Novel Sparteine-Mediated Enantio-Dichotomic Formal Synthesis of (*R*)-(−)- and (*S*)-(+)-Curcuphenol

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Received October 17, 2000

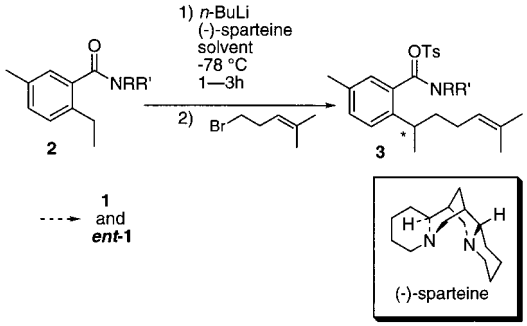
High and opposite enantiodiscriminations were observed between tertiary amides and secondary amides in the sparteine-mediated lateral metalation−allylation of 2-ethyl-*m*-toluamide derivatives (**2a**, **2e**). The results described above have been applied for the formal synthesis of both enantiomers of curcuphenol. The brief mechanistic studies suggested that stereoinformation was introduced after the deprotonation step.

Introduction

The recent progress in various aspects of chiral ligand-mediated organometallic chemistry has brought great benefits to the asymmetric synthesis of optically active compounds including natural products and related biologically active compounds.[1] In general, one of the two antipodal chiral ligands produces adducts with either an (*R*) or (*S*) configuration, although there are a few exceptional examples affording both enantiomers of adducts by only one of the two antipodal ligands.[2] In previous study, we reported that the opposite enantioselectivity was observed between *N*,*N*-diisopropyl *o*-allyloxymethylbenzamide and *N*,*N*-diethyl *o*-allyloxymethylbenzamide on the (−)-sparteine-mediated enantioselective [2,3]-Wittig rearrangement of *N*,*N*-dialkyl *o*-allyloxymethylbenzamides.[3] We presently report on the moderate to high and opposite enantiodiscrimination between tertiary amides and secondary amides in the (−)-sparteine-mediated lateral metalation−substitution reactions (Table 1, Scheme 1). We applied these findings for the formal synthesis of both enantiomers of curcuphenol (**1** and *ent*-**1**). The findings of a brief mechanistic study suggested that an enantiodetermining step in both sequences (**2a** → **4a**, **2e** → **4e** in Scheme 1) occurred after deprotonation. This method makes it possible to carry out a preparation of a pair of optically active compounds with opposite configurations at the stereogenic center. In medicinal chemistry, the high optical purity of each target molecule is of course crucial and preparations of both of the (*R*) and (*S*) enantiomers of the molecules are often needed. A pair of enantiomers showing these factors is curcuphenol (**1** and *ent*-**1**).

Even though much attention has been paid to these bisabolane sesquiterpenes which showed different activities between each enantiomers,[4] only two enantioselective syntheses of curcuphenol have been reported.[4c,4d] In the present study, we attempted to synthesize both enantiomers of curcuphenol by the (−)-sparteine-mediated enantioselective lateral metalation−substitution reactions of *o*-ethylbenzamide derivatives, following precedents developed by Beak et al.[2]

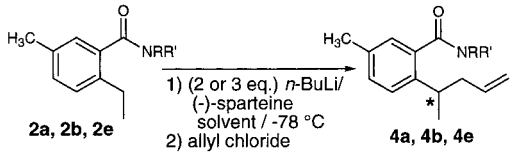
Table 1. Opposite Enantioselectivity between Tertiary Amides (2a, 2b) and Secondary Amides (2c−e) in the Sparteine-Mediated Lateral Metalation Substitutions



entry	product	R	R′	solvent[a]	yield (%)	ee (%)	$[\alpha]_D$
1[b]	**3a**	*i*-Pr	*i*-Pr	pentane	66	92	+9.39
2	**3b**	Et	Et	pentane	43	25	+2.2
3[c]	**3c**	H	*i*-Pr	pentane/MTBE (10/1)	55	16	−1.56
4[c]	**3d**	H	*c*-Hex	pentane/MTBE (5/1)	31	15	−1.3
5[c]	**3e**	H	*n*-Oct	pentane	51	44	−5.5

[a] MTBE = *tert*-butyl methyl ether. [b]With 2.2 equiv of *sec*-BuLi, 55% of **3a** with 48% ee was obtained. [c]3.3 Equivalents of *n*-BuLi and (−)-sparteine were used for effective metalation.

Scheme 1. Enantioselective Metalation−Allylation of 2a, 2b, 2c



product	R	R'	solvent	yield(%)	$[\alpha]_D$	ee (%)
4a	*i*-Pr	*i*-Pr	pentane	78	+6.8	n. d.*
4b	Et	Et	toluene	50	+7.8	n. d.*
4e	H	Octyl	pentane	56	- 6	80%

n.d.* = Optical yield was not determined at this stage.

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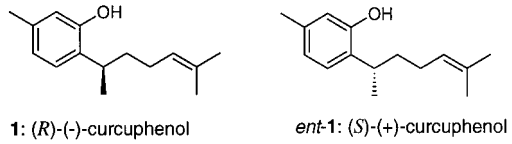
10.1021/jo001485c CCC: $20.00
Published on Web 03/20/2001

Chart 1. Structure of Curcuphenol



1: (*R*)-(-)-curcuphenol *ent*-**1**: (*S*)-(+)-curcuphenol

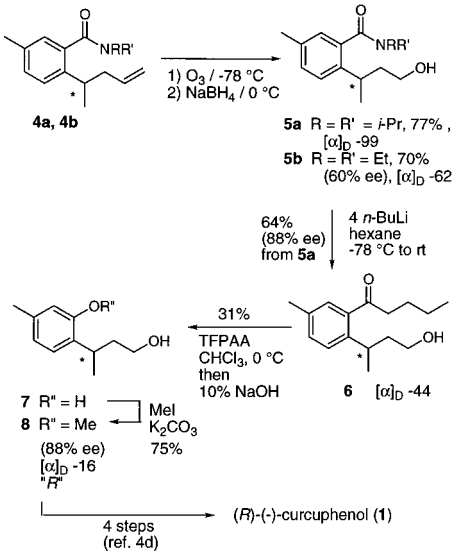
Results and Discussions

Our initial goal of preparing both enantiomers of curcuphenol envisioned an enantioselective introduction of a side chain and a stereogenic center in a single step (Table 1). According to Beak's procedure, lithiation of a series of *o*-ethylbenzamide derivatives (**2a**−**e**) with *n*-BuLi in the presence of (−)-sparteine at −78 °C and careful treatment with 5-bromo-2-methyl-2-pentene afforded the optically active intermediates (**3a**−**e**) in moderate to high enantiomeric ratios (Table 1).

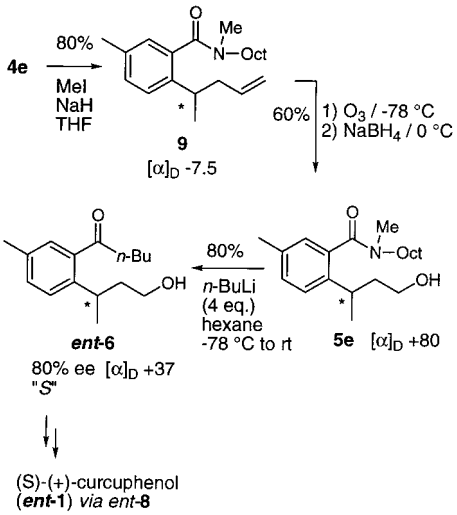
The *N*,*N*-diisopropyl carbamyl group resulted in highly enantioselective alkylation to afford **3a** (92% ee) (entry 1), but the subsequent conversions of the *N*,*N*-diisopropyl carbamyl group to a hydroxyl group by way of acidic or basic hydrolysis or reduction with DIBAH, or cleavage with $La(OTf)_3$−MeLi[5]-mediated alkylation, MeLi, or *n*-BuLi[6] could not be realized. It is noted that **2a** and **2b** showed a similar configurational selectivity in this alkylation and afforded the products with similar signs of optical rotation (see entries 2, 3), while the substrates with one *N*-alkyl group afforded the products with an opposite sign of optical rotation compared with those of **3a** and **3b** (entries 3−5). These findings differ from our enantioselective [2,3]-Wittig rearrangement analogy.[7] The results in Table 1 (entries 3−5) also show that the *N*-octyl group was the most suitable director in all three *N*-alkyl groups because it could form the most enantioenriched product in all three. From these preliminary results, we reexamined the strategy for the synthesis of curcuphenol and carried out an alternative approach shown in Scheme 1, Scheme 2, and Scheme 3. Presently, we attempted to obtain enantiomerically enriched **8** and *ent*-**6** to complete the formal synthesis of both enantiomers of curcuphenol. Compound **8** is an enantiomer of a reported intermediate and is known to have an (*R*)-configuration.[4d]

Metalation of *N*,*N*-diisopropyl-2-ethyl-*m*-toluamide (**2a**) and *N*,*N*-diethyl-2-ethyl-*m*-toluamide (**2b**) at −78 °C in the presence of (−)-sparteine followed by the careful treatment with allyl chloride afforded optically active allyl adducts (**4a**, **4b**). The compounds (**4a**, **4b**) were subsequently exposed to ozonolysis and in situ reduction by sodium borohydride to afford optically active alcohols

Scheme 2. Application for the Formal Synthesis of (*R*)-(−)-Curcuphenol



Scheme 3. Application for the Formal Synthesis of (S)-(+)-Curcuphenol



(**5a**, **5b**) (Scheme 2). The % ee of **5b** (60%) was obtained by HPLC analysis using a CHIRALCEL OD column. Although the % ee of **5a** was not found at this stage, it was found to be 88% when **5a** was converted to **6** by excess amounts of *n*-BuLi (Scheme 2).

Baeyer−Villiger oxidation of **6** by trifluoroperacetic acid (TFPAA) and successive hydrolysis afforded a phenol (**7**) in moderate yields (31%). Conversion by MeI/K_2CO_3 gave a desired substituted anisole (**8**). The absolute configuration of **8** was found to be (*R*) by the comparison of the optical rotation reported by Serra et al.[4d] Next, (−)-sparteine-mediated lateral metalation−substitution of *N*-octylbenzamide derivative (**2e**) was carried out. Metalation at −78 °C with 3.3 equiv of *n*-BuLi−(−)-sparteine mixture, and the following careful treatment with allyl chloride afforded an adduct (**4e**) in 56% yields (80% ee) (Scheme 1). The adduct **4e** was converted to an *N*-methyl-*N*-octylamide derivative (**9**) which led to **5e** that was further converted to an *ent*-**6** by alkylation with *n*-BuLi (Scheme 3).

According to the same experimental procedures used in the synthesis of **8**, *ent*-**6** can be transformed to *ent*-**8**. In conclusion, we achieved the (−)-sparteine-mediated

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(7) In the case of the (−)-sparteine-mediated [2,3]-Wittig rearrangement of *N*,*N*-dialkyl and *N*-alkyl *o*-allyloxymethylbenzamides, an opposite enantioselectivity was observed between the *N*,*N*-diisopropyl carbamyl group and the *N*,*N*-diethyl carbamyl group, and the *N*,*N*-diethyl carbamyl group showed the same selectivity as the *N*-isopropyl carbamyl group.

enantioselective formal synthesis of both enantiomers of curcuphenol because the efficient synthesis of *ent*-**1** from *ent*-**8** in four steps is known.[4d]

To interpret the opposite configurational result s in this sparteine-mediated lateral metalation−substitution, the following experiment was carried out. (−)-Sparteine (3.3 equiv) was added to a solution of racemic lithiated **2e** followed by quenching with allyl chloride. As a result, the enantioenriched product (**4e**) in 54% yields (68% ee) with an (*S*) configuration was formed. This result indicates that stereoinformation is transferred after deprotonation. This result is also consistent with that of Beak's mechanistic studies of sparteine-mediated lateral metalation−substitution of *N*,*N*-dialkyl *o*-ethylbenzamides. However, further investigations are required to confirm whether enantioenrichment in the sequence with lithiated **2e**-(−)-sparteine arises from a dynamic kinetic resolution or a dynamic thermodynamic resolution.

Experimental Section

^{1}H NMR spectra were recorded on a JEOL JNM-FX-270 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm) relative to TMS. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of a doublet; m, multiplet; b, broad. ^{13}C NMR spectra were proton decoupled and recorded on a JEOL-FX-270 spectrometer using a carbon signal of the deuterated solvents as an internal standard. Mass spectra (MS) were obtained on JMS-HX/HX-110A instruments. Elemental analyses were performed by the Center for Organic Elemental Microanalysis in Kyoto University. Optical rotations were measured on a DIP 360 (Japan Spectroscopic Co.) polarimeter at the sodium D-line and ambient temperature. Analytical HPLC was performed on a Waters 510/486 unit, and the wavelength detector was operated at 254 nm. Chiral HPLC analyses were performed using CHIRALCEL OD columns at room temperature unless stated otherwise. Enantiomeric purity assays using chiral HPLC columns were completed with both racemic and enantioenriched materials and repeated at least once to ensure accuracy of the method used. Melting points were measured on a Yanagimoto micro melting point apparatus without correction. Flash chromatography was performed with silica gel (C-200) obtained from Wakenyaku Co. Analytical thin-layer chromatography was performed on Merck Silica gel 60 F_{254} aluminum sheets and the visualization was accomplished using a UV lamp. THF was distilled from sodium/benzophenone under an argon atmosphere. Pentane and diethyl ether were distilled from calcium hydride under an argon atmosphere. Toluene was distilled from sodium. (−)-Sparteine and *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under nitrogen and stored under argon. Solution of *n*-BuLi in hexane and *sec*-BuLi in cyclohexane were obtained from KANTO CHEMICAL CO. or Aldrich and titrated periodically according to the method of Watson and Eastham.[9] A −78 °C bath refers to a mixture of dry ice in acetone.

Synthesis of 3a. Typical Procedure (sparteine-mediated lateral metalation−substitution). To a solution of (−)-sparteine (0.25 mL, 1.1 mmol) in freshly distilled pentane (15 mL) at −78 °C was added *n*-BuLi (0.76 mL, 1.1 mmol). The reaction mixture was stirred for 10 min, and then a precooled solution of *N*,*N*-diisopropyl-2-ethyl-5-methylbenzamide (**2a**) (123 mg, 0.5 mmol) in pentane (15 mL) was added via a cannula. The resulting burgundy solution was stirred for 1 h at −78 °C, and then 0.27 mL (2.0 mmol) of 5-bromo-2-methyl-2-pentene in 5 mL of pentane was added. After the reaction was completed, methanol was added to the reaction mixture, and then the mixture was treated with saturated aqueous NH_4-Cl and then separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with 5% HCl, water, and then brine. The organic layer was dried over $MgSO_4$ and concentrated to a small volume. Purification by flash chromatography afforded a pure compound (**3a**) as a colorless oil (108 mg, 66% yield); $[\alpha]_D$ +9.4 (*c* 1.64 in $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06−1.26 (m, 9H), 1.56−1.66 (m, 14H), 1.90 (m, 2H), 2.30 (s, 3H), 2.75 (m, 1H), 3.46 (m, 1H), 3.73 (m, 1H), 5.12 (m, 1H), 6.87 (d, 1H, J = 7.59 Hz), 7.17(dd, 1H, J = 1.98 Hz, J = 7.59 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.5, 20.3, 20.4, 20.7, 20.8, 20.9, 22.4, 25.6, 25.9, 34.9, 35.8, 45.5, 50.4, 124.1, 125.1, 126.1, 129.0, 131.1, 135.3, 136.9, 139.8, 170.4. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.24; H, 10.64; N, 4.26. Found: C, 79.95; H, 10.65; N, 4.17. The enantiomeric excess was found to be 92% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 200/1 as eluent (flow rate 0.5 mL/min) at 254 nm. The major enantiomer was eluted after 11.5 min, and the minor enantiomer was eluted after 15.8 min.

Synthesis of Optically Active 3b from 2b According to the typical procedure for the synthesis of **3a**, the reaction was carried out using 0.5 mmol (109 mg) of *N*,*N*-diethyl-2-ethyl-5-methylbenzamide (**2b**), (−)-sparteine (0.25 mL, 1.1 mmol), and *n*-BuLi (0.76 mL, 1.1 mmol). The resulting burgundy solution was stirred for 1 h at −78 °C and then quenched with 0.27 mL (2.0 mmol) of 5-bromo-2-methyl-2-pentene in 5 mL of pentane. Purification by flash chromatography afforded a pure compound (**3b**) as a colorless oil; 64 mg (43%). $[\alpha]^{20}_D$ +2.2 (*c* 2.7 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01−1.33 (m, 9H), 1.55(s, 3H), 1.67 (s, 3H), 1.63 (m, 2H), 1.90 (m, 2H), 2.31 (s, 3H), 2.71 (m, 1H), 3.01−3.20 (m, 2H), 3.35 (m, 1H), 3.83 (m, 1H), 5.08 (m, 1H), 6.93 (s, 1H), 7.15 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.8, 14.0, 17.6, 20.7, 22.7, 25.6, 26.3, 34.7, 38.1, 42.3, 43.3, 124.4, 125.5, 126.1, 130.1, 131.3, 135.6, 136.5, 140.0, 172.2. HRMS (FAB+) Calcd for $C_{20}H_{31}NO$ (302.24856, MH^+); Found: 302.2483. The enantiomeric excess was found to be 25% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.5 mL/min) at 254 nm. The major enantiomer was eluted after 23.5 min, and the minor enantiomer was eluted after 29 min.

Synthesis of 3c from 2c According to the typical procedure for the synthesis of **3a**, the reaction was carried out using 1.46 mmol (300 mg) of **2c**, (−)-sparteine (1.1 mL, 4.8 mmol), and *n*-BuLi (3.4 mL, 4.8 mmol) in freshly distilled pentane/MTBE (10/1) (30 mL). The resulting burgundy solution was stirred for 1 h at −78 °C and then quenched with 0.8 mL (6.0 mmol) of 5-bromo-2-methyl-2-pentene in 5 mL of solvent. Purification by flash chromatography afforded a pure compound (**3c**) as a white solid; 231 mg (55%). $[\alpha]^{21}_D$ −1.34 (*c* 0.9 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (m, 9H), 1.51 (s, 3H), 1.64 (s, 3H), 1.59 (m, 2H), 1.90 (m, 2H), 2.32 (s, 3H), 3.08 (m, 1H), 4.27 (m, 1H), 5.07 (m, 1H), 5.51 (m, 1H), 7.07 (m, 1H), 7.17 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.5, 20.7, 22.5, 22.6, 22.7, 25.6, 26.3, 34.6, 38.1, 41.6, 124.3, 126.1, 126.8, 130.3, 131.2, 135.0, 137.0, 142.0, 170.0. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.38; H, 10.17; N, 4.87. Found: C, 79.28; H, 10.08; N, 4.73. The enantiomeric excess was found to be 16% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.5 mL/min) at 254 nm. The major enantiomer was eluted after 34 min, and the minor enantiomer was eluted after 24 min.

Synthesis of 3d from 2d According to the typical procedure for the synthesis of **3a**, the reaction was carried out using 1 mmol (245 mg) of **2d**, (−)-sparteine (0.76 mL, 3.3 mmol) and *n*-BuLi (2.3 mL, 3.3 mmol) in freshly distilled pentane/MTBE (5/1) (25 mL) at −78 °C. The resulting burgundy solution was stirred for 1 h at −78 °C and then 0.67 mL (5.0 mmol) of 5-bromo-2-methyl-2-pentene in 5 mL of pentane was added.

(8) Sparteine-mediated lateral metalation−substitutions of *o*-ethylbenzamides are known to proceed via an asymmetric substitution pathway (dynamic kinetic resolution), and this suggested that the stereoinformation of **4a** and **4b** are also determined after deprotonation of **2a** and **2b**, respectively. See ref 2c.

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Purification by flash chromatography afforded a pure compound (**3d**) as a white solid; 100 mg (31%). $[\alpha]_D^{25}$ −1.84 (*c* 0.87 $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (d, 3H, J = 6.93 Hz), 1.44 (s, 3H), 1.57 (s, 3H), 1.10−2.20 (m, 14H), 2.23 (s, 3H), 2.98 (m, 1H), 3.88 (m, 1H), 4.98 (m, 1H), 5.50 (m, 1H), 6.99 (s, 1H), 7.10 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.6, 20.8, 22.7, 24.8, 24.8, 25.5, 25.7, 26.3, 33.1, 33.2, 34.7, 38.1, 48.4, 124.4, 126.2, 126.9, 130.4, 131.3, 135.1, 137.1, 142.0, 169.7. Anal. Calcd for $C_{22}H_{33}NO$: C, 80.67; H, 10.16; N, 4.28. Found: C, 80.83; H, 10.45; N, 4.25. The enantiomeric excess was found to be 15% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 50/1 as eluent (flow rate 0.7 mL/min) at 254 nm. The major enantiomer was eluted after 28 min, and the minor enantiomer was eluted after 16 min.

Synthesis of 3e from 2e According to the typical procedure for the synthesis of **3a**, the reaction was carried out using 1 mmol (275 mg) of **2e**, (−)-sparteine (0.77 mL, 3.3 mmol) and *n*-BuLi (2.3 mL, 3.3 mmol) in freshly distilled pentane (20 mL) at −78 °C. The resulting clear green solution was stirred for 1 h at −78 °C and then quenched with 0.67 mL (5.0 mmol) of 5-bromo-2-methyl-2-pentene. Purification by flash chromatography afforded a pure compound (**3e**) as a colorless oil; 182 mg (51%). $[\alpha]_D^{20}$ −5.5 (*c* 2.2 $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.22 (d, 3H, J = 6.93 Hz), 1.28 (m, 11H), 1.50 (s, 3H), 1.65 (s, 3H), 1.56 (m, 3H), 1.89 (m, 2H), 2.31 (s, 3H), 3.05 (m, 1H), 3.41 (m, 2H), 5.07 (m, 1H), 5.69 (m, 1H), 7.08 (s, 1H), 7.18 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 17.6, 20.8, 22.6, 22.8, 25.6, 26.3, 27.0, 29.0, 29.2, 29.3, 29.7, 31.8, 34.7, 38.1, 39.8, 124.5, 126.2, 127.0, 130.5, 131.3, 135.1, 137.0, 142.0, 170.5.Anal. Calcd for $C_{24}H_{39}NO$: C, 80.60; H, 11.00; N, 3.92. Found: C, 80.50; H, 11.04; N, 3.82. The enantiomeric excess was found to be 44% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.5 mL/min) at 254 nm. The major enantiomer was eluted after 59 min, and the minor enantiomer was eluted after 42 min.

***N,N*-Diisopropyl-2-(1-allyl)ethyl-5-methylbenzamide (4a)** To a −78 °C solution of *n*-BuLi (0.56 mL, 0.9 mmol, 1.6 M solution in hexane) and (−)-sparteine (0.21 mL, 0.9 mmol) in pentane (15 mL) was added **2a** (124 mg, 0.5 mmol) in pentane (15 mL) via a cannula. (**2a** in pentane was precooled to −40 °C before cannulation.) The resulting purple solution was kept under −50 °C for 1.5 h and then cooled to −78 °C and quenched with allyl chloride (0.082 mL, 1.0 mmol) in pentane (allyl chloride solution was cooled to −78 °C before cannulation) at this temperature. The mixture was stirred for 5 h at −78 °C. When the solution turned colorless, methanol was added to the resulting colorless solution followed by extractive work up with ethyl acetate and NH_4Cl aq. The aqueous layer was extracted twice with ethyl acetate, and the organic layers were combined. The organic layer was washed with 5% HCl, brine, dried over $MgSO_4$, and then concentrated. The crude product was purified by flash chromatography to afford pure *N,N*-Diisopropyl-2-(1-allyl)ethyl-5-methylbenzamide (**4a**) as a colorless oil (111 mg, 78%); $[\alpha]_D^{22}$ +6.8 (*c* 3.02 $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (d, 6H, J = 6.6 Hz), 1.22 (m, 3H), 1.55 (d, 3H, J = 6.93 Hz), 1.56 (d, 3H, J = 6.93 Hz), 2.30 (s, 3H), 2.10−2.52 (m, 2H), 2.85 (m, 1H), 3.48 (m, 1H), 3.72 (m, 1H), 5.0 (m, 2H), 5.73 (m, 1H), 6.88 (s, 1H), 7.09−7.26 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.1, 20.4, 20.5, 20.6, 20.7, 20.8, 35.0, 41.4, 45.5, 50.4, 115.8, 125.1, 125.9, 128.9, 135.1, 137.0, 137.7, 140.0, 170.4. HRMS (FAB+) Calcd for $C_{19}H_{30}NO$ (288.2329, MH^+); Found: 288.2323.

