Enantiomerically Pure Dimethyl (2S)-N-(9-Phenyl~uoren-9-yl)-3,4-didehydroglutamate as Chiral Educt. Chirospecific Synthesis of (+)-5-O-Carbamoylpolyoxamic Acid and 3-Alkylglutamate...

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Enantiomerically Pure Dimethyl (2S)-N-(9-Phenylfluoren-9-yl)-3,4-didehydroglutamate as Chiral Educt. Chirospecific Synthesis of (+)-5-O-Carbamoylpolyoxