Asymmetric Synthesis of Optically Active Phthalides *via ortho*-Lithiation and Cyclization of Chiral *N*-Monosubstituted Benzamides

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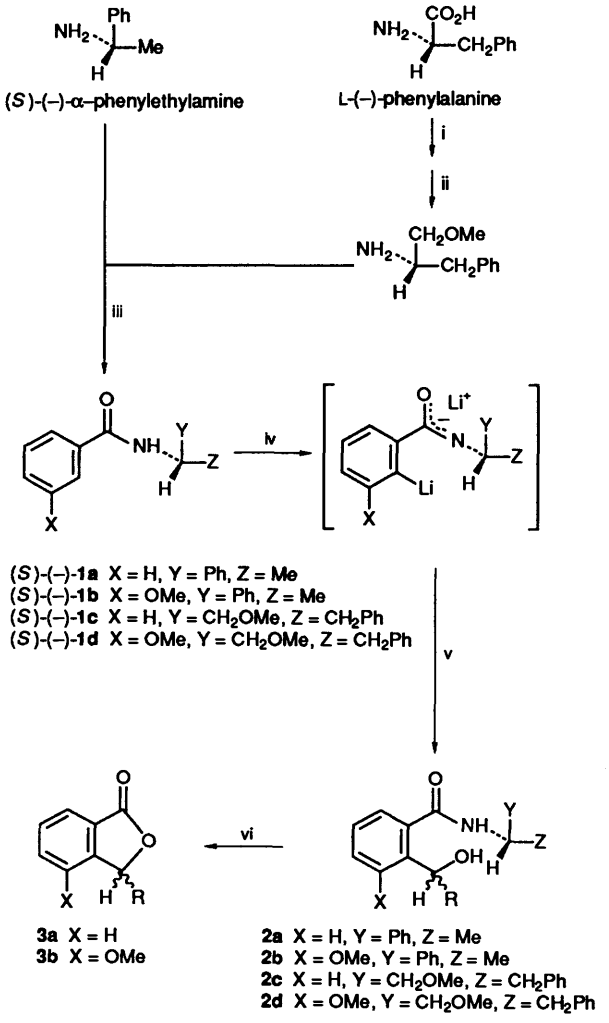
The chiral *N*-monosubstituted benzamides **1a–d**, derived from (*S*)-(−)-α-phenylethylamine and L-(−)-phenylalanine, gave the *ortho*-lithiated species on treatment with butyllithium (2.2 equiv.) and TMEDA in THF at 0 °C. The resulting lithio amides reacted smoothly with aldehydes to afford the expected *ortho* substituted products **2a–d** as diastereoisomeric mixtures, which were converted quantitatively into the phthalides **3a, b** on acidic hydrolysis. Use of (*S*)-(−)-*N*-benzoyl-*O*-methylphenylalaninol **1c** and (*S*)-(−)-*N*-(3-methoxybenzoyl)-*O*-methylphenylalaninol **1d** as the amide resulted in consistently high diastereoselectivities. The reaction of the dianions derived from **1c** with valeraldehyde gave, after cyclization, (*S*)-(−)-3-butylphthalide, an essential oil of celery, with 83% e.e.

In recent years, much attention has been focussed on the *ortho*-directed metallations of benzene derivatives because of their great synthetic utility.[1] In particular, the asymmetric synthesis of optically active phthalides using ortho-metallation of chiral benzamides has proved attractive since these compounds both occur as biologically active natural products[2] and serve as useful synthetic intermediates.[1,2] Although several asymmetric syntheses of these compounds have been reported, few have provided chiral phthalides with high optical purity.[3] We have been interested in using dianions in the synthesis of α, β-unsaturated esters and lactones,[4] and have initiated our studies on the asymmetric synthesis of optically active phthalides using *ortho*-metallation of chiral *N*-monosubstituted benzamides **1a–d**. However, the optical yields of 3-substituted phthalides **3** obtained by the reaction of dianions derived from (*S*)-(−)-*N*-benzoyl-α-phenylethylamine **1a** and (*S*)-(−)-*N*-(3-methoxybenzoyl)-α-phenylethylamine **1b** with aldehydes were too low to be of practical use. In contrast, the use of **1c** and **1d** as the amide has enhanced remarkably the optical yields of **3**. It is noteworthy that the amides **1c** and **1d** are more effective in inducing asymmetry than the amides **1a** and **1b**.

