Articles

Synthesis of the Chromophore of Pseudobactin, a Fluorescent Siderophore from *Pseudomonas*

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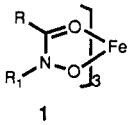
Protected forms of dihydroxyphenylalanine (DOPA) were converted to the corresponding dihydroquinolin-2-ones 13 by nitration and reductive cyclization. Subsequent N-alkylation with α-halo-γ-aminobutryic acid derivatives provided the carbon framework 12 for the chromophore of pseudobactin. Conversion to protected forms of the fluorescent chromophore 5 was accomplished by reaction of 12 with Lawesson's reagent to produce the corresponding thioamide which was cyclized by reaction with mercuric acetate.

Introduction

Each strain of *Pseudomonas* apparently produces a unique water-soluble fluorescent pigment which serves as a siderophore. Siderophores are growth promoting compounds which are synthesized by organisms, especially under iron-deficient conditions, to bind iron and promote its transport into cells.[1-3] Most microbial siderophores contain multiple hydroxamic acid (1) and/or catechol (2) derivatives which effectively chelate ferric ion. The



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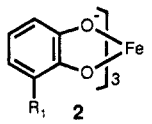

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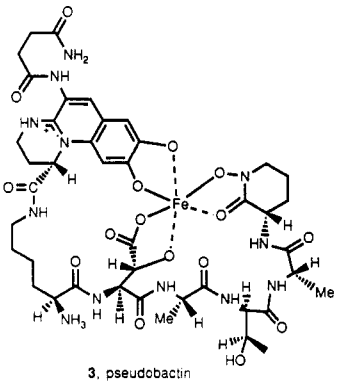
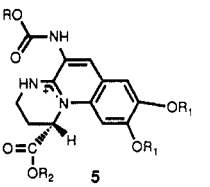
fluorescent siderophores of the individual strains of *Pseudomonas* are most frequently referred to as pyoverdines,[4-10] although the term pseudobactin has been used for the related fluorescent siderophore from *Pseudomonas fluorescensputida*.[11-14] Some *Azotobacter*, such as *Azotobacter vinlandii*, also produce a fluorescent yellow-green peptide called azotobactin.[7,15,16] Each of these iron chelating agents contains three bidentate ligands arranged in a novel peptide. Structures of pseudobactin 3 and azotobactin 4 illustrate the apparent complexity of these important microbial growth factors.



3, pseudobactin



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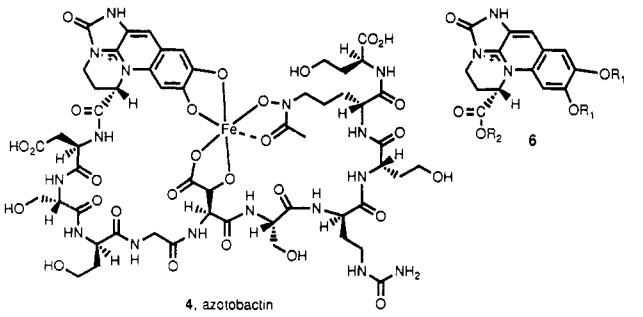

4, azotobactin

6

Since the discovery of the pyoveridines, pseudobactin, and azotobactin, considerable effort has been expended to understand and influence their essential role in promoting the growth of their parent organisms. This is especially appropriate since several strains of *Pseudomonas* are severe human pathogens.[17,18] *Pseudomonas aeruginosa* causes cystic fibrosis and septicemia in weakened patients. Pseudomonal infections are often the most difficult to treat, even with modern antibiotics. On the other hand, specific strains of *Pseudomonas putida* and *Pseudomonas fluorescens* rapidly colonize the roots of

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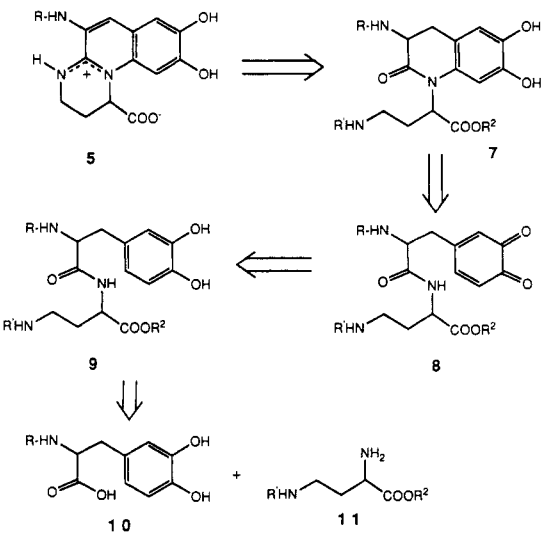
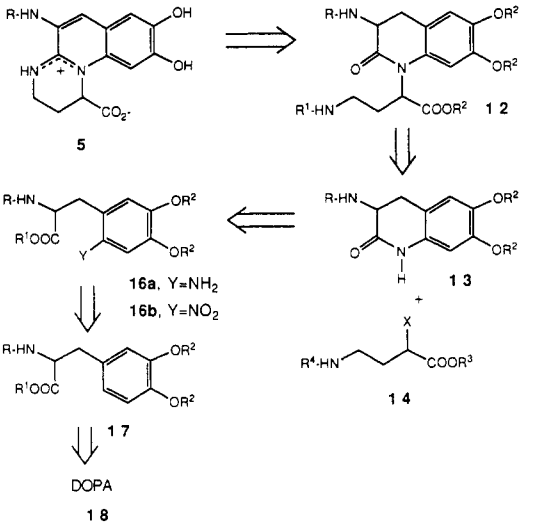
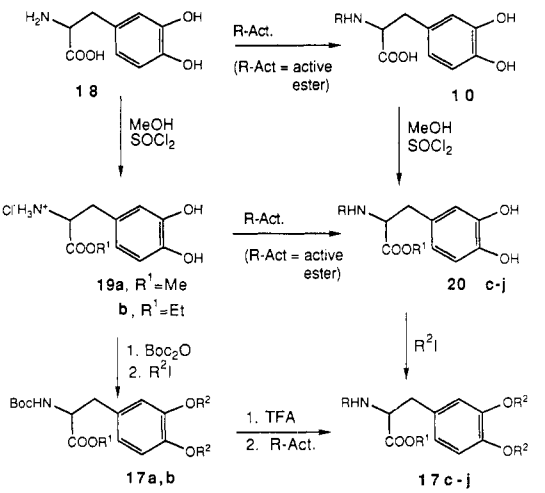
Scheme I



Scheme II



Scheme III



several types of plants and cause statistically significant increases in crop yields.[11,19-21] These bacteria, often called plant growth-promoting rhizobacteria (PGPR), produce pseudobactin (3) which strongly complexes ferric ion (pK_{assoc} = 30–32) and make it unavailable for the growth of other potentially harmful microorganisms. Pseudobactin contains an unusual linear peptide with alternating L- and D-amino acids which presumably minimizes its susceptibility to various proteases. The iron-chelating groups consist of a hydroxamic acid, incorporated as cyclo-δ-*N*-hydroxyornithine, an α-hydroxy acid, from β-hydroxyaspartic acid, and a catechol derivative. The catechol is incorporated in the characteristic fluorescent quinoline component which is nearly invariant, and perhaps essential, among the largest group of pseudomonal siderophores. A minor, but notable variation, is pseudobactin A,[22] a colorless siderophore isolated from *Pseudomonas* B_{10} which contains a dihydroquinoline moiety. Pseudobactin A readily oxidizes to the fluorescent pseudobactin.[22]

We have initiated a program to synthesize and study pseudomonal siderophores with the long term intent to design and develop agriculturally and therapeutically effective agents. This paper describes in detail[23] our successful efforts to synthesize protected forms of the key fluorescent component **5** of the pseudomonal siderophores and the related fluorescent component **6** of azotobactin.

Results and Discussion

The resemblance of fluorescent fragments **5** and **6** to the physiologically important amino acid dihydroxyphenylalanine (DOPA, **10**) prompted us to use it as the basis for our retro synthetic analyses. The most direct synthetic approach (Scheme I) was anticipated to involve simple coupling of protected forms of DOPA **10** and diaminobutyric acid **11** to give dipeptide **9**, followed by oxidation to the quinone **8**, subsequent cyclization to **7**, and final reductive elaboration to **5**. Chemical and enzymatic mediated oxidations of DOPA and a number of its derivatives to DOPA quinone have ample precedent.[24] The susceptibility of DOPA quinone to nucleophiles has also been exploited. While intermolecular nucleophilic addition reactions occur predominantly at positions ortho to either of the original catechol hydroxyl groups,[25] intramolecular delivery of nucleophiles can be controlled to give the desired meta type substitution products.[26-28] However, preliminary attempts to apply an oxidative approach to the synthesis of the pseudobactin chromophore failed. The substrates were readily prepared by synthesizing appropriately protected diaminobutyric acid derivatives (**11**) and coupling them to the α-amino protected DOPA (**10**). Oxidation of the product was attempted chemically with ceric ammonium nitrate,[27] other oxidants, and enzymatically with mushroom tyrosinase.[26] The chemical oxidations produced a multitude of products along with unreacted substrate. The enzymatic attempt was hindered by poor substrate solubility. Further studies, using the enzyme in organic solvents,[29] are being considered.

An alternate synthetic approach, summarized in Scheme II, is the main focus of this paper. Conceptually, this approach first required amination of the aromatic ring of DOPA to produce **16a**. Subsequent cyclization to amide

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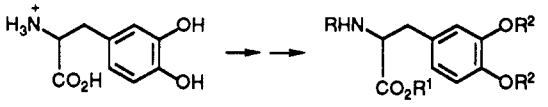
Table I