***N,N*-Diisopropyl-2-(1-hydroxyethyl)ethyl-5-methylbenzamide (5a)** To a −78 °C solution of *N,N*-diisopropyl-2-(1-allylethyl)-5-methylbenzamide (**4a**) (61 mg, 0.21 mmol, $[\alpha]_D$ +6.8) in MeOH (15 mL), O_3 gas was passed through for 30 min. After the reaction was completed, excess amounts of $NaBH_4$ (500 mg) was added at −10 °C. Saturated NH_4Cl aq was added to the reaction mixture, and the mixture was concentrated in vacuo. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with 5% HCl, water, and brine and concentrated after drying over $MgSO_4$. Purification by flash chromatography afforded 47 mg (77%) of pure **5a** as a colorless oil; $[\alpha]_D^{25}$ −99 (*c* 2.92 $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.13 (d, 6H, J = 6.93 Hz), 1.25 (d, 3H, J = 6.93 Hz), 1.57 (m, 6H), 1.94 (m, 1H), 2.32 (s, 3H), 2.94 (m, 1H), 3.14 (m, 1H), 3.41−3.56 (m, 2H), 3.78 (m, 1H), 4.50 (m, 1H), 6.86 (s, 1H), 7.16 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.2, 20.3, 20.7, 20.8, 20.9, 23.4, 31.7, 42.4, 46.2, 51.2, 59.2, 124.7, 126.5, 129.8, 135.7, 138.0, 139.3, 172.4. HRMS (FAB+) Calcd for $C_{18}H_{30}NO_2$ (292.2278, MH^+); Found: 292.2286.

(−)-2-(1-Hydroxyethyl)ethyl-5-methylvalerophenone (6) To a solution of **5a** (370 mg, 1.27 mmol) in 20 mL of hexane in −78 °C was slowly added *n*-BuLi (3.6 mL, 5.1 mmol, 1.4 M solution in hexane). A white precipitate was formed, and the reaction mixture was continuously stirred for 16 h at room temperature. The reaction mixture was worked up with saturated NH_4Cl aq and then separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated to a small volume. Purification by flash chromatography afforded 202 mg (64%) of the desired 2-(1-hydroxyethyl)ethyl-5-methylvalerophenone (**6**) as a colorless oil; $[\alpha]_D^{21}$ −44.0 (*c* 0.38 $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.26 Hz), 1.20 (d, 3H, J = 6.93 Hz), 1.38 (m, 2H), 1.68 (m, 3H), 1.95 (m, 1H), 2.36 (s, 3H), 2.87 (m, 2H), 3.25 (m, 2H), 3.48 (m, 1H), 7.24 (m, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 20.9, 22.3, 23.7, 26.5, 30.2, 41.8, 42.7, 60.1, 127.3, 127.4, 132.0, 135.2, 139.1, 141.9, 208.8. HRMS (FAB+) Calcd for $C_{16}H_{25}O_2$ (249.18555, MH^+); Found: 249.1860. The enantiomeric excess was found to be 88% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.5 mL/min) at 254 nm. The major enantiomer was eluted after 48 min, and the minor enantiomer was eluted after 43 min.

2-(1-Hydroxyethyl)ethyl-5-methylphenol (7). 2-(1-Hydroxyethyl)ethyl-5-methylvalerophenone (**6**) (100 mg, 0.4 mmol) in chloroform (2.5 mL) was added at 0 °C to a solution of trifluoroperacetic acid (TFPAA) in chloroform. (TFPAA was prepared by adding trifluoroacetic anhydride (0.56 mL, 4 mmol) to 30% aq H_2O_2 (0.6 mL) in chloroform (3.7 mL) at 0 °C.) The mixture was stirred at room temperature for 1 h and then poured into 2% aqueous potassium carbonate and extracted with chloroform. The extract was vigorously stirred with a few drops of 10% NaOH at 0 °C for 5 min and then acidified with 5% HCl. The chloroform layer was separated and washed with water and brine and then dried over $MgSO_4$. Concentration in vacuo and purification by flash chromatography afforded pure **7** (21 mg, 31%) as a pale yellow oil; $[\alpha]_D^{21}$ −24 (c, 2.3, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.93 Hz), 1.53 (m, 1H), 2.03 (m, 1H), 2.27 (s, 3H), 2.72 (m, 1H), 3.26−3.43 (m, 2H), 3.68 (m, 1H), 6.67(s, 1H), 6.74 (d, 1H, J = 7.59 Hz), 7.05 (d, 1H, J = 7.59 Hz). HRMS (FAB+) Calcd for $C_{11}H1_6O_2$ (180.11508, MH^+); Found; 180.1152.