Results and Discussion

Our synthesis of optically active phthalides involves the *ortho* lithiation of chiral *N*-monosubstituted benzamides **1a–d** followed by the diastereoselective reaction of the resulting lithio amides with aldehydes to induce a new asymmetric centre (see Scheme 1). The amides **1a, b** and **1c, d** were prepared from (*S*)-(−)-α-phenylethylamine and L-(−)-phenylalanine, respectively. Treatment of **1a–d** with BuLi/TMEDA (2.2 equiv) in dry THF at −78 °C for 15 min and at 0 °C for 30 min produced the lithio amides which reacted with aldehydes to afford the adducts **2a–d** in moderate to good yields. Treatment of **2a–d** with 5% HCl in refluxing dioxane for 4 h resulted in smooth cyclization to the phthalides **3a–d** in quantitative yields. The results were summarized in Table 1.

The results showed that *ortho* lithiation of **1** proceeded smoothly under the described conditions and that all the adducts **2a–d** were obtained as diastereoisomeric mixtures. The diastereomeric ratios of **2**, summarized in Table 1, were determined by ^{1}H NMR and/or HPLC. For example, the ^{1}H NMR spectrum of **2a–2** obtained by the reaction of the lithiated (*S*)-(−)-**1a** with benzaldehyde exhibited doublet signals for the



Scheme 1 *Reagents and conditions:* i, $LiAlH_4$, THF, reflux, 4 h, 10% KOH, then H_2O, reflux, 0.5 h (79%); ii, NaH, THF, room temp., 10 h, MeI, room temp., 3 h (65%), iii, **1a**: Et_3N, PhCOCl, THF, room temp., 16 h (90%); **1b**: Et_3N, *m*-$MeOC_6H_4COCl$, THF, room temp., 16 h (87%); **1c**; Et_3N, PhCOCl, THF, room temp., 16 h (73%); **1d**; Et_3N, *m*-$MeOC_6H_4COCl$, THF, room temp., 16 h (69%); iv, BuLi, TMEDA, THF, −78 °C to 0 °C; v, RCHO, THF, −78 °C, 4 h; vi, 5% HCl, dioxane, reflux, 4 h.

Table 1 Reactions of lithio amides derived from **1a–d** with aldehydes and subsequent cyclization into 3-substituted phthalides **3**