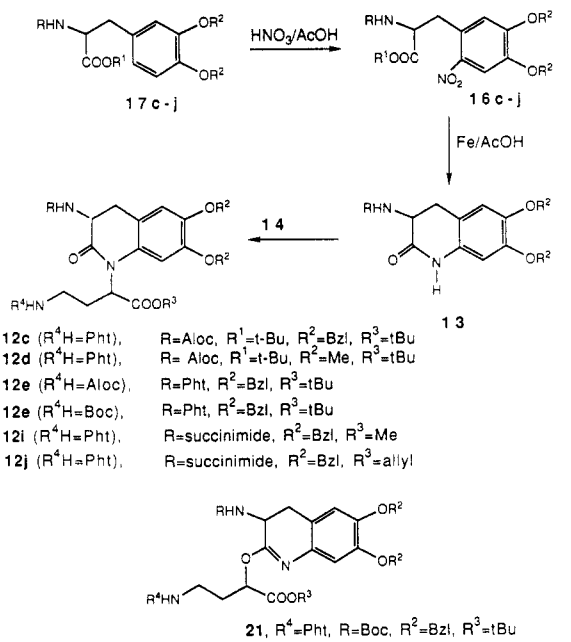


18 17

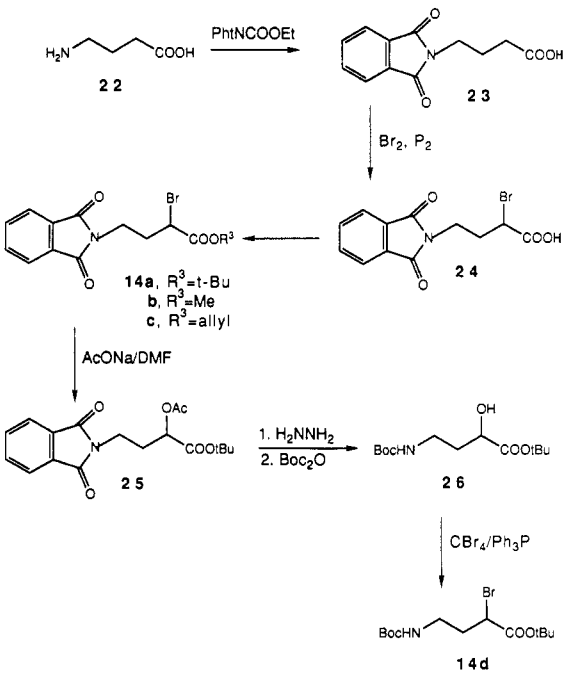
no.	R	R^1	R^2	conf.	method	overall yield, %	mp, °C	acylating agent
				L	A	97	88–90	
17a	Boc	Et	CH_2Ph	D	A	96	96–7	Boc_2O[a]
				L	A	80	65–7	
17b	Boc	Et	Me	DL	A	90	85–6	Boc_2O
				L	B	100	61–2	
					A	90	62–4	Allyloxycarbonyl
17c	Aloc	Et	CH_2Ph	DL	B	79	61–2	chloride
				L	B	100	55–6	
17d	Aloc	Et	Me	DL	B	100	44–6	AlocCl
				L	A[b]	70	oil	
					A	66	oil	*N*-(carboethoxy)phthalimide
17e	Pht	Et	CH_2Ph	DL	B[c]	75	oil	
					A	38	64–8	
17f	$MeO_2CCH_2CH_2CO$	Et[d]	CH_2Ph	DL	B	93	66–7	$MeO_2C(CH_2)_2CO_2Su$[f]
17g	$MeO_2CCH_2CH_2CO$	Me[d]	CH_2Ph	DL	A	57	88–90	$MeO_2C(CH_2)_2CO_2Su$[f]
17h	$EtO_2CCH_2CH_2CO$	Et[e]	CH_2Ph	DL	A	38	90–92	$MeO_2C(CH_2)_2CO_2Su$[f]
17i	Succinimide	Et[e]	CH_2Ph	DL	A	52	118–20	$MeO_2C(CH_2)_2CO_2Su$[f]
17j	Succinimide	Me[d]	CH_2Ph	DL	A	25	114–17	$MeO_2C(CH_2)_2CO_2Su$[f]

[a] Di-*tert*-butyl dicarbonate. [b] Dopa was first acylated and then esterified and finally alkylated. [c] Acylation was done in CH_3CN in the presence of DMAP. [d] Alkylation reaction was done in acetone. [e] Alkylation was accomplished in ethanol. [f] Su = N-succinimidyl.

Scheme IV



Scheme V



13 and alkylation with a protected α-halo-γ-aminobutyric acid derivative **14** would produce **12** which contains the requisite carbon framework for completion of the synthesis of the fluorescent chromophore **5**. The successful implementation of this plan and its extension to the synthesis of the azotobactin chromophore **6** is described next.

As shown in Table I and Scheme III, a number of fully protected DOPA derivatives **17** were prepared by standard techniques in excellent overall yields. The first additional nitrogen required was introduced nearly quantitatively as a nitro group by treating various forms of **17** with nitric acid in acetic acid at 0 °C for 2 to 3 h (Scheme IV). Subsequent heating of the nitro derivatives with iron powder in acetic acid[30] resulted in clean reduction to the amino group and cyclization to the dihydroquinoline derivatives **13** when the allyloxycarbonyl or phthaloyl protected substrates were used. Other α-amino protecting groups, including the Boc and troc ((trichloroethoxy)-carbonyl) groups, were incompatible with the nitration, reduction, and cyclization conditions. Early incorporation of the succinoyl side chain, eventually needed at the α-amino position of the pseudobactin chromophore, also was incompatible with this reaction sequence, since predominant cyclization to the corresponding succinimide was observed.

As shown in Schemes II and IV, elaboration of the protected dihydroquinoline **13** required introduction of another four carbon frgment and eventual cyclization to the chromophore skeleton **5**. The first step in realizing these goals was anticipated to be N-alkylation of **13** with

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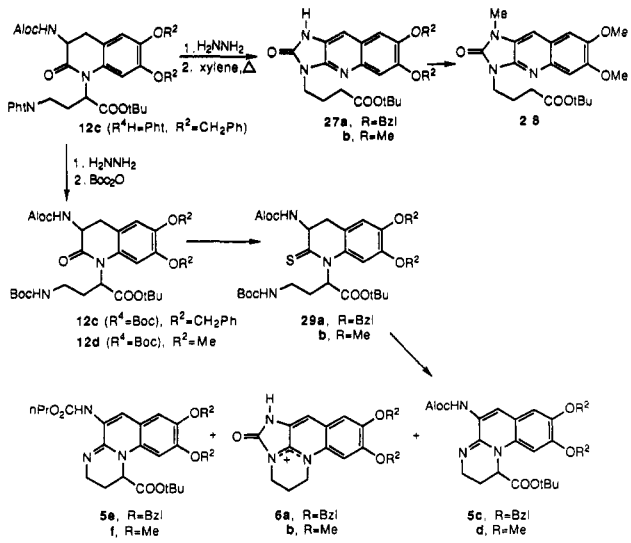
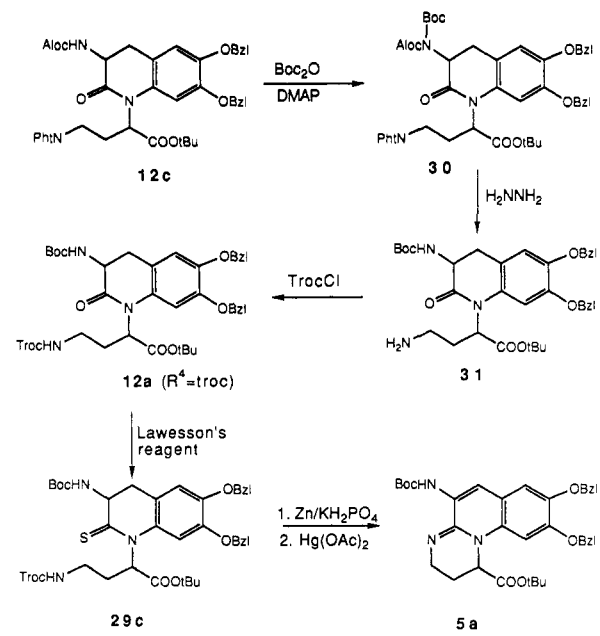
Scheme VI



Scheme VII



a suitably protected α-halo-γ-aminobutyric acid.[31] This fragment was prepared initially in racemic form by the process shown in Scheme V. Thus, the amino group of γ-aminobutyric acid (**22**) was first protected as the corresponding phthalimide **23**. α-Bromination produced **24** which was readily converted to the corresponding *tert*-butyl (**14a**), methyl (**14b**), and allyl (**14c**) esters. With the intent of eventually preparing samples of the pseudobactin chromophore with different modes of protection on each functional group suitable for sequential elaboration to pseudobactin itself, the *tert*-butyl ester **14a** was chosen for the alkylation studies. Treatment of **13** with sodium hydride in THF followed by addition of **14a** cleanly produced the expected diastereomeric mixture of the desired N-alkylation product **12c** (R^4 = Pht, Scheme IV) in over 90% yield, despite requiring 72–96 h to complete the reaction.

Removal of the phthaloyl group from **12c** (R^4 = Pht, Scheme VI) with hydrazine produced the corresponding free amine. Attempted cyclization of the free amine to the ring system corresponding to **5** by refluxing it in xylene produced the alternate tricycle **27a** instead. Apparently, the intended first cyclization occurred followed by reaction of the intermediate amine with the allyloxy protecting group to give an imide with concomitant aromatization and cleavage of the C–N bond formed in the earlier alkylation reaction. Cyclization reactions using milder conditions were ineffective. Thus, an alternative process was developed (Scheme VI).

This route relied on the use of the corresponding thioamide (**29**) to facilitate the desired cyclization. As before, the phthaloyl group of **12c,d** (R^4 = Pht) was removed with hydrazine and the resulting free amine was reprotected as its Boc derivative **12c,d** (R^4 = Boc). Reaction of **12c,d** with Lawsson's reagent[34] in refluxing benzene provided the desired thioamides **29a,b** nearly quantitatively after column chromatography. Careful removal of the Boc group with *p*-toluenesulfonic acid proceeded without loss of the *tert*-butyl ester.[35] Treatment of the resulting amine with mercuric acetate in a mixture of benzene and THF, and a small amount of ethanol to accelerate the reaction, produced three fluorescent products. The three were identified as the desired protected pseudobactin chromophore (**5c,d**), the same chromophore, but with reduction of the double bond of the (allyloxy)carbonyl protecting group (**5e,f**), and the tetracycle (**6a,b**) corresponding to the chromophore of azotobactin.

Use of a more bulky amino protecting group (i.e., phthaloyl or Boc) on the penultimate product was anticipated to avoid further cyclization to the azotobactin chromophore (**6**). As already indicated, the [(allyloxy)carbonyl]amino and phthaloylamino protecting groups were most compatible with the sequence developed for the synthesis of the desired 3-amino-6,7-bis(benzyloxy)quinolin-2-one derivatives. Use of the phthaloyl protecting group was tested by alkylation of **13e** (Scheme IV) with α-bromo-γ-[(*tert*-butoxycarbonyl)amino]butyric acid (**14d**). Interestingly, a mixture of O- and N-alkylated products (**21** and **12e**) were isolated in 58% combined yield. Separation and attempted thioamidation of **21** resulted in complete decomposition. This prompted use of the bulky and less reactive Boc group.

Since the Boc group was incompatible with some of the early synthetic steps utilized for the preparation of precursors of **5**, it was introduced at a later stage. Thus, *tert*-butoxycarbonylation of **12c** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of DMAP[36] gave the fully protected amine **30** in quantitative yield (Scheme VII). Treatment of **30** with hydrazine hydrate removed both the phthaloyl and aloc groups to provide **31** in 90% yield. The free amine of **31** was protected as the trichloroethoxy (troc) carbamate to give **12a** (R^4 = troc), also in 90% yield. Surprisingly, **5a** and **6a** were also formed in 8% and 2% yield respectively. Amide **12a** (R^4 = troc) was converted to the corresponding thioamide **29c** in 64% yield by reaction with Lawesson's reagent. The troc group was removed with zinc in an aqueous monopotassium phosphate solution, and the resulting free amine was immediately cyclized by treatment with mercuric acetate in ethanol to produce **5a** in 90% overall yield from **29c**.

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In summary, protected forms of the fluorescent chromophore of pseudobactin (5) and azotobactin (6) have been prepared for the first time. The resemblance of the chromophores to dihydroxyphenylalanine (DOPA) and their ease of synthesis from DOPA further implicates this amino acid in the biosynthesis of the pseudomonal chromophores. Detailed studies of the biosyntheses of the chromophores are also in progress.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 spectrophotometer. Proton NMR spectra were obtained on Varian EM-90, Nicolet NB-300, or GE-300 spectrophotometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ units). Mass spectra were recorded on DuPont DP102 and Finnigan MAT Model 8430 spectrometers. Optical rotations were determined with a Rudolph Autopol III instrument. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All solvents were distilled and dried by standard methods.

