A New Route to the Synthesis of Amino Acids through the Mercury Cyclization of Chiral Amidals

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By means of the mercury cyclization of the unsaturated amidals **3a–e**, obtained from the reaction of 1,3,5-tris-[(*S*)-phenylethyl]hexahydrotriazine (1) and α,β-unsaturated acyl chlorides, diastereomeric mixtures of imidazolidin-4-ones **5–8** and perihydropyrimidin-4-ones **9–10** have been synthesized and easily separated by flash chromatography. The subsequent hydrolysis under acid conditions of the separated heterocycles affords respectively D or L α- and β-amino acids. The regiochemistry of the cyclization has been studied, depending on the substituents of the double bond. Furthermore the absolute configuration of the newly introduced stereogenic center has been attributed on the basis of the ^{1}H NMR spectra of the heterocycles.

Introduction

Recently many synthetic procedures describing the electrophile-promoted cyclofunctionalization of unsaturated substrates containing an internal nucleofile has been reported.[1]

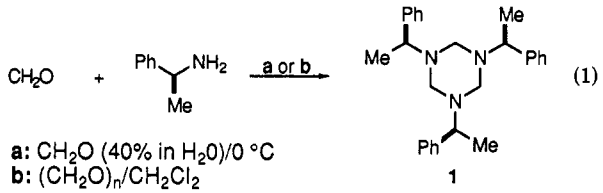
In the last years we have been interested in this kind of approach, associated to the use of commercially available (*S*)-1-phenylethylamine as a chiral source to synthesize enantiomerically pure compounds. This strategy affords diastereomeric mixtures of heterocycles that can be easily separated by flash chromatography. Moreover, starting from the appropriate unsaturated carbamate, urea, or amide,[2] cyclic compounds have been synthesized, with the carbon–hydrogen bond of the phenylethyl group eclipsing the adjacent carbonyl function of the heterocycle. This particular situation favors the identification of the absolute configuration of the newly formed stereogenic center through the comparison of ^{1}H NMR shifts of the couples of diastereomers.

In a preliminary account of this work[3] we reported the synthesis of D- and L-alanine starting from chiral amidals.[4–6] Now we report an extension of this strategy to substrates containing substituted double bonds, further transformations of the organometallic intermediates, and the experimental details, in order to extend this method to the synthesis of α- and β-amino acids.

Results and Discussion

A. Synthesis and Separation of 5-Substituted Imidazolidin-4-ones and 6-Substituted Perihydropyrimidin-4-ones.

The amidals **3a–e** have been obtained through simple steps, starting from the chiral 1,3,5-tris-[(*S*)-1-phenylethyl]hexahydrotriazine, 1.[7] It is known that 1,3,5-hexahydrotriazines are highly reactive compounds which afford, by treatment with acyl chlorides, the corresponding *N*-alkyl-*N*-(chloromethyl)amides in quantitative yields.[8] Thus 1 was obtained simply by treating (*S*)-1-phenylethylamine either with a 40% aqueous solution of formaldehyde or with solid paraformaldehyde in dichloromethane. This compound can be utilized without further purification, nevertheless, the crystallization from petroleum ether afforded a white solid (mp 52–54 °C; $[\alpha]_D$ −70.3°; c = 2, $CHCl_3$).



(1)

a: CH_2O (40% in H_2O)/0 °C
b: $(CH_2O)_n/CH_2Cl_2$

1

The hexahydrotriazine 1 reacted smoothly with 2,3-unsaturated acyl chlorides in dry dichloromethane at 0 °C under argon to give the corresponding *N*-[(*S*)-1-phenylethyl]-*N*-(chloromethyl)amides **2a–e**. The displacement of the chloride group was performed directly by adding the mixture to a saturated solution of ammonia in dry dichloromethane and continuing to bubble gaseous ammonia in the reaction mixture for 20 min. After filtration of ammonium chloride and concentration of the liquid, the amino group was protected by reaction with benzyl chloroformate in a heterogeneous solution of dichloromethane and aqueous $NaHCO_3$ at 0 °C. The amidals **3a–e** were purified by chromatography on neutral alumina or silica gel and obtained as colorless oils in yields ranging from 60 to 80% from the triazine 1.

The synthesis of enantiomerically pure (*R*)- or (*S*)-α-amino acids draws increasing attentions in the recent years.[9] Thus in order to synthesize the optically active *N*-substituted imidazolidin-4-ones that are protected forms of α-amino acids, the amidal **3a** was cyclized in dry dichloromethane, utilizing $Hg(TFA)_2$ (1.1 equiv) as electrophile.[5] The reaction was complete in 20 min at room

(1) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(2) For carbamates, see: (a) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1987**, *43*, 2505. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron* **1987**, *43*, 4377. For ureas and isoureas see: (c) Bruni, E.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron Lett.* **1989**, *30*, 1679. (d) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Synlett* **1990**, 543. (e) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1991**, *47*, 2263. For amides see: (f) Cardillo, G.; Hashem, M. A.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1487.

(3) Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* **1990**, *31*, 6413.

(4) For the use of acetals to extend the nucleophilicity of an hydroxyl group, see: (a) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1974**, *39*, 1474. (b) Stork, G., Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258.