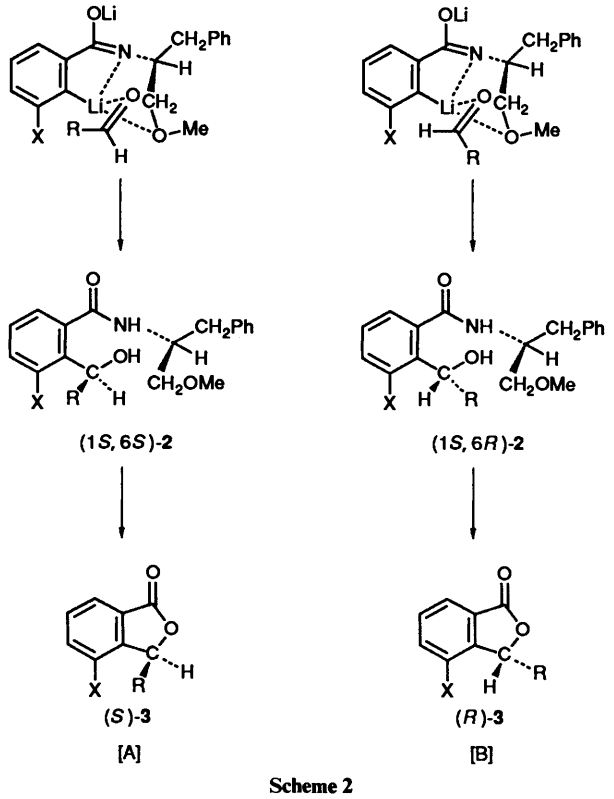
Entry	Starting[a] material	Aldehyde	Yield of **2** (%)[b]	Diastereoisomeric ratio of **2** (I/II)[c]	Yield of **3** (%)[d]	$[\alpha]_D$ (°C, *c* in $CHCl_3$)	% E.e. of **3**
1	(*S*)-(−)-**1a**	C_4H_9CHO	63 **2a–1**	45/55	93 **3a–1**	+3.5 (20, 0.95)	13[e], 12[f]
				97/3[g]	91 **3a–1**	−54.0 (19, 1.17)	95[e], 95[f]
2	(*S*)-(−)-**1a**	C_6H_5CHO	74 **2a–2**	57/43	90 **3a–2**	−6.2 (23, 0.88)	15[f]
3	(*S*)-(−)-**1a**	$C_7H_{15}CHO$	73 **2a–3**	53/47	85 **3a–3**	−2.7 (20, 1.05)	6[f]
4	(*S*)-(−)-**1a**	C_4H_9CHO	13[h] **2a–1**	55/45	—	—	—
5	(*S*)-(−)-**1b**	C_4H_9CHO	72 **2b–1**	48/52	92 **3b–1**	+1.4 (20, 1.17)	0[f]
6	(*S*)-(−)-**1b**	C_6H_5CHO	64 **2b–2**	54/46	90 **3b–2**	−7.0 (19, 1.10)	7[f]
7	(*S*)-(−)-**1c**	C_4H_9CHO	57 **2c–1**	90/10	95 **3a–1**	−47.3 (17, 0.73)	83[e], 81[f]
8	(*S*)-(−)-**1c**	C_6H_5CHO	60 **2c–2**	81/19	87 **3a–2**	−39.5 (19, 1.00)	65[f]
9	(*S*)-(−)-**1d**	C_4H_9CHO	49 **2d–1**	85/15	91 **3b–1**	−41.4 (20, 1.10)	73[f]
10	(*S*)-(−)-**1d**	C_6H_5CHO	48 **2d–2**	87/13	88 **3b–2**	−46.0 (21, 1.03)	76[f]

[a] Absolute configurations of **1** are based on the absolute configuration of α-phenylethylamine and the sign of the specific rotation. [b] Mixture of faster eluting and slower eluting diastereoisomers isolated by column chromatography on silica gel with hexane–ethyl acetate (5:1) as eluent. [c] Numerals I and II indicate the elution order of diastereoisomers, the ratio was determined by HPLC (SUMICHIRAL OA-2500 column, 70:29:1 hexane–1,2-dichloroethane–ethanol eluent, flow rate 1 ml min^{-1}) and/or ^1H NMR. [d] Isolated yields for cyclization of **2** into **3**. [e] Optically pure (*S*)-(−)-3-butylphthalide is reported to have $[\alpha]_D = -57$ (*c* 1.96, $CHCL_3$).[2] [f] Determined by HPLC (SUMICHIRAL OA-2500 column hexane–ethyl acetate–ethanol (70:29:1) eluent, flow rate 1 ml min^{-1}). [g] One fraction from column purification of **2a–1**, prepared in 45:55 diastereoisomer ratio. [h] The lithiation of **1** was carried out at −78 °C. In other reactions, the reaction temperature was raised to 0 °C from −78 °C.