Esters of *N*-Acyl-3,4-dialkoxyphenylalanine (17). General Procedure. Method A. To a solution of 0.1 mol of DOPA (18) in 400 mL of methanol at −40 °C was added 0.11 mol of thionyl chloride dropwise, and the reaction mixture was stirred for 2 days at room temperature. The methanol was removed under reduced pressure, and the residue was dissolved in 200 mL of H_2O. To this solution was added 0.2 mol of $NaHCO_3$, followed by 0.11 mol of an acylating agent in 150 mL of THF, and the reaction mixture was stirred overnight. The THF was removed under reduced pressure. The aqueous suspension of product **20** was filtered. The solid was washed with H_2O and dried under vacuum. Next, 0.1 mol of **20** was dissolved in 500 mL of absolute ethanol, and 0.22 mol of anhydrous K_2CO_3, 10 mmol of NaI, and 0.210 mol of alkyl halide were added. The reaction mixture was refluxed for 4 h. The reaction mixture was then cooled to room temperature and poured into 2 L of H_2O with vigorous stirring. The precipitated product was filtered off, washed with H_2O, dried under vacuum, and recrystallized from ethanol. The results are presented in Table I.

Method B. To the 0.1 mol of **17a** in 100 mL of CH_2Cl_2 was added 0.4 mol of TFA, and the reaction mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure, and 0.2 mol of $NaHCO_3$ in 100 mL of H_2O followed by 0.11 mol of acylating agent in 100 mL of ethyl acetate was added. The reaction mixture was stirred at room temperature overnight. The ethyl acetate layer was separated, washed with H_2O, 1 N HCl, H_2O, and brine, and dried over $MgSO_4$. After the ethyl acetate was removed under reduced pressure, the residue was recrystallized from ethanol (see Table I).

DL-**17a**: NMR (90 MHz, $CDCl_3$) δ 1.2 (t, 3 H, J = 7 Hz), 1.43 (s, 9 H), 3.0 (d, 2 H, J = 7 Hz), 4.1 (q, 2 H, J = 7 Hz), 4.5 (m, 1 H), 5.2 (s, 4 H), 6.9 (m, 3 H), 7.5 (m, 10 H); IR (Nujol) 3380, 1755, 1680 cm^{-1}; MS (Cl-*i*-Bu) m/e 506 (M + 1), 450 (M − 56).

L-**17a**: NMR identical to that given above; $[\alpha]_D$ = +25.0 (c = 2, CH_2Cl_2).

DL-**17b**: NMR (90 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz), 1.4 (s, 9 H), 3.02 (m, 2 H), 3.85 (s, 6 H), 4.17 (q, 2 H, J = 7 Hz), 4.53 (m, 1 H), 5.0 (d, 1 H), 6.66 (d, 2 H), 6.8 (d, 1 H); IR (Nujol) 3320, 1730, 1700 cm^{-1}; MS (CI with isobutane) m/e 354 (M + 1), 298 (M − 56).

L-**17b**: NMR (90 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 1.4 (s, 9 H), 3.02 (m, 2 H), 3.86 (s, 6 H), 4.16 (q, 2 H, J = 7 Hz), 4.5 (m, 1 H), 5.0 (d, 1 H), 6.67 (d, 2 H), 6.78 (d, 1 H); $[\alpha]_D$ = +34.2 (c = 2.2, CH_2Cl_2).

DL-**17c**: NMR (90 MHz, $CDCl_3$) δ 1.16 (t, 3 H, J = 7 Hz), 3.0 (d, 2 H, J = 7 Hz), 4.1 (q, 2 H, J = 7 Hz), 4.53 (d, 2 H, J = 6 Hz), 5.1 (s + m, 6 H), 5.77 (m, 1 H), 6.72 (m, 3 H), 7.4 (m, 10 H); IR (Nujol) 3340, 1745, 1685 cm^{-1}; MS (CI with isobutane) m/e 490 (M + 1).

L-**17c**: NMR identical with that given above for the racemic material; $[\alpha]_D$ = +31.1 (c = 2, CH_2Cl_2).

DL-**17d**: NMR (90 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 3.05 (m, 2 H), 3.85 (s, 6 H), 4.16 (q, 2 H, J = 7 Hz), 4.6 (m, 3 H), 5.22 (m, 3 H), 5.9 (m, 1 H), 6.62 and 6.82 (two d, 3 H, J = 8 Hz); IR (Nujol) 3320, 1750, 1690 cm^{-1}; MS (EI) m/e 337 (M$^+$), 236, 151; high-resolution MS for $C_{17}H_{23}NO_6$ calcd 337.1525, found 337.1520–337.1535.

L-**17d**: NMR (90 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 3.10 (m, 2 H), 3.83 (two s, 6 H), 4.16 (q, 2 H, J = 7 Hz), 4.62 (m, 3 H), 5.25 (m, 3 H), 5.88 (m, 1 H), 6.62 (d, 2 H, J = 7 Hz), 6.78 (d, 1 H, J = 8 Hz); $[\alpha]_D$ = +40.7 (c = 2, CH_2Cl_2).

DL-**17e**: NMR (90 MHz, $CDCl_3$) δ 1.2 (t, 3 H, J = 7 Hz), 3.13 (d, 2 H, J = 8 Hz), 4.23 (q, 2 H, J = 7 Hz), 4.95 and 5.0 (two s, 4 H), 5.1 (m, 1 H), 6.72 (m, 3 H), 7.4 (m, 10 H), 7.72 (m, 4 H); IR (Nujol) 1770, 1735, 1725 cm^{-1}; MS (CI with isobutane) m/e 536 (M + 1), 535 (M$^+$).

L-**17e**: NMR (90 MHz, $CDCl_3$) δ 1.13 (t, 3 H, J = 7 Hz), 3.45 (d, 2 H, J = 7 Hz), 4.1 (q, 2 H, J = 7 Hz), 4.95 (two s, 4 H), 5.05 (m, 1 H), 6.67 (m, 3 H), 7.3 (m, 10 H), 7.7 (m, 4 H).

17f: NMR (90 MHz, $CDCl_3$) δ 1.1 (t, 3 H, J = 7 Hz), 2.45 (m, 4 H), 3.0 (d, 2 H, J = 6 Hz), 3.72 (s, 3 H), 4.1 (q, 2 H, J = 7 Hz), 4.8 (m, 1 H), 5.1 (two s, 4 H), 6.2 (d, 1 H, J = 8 Hz), 6.75 (m, 3 H), 7.35 (m, 10 H); IR (Nujol) 3320, 1730, 1710, 1650 cm^{-1}; MS (EI) m/e 519 (M$^+$), 388, 91.

17g: NMR (90 MHz, $CDCl_3$) δ 2.47 (m, 4 H), 3.0 (d, 2 H, J = 6 Hz), 3.66 (two s, 6 H), 4.8 (m, 1 H), 5.1 (two s, 4 H), 6.17 (d, 1 H, J = 7 Hz), 6.75 (m, 3 H), 7.4 (m, 10 H); IR (Nujol) 3320, 1740, 1720, 1650 cm^{-1}; MS (EI) m/e 505 (M$^+$), 374, 91.

17h: NMR (90 MHz, $CDCl_3$) δ 1.15 (two t, 6 H, J = 7 Hz), 2.48 (m, 4 H), 3.0 (d, 2 H, J = 6 Hz), 4.1 (two q, 4 H, J = 7 Hz), 4.86 (m, 1 H), 5.1 (two s, 4 H), 6.3 (d, 1 H, J = 7 Hz), 6.72 (m, 3 H), 7.33 (m, 10 H); IR (Nujol) 3300, 1740, 1720, 1640 cm^{-1}; MS (CI with isobutane) m/e 534 (M + 1), 488.

17i: NMR (90 MHz, $CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 2.4 (s, 4 H), 3.4 (m, 2 H), 4.2 (q, 2 H, J = 7 Hz), 4.95 (m, 1 H), 5.1 (s, 4 H), 6.72 (m, 3 H), 7.4 (m, 10 H); IR (Nujol) 1770, 1740, 1700 cm^{-1}; MS (Cl-*i*-Bu) m/e 488 (M + 1), 442; mp 118–120 °C.

17j: NMR (90 MHz, $CDCl_3$) δ 2.4 (s, 4 H), 3.36 (d, 2 H, J = 7 Hz), 3.72 (s, 3 H), 4.97 (m, 1 H), 5.1 (s, 4 H), 6.71 (m, 3 H), 7.4 (m, 10 H); IR (Nujol) 1770, 1740, 1700 cm^{-1}; MS (EI) m/e 473 (M$^+$), 374, 91.

***N*-Acyl-3,4-dialkoxy-6-nitrophenylalanine Esters (16c–j). General Procedure.** To a solution of 0.1 mol of **17c–j** in 200 mL of glacial acetic acid at 0 °C was added 75 mL of nitric acid (d = 1.4) dropwise, and the reaction was stirred at this temperature for 2 h. The solution was poured into 1 L of H_2O, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with H_2O, 10% $NaHCO_3$ solution, H_2O, and brine, dried over anhydrous $MgSO_4$, and filtered. After the ethyl acetate was removed under reduced pressure, the residue was recrystallized from ethanol to provide the nitrated product **16**.

DL-**16c**: 88% yield; mp 105–107 °C; NMR (90 MHz, $CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz), 3.4 (m, 2 H), 4.1 (q, 2 H, J = 7 Hz), 4.82 (m, 3 H), 5.17 (m, 4 H), 5.82 (m, 1 H), 6.82 (s, 1 H), 7.4 (m, 10 H), 7.72 (s, 1 H); IR (Nujol) 3340, 1745, 1680 cm^{-1}; MS (CI with isobutane) m/e 535 (M + 1).

L-**16c**: 95% yield; mp 105–106 °C.

DL-**16e**: 76% yield; NMR (90 MHz, $CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 3.42 (m, 1 H), 4.05 (m, 1 H), 4.18 (q, 2 H, J = 7 Hz), 4.76 (d, 2 H, J = 6 Hz), 5.06 (s, 4 H), 5.4 (dd, 1 H), 7.0 (s, 1 H), 7.33 (m, 10 H), 7.7 (m, 5 H); MP 140–141 °C; IR (Nujol) 1780, 1735, 1710 cm^{-1}; MS (CI with isobutane) m/e 581 (M + 1), 580 (M).

L-**16e**: 75% yield; oil.

DL-**16d**: 85% yield; mp 98–100 °C; NMR (90 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 3.33 (dd, 1 H, J = 7 and 15 Hz), 3.52 (dd, 1 H, J = 7 and 15 Hz), 3.94 (s, 6 H), 4.16 (q, 2 H, J = 7 Hz), 4.5 (d, 2 H, J = 6 Hz), 4.65 (m, 1 H), 5.25 (m, 2 H), 5.55 (d, 1 H, J = 8 Hz), 5.85 (m, 1 H), 6.75 (s, 1 H), 7.62 (s, 1 H); IR (Nujol) 3325, 1740, 1680 cm^{-1}; MS (CI with isobutane) m/e 383 (M + 1).

L-**16d**: 74% yield; mp 103–105 °C; NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 3.33 (m, 1 H), 3.55 (dd, 1 H, J = 9 Hz and 15 Hz), 3.85 (s, 6 H), 4.15 (q, 2 H, J = 7 Hz), 4.5 (d, 2 H, J = 6 Hz), 4.62 (m, 1 H), 5.2 (m, 2 H), 5.6 (d, 1 H, J = 8 Hz), 5.8 (m, 1 H), 6.73 (s, 1 H), 7.6 (s, 1 H).

16g: 61% yield; mp 137–140 °C; NMR (90 MHz, $CDCl_3$) δ 2.5 (m, 2 H), 3.4 (m, 2 H), 3.66 (two s, 6 H), 4.82 (m, 1 H), 5.15 and 5.22 (two s, 4 H), 6.45 (d, 1 H), 6.92 (s, 1 H), 7.45 (m, 10 H), 7.7 (s, 1 H); IR (Nujol) 3300, 1745, 1720, 1649 cm^{-1}; MS (CI with isobutane) m/e 551 (M + 1), 240, 201.