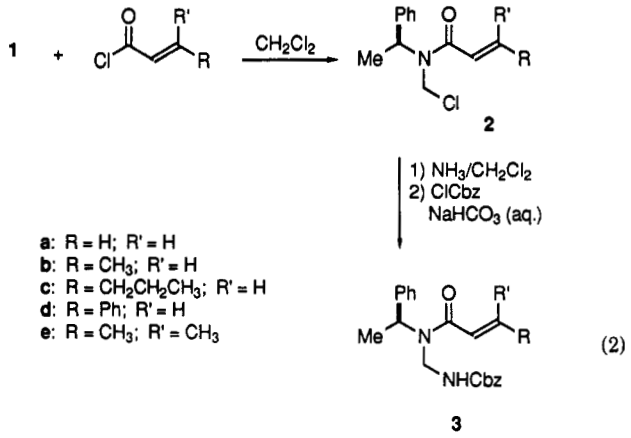
(5) For the use of amidals in cyclofunctionalization reactions, see: Harding, K. E.; Marman, T. H.; Nam, D. H. *Tetrahedron* **1988**, *44*, 5605 and references therein.

(6) For an alternative strategy for the synthesis of amino acids starting from chiral amidals, see: (a) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622. (b) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach,

(7) Zaugg, H. E. *Synthesis* **1984**, 85 and 181.

(8) Gronowitz, S.; Lidert, Z. *Synthesis* **1979**, 810.

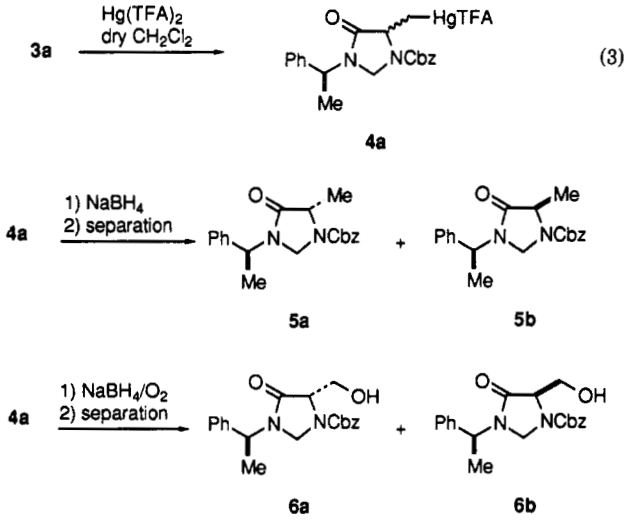
(9) (a) O'Donnell, M. J., Ed. *α-Amino Acids Synthesis*; *Tetrahedron Simposia in Print number 33*; Pergamon: Oxford, 1988; p 5253. (b)



(2)

temperature, and then the solvent was evaporated and replaced with dry acetonitrile. The cleavage of the C–Hg bond was performed under the usual conditions[10b] by adding 1.1 equiv of $NaBH_4$ at 0 °C. The mercury was removed by filtration, and the analysis of the crude mixture by ^1H NMR and capillary column gas chromatography showed, as expected,[10] the signals of two diastereomers in 1:1 ratio. The diastereomeric mixture, separated on silica gel, afforded pure **5a** and **5b** in 80% total yield. The enantiomeric purity and the absolute configuration of each compound were established by ^1H NMR analysis.

When the organomercury compound **4a** was treated with $NaBH_4$ in DMF under O_2,[11] a 1:1 mixture of 5-(hydroxymethyl)imidazolidin-4-ones **6a** and **6b** was obtained. After the usual workup, the mixture was separated on silica gel (cyclohexane/ethyl acetate, 8:2, as eluant), and **6a** and **6b** have been obtained in 60% overall yield.



(3)

In order to establish the influence of a substituent on the double bond for the ring size formation, the amidals **3b** and **3c** have been cyclized with $Hg(TFA)_2$ in dry dichloromethane. The cyclization proceeds with the formation of imidazolidin-4-ones as proven by the IR absorption at 1690 cm^{-1}, characteristic of five-membered rings of this class of compounds.

When electron factors are overwhelming, as in the amidals **3d** and **3e**, the cyclization proceeds with the formation of six-membered rings. The cyclization of **3d** with

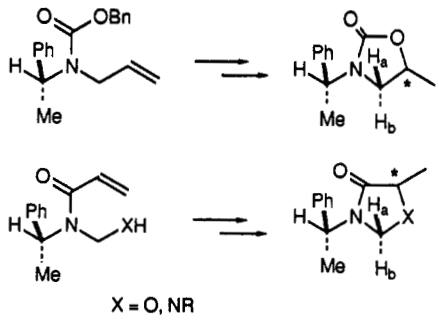


Figure 1.

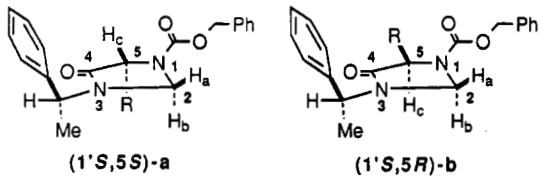
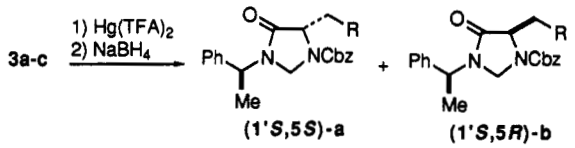


Figure 2.

