Synthetic Applications of the β-Lithiation of β-Aryl Secondary Amides: Diastereoselective and Enantioselective Substitutions†

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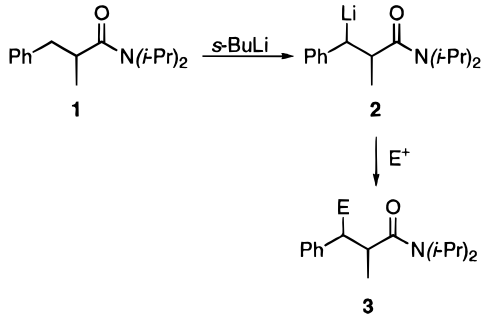
The sequence of β-lithiation and electrophilic substitution of β-aryl secondary amides is reported. The lithiations occur regioselectively at the β-position, and the resulting lithiated intermediates can be reacted with a wide range of electrophiles to give substituted products. Reactions of β-lithiated amides bearing an α-substituent provide substituted products with high diastereoselectivity. Electrophilic substitutions of β-lithiated *N*-methylamides in the presence of the chiral diamine (−)-sparteine provide highly enantioenriched products. The methodology is used to synthesize enantioenriched β-aryl β-substituted amides, acids, and lactones.

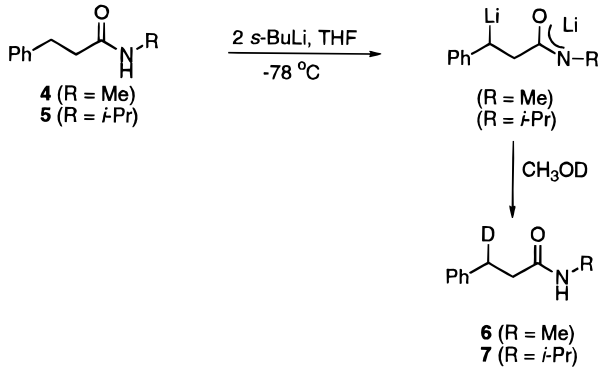
The β-lithiation of carboxamides provides lithiated intermediates which are synthetic equivalents of homoenolates.[1] We have previously reported β-lithiations of α-substituted diisopropylamides **1**.[2] These reactions are characterized by a kinetically directed deprotonation of a β-hydrogen instead of deprotonation of the thermodynamically more acidic hydrogen α to the amide carbonyl.[3] The lithiated intermediate **2** was shown to react with electrophiles to provide the β-substituted products **3** with high diastereoselectivity. The relative stereochemistry of **3** was found to be dependent on the electrophile.



The synthetic utility of these reactions is limited by the difficulty in removing the diisopropylamide functionality. As part of an ongoing effort to extend remote directed lithiation/substitution methodology, we have investigated β-aryl secondary amides. In this report, we show that lithiations of these compounds occur regioselectively in the β-position. Substitution reactions of the lithiated intermediates proceed with high diastereoselectivity in the presence of α-substituents. In the absence of α-substituents and in the presence of the chiral diamine (−)-sparteine the β-substituted products are formed with high enantioenrichments.[4] These reactions can be used to provide diastereoenriched and enantioenriched lactone and lactam products.

Results and Discussion

Lithiations of β-Phenyl Secondary Amides. Lithiations of β-phenyl tertiary amides which do not have an α-substituent occur at the α-position.[2] We expected that lithiation of the corresponding secondary amides would result in the initial formation of the *N*-lithio species which should discourage formation of the enolate species. As shown below, lithiation of either *N*-methyl-3-phenylpropanamide (**4**) or *N*-isopropyl-3-phenylpropanamide (**5**) with 2 equiv of *s*-BuLi in THF at −78 °C for 1 h produced a dianion which on reaction with CH_3OD provided either the β-substituted product **6** in 88% yield and 97% d_1 or **7** in 98% yield and 96% d_1.



A wide range of electrophiles have been assayed in this reaction, and formation of products **8**−**30** is summarized in Table 1. Most of these electrophilic substitutions proceed in good yield from either **4** or **5** with no detectable substitution at the anionic amide nitrogen. The dilithiated intermediate reacts with alkyl halides in good yields (Table 1, entries 1−10). Reactions with bromochloroalkanes (Table 1, entries 5−7) illustrate that alkyl chlorides remain intact under the reaction conditions. Alkylations using the corresponding dibromoalkanes provided lower yields of the desired products and sideproducts including debrominated material and cross-coupling products.

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) For leading references and reviews on homoenolates, see: Kuwajima, I.; Nakamura, E. *Topics Curr. Chem.* **1991**, *155*, 1. Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409.

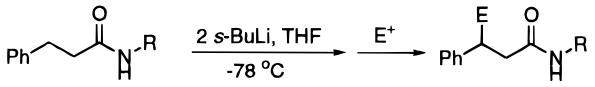
(2) Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938. Beak, P.; Hunter, J. E.; Jun, Y. M.; Wallin, A. P. *J. Am. Chem. Soc.* **1987**, *109*, 5403. Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350.

(3) Kinetic deprotonation of a less thermodynamically acidic hydrogen has been rationalized in terms of a complex-induced proximity effect (CIPE). Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(4) For a preliminary report of this work, see: Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516.

S0022-3263(95)02223-7 CCC: $12.00

Table 1. β-Lithiations and Electrophilic Substitutions of 4 and 5



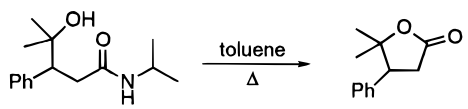
4 (R = Me)
5 (R = *i*-Pr)

8 - 30

entry	R	E^+	E	product	yield[a] (%)
1	Me	CH_3I	CH_3	**8**	93
2	*i*-Pr	CH_3I	CH_3	**9**	70
3	Me	*n*-BuI	*n*-Bu	**10**	94
4	*i*-Pr	*n*-BuI	*n*-Bu	**11**	93
5	*i*-Pr	$Cl(CH_2)_3Br$	$Cl(CH_2)_3$	**12**	79
6	*i*-Pr	$Cl(CH_2)_4Br$	$Cl(CH_2)_4$	**13**	80
7	*i*-Pr	$Cl(CH_2)_5Br$	$Cl(CH_2)_5$	**14**	77
8	Me	$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2$	**15**	78
9	Me	$PhCH_2Cl$	$PhCH_2$	**16**	55
10	*i*-Pr	$PhCH_2Cl$	$PhCH_2$	**17**	91
11	Me	TMSCl	TMS	**18**	87
12	*i*-Pr	TMSCl	TMS	**19**	75
13	Me	$Me_2PhSiCl$	Me_2PhSi	**20**	78
14	Me	Bu_3SnCl	Bu_3Sn	**21**	82
15	Me	Ph_2CO	$Ph_2C(OH)$	**22**	90
16	*i*-Pr	Ph_2CO	$Ph_2C(OH)$	**23**	96
17	Me	PhCHO	PhCH(OH)	**24**	78[b]
18	*i*-Pr	PhCHO	PhCH(OH)	**25**	81[b]
19	Me	$(CH_3)_2CO$	$(CH_3)_2C(OH)$	**26**	50
20	*i*-Pr	$(CH_3)_2CO$	$(CH_3)_2C(OH)$	**27**	>48[c]
21	Me	$(CH_2)_5CO$	$(CH_2)_5COH$	**28**	67
22	*i*-Pr	$PhCO_2CH_3$	PhCO	**29**	70
23	*i*-Pr	*n*-BuCOCl	*n*-BuCO	**30**	53

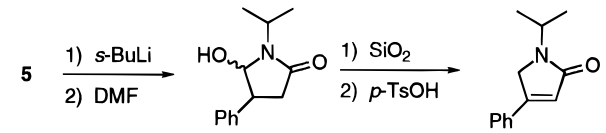
[a] Yield of isolated material unless otherwise noted. [b] Obtained as a 1:1 mixture of diastereomers. [c] Product **27** was not purified but converted to the lactone **31** in 48% overall yield.

Lithiation/substitution of **4** using TMSCl as an electrophile (Table 1, entry 11) provided the expected product **18** in 87% yield, while the lithiation/substitution of **5** with TMSCl (Table 1, entry 12) provided a 75% yield of **19**. Carbonyl compounds also functioned as efficient electrophiles (Table 1, entries 15−23). Use of benzophenone and benzaldehyde (Table 1, entries 15−18) provided good yields of substituted products. The initial product **27** from the use of acetone as the electrophile was not purified but was cyclized to lactone **31** in 48% overall yield.



27 **31**

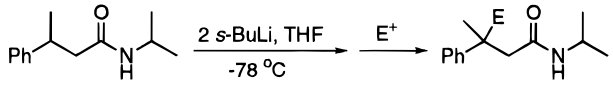
When DMF was used as the electrophile the unstable lactam **32** was found to be the major product. Treatment of crude **32** sequentially with silica gel and *p*-toluenesulfonic acid provided the α,β-unsaturated lactam **33** in 88% overall yield from **5**.



32 **33**

The sequence of lithiation/substitution at the tertiary benzylic position of **9** was investigated. Treatment of **9** with 2 equiv of *s*-BuLi followed by reactions with electrophiles provided moderate to good yields of β-substituted products **34**−**38** as shown in Table 2. Use of

Table 2. β-Lithiation and Electrophilic Substitution of 9



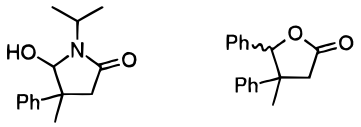
9 **34-38**

entry	E^+	E	product	yield[a] (%)
1	CH_3OD	D	**34**	87 (86 d_1)
2	CH_3I	CH_3	**35**	91
3	Ph_2CO	$Ph_2C(OH)$	**36**	61
4	PhCHO	PhCH(OH)	**37**	66[b]
5	DMF		**38**	71[c]

[a] Isolated yields of analytically pure material unless otherwise noted. [b] Isolated as lactone **39** as two diastereomers in 66% overall yield. [c] Isolated as lactam **38** in 71% yield.

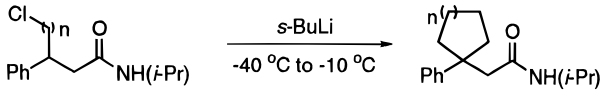
methanol-*d* and methyl iodide as electrophiles (Table 2, entries 1 and 2) provided 87% and 91% yields of **34** and **35**, respectively. Use of benzophenone and benzaldehyde as electrophiles (Table 2, entries 3 and 4) provided moderate yields of substituted products.

The crude product **37** from reaction with benzaldehyde was converted to lactone **39** to provide two separable diastereomers in 66% overall yield. Use of DMF as the electrophile (entry 5) provided a 71% yield of **38** as one diastereomer of undetermined relative stereochemistry.



38 **39**

The chloro derivatives **13** and **14** (Table 1, entries 6 and 7) were found to undergo β-lithiation followed by an intramolecular cyclization on warming to provide the cyclopentane derivative **40** and the cyclohexane derivative **41**. When the deprotonation-cyclization sequence was attempted at −78 °C, only unchanged starting materials were recovered. Addition of the *s*-BuLi to **13** and **14** at −40 °C followed by very gradual warming to −10 °C overnight afforded the desired cyclized products **40** and **41** in 95% and 79% yields, respectively.

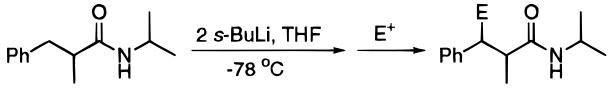


13, n = 4
14, n = 5

40, n = 1
41, n = 2

Diastereoselectivity in the Presence of α-Substituents. The diastereoselectivity of the β-lithiation in the presence of an α-methyl substituent was investigated. Amide **42** was lithiated with 2−2.3 equiv of *s*-BuLi in THF at −78 °C for 30 min followed by reaction with an electrophile to provide the β-substituted amides **43**−**47** (Table 3) in 70−95% yields with moderate to high diastereoselectivity. As shown in entry 1 (Table 3), the addition of CH_3OD provided the β-deuterated amide **43** in 95% yield as 92.5% d_1 material. Amide **43** was obtained as a 75:25 mixture of diastereomers based on the ^1H NMR spectrum. The β-protons of **42** appear as two distinct sets of doublets of doublets at 2.67 and 2.92 ppm while the β-proton of **43** appears as a multiplet at 2.65 ppm which integrates as 0.25 of a proton and as a doublet at 2.90 ppm which integrates as 0.75 of a proton. The position of deuteration was further verified by the

Table 3. β-Lithiation and Electrophilic Substitution of 42



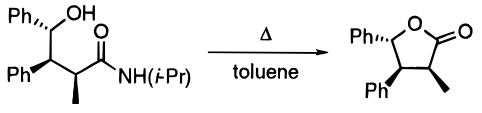
42 **43-47**

entry	E^+	E	product	yield[a] (%)
1	CH_3OD	D	**43**	95 (93 d_1)
2	CH_3I	CH_3	(*R*,S**)-**44**	87[b]
3	$Br(CH_2)_4Br$	$Br(CH_2)_3CH_2$	(*R*,S**)-**45**[c]	79
4	Ph_2CO	$Ph_2C(OH)$	(*R*,S**)-**46**[c]	95
5	PhCHO	PhCH(OH)	**47**	70[d]

[a] Isolated yield of analytically pure material. [b] Yield corrected for 14% recovered starting material. [c] Relative stereochemistry assigned by analogy to **44**. [d] Yield corrected for 22% recovered starting material.

observance of a triplet for the β-carbon resonance at 40.3 ppm in the ^{13}C NMR spectrum of **43**. The stereochemistries of the diastereomers were not assigned. The assignment of the regiochemistry for the remainder of the products in Table 3 was similarly based upon ^1H and ^{13}C NMR spectra and upon analogy to the β-deuterated product **43**. Use of methyl iodide as the electrophile provided the α,β-dimethyl amide **44** in 75% yield. The amide **44** was obtained as a single diastereomer and was determined to be of the *R*,S** configuration based upon ^1H and ^{13}C NMR comparison to authentic *R*,R** material.[5]

The β-lithiated intermediate from **42** reacts with $Br(CH_2)_4Br$ to provide the bromide **45** in 79% yield as a single diastereomer based on ^1H NMR and ^{13}C NMR analysis. Use of benzophenone as the electrophile afforded **46** in 95% yield also as a single diastereomer as shown in entry 4 (Table 3). The relative configurations of **45** and **46** are tentatively assigned as (*R*,S**) by analogy to **44**. The corresponding reaction sequence using benzaldehyde provided only one of the four possible diastereomers of **47** in 55% yield. The assignment of the relative stereochemistry of **47** is based on an X-ray crystal structure of the lactone **48** resulting from cyclization of **47**. The formation of **47** as a single diastereomer illustrates the potential of this reaction to be used for diastereoselective synthesis of three contiguous stereogenic centers in a single transformation.