16f: 90% yield; mp 129–130 °C; NMR (90 MHz, $CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz), 2.45 (m, 4 H), 3.4 (dd, 2 H), 3.63 (s, 3 H), 4.1 (q, 2 H, J = 7 Hz), 4.82 (m, 1 H), 5.2 (two s, 4 H), 6.45 (d, 1 H, J = 8 Hz), 6.95 (s, 1 H), 7.4 (s, 10 H), 7.72 (s, 1 H).

16h: 88% yield; mp 133–135 °C; NMR (90 MHz, $CDCl_3$) δ 1.2 (two t, 6 H, J = 7 Hz), 2.46 (m, 4 H), 3.1 (m, 2 H), 4.1 (two q, 4 H, J = 7 Hz), 4.8 (m, 1 H), 5.15 and 5.22 (two s, 4 H), 6.14 (d, 1 H), 6.93 (s, 1 H), 7.43 (m, 10 H), 7.72 (s, 1 H); IR (Nujol) 3300, 1730, 1710, 1640 cm^{-1}; MS (CI with isobutane) m/e 579 (M + 1).

16i: 94% yield; NMR (90 MHz, $CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 2.37 (s, 4 H), 3.47 (m, 1 H), 3.98 (m, 1 H), 4.15 (q, 2 H, J = 7 Hz), 5.15 (s + m, 5 H), 6.7 (s, 1 H), 7.42 (m, 10 H), 7.74 (s, 1 H); IR (Nujol) 1730, 1700 cm^{-1}; MS (CI with isobutane) m/e 533 (M + 1), 443 (M − 90).

16j: 88% yield; mp 124–125 °C; NMR (90 MHz, $CDCl_3$) δ 2.4 (s, 4 H), 3.4 (m, 1 H), 3.76 (s, 3 H), 3.95 (m, 1 H), 5.16 (s + m, 5 H), 6.66 (s, 1 H), 7.4 (m, 10 H), 7.75 (s, 1 H); MS (CI with isobutane) m/e 519 (M + 1), 518 (M).

3-(Acylamino)-6,7-dialkoxy-3,4-dihydroquinolin-2-one (13). General Procedure. To a solution of 0.1 mol of **16** in 500 mL of glacial acetic acid was added 100 g of iron powder, and the reaction mixture was refluxed at 90–100 °C for 3 h. The mixture was poured into water, and the product was filtered off, washed with water, and redissolved in tetrahydrofuran (250 mL). The insoluble material was filtered off, and the filtrate was concentrated to 100 mL. The concentrate was poured into 500 mL of water, and the precipitated product was collected, washed with water, and dried under reduced pressure. Crystallization from ethanol gave pure product.

DL-**13c**: 90% yield; mp 159–160 °C; NMR (90 MHz, $CDCl_3$) δ 2.7 (t, 1 H, J = 15 Hz), 3.3 (dd, 1 H, J = 9 and 15 Hz), 4.15 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 5.07 (two s, 4 H), 5.2 and 5.3 (two d, 2 H, J = 6 and 15 Hz), 5.9 (m, 2 H), 6.22 (s, 1 H), 6.75 (s, 1 H), 7.4 (m, 10 H), 8.95 (s, 1 H); IR (Nujol) 3300, 1670 cm^{-1}; MS (CI with isobutane) m/e 459 (M + 1), 458 (M).

L-**13c**: 68% yield; mp 138–141 °C; $[\alpha]_D$ = −10.75 (c = 2, $CHCl_3$); $[\alpha]_D$ = −68.5 (c = 1, acetone). Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.74; H, 5.68; N, 6.11. Found: C, 70.83; H, 5.57; N, 6.12.

DL-**13d**: 80% yield; mp 152–155 °C; NMR (90 MHz, $CDCl_3$) δ 2.8 (t, 1 H, J = 15 Hz), 3.4 (dd, 1 H, J = 9 and 15 Hz), 3.83 (s, 6 H), 4.38 (m, 1 H), 4.62 (d, 2 H, J = 6 Hz), 5.2 and 5.3 (two d, 2 H, J = 6 and 15 Hz), 5.97 (m, 2 H), 6.4 (s, 1 H), 6.7 (s, 1 H), 8.94 (d, 1 H, J = 15 Hz). Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.88; N, 9.15. Found: C, 59.00; H, 6.04; N, 9.11.

L-**13d**: 78% yield; mp 123–125 °C; $[\alpha]_D$ = −18.4 (c = 1, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 2.8 (t, 1 H, J = 15 Hz), 3.4 (dd, 1 H, J = 8 and 15 Hz), 3.83 (s, 6 H), 4.4 (m, 1 H), 4.63 (d, 2 H, J = 6 Hz), 5.16 and 5.33 (two d, 2 H, J = 6 and 15 Hz), 5.98 (m, 2 H), 6.47 (s, 1 H), 6.7 (s, 1 H), 9.38 (d, 1 H, J = 15 Hz); IR (Nujol) 3300, 3200, 1700, 1670 cm^{-1}; exact mass calcd for $C_{15}H_{18}N_2O_5$ 306.1216, found 306.1216.

DL-**13e**: 57% yield; mp 191–192 °C; NMR (300 MHz, $CDCl_3$) δ 2.9 (dd, 1 H, J = 7 and 15 Hz), 3.8 (t, 1 H, J = 15 Hz), 5.1 (two s, 4 H), 5.2 (dd, 1 H, J = 7 and 15 Hz), 6.6 (s, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H), 7.8 and 7.9 (two m, 4 H), 9.7 (br s, 1 H); IR (Nujol) 3200, 1780, 1720, 1690 cm^{-1}; MS (CI with isobutane) m/e 505 (M + 1), 504 (M). Anal. Calcd for $C_{31}H_{24}N_2O_5$: C, 73.81; H, 4.76; N, 5.56. Found: C, 73.91; H, 4.94; N, 5.56.

L-**13e**: 52% yield; mp 192–193 °C; $[\alpha]_D$ = −1.4 (c = 5, DMF); NMR (300 MHz, $CDCl_3$) δ 2.93 (dd, 1 H, J = 7 Hz), 3.83 (t, 1 H, J = 4.5 Hz), 5.05 (s, 4 H), 5.13 (dd, 1 H, J = 4.5 Hz), 6.7 (s, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H), 7.83 (m, 2 H), 7.93 (m, 2 H), 9.7 (s, 1 H); MS (CI with isobutane) m/e 505 (M + 1).

13f: 90% yield; mp 187–190 °C; NMR (90 MHz, $CDCl_3$) δ 2.8 (s + m, 5 H), 3.1 (m, 1 H), 3.8 (s, 3 H), 4.76 (m, 1 H), 5.1 (s, 4 H), 6.6 (s, 1 H), 6.9 (s, 1 H), 7.38 (s, 10 H), 9.43 (s, 1 H); IR (Nujol) 3300, 1730, 1680, 1630 cm^{-1}; MS (CI with isobutane) m/e 489 (M + 1).

13i: 88% yield; mp 212–213 °C; NMR (90 MHz, $CDCl_3$) δ 2.76 (dd, 1 H, J = 7 and 15 Hz), 3.0 (s, 4 H), 3.76 (t, 1 H, J = 15 Hz), 5.15 (s + m, 5 H), 6.56 (s, 1 H), 6.8 (s, 1 H), 7.45 (s, 10 H), 9.56 (br s, 1 H); IR (Nujol) 3300, 1740, 1680 cm^{-1}; MS (CI with isobutane) m/e 457 (M + 1), 456 (M), 366 (M − 91); exact mass calcd for $C_{27}H_{24}N_2O_5$ 456.1685, found 456.1686.

Alkylation of 3-(Aminoacyl)-6,7-dialkoxy-3,4-dihydroquinolin-2-one (13) with 14 To Give 12. General Procedure. To a solution of 10 mmol of **13** in 200 mL of anhydrous THF was added 12 mmol of 60% NaH in oil. After 30 min, 15 mmol of bromo ester **14** was added, and the reaction mixture was stirred while refluxing under nitrogen for 72 h. The THF was then removed under reduced pressure, and the residue was separated on a silica gel column with CH_2Cl_2–ethyl acetate (19:1) as the eluent to provide the diastereomeric products (designated I and II, when separable).

I-12c (R^4H = Pht, R^2 = CH_2Ph): 46% yield; mp 114–116 °C; NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.86 (m, 1 H), 2.6 (m, 1 H), 3.0 (m, 1 H), 3.24 (dd, 1 H, J = 8 and 15 Hz), 3.5 (m, 2 H), 4.27 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 5.1 (d, 1 H), 5.14 (s, 4 H), 5.25 (m, 2 H), 5.85 (br d, 1 H), 5.95 (octet, 1 H, J = 6 Hz), 6.4 (s, 1 H), 6.83 (s, 1 H), 7.4 (m, 10 H), 7.7 (m, 2 H), 7.83 (m, 2 H); IR (film) 3420, 1775, 1720, 1680 cm^{-1}; MS exact mass calcd for $C_{43}H_{43}N_3O_9$ 745.2999, found 745.300.

II-12c (R^4H = Pht, R^2 = CH_2Ph): 46% yield; oil; NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 2.18 (m, 1 H), 2.7 (t, 1 H, J = 15 Hz), 3.2 (dd, 1 H, J = 8 and 15 Hz), 3.73 (t, 2 H, J = 8 Hz), 4.2 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 5.0 (m, 1 H), 5.05 (s, 2 H), 5.1 (d, 2 H, J = 12 Hz), 5.22 (m, 2 H), 5.88 (m + br d, 2 H), 6.53 (s, 1 H), 6.7 (s, 1 H), 7.4 (m, 10 H), 6.67 (m, 2 H), 7.8 (m, 2 H); IR (film) 3320, 1770, 1720, 1670, 1610 cm^{-1}; MS exact mass calcd for $C_{43}H_{43}N_3O_9$ 745.2999, found 745.300.

The alkylation of the quinoline derivative made from L-DOPA gave exactly the same yield of two diastereomeric products. The IR and NMR spectra were the same as for the compounds derived from DL-DOPA. Anal. Calcd for $C_{43}H_{43}N_3O_9$: C, 69.26; H, 5.77; N, 5.64. Found for I: C, 69.16; H, 5.82; N, 5.52. Found for II: C, 69.29; H, 5.73; N, 5.25.

I-12d (DL) (R^4H = Pht, R^2 = Me): 42% yield; oil; NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 2.2 (m, 1 H), 2.75 (sextet, 1 H, J = 7 Hz), 2.95 (t, 1 H, J = 15 Hz), 3.18 (dd, 1 H, J = 7 and 15 Hz), 3.6 (m, 2 H), 3.75 and 3.8 (two s, 6 H), 3.7 (m, 1 H), 4.2 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 5.18 (d, 1 H), 5.3 (two d, 2 H), 5.9 (m, 2 H), 6.32 (s, 1 H), 6.67 (s, 1 H), 7.7 and 7.8 (two m, 4 H); IR (Nujol) 3340, 1770, 1720, 1670, 1616 cm^{-1}; ^{13}C NMR δ 169.438, 169.266, 169.148, 168.243, 155.897, 148.166, 145.389, 134.009, 132.808, 132.006, 123.380, 123.194, 117.759, 117.511, 117.435, 112.289, 101.762, 82.514, 66.723, 65.747, 56.153, 56.070, 51.139, 34.991, 31.526, 27.867, 22.363, 10.373.