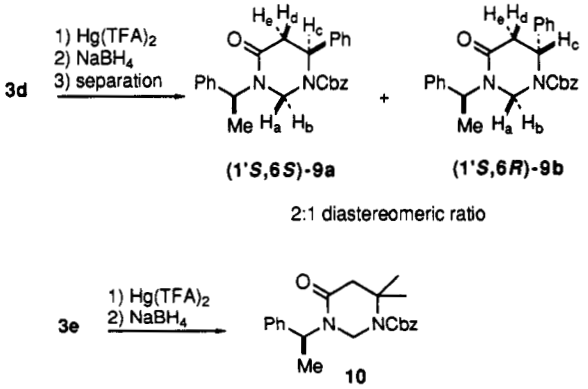
Table I. Synthesis of 5-Substituted Imidazolidin-4-ones



product	R	total yield, %	$[\alpha]_D$, deg a	$[\alpha]_D$, deg b
5	H	78	−89.3	−43.7
6	OH	61	−88.2	−20.9
7	CH_3	73	+95.3	−92.0
8	$(CH_2)_2CH_3$	81	−26.7	−95.1

$Hg(TFA)_2$ in dichloromethane was complete in 2 h. After reduction with $NaBH_4$, a mixture of 6-phenylperihydropyrimidin-4-ones, **9a** and **9b**, was obtained in 80% yield and 2:1 diastereomeric ratio, as shown by GC–MS and ^1H NMR analyses. The chromatographic separation appeared to be troublesome, and only the more abundant diastereomer **9a** could be obtained pure. The IR absorption at 1650 cm^{-1} confirmed the formation of six-membered rings.

Similar results have been obtained starting from **3e**. In fact, after cyclization with $Hg(TFA)_2$ and reduction with $NaBH_4$, the perihydropyrimidin-4-one **10** was obtained pure in 80% overall yield.

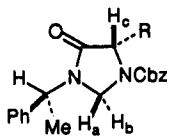


(4)

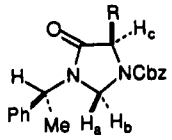
B. ^1H NMR Study on 5-Substituted Imidazolidin-4-ones and 6-Substituted Perihydropyrimidin-4-ones. In preceding works it has been hypothesized through ^1H NMR analysis that the (*S*)-phenylethyl group assumes a

(10) For enantioselective cyclizations starting from chiral amidals, see: (a) Harding, K. E.; Hollingsworth, D. R.; Reibenspies, J. *Tetrahedron Lett.* **1989**, *30*, 4775. (b) Takacs, J. M.; Helle, M. A.; Yang, L. *Tetrahedron Lett.* **1989**, *30*, 1777. (c) Amoroso, R.; Cardillo, G.; Tomasini, C.

Table II. ^{1}H NMR Data of Imidazolidin-4-ones 5–8 in $CDCl_3$ at 300 MHz



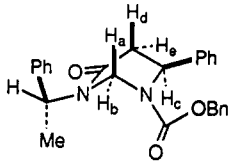
(1'S,5S) a



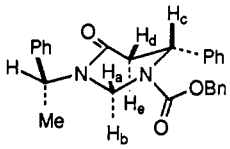
(1'S,5R) b

product	R	δ_{Ha}	δ_{Hb}	δ_{Hc}	$J_{Ha,Hb}$, Hz
5a	CH_3	4.41–4.48[a]	4.70	4.20	6.5
6a	CH_2OH	4.42–4.50[a]	4.70–4.72[a]	4.16–4.27[a]	5.6
7a	CH_2CH_3	4.44–4.51[a]	4.65–4.66[a]	4.25–4.32[a]	6.0
8a	$(CH_2)_3CH_3$	4.45–4.50[a]	4.64–4.65[a]	4.25–4.32[a]	6.0
5b	CH_3	4.31	4.74–4.81[a]	4.24	6.5
6b	CH_2OH	4.35	4.72–4.80[a]	4.19–4.29[a]	6.0
7b	CH_2CH_3	4.27	4.77–4.85[a]	4.32	6.0
8b	$(CH_2)_3CH_3$	4.25	4.77–4.85[a]	4.32	5.7

[a] Owing to the presence of two conformers, two chemical shift values are reported.



(1'S,6S)-9a



(1'S,6R)-9b

Figure 3.

firmed by MM2P[12] calculations for perihydrooxazin-2-ones and oxazolidin-2-ones containing the (*S*)-1-phenylethylamine moiety.[13]

In a similar way as a result of this conformation, the absolute configuration at C_5 of imidazolidin-4-ones **5–8** may be easily attributed on the basis of the shielding effect exerted by the phenyl group of the (*S*)-1-phenylethylamine on H_a of the heterocycle. Moreover an additional shielding effect is exerted by the substituent R, which shifts upfield H_b in compounds **5–8a** and H_a in compounds **5–8b**. The combination of those two effects yields a $\Delta\delta_{Ha,Hb}$ larger in **5–8b** then in **5–8a**.

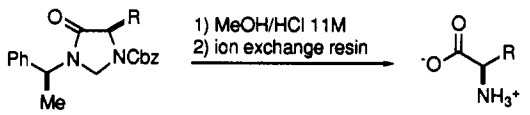
Moreover, due to the presence of the *N*-carbamate protecting group, the ^{1}H NMR spectra recorded at room temperature in $CDCl_3$ at 300 MHz show a mixture of rotamers in ratios ranging from 2:1 to 1:1.[14] In Table II are collected the more significant ^{1}H NMR data for imidazolidin-4-ones **5–8a** and **5–8b**.