methyl protons of the *N*-substituent at δ 1.14 and 1.44. The diastereoisomeric ratio (56:44) determined from the ^1H NMR spectrum was in good agreement with that (57:43) determined by HPLC. The adducts **2a–b** obtained from the amides **1a, b** exhibited consistently low diastereoselectivity. The reaction of lithiated (*S*)-(−)-**1a** with valeraldehyde (Entry 1) afforded **2a-1** as a 45:55 mixture of diastereoisomers which upon cyclization gave 3-butylphthalide **3a–1** of poor optical purity. The mixture of diastereoisomers of **2a–1** were readily separated by open-column chromatography to yield a 97:3 mixture of diastereoisomers as the faster eluting fraction. It was cyclized to afford **3a–1**, $[\alpha]_D^{19}$ − 54.0 (*c* 1.17, $CHCl_3$). Since enantiomerically pure (*S*)-(−)-3-butylphthalide is reported to have a value of $[\alpha]_D$ − 57 (*c* 1.96, $CHCl_3$),[2] we chose valeraldehyde as a representative electrophile. Therefore, the absolute configuration of **3a–1** prepared in this experiment was determined as S on the basis of the sign of the specific rotation. Thus, in the present reactions in which the *S* amide was used, the faster eluting diastereoisomer was found to yield the *S* 3-substituted phthalide.

On the other hand, the reaction of the lithiated (*S*)-(−)-**1c** with valeraldehyde (Entry 7) afforded the adduct **2c–2** as a 90:10 mixture of diastereoisomers which upon cyclization gave (*S*)-(−)-3-butylphthalide, an essential oil of celery, with 83% e.e. The enantiomeric excess of **3a–1** obtained by the reaction of the lithiated (*S*)-(−)-**1a** or (*S*)-(−)-**1c** with valeraldehyde was calculated from the specific rotation {$[\alpha]_D$ − 57 (*c* 1.96, $CHCl_3$)} of enantiomerically pure (*S*)-(−)-3-butylphthalide. These enantiomeric excesses (Entries 1 and 7) were in good agreement with those determined by HPLC using the chiral stationary phase (SUMICHIRAL OA-2500). However, since all the chiral 3-substituted phthalides so obtained were unknown compounds except for **3a–1**, the enantiomeric excess of each phthalides, (see Table 1), was determined by HPLC as described above. The enantiomeric excess of **3** almost corresponded to the diastereoselectivity of **2**. This indicates that no racemization took place during the cyclization of **2** to **3**. Thus the absolute configuration of mobile diastereoisomer **2**, leading to (*S*)-(−)-**3** by cyclization, was established as (1*S*,6*S*)-**2**.

Interestingly, an enhancement of the asymmetric induction in the reaction of the lithio amides with aldehydes was observed when (*S*)-(−)-**1c** and (*S*)-(−)-**1d** bearing a methoxy function on the *N*-substituent was employed as the amide. The asymmetric induction which occurs in the reactions of the *ortho* lithiated amides **1c, d** with aldehydes would, most reasonably, be attributed to kinetic control in the diastereoisomeric transition states leading to the adducts **2c, d**. A rigid bicyclic transition state resulting from intramolecular coordination of the methoxy oxygen and amide nitrogen to lithium metal is postulated which would be effective for differentiation of the enantioface of the approaching aldehyde (Scheme 2). Thus the aldehyde approaches from the less-hindered front side *via* path (A), to give predominant formation of (1*S*,6*S*)-**2**.



Scheme 2

Experimental

General Methods. Tetrahydrofuran (THF) was dried by distillation from calcium hydride and by subsequent distillation from lithium aluminium hydride under a nitrogen atmosphere. A hexane solution of BuLi (Aldrich) was titrated by using diphenylacetic acid.[5] *N,N,N',N'*-Tetramethylethylenediamine

(TMEDA) was distilled from calcium hydride and stored over molecular sieves. Aldehydes were purified by distillation under a nitrogen atmosphere. The glassware was dried by flaming in a nitrogen stream. All reactions were carried out under a nitrogen atmosphere.