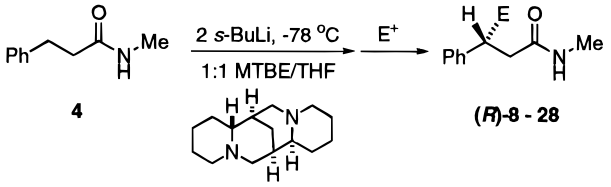
47 **48**

Enantioselectivity in the Presence of (−)-Sparteine. We have previously reported as preliminary results observations that the lithiation/substitutions of **4** provide β-substituted products in high enantioselectivities when the reactions are carried out in the presence of the chiral diamine (−)-sparteine (**49**).[4,6] If the lithiation reactions were carried out in the absence of (−)-sparteine and the chiral diamine was added to the reaction mixture prior to the addition of the electrophile, the products were obtained in high enantiomeric excess.[7]

(5) Hunter, J. E. Ph.D. Dissertation, University of Illinois at Urbana−Champaign, 1986.

(6) For related work, see: Hoppe, D.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158 and references cited therein.

Table 4. Yields and enantioselectivities for the lithiation of 4 in the presence of 49



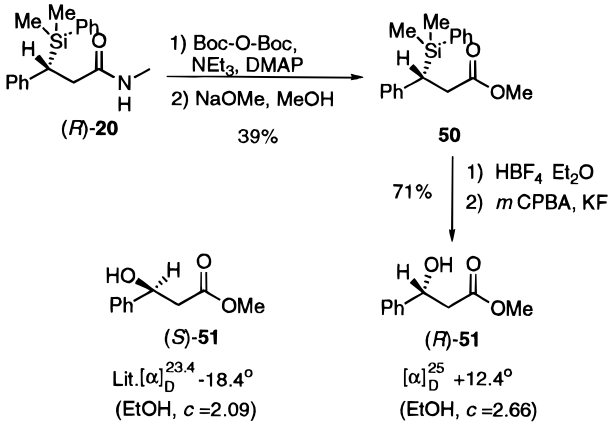
4 **(*R*)-8 - 28**

49

entry	E^+	E	product	yield[a] (%)	ee[c] (%)
1	CH_3I	CH_3	(*R*)-**8**	84[b]	78
2	$(CH_3)_2SO_4$	CH_3	(*R*)-**8**	80	59
3	*n*-C_4H_9I	*n*-C_4H_9	(*R*)-**10**	77[b]	88
4	*n*-C_4H_9Cl	*n*-C_4H_9	(*R*)-**10**	76	10
5	$PhCH_2Br$	$PhCH_2$	(*R*)-**16**	78[b]	80
6	$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2$	(*R*)-**15**	74	80
7	$(CH_3)_3SiCl$	$(CH_3)_3Si$	(*R*)-**18**	86[b]	94
8	$(CH_3)_2PhSiCl$	$(CH_3)_2PhSi$	(*R*)-**20**	68	80
9	$(n\text{-}C_4H_9)_3SnCl$	$(n\text{-}C_4H_9)_3Sn$	(*R*)-**21**	84	60
10	PhCHO	PhCH(OH)	(*R*)-**24**	63[b]	65[d]
11	$Ph_2C(O)$	$Ph_2C(OH)$	(*R*)-**22**	84[b]	73[e]
12	$(CH_2)_5C(O)$	$(CH_2)_5C(OH)$	(*R*)-**28**	65	54
13	$(CH_3)_2C(O)$	$(CH_3)_2C(OH)$	(*R*)-**26**	45	60

[a] Isolated yields. [b] From ref 4. [c] The ee's and absolute configurations were determined as described in the text. [d] The ee of the product was determined by conversion of **24** to **53** as described in the text and analysis by CSP HPLC. [e] Recrystallization of the product **22** from EtOAc provided 84% ee.

Yields and enantioselectivities for the lithiation/substitution of **4** in the presence of (−)-sparteine are summarized in Table 4. As can be seen in Table 4, yields are generally good, and the products can be obtained in 54−94% enantiomeric excesses. The degree of enantioenrichment was a function of the electrophile. For example, the use of methyl iodide (Table 4, entry 1) provides 84% yield of (*R*)-**8** in 78% ee, whereas dimethyl sulfate (Table 4, entry 2) provides comparable yields but a 59% ee. The difference between the use of *n*-butyl iodide (88% ee, Table 4, entry 3) and *n*-butyl chloride (10% ee, Table 4, entry 4)) also illustrates this effect. In general, electrophilic substitution with alkyl or silyl halides proceeded in good yield and enantioselectivities. In contrast, stannyl and carbonyl electrophiles (Table 4, entries 9−13) gave somewhat lower enantiomeric excesses. Electrophilic substitution with benzaldehyde (Table 4, entry 10) provided a 1:1 mixture of diastereomers.



(*R*)-**20** **50** (*S*)-**51** (*R*)-**51**

Lit.$[\alpha]_D^{23.4}$ -18.4° (EtOH, *c* =2.09)

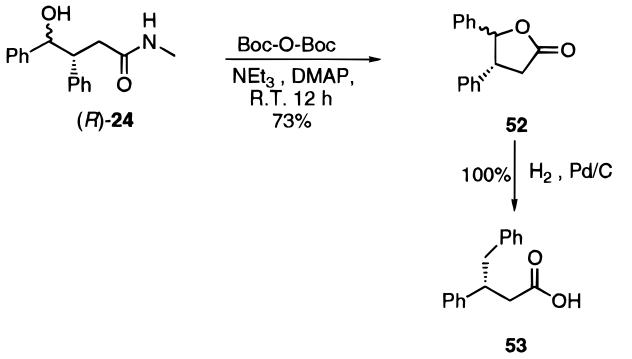
$[\alpha]_D^{25}$ +12.4° (EtOH, *c* =2.66)

The enantiomeric excesses for (*R*)-**8**, (*R*)-**10**, and (*R*)-**16** were determined by hydrolysis of the methyl amides to the corresponding acids as discussed below. Amidation

with 3,5-dimethylaniline provided the dimethylanilide derivatives which were analyzed by chiral stationary phase (CSP) HPLC. The absolute stereochemistries of (*R*)-**8**, (*R*)-**10**, and (*R*)-**16** were assigned by comparison of the optical rotations of the acids to known values. The enantiomeric excess of (*R*)-**15** was determined directly by CSP HPLC and the absolute stereochemistry assigned by analogy with (*R*)-**8**, (*R*)-**10**, and (*R*)-**16**.

The enantiomeric excesses of (*R*)-**18**, (*R*)-**20**, and (*R*)-**21** were determined directly by CSP HPLC analysis. Amide (*R*)-**20** was converted to the ester **50**, which was then oxidized using HBF_4 and *m*-CPBA to the hydroxy ester **51**.[9,10] Assignment of the absolute stereochemistry of (*R*)-**51** was based on comparison of the optical rotation literature values.[11] The assignments of absolute stereochemistry to (*R*)-**18** and (*R*)-**21** were made by analogy to (*R*)-**20**.

The ee's of (*R*)-**26** and (*R*)-**28** were determined by conversion to the corresponding lactones (*vida infra*) and analysis by CSP HPLC. The benzaldehyde adduct (*R*)-**24** was converted to the known acid **53** by treatment of the 1:1 mixture of diastereomers with Boc-O-Boc under basic conditions to provide a mixture of diastereomeric lactones **52**. Hydrogenolysis provided the known acid **53**. The dimethylanilide derivative of **53** was determined by CSP HPLC analysis to be of 65% ee. Comparison of the optical rotation of **53** led to the absolute stereochemistry of the β-benzylic carbon assignment as *R*. Assignments of the absolute stereochemistry of (*R*)-**22**, (*R*)-**26**, and (*R*)-**28** are made by analogy to (*R*)-**24**.



A series of reactions carried out to optimize the lithiation conditions for the formation of (*R*)-**18** from **4** are summarized in Table 5. Entries 1−4 illustrate the effect of increasing the amount of (−)-sparteine. Some improvement in enantiomeric excess was found upon increasing the equivalents of (−)-sparteine to 2.5, but additional (−)-sparteine had little effect. The reaction

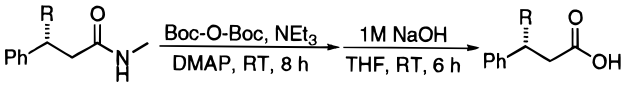
Table 5. Effect of Lithiation Conditions on the Formation of (*R*)-18 from the Lithiation/Substitution of 4 in the Presence of (−)-Sparteine (49)

entry	base[a]	solvent	equiv of **49**[b]	condns[c] (*T* (°C), time (h))	yield (%)	ee (%)
1	*s*-BuLi	THF	1.1	−78, 1.5	79	82
2	*s*-BuLi	THF	2.5	−78, 1.5	78	88
3	*s*-BuLi	THF	5	−78, 1.5	74	90
4	*s*-BuLi	THF	10	−78, 1.5	67	89
5	*t*-BuLi	THF	2.5	−78, 1.5	82	80
6	*s*-BuLi	Et_2O	2.5	−78, 1.5		
6	*s*-BuLi	THF/Et_2O (1:1)	2.5	−78, 1.5	73	86
7	*s*-BuLi	THF/MTBE (1:1)	2.5	−78, 1.5	84	92
8	*s*-BuLi	THF/MTBE (1:1)	5	−78, 1.5	86	94
9	*s*-BuLi	THF/MTBE (1:1)	5	−40, 1.5	70	82

[a] 2.2 equiv of organolithium was used for the deprotonation. [b] Number of equivalents relative to **4**. [c] Conditions for the lithiation reaction.

could also be carried out with *t*-BuLi (Table 5, entry 5). The reaction did not proceed in Et_2O where a precipitate, which is most likely the initially deprotonated amide, is formed. Mixed solvents of THF/Et_2O or THF/MTBE were found to provide good yields and enantiomeric excesses of (*R*)-**18**. The optimum conditions for the conversion of **4** to (*R*)-**18**, listed as entry 8 (Table 5), utilize a 1:1 THF/MTBE solvent mixture, 5 equiv of (−)-sparteine, and 2.5 equiv of *s*-BuLi and provide a 94% ee as compared to the reaction in THF with 1.2 equiv of (−)-sparteine which provided 82% ee. The reaction possesses some tolerance for higher temperatures as shown by entry 9 (Table 5) in which carrying out the lithiation and substitution steps at −40 °C provides (*R*)-**18** in 70% yield and 82% ee.

Synthetic Transformations of the Enantioenriched Products. Conversions of the enantioenriched β-substituted carboxamides into other chiral compounds have been carried out. Asymmetric syntheses of (*R*)-3-phenylalkanoic acids (*R*)-**54**, (*R*)-**55**, and (*R*)-**53** are shown below. The syntheses of these compounds have previously utilized chiral auxiliary methodologies involving Michael additions of organometallic reagents to chiral α,β-unsaturated amides,[12−14] esters,[15] and oxazolines.[16] The enantioenriched amides **8**, **10**, and **16** were converted to the *N*-Boc derivatives and then treated with 1 M NaOH in THF at room temperature[17] to provide the known acids (*R*)-**54**, (*R*)-**55**, and (*R*)-**53** in 60%, 58%, and 62% yields and 78%, 88%, and 80% enantiomeric excesses, respectively.



(*R*)-**8**, R = CH_3
(*R*)-**10**, R = *n*-Bu
(*R*)-**16**, R = CH_2Ph

(*R*)-**54**, R = CH_3
(*R*)-**55**, R = *n*-Bu
(*R*)-**53**, R = CH_2Ph

The alcohols produced by electrophilic substitution with ketones could be cyclized to the enantioenriched

(7) These results indicated that these reactions proceed through an asymmetric substitution pathway in which the chiral diamine induces asymmetry in the substitution step. This is in contrast to an asymmetric deprotonation pathway.[8] Work is currently underway exploring the mechanistic issues of these asymmetric substitution reactions, and the results will be presented in due course.

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(9) The phenyldimethylsilyl group can be converted in two steps into a hydroxyl group with retention of configuration. This oxidation procedure is known to proceed with retention of configuration. [10]

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(12) Touet, J.; Baudouin, S.; Brown, E. *Tetrahedron: Asymmetry* **1992**, *3*, 587−590.

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(14) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 913−916.

(15) Fang, C.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymetry* **1991**, *2*, 389−398.

(16) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250−2254. Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266−6267.

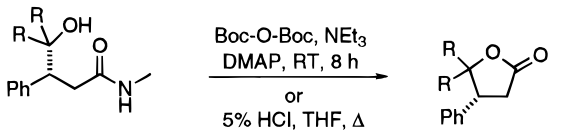
(17) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

Table 6. Lithiation of 60 with *s*-BuLi/49 and Asymmetric Syntheses of (*R*)-4-Substituted Hydrocoumarins 66−68

R	product amide	yield of amide[a] (%)	ee of amide[b] (%)	product coumarin[c]	yield of coumarin (%)
$PhCH_2$	**61**	71	80	**66**	51
CH_3	**62**	63	80	**67**	49
Bu	**63**	67	83	**68**	46
TMS	**64**	68	80		
$H_2C{=}CHCH_2$	**65**	67	86		

[a] Isolated yields. [b] For determination of enantiomeric excesses, see ref 21. [c] Overall isolated yield from the substituted amides **61**−**63**.