Owing to the same conformational effect of the phenylethyl moiety, the absolute configuration of perihydropyrimidin-4-ones **9a** and **9b** can be attributed. The structural assignment of **9a** and **9b** is made on the basis of the nonequivalence of H_a and H_b, assuming that the chemical shift of the hydrogen resonating upfield strongly depends on the shielding of the phenyl ring of the 1'*S* stereogenic center.

The phenyl group on 1'*S* shields H_a, which resonates always upfield in **9a** and **9b** [**9a**, δ_{Ha} 4.31, δ_{Hb} 5.05; **9b**, δ_{Ha} 4.58, δ_{Hb} 4.95]; moreover, due to the additional shielding effect of the substituent at C_6, $\Delta\delta_{Ha,Hb}$ in **9a** is larger then in **9b**. The result of a nuclear Overhauser effect (NOEDIF) experiment performed on **9a** confirmed the stereochemical assignment. In fact the irradiation of H_d (δ 2.71) caused the enhancement of H_a (δ 4.31), showing the cis relationship between H_d and H_a.

Furthermore the coupling constants of H_c–H_d and H_c–H_e in **9a** ($J_{Hc,Hd}$ = 11 Hz, $J_{Hc,He}$ = 6 Hz) show that the phenyl substituent occupies the equatorial position. The same trend is observed for **9b** ($J_{Hc,Hd}$ = 5.5 Hz, $J_{Hc,He}$ = 10 Hz).

Table III. Hydrolysis of Compounds 5–8b



(1'S,5R)-b (R)-(-)

starting material	R	product	yield, %	$[\alpha]_D$,[a] deg
5b	CH_3	**11**	73	−14.1
6b	CH_2OH	**12**	65	−13.9
7b	CH_2CH_3	**13**	71	−7.6
8b	$(CH_2)_3CH_3$	**14**	80	−20.5

[a] The $[\alpha]_D$ values are in agreement with those of commercial samples.

D. Hydrolysis of Imidazolidin-4-ones 5–8b and Perihydropyrimidin-4-ones 9–10. The correct attribution of the stereochemistry of the imidazolidin-4-ones is confirmed by the hydrolysis of the compounds (1'*S*,5*R*)-**5–8b**. The hydrolysis was conducted under acid conditions to avoid racemization and represents an easy step to the synthesis of α-amino acids. Thus the imidazolidin-4-ones, dissolved in methanol and 11 M HCl, were refluxed for 24 h to furnish in quantitative yield a mixture of the corresponding α-amino acids hydrochlorides and (*S*)-1-phenylethylamine hydrochloride.

The (*S*)-1-phenylethylamine was separated during the workup, by treatment with aqueous sodium carbonate followed by extraction with ethyl acetate. On the other hand the purification of the amino acid from sodium chloride was performed on a column of BIORAD AG 50W-X2 resin using NH_4OH (0.015 M) as eluant. The results of the hydrolysis of compounds **5–8b** are reported in Table III. The values of $[\alpha]_D$ are in perfect agreement with those reported for commercial samples.

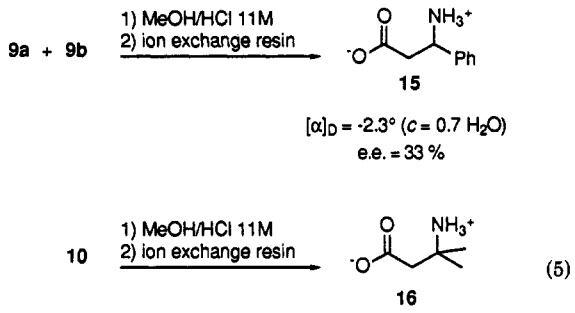
The hydrolysis under acid conditions of the 2:1 mixture of (1'*S*,6*S*)-**9a** and (1'*S*,6*R*)-**9b** afforded the β-phenylalanine **15**. In fact after elution from the column resin with

(12) Allinger, N. L.; Yuh, Y. H. *Program MM2P (QCPE)*, updated by Rohrer D. C. (1984).

(13) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chemistry Lett.* 1988, 87.

confirming that the more abundant heterocycle **9a** has a 1′*S*,6*S* configuration.

In the same manner from the 6,6-dimethylperihydropyrimidin-4-one, **10**, the 3-amino-3-methylbutanoic acid, **16**, was obtained in 75% yield.



In conclusion this work describes the preparation of enantiomerically pure amino acids through simple steps and under mild conditions, by means of the formation of intermediate chiral imidazolidin-4-ones and perihydropyrimidin-4-ones. Nevertheless the cyclofunctionalization of substrates containing electron-deficient double bonds requires the use of $Hg(TFA)_2$ as electrophile.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent. Infrared spectra were recorded with a Perkin-Elmer 682 infrared spectrometer. Melting points were determined in open capillaries and are uncorrected. GCMS analyses were performed with a cross-linked methyl silicone column. Flash chromatography was performed with silica gel 60 (230–400 mesh). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methylene chloride and DMF were distilled over CaH_2 and stored over molecular sieves. Other solvents were used as purchased. (*S*)-1-Phenylethylamine was purchased by Janssen and distilled.

1,3,5-Tris[(*S*)-phenylethyl]hexahydrotriazine, 1. Method A. To an aqueous solution of formaldehyde (40%, 133 mmol, 10 mL) was added (*S*)-1-phenylethylamine (100 mmol, 12.9 mL) at 0 °C. The solution was stirred for 15 min until a yellowish solid precipitated. After 30 min CH_2Cl_2 was added, and the organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. Hexahydrotriazine **1** was obtained pure in quantitative yield (3.95 g) as a low-melting solid and directly used without further purification. Recrystallization from petroleum ether afforded a white solid.