IR spectra were recorded on a Hitachi Model 260–30 spectrophotometer. NMR spectra were obtained on a JEOL Model EX-90 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard; J values are recorded in Hz. Optical rotations were measured in 0.5 dm path-length cell of 4 cm^3 capacity on a JASCO Model DIP-390 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University. Analytical TLC was performed on glass pre-coated silica gel plates (Merck F-254). Column chromatography was performed by using Silica gel (Wakogel) of 300 mesh size. High pressure liquid chromatography was carried out on a TOYO SODA Model CCPE liquid chromatograph using the chiral stationary phase (SUMICHIRAL OA-2500).

(S)-(−)-N-*Benzoyl-α-phenylethylamine* **1a**.—To a solution of (*S*)-(−)-α-phenylethylamine (2.9 g, 23.9 mmol) and triethylamine (2.9 g, 28.7 mmol) in THF (50 cm^3) was added dropwise benzoyl chloride (3.3 g, 23.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h after which the precipitated salts were filtered off through a glass filter. The filtrate was concentrated under reduced pressure and the residue recrystallized from ethyl acetate–hexane to afford the amide **1a** as a white crystalline solid (4.74 g, 90%); m.p. 123.0–123.5 °C; $[\alpha]_D^{20}$ − 23.5 (*c* 0.96, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1760; δ_H(90 MHz, $CDCl_3$) 6.40–7.80 (m, 1 H), 5.06 (q, *J* 7, 1 H) and 1.43 (d, *J* 7, 3 H) (Found: C, 79.9; H, 6.8; 6.2. Calc. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22%).

(S)-(−)-N-(3-*Methoxybenzoyl*)-α-*phenylethylamine* **1b**.—Thionyl chloride (15 cm^3, 206 mmol) was added to *m*-anisic acid (7.8 g, 51 mmol) and the reaction mixture was refluxed at 100–110 °C for 4.5 h. It was then distilled under reduced pressure (110–112 °C/1.0 Torr) to afford *m*-anisoyl chloride (8.0 g, 92%) as a colourless oil. By the procedure described for the preparation of amide **1a**, (*S*)-(−)-α-phenylethylamine (2.9 g, 23.9 mmol), triethylamine (28.7 mmol) and *m*-anisoyl chloride (4 g, 23.4 mmol) in THF (50 cm^3) afforded, after recrystallization from ethyl acetate–hexane, the amide **1b** as a white crystalline solid (5.19 g, 87%); m.p. 125.0–126.0 °C; $[\alpha]_D^{20}$ − 28.6 (*c* 1.50, $CDCl_3$); ν_{max}(KBr)/cm^{-1}; 1760; δ_H(90 MHz, $CDCl_3$) 6.04–7.20 (m, 10 H), 4.96 (q, *J* 1 H), 3.52 (s, 3 H) and 1.44 (d, *J* 7, 3 H) (Found: C, 74.9; H, 6.7; N, 5.4. Calc. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%).