II-12d (DL) (R^4H = Pht, R^2 = Me): 42% yield; oil; NMR (300 MHz, $CDCl_3$) δ 1.3 (s, 9 H), 2.3 (sextet, 1 H, J = 7 Hz), 2.65 (t, 1 H, J = 12 Hz), 2.78 (sextet, 1 H, J = 7 Hz), 3.15 (dd, 1 H, J = 7 and 15 Hz), 3.75 (two s + m, 8 H), 4.15 (m, 1 H), 4.55 (d, 2 H, J = 6 Hz), 4.97 (m, 1 H), 5.14 (d, 1 H, J = 12 Hz), 5.25 (d, 1 H, J = 18 Hz), 5.85 (m, 2 H), 6.42 (s, 1 H), 6.53 (s, 1 H), 7.55 and 7.70 (two m, 4 H); IR (Nujol) 3340, 1770, 1710, 1670, 1610 cm^{-1}; ^{13}C NMR δ 168.542, 168.453, 148.340, 145.319, 133.822, 132.745, 131.957, 123.065, 117.700, 117.218, 111.862, 101.048, 82.310, 65.730, 56.104, 51.136, 51.086, 36.086, 36.046, 31.771, 29.887, 27.766, 22.342, 10.354.

I-12d (L) (R^4H = Pht, R^2 = Me): 43% yield; NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 2.3 (m, 1 H), 2.85 (m, 1 H), 3.05 (t, 1 H, J = 15 Hz), 3.27 (dd, 1 H, J = 7 and 15 Hz), 3.68 (m, 2 H), 3.7 (s, 3 H), 3.74 (s, 3 H), 4.13 (t, 1 H), 4.28 (m, 1 H), 4.63 (d, 2 H, J = 6 Hz), 5.25 (d, 1 H, J = 12 Hz), 5.32 (d, 1 H, J = 18 Hz), 5.97 (m + br d, 2 H), 6.4 (s, 1 H), 6.7 (s, 1 H), 7.7 (two m, 4 H); IR (film) 3380, 1770, 1710, 1620 cm^{-1}; exact mass calcd for $C_{31}H_{35}N_3O_9$ 593.2373, found 593.2387.

II-12d (L) (R^4H = Pht, R^2 = Me): 43% yield; NMR (300 MHz, $CDCl_3$) δ 1.3 (s, 9 H), 1.65 (sextet, 1 H, J = 7 Hz), 2.40 (sextet, 1 H, J = 7 Hz), 2.73 (t, 1 H, J = 15 Hz), 2.85 (sextet, 2 H, J = 7 Hz), 3.25 (dd, 1 H, J = 7 and 15 Hz), 3.76 (two s, 6 H), 4.05 (t, 1 H, J = 6 Hz), 4.2 (two t, 1 H, J = 5.5 Hz), 4.63 (d, 2 H, J = 6 Hz), 5.05 (m, 1 H), 5.25 (d, 1 H, J = 12 Hz), 5.32 (d, 1 H, J = 18 Hz), 5.94 (m, 2 H), 6.5 (s, 1 H), 6.6 (s, 1 H), 7.75 (two m, 4 H); IR (Nujol) 3350, 1770, 1710, 1675, 1620 cm^{-1}; MS exact mass calcd for $C_{31}H_{35}N_3O_9$ 593.2373, found 593.2361.

12e + 21e (R^4 = Aloc): 29% yield; NMR (300 MHz, $CDCl_3$) δ 1.25 and 1.5 (two s, ratio 1:2, 9 H), 2.3 (m, 1 H), 2.8 (m, 2 H), 3.23 (m, 1 H), 3.9 (dd, 2 H, J = 15 Hz), 4.5 (two d, ratio 1:2, 2 H, J = 6 Hz), 5.1 (m, 6 H), 5.3 (m, 2 H), 5.88 (m, 1 H), 6.45 and 6.62 (two s, ratio 2:1, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H), 7.78 and 7.85 (two m, 4 H); IR (Nujol) 3370, 1775, 1715, 1685, 1615 cm^{-1}.

12i (R^4H = Pht, R^3 = allyl): 42% yield; mp 70–73 °C; NMR (90 MHz, $CDCl_3$) δ 2.55 (m, 2 H), 2.76 (s + m, 5 H), 3.85 (m, 3 H), 4.6 (m, 2 H), 4.8 (m, 1 H), 5.1 (m, 7 H), 5.8 (m, 1 H), 6.4–6.8 (4s, 2 H), 7.43 (m, 10 H), 7.7 (m, 4 H); IR (Nujol) 1770, 1740, 1700, 1680 cm^{-1}; MS (EI) *m/e* 727 (M^+), 636, 578. MS exact mass calcd for $C_{42}H_{37}N_3O_9$ 727.2529, found 727.2526.

I-12j (R^4H = Pht, R^3 = Me): 24% yield; NMR (90 MHz, $CDCl_3$) δ 2.26 (m, 2 H), 2.56 (m, 2 H), 2.9 (s, 4 H), 3.6 (s + t, 5 H), 3.9 (m, 1 H), 5.1 (s, 4 H), 5.2 (m, 1 H), 6.62 (s, 1 H), 6.68 (s, 1 H), 7.35 (m, 10 H), 7.85 (m, 4 H); IR (Nujol) 1760, 1700, 1650 cm^{-1}; exact mass calcd for $C_{40}H_{35}N_3O_9$ 701.2373, found 701.2371.

II-12j (R^4H = Pht, R^3 = Me): 24% yield; NMR (90 MHz, $CDCl_3$) δ 2.2 (m, 2 H), 2.68 (m, 2 H), 2.97 (s, 4 H), 3.66 (s + m, 6 H), 5.13 (s, 4 H), 5.27 (m, 1 H), 6.63 (s, 1 H), 6.72 (s, 1 H), 7.45 (m, 10 H), 7.8 (m, 4 H); MS exact mass calcd for $C_{40}H_{35}N_3O_9$ 701.2373, found 701.237.

α-Bromo-γ-(*N*-phthaloylamino)butyric Acid (24) was prepared in two steps (75% yield overall) from α-aminobutyric acid **22** as described by Itoh et al.,[31] with slight modification, as follows.

To a solution of 20.6 g (0.2 mol) γ-aminobutyric acid (**22**, Aldrich) and 22 g (0.21 mol) of Na_2CO_3 in 500 mL of water was added 48.2 g (0.22 mol) of *N*-carbethoxyphthalimide, and the reaction mixture was stirred vigorously at room temperature for 5 h. The solution was then acidified and cooled for 2 h in an ice bath, and the precipitated solid was removed by filtration. The filtrate was washed with water and dried under reduced pressure to provide 37 g (80%) of product **23**: mp 101–103 °C (lit.[31] mp 119–121 °C); NMR (90 MHz, $CDCl_3$) δ 2.0 (m, 2 H), 2.4 (m, 2 H), 2.72 (t, 2 H, *J* = 7 Hz), 7.72 (m, 4 H), 10.33 (br s, 1 H); IR (Nujol) 3200–2500, 1770, 1700 cm^{-1}; MS (CI with isobutane) *m/e* 234 (M + 1), 216 (M − 17).

The crude product obtained from the procedure described above was used directly, without further purification, in the next reaction. To a boiling solution of 11.7 g (50 mmol) of **23** and 4.5 g of red phosphorous in 75 mL of anhydrous CCl_4 was added 25 mL of Br_2 dropwise at such rate that no excess bromine was present in the solution. After 30 min an additional 25 mL of Br_2 was added, as before, and refluxing was continued until no more bromine was consumed (6–8 h). The solution was cooled down, washed with H_2O, 10% Na_2SO_3, H_2O, and finally with 10% $NaHCO_3$. The bicarbonate solution was acidified with 2 N HCl, and the product was removed by filtration, washed with water and cold ethanol, and dried under reduced pressure. The reaction provided 15 g (96%) of **24** as a white solid: mp 147–149 °C (lit.[31] mp 159–161 °C); ^1H NMR (90 MHz, $CDCl_3$) δ 2.5 (m, 2 H, *J* = 7 Hz), 3.97 (t, 2 H, *J* = 7 Hz), 4.33 (t, 1 H, *J* = 7 Hz), 7.9 (m, 4 H); IR (Nujol) 3220, 2500, 1770, 1730, 1690 cm^{-1}.

***tert*-Butyl α-Bromo-γ-*N*-phthalimidobutyrate (14a).** The *tert*-butyl ester was prepared according to known procedures[32,33] with the following adaptation of the *tert*-butyl acetate procedure preferred.

A solution of 3.12 g (10 mmol) of **24** and 0.1 mL of 70% of $HClO_4$ in 25 mL of dioxane and 30 mL *tert*-butyl acetate was left for 2 days at room temperature in a tightly closed flask. The flask was carefully opened, and the reaction mixture was poured slowly into a saturated solution of $NaHCO_3$. Then, 100 mL of ethyl ether was added. The organic layer was separated, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to provide 2.7 g (73%) of solid: mp 77–79 °C (after crystallization from ethyl acetate–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 2.23 (m, 1 H, *J* = 7 Hz), 2.38 (m, 1 H, *J* = 6 Hz), 3.83 (t, 2 H, *J* = 7 Hz), 4.18 (dd, 1 H, *J* = 5.6 Hz), 7.69 (dd, 2 H, *J* = 3 Hz), 7.83 (dd, 2 H, *J* = 3 Hz); IR (Nujol) 1700 cm^{-1}; MS (CI with isobutane) *m/e* 370 (M + 2), 368 (M), 314.

Methyl α-Bromo-γ-*N*-phthalimidobutyrate (14b). To a solution of 3.12 g (10 mmol) of **24** in 50 mL of methanol was added 11 mmol of thionyl chloride at −15 °C, and the reaction mixture was allowed to stand for 48 h at room temperature. The methanol was removed under reduced pressure, and the residue was recrystallized from ethyl acetate–hexanes to provide the product quantatively: mp 52–54 °C. NMR (90 MHz, $CDCl_3$) δ 2.43 (m, 2 H), 3.8 (s + t, 5 H), 4.3 (t, 1 H, *J* = 7 Hz), 7.76 (m, 4 H); IR (Nujol) 1770, 1720 cm^{-1}.

Allyl α-Bromo-γ-*N*-phthalimidobutyrate (14c). To a solution of 3.12 g (10 mmol) of **24** and 840 mg (10 mmol) of $NaHCO_3$ in 30 mL of DMF was added 3.63 mL (30 mmol) of allyl bromide, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into water. The product was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure to give the allyl ester, quantitatively, as an oil: NMR (90 MHz, $CDCl_3$) δ 2.4 (m, 2 H), 3.87 (t, 2 H, *J* = 7 Hz), 4.3 (t, 1 H, *J* = 7 Hz), 4.63 (d, 2 H, *J* = 6 Hz), 5.33 (m, 2 H), 5.85 (octet, 1 H, *J* = 6 Hz), 7.8 (m, 4 H); IR (film) 1770, 1720 cm^{-1}.

***tert*-Butyl α-Acetoxy-γ-*N*-phthalimidobutyrate (25).** To a solution of 9.7 g (30 mmol) of **14a** in 75 mL of DMF was added 8.2 g (100 mmol) of fused sodium acetate, and the reaction mixture was stirred at 50 °C for 16 h. The solution was poured into 250 mL of water, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine and dried over $MgSO_4$. The ethyl acetate was removed under reduced pressure, and the product was recrystallized from ethyl acetate–hexanes to provide 10 g (96%) of product **25**: mp 75–77 °C; NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 9 H), 2.15 (s, 3 H), 2.22 (m, 2 H), 3.79 (m, 1 H, *J* = 6 Hz), 3.89 (quintet, 1 H, *J* = 7 Hz), 4.9 (dd, 1 H, *J* = 4 and 9 Hz), 7.7 and 7.8 (two m, 4 H); IR (Nujol) 1775, 1740, 1720 cm^{-1}; MS (CI with isobutane) *m/e* 348 (M + 1), 292 (M − 56).