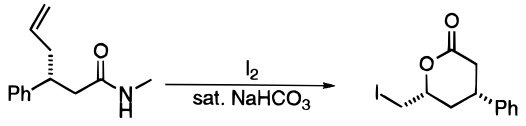
lactones using either 5% HCl in THF or by treatment with Boc-O-Boc. Using the latter procedure, (*R*)- **22** was converted to lactone (*R*)-**56** in 87% yield and 84% ee. Similarly, treatment of (*R*)-**26** and (*R*)-**28** provided 82% and 79% yields of (*R*)-**57** and (*R*)-**58** in 60% ee and 54% ee, respectively. The enantiomeric excesses of **56**−**58** were determined directly by CSP HPLC and the absolute configurations assigned by analogy to (*R*)-**24**.



(*R*)-**22**, R = Ph
(*R*)-**26**, R = CH_3
(*R*)-**28**, R = $(CH_2)_5$

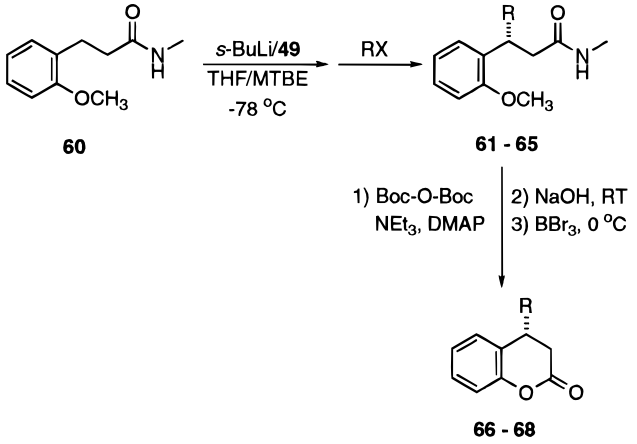
(*R*)-**56**, R =Ph
(*R*)-**57**, R = CH_3
(*R*)-**58**, R = $(CH_2)_5$

Iodolactonization[18] of the β-allyl-substituted amide (*R*)-**15** provided only the *syn*-diastereomer of β,δ-disubstituted-δ-lactone **59** in 67% yield.[19] The cis stereochemistry was assigned by ^{1}H NMR spectroscopy using NOE effects and the enantiomeric excess is assigned as 74% ee based on that of the starting amide (*R*)-**15**.



(*R*)- **15** **59**

Enantioenriched 4-substituted hydrocoumarins can be synthesized using this methodology.[20] Treatment of *o*-methoxy-substituted amide **60** with *s*-BuLi/**49** in 1:1 MTBE/THF at −78 °C followed by electrophilic substitution provides the (*R*)-substituted products **61**−**65** in 63−71% yields and 80−86% enantiomeric excesses.[21] Substituted products **61**−**64** were hydrolyzed to the corresponding carboxylic acids by treatment with Boc-O-Boc, followed by 1 M NaOH. Demethylation of **61**−**63** and cyclization with BBr_3 provided enantioenriched 4-substituted hydrocoumarin products **66**−**68** in moderate yields over the three steps (42−51%). Attempted demethylation and cyclization of the allyl-substituted product **65** resulted in the formation of an intractable mixture. The results of the lithiation and hydrocoumarin-forming reactions are presented in Table 6.



We have briefly investigated other β-aryl-substituted systems. The *p*-methoxy-substituted amide **69** was lithiated using *s*-BuLi/(−)-sparteine to provide **72** in 88% yield and 80% ee. Use of the *o*-methyl- and *o*-chloro-substituted amides **70** and **71** provided 66% isolated yields of **73** and **74**, but the enantiomeric excesses of the products were 0% and 15% for **73** and **74**, respectively. Although the lithiation/substitution protocol was successful with the *o*-methoxy group present, this methodology is apparently not general for all ortho-substituted systems.

69, X = *p*-OMe
70, X = *o*-CH_3
71, X = *o*-Cl

72, X = *p*-OMe (80% ee)
73, X = *o*-CH_3 (0% ee)
74, X = *o*-Cl (15% ee)

In summary, the present work shows that lithiation/substitution sequences with β-phenyl secondary amides can be carried out with high regioselectivity, diastereoselectivity, and enantioselectivity under controlled reaction conditions. The applications of this methodology should provide useful approaches for the enantioselective syntheses of β-aryl-substituted amides, acids, and lactones.

Experimental Section

All reactions involving organometallic reagents were carried out under a nitrogen or argon atmosphere in glassware which was either flame dried or dried in an oven and cooled under a nitrogen atmosphere. All solvents and reagents were obtained from commercial sources and were used without further purification except where noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under a nitrogen atmosphere before use. The *s*-BuLi solutions were titrated using the method of Suffert.[22]

(18) For recent reports on highly diastereoselective iodolactonization see: Hoffmann, R. W.; Stürmer, R.; Harms, K. *Tetrahedron Lett.* **1994**, *35*, 6263−6266. Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888−4895. Pearson, A. J.; Hsu, S-Y. *J. Org. Chem.* **1986**, *51*, 2505−2511. Metz, P. *Tetrahedron* **1993**, *49*, 6367−6374.

(19) The relative configuration of **59** was determined by a difference ^{1}H NMR NOE experiment detailed in the Experimental Section.

(20) Previous asymmetric syntheses of 4-substituted hydrocoumarins: Grimshaw, J.; Millar, P. G. *J. Chem. Soc.* **1970**, 2324. Abe, S.; Nonaka, T.; Fuchigami, T. *J. Am. Chem. Soc.* **1983**, *105*, 3630−3632. Schoo, N.; Schafer, H.-J. *Liebig. Ann. Chem.* **1993**, 601−607. Syntheses of racemic 4-substituted hydrocoumarins: Bergdahl, M.; Eriksson, M.; Nisson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238−7244. Patra, A.; Misra, S. K. *Indian J. Chem.* **1988**, 272−273.

(21) The enantiomeric excesses of amides **61**−**65** were determined by hydrolysis of the amides to the corresponding acids and then formation of the (*S*)-α-methylbenzylamide derivatives, which were analyzed for diastereomeric excess by gas chromatography. The absolute configuration of **62** and **67** was determined by comparison of the optical rotation of (*R*)-**67** to the known rotation for (*R*)-**67**.[20] The absolute configurations of **61**, **63**−**66**, **68**, and **69** are assigned by analogy to (*R*)-**67**.

(22) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

High-pressure liquid chromatography (HPLC) was performed using Rainin HPXL pump systems. Preparative scale HPLC was performed on a Dynamax 60-A 8 μm silica column (Rainin Instrument Co., Woburn, MA, 25 cm × 21.4 mm i.d.). Flash chromatography was performed with Merck 50−200 μm silica gel. Medium-pressure liquid chromatography (MPLC) was performed using columns of different sizes packed with Merck silica gel (32−63 mesh) whose length and diameter depended on the amount of material and the difficulty of the separation.

Compounds were fully characterized as either the racemic mixtures or as enantiomerically enriched material. When microanalysis data were not available, the purity of title compounds was judged to be >90% by ^{1}H-NMR, GC analysis, and/or ^{13}C-NMR unless otherwise stated.

Enantiomeric Purity Analyses. Enantiomeric purity analyses were carried out with both racemic and enantioenriched compounds. Optical rotations were obtained on a JASCO Model DIP-370 digital polarimeter (JASCO Inc., Easton, MD) in a cylindrical glass cell (3.5 mm i.d. × 50 mm) with quartz windows. Analytical chiral stationary phase (CSP) HPLC was performed on Pirkle-concept chiral columns (Regis Chemical Co., Morton Grove, IL, 25 cm × 4.6 mm i.d.): (*R,R*)-β-Gem 1, D-phenylglycine or (*S,S*)-Whelk-O1 columns using mixtures of 2-propanol (*i*-PrOH) and hexane. Diastereomeric purity analyses determined by GC were performed on an HP-5 fused silica column.

General Procedure for the Lithiation of 4 or 5 with *s*-BuLi in THF. To a stirring solution of **4** or **5** (0.05 M in THF) cooled to −78 °C was added 2.2 equiv of *s*-BuLi. The solution was allowed to stir for 0.5−1.4 h, and then the electrophile (1.1−1.5 equiv) was added. The solution was allowed to warm slowly to room temperature before 2% HCl and Et_2O were added. The aqueous layer was washed twice with 10 mL portions of Et_2O . The combined Et_2O layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude products, which were purified as indicated below.

3-Deuterio-*N*-methyl-3-phenylpropanecarboxamide (6) was obtained using methanol-*d* as the electrophile in 93% yield and was found to contain 96% d_1 and 4% d_0 material by FIMS isotope ratios: ^{1}H NMR (300 MHz) δ 2.52 (d, J = 7.8 Hz, 2H), 2.75 (bs, 3H), 2.94 (t, J = 7.5 Hz, 1H), 6.40−6.70 (b, 1H), 7.15−7.30 (om, 5H); ^{13}C NMR (75 MHz) δ 26.33, 31.42 (t, J = 19.7 Hz), 37.81, 126.17, 128.18, 128.41, 140.52, 173.43.

3-Deuterio-*N*-isopropyl-3-phenylpropanamide (7) was obtained using methanol-*d* as the electrophile in 98% yield as a thick oil which was found to contain 96.0% d_1 and 4.0% d_0 material by FIMS isotope ratios: ^{1}H NMR (200 MHz) δ 1.06 (d, J = 6.7 Hz, 6H), 2.41 (d, J = 8.1 Hz, 2H), 2.93 (bt, 1H), 4.02 (m, J = 6.7 Hz, 1H), 5.38−5.53 (bs, 1H), 7.15−7.35 (om, 5H): ^{13}C NMR (50 MHz) 22.58, 31.44 (t, J = 20 Hz), 38.54, 41.11, 126.07, 128.27, 128.36, 140.79, 171.12.

***N*-Methyl-3-phenylbutanamide (8)** was obtained using methyl iodide as the electrophile and was purified by MPLC (35% EtOAc/hexane) to give an 84% yield of **8** as a white solid: mp 61−63 °C; ^{1}H NMR (300 MHz) δ 1.29 (d, J = 7.0 Hz, 3H), 2.34−2.48 (m, AB portion of an ABX spin system, 2H), 2.69 (d, J = 4.8 Hz, 3H), 3.26−3.33 (m, 1H), 5.60−5.80 (b, 1H), 7.15−7.35 (om, 5H); ^{13}C NMR (75 MHz) δ 21.48, 26.10, 36.80, 45.55, 126.27, 126.62, 128.44, 145.91, 172.34. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.59; H, 8.54; N, 7.90.

***N*-Isopropyl-3-phenylbutanamide (9)**[23] was obtained using methyl iodide as the electrophile and was purified by MPLC (40% EtOAc/hexane) to afford a 93% yield of **9** as a white solid: mp 43−45 °C; ^{1}H NMR (200 MHz) δ 0.95 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3 Hz), 2.39 (d, J = 7.6 Hz, 2H), 3.29 (m, 1H), 4.00 (m, 1H), 5.80−6.20 (b, 1H), 7.10−7.30 (om, 5H); ^{13}C NMR (50 MHz) 21.20, 22.15, 22.28, 36.79, 40.72, 45.38, 125.98, 126.51, 128.13, 145.71, 170.67. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.10; H, 9.31; N, 6.89.

***N*-Isopropyl-3-phenylheptanamide (11)** was obtained using butyl iodide as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford a 93% yield of **11**: ^{1}H NMR (300 MHz) δ 0.82 (t, J = 7.2 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.07−1.37 (om, 4H), 1.55−1.75 (m, 2H), 2.31 (dd, J_1 = 13.7 Hz, J_2 = 8.9 Hz, 1H), 2.47 (dd, J_1 = 13.5 Hz, J_2 = 6.4 Hz, 1H), 3.02−3.12 (m, 1H), 3.92 (m, J = 6.6 Hz, 1H), 5.35−5.47 (bd, 1H), 7.10−7.35 (om, 5H); ^{13}C NMR (75 MHz) δ 13.77, 22.25, 22.42, 29.40, 35.62, 40.77, 42.88, 44.80, 126.15, 127.34, 128.24, 144.24, 170.69. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.69; H, 10.19; N, 5.66. Found: C, 77.89; H, 10.00; N, 5.71.

6-Chloro-*N*-isopropyl-3-phenylhexanamide (12) was obtained using 1-bromo-3-chloropropane as the electrophile and was purified by recrystallization from hexane/EtOAc to afford a 79% yield of **12** as a white solid: mp 108−110 °C; ^{1}H NMR (300 MHz) δ 0.85 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.55−1.95 (om, 4H), 2.31 (dd, J_1 = 13.6 Hz, J_2 = 8.6 Hz, 1H), 2.46 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 3.05−3.15 (m, 1H), 3.46 (t, J = 6.2 Hz, 2H), 3.93 (m, J = 6.7 Hz, 1H), 4.95−5.10 (b, 1H), 7.15−7.25 (om, 3H), 7.25−7.35 (m, 2H); ^{13}C NMR (75 MHz) δ 22.43, 22.58, 30.41, 33.03, 41.01, 42.44, 44.95, 45.06, 126.67, 127.39, 128.61, 143.36, 170.30. Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.28; H, 8.28; N, 5.23; Cl, 13.24. Found: C, 67.38; H, 8.34; N, 5.20; Cl, 13.32.

