Radical recombination occurs therefore exclusively between two radicals of equal or opposite absolute configuration in conformation **a** by way of the face opposite to the pivaloyloxymethyl substituent.

The dependence of the product ratio on the aryl substituent is less readily understood. Statistically, **A** and **B** isomers would be expected to be formed in a 1:1 ratio. Subtle differences in the energies of the gauche interactions between the three combinations of aryl and indolinyl groups appear to be at work. In compound **11B** containing a 4-substituted phenyl group, the two indolinyl groups and the two aryl groups are each arranged in a gauche relationship. This compound predominates over its isomer **11A**, indicating that the sum of the steric interaction energies between two phenyl and two indolinyl groups is smaller than twice the steric interaction energy between a phenyl and an indolinyl group as long as no bulky *ortho*-substituent is present. It may be assumed that the introduction of such a substituent as in compounds **12** and **13** increases the steric interaction energy between the two aryl groups, thus favoring the **A** isomer in which the orientation of these groups is anti-periplanar while two gauche interactions occur between the indolinyl and aryl substituents.

Finally, we note that the homochiral nature of the starting material **1** renders an **A**-type structure, which is a meso form, impossible for compound **8**. It is therefore likely that this compound possesses a **B**-type structure with the

absolute stereochemistry opposite to that depicted in Figures 1 and 3. The high degree of stereochemical induction observed for the present reaction may find application in a simple synthesis of homochiral ligands of the 1,2-diamino-1,2-diarylethane class potentially useful in enantioselective catalysis.

EXPERIMENTAL

Thin-layer chromatography was performed in a solvent-vapor-saturated chamber on silica gel 60 F_{254} plates. Spots were visualized by UV light. Melting points (uncorrected) were determined in open capillaries on a Thomas-Hoover Unimelt apparatus. Infrared spectra were obtained on an ATI Mattson Genesis Series spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired at a field strength corresponding to a proton frequency of 300 MHz. Elemental Analyses were performed by Micro-Analysis, Inc. Mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer using a direct inlet probe and an electron beam energy of 70 eV. Optical rotations were measured with a Rudolph Research Automatic Polarimeter.

Single-crystal X-ray Diffraction Analysis of Compounds **11B** and **12A**.

Compound **11B**: $C_{42}H_{44}N_4O_8Br_2$, F.W. = 892.64, monoclinic space group C2/c, a = 27.884(1), b = 10.274(1), c = 17.559(1) Å, β = 126.23(1)°, V = 4057.45(8) Å^3, Z = 4, ρ_{calc} = 1.461 mg mm^{-3}, λ(Cu K$_\alpha$) = 1.54178 Å, μ = 3.010 mm^{-1}, F (000) = 1832, T = 293 K. A yellow 0.40 x 0.07 x 0.04-mm crystal was used for data collection with a Bruker SMART [15] 6K CCD detector on a Platform goniometer. The Rigaku rotating Cu anode source was equipped with an incident beam Gobel mirror. Lattice parameters were determined using SAINT [15] from 5003 reflections within 7.9<2θ < 133.7°. The data collection range had a {(sin θ)/λ}$_{max}$ = 0.59. A set of 9139 reflections was collected in the ω scan mode. There were 3302 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL [16] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 used 3 restraints and varied 267 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C-H distances set to 0.96 to 0.93 Å, H angles idealized, U_{iso} (H) were set to 1.2 to 1.5 U_{eq}(C). Final residuals were R1 = 0.041 for the 2932 observed data with F_o>4σ(F_o) and 0.045 for all data. Final difference Fourier excursions were 0.47 and -0.48 eÅ^{-3}. The *t*-butyl moiety is disordered over two sites at occupancies of 79:21. The bond and next nearest neighbor distances of the *t*-butyl carbons for the lower occupancy positions were restrained to those of the higher occupancy positions. The molecule sits on an inversion center and has C_i symmetry.

Compound (**12A**): $C_{42}H_{44}N_4O_8Br_2$, F.W. = 892.64, triclinic space group P1bar, a = 9.326(2), b = 9.327(2), c 13.592(2) Å, α = 74.632(3), β = 71.321(3), and γ = 63.166(3)°. V = 989.3(3) Å^3, Z = 1, ρ_{calc} = 1.498 mg mm^{-3}, λ(Mo K$_\alpha$) = 0.71073 Å, μ = 2.108 mm^{-1}, F(000) = 458, T = 93 K. A yellow 0.32 x 0.16 x 0.08-mm crystal was used for data collection with a Bruker SMART [15] 1K CCD detector on a four-circle goniometer. The Mo-K$_\alpha$ source was equipped with an incident beam graphite monochromator. Lattice parameters were determined using SAINT [15] from 5003 reflections within 4.9° < 2θ < 58.1°. The data collection range had a {(sin θ)/λ}$_{max}$ = 0.68. A set of 7554 reflections was collected in the ϕ and ω scan mode. There were 4799 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL [16] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 varied 253 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C-H distances set to 0.96 to 0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2 to 1.5 U_{eq}(C). Final residuals were R1 = 0.038 for the 3976 observed data with F_o >4σ(F_o) and 0.050 for all data. Final difference Fourier excursions were 1.07 and -0.82 eÅ^{-3}. The molecule sits on an inversion center and has C_i symmetry.

(*S*)-(-)-2-(Hydroxymethyl)indoline.

This compound was prepared from (*S*)-(-)-indoline-2-carboxylic acid following the published general procedure; [17] colorless plates, mp 59-61 ºC; ir: 3278, 3195, 1608, 1463, 1077, 1047, 828, 778, 744 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.39 (br s, 2H), 2.85 (dd, 1H, J = 8.0, 15.8 Hz), 3.12 (dd, 1H, J = 9.2, 16.1 Hz), 3.59 (dd, 1H, J = 6.3, 10.8 Hz), 3.74 (dd, 1H, J = 3.8, 11.0 Hz), 4.06 (m, 1H), 6.65-6.76 (m, 2H); 7.01-7.11 (m, 2H); ^{13}C nmr ($CDCl_3$): δ 31.7, 60.1, 65.1, 109.7, 118.8, 124.5, 127.1, 128.4, 150.1; ms: m/z 149 (53), 118 (100), 91 (55); $[\alpha]^{25}_D$ = +49.4 (c = 0.88, MeOH).

(*S*)-(-)-2-(Acetoxymethyl)-*N*-(ethoxycarbonyl)indoline.

To a suspension of (*S*)-(-)-2-(hydroxymethyl)indoline (4.5 g, 30 mmol) and Na_2CO_3 (3.8 g, 36 mmol) in water (100 mL) were added EtOCOCl (4.6 mL, 48 mmol) and EtOAc (5 mL) in one portion. The mixture was stirred at room temperature for 4 hours and extracted with AcOEt (4 x 50 mL). The organic layer was dried over Na_2SO_4 and evaporated to give an oil which was dissolved in Et_3N (8.3 mL, 60 mmol) and Ac_2O (3.4 mL, 60 mmol). The mixture was stirred for 4 hours at room temperature and then partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was extracted with CH_2Cl_2 (2 x 100 mL) and dried over Na_2SO_4. Evaporation and column chromatography (silica gel, ethyl acetate:hexane = 1:2) provided 7.1 g (90 %) of the product, ir: 2985, 1746, 1709, 1486, 1410, 1194, 1057, 755 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.37 (t, 3H, J = 7.0 Hz), 1.94 (s, 3H), 2.90 (d, 1H, J = 16.6 Hz), 3.33 (dd, 1H, 9.9, 16.2 Hz), 4.20 (m, 2H), 4.30 (q, 2H, J = 7.0 Hz), 4.71 (br s, 1H), 6.92-7.01 (m, 1H); ^{13}C nmr ($CDCl_3$): δ 14.5, 20.5, 31.3, 57.4, 61.6, 64.6, 115.2, 122.8, 124.6, 127.4, 129.6, 141.8, 153.0, 170.7; ms: m/z 263 (7), 203 (15), 190 (18), 130 (28), 118 (100), 91 (20); $[\alpha]^{25}_D$ = -56.6 (c = 1.25, $CHCl_3$).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.54; H, 6.63; N, 5.51.

(*S*)-(-)-2-(Acetoxymethyl)-*N*-(ethoxycarbonyl)-5-nitroindoline.

To a solution of (*S*)-(-)-2-(acetoxymethyl)-*N*-(ethoxycarbonyl)indoline (15.8 g, 60 mmol) in Ac_2O (250 mL) was added nitric acid (35 mL, 275 mmol) dropwise at -15 ºC. The mixture was allowed to warm to 0 ºC within 30 minutes and was poured onto crushed ice (500 g). After warming to ambient temperature,

the product was extracted into EtOAc (5 x 100 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated. Column chromatography (500 g of silica gel, ethyl acetate:hexane = 1:2) followed by crystallization from methanol provided pure product (12.0 g, 65%), mp 94-96 ºC; ir: 1743, 1716, 1513, 1487, 1341, 1301, 1273, 1236, 1055, 1045 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.38 (t, 3H, J = 7.1 Hz), 1.90 (s, 3H), 9.04 (dd, 1H, J = 2.1, 16.7 Hz), 3.41 (dd, 1H, J = 10.1, 16.7 Hz), 4.18 (dd, 1H, J = 3.7, 11.5 Hz), 3.29-4.40 (m, 3H), 4.80(m, 1H), 7.80 (br s, 1H), 8.00 (s, 1H), 8.10 (dd, 1H, J = 2.3, 8.9 Hz); ^{13}C nmr ($CDCl_3$): δ 14.3, 20.4, 30.6, 58.6, 62.5, 64.4, 114.3, 120.2, 124.5, 131.1, 143.0, 147.7, 152.4, 170.6; ms: m/z 308 (2), 248 (12), 235 (6), 175 (7), 117 (44), 43 (100); $[\alpha]^{25}_D$ = -49.0 (c = 1.12, MeOH).

Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.67; H, 5.43; N, 9.34.

(*S*)-(-)-*N*-(Ethoxycarbonyl)-2-(hydroxymethyl)-5-nitroindoline.

To a vigorously stirred mixture of (*S*)-(-)-2-(acetoxymethyl)-*N*-(ethoxycarbonyl)-5-nitroindoline (10.0 g, 32.5 mmol) in MeOH (1.5 L) and THF (100 mL) was added Na_2CO_3 (24.1 g, 227 mmol) in water (500 mL). After stirring for 1.5 hour, the organic solvents were evaporated under reduced pressure, and the residue was brought with HCl to pH 7. Ethyl acetate extraction and drying followed by concentration provided an oil which was chromatographed on silica gel (ethyl acetate:hexane = 1:2) to provide a pale yellow solid (7.7 g, 89%). An analytically pure sample was obtained by crystallization from toluene, mp 115-117 ºC; ir: 3257, 1701, 1516, 1484, 1319, 1260 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.43 (t, 1H, J = 7.1 Hz), 2.43 (br s, 1H), 3.12 (d, 1H, J = 16.8 Hz), 3.43 (dd, 1H, J = 10.3, 16.8 Hz), 3.84 (m, 2H), 4.39 (q, 2H, J = 7.1 Hz), 4.73 (m, 1H), 7.78 (br s, 1H), 8.04 (s, 1H), 8.12 (dd, 1H, J = 2.3, 8.9 Hz); ms: m/z 266 (37), 235 (100), 163 (45), 145 (36), 130 (32), 117 (60), 84 (31); ^{13}C nmr ($CDCl_3$): δ 14.3, 30.3, 61.5, 62.6, 64.1, 114.4, 120.4, 124.0, 131.8, 143.0, 147.8, 153.3; $[\alpha]^{25}_D$ = -100.3 (c = 0.955, MeOH).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.96; H, 5.47; N, 10.38.

(*S*)-(-)-*N*-Benzyl-2-(hydroxymethyl)-5-nitroindoline.

A round bottom flask fitted with a dropping funnel was charged with NaH (5.2 g, 216 mol) and benzyl bromide (22.2 g, 130 mmol) and cooled to -30 ºC. DMF (100 mL) was added with stirring under a nitrogen atmosphere. Then (*S*)-(-)-*N*-(ethoxycarbonyl)-2-(hydroxymethyl)-5-nitroindoline (19.9 g, 86.5 mmol) in DMF (200 mL) was slowly added within 30 minutes to the resulting suspension. The reaction mixture was allowed to warm to room temperature, and water (50 mL) was added cautiously to destroy the excess of NaH. Addition of more water (600 mL) was followed by neutralization with 6 *M* HCl and extraction with ethyl acetate (4 x 200 mL). The combined organic extracts were concentrated, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2) to give 16.3 g (66%) of the product, ir: 3427, 1609, 1509, 1496, 1314, 1267 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.04 (dd, 1H, J = 7.3, 16.6 Hz), 3.22 (dd, 1H, J = 10.4, 16.5 Hz), 3.68 (dd, 1H, J = 4.0, 11.6 Hz), 3.81 (dd, 1H, J = 3.9, 11.7 Hz), 4.05 (m, 1H), 4.50 (d, 1H, J = 16.4 Hz), 4.59 (d, 1H, J = 16.4 Hz), 6.30 (d, 1H, J = 8.8 Hz), 7.21-7.38 (m, 5 Hz), 7.86 (s, 1H), 7.98 (dd, 1H, J = 1.7, 8.8 Hz); ^{13}C nmr ($CDCl_3$): δ 30.1, 49.2, 62.8, 64.8, 103.7, 120.5, 126.5, 126.8, 127.5, 128.6, 136.6, 137.7, 157.4; ms: m/z 284 (25), 253 (100), 91 (97); $[\alpha]^{25}_D$ = +155.7 (c = 0.61, MeOH).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.32; H, 5.91; N, 9.53.

(*S*)-(+)-*N*-Benzyl-2-[[[*N*-(*tert*-butoxycarbonyl)-L-valyl]oxy]-methyl]-5-nitroindoline (**1**).

To a stirred solution of (*S*)-(-)-*N*-benzyl-2-(hydroxymethyl)-5-nitroindoline (11.0 g, 38.7 mmol) and triethylamine (10.8 mL, 77.4 mmol) in dry CH_2Cl_2 (150 mL) was added *N*-(*tert*-butoxycarbonyl)-*L*-valyl fluoride [18] (12.7 g, 58.1 mmol) under nitrogen. The reaction mixture was left for 11 hours at room temperature, then evaporated to dryness, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to give the product (9.9 g, 53%), ir: 3408, 1742, 1716, 1708, 1609, 1498, 1385, 1317, 1174 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.77 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.8 Hz), 1.43 (s, 3H), 1.91 (m, 1H), 2.96 (d, 1H, J = 5.7, 16.7 Hz), 3.34 (d, 1H, J = 10.1, 16.7 Hz), 4.08-4.25 (m, 2H), 4.32-4.40 (m, 1H), 4.47 (d, 1H, J = 16.7 Hz), 4.64 (d, 1H, J = 16.7 Hz), 4.86 (d, 1H, J = 9.0 Hz), 6.31 (d, 1H, J = 8.8 Hz), 7.22-4.38 (m, 5H), 7.92 (s, 1H), 8.03 (dd, 1H, J = 2.2, 8.8 Hz); ^{13}C nmr ($CDCl_3$): δ 17.3, 19.0, 28.2, 30.8, 31.1, 49.6, 58.5, 62.0, 65.2, 79.9, 104.2, 120.6, 126.6, 126.8, 127.7, 128.9, 136.3, 138.7, 155.6, 156.8, 172.2; ms: m/z 483 (10), 410 (10), 266 (31), 253 (100), 91 (93); $[\alpha]^{25}_D$ = +126.6 (c = 1.25, MeOH).

Anal. Calcd for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88; N, 8.69. Found: C, 64.42; H, 7.11; N, 8.56.

Dimerization Reaction of Compound (**1**).

Compound **1** (12.0 g, 24.8 mmol), *N*-methylmorpholine (17.6 g, 173.9 mmol) and dry THF (450 mL) were placed in a 1 L round bottom flask under nitrogen. The flask was cooled to -78 ºC, and sodium hexamethyldisilazide (124 mL of a 1 *M* solution in THF) was added slowly with vigorous stirring. After the addition was completed (35 minutes), the solution was allowed to warm to 0 ºC within 3.3 hours. Then saturated aqueous NH_4Cl (150 mL) and water (150 mL) were added. The layers were separated, and the aqueous phase was extracted with ethyl acetate (4 x 100 mL). The combined organic phases were evaporated to dryness, and the residue was chromatographed on silica gel (ethyl acetate:hexane = 1:10, then 1:5) to provide compound **1** as a yellow oil (6.15 g, 51%), ir: 3427, 1742, 1716, 1707, 1604, 1499, 1385, 1322, 1173 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.72 (d, 6H, J = 6.6 Hz), 0.82 (d, 6H, J = 6.6 Hz), 1.43 (s, 18H), 1.85 (m, 2H), 2.06 (dd, 2H, J = 10.0, 16.1 Hz), 2.51 (d, 2H, J = 16.6 Hz), 2.93 (dd, 2H, J = 8.6, 10.5 Hz), 3.29 (d, 2H, J = 9.0 Hz), 3.95-4.06 (m, 4H), 4.81 (d, 2H, J = 8.5 Hz), 5.92 (s, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.20-7.45 (m, 10H), 7.81 (s, 2H), 8.16 (dd, 2H, J = 1.7, 8.8 Hz); ^{13}C nmr ($CDCl_3$): δ 17.4, 18.9, 28.3, 30.9, 31.3, 57.4, 58.0, 58.3, 64.7, 80.0, 103.5, 121.4, 126.6, 127.8, 128.2, 129.0, 129.3, 136.8, 139.0, 155.4, 155.5, 172.1; ms: m/z 482 (5), 426 (3), 91 (8), 56 (31), 41 (100); $[\alpha]^{25}_D$ = -260.8 (c = 0.365, MeOH).

Anal. Calcd. for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88; N, 8.69. Found: C, 64.33; H, 7.09; N, 8.81.

The syntheses of the racemic amines **3**-**8** were carried out in a similar way as that of **1**. The products were only partially characterized (^1H nmr, ms) and then subjected to the action of base.

Representative Example for the Synthesis of the Dimers (**9**-**13**).

To a solution of amine **5** (30 mg, 0.08 mmol) and *N*-methylmorpholine (58 mg, 0.57 mmol) in dry THF (2 mL) was added a 1 *M* solution of NaHMDS in THF (0.41 mL) at -78 °C under nitrogen. The reaction mixture was allowed to warm to 0 °C

within 1.5 hour and then quenched with saturated NH_4Cl (10 mL). Extraction with ethyl acetate (4 x 20 mL) followed by preparative TLC on silica gel (ethyl acetate:hexane = 1:3) provided a mixture of the dimers **10A** and **10B** (20 mg, 67%) as a yellow oil, ms: m/z 367, 265, 219, 57.

Dimers (**9A**) and (**9B**).

These compounds gave ms: m/z 387, 176, 179, 105.

Dimer (**11B**).