***tert*-Butyl γ-[*N*-(*tert*-Butoxycarbonyl)amino]-α-hydroxybutyrate (26).** A mixture of 30 g (90 mmol) of **25** and 13.6 mL (270 mmol) of hydrazine hydrate in 150 mL of ethanol was refluxed for 30 min, and the precipitated solid was dissolved in 10% Na_2CO_3. The product was extracted with 5 × 100 mL of ethyl ether. The ethyl ether extracts were dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was treated with 15 g of di-*tert*-butyl dicarbonate in 100 mL of ethyl acetate and 5.7 g (70 mmol) of $NaHCO_3$ in 50 mL of water for 16 h. The product was extracted with ethyl acetate and purified on a silica gel column with hexanes–ethyl acetate (4:1) as the eluent to provide 5.3 g (25%) of **26**: NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.54 (s, 9 H), 1.76 (m, 1 H, *J* = 8 Hz), 2.0 (m, 1 H), 3.26 and 3.33 (two m + b s, 3 H), 4.12 (m, 1 H, *J* = 4 and 6 Hz), 5.0 (br s, 1 H); IR (neat) 3400, 1740, 1700 cm^{-1}; MS (CI with isobutane) *m/e* 276 (M + 1).

***tert*-Butyl α-Bromo-γ-(*tert*-butoxycarbonyl)butyrate (14d).** To a solution of 1.75 g (6.4 mmol) of **26** and 6.8 g (20 mmol) of carbon tetrabromide in 100 mL of dry THF was added 5.24 g (20 mmol) of Ph_3P, and the reaction mixture was stirred at room temperature under nitrogen overnight. The THF was removed under reduced pressure, and the residue was chromatographed on a silica gel column with hexanes–ethyl acetate (3:1) as the eluent to provide 2.1 g (96%) of **14d**: NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.4 (s, 9 H), 2.0 (m, 1 H, *J* = 6 Hz), 2.16 (m, 1 H, *J* = 7 Hz), 3.2 (octet, 1 H, *J* = 7 Hz), 3.4 (m, 1 H, *J* = 6 Hz), 4.2 (dd, 1 H, *J* = 6 Hz), 4.95 (t, 1 H, *J* = 6 Hz); IR (neat) 3340, 1700 cm^{-1}; MS (CI with isobutane) *m/e* 340, 338 (M + 1), 284, 282, 228, 226.

Attempts To Transform 12 into Fluorescent Chromophore 5. A. To a solution of 745 mg (1 mmol) of **12c** in 25 mL of ethanol was added 0.25 mL (4 mmol) of hydrazine hydrate, and the reaction mixture was refluxed for 25 min. The reaction mixture was poured into an aqueous solution of 10% Na_2CO_3, and the product was extracted with ethyl acetate. After removing the ethyl acetate under reduced pressure, the residue was dissolved in 50 mL of xylene, and the resulting solution was refluxed under a Dean-Stark trap for 40 h. After that, the xylene was removed under reduced pressure, and the residue was separated on a silica gel column with CH_2Cl_2–ethyl acetate (3:1) to provide 250 mg (47%) of **27a** and 120 mg (20%) of unreacted amino compound.

27a: mp 161–163 °C; NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 2.2 (quintet, 2 H, *J* = 7.5 Hz), 2.4 (t, 2 H, *J* = 7.5 Hz), 4.1 (t, 2 H, *J* = 7.5 Hz), 5.26 (s, 2 H), 5.33 (s, 2 H), 7.12 (s, 1 H), 7.4 (m, 6 H), 7.44 (s, 1 H), 7.5 (m, 5 H), 9.9 (br s, 1 H); decoupling at 2.2 ppm gave two singlets at 2.4 and 4.1 ppm; IR (Nujol) 3200, 1710 with shoulder 1725 cm^{-1}; MS (CI with isobutane) *m/e* 540 (M + 1), 539 (M). Anal. Cacld for $C_{32}H_{33}N_3O_5$: C, 71.24; H, 6.12; N, 7.79; Found: C, 71.26; H, 6.10; N, 7.61.

B. Compound **27b** was obtained in 24% yield from **12b** as described above.

27b: mp 176–178 °C; NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 2.22 (quintet, 2 H, *J* = 7 Hz), 2.4 (t, 2 H, *J* = 7 Hz), 4.0 and 4.03

(two s, 6 H), 4.14 (t, 2 H, J = 7 Hz), 7.04 (s, 1 H), 7.35 (s, 1 H), 7.6 (s, 1 H); decoupling at 2.22 ppm gave two singlets at 2.4 and 4.14 ppm; IR (Nujol) 3140, 1720, 1700 cm^{-1}; MS (EI) m/e 387 (M), 331, 259; exact mass calcd for $C_{20}H_{25}N_3O_5$ 387.179422, experimental 387.1789.

Compound 28, *N*-Methyl Derivatives of 27. A. 100 mg (0.185 mmol) of **27a** in 20 mL of ethanol was mixed with 50 mg of 10% Pd–C, and hydrogen was passed through the mixture until TLC analysis indicated that all of the starting material was consumed. Then, the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue was dissolved in 25 mL of THF. To this solution were added 24 mg (0.6 mmol) of 60% NaH and 0.13 mL (2 mmol) of methyl iodide, and the solution was stirred at room temperature for 24 h. After evaporation of the THF under reduced pressure, the residue was dissolved in ethyl acetate, washed with H_2O and brine, dried over $MgSO_4$, and filtered. Removal of the ethyl acetate under reduced pressure and separation of the crude product on a silica gel column gave 30 mg (40%) of **28** as a viscous oil: NMR (in $CDCl_3$) δ 1.48 (s, 9 H), 2.2 (quintet, 2 H, J = 7.5 Hz), 2.4 (t, 2 H, J = 7.4 Hz), 3.5 (s, 3 H), 4.05 (two s, 6 H), 4.13 (t, 2 H, J = 7.5 Hz), 7.1 (s, 1 H), 7.35 and 7.4 (two s, 2 H); IR (Nujol) 1720, 1660, 1620, 1610 cm^{-1}.

B. To a solution of 155 mg (0.4 mmol) of **27b** in 25 mL of acetone were added 0.25 mL (4 mmol) of methyl iodide and 138 mg (1 mmol) of anhydrous K_2CO_3, and the reaction mixture was refluxed for 6 h. The acetone was removed under reduced pressure, and the residue was separated on a silica gel column with CH_2Cl_2–ethyl acetate (3:1) as the eluent giving 162 mg (100%) of **28**: exact mass calcd for $C_{21}H_{27}N_3O_5$ 401.1951, found 401.1952.

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)-amino]propyl]-3-[(allyloxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinolin-2-one (I-12c) (R^4 = Boc). To 1.79 g (2.4 mmol) of **I-12c** (RH^4 = Pht) in 60 mL of ethanol was added 0.4 mL (8 mmol) of hydrazine hydrate, and the reaction mixture was refluxed for 15 min. Then, the precipitated solid was dissolved in 10% Na_2CO_3 solution, and the product was extracted with ethyl ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated. To the residue were added 252 mg (3 mmol of $NaHCO_3$ in 30 mL of H_2O and 872 mg (4 mmol) of Boc_2O in 70 mL of ethyl acetate, and the reaction mixture was stirred overnight at room temperature. Then, the ethyl acetate layer was separated, washed with H_2O, and brine, dried over $MgSO_4$ and filtered. Evaporation of the ethyl acetate under reduced pressure, followed by purification of the residue on a silica gel column with CH_2Cl_2–ethyl acetate (9:1) as the eluent gave 1.15 g (67%) of product **I-12c** (R^4 = Boc) and 150 mg of **5a** (UV fluorescent compound), which was eluted with ethyl acetate.

I-12c (R^4 = Boc): NMR (300 MHz, $CDCl_3$) δ 1.4 and 1.42 (two s, 18 H), 1.65 (m, 1 H), 2.07 (m, 1 H), 2.9 (m, 3 H), 3.25 (d + m, 1 H), 4.28 (m, 1 H), 4.6 (m, 1 H), 4.63 (d, 2 H, J = 6 Hz), 5.15 (d + dd, 4 H), 5.2–5.4 (4d, 2 H, J = 1.5 Hz), 5.93 (m, 2 H), 6.4 (s, 1 H), 6.83 (s, 1 H), 7.4 (m, 10 H); IR (Nujol) 3325, 1720, 1680, 1620 cm^{-1}; MS (CI with ammonia) m/e 733 (M + NH_4^+), 716 (M + 1), 677 (M + NH_4^+ − 56), 598, 543.

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)-amino]propyl]-3-[(allyloxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinolin-2-one (II-12c) (R^4 = Boc). To a solution of 1.21 g (1.6 mmol) of **II-12c** (R^4H = Pht) in 40 mL of ethanol–benzene (1:1) was added 0.24 mL (5 mmol) of hydrazine hydrate, and the reaction mixture was refluxed for 15 min. The precipitated solid was dissolved in 10% Na_2CO_3, and the product was extracted with ethyl ether. The ether extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was treated with 168 mg (2 mmol) of $NaHCO_3$ in 25 mL of H_2O and 654 mg (3 mmol) of Boc_2O in 50 mL of ethyl acetate, and the solution was stirred overnight. The ethyl acetate layer was washed with water and brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography, with CH_2Cl_2–ethyl acetate (9:1) as the eluent, to provide 1.1 g (95%) of **II-12c** (R^4 = Boc) and 40 mg of fluorescent compound **5a** which was eluted with ethyl acetate only.

II-12c (R^4 = Boc): NMR (300 MHz, $CDCl_3$) δ 1.2 (s, 9 H), 1.43 (s, 9 H), 1.9 (m, 1 H), 2.3 (m, 1 H), 2.7 (t, 1 H, J = 15 Hz), 2.8 (m, 2 H), 3.3 (m, 2 H), 4.26 (m, 1 H), 4.6 (m, 2 H, J = 6 Hz), 5.05 (t, 2 H, J = 12 Hz), 5.15 (t, 2 H, J = 4.5 Hz), 5.2–5.4 (m, 3 H), 5.9 (m, 2 H), 6.55 (s, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H); IR (Nujol) 3330, 1725, 1675, 1615 cm^{-1}; MS (CI with ammonia) m/e 733 (M + NH_4^+), 716 (M + 1), 677, 598, 350, 168.

5a (fluorescent): mp 157–159 °C; NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.5 (s, 9 H), 1.97 (m, 1 H), 2.3 (dd, 1 H, J = 2 and 12 Hz), 3.4 (d, 1 H, J = 3 and 12 Hz), 3.6 (dd, 1 H, J = 2 and 12 Hz), 4.6 (d + m, 1 H, J = 6 Hz), 5.1 (s + q, 4 H), 6.5 (s, 1 H), 6.9 (s, 1 H), 7.4 (m, 11 H), 7.78 (s, 1 H); decoupling at 2.3 ppm simplified the multiplet at 1.97 ppm; four doublets at 3.4 ppm were converted to a triplet, J = 12 Hz; the dd at 3.6 ppm and dm at 4.6 ppm were transformed into doublets, J = 6 Hz; decoupling at 1.97 ppm transformed the dd at 2.3 ppm and dm at 3.6 ppm into singlets; the dd at 3.6 ppm was changed into doublet, and four d at 3.4 ppm were converted to a triplet; decoupling at 3.4 ppm gave a singlet at 3.6 ppm, doublet at 2.3 ppm and simplified the multiplet at 1.97 ppm to triplet doublet; decoupling at 3.6 ppm changed the multiplet at 1.97 ppm to td (J = 7 Hz); the dd at 2.3 ppm collapsed into a doublet, and four doublets at 3.4 ppm were transformed into a doublet; decoupling at 4.6 ppm converted a multiplet at 1.97 ppm to a triple doublet and changed the broad dd at 2.3 ppm to a nice sharp dd; IR (Nujol) 3320, 1737, 1720, 1650, 1590 cm^{-1}; MS exact mass calcd for $C_{36}H_{41}N_3O_6$ 611.2995, found 611.2991–611.3003.