2-(1-Hydroxyethyl)ethyl-5-methylanisole (8) To a stirred solution of **7** (23 mg, 0.14 mmol) in acetone (3 mL) were added potassium carbonate (100 mg) and iodomethane (50 μL). The mixture was refluxed for 3 h and then filtered. The filtrate was concentrated in vacuo, and the residue was diluted with ethyl acetate, washed with $Na_2S_2O_3$ aq, water, and brine, and then dried over $MgSO_4$. Solvent was removed in vacuo and purified by flash chromatography to afford 19 mg (75%) of 2-(1-hydroxyethyl)ethyl-5-methylanisole (**8**) as a colorless oil. The absolute configuration of this compound was determined as (*R*) by the negative sign of an optical rotation value. ^1H NMR (270 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.26 Hz), 1.64 (m, 1H), 1.90 (m, 1H), 2.0 (m, 1H), 2.33 (s, 3H), 3.31−3.57 (m, 3H), 3.82 (s, 3H), 6.76 (s, 1H), 6.77 (d, 1H, J = 7.91 Hz), 7.08 (d, 1H, J = 7.91 Hz). $[\alpha]_D^{20}$ −16 (*c* 1.58 $CHCl_3$). LRMS (FAB+) *m/z* (M^+) 194. The enantiomeric excess was found to be 88% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.7 mL/min) at 254 nm. The *R*-enantiomer was eluted after 66 min, and the *S*-enantiomer was eluted after 59 min.

***N,N*-Diethyl-2-(1-allyl)ethyl-5-methylbenzamide (4b).** According to the procedure described in the synthesis of *N,N*-diisopropyl-2-(1-allyl)ethyl-5-methylbenzamide (**4a**), 200 mg (0.91 mmol) of *N,N*-diethyl-2-ethyl-5-methylbenzamide (**2b**) was lithiated in toluene instead of hexane at −78 °C and 113 mg (48%) of **4b** was obtained; $[\alpha]^{26}_D$ +7.8 (*c* 2.2, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85−1.37 (m, 9H), 2.15−2.55 (m, 2H), 2.31 (s, 3H), 2.79 (m, 1H), 3.03−3.42 (m, 3H), 3.80 (m, 1H), 4.91−5.03 (m, 2H), 5.71 (m, 1H), 6.93 (m, 1H), 7.17 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.4, 13.6, 20.0, 22.3, 34.8, 37.9, 41.3, 42.6, 115.7, 125.5, 125.8, 129.2, 135.0, 136.1, 136.6, 139.7, 170.5. Anal. Calcd for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.41. Found: C, 78.48; H, 9.83; N, 5.22.

***N,N*-Diethyl-2-(1-hydroxyethyl)ethyl-5-methylbenzamide (5b)** According to the procedure described in the synthesis of **5a**, 70 mg (0.27 mmol) of **4b** was exposed to ozonolysis and the following reduction by $NaBH_4$ to afford 68 mg (98%) of *N,N*-diethyl-2- (1-hydroxethyl)ethyl-5-methylbenzamide (**5b**) was obtained; $[\alpha]^{26}_D$ −61.6 (*c* 1.48 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.03−1.36 (m, 10H), 1.88 (m, 1H), 2.34 (s, 3H), 2.84 (m, 1H), 3.07−3.90 (m, 7H), 6.91 (s, 1H), 7.18-(m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.8, 14.0, 20.9, 23.2, 31.7, 39.1, 42.4, 43.3, 59.3, 125.5, 126.5, 130.1, 135.6, 1365, 139.6, 172.3. HRMS (FAB+) Calcd for $C_{16}H_{26}NO_2$ (264.19648, MH^+); Found: 264.1961. The enantiomeric excess was found to be 60% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 400/3 as eluent (flow rate 0.7 mL/min) at 254 nm. The major enantiomer was eluted after 77.5 min, and the minor enantiomer was eluted after 68.5 min.