(S)-(−)-N-*Benzoyl*-O-*methylphenylalaninol* **1c**.—To a solution of lithium aluminium hydride (8.2 g, 216 mmol) in THF (220 cm^3) was added L-phenylalanine (25 g, 151 mmol) over a period of 1 h. The reaction mixture was refluxed for 4 h and cooled to room temperature. To this was added dropwise 10% aqueous potassium hydroxide (9.2 cm^3) followed by water (9.2 cm^3). The mixture was refluxed for 30 min after which the precipitate was filtered off. The filtrate was concentrated under reduced pressure and distilled under reduced pressure to afford L-phenylalaninol as a viscous oil (18 g, 79%). To a solution of sodium hydride (4.8 g, 120 mmol) in THF (90 cm^3) was added dropwise a solution of L-phenylalaninol (16.6 g, 110 mmol) in THF (20 cm^3). The mixture was stirred at room temperature for 10 h when methyl iodide (15.3 g, 108 mmol) was added over a period of 2 h. The reaction mixture was stirred at room temperature for 3 h, poured into ice-cooled water and extracted with ether (100 × 3 cm^3). The combined extracts were washed with brine (×2), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (5:1, hexane–ethyl acetate) of the resulting oil afforded (*S*)-(−)-2-amino-1-methoxy-3-phenylpropane as a viscous oil (11.8 g, 65%). By the procedure described above (*S*)-(−)-1-methoxy-2-amino-3-phenylpropane (4.0 g, 24.2 mmol), triethylamine (2.9 g, 28.7 mmol), and benzoyl chloride (3.3 g, 23.4 mmol) in THF (50 cm^3) afforded, after column chromatography (5:1, hexane/ethyl acetate), the amide **1c** as a white crystalline solid (4.6 g, 73%); $[\alpha]_D^{25}$ − 66.1 (*c* 1.14, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1755; δ_H(90 MHz, $CDCl_3$) 5.84–7.32 (m, 11 H), 4.00–4.25 (m, 1 H), 3.08–3.32 (m, 5 H) and 2.66–3.25 (m, 2 H) (Found: C, 76.0; H, 7.0; N, 5.2. Calc. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%).

(S)-(−)-N-(3-*Methoxybenzoyl*)-O-*methylphenylalaninol* **1d**.—By the procedure described above (*S*)-(−)-2-amino-1-methoxy-3-phenylpropane (4.0 g, 24.2 mmol); triethylamine (2.9 g 28.7 mmol) and *m*-anisoyl chloride (4 g, 23.4 mmol) in THF (50 cm^3) afforded, after column chromatography (5:1, hexane–ethyl acetate), the amide **1d** as a white crystalline solid (4.83 g, 69%); $[\alpha]_D^{25}$ − 67.9 (*c* 1.50, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1755; δ_H(90 MHz, $CDCl_3$) 6.28 (m, 10 H), 4.16–4.60 (m, 1 H), 3.76 (s, 3 H), 3.20–3.52 (m, 5 H) and 2.78–3.08 (m, 2 H) (Found: C, 72.65; H, 7.0; N, 4.3. Calc. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68%).

General Procedure for Amide Lithiation and Preparation of Aldehyde Adducts.—2-(α-*Hydroxypentyl*)-N-α-*phenylethylbenzamide* **2a–1**. (*S*)-(−)-*N*-Benzoyl-α-phenylethylamine **1a** (0.900 g, 4 mmol) in THF (5 cm^3) was added dropwise to stirred mixture of BuLi (0.562 g, 8.8 mmol) and TMEDA (1.02 g, 8.8 mmol) in THF (30 cm^3) at −78 °C. The mixture was stirred for 30 min at −78 °C, warmed to 0 °C, stirred for 30 min, and cooled to −78 °C. After the mixture had been stirred for 30 min at −78 °C, a solution of valeraldehyde (0.345 g, 4 mmol) in THF (3 cm^3) was added dropwise, and stirring at −78 °C continued for 4 h. Saturated aqueous ammonium chloride (5 cm^3) was added to the mixture which was then poured into dilute hydrochloric acid (20 cm^3). The resultant mixture was extracted with ether (3 × 20 cm^3) and the combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (5:1) as eluent to afford **2a–1** (0.78 g, 63%) as a 45:55 mixture of diastereoisomers; ν_{max}(neat)/cm^{-1} 3300 and 1760; δ_H(90 MHz, $CDCl_3$) 6.90–8.35 (m, 10 H), 5.08–5.60 (m, 1 H), 4.65 (br s, 1 H), 4.10 (s, 1 H) and 0.40–2.25 (m, 12 H) (Found: C, 77.0; H, 8.2; N, 4.4. Calc. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50 %).

The adduct **2a-1** (0.46 g) were further separated by column chromatography on silica gel with hexane–ethyl acetate (5:1) as eluent to afford **2a-1** (0.20 g) (diastereomeric ratio I/II = 97:3) as the faster eluting diastereoisomer; ν_{max}(neat)/cm^{-1} 3300 and 1760; δ_H(90 MHz, $CDCl_3$) 6.80–8.30 (m, 10 H), 5.05–5.50 (m, 1 H), 4.65 (br s, 1 H), 4.08 (s, 1 H) and 0.42–2.30 (m, 12 H).