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)-amino]propyl]-3-[(allyloxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinoline-2-thione (29a). To 1.0 g (1.4 mmol) of **I-12c** (R^4 = Boc) in 25 mL of benzene was added 566.3 mg (1.4 mmol) of Lawesson's reagent and the reaction mixture was refluxed overnight. Then, the solution was concentrated under reduced pressure, and the residue was passed through a silica gel column with CH_2Cl_2–ethyl acetate (24:1) as the eluent to provide 906 mg (93%) of product: NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.45 (s, 9 H), 1.6 (m, 1 H), 2.05 (m, 1 H), 2.6 (m, 2 H), 2.9 (m, 1 H), 3.15 (m, 1 H), 4.2 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 5.05 (m, 1 H), 5.2 (m, 6 H), 5.95 (m, 1 H), 6.45 (m, 1 H), 6.65 (br s, 1 H), 6.83 (s, 1 H), 6.95 (br s, 1 H), 7.4 (m, 10 H); IR (Nujol) 3330, 1730, 1715, 1620 cm^{-1}; MS (EI) m/e 731 (M^+), 598, 541; exact mass calcd for $C_{40}H_{49}N_3O_8S$ 731.324040, found 731.3229.

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)-amino]propyl]-3-[(allyloxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinoline-2-thione (29a). To 1.05 g (1.46 mmol) of **II-12c** (R^4 = Boc) in 27 mL of benzene was added 594 mg (1.46 mmol) of Lawesson's reagent, and the reaction mixture was refluxed overnight. The reaction mixture was directly chromatographed on a silica gel column to give 920 mg (86%) of product: NMR (300 MHz, $CDCl_3$) δ 1.2 (s, 9 H), 1.43 (s, 9 H), 2.0 (m, 1 H), 2.4 (m, 1 H), 2.55 (t, 1 H, J = 15 Hz), 3.2 (m, 3 H), 4.3 (m, 1 H), 4.52 (d, 2 H, J = 6 Hz), 4.58 (m, 1 H), 5.2 (m, 7 H), 5.95 (octet, 1 H, J = 6 Hz), 6.45 (br s, 1 H), 6.65 (s, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H); IR (Nujol) 3320, 1725, 1710 with shoulder 1680, 1615 cm^{-1}; MS (EI) m/e 731 (M^+), 598, 541, 485.

5-[*N*-(Allyloxycarbonyl)amino]-2,3-dihydro-8,9-bis(benzyloxy)-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylic Acid *tert*-Butyl Ester (5c). To 110 mg (0.15 mmol) of **29a** in 4 mL of CH_3CN was added 57 mg (0.3 mmol) of $TsOH·H_2O$, and after 1.5 h an additional 57 mg of $TsOH·H_2O$ was added, and the reaction was continued for 1.5 h longer. The acetonitrile was removed under reduced pressure, $NaHCO_3$ solution was added, and the product was extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. To the residue were added 20 mL of benzene, 10 mL of THF, 25 mg (0.3 mmol) of $NaHCO_3$, 0.5 mL of allyl alcohol, and 100 mg (0.3 mmol) of $Hg(OAc)_2$. The reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with CH_2Cl_2–ethyl acetate (9:1) as the eluent to give 70 mg of **5c** contaminated with **5e** and 20 mg of **6a**. Final purification of 110 mg of the mixture gave 35 mg of **5c**, 60 mg of **6a**, and 10 mg of **5e**.

5c: mp 128–130 °C; NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 2.0 (m, 1 H), 2.35 (dm, 1 H, J = 12 Hz), 3.4 (td, 1 H, J = 4 and 12 Hz), 3.65 (dm, 1 H, J = 12 Hz), 4.66 (d, 2 H, J = 6 Hz), 5.14 (s + dd + m, 5 H), 5.2–5.4 (4d, 2 H, J = 1.5 Hz), 5.95 (octet, 1 H, J = 6 Hz), 6.5 (s, 1 H), 6.93 (s, 1 H), 7.4 (m, 11 H), 7.8 (s, 1 H); IR (Nujol) 3300, 1737 with shoulder 1725, 1650, 1590 cm^{-1};

MS (EI) m/e 595 (M), 537 (M - 58). Anal. Calcd for $C_{35}H_{37}N_3O_6$: C, 70.59; H, 6.22; N, 7.06. Found: C, 70.50; H, 6.38; N, 6.85.

6a: mp 168–170 °C; NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 2.5 (m, 1 H), 2.8 (dm, 1 H, J = 14 Hz), 3.5 (3d, 1 H, J = 3, 4, and 5 Hz), 4.25 (2d, 1 H, J = 5 and 4 Hz), 5.17 (s, 2 H), 5.25 (s, 2 H), 5.45 (d + m, 1 H, J = 5 Hz), 7.05 (s, 1 H), 7.17 (s, 1 H), 7.4 (m, 11 H); IR (Nujol) 3340, 1740, 1680, 1560 cm^{-1}; MS (FAB) m/e 538 (M + 1), 482 (M - 56). Anal. Calcd for $C_{32}H_{31}N_3O_5$: C, 69.27; H, 5.78; N, 7.82. Found: C, 69.07; H, 5.85; N, 7.62.

5e: mp 120–123 °C; NMR (90 MHz, $CDCl_3$) δ 1.0 (t, 3 H, J = 7 Hz), 1.45 (s, 9 H), 1.7 (m, 2 H), 2.1 and 2.5 (two m, 2 H), 3.5 and 3.8 (two m, 2 H), 4.1 (t, 2 H, J = 7 Hz), 4.82 (m, 1 H), 5.2 (s + dd, 4 H), 6.63 (s, 1 H), 6.95 (br s, 1 H), 7.0 (s, 1 H), 7.4 (m, 10 H), 7.6 (s, 1 H); IR (Nujol) 3360, 1735, 1660, 1575 cm^{-1}; MS exact mass calcd for $C_{35}H_{39}N_3O_6$ 597.284, found 597.285–597.287.

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]propyl]-3-[(allyloxycarbonyl)amino]-5,6-dimethoxytetrahydroquinolin-2-one (12b). A solution of 360 mg (0.6 mmol) of **I-12d** (R^4H = Pht) and 0.097 mL (2 mmol) of $H_2NNH_2 \cdot H_2O$ in 20 mL of benzene–EtOH (1:1) was refluxed 15 min, and then the precipitated solid was dissolved in 10% Na_2CO_3. The free amine was extracted with ethyl acetate, dried over $MgSO_4$, and filtered. The ethyl ether was removed under reduced pressure, and to the residue were added 50 mg (0.6 mmol) of $NaHCO_3$ in 10 mL of H_2O and 219 mg (1 mmol) of Boc_2O in 20 mL of THF, and the reaction mixture was stirred overnight. The ethyl acetate was separated, washed with brine, dried over $MgSO_4$, and filtered. After the THF was removed under reduced pressure, the product was extracted with ethyl acetate. The ethyl acetate solution was dried over $MgSO_4$, filtered, and evaporated. The residue was purified on a silica gel column with CH_2Cl_2–ethyl acetate (19:1) to provide 140 mg (42%) of product **12b** and 6 mg of fluorescent compound **5b**.

12b: NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.46 (s, 9 H), 2.05 (m, 1 H, J = 5 Hz), 2.38 (m, 1 H), 3.0 (m, 2 H), 3.1 (m, 1 H), 3.3 (dd, 1 H, J = 5 Hz), 3.82 (s, 3 H), 3.88 (s, 3 H), 4.3 (sextet, 1 H, J = 4 Hz), 4.6 (d, 2 H, J = 6 Hz), 4.74 (br s, 1 H), 5.3 (4d, 2 H, J = 2 Hz), 6.45 (s, 1 H), 6.75 (s, 1 H), 6.95 (m, 2 H); IR (Nujol) 3330, 1730, 1680, 1618 cm^{-1}; MS (CI with ammonia) m/e 581 (M + NH_4^+), 583 (reduced allyl + NH_4^+).

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]propyl]-3-[(allyloxycarbonyl)amino]-5,6-dimethoxytetrahydroquinolin-2-one (12d) (R^4 = Boc). A mixture of 400 mg (0.674 mmol) of **II-12d** (R^4H = Pht) and 0.14 mL (3 mmol) of hydrazine hydrate in 20 mL of benzene–EtOH (1:1) was refluxed for 15 min. Then, after cooling, the reaction mixture was mixed with a 10% aqueous solution of Na_2CO_3, and the product was extracted with ethyl ether. The ether was removed under reduced pressure, and 60 mg (0.7 mmol) of $NaHCO_3$ in 15 mL of H_2O and 438 mg (2 mmol) of Boc_2O in 30 mL of THF were added. The new reaction mixture was stirred overnight. The THF was removed. The product was extracted with ethyl acetate. The ethyl acetate extracts were dried over $MgSO_4$, filtered, and evaporated. Purification of the crude product by silica gel column chromatography provided product **12d** (R^4 = Boc), 310 mg (82%), contaminated with *n*-propoxycarbonyl derivative **5f**.

12d (R^4 = Boc): NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.43 (s, 9 H), 2.2 (m, 1 H), 2.45 (m, 1 H), 2.75 (t, 1 H, J = 15 Hz), 2.95 (m, 1 H), 3.37 (m, 2 H), 3.8 (two s, 6 H), 4.3 (m, 1 H), 4.62 (d, 2 H, J = 6 Hz), 5.12 (m, 1 H), 5.25 (m, 1 H), 5.35 (m, 1 H), 5.9 (m, 1 H), 6.0 (m, 1 H), 6.6 (s, 1 H), 6.77 (s, 1 H); IR (Nujol) 3320, 1725, 1680, 1618 cm^{-1}; MS (CI with ammonia) m/e 581 (M + NH_4^+), 564 (M + 1).

1-[1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]propyl]-3-[(allyloxycarbonyl)amino]-5,6-dimethoxytetrahydroquinoline-2-thione (29b). A solution of 90 mg (0.16 mmol) of **I-12d** (R^4 = Boc) and 81 mg (0.2 mmol) of Lawesson's reagent in 5 mL of benzene was refluxed 12 h. After cooling, the mixture was purified on a silica gel column with CH_2Cl_2–ethyl acetate (9:1) as the eluent to provide 91 mg (98%) of product: NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.48 (s, 9 H), 2.15 (m, 1 H), 2.4 (m, 1 H), 2.7 (m, 1 H), 2.9 (m, 1 H), 3.2 (m, 2 H), 3.83 (s, 3 H), 3.9 (s, 3 H), 4.3 (m, 1 H), 4.62 (d, 2 H, J = 6 Hz), 4.74 (br s, 1 H), 5.45 (two m, 1 H), 5.7 (two m, 1 H), 5.95 (octet, 1 H, J = 6 Hz), 6.5 (br s, 2 H), 6.7 and 6.78 (two s, 2 H); IR (Nujol) 3320, 1720, with shoulder 1708, 1620 cm^{-1}; MS (EI) m/e 579 (M), 445, 389; exact mass calcd for $C_{28}H_{41}N_3O_8S$ 579.261440, found 579.2606.