7-Chloro-*N*-isopropyl-3-phenylheptanamide (13) was obtained using 1-bromo-4-chlorobutane as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford an 80% yield of **13** as a clear oil: ^{1}H NMR (300 MHz) δ 0.85 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.20−1.40 (m, 2H), 1.60−1.80 (om, 4H), 2.31 (dd, J_1 = 13.6 Hz, J_2 = 8.7 Hz, 1H), 2.46 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 3.02−3.17 (m, 1H), 3.44 (t, J = 6.7 Hz, 2H), 3.92 (m, J = 6.7 Hz, 1H), 5.10−5.25 (b, 1H), 7.15−7.37 (om, 5H); ^{13}C NMR (75 MHz) δ 22.35, 22.49, 24.56, 32.30, 35.00, 40.90, 42.71, 44.68, 44.82, 126.44, 127.33, 128.44, 143.71, 170.46. Anal. Calcd for $C_{16}H_{24}ClNO$: C, 68.19; H, 8.58; N, 4.97; Cl, 12.58. Found: C, 68.28; H, 8.61; N, 4.96; Cl, 12.65.

8-Chloro-*N*-isopropyl-3-phenyloctanamide (14) was obtained using 1-bromo-5-chloropentane as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford a 77% yield of **14** as a white solid: mp 45−46 °C; ^{1}H NMR (300 MHz) δ 0.85 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.07−1.27 (m, 2H), 1.27−1.47 (m, 2H), 1.57−1.80 (om, 4H), 2.30 (dd, J_1 = 13.6 Hz, J_2 = 8.7 Hz, 1H), 2.45 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 3.02−3.17 (m, 1H), 3.45 (t, J = 6.7 Hz, 2H), 3.92 (m, J = 6.7 Hz, 1H), 5.23 (bd, 1H), 7.15−7.35 (om, 5H); ^{13}C NMR (75 MHz) δ 22.31, 22.46, 26.51, 26.60, 32.26, 35.64, 40.84, 42.79, 44.87, 126.32, 127.32, 128.36, 143.93, 170.53. Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.02; H, 8.86; N, 4.73; Cl, 11.98. Found: C, 68.94; H, 8.90; N, 4.71; Cl, 12.08.

3,4-Diphenyl-*N*-isopropylbutanecarboxamide (17) was obtained using benzyl chloride as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford a 91% yield of **17** as a white solid: mp 96−98 °C; ^{1}H NMR (300 MHz) δ 0.82 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 2.37 (dd, J_1 = 13.8 Hz, J_2 = 9.0 Hz, 1H), 2.51 (dd, J_1 = 13.8 Hz, J_2 = 6.2 Hz, 1H), 2.9−3.0 (om, 2H), 3.41 (m, 1H), 3.90 (m, J = 6.8 Hz, 1H), 5.50−5.90 (b, 1H), 6.95−7.30 (om, 10H); ^{13}C NMR (75 MHz) δ 22.14, 22.24, 40.65, 42.40, 42.89, 44.43, 125.72, 126.19, 127.33, 127.82, 128.05, 128.92, 139.38, 143.21, 170.32. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.12; H, 8.29; N, 4.92.

***N*-Isopropyl-3-phenyl-3-trimethylsilylpropanamide (19)** was obtained using TMSCl as the electrophile, and the reaction mixture was purified by MPLC (30% EtOAc/hexane) to afford a 75% yield of **19** as a white solid: mp 64−68 °C; ^{1}H NMR (300 MHz, the internal $Si(CH_3)_3$ signal was set to be 0.00 ppm) δ 0.00 (s, 9H), 0.69 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H), 2.40−2.60 (om, 3H), 3.74 (m, J = 6.7 Hz, 1H), 5.45 (bd, 1H), 6.90−7.00 (m, 3H), 7.10−7.20 (m, 2H); ^{13}C NMR (75 MHz) δ −3.27, 22.18, 22.24, 33.11, 36.76, 40.72, 124.67, 127.20, 128.11, 142.17, 171.38. Anal. Calcd for $C_{15}H_{25}NOSi$: C, 68.39; H, 9.56; N, 5.32. Found: C, 68.66; H, 9.72; N, 5.30.

(23) The ^{1}H and ^{13}C NMR spectra of **9** were consistent with previously reported data. De Kimpe, N.; Sulmon, P.; Moens, L.; Schamp, N.; Declercq, J.-P.; Meerssche, M. V. *J. Org. Chem.* **1986**, *51*, 3839.

4-Hydroxy-*N*-isopropyl-3,4,4-triphenylbutanamide (23) was obtained using benzophenone as the electrophile and was purified by MPLC (first 5% EtOAc/hexane, then 30% EtOAc/hexane) to afford a 96% yield of **23** as a white solid: mp 160−162 °C; ^{1}H NMR (200 MHz) δ 0.74 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 2.50−2.72 (m, AB portion of ABX system, 2H), 3.75 (m, J = 6.7 Hz, 1H), 4.32 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, X portion of ABX system, 1H), 4.51 (s, 1H), 5.17 (bd, 1H), 6.90−7.40 (om, 13H), 7.65−7.75 (m, 2H); ^{13}C NMR (75 MHz) δ 22.13, 22.14, 39.47, 41.09, 50.55, 80.13, 125.72, 125.97, 126.05, 126.58, 127.49, 127.71, 128.26, 129.91, 139.51, 145.87, 146.37, 171.34. Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.17; H, 7.45; N, 3.66.

3,4-Diphenyl-4-hydroxy-*N*-isopropylbutanamide (25) was obtained using benzaldehyde as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford a 42% yield of the less polar diastereomer of **25** as a white solid: mp 128−130 °C; ^{1}H NMR (300 MHz) δ 0.87 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 2.37 (dd, J_1 = 8.2 Hz, J_2 = 14.3 Hz, 1H), 2.52 (dd, J_1 = 6.6 Hz, J_2 = 14.3 Hz, 1H), 2.75−2.95 (b, 1H), 3.49 (m, J_1 = 6.6 Hz, J_2 = 8.2 Hz, J_3 = 6.3 Hz, 1H), 3.80−4.00 (m, 1H), 4.92 (d, J = 6.3 Hz, 1H), 5.00−5.20 (bd, 1H), 7.10−7.35 (om, 10H); ^{13}C NMR (75 MHz) δ 22.45, 22.50, 35.95, 39.82, 41.23, 50.06, 77.37, 126.76, 127.08, 127.63, 128.08, 128.38, 128.78, 139.91, 141.70, 170.63. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.70; H, 7.75; N, 4.72. The MPLC separation also gave 39% yield of the more polar diastereomer of **25** as a white solid: mp 127−129 °C; ^{1}H NMR (300 MHz) δ 0.93 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 2.60 (dd, J_1 = 6.3 Hz, J_2 = 14.8 Hz, 1H), 2.79 (dd, J_1 = 6.3 Hz, J_2 = 14.8 Hz, 1H), 3.34 (m, J_1 = 6.3 Hz, J_2 = 6.3 Hz, J_3 = 7.9 Hz, 1H), 3.80−4.00 (m, 1H), 4.20−4.60 (b, 1H),4.80 (d, J = 7.9 Hz, 1H), 5.40-5.55 (b, 1H), 7.00−7.30 (om, 10H). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.75; H, 7.79; N, 4.73.

***N*-Isopropyl-4-keto-3-phenylheptanamide (30)** was prepared using butyryl chloride as the electrophile and was purified by MPLC separation (35% EtOAc/hexane) to give 0.18 g (53% yield) of **30** as a clear oil: ^{1}H NMR (300 MHz) δ 0.78 (t, J = 7.5 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H), 1.42−1.60 (m, 2H), 2.30−2.50 (om, 3H), 2.99 (dd, J_1 = 9.3 Hz, J_2 = 14.7 Hz, 1H), 3.98 (m, J = 6.7 Hz, 1H), 4.28 (dd, J_1 = 9.3 Hz, J_2 = 5.4 Hz, 1H), 5.60−5.75 (b, 1H), 7.20−7.35 (om, 5H); ^{13}C NMR (75 M Hz) δ 13.36, 16.97, 22.44, 39.54, 41.14, 43.54, 54.44, 127.32, 128.09, 128.86, 137.95, 170.03, 209.71. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.42; H, 8.80; N, 5.30.

4-Hydroxy-4-methyl-3-phenylpentanoic acid γ-lactone (31).[24] Lithiation of **5** followed by electrophilic substitution with acetone provided a crude oil. The oil was dissolved in 10 mL of toluene, and the solution was heated at reflux temperatures for 18 h. After the toluene was removed under reduced pressure, the crude product was purified by MPLC (15% EtOAc/hexane) to give a 48% yield of **31** as a white solid: mp 89−91 °C; ^{1}H NMR (200 MHz) δ 1.04 (s, 3H), 1.55 (s, 3H), 2.95 [center of AB portion of an ABX spin system, J_{AB} = 17.6 Hz, J_{AX} = 8.5 Hz, J_{BX} = 9.6 Hz, ($\nu_A - \nu_B$) = 31.5 Hz, 2H], 3.52 (center of X portion of ABX spin system, 1H), 7.15−7.45 (om, 5H); ^{13}C NMR (50 MHz), 23.08, 27.57, 34.34, 51.01, 87.12, 127.61, 127.67, 128.54, 136.54, 175.30. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.86; H, 7.52.

3,4-Diphenyl-*N*-isopropyl-4-ketobutanamide (29) was obtained using methyl benzoate as the electrophile and was purified by MPLC (30% EtOAc/hexane) to afford a 70% yield of **29** as a white solid: mp 111−114 °C; ^{1}H NMR (200 MHz) δ 1.01 (d, J = 6.3 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 2.56 (dd, J_1 = 14.5 Hz, J_2 = 5.7 Hz, 1H), 3.11 (dd, J_1 = 14.5 Hz, J_2 = 9.0 Hz, 1H), 3.98 (m, 1H), 5.20 (dd, J_1 = 8.9 Hz, J_2 = 5.7 Hz, 1H), 5.40−5.60 (bd, 1H), 7.10−7.50 (om, 8H), 7.97 (d, J = 7.1 Hz, 2H); ^{13}C NMR (50 MHz) δ 22.54, 41.11, 41.28, 50.01, 127.25, 128.04, 128.40, 128.84, 129.05, 132.92, 136.12, 138.50, 170.07, 199.22. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.01; H, 7.28; N, 4.84.

Preparation of 3,4-Didehydro-1-isopropyl-4-phenyl-2-pyrrolidinone (33). To a stirring solution of 0.482 g (2.52 mmol) of **5** in 50 mL of THF at −78 °C was added 5.0 mL (5.5 mmol) of *s*-BuLi. After 50 min, 0.58 mL (7.5 mmol) of *N*,*N*-dimethylformamide (DMF) was added. After 1 h, 30 mL of saturated NH_4Cl in 2% HCl was added, and the mixture was allowed to warm to room temperature overnight before 30 mL of ether was added. The layers were separated, and the aqueous layer was washed with 30 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude solid. To a stirring solution of the solid in 20 mL of EtOAc was added 2 g of silica gel. The mixture was allowed to stir for 5 h before the silica gel was removed by filtration. The EtOAc was concentrated under reduced pressure to afford an off-white solid. To a stirring solution of the off-white solid in 40 mL of benzene was added 0.85 g (4.5 mmol) of *p*-toluenesulfonic acid monohydrate. After the solution was allowed to stir overnight, 20 mL of saturated $NaHCO_3$ was added. The benzene was removed under reduced pressure before 20 mL of ether was added. The layers were separated, and the aqueous layer was washed twice with 20 mL portions of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude solid. The solid was purified by MPLC separation using 20% EtOAc/hexane as the eluant. The EtOAc backwash was collected and concentrated under reduced pressure to give 0.45 g (88% yield) of **33** as a white solid: ^{1}H NMR (300 MHz) δ 1.27 (d, J = 6.8 Hz, 6H), 4.30 (d, J = 0.9 Hz, 2H), 4.52 (m, J = 6.8 Hz, 1H), 6.41 (s, 1H), 7.40−7.48 (m, 3H), 7.48−7.57 (m, 2H); ^{13}C NMR (75 MHz) δ 20.88, 42.22, 47.39, 120.61, 125.53, 128.81, 129.87, 131.83, 153.77, 170.84. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.51; H, 7.52; N, 6.98.

Representative Lithiation of Carboxamide 9: Preparation of 3-Deuterio-*N*-isopropyl-3-phenylbutanamide (34). To a stirring solution of 0.074 g (0.36 mmol) of **9** in 7.4 mL of THF at −78 °C was added 0.56 mL (0.79 mmol) of *s*-BuLi. The solution was allowed to stir for 1 h before 0.20 mL (4.8 mmol) of CH_3OD was added. After the solution was allowed to stir for 1 h, 10 mL of saturated NH_4Cl in 2% HCl and 10 mL of ether were added. The layers were separated, and the aqueous layer was washed with 10 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 0.064 g (87% yield) of **34** which was determined to contain 86% d_1 and 14% d_0 material by FIMS isotope ratios: ^{1}H NMR (200 MHz) δ 0.93 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.30 (s, 3H), 2.39 (s, 1H), 3.29 (m, 0.1H), 3.97 (m, J = 6.7 Hz, 1H), 5.45−5.62 (b, 1H), 7.15−7.35 (om, 5H); ^{13}C NMR (50 MHz) δ 21.38, 22.41, 22.56, 41.16, 45.78, 126.36, 126.76, 128.46, 145.68, 170.90.

***N*-Isopropyl-3-methyl-3-phenylbutanamide (35)** was obtained using methyl iodide as the electrophile following a procedure similar to that reported for the preparation of **34**. The crude product was purified by MPLC (30% EtOAc/hexane) to afford a 91% yield of **35** as a clear oil: ^{1}H NMR (200 MHz) δ 0.83 (d, J = 6.8 Hz, 6H), 1.45 (s, 6H), 2.44 (s, 2H), 3.83 (m, J = 6.8 Hz, 1H), 4.70−4.85 (b, 1H), 7.15−7.45 (om, 5H); ^{13}C NMR (50 MHz) δ 22.22, 28.60, 37.28, 40.51, 51.58, 125.64, 126.00, 128.29, 147.91, 169.75. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.32; H, 9.64; N, 6.53.