This compound was obtained as yellow prisms after several recrystallizations from MeOH-CH_2Cl_2, mp 292-294 ºC; ir: 1730, 1603, 1493, 1315, 1271, 1152 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.00 (s, 18H), 2.12 (dd, 2H, J = 9.9, 16.2 Hz), 2.55 (d, 2H, J = 16.1 Hz), 2.89 (dd, 2H, J = 7.8, 10.5 Hz), 3.49 (dd, 2H, J = 2.7, 8.5 Hz), 3.93 (m, 2H), 5.80 (s, 2H), 6.90 (s, 2H, J = 9.0 Hz), 7.23-7.45 (m, 8H), 7.82 (s, 2H), 8.16 (dd, 2H, J = 2.2, 8.8 Hz); ^{13}C nmr ($CDCl_3$): δ 26.9; 31.3; 38.6; 56.9; 58.2; 64.2; 103.5; 121.4; 123.1; 126.2; 128.1; 129.8; 132.5; 136.0; 139.2; 155.3; 178.2; ms: m/z 445, 417, 178, 57.

Anal. Calcd. for $C_{42}H_{44}Br_2N_4O_8$: C, 56.51; H, 4.97; N, 6.28. Found: C, 56.04; H, 4.88; N, 6.05.

Dimer (**12A**).

This compound was obtained as yellow prisms after several recrystallizations from MeOH-CH_2Cl_2, mp 250-252 ºC; ir: 1729, 1603, 1492, 1318, 1259, 1150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.01 (s, 18H), 3.67 (d, 2H, J = 16.2 Hz), 2.90 (dd, 2H, J = 10.0, 16.4 Hz), 3.78 (dd, 2H, J = 6.2, 11.2 Hz), 3.76 (dd, 2H, J = 2.7, 11.2 Hz), 4.23 (m, 2H), 6.16 (s, 2H), 6.82 (d, 2H, J = 8.8 Hz), 7.08-7.20 (m, 4H), 7.56 (dd, 2H, J = 1.5, 7.8 Hz), 7.65 (dd, 2H, J = 1.7, 7.8 Hz), 7.70 (s, 2H), 7.95 (dd, 2H, J = 2.2, 8.8 Hz); ^{13}C nmr ($CDCl_3$): δ 26.9, 31.9, 38.7, 58.9, 61.7, 64.9, 107.5, 120.4, 125.4, 125.5, 128.2, 128.9, 129.3, 130.8, 133.6, 135.6, 139.4, 155.3, 178.1; ms: m/z 445, 207, 178, 57.

Anal. Calcd. for $C_{42}H_{44}Br_2N_4O_8$: C, 56.51; H, 4.97; N, 6.28. Found: C, 56.34; H, 4.71; N, 6.12.

Dimer (**13A**).

This compound was obtained as yellow needles after several recrystallizations from MeOH-CH_2Cl_2, mp 253-255 ºC; ir: 1728, 1603, 1487, 1318, 1257, 1147 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.01 (s, 18H), 2.69 (d, 2H, J = 16.2 Hz), 2.96 (dd, 2H, J = 9.8, 16.1 Hz), 3.35 (dd, 2H, J = 6.2, 11.2 Hz), 3.74 (dd, 2H, J = 2.7, 11.2 Hz), 4.26 (m, 2H), 5.95 (s, 2H), 6.91 (d, 2H, J = 9.0 Hz), 6.90-7.25 (m, 4H), 7.65 (dd, 2H, J = 1.4, 7.8 Hz), 7.70 (s, 2H), 7.83 (d, 2H, J = 8.0 Hz), 7.93 (dd, 2H, J = 2.3, 9.0 Hz); ^{13}C nmr ($CDCl_3$): δ 27.0; 31.9; 38.7; 59.0; 64.8; 67.6; 102.4; 108.3; 120.4; 125.2; 129.0; 129.0; 129.3; 131.0; 138.6; 139.3; 140.5; 155.2; 178.1; ms: m/z 493, 391, 178, 57.

Anal. Calcd. for $C_{42}H_{44}I_2N_4O_8$: C, 51.13; H, 4.50; N, 5.68. Found: C, 51.03; H, 4.34; N, 5.50.

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