5-[*N*-(Allyloxycarbonyl)amino]-2,3-dihydro-8,9-dimethoxy-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylic Acid *tert*-Butyl Ester (5d). To 145 mg (0.25 mmol) of **29b** was added 10 mL of 88% formic acid, and the mixture was allowed to stir for 5 h at which time TLC analysis indicated that all of the starting material was consumed. The solution was then dissolved in ethyl acetate, and the formic acid was washed out with an aqueous $NaHCO_3$ solution. The ethyl acetate was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dissolved in 20 mL of THF, and 95 mg (0.2 mmol) of $Hg(OAc)_2$ and 0.032 mL (0.4 mmol) of pyridine were added. The new reaction mixture was stirred at room temperature for 24 h. The THF was removed under reduced pressure, and the residue was purified on a silica gel column initially eluting with CH_2Cl_2–ethyl acetate (1:1) and then with ethanol to provide 30 mg of **5d**, 40 mg of **6b**, and 10 mg of **5f**.

5d: NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 2.0 (m, 1 H), 2.4 (d + m, 1 H, J = 14 Hz), 3.4 (m, 1 H), 3.68 (d + m, 1 H), 3.87 (two s, 6 H), 4.63 (d, 2 H, J = 6 Hz), 4.9 (m, 1 H), 5.3 (4m, 2 H), 5.95 (octet, 1 H, J = 6 Hz), 6.6 (s, 1 H), 6.9 (s, 1 H), 7.8 (s, 1 H); exact mass calcd for $C_{23}H_{31}N_3O_6$ 445.221, found 445.220.

5f: NMR (300 MHz, $CDCl_3$) δ 1.0 (t, 3 H, J = 7 Hz), 1.45 (s, 9 H), 1.7 (sextet, 2 H, J = 7 Hz), 2.17 (m, 1 H), 2.43 (d + m, 1 H, J = 14 Hz), 3.44 (t, 1 H, J = 9 Hz), 3.75 (d, 1 H, J = 9 Hz), 3.9 (s, 6 H), 4.13 (t, 2 H, J = 7 Hz), 4.9 (m, 1 H), 6.5 (s, 1 H), 6.9 (s, 1 H), 7.9 (s, 1 H); IR (Nujol) 3300, 1740, 1640, 1595 cm^{-1}. Compound **6b** was treated with Boc_2O in the presence of $NaHCO_3$ to give 10 mg of **5a**: NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.5 (s, 9 H), 2.35 (m, 1 H), 2.6 (m, 2 H), 3.65 (m, 1 H), 4.04 (two s, 6 H), 4.5 (s, 1 H), 5.1 (t, 1 H, J = 6 Hz), 7.15 (s, 1 H), 7.45 (s, 1 H), 8.1 (s, 1 H).

N-*tert*-Butoxycarbonylation of 12c (R^4H = Pht). To a solution of 745 mg (1 mmol) of **12c** (R^4H = Pht) and 436 mg (2 mmol) of BOC_2O in 15 mL of dry acetonitrile was added 61 mg (0.5 mmol) of DMAP, and the reaction mixture was left overnight in tightly closed flask. The CH_3CN was removed under reduced pressure, the residue was dissolved in ethyl acetate, washed with 10% citric acid, H_2O, and brine, dried over $MgSO_4$, and filtered. The product, **30** (mp 126–128 °C), was obtained quantitatively after removing the ethyl acetate under reduced pressure.

30: NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 18 H), 1.7 (m, 2 H), 2.5 (m, 2 H), 3.7 (m, 3 H), 4.66 (d, 2 H, J = 6 Hz), 5.15 (m, 5 H), 5.9 (m, 1 H), 6.4 (s, 1 H), 6.8 (s, 1 H), 7.4 (m, 10 H), 7.76 (m, 4 H); IR (Nujol) 1760, 1725, 1700, 1685 cm^{-1}; MS (EI) 845 (M^+), 220, 205.

Hydrazinolysis of 30. A solution of 845 mg (1 mmol) of **30** and 0.19 mL (3 mmol) of hydrazine hydrate was refluxed for 30 min. Then, the precipitated solid was dissolved in 10% aqueous Na_2CO_3, and the product was extracted with ethyl ether. The ethyl ether layer was washed twice with H_2O and once with brine and dried over $MgSO_4$. After filtration, the ether was removed under reduced pressure to give 570 mg (90%) of **31**: mp 130–133 °C; NMR (300 MHz, $CDCl_3$) δ 1.43 (two s, 18 H), 2.33 (m, 4 H), 3.4 (m, 2 H), 4.16 (m, 1 H), 4.6 (m, 1 H), 5.1 (s, 4 H), 6.3, 6.5, and 6.8 (3s, 3 H), 7.33 (m, 10 H); IR (Nujol) 3380, 1720, 1640 cm^{-1}; MS (CI with isobutane) m/e 632 (M + 1), 614.

1-[1-(*tert*-Butoxycarbonyl)-3-[(trichloroethoxycarbonyl)amino]propyl]-3-[(*tert*-butoxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinolin-2-one (12a) (R^4 = troc). To a solution of 3.5 g (4 mmol) of **30** in 50 mL of ethanol–benzene (1:1) was added 1.6 mL (32 mmol) of hydrazine hydrate, and the resulting mixture was refluxed for 15 min. The precipitated solid was dissolved in 10% aqueous sodium carbonate, and the product was extracted with several portions of ethyl ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was treated with 0.64 mL (5 mmol of trichloroethoxycarbonyl chloride in 45 mL of ethyl acetate and 840 mg (10 mmol) of $NaHCO_3$ in 15 mL of water for 12 h. The ethyl acetate layer was separated, dried over $MgSO_4$, and filtered. Removal of the ethyl acetate under reduced pressure and purification of the crude product on a silica gel column (CH_2Cl_2–ethyl acetate 19:1 as the eluent) gave 3 g (89%) of **12a** (R^4 = troc) as a mixture of two diastereoisomers, 200 mg (9%) of **5a** and 50 mg (2%) of **6a**.

I-12a (R^4 = troc): NMR (300 MHz, $CDCl_3$) δ 1.46 (two s, 18 H), 1.64 (m, 2 H), 2.15 (m, 1 H), 2.72 (t, 1 H, J = 12 Hz), 2.96 (m, 1 H), 3.1 (m, 1 H), 3.25 (d + m, 1 H), 4.2 (m, 1 H), 4.7 (s, 2 H), 5.1 (m + br s, 5 H), 5.7 (br s, 1 H), 6.35 (s, 1 H), 6.83 (s, 1 H), 7.4 (m, 10 H); IR (neat) 3320 with shoulder 3400, 1725, 1665 cm^{-1}; MS (CI with isobutane) m/e 808 (M + 1), 806, 752, 750, 708, 706.

II-12a (R^4 = troc): NMR (300 MHz, $CDCl_3$) δ 1.2 (s, 9 H), 1.4 (s, 9 H), 1.9 (m, 2 H), 2.2 (m, 1 H), 2.63 (t, 1 H, J = 11 Hz), 2.9 (m, 1 H), 3.23 (m, 1 H), 3.4 (m, 1 H), 4.2 (m, 1 H), 4.7 (dd, 1 H, J = 12 Hz), 4.8 (s, 1 H), 5.2 (m, 5 H), 5.4 (m, 1 H), 6.5 (s, 1 H), 7.4 (m, 10 H); IR (film) 3320 with shoulder 3400, 1730, 1660 cm^{-1}; MS (CI with isobutane) m/e 809, 808 (MH), 806, 752.

1-[1-(*tert*-Butoxycarbonyl)-3-[(trichloroethoxycarbonyl)amino]propyl]-3-[(*tert*-butoxycarbonyl)amino]-6,7-bis(benzyloxy)tetrahydroquinoline-2-thione (29c). A solution of 323 mg (0.4 mmol) of **12a** (R^4 = troc) and 162 mg (0.4 mmol) of Lawesson's reagent in 15 mL of benzene was refluxed overnight under nitrogen. The reaction mixture was passed through a silica gel column with hexanes-ethyl acetate (3:1) as the eluent to provide 210 mg (64%) of product **29c**. A number of unidentified compounds, resulting from decomposition of **12a** (R^4 = troc), were also observed. **29c**: NMR (300 MHz, $CDCl_3$) δ 1.45 (3s, 18 H), 2.5 (m, 2 H), 2.8 (m, 1 H), 3.0 (m, 1 H), 3.2 (m, 2 H), 3.35 (m, 1 H), 4.2 (m, 1 H), 4.7 (two s, 2 H), 5.2 (m, 6 H), 6.2 and 6.4 (two s, 1 H), 6.42 and 6.85 (two s, 1 H), 7.4 (m, 10 H); IR (neat) 3340, broad 1710 with shoulders 1730 and 1690 cm^{-1}; MS (CI with isobutane) m/e 826, 824 (M + 1), 822, 768, 766.

5-[*N*-(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-8,9-bis(benzyloxy)-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylic Acid *tert*-Butyl Ester (5a). To 823 mg (1 mmol) of **29c** in 50 mL of THF was added with vigorous stirring 1.5 g of zinc powder followed by addition of 10 mL 1 M KH_2PO_4, and the course of the reaction was followed by TLC analysis. After 2 h, 50 mL of THF, 1.5 g of Zn powder, and 10 mL of 1 M KH_2PO_4 were added, and the reaction was continued for 2 h more. The product was extracted with ethyl acetate, washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was evaporated under reduced pressure. The residue was dissolved in 25 mL of ethanol and treated with mercuric acetate under reflux for 2 h. The ethanol was removed under reduced pressure, and the crude reaction mixture was chromatographed on a silica gel column with CH_2Cl_2-EtOH (9:1) as the eluent to give 440 mg (90%) of **5a**: mp 152-154 °C; NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.53 (s, 9 H), 2.0 (m, 1 H), 2.3 (dm, 1 H), 3.4 (dd, 1 H, J = 12 Hz), 3.63 (dm, 1 H), 4.6 (m, 1 H), 5.15 (dd, 2 H), 6.5 (s, 1 H), 6.9 (s, 1 H), 7.4 (m, 11 H), 7.8 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.604, 27.469, 27.877, 39.321, 55.602, 71.197, 71.515, 79.777, 82.382, 98.566, 113.311, 114.798, 126.834, 126.964, 127.400, 127.594, 128.054, 128.143, 130.741, 136.371, 136.589, 143.036, 143.988, 148.311, 152.547, 169.615. Anal. Calcd for $C_{36}H_{41}N_3O_6$: C, 70.70; H, 6.71; N, 6.87; Found: C, 70.74; H, 6.70; N, 6.71.

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Lewis Acid Catalyzed Reactions of α,β-Unsaturated *N,N*-Dimethylhydrazones with 1,4-Benzoquinone. Formation of Indoles by a Novel Oxidative Rearrangement

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The Diels-Alder reaction of quinones and (*E*)-3-arylpropenal *N,N*-dimethylhydrazones only proceeds with 1,4-naphthoquinone as the dienophile. The addition of Lewis acids leads to the formation of *trans*-2,3-dihydrobenzofurans in a highly regioselective [3 + 2] process. When [*o*-(acylamino)phenyl]propenal *N,N*-dimethylhydrazones **4** and **5** were allowed to react with 1,4-benzoquinone and boron trifluoride, an unprecedented oxidative rearrangement took place yielding indole-3-carboxaldehyde *N,N*-dimethylhydrazones **7** and **8**, respectively.

The ability of α,β-unsaturated hydrazones to react with electrophilic reagents at C-3[1] has been successfully exploited in their utilization as 1-azadienes[2,3] in Diels-Alder cycloaddition reactions with electron-deficient dienophiles.[4] In an effort to apply this annulation strategy as a key step in the synthesis of polycyclic marine alkaloids,[5,6] the cy-

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