4-Hydroxy-*N*-isopropyl-3-methyl-3,4,4-triphenylbutanamide (36) was obtained using benzophenone as the electrophile following a procedure similar to that reported for the preparation of **34**. The crude mixture was purified by MPLC (20% EtOAc/hexane, the solid was dissolved in CH_2Cl_2 before being loaded onto the MPLC column) to afford a 61% yield of **36** as a white solid: mp 176−178 °C; ^{1}H NMR (200 MHz) δ 0.87 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H),1.57 (s, 3H), 2.68 (d, J = 13.9 Hz, 1H), 3.05 (d, J = 13.9 Hz, 1H), 3.90 (m, J = 6.7 Hz, 1H), 4.90−5.05 (bd, 1H), 5.70 (s, 1H), 6.90−7.00 (m, 2H), 7.10−7.30 (om, 9H), 7.30−7.40 (m, 2H), 7.40−7.52 (m, 2H) ^{13}C NMR ($CDCl_3$/DMSO, 50 MHz) δ 21.58, 21.65, 21.79, 40.72, 45.89, 49.51, 81.62, 125.81, 125.89, 126.00, 126.16, 126.33, 126.46, 128.25, 128.41, 128.97, 144.18, 144.90,

(24) The melting point, ^{1}H NMR spectrum, and mass spectrum of **31** were consistent with previously reported data. Campaigne, E.; Ellis, R. L. J. *Org. Chem.* **1967**, *32*, 2372. Baumann, N.; Sung, M.; Ulman, E. F. *J. Am. Chem. Soc.* **1968**, *90*, 4157.

145.02, 171.73. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.19; H, 7.46; N, 3.57.

Preparation of 5-Hydroxy-1-isopropyl-4-methyl-4-phenyl-2-pyrrolidinone (38). To a stirring solution of 0.269 g (1.31 mmol) of **9** in 26 mL of THF at −78 °C was added 2.1 mL (2.9 mmol) of *s*-BuLi. The solution was allowed to stir for 45 min before 0.30 mL (3.9 mmol) of DMF was added. After the solution was allowed to stir at ambient temperature overnight, 20 mL of saturated NH_4Cl in 2% HCl and 20 mL of ether were added. The layers were separated, and the aqueous layer was washed with two 20 mL portions of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude solid. The crude solid was purified by recrystallization from hexane/EtOAc to afford 0.22 g (71% yield) of **38** as a white solid: mp 135−136 °C; ^{1}H NMR (300 MHz) δ 1.00 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.52 (s, 3H), 2.75 (AB quartet, $\Delta\sqrt{}_{AB}$ = 28.6 Hz, 33.1 Hz, 2H), 3.83 (d, J = 8.2 Hz, 1H), 4.18 (m, J = 6.8 Hz, 1H), 5.11 (d, J = 8.2 Hz, 1H), 7.20−7.45 (om, 5H); ^{13}C NMR (75 MHz) δ 19.33, 21.76, 22.70, 43.06, 43.42, 45.20, 89.31, 125.46, 126.73, 128.59, 145.77, 173.91. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found C, 72.14; H, 8.18; N, 6.01.

Preparation of 3,4-Diphenyl-4-hydroxy-3-methylbutanoic Acid γ-Lactone (39a,b). To a stirring solution of 0.41 g (2.0 mmol) of **9** in 40 mL of THF at −78 °C was added 3.2 mL (4.4 mmol) of *s*-BuLi. The solution was allowed to stir for 50 min before 0.48 mL (4.6 mmol) of benzaldehyde was added. After the solution was allowed to warm to ambient temperature overnight, 25 mL of saturated NH_4Cl in 2% HCl and 30 mL of ether were added. The layers were separated, and the aqueous layer was washed with 30 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **37** as a crude oil. The crude mixture was partially purified by MPLC separation using 30% EtOAc/hexane as the eluant to afford a clear oil. The oil was dissolved in 10 mL of toluene, and the solution was heated at reflux temperatures for 18 h. After the toluene was removed under reduced pressure, the crude product was purified by MPLC separation using 30% EtOAc/hexane as the eluant to give 0.21 g (42% yield) of **39a** as a white solid: mp 133−135 °C; ^{1}H NMR (300 MHz) δ 1.15 (s, 3H), 2.72 (d, J = 17.1 Hz, 1H), 3.31 (d, J = 17.1 Hz, 1H), 5.66 (s, 1H), 6.98 (d, J = 6.4 Hz, 2H), 7.23−7.44 (om, 8H); ^{13}C NMR (75 MHz) δ 20.50, 45.28, 47.69, 89.47, 125.68, 126.30, 127.37, 128.02, 128.21, 128.79, 134.45, 141.51, 175.25. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.19; H, 6.15. The MPLC separation also gave 0.12 g (24% yield) of **39b** as a white solid: mp 112−114 °C; ^{1}H NMR (300 MHz) δ 1.72 (s, 3H), 2.81 (d, J = 17.2 Hz, 1H), 3.26 (d, J = 17.2 Hz, 1H), 5.41 (s, 1H), 6.80−6.90 (om, 4H), 7.05−7.18 (om, 6H); ^{13}C NMR (75 MHz) δ 25.78, 43.05, 48.67, 90.58, 126.08, 126.51, 126.86, 127.64, 127.90, 128.06, 134.82, 140.16, 176.37. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.11; H, 6.06.

Preparation of 1-Phenyl-1-[[(*N*-isopropylamino)carboxy]methyl]cyclopentane (40). To a stirring solution of 0.149 g (0.529 mmol) of **13** in 11 mL of THF at −40 °C was added 0.94 mL (1.2 mmol) of *s*-BuLi. The solution was allowed to stir overnight at −40 to −10 °C before 10 mL of saturated NH_4Cl in 2% HCl and 10 mL of ether were added. The layers were separated and the aqueous layer was washed twice with 10 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 0.124 g (95% yield) of **40** as a white solid: mp 58−60 °C; ^{1}H NMR (200 MHz) δ 0.79 (d, J = 6.3 Hz, 6H), 1.60−1.90 (om, 4H), 1.90−2.20 (om, 4H), 2.40 (s, 2H) 3.78 (m, J = 6.6 Hz, 1H), 4.37−4.52 (b, 1H), 7.15−7.40 (om, 5H); ^{13}C NMR (50 MHz) δ 22.25, 22.73, 37.38, 40.58, 48.86, 50.13, 125.99, 126.79, 128.22, 147.32, 170.06. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.10; H, 9.60; N, 5.44.

Preparation of 1-Phenyl-1-[[(*N*-isopropylamino)carboxy]methyl]cyclohexane (41). To a stirring solution of 0.128 g (0.433 mmol) of **14** in 9 mL of THF at −70 °C was added 0.80 mL (1.0 mmol) of *s*-BuLi. The resulting solution was allowed to warm to −40 °C and was then allowed to stir overnight at −40 to −10 °C before 10 mL of saturated NH_4Cl in 2% HCl and 10 mL of ether were added. The layers were separated, and the aqueous layer was washed with two 10 mL portions of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a clear oil. The crude material was purified by MPLC separation using 30% EtOAc/hexane as the eluant to afford 0.089 g (79% yield) of **41** as a white solid: mp 72−74 °C; ^{1}H NMR (300 MHz) δ 0.78 (d, J = 6.5 Hz, 6H), 1.35−1.52 (om, 4H), 1.52−1.68 (m, 2H), 1.68−1.83 (m, 2H), 2.13−2.24 (m, 2H), 2.35 (s, 2H) 3.76 (m, J = 6.6 Hz, 1H), 4.17−4.30 (b, 1H), 7.19−7.40 (om, 5H); ^{13}C NMR (75 MHz) δ 22.21, 22.32, 26.19, 36.13, 40.62, 41.02, 51.74, 125.96, 126.88, 128.50, 145.71, 169.60. Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.44; H, 9.62; N, 5.22.

Representative Lithiation of Carboxamide 42: Preparation of (*R*,S)-*N*-isopropyl-2-methyl-3-phenylbutanamide ((*R*,S**)-44).** To a stirring solution of 0.384 g (1.87 mmol) of **42** in 37 mL of THF at −78 °C was added 2.7 mL of *s*-BuLi. After 50 min, 0.13 mL (2.1 mmol) of iodomethane was added. After 1.5 h, 20 mL of saturated NH_4Cl in 2% HCl and 20 mL of ether were added. The aqueous layer was washed twice with 20 mL portions of ether. The three combined ether layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude solid. Purification was accomplished by MPLC separation using 30% EtOAc/hexane followed by HPLC separation using 25% EtOAc/hexane as the eluant to give 0.053 g (14% recovery) of **42** and 0.31 g (75% yield) of (*R*,S**)-**44** as a white solid: mp 107−109 °C; ^{1}H NMR (200 MHz) δ 0.62 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H), 2.23 (dq, J_1 = 6.6 Hz, J_2 = 9.5 Hz, 1H), 2.92 (dq, J_1 = 6.9 Hz, J_2 = 9.9 Hz, 1H), 3.77 (m, J = 6.7 Hz, 1H), 4.80−5.00 (bd, 1H), 7.10−7.35 (om, 5H); ^{13}C NMR (50 MHz) δ 15.28, 18.37, 22.14, 22.43, 40.44, 40.52, 43.08, 49.34, 126.16, 127.21, 128.22, 145.70, 174.22. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.77; H, 9.64; N, 6.41.

3-Deuterio-*N*-isopropyl-2-methyl-3-phenylpropanamide (43) was obtained using methanol-*d* as the electrophile following a procedure similar to that reported for the preparation of **44**. The deuterated product **43** was obtained in 95% yield as a white solid which was determined to contain 93% d_1 and 8% d_0 material by FIMS isotope ratios: mp 114−116 °C; ^{1}H NMR (200 MHz) δ 0.91 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 2.34 (m, 1H), 2.65 (m, 0.25H), 2.90 (d, J = 8.6 Hz, 0.75H), 3.96 (d, J = 6.1 Hz, 0.5H), 4.00 (d, J = 6.1 Hz, 0.5H), 5.00−5.10 (bs, 1H), 7.10−7.35 (om, 5H); ^{13}C NMR (50 MHz) δ 17.64, 22.55, 22.64, 40.3 (t), 40.90, 43.90, 126.16, 128.29, 128.92, 139.89, 174.6;7.75, 128.37, 128.49, 131.55, 135.07, 141.87, 172.58.

7-Bromo-*N*-isopropyl-2-methyl-3-phenylheptanamide (45) was obtained using 1,4-dibromobutane as the electrophile following a procedure similar to that reported for the preparation of **44**. The crude oil was purified by MPLC (30% EtOAc/hexane) to afford a 79% yield of **45** as a white solid: mp 68−70 °C; ^{1}H NMR (200 MHz) δ 0.58 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.05−1.28 (m, 2H), 1.45−1.68 (m, 1H), 1.70−1.95 (om, 3H), 2.28 (dq, J_1 = 9.9 Hz, J_2 = 6.9 Hz, 1H), 2.74 (om, J_1 = 3.0 Hz, J_2 = 10.6 Hz, J_3 = 10.0 Hz, 1H), 3.29 (t, J = 7.0 Hz, 2H), 3.74 (m, J = 6.7 Hz, 1H), 4.85−5.05 (bd, 1H), 7.10−7.30 (om, 5H); ^{13}C NMR (50 MHz) δ 15.55, 22.01, 22.30, 25.87, 30.97, 32.53, 33.38, 40.38, 48.35, 48.84, 126.25, 127.92, 128.16, 143.01, 173.98. Anal. Calcd for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70; N, 4.12; Br, 23.48. Found: C, 60.02; H, 7.72; N, 4.08; Br, 23.23.

4-Hydroxy-*N*-isopropyl-2-methyl-3,4,4-triphenylbutanamide (46) was obtained using benzophenone as the electrophile following a procedure similar to that reported for the preparation of **44**. The crude product was purified by MPLC (first 5% EtOAc/hexane, then 40% EtOAc/hexane) to afford a 95% yield of **46** as a white solid: mp 158−162 °C; ^{1}H NMR (200 MHz) δ 0.78 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 3.02 (dq, J_1 = 1.2 Hz, J_2 = 7.4 Hz, 1H), 3.78 (s,1H), 3.89 (m, J_1 = 7.9 Hz, J_2 = 6.7 Hz, 1H), 5.01 (bd, J = 7.9 Hz, 1H), 6.85−7.25 (om, 7H), 7.30−7.50 (om, 6H), 7.80−7.88 (om, 2H); ^{13}C NMR (75 MHz) δ 17.17, 21.64, 22.19, 41.48, 41.71, 58.11, 80.14, 125.36, 125.55, 125.75, 126.23,

126.40, 127.19, 127.36, 128.23, 131.01, 136.99, 145.98, 148.63, 174.77. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.69; H, 7.61; N, 3.34.

3,4-Diphenyl-4-hydroxy-*N*-isopropyl-2-methylbutanamide (47) was obtained using benzaldehyde as the electrophile following a procedure similar to that reported for the preparation of **44**. The crude oil was purified by MPLC (30% EtOAc/hexane) to afford a 22% recovery of the starting amide **42** and 55% yield of **47** as a white solid: mp 107−108 °C; ^{1}H NMR (200 MHz) δ 1.05 (d, J = 7.4 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H), 3.03 (dd, J_1 = 9.3 Hz, J_2 = 4.7 Hz, 1H), 3.18 (dq, J_1 = 7.4 Hz, J_2 = 4.7 Hz, 1H), 4.11 (m, J = 6.2 Hz, 0.5H), 4.15 (m, J = 6.7 Hz, 0.5H), 5.07 (dd, J_1 = 9.3 Hz, J_2 = 4.5 Hz, 1H), 5.27 (d, J = 4.5 Hz, 1H), 5.45−5.55 (bd, 1H), 6.90−7.05 (om, 2H), 7.05−7.20 (om, 8H); ^{13}C NMR (75 MHz) δ 15.32, 22.29, 22.57, 41.31, 41.46, 57.99, 75.58, 126.56, 126.82, 126.95, 127.79, 127.92, 129.33, 139.04, 143.17, 174.37. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.90; H, 8.13; N, 4.43.