2-(α-*Hydroxybenzyl*) N-(α-*phenylethyl*)*benzamide* **2a–2**. ν_{max}(neat)/cm^{-1} 3280 and 1760; δ_H(90 MHz, $CDCl_3$) 6.82–7.84 (m, 14 H), 6.46–6.72 (m, H), 5.76 (s, 0.43 H), 5.70 (s, 0.57 H), 4.76–5.18 (m, 2 H), 1.44 (d, *J* 7, 1.29 H) and 1.14 (d, *J* 7, 1.71 H) (Found: C, 79.5; H, 6.5; N, 4.4. Calc. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23%).

2-(α-*Hydroxyoctyl*)-N-(α-*phenylethyl*)*benzamide* **2a–3**. ν_{max}(neat)/cm^{-1} 3300, 1760 and 1705; δ_H(90 MHz, $CDCl_3$) 7.10–8.05 (m, 10 H), 6.65 (br s, 1 H), 5.12–5.65 (m, 1 H), 4.72 (s, 1 H) and 0.78–2.20 (m, 18 H) (Found: C, 77.9; H, 8.8; N, 4.0. Calc. for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84; N, 3.96%).

2-(α-*Hydroxypentyl*)-3-*methoxy*-N-(α-*phenylethyl*)*benzamide* **2b–1**. ν_{max}(neat)/cm^{-1} 3310 and 1755; δ_H(MHz, $CDCl_3$) 6.70–7.85 (m, 9 H), 5.05–5.24 (m, 1 H), 4.58 (br s, 1 H), 3.45–4.10

(m, 4 H) and 0.50–2.16 (m, 12 H) (Found: C, 73.8; H, 7.8; N, 4.0. Calc. for $C_{21}H_{27}NO_2$: C, 73.87; 7.97; N, 4.10%).

2-(α-*Hydroxybenzyl*)-3-*methoxy*-N-(α-*phenylethyl*)*benzamide* **2b–2**. ν_{max}(neat)/cm^{-1} 3310 and 1752; δ_H(MHz, $CDCl_3$) 6.36–7.44 (m, 14 H), 5.83–6.37 (m, 1 H), 5.44–5.82 (br s, 1 H), 4.60 (q, *J* 7, 1 H), 3.56 (s, 3 H), 1.36 (d, *J* 7, 1.62 H) and 0.94 (d, *J* 7, 1.38 H) (Found: C, 76.6; H, 6.3; N, 3.8. Calc. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%).

N-(α-*Benzyl*-β-*methoxyethyl*)-2-(α-*hydroxypentyl*)*benzamide* **2c–1**. ν_{max}(neat)/cm^{-1} 3290, 1740 and 1635; δ_H(90 MHz, $CDCl_3$) 6.95–8.00 (m, 9 H), 6.38–6.60 (m, 1 H), 4.36–4.70 (m, 2 H), 2.70–3.95 (m, 8 H) and 0.65–2.05 (m, 9 H) (Found: C, 74.3; H, 8.4; N, 3.8. Calc. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94%).

N-α-*Benzyl*-β-*methoxyethyl*-2-(α-*hydroxybenzyl*)*benzamide* **2c–2**. ν_{max}(neat)/cm^{-1} 3310, 1760 and 1640; δ_H(90 MHz, $CDCl_3$) 6.20–7.62 (m, 15 H), 3.68–4.24 (m, 3 H) and 2.50–3.42 (m, 7 H) (Found: C, 76.5; H, 6.8; N, 3.7. Calc. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73%).