Method B. To a solution of (*S*)-1-phenylethylamine (100 mmol, 12.9 mL) in CH_2Cl_2 (30 mL) was added solid paraformaldehyde (100 mmol, 3.00 g). The homogeneous solution was dried over sodium sulfate and concentrated. Hexahydrotriazine **1** was obtained in quantitative yield (3.9 g) as a low-melting solid and directly used without further purification. Recrystallization from petroleum ether afforded a white solid: mp 52–54 °C; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, J = 7 Hz, NCHCH_3), 3.35 (s, 2 H, NCHN), 3.70 (q, 1 H, J = 7 Hz, NCHCH$_3$), 7.20 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.08, 59.38, 69.98, 126.67, 127.31, 128.06, 144.29; $[\alpha]_D$ −70.3° (c = 2, $CHCl_3$). Anal. Calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.09; H, 8.29; N, 10.49.

General Procedure for the Preparation of Amidal 3. A solution of acyl chloride (45 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of hexahydrotriazine **1** (15 mmol, 5.98 g) in dry CH_2Cl_2 (30 mL) at 0 °C and under argon. After 20 min at 0 °C, TLC analysis of the reaction mixture showed a single spot corresponding to the *N*-(chloromethyl)-*N*-[(*S*)-phenylethyl]amide **2**.

Meanwhile in a 500-mL four-necks flask dry CH_2Cl_2 (200 mL) was saturated with gaseous NH_3. The solution of *N*-(chloromethyl)-*N*-[(*S*)-phenylethyl]amide **2** in CH_2Cl_2 was added dropwise at 0 °C, bubbling NH_3. After 20 min a white precipitate (ammonium chloride) was formed and the bubbling was stopped. The mixture was filtered, and the white solid was washed with CH_2Cl_2. The liquid was concentrated under vacuum, and the corresponding *N*-(aminomethyl)-*N*-[(*S*)-phenylethyl]amide was obtained.

To a solution of *N*-(aminomethyl)-*N*-[(*S*)-phenylethyl]amide in CH_2Cl_2 (50 mL) and aqueous $NaHCO_3$ (50 mL) was added benzyl chloroformate (18 mmol, 2.55 mL) in CH_2Cl_2 (10 mL) dropwise at 0 °C. The mixture was stirred for 10 min at room temperature and then separated in a funnel. The organic layer was dried over Na_2SO_4 and concentrated, and the residue was chromatographed on silica gel or neutral alumina (cyclohexane/ethyl acetate in different ratios). The amidal **3** was obtained in good yield as a colorless oil.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-[[(benzyloxycarbonyl)amino]methyl]acrylamide (3a): chromatography on neutral alumina (cyclohexane/ethyl acetate, 9:1); 60% yield from hexahydrotriazine **1**; IR (film) 3440, 3300, 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (d, 3 H, J = 7.1 Hz, NCHCH_3), 4.58 (s, 2 H, NCH_2N), 5.06 (s, 2 H, OCH_2Ph), 5.23 (q, 1 H, J = 7.1 Hz, CH$_3$CHN), 5.75 (d, 1 H, J = 10 Hz, NCOCH=CHH), 6.06 (bs, 1 H, NH), 6.39 (d, 1 H, J = 15 Hz, COCH=CHH), 6.64 (dd, 1 H, J = 10 Hz, J = 15 Hz, NCOCH=CH$_2$), 7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.12, 50.40, 55.16, 66.45, 126.75, 127.73, 127.87, 128.09, 128.31, 128.47, 128.75, 128.91, 136.40, 140.18, 155.59, 168.37; $[\alpha]_D$ −115.4° (c = 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.94; H, 6.49; N, 8.24.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-[[(benzyloxycarbonyl)amino]methyl]crotonamide (3b): chromatography on silica gel (cyclohexane/ethyl acetate, 9:1); 67% yield from hexahydrotriazine **1**; IR (film) 3440, 3300, 1730, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (d, 3 H, J = 7.1 Hz, CH_3CHN), 1.84 (d, 3 H, J = 6 Hz, CH_3CH=CH), 4.53 (m, 2 H, NCH_2N), 5.01 (s, 2 H, OCH_2Ph), 5.18 (q, 1 H, J = 7.1 Hz, CH$_3$CHN), 6.08 (bs, 1 H, NH), 6.31 (d, 1 H, J = 11 Hz, OCCH=CH), 6.95 (dq, 1 H, J = 6 Hz, J = 11 Hz, OCCH=CH), 7.28 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.47, 18.27, 50.44, 55.02, 66.58, 121.63, 126.75, 127.22, 127.60, 127.83, 128.01, 128.41, 128.65, 140.21, 142.97, 155.27, 168.20; $[\alpha]_D$ −111.5° (c = 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.49; H, 6.79; N, 7.88.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-[[(benzyloxycarbonyl)amino]methyl]hex-2-enamide (3c): chromatography on silica gel (cyclohexane/ethyl acetate, 9:1); 72% yield from hexahydrotriazine **1**; IR (film) 3440, 3300, 1730, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.4, Hz, CH_3CH$_2$CH$_2$), 1.49 (m, 2 H, CH$_3$CH_2CH$_2$), 1.69 (d, 3 H, J = 7.0 Hz, CH_3CHN), 2.19 (q, 2 H, J = 7.4 Hz, CH$_3$CH$_2$CH_2), 4.54 (m, 2 H, NCH_2N), 5.01 (s, 2 H, OCH_2Ph), 5.22 (q, 1 H, J = 7.0 Hz, CH$_3$CHN), 6.08 (bs, 1 H, NH), 6.31 (d, 1 H, J = 11 Hz, OCCH=CH), 6.95 (dq, 1 H, J = 7 Hz, J = 11 Hz, OCCH=CH), 7.28 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.36, 18.17, 21.13, 34.19, 50.34, 54.84, 66.20, 120.15, 126.39, 127.21, 127.50, 127.65, 128.06, 128.30, 136.10, 140.11, 147.35, 155.18, 168.10; $[\alpha]_D$ −95.5° (c = 1.8, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.58; H, 7.39; N, 7.32.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-[[(benzyloxycarbonyl)amino]methyl]cinnamamide (3d): chromatography on silica gel (cyclohexane/ethyl acetate, 9:1); 80% yield from hexahydrotriazine **1**; IR (film) 3420, 3300, 1720, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (d, 3 H, J = 6.8 Hz, NCHCH_3), 4.78 (m, 2 H, NCH_2N), 5.10 (s, 2 H, OCH_2Ph), 5.36 (q, 1 H, J = 6.8 Hz, NCHCH$_3$), 6.12 (bs, 1 H, NH), 6.91 (d, 1 H, OCCH=CH), 7.35 (m, 15 H, Ph), 7.75 (d, 1 H, OCCH=CH); ^{13}C NMR ($CDCl_3$) δ 18.75, 51.03, 55.57, 66.74, 117.38, 126.77, 127.94, 128.12, 128.50, 128.84, 129.88, 135.00, 140.37, 143.69, 157.28, 169.12; $[\alpha]_D$ = −148.9° (c = 2, $CHCl_3$). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.30; H, 6.28; N, 6.71.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-[[(benzyloxycarbonyl)amino]methyl]-3-methylcrotonamide (3e): chromatography on silica gel (cyclohexane/ethyl acetate, 85:15); 72% yield from hexahydrotriazine **1**; IR (film) 3440, 3300, 1730, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (d, 3 H, J = 7.1 Hz, CH_3CHN), 1.86 (s, 3 H, CH$_3$C=), 2.01 (s, 3 H, CH$_3$C=), 4.53 (ABX, 2 H, J = 4.2 Hz, J = 13.5 Hz, NCH$_2$N), 5.07 (s, 2 H, OCH_2Ph), 5.19 (q, 1 H,