Representative Lithiation of Carboxamide 4 with *s*-BuLi/(−)-Sparteine: Preparation of (*R*)-*N*-Methyl-3-phenylbutanamide ((*R*)-8). To (−)-sparteine (1 mL, 3.8 mmol) in THF (4 mL) at −78 °C was added *s*-BuLi (2.8 mL, 3.4 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was transferred to a solution of *N*-methyl-3-phenylpropanamide (**4**) (222 mg, 1.36 mmol) in THF (8 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 50 min, and then iodomethane (0.14 mL, 2.2 mmol) was added. This mixture was allowed to stir for 2 h at −78 °C. HCl (5%, 15 mL) and Et_2O (20 mL) were added. The mixture was allowed to warm to ambient temperature, and then the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by MPLC (30% EtOAc/hexane) to give (*R*)-**8** as a white solid (216 mg, 89%): mp 61−63 °C; ^{1}H and ^{13}C NMR spectral data were consistent with the racemic product reported above; $[\alpha]^{22}_D$ −25.4° (c = 1.68, $CHCl_3$). The enantiomeric excess of (*R*)-**8** was determined to be 78% by hydrolysis to the acid **54**, conversion of **54** to the dimethylanilide derivative, and CSP HPLC analysis as described below.

Representative Hydrolysis of the Amides to the Corresponding Acids and Preparation of the Dimethylanilide Derivatives: Preparation of (*R*)-3-Phenylbutyric Acid ((*R*)-54). To a 0.5 M solution of (*R*)-**8** (194 mg, 1.09 mmol) in methylene chloride was added triethylamine (0.15 mL, 1.09 mmol), di-*tert*-butyl dicarbonate (0.5 mL, 2.18 mmol), and 4-(dimethylamino)pyridine (150 mg, 1.11 mmol). The solution was stirred for 8 h at room temperature. The volatiles were removed, and the residue was purified by flash chromatography (1/20 (v/v) EtOAc/hexane) to afford the desired (*R*)-*N*-Boc-*N*-methyl-3-phenylbutanamide (210 mg, 70%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, J = 6.9 Hz, 3H, CH_3), 1.52 (s, 9H, O-*t*-Bu), 3.07 (s, 3H, NCH_3), 3.10−3.38 (m, 3H, $CHCH_2$), 7.18−7.29 (m, 5H, Ar).

A 0.2M solution of *N*-Boc derivative (175 mg, 0.63 mmol) in THF (4 mL), under N_2 atmosphere, was cooled to 0 °C. To this solution was added 1 N lithium hydroxide (2.0 mL, 2.0 mmol). The reaction mixture was allowed to stir for 6 h. After removal of THF *in vacuo*, the basic residue was acidified with 5% HCl and extracted with ether (3 × 15 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (110−120 °C /1.2 mmHg) to give the desired acid (*R*)-**54** (85 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, 3H, J = 7.0 Hz, CH_3), 2.46−2.75 (m, 2H, CH_2), 3.28−3.35 (m, 1H, CH), 7.22−7.37 (m, 5H, Ar), 10.78 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.80, 36.07, 42.56, 126.44, 126.64, 128.50, 145.36, 178.78. The absolute configuration of **54** was assigned as *R* by comparison of the optical rotation of **54** [$[\alpha]^{22}_D$ −39.2° (c = 2.33, benzene)] to the known rotation for (*R*)-**54** [$[\alpha]^{23}_D$ −54.5° (c = 10, benzene)].[25]

The acid was converted to the 3,5-dimethylanilide according to Pirkle's method.[26] To a solution of (*R*)-**54** (48 mg, 0.29 mmol) in methylene chloride (6 mL) were added dicyclohexylcarbodiimide (64 mg, 0.30 mmol) and 3,5-dimethylaniline (50 μL, 0.40 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. The resulting mixture was then dissolved in 1/1 (v/v) EtOAc/hexane and passed through a short plug of silica to give a light yellow oil. Purification by flash chromatography (5% EtOAc/hexane) gave the 3,5-dimethylanilide derivative as a colorless oil (50 mg, 65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (d, 3H, J = 6.9 Hz, CH_3), 2.26 (s, 6H, CH_3Ar), 2.53−2.65 (m, 2H, CH_2), 3.34−3.41 (m, 1H, CH), 6.72 (s, 1H, NH), 6.89 (s, 1H, Ar), 6.99 (s, 2H, Ar), 7.20−7.35 (m, 5H, Ar). The enantiomeric excess of the 3,5-dimethylanilide derivative was determined to be 78% by CSP HPLC ((*R*,*R*)-β-Gem column, 24/1 hexane/*i*-PrOH, 2.0 mL/min). The major enantiomer (*R*) had a retention time of 36.4 min and the minor enantiomer (*S*) had a retention time of 45.8 min.

(*R*)-*N*-Methyl-3-phenylheptanamide ((*R*)-10) was obtained using butyl iodide as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 77% yield of (*R*)-**10** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J = 7.1 Hz, CH_3), 1.06−1.29 (m, 4H, CH_2CH_2), 1.55−1.68 (m, 2H, CH_2), 2.35 (dd, 1H, J = 5.7 Hz, J = 8.2 Hz, CH_2), 2.47 (dd, 1H, J = 7.3 Hz, J = 6.7 Hz, CH_2), 2.63 (d, 3H, J = 4.8 Hz, NCH_3), 3.03−3.13 (m, 1H, CH), 5.48 (bs, 1H, NH), 7.15−7.29 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.86, 22.53, 26.06, 29.51, 35.66, 42.68, 44.61, 126.26, 127.32, 128.33, 144.44, 172.37; $[\alpha]^{26}_D$ −22.8° (c = 2.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.38. Found: C,76.54; H, 9.73; N, 6.44. The absolute configuration and enantiomeric excess of (*R*)-**10** was determined following the hydrolysis/dimethylanilide derivatization protocol described above for (*R*)-**8**. The acid **55** was assigned the absolute configuration of (*R*) by comparison of the optical rotation of **55** [$[\alpha]^{20}_D$ −31.4° (c = 2.20, benzene)] to the known rotation for (*R*)-**55** [$[\alpha]^{23}_D$ −35.2° (c = 8, benzene)].[25] The dimethylanilide of **55** was analyzed by CSP HPLC ((*R*,*R*)-β-Gem column, 24/1 hexane/*i*-PrOH, 2.0 mL/min) and found to have an enantiomeric excess of 88%. The major enantiomer (*R*) had a retention time of 30.5 min, and the minor enantiomer (*S*) had a retention time of 42.6 min.

(*R*)-*N*-Methyl-3-phenyl-5-hexenamide ((*R*)-15) was obtained using allyl chloride as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 74% yield of (*R*)-**15** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32−2.50 (m, 3H, CH_2 and 1H of CH_2), 2.53−2.64 (m , 1H, 1H of CH_2), 2.63 (d, 3H, J = 5.1 Hz, CH_3), 3.18−3.27 (m, 1H, CH), 4.92−5.00 (m, 2H, CH_2), 5.51−5.71 (m, 2H, CH and NH), 7.16−7.30 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.11, 40.26, 42.17, 43.26, 116.63, 126.44, 127.33, 128.41, 136.01, 143.73, 172.16. Anal. Calcd for $C_{17}H_{19}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.81; H, 8.45; N, 6.90. The enantiomeric excess of (*R*)-**15** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 15% *i*-PrOH/hexane, 2.0 mL/min) to be 74%. The major enantiomer (*R*)-**15** had a retention time of 6.6 min, and the minor enantiomer (*S*)-**15** had a retention time of 7.8 min.

(*R*)-*N*-Methyl-3,4-diphenylbutanamide ((*R*)-16) was obtained using benzyl bromide as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 78% yield of (*R*)-**16** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (dd, 1H, J = 5.6, 8.7 Hz, CH_2), 2.55 (dd, 1H, J = 8.2, 6.1 Hz, CH_2), 2.62 (d, 3H, J = 4.9 Hz, NCH_3), 2.87−3.00 (m, 2H, CH_2), 3.39−3.46 (m, 1H, CH), 5.16−5.23 (bs, 1H, NH), 7.03−7.28 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.14, 42.66, 42.90, 44.30, 126.01, 126.50, 127.47, 128.09, 129.19, 139.56, 143.60, 172.03; $[\alpha]^{26}_D$ +27.8° (c = 1.94, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53.

(25) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 913−916.

(26) Pirkle, W. H.; McCune, J. F. *J. Chromatogr.* **1989**, *479*, 419.

Found: C, 80.30; H, 7.68; N, 5.49. The absolute configuration and enantiomeric excess of (*R*)-**16** were determined following the hydrolysis/ dimethylanilide derivatization protocol described above for (*R*)-**8**. The acid **53** was assigned the absolute configuration of *R* by comparison of the optical rotation of **53** [$[\alpha]^{22}_D$ +52.5° (*c* = 1.07, benzene)] to the known rotation for (*S*)-**53** [$\alpha]^{22}_D$ −60° (benzene)].[27] The enantiomeric excess was determined to be 80% by CSP HPLC ((*R*,*R*)-β-Gem column, 24/1 hexane/*i*-PrOH, 2.0 mL/min) analysis of the dimethylanilide of **53**. The major enantiomer (*R*) had a retention time of 42.0 min, and the minor enantiomer (*S*) had a retention time of 66.2 min.

(*R*)-*N*-Methyl-3-phenyl-3-(trimethylsilyl)propanamide ((*R*)-18) was obtained using TMSCl as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to give an 86% yield of (*R*)-**18** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0 (s, 9H, $Si(CH_3)_3$), 2.57−2.70 (m, 6H, CH_2CH_2 and NCH_3), 5.26−5.42 (bs, 1H, NH), 7.06−7.32 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −3.14, 26.18, 32.92, 36.66, 124.9, 127.17, 128.27, 142.29, 173.17. $[\alpha]^{26}_D$ −17.6° (*c* = 2.82, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}NOSi$: C, 66.33; H, 8.99; N, 5.95. Found: C, 66.42; H, 8.96; 5.81. The enantiomeric excess of (*R*)-**18** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) to be 94%. The major enantiomer (*R*)-**18** had a retention time of 13.5 min, and the minor enantiomer (*S*)-**18** had a retention time of 9.0 min.

(*R*)-*N*-Methyl-3-phenyl-3-(dimethylphenylsilyl)propanamide ((*R*)-20) was obtained using dimethylphenylsilyl chloride as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 68% yield of (*R*)-**20** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.23 (s, 3H, $SiCH_3$), 0.24 (s, 3H, $SiCH_3$), 2.52−2.59 (m, 5H, NCH_3 and CH_2), 2.76−2.81 (m, 1H, CH), 5.41 (bs, 1H, NH), 7.07−7.40 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.46, −4.24, 25.95, 32.37, 36.41, 124.83, 127.34, 127.50, 128.04,129.08, 133.94, 136.29, 141.51,172.76. Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.68; H, 7.79; N, 4.71. Found: C, 72.75; H, 7.82; N, 4.75. The enantiomeric excess of (*R*)-**20** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) to be 80%. The major enantiomer (*R*)-**20** had a retention time of 16.1 min, and the minor enantiomer (*S*)-**20** had a retention time of 11.2 min.

(*R*)-*N*-Methyl-3-phenyl-3-(tributylstannyl)propanamide ((*R*)-21) was obtained using tributyltin chloride as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (30% EtOAc/hexane) to provide an 84% yield of (*R*)-**21** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67−0.93 (m, 15H, $3CH_3CH_2$), 1.10−1.29 (m, 6H, $3CH_2$), 1.30−1.46 (m, 6H, $3CH_2$), 2.67 (d, 3H, *J* = 4.9 Hz, NCH_3), 2.69−2.97 (m, 3H, $CHCH_2$), 5.45 (bs, 1H, NH), 6.98−7.269 (m, 5H, C_6H_5); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 9.40, 13.62, 26.26, 27.41, 28.94, 29.3, 38.95, 123.89, 125.59, 145.69, 173.46. Anal. Calcd for $C_{22}H_{39}SnNO$: C, 58.43; H, 8.69; N, 3.10; Sn, 26.25. Found: C, 58.44; H, 8.74; N, 3.16; Sn, 26.16. The enantiomeric excess of (*R*)-**21** was determined directly by CSP HPLC analysis (D-phenylglycine, 10% *i*-PrOH/hexane, 1.0 mL/min) to be 60%. The major enantiomer (*R*)-**21** had a retention time of 55.1 min, and the minor enantiomer (*S*)-**21** had a retention time of 63.6 min.

(*R*)-*N*-Methyl-4-hydroxy-3,4,4-triphenylbutanamide ((*R*)-22) was obtained using benzophenone as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was recrystallized from EtOAc to provide an 84% yield of (*R*)-**22** as a white solid: mp 182−184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56 (d, 3H, *J* = 4.8 Hz, CH_3), 2.67 (m, 2H, CH_2), 3.87 (s, 1H, OH), 4.39 (dd, 1H, *J* = 5.7Hz, *J* = 1.5 Hz, CH), 5.07−5.16 (bs, 1H, NH), 7.00−7.73 (m, 15H, Ar); ^{13}C NMR (d_6-acetone, 75 MHz) δ 25.92, 39.68, 50.69, 80.82, 126.10, 126.52, 126.69, 126.97, 127.84, 128.71, 131.08, 141.48, 147.83, 149.08, 172.91. $[\alpha]^{22}_D$ 105.5° (*c* = 0.47, EtOH). Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.63; H, 6.76; N, 4.06. The enantiomeric purity of (*R*)-**22** was determined to be 84% by CSP HPLC of the corresponding γ-lactone **56** as described below.