***N*-Octyl-2-(1-allyl)ethyl-5-methylbenzamide (4e).** According to the procedure described in the synthesis of **4a**, with 3.3 equiv of *n*-BuLi and (−)-sparteine, 200 mg (0.7 mmol) of *N*-octyl-2-ethyl-5-methylbenzamide (**2e**) was lithiated in pentane at −78 °C and 126 mg (56%) of **4e** was obtained; $[\alpha]^{21}_D$ −6 (*c* 3.9 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.23 (d, 3H, J = 6.6 Hz), 1.28 (m, 10H), 1.57 (m, 2H), 2.30 (s, 3H), 2.36 (m, 2H), 3.16 (m, 1H), 3.39 (m, 2H), 4.93 (m, 2H), 5.6−5.79 (m, 2H), 7.08 (bs, 1H), 7.18 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 20.7, 21.8, 22.5, 26.8, 29.0, 29.1, 29.5, 31.7, 34.7, 39.7, 42.4, 115.9, 126.2, 127.0, 130.3, 135.1, 136.7, 137.1, 141.2, 170.4. HRMS (FAB+) Calcd for $C_{21}H_{34}NO$ (MH^+, 316.26422); Found: 316.2630. The enantiomeric excess was found to be 80% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 400/3 as eluent (flow rate 0.5 mL/min) at 254 nm. The *R*-enantiomer was eluted after 76.5 min, and the *S*-enantiomer was eluted after 83 min.

***N*-Methyl-*N*-octyl-2-(1-allyl)ethyl-5-methylbenzamide (9).** To a 0 °C suspension of NaH (8 mg, 0.2 mmol, 60% oil suspension) in 0.5 mL of DMF was slowly added **4e** (35 mg, 0.1 mmol) in DMF, and the mixture was stirred for 30 min at room temperature. Iodomethane (25 mL, 0.4 mmol) was added, and the mixture was continuously stirred for 12 h. The reaction mixture was poured into NH_4Cl aq with ice and then extracted three times with diethyl ether. The combined ether layer was washed with water and brine and dried over $MgSO_4$. Concentration and purification by flash chromatography afforded 28.5 mg (80%) of **9**; $[\alpha]^{21}_D$ −7.5 (*c* 2.8 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.14−1.70 (m, 15H), 2.30 (s, 3H), 2.35 (m, 2H), *2.78 and *3.08 (s, totally 3H), 3.41−3.66 (m, 2H), 4.95 (m, 2H), 5.70 (m, 1H), 6.92 (s, 1H), 7.16 (m, 2H). Asterisks indicate the separated singlet methyl proton signals of diastereomers at the N atom. HRMS (FAB+) Calcd for $C_{22}H_{36}NO$ (330.27988, MH^+); Found: 330.2793.

***N*-Methyl-*N*-octyl-2-(1-hydroxyethyl)ethyl-5-methylbenzamide (5e)**. According to the procedure for the synthesis of **5a**, a −78 °C solution of *N*-methyl-*N*-octyl-2-(1-allyl)ethyl-5-methylbenzamide (**9**) (26 mg, 0.08 mmol, $[\alpha]_D$ −7.5) in MeOH (15 mL) was exposed to O_3 and then reduced by $NaBH_4$. The resulting residue after workup was purified by flash chromatography to provide 15.4 mg (60%) of **5e** as a colorless oil; $[\alpha]^{21}_D$ +80.4 (*c* 1.54 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.23 (d, 3H, J = 6.93 Hz), 1.21−1.93 (m, 14H), 2.32 (s, 3H), 2.83 and 3.09 (s, 3H), 2.90 (m, 1H), 3.15 (m, 2H), 3.56 (m, 2H), 6.91 (m, 1H), 7.18 (m, 2H). HRMS (FAB+) Calcd for $C_{21}H_{36}NO_2$ (334.2748, MH^+); Found: 334.2750.

***(S)*-(+)-2-(1-Hydroxyethyl)ethyl-5-methylvalerophenone (*ent*-6).** To a solution of **5e** (15 mg, 45 μmol) in 1 mL of hexane at −78 °C was slowly added *n*-BuLi (0.1 mL, 0.16 mmol, 1.6 M solution in hexane). White precipitates were formed, and the reaction mixture was continuously stirred for 4 h at room temperature. The reaction mixture was worked up with saturated NH_4Cl aq and then separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated to a small volume. Purification by preparative thin-layer chromatography (20 × 20 cm) (hexane: ethyl acetate = 4:1) afforded 8.3 mg (71%) of desired *ent*-**6**. The absolute configuration was determined as (*S*) from the positive sign of the optical rotation value; $[\alpha]^{21}_D$ +37 (*c* 0.83 $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.26 Hz), 1.20 (d, 3H, J = 6.93 Hz), 1.38 (m, 2H), 1.68 (m, 3H), 1.95 (m, 1H), 2.36 (s, 3H), 2.87 (m, 2H), 3.25 (m, 2H), 3.48 (m, 1H), 7.24 (m, 3H). LRMS (FAB+) *m*/*z* (MH^+) 249. The enantiomeric excess was found to be 80% and was obtained by HPLC on a Chiralcel OD column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 100/1 as eluent (flow rate 0.5 mL/min) at 254 nm.

Acknowledgment. We thank Professor Victor Snieckus (Department of Chemistry, Queen's University, Canada) for informative discussions and advice.

Supporting Information Available: Detailed description of experimental procedures and ^{1}H NMR, ^{13}C NMR spectral data, and analytical data for *N,N*-dialkyl-2,5-dimethylbenzamides, *N*-alkyl-*m*-toluamides, **2a**, **2b**, **2c**, **2d**, and **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001485C