21.75, 48.13, 55.47, 66.50, 118.41, 126.07, 127.02, 127.47, 128.36, 128.44, 128.56, 140.11, 148.49, 155.27, 165.91; $[\alpha]_D$ −110.8° (*c* = 2, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.13; H, 7.17; N, 7.67.

General Procedure for Cyclization. To a stirred solution of amidal **3** (3.0 mmol) in dry CH_2Cl_2 (60 mL) was added $Hg(TFA)_2$ (3.2 mmol) at room temperature and under argon. After 20 min the reaction was complete, and the solvent was evaporated and replaced with CH_3CN (200 mL). The solution was cooled at 0 °C, and solid $NaBH_4$ (3.2 mmol, 121 mg) was added. After 30 min at 0 °C, elemental mercury precipitated and was filtered, water was added, and the organic layer was separated, dried, and concentrated under vacuum, and the crude product was chromatographed on silica gel (cyclohexane/ethyl acetate in different ratios). The heterocycles **5** and **7–10** were obtained as liquids or low melting solids.

1-(Benzyloxycarbonyl)-3-(1′-phenyleth-1′-yl)-5-methylimidazolidin-4-ones (5a and 5b): overall yield 78%; isolated ratio 1:1.

(1′*S*,5*S*)-5a: IR (film) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 1.44 (d, 3 H, *J* = 6.8 Hz, OCCHCH_3, major rotamer), 1.50 (d, 3 H, *J* = 6.8 Hz, OCCHCH_3, minor rotamer), 1.56 (d, 3 H, *J* = 7.1 Hz, NCHCH_3), 4.20 (q, 1 H, *J* = 6.8 Hz, H_c), 4.41 (d, 1 H, *J* = 6.5 Hz, H_a, minor rotamer), 4.48 (d, 1 H, *J* = 6.5 Hz, H_a, major rotamer), 4.70 (d, 1 H, *J* = 6.5 Hz, H_b), 5.09 (AB, 2 H, OCH_2Ph, minor rotamer), 5.16 (AB, 2 H, OCH_2Ph, major rotamer), 5.54 (q, 1 H, *J* = 7.1 Hz, NC*H*CH_3), 7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 16.00, 17.39, 48.89, 54.91, 57.98, 67.31, 127.18, 128.18, 128.42, 128.67, 128.94, 136.04, 138.78, 154.03, 170.47; (minor rotamer) 16.00, 16.48, 48.66, 55.07, 57.65, 67.13, 127.18, 128.18, 128.42, 128.67, 128.94, 136.04, 138.78, 153.27, 170.47; $[\alpha]_D$ −89.3° (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.04; H, 6.58; N, 8.34.