(3*R*)-*N*-Methyl-4-hydroxyl-3,4-diphenylbutanamide ((3*R*)-24) was obtained using benzaldehyde as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by HPLC (60% EtOAc/hexane) to give the less polar diastereomer as a semisolid (33%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57−2.7 (m, 4H, CH_3 and CH_2), 2.82 (dd, 1H, *J* = 15.1, 6.4 Hz, CH_2), 3.31−3.37 (m, 1H, CH), 4.7−5.5 (bs, 1H, OH), 4.76 (d, 1H, *J* = 7.8 Hz, CH), 6.99 (s, 1H, NH), 7.03−7.35 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.30, 39.06, 50.14, 78.26, 126.42, 126.59, 127.10, 127.84, 128.14, 128.22, 141.58, 143.02, 173.56. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.59; H, 7.16; N, 5.05. The more polar diastereomer (30%) was isolated as a semisolid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40 (dd, 1H, *J* = 14.6, 7.5 Hz, CH_2), 2.55−2.62 (m, 4H, CH_2 and CH_3N), 3.20 (bs, 1H, OH), 3.46−3.53 (m, 1H, CH), 4.89 (d, 1H, *J* = 5.9 Hz, CH), 5.64 (s, 1H, NH), 7.05−7.27 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.26, 39.10, 49.65, 77.08, 126.71, 126.96, 127.50, 127.96, 128.26, 128.71, 139.92, 141.68, 172.41. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.54; H, 7.13; N, 5.13.

Stereochemistry and Enantiomeric Purity Assay of (3*R*)-*N*-Methyl-4-hydroxyl-3,4-diphenylbutanamide ((3*R*)-24): Synthesis of 52. To a solution of the less polar diastereomer of (3*R*)-**24** (98 mg, 0.36 mmol) in methylene chloride (5 mL) were added triethylamine (0.05 mL, 0.35 mmol), di-*tert*-butyl dicarbonate (0.16 mL, 0.70 mmol), and 4-(dimethylamino)pyridine (46 mg, 0.35 mmol). The solution was stirred for 12 h at room temperature. The volatile materials were removed *in vacuo*, and the residue was purified by flash chromatography (1/10 (v/v) EtOAc/hexane) to afford the desired γ-lactone **52** (62 mg, 73%) as a white solid: mp 107−109 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.93 (m, 1H, CH_2), 3.07 (m, 1H, CH_2), 3.56−3.62 (m, 1H, CH), 5.43 (d, 1H, *J* = 8.6 Hz, CH), 7.17−7.39 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.10, 50.53, 87.39, 125.58, 127.32, 127.84, 128.60, 129.06, 137.66, 137.85, 175.30.

To a solution of the γ-lactone **52** (97 mg, 0.41 mmol) in EtOH (10 mL) was added 5% Pd in carbon (80 mg). The mixture was allowed to stir under H_2 atmosphere for 4 h and then passed through a short plug of Celite. The resulting solution was concentrated to give **53** (96 mg, quantitative yield) as a colorless oil. $[\alpha]^{22}_D$ +41.4° (*c* = 2.62, benzene). Acid **53** was converted to the 3,5-dimethylanilide and the enantiomeric excess determined to be 65% by CSP HPLC as described above.

(*R*)-*N*-Methyl-4-hydroxy-4-methyl-3-phenylpentanamide ((*R*)-26) was obtained using acetone as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was recrystallized from EtOAc to provide 45% of (*R*)-**26** as a white solid: mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.53−2.62 (m, 4H, CH_3 and 1H of CH_2), 2.87−2.94 (m, 1H, 1H of CH_2), 3.16−3.21 (m, 1H, CH), 5.75 (bs, 1H, NH), 7.18−7.30 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.30, 26.65, 29.27, 34.49, 37.92, 51.16, 52.88, 72.36, 126.74, 128.16, 129.02, 141.51, 173.43. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.32. Found: C, 70.46; H, 8.54; N, 6.09. The enantiomeric purity of (*R*)-**26** was determined to be 60% by CSP HPLC of the corresponding γ-lactone **57** as described below.

(*R*)-*N*-Methyl-3-(1-hydroxycyclohexyl)-3-phenylpropanamide ((*R*)-28) was obtained using cyclohexanone as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**8**. The crude product was purified by MPLC (50% EtOAc/hexane) to afford a 65% yield of (*R*)-**28** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08−1.71 (m, 10H, $(CH_2)_5$), 2.28 (bs, 1H, OH), 2.51−2.59 (m, 4H, CH_3 and 1H of CH_2), 2.86 (dd, *J* = 5.2 Hz, *J* = 9.4 Hz, 1H, 1H of CH_2), 3.13−3.18 (m, 1H, CH), 5.69 (bs, 1H, NH), 7.17−7.29 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.70, 21.91, 25.53, 26.27, 35.25, 36.18, 37.28, 52.28, 72.72, 126.64, 128.12, 129.28, 141.21, 173.36. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87; N, 5.36. Found: C, 73.22; H, 8.83; N, 5.46. The enantiomeric purity

(27) Touet, J.; Baudouin, S.; Brown, E. *Tetrahedron: Asymmetry* **1992**, *3*, 587−590.

of (*R*)-**28** was determined to be 54% by CSP HPLC of the corresponding γ-lactone **58** as described below.

Stereochemical Assay of (R)-*N*-Methyl-3-phenyl-3-(dimethylphenylsilyl) propanamide ((*R*)-20): Synthesis of (*R*)-51. To a 0.5 M solution of (*R*)-**20** (947 mg, 3.18 mmol) in methylene chloride were added triethylamine (0.44 mL, 3.18 mmol), di-*tert*-butyl dicarbonate (1.39 g, 6.36 mmol), and 4-(dimethylamino)pyridine (388 mg, 3.18 mmol). The solution was stirred for 7 h at room temperature. The volatiles were removed *in vacuo,* and the residue was purified by flash chromatography (1/20 (v/v) EtOAc/Hexane) to afford the desired (*R*)-*N*-Boc-*N*-methyl-3-(dimethylphenylsilyl)-3-phenylpropanamide (850 mg, 67%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 3H, $SiCH_3$), 0.26 (s, 3H, $SiCH_3$), 1.51 (s, 9H, O-*t*-Bu), 2.91 (s, 3H, NCH_3), 2.97−3.15 (m, 2H, CH_2), 3.40−3.50 (m, 1H, CH), 6.95−7.43 (m, 10H, Ar).

A solution of the *N*-Boc derivative (530 mg, 1.33 mmol) in methanol (3 mL), under N_2 atmosphere, was cooled to 0 °C. To this solution was added 0.5 mL (2.44 mmol) of a 25 wt % solution of sodium methoxide in methanol. The reaction mixture was stirred for 40 min and then poured into 15 mL of brine. The layers were separated, and the aqueous layer was extracted with ether (3 × 15 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1/50 (v/v) EtOAc/hexane) to give (*R*)-**50** (226 mg, 57%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.21 (s, 3H, $SiCH_3$), 0.24 (s, 3H, $SiCH_3$), 2.60−2.87 (m, 3H, $CHCH_3$), 3.46 (s, 3H, OCH_3), 6.93−7.41 (m, 10H, Ar).

To a 0.1 M solution of (*R*)-**50** (183 mg, 0.6 mmol) in methylene chloride was added tetrafluoroboric acid−diethyl ether complex (1 g, 6 mmol). The mixture was stirred at room temperature for 3 h. The volatile materials were removed *in vacuo* to give (*R*)-3-(fluorodimethylsilyl)-3-phenyl propyl methyl ester (105 mg) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14 (d, *J* = 7.5 Hz, 3H, $SiCH_3$), 0.19 (d, *J* = 7.4 Hz, 3H, $SiCH_3$), 2.79−2.87 (m, 3H, $CHCH_2$), 3.58 (s, 3H, OCH_3), 7.09−7.29 (m, 5H, Ar). The material was used without further purification.

To a solution of the crude fluorosilane (100 mg, 0.42 mmol) in DMF (1.2 mL) were added *m*-chloroperbenzoic acid (624 mg, 3.6 mmol) and anhydrous potassium fluoride (133 mg, 2.3 mmol). The mixture was stirred at room temperature for 5 h. The crude product was purified by MPLC (10% EtOAc/hexane) to afford (*R*)-3-hydroxy-3-phenylpropyl methyl ester ((*R*)-**51**) (70 mg, 71% total) as an oil: $[\alpha]^{25}_D$ +12.4° (*c* = 2.66, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73−2.77 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.2−4.7 (bs, 1H, OH), 5.12−5.17 (dd, 1H, *J* = 4.2 Hz, *J* = 4.5 Hz, CH), 7.29−7.39 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.1, 51.9, 70.27, 125.61, 127.81, 128.53, 142.39, 172.78. The $[\alpha]^{25}_D$ for (*S*)-**51** was reported to be −18.4.[11]

Representative Synthesis of Butyrolactones: Preparation of (*R*)-3,4,4-Triphenylbutyrolactone ((*R*)-56). To a 0.5 M solution of (*R*)-**22** (121 mg, 0.35 mmol) in methylene chloride were added triethylamine (0.05 mL, 0.35 mmol), di-*tert*-butyl dicarbonate (0.16 mL, 0.70 mmol), and 4-(dimethylamino)pyridine (43 mg, 0.35 mmol). The solution was stirred for 8 h at room temperature. The volatiles were removed, and the residue was purified by flash chromatography (1/20 (v/v) EtOAc/hexane) to afford the desired γ-lactone (*R*)-**56** (96 mg, 87%): mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (dd, 1H, *J* = 17.5, 4.6 Hz, CH_2), 3.00 (dd, *J* = 17.5, 8.0 Hz, CH_2), 4.47−4.51 (m, 1H, CH), 6.93−7.67 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.39, 50.90, 92.91, 126.02, 126.19, 127.14, 127.28, 127.62, 128.13, 128.29, 128.49, 128.64, 138.43, 139.87, 143.05, 175.79. The enantiomeric excess of (*R*)-**56** was determined directly by CSP HPLC analysis (D-phenylglycine, 200/1 (v/v) *i*-PrOH/hexane, 1.0 mL/min) to be 60%. The major enantiomer (*R*)-**56** had a retention time of 51.6 min, and the minor enantiomer (*S*)-**56** had a retention time of 57.1 min.

(*R*)-4,4-Dimethyl-3-phenyl-γ-butyrolactone ((*R*)-57) was prepared from (*R*)-**26** following a procedure similar to that reported for the preparation of (*R*)-**56**. The crude product was purified by MPLC (30% EtOAc/hexane) to provide an 85% yield of (*R*)-**57** as a white solid: mp 100−102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.84−3.06 (m, 2H, CH_2), 3.49−3.55 (m, 1H, CH), 7.20−7.39 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.22, 27.74, 34.52, 51.20, 87.26, 127.79, 128.70, 136.69, 175.39. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.80; H, 7.44. The enantiomeric excess of (*R*)-**57** was determined to be 54% by CSP HPLC analysis (1% *i*-PrOH/hexane, 2.0 mL/min) using a prototype CSP HPLC column from Professor William Pirkle. The major enantiomer (*R*)-**57** had a retention time of 19.3 min, and the minor enantiomer (*S*)-**57** had a retention time of 22.2 min.

(*R*)-4-(*spiro*-Cyclohexyl)-3-phenyl-γ-butyrolactone ((*R*)-58) was prepared from (*R*)-**28** following a procedure similar to that reported for the preparation of (*R*)-**56**. The crude product was purified by MPLC (30% EtOAc/hexane) to provide a 79% yield of (*R*)-**58** as a white solid: mp 95−96 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 0.86−1.92 (m, 10H, $(CH_2)_5$), 2.94 (d, 2H, *J* = 8.6 Hz, CH_2), 3.40 (t, 1H, *J* = 8.9 Hz, CH), 7.16−7.38 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.63, 22.55, 24.88, 32.29, 34.71, 36.73, 51.16, 88.55, 127.63, 128.10, 128.59, 137.05, 175.80. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.19; H, 7.87. The enantiomeric excess of (*R*)-**58** was determined to be 54% by CSP HPLC analysis (1% *i*-PrOH/hexane, 2.0 mL/min) using a prototype CSP HPLC column from Professor William Pirkle. The major enantiomer (*R*)-**58** had a retention time of 16.3 min, and the minor enantiomer (*S*)-**58** had a retention time of 21.1 min.

Preparation of (3*R*,5*S*)-3-Phenyl-5-(iodomethyl)-δ-lactone (59). To a stirring solution of (*R*)-**15** (182 mg, 0.89 mmol) in THF (8 mL) and Et_2O (8 mL) was added saturated $NaHCO_3$ solution (16 mL). The mixture was allowed to stir for 10 min before being cooled to 0 °C. Iodine (909 mg, 3.58 mmol) was added, and the mixture was stirred overnight at 0 °C. Et_2O (150 mL) was added, and the organic layer was washed with NaS_2O_3 solution (50 mL), H_2O (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by MPLC (25% EtOAc/hexane) gives the product as a yellow semisolid (189 mg, 67% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 1H, 1H of CH_2), 2.41 (m, 1H, 1H of CH_2), 2.56 (m, 1H, 1H of CH_2), 2.91 (m, 1H, 1H of CH_2), 3.23 (m, 1H, CH), 3.44 (m, 2H, CH_2), 4.40 (m, 1H, CH), 7.20−7.39 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) 7.81, 36.18, 36.85, 37.11, 78.330, 126.32, 127.33, 128.94, 141.98, 169.66. The relative configuration was determined by a difference ^{1}H NMR NOE experiment. Irradiation at δ_H 3.23 ppm (1H, benzylic CH) caused enhancement at δ_H 4.40 ppm (1H, CH, 10.2%). Irradiation at δ_H 4.40 ppm (1H, CH) caused enhancement at δ_H 3.23 ppm (1H, benzylic CH, 11.0%). Anal. Calcd for $C_{13}H_{16}NO_2I$: C, 45.59; H, 4.16. Found: C, 45.88; H, 4.16.