N-(α-*Benzyl*-β-*methoxyethyl*)-2-(α-*hydroxypentyl*)-3-*methoxybenzamide* **2d–1**. ν_{max}(neat)/cm^{-1} 3290, 1745 and 1640; δ_H(90 MHz, $CDCl_3$) 5.96–7.52 (m, 9 H), 4.02–4.36 (m, 1 H), 3.66 (br s, 1 H), 2.36–3.46 (m, 11 H) and 0.52–2.16 (m, 9 H) (Found: C, 71.4; H, 8.1; N, 3.7. Calc. for $C_{23}H_{31}NO_4$: C, 71.69; H, 8.11; N, 3.64%).

N-(α-*Benzyl*-β-*methoxyethyl*)-2-(α-*hydroxybenzyl*)-3-*methoxybenzamide* **2d–2**. ν_{max}(neat)/cm^{-1} 3310, 1760 and 1635; δ_H(90 MHz, $CDCl_3$) 5.84–7.48 (m, 14 H), 3.80–4.18 (m, 2 H) and 2.30–3.78 (m, 11 H) (Found: C, 73.9; H, 6.5; N, 3.6. Calc. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.46%).

General Procedure for Preparation of Optically Active 3-*Substituted Phthalides*.—3-*Butylphthalide* **3a–1** (*Entry 7*). A solution of the adduct **2c–1** (diastereoisomeric ratio I/II = 90:10) (0.40 g, 1.13 mmol) in dioxane (20 cm^3) containing 5% HCl (3 cm^3) was heated at reflux for 3 h. After cooling, the acidic solution was extracted with ether (3 × 20 cm^3) and the extract dried and concentrated. Column chromatography of the residue on silica gel with hexane–ethyl acetate (7:1) as eluent afforded **3a–1** as a pale yellow oil (0.20 g, 95%): b.p. 131.0–132.0 °C/1.0 Torr; $[\alpha]_D^{17}$ − 47.3 (*c* 0.73, $CDCl_3$); ν_{max}(neat)/cm^{-1} 2960 and 1765; δ_H(90 MHz, $CDCl_3$) 7.20–8.30 (m, 4 H), 5.35–5.80 (m, 1 H) and 0.64–2.40 (m, 9 H) (Found: C, 75.6; H, 7.5. Calc. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%).

3-*Phenylphthalide* **3a–2** (*Entry 8*). M.p. 117.0–118.0 °C; $[\alpha]_D^{19}$ − 39.5 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2950 and 1770; δ_H(90 MHz, $CDCl_3$) 6.54–7.26 (m, 9 H) and 5.80 (s, 1 H) (Found: C, 79.8; H, 4.8. Calc. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79%).

3-*Heptylphthalide* **3a–3** (*Entry 3*). B.p. 168.0–160.0 °C)/0.9 Torr; $[\alpha]_D^{20}$ −2.7(*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2965 and 1763; δ_H(90 MHz, $CDCl_3$) 7.14–7.93 (m, 4 H), 5.30–5.53 (m, 1 H) and 0.68–2.20 (m, 15 H) (Found: C, 77.4; H, 8.7. Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%).

3-*Butyl*-5-*methoxyphthalide* **3b–1** (*Entry 9*). B.p. 159.0–160.0 ° C/0.8 Torr; $[\alpha]_D^{20}$ − 41.4 (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2960 and 1770; δ_H(90 MHz, $CDCl_3$) 6.92–7.73 (m, 3 H), 5.25–5.63 (m, 1 H), 3.92 (s, 3 H) and 0.55–2.52 (m, 9 H) (Found: C, 70.8; H, 7.5. Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%).

5-*Methoxy*-3-*phenylphthalide* **3b–2** (*Entry 10*). M.p. 147.0–148.0 °C; $[\alpha]_D^{21}$ − 46.0 (*c* 1.03, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2950 and 1772; δ_H(90 MHz, $CDCl_3$) 6.40–7.24 (m, 8 H), 5.98 (s, 1 H) and 3.48 (s, 3 H) (Found: C, 74.7; H, 5.2. Calc. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%).

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