(1′*S*,5*R*)-5b: IR (film) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 1.38 (d, 3 H, *J* = 6.4 Hz, OCCHCH_3, major rotamer), 1.46 (d, 3 H, *J* = 6.4 Hz, OCCHCH_3, minor rotamer), 1.56 (d, 3 H, *J* = 7.1 Hz, NCHCH_3), 4.24 (q, 1 H, *J* = 6.4 Hz, H_c), 4.31 (d, 1 H, *J* = 6.5 Hz, H_a), 4.74 (d, 1 H, *J* = 6.5 Hz, H_b, minor rotamer), 4.81 (d, 1 H, *J* = 6.5 Hz, H_b, major rotamer), 5.13 (AB, 2 H, OCH_2Ph, minor rotamer), 5.17 (AB, 2 H, OCH_2Ph, major rotamer), 5.54 (q, 1 H, *J* = 7.1 Hz, NC*H*CH_3), 7.33 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 15.93, 17.41, 48.67, 54.94, 57.97, 67.32, 126.95, 128.17, 128.45, 128.70, 128.97, 136.08, 138.93, 154.05, 170.53; (minor rotamer) 15.93, 16.57, 48.38, 55.08, 57.58, 67.32, 126.95, 128.17, 128.45, 128.70, 128.97, 136.08, 138.93, 153.27, 170.53; $[\alpha]_D$ −43.7° (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.98; H, 6.43; N, 8.27.

1-(Benzyloxycarbonyl)-3-(1′-phenyleth-1′-yl)-5-ethylimidazolidin-4-ones (7a and 7b): overall yield 73%; isolated ratio 1:1.

(1′*S*,5*S*)-7a: mp 55–57 °C; IR (film), 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 0.83 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3, major rotamer), 0.85 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3, minor rotamer), 1.58 (d, 3 H, *J* = 7.1 Hz, NCHCH_3), 1.98 and 2.08 (m, 2 H, CH_2CH_3), 4.25 (t, 1 H, *J* = 6.2 Hz, H_c, major rotamer), 4.32 (t, 1 H, *J* = 6.2 Hz, H_c, minor rotamer), 4.44 (d, 1 H, H_a, *J* = 6.0 Hz, minor rotamer), 4.51 (d, 1 H, H_a, *J* = 6.0 Hz, major rotamer), 4.65 (d, 1 H, H_b, *J* = 6.0 Hz, major rotamer), 4.66 (d, 1 H, H_b, *J* = 6.0 Hz, minor rotamer), 5.13 (AB, 2 H, OCH_2Ph), 5.56 (q, 1 H, NC*H*CH_3, *J* = 7.1 Hz), 7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 7.17, 16.11, 23.82, 48.96, 58.93, 59.65, 67.33, 127.23, 128.10, 128.21, 128.40, 128.67, 128.94, 136.03, 138.67, 154.12, 169.60; (minor rotamer) 7.31, 16.11, 22.89, 48.69, 58.51, 59.78, 67.11, 127.23, 128.10, 128.21, 128.40, 128.67, 128.94, 136.03, 138.67, 154.12, 169.60; $[\alpha]_D$ +95.3° (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.61; H, 6.88; N, 7.97.

(1′*S*,5*R*)-7b: IR (film) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 0.68 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3, major rotamer), 0.75 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3, minor rotamer), 1.59 (d, 3 H, *J* = 7.1 Hz, NCHCH_3), 1.92 (m, 2 H, CH_2CH_3), 4.27 (d, 1 H, *J* = 6.0 Hz, H_a), 4.32 (t, 1 H, *J* = 6.1 Hz, H_c), 4.77 (d, 1 H, *J* = 6.0 Hz, H_b, minor rotamer), 4.85 (d, 1 H, *J* = 6.0 Hz, H_b, major rotamer), 5.16 (AB, 2 H, OCH_2Ph), 5.57 (q, 1 H, *J* = 7.1 Hz, NC*H*CH_3), 7.32 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 7.41, 15.93, 23.05, 48.61, 58.45, 59.89, 67.41, 127.20, 128.14, 128.28, 128.49, 128.76, 128.95, 136.14, 138.98, 154.12, 169.74; $[\alpha]_D$ −92.0° (*c* = 0.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.61; H, 6.92; N, 7.98.

1-(Benzyloxycarbonyl)-3-(1′-phenyleth-1′-yl)-5-butylimidazolidin-4-ones (8a and 8b): overall yield 81%; isolated ratio 1:1.

(1′*S*,5*S*)-8a: mp 50–52 °C; IR (film) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 0.85 (t, 3 H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$, major rotamer), 0.87 (t, 3 H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$, minor rotamer), 1.26 (m, 4 H, $CH_3CH_2CH_2CH_2$), 1.59 (d, 3 H, *J* = 7.2 Hz, NCHCH_3), 1.92 (m, 2 H, $CH_3CH_2CH_2CH_2$), 4.25 (t, 1 H, *J* = 6.3 Hz, H_c, major rotamer), 4.32 (t, 1 H, *J* = 6.3 Hz, H_c, minor rotamer), 4.45 (d, 1 H, *J* = 6.0 Hz, H_a, minor rotamer), 4.50 (d, 1 H, *J* = 6.0 Hz, H_a, major rotamer), 4.64 (d, 1 H, *J* = 6.0 Hz, H_b, major rotamer), 4.65 (d, 1 H, *J* = 6.0 Hz, H_b, minor rotamer), 5.13 (AB, 2 H, OCH_2Ph), 5.55 (q, 1 H, *J* = 7.2 Hz, NC*H*CH_3), 7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 13.72, 15.93, 20.42, 25.14, 30.45, 48.77, 58.69, 58.83, 66.98, 126.73, 127.71, 127.88, 128.14, 128.42, 135.82, 138.40, 153.75, 169.16; (minor rotamer) 13.46, 15.93, 22.11, 25.35, 29.30, 48.55, 58.57, 59.64, 66.74, 126.73, 127.71, 127.88, 128.14, 128.42, 135.82, 138.40, 153.75, 169.16; $[\alpha]_D$ −26.7° (*c* = 2, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42, N, 7.36. Found: C, 72.66; H, 7.48; N, 7.40.