Representative Lithiation of *N*-Methyl-3-(*o*-methoxyphenyl)propanamide (60): Preparation of (*R*)-*N*-Methyl-3-(*o*-methoxyphenyl)-4-phenylbutanamide ((*R*)-61). To (−)-sparteine (0.64 mL, 2.78 mmol) in THF (5 mL) and *tert*-BuOMe (5 mL) at −78 °C was added *s*-BuLi (2.43 mL, 2.55 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was transferred to a solution of *N*-methyl-3-(*o*-methoxyphenyl)propanamide (**60**) (214 mg, 1.11 mmol) in THF (5 mL) and *tert*-BuOMe (5 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 1 h, and then benzyl bromide (0.17 mL, 1.44 mmol) was added. This mixture was then allowed to warm to ambient temperature overnight. HCl (5%, 5 mL) was added, and then the layers were separated. The aqueous layer was extracted with ether (3 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (30% EtOAc/hexane) to give (*R*)-**61** as an oil (223 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55−2.58 (m, 2H, CH_2Ph), 2.62 (d, 3H, *J* = 4.8 Hz, CH_3), 2.87−3.00 (m, 2H, CH_2CO), 3.72−3.82 (m, 4H, OCH_3 and CH), 5.41 (bs, 1H, NH), 6.81−6.89 (m, 2H, Ar), 7.05−7.26 (m, 7H, Ar and C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.15, 38.01, 41.08, 41.27, 55.43, 110.83, 120.75, 125.86, 127.47, 127.97, 128.15, 129.21, 131.54, 140.12, 157.00, 172.45; $[\alpha]^{22}_D$ 28.1° (*c* = 1.2, $CHCl_3$). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.27; H, 7.66; N, 4.85. The enantiomeric excess of (*R*)-**61** was determined to be 80% by conversion to the (*S*)-α-methylbenzylamide derivative and analysis by GC.[21]

(*R*)-*N*-Methyl-3-(*o*-methoxyphenyl)butanamide ((*R*)-62) was obtained using methyl iodide as the electrophile

following a procedure similar to that reported for the preparation of (*R*)-**61**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 63% yield of (*R*)-**62** as an oil which solidified upon standing: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (δ, 3H, J = 7.0 Hz, CH_3), 2.31−2.39 (m, 1H, CH_2), 2.46−2.60 (m, 1H, CH_2), 2.73 (d, 3H, J = 4.8 Hz, CH_3), 3.58−3.65 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 5.49 (bs, 1H, NH), 6.85−6.94 (m, 2H, Ar), 7.16−7.26 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 20.12, 26.19, 30.34, 43.93, 55.31, 110.52, 120.70, 126.89, 127.24, 133.84, 156.63, 172.77. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.75. Found: C, 69.80; H, 8.32; N, 6.72. The enantiomeric excess of (*R*)-**62** was determined to be 80% by conversion to the (*S*)-α-methylbenzylamide derivative and analysis by GC.[21]

(*R*)-*N*-Methyl-3-(*o*-methoxyphenyl)heptanamide ((*R*)-63) was obtained using butyl iodide as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**61**. The crude product was purified by MPLC (35% EtOAc/hexane) to give a 67% yield of (*R*)-**63** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, 3H, J = 7.1 Hz, CH_3), 1.03−1.30 (m, 4H, CH_2CH_2), 1.61−1.668 (m, 2H, CH_2), 2.48 (d, 2H, J = 7.4 Hz, CH_2), 2.66 (d, 3H, J = 4.8 Hz, CH_3), 3.40−3.47 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 5.50 (s, 1H, NH), 6.84−6.94 (m, 2H, Ar), 7.11−7.26 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.96, 22.60, 26.15, 29.56, 34.54, 35.75, 43.10, 43.15, 55.41, 110.69, 1120.79, 127.18, 127.85, 132.32, 157.10, 172.80. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.30; H, 9.27; N, 5.64. $[\alpha]^{22}_D$ 11.1° (c = 1.5, $CHCl_3$). The enantiomeric excess of (*R*)-**63** was determined to be 83% by conversion to the (*S*)-α-methylbenzylamide derivative and analysis by GC.[21]

(*R*)-*N*-Methyl-3-(*o*-methoxyphenyl)-3-trimethylsilyl propanamide ((*R*)-64) was obtained using TMSCl as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**61**. The crude product was purified by MPLC (30% EtOAc/hexane) to give a 68% yield of (*R*)-**64** as a white solid: mp 111−113 °C. $[\alpha]^{22}_D$ −13.0° (c = 1.5, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ −0.06 (s, 9H, $Si(CH_3)_3$), 2.58−2.77 (m, 5H, CH_2 and CH_3), 2.90−2.97 (m, 1H, CH), 3.81 (s, 3H, OCH_3), 5.57 (bs, 1H, NH), 6.81−6.91 (m, 2H, Ar), 7.00−7.21 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) −2.99, 24.49, 26.19, 36.31, 55.05, 110.15, 120.70, 125.70, 127.20, 130.61, 156.12, 173.38. Anal. Calcd for $C_{14}H_{23}NO_2Si$: C, 63.35; H, 8.73; N, 5.28. Found: C, 63.32; H, 8.74; N, 5.28. The enantiomeric excess of (*R*)-**64** was determined to be 80% by conversion to the (*S*)-α-methylbenzylamide derivative and analysis by GC.[21]

(*R*)-*N*-Methyl-3-(*o*-methoxyphenyl)-5-hexenamide ((*R*)-65) was obtained using allyl chloride as the electrophile following a procedure similar to that reported for the preparation of (*R*)-**61**. The crude product was purified by MPLC (40% EtOAc/hexane) to give 67% yield of (*R*)-**65** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39−2.44 (m, 2H, CH_2), 2.49−2.52 (m, 2H, CH_2), 2.65 (d, 3H, J = 4.8 Hz, CH_3), 3.55−3.60 (m, 1H, CH), 3.81 (s, 3H, OCH_3), 4.88−4.98 (m, 2H, CH_2), 5.57−5.71 (m, 2H, NH and C*H*=CH_2), 6.83−6.91 (m, 2H, Ar), 7.12−7.20 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.09, 35.71, 38.86, 41.59, 55.35, 110.72, 116.14, 120.63, 127.35, 127.95, 131.63, 136.50, 156.97, 171.57; $[\alpha]^{22}_D$ −19.4° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.01. Found: C, 71.92; H, 8.19; N, 6.00. The enantiomeric excess of (*R*)-**65** was determined to be 86% by conversion to the (*S*)-α-methylbenzylamide derivative and analysis by GC.[21]

Representative Conversion of an (*o*-Methoxyphenyl)-propanamide to a Hydrocoumarin: Preparation of (*R*)-4-Benzylhydrocoumarin ((*R*)-66). To a solution of (*R*)-**61** (223 mg, 0.79 mmol) in methylene chloride (3 mL) were added triethylamine (0.12 mL, 0.79 mmol), di-*tert*-butyl dicarbonate (345 mg, 1.58 mmol), and 4-(dimethylamino)pyridine (98 mg, 0.79 mmol). The solution was stirred overnight at room temperature. The volatile materials were removed, and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford (*R*)-*N*-Boc-*N*-methyl-3-(*o*-methoxyphenyl)-4-phenylbutanamide.

A solution of the *N*-Boc derivative in THF (2.5 mL), under N_2 atmosphere, was cooled to 0 °C. To this solution was added 10% NaOH (1.0 mL). The reaction mixture was allowed to stir overnight. After removal of THF *in vacuo*, the basic residue was acidified with 10% HCl and extracted with ether (3 × 15 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude acid (134 mg, 63% yield) was obtained as an oil which was not purified but was used for cyclization.

To a solution of the acid (112 mg, 0.41 mmol) in dry methylene chloride (12 mL) at 0 °C was added BBr_3 (0.11 mL, 1.20 mmol) under N_2 atmosphere. The reaction mixture was stirred for 2.5 h, and then H_2O (3 mL) was added. The resulting mixture was allowed to warm to ambient temperature and neutralized by saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and EtOAc (15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (15% EtOAc/hexane) to give (*R*)-**66** as an oil (80 mg, 82% yield, 52% overall yield from (*R*)-**61**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70−2.78 (m, 3H, CH_2 and 1H of CH_2CO), 2.94−3.01 (dd, 1H, J = 6.6, 13.5 Hz, CH_2CO), 3.20−3.28 (m, 1H, CH), 7.01−7.10 (m, 2H, Ar), 7.22−7.33 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 33.73, 37.31, 41.25, 117.06, 124.32, 125.92, 126.77, 127.78, 128.48, 128.57, 129.21, 137.80, 151.26, 168.03. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.49; H, 5.88.

(*R*)-4-Methylhydrocoumarin ((*R*)-67) was prepared from (*R*)-**62** following the procedure detailed above for (*R*)-**66**. The crude product was purified by MPLC (15% EtOAc/hexane) to give (*R*)-**67** as an oil in 49% overall yield from (*R*)-**62**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (d, 3H, J = 7.0 Hz, CH_3), 2.55−2.62 (dd, 1H, J = 7.2 Hz, J = 15.6 Hz, CH_2), 2.81−2.88 (dd, 1H, J = 5.4 Hz, J = 15.8 Hz, CH_2), 3.15−3.22 (m, 1H, CH), 7.04−7.29 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.88, 29.46, 36.77, 116.97, 124.57, 126.48, 127.82, 128.24, 151.20, 168.35. The absolute configuration of (*R*)-**67** was determined by comparison of the optical rotation($[\alpha]^{22}_D$ 26.1° (c = 1.07, benzene) with the literature value ($[\alpha]^{20}_D$ 32°) for (*R*)-**67**.[20]

(*R*)-4-Butylhydrocoumarin (68) was prepared from (*R*)-**63** following the procedure detailed above for (*R*)-**66**. The residue was purified by MPLC (15% EtOAc/hexane) to give (*R*)-**68** as an oil in 46% overall yield from (*R*)-**63**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 0.93−1.40 (m, 4H, CH_2CH_2), 1.50−1.63 (m, 2H, CH_2), 2.71−2.87 (m, 2H, CH_2CO), 2.93−2.99 (m, 1H, CH), 7.04−7.29 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.89, 22.52, 28.78, 34.34, 34.73, 35.11, 117.08, 124.25, 126.85, 127.78, 128.18, 151.24, 168.50. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.17; H, 8.13.

***N*-Methyl-3-(*p*-methoxyphenyl)-3-(trimethylsilyl)propanamide (72)** was obtained starting from amide **69** and by following the lithiation/substitution procedure described above for the preparation of (*R*)-**8**, using TMSCl as the electrophile. The crude product was purified by MPLC (40% EtOAc/hexane) to give **72** as a white solid: mp 55−57 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.08 (s, 9H, $Si(CH_3)_3$), 2.43−2.59 (m, 6H, $CHCH_2$ and CH_3), 3.74 (s, 3H, OCH_3), 5.58 (bs, 1H, NH), 6.75−6.79 (m, 2H, Ar), 6.92−6.96 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) −3.18, 26.13, 31.73, 36.76, 55.01, 113.74, 127.98, 134.05, 156.90, 173.32. Anal. Calcd for $C_{14}H_{23}NO_2Si$: C, 63.35; H, 8.73; N, 5.28. Found: C, 63.36; H, 8.76; N, 5.24. The enantiomeric excess of **72** was determined to be 80% by conversion to the *N*-α-(methylbenzyl)amide derivative followed by analysis of the diastereomeric excess by gas chromatography.[21]

***N*-Methyl-3-(*o*-methylphenyl)-3-(trimethylsilyl)propanamide (73)** was obtained starting from amide **70** and by following the lithiation/substitution procedure described above for the preparation of (*R*)-**8**, using TMSCl as the electrophile. The crude product was purified by MPLC (30% EtOAc/hexane) to give **73** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 6H, $Si(CH_3)_3$), −0.05 (s, 3H, $Si(CH_3)_3$), 2.29−2.30 (bs, 3H, CH_3-Ar), 2.51−2.61 (m, 5H, CH_2 and CH_3), 2.85−2.90 (, m, 1H, CH), 5.35 (bs, 1H, NH), 6.97−7.12 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) −2.87, 20.53, 26.20, 27.33, 37.70, 124.56, 125.59, 125.91, 130.52, 135.62, 141.24, 173.32. Anal. Calcd for $C_{14}H_{23}NOSi$: C, 67.41; H, 9.29; N, 5.62. Found: C, 67.38; H, 9.31;

N, 5.60. CSP HPLC analysis ((*S, S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) indicated 0% ee.

***N*-Methyl-3-(*o*-chlorophenyl)-3-(trimethylsilyl)propanamide (74)** was obtained starting from amide **71** and by following the lithiation/substitution procedure described above for the preparation of (*R*)-**8**, using TMSCl as the electrophile. The residue was purified by MPLC (30% EtOAc/hexane) to give **74** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 6H, Si-$(CH_3)_3$), 2.58−2.75 (m, 5H, $CH_2$and CH_3), 3.17−3.23 (m, 1H, CH), 5.81 (bs, 1H, NH), 6.97−7.32 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 75 MHz) −3.06, 26.20, 28.10, 36.65, 125.83, 126.77, 127.16, 129.61, 133.14, 140.36, 172.52. Anal. Calcd for $C_{13}H_{20}$-NOSiCl: C, 57.86; H, 7.47; N, 5.19. Found: C, 57.91; H, 7.37; N, 5.13. The enantiomeric excess of **74** was determined to be 0% by conversion to the *N*-α-(methylbenzyl)amide derivative followed by analysis of the diastereomeric excess by gas chromatography.[21]

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Supporting Information Available: Preparations of amides **4**, **5**, **42**, **60**, **69**, **70**, and **71** and the X-ray crystal structure for **48** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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