(1′*S*,5*R*)-8b: IR (film) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 0.76 (t, 3 H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$, minor rotamer), 0.85 (t, 3 H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$, major rotamer), 1.20 (m, 2 H, $CH_3CH_2CH_2CH_2$), 1.60 (d, 3 H, *J* = 7.0 Hz, NCHCH_3), 1.88 (m, 2 H, $CH_3CH_2CH_2CH_2$), 2.15 (m, 2 H, $CH_3CH_2CH_2$), 4.25 (d, 1 H, *J* = 5.7 Hz, H_a), 4.32 (t, 1 H, *J* = 6.3 Hz, H_c), 4.77 (d, 1 H, *J* = 5.7 Hz, H_b, minor rotamer), 4.85 (d, 1 H, *J* = 5.7 Hz, H_b, major rotamer), 5.14 (AB, 2 H, OCH_2Ph), 5.58 (q, 1 H, *J* = 7.0 Hz, NC*H*CH_3), 7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ (major rotamer) 13.85, 16.11, 22.42, 25.51, 29.65, 48.98, 58.81, 59.11, 67.40, 126.21, 127.01, 128.07, 128.30, 128.54, 128.69, 135.89, 138.35, 144.90, 169.60; (minor rotamer) 13.68, 16.11, 21.60, 25.75, 30.08, 48.57, 58.34, 59.26, 67.40, 126.21, 127.01, 128.07, 128.30, 128.54, 128.69, 135.89, 138.35, 144.90, 169.60; $[\alpha]_D$ −95.1° (*c* = 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.62; H, 7.50, N, 7.38.

1-(Benzyloxycarbonyl)-3-(1′-phenyleth-1′-yl)-6-phenylperihydropyrimidin-4-ones (9a and 9b): overall yield 80%; isolated ratio 2:1.

(1′*S*,6*S*)-9a: IR (film) 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (d, 3 H, *J* = 7.2 Hz, NCHCH_3), 2.71 (dd, 1 H, $J_{Hd,Hc}$ = 11 Hz, $J_{Hd,He}$ = 15.5 Hz, H_d), 2.95 (dd, 1 H, $J_{He,Hc}$ = 6 Hz, $J_{He,Hd}$ = 15.1 Hz, H_e), 4.31 (d, 1 H, *J* = 13.2 Hz, H_a), 5.05 (d, 1 H, *J* = 13.2 Hz, H_b), 5.10 (m, 3 H, H_c + OCH_2Ph), 5.86 (q, 1 H, *J* = 7.2 Hz, NC*H*CH_3), 7.35 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.26, 50.51, 53.20, 67.74, 125.55, 125.73, 127.10, 127.31, 127.72, 127.84, 127.96, 128.09, 128.28, 128.40, 128.58, 128.74, 128.79, 128.88, 135.72, 139.13, 159.20, 169.50; $[\alpha]_D$ −45.9° (*c* = 0.5, $CHCl_3$). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.38; H, 6.34; N, 6.81.

(1′*S*,6*R*)-9b: IR (film) 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (d, 3 H, *J* = 7.2 Hz, NCHCH_3), 2.79 (dd, 1 H, $J_{He,Hc}$ = 10 Hz, $J_{He,Hd}$ = 15 Hz, H_e), 2.98 (dd, 1 H, $J_{Hd,Hc}$ = 5.5 Hz, $J_{Hd,He}$ = 15 Hz, H_d), 4.58 (d, 1 H, *J* = 12.1 Hz, H_a), 4.95 (d, 1 H, *J* = 12.1 Hz, H_b), 5.02 (m, 3 H, H_c + OCH_2Ph), 5.93 (q, 1 H, *J* = 7.2 Hz, NC*H*CH_3), 7.35 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.26, 50.51, 54.65, 67.99, 125.55, 127.10, 127.31, 127.59, 127.72, 127.84, 127.96, 128.09, 128.28, 128.40, 128.58, 128.74, 128.79, 128.88, 135.72, 139.13, 159.50, 169.50.

1-(Benzyloxycarbonyl)-3-(1′-phenyleth-1′-yl)-6,6-dimethylperihydropyrimidin-4-ones (10): yield 75%; IR (film) 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H, CH_3CN), 1.47 (s, 3 H, CH_3CN), 1.48 (d, 3 H, *J* = 7.1 Hz, CH_3CHN), 2.54 (AB, 2 H, $OCCH_2C$), 4.50 (d, 1 H, *J* = 13.2 Hz, H_a), 4.81 (d, 1 H, *J* = 13.2 Hz, H_b), 5.05 (AB, 2 H, OCH_2Ph), 5.82 (q, 1 H, *J* = 7.1 Hz, NC*H*CH_3), 7.26 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.38, 26.48, 47.85, 49.75, 53.09, 55.35, 66.99, 126.94, 127.48, 127.88, 127.99, 128.34, 128.39, 135.94, 139.60, 169.50; $[\alpha]_D$ −51.7° (*c* = 3, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.17; H, 7.20; N, 7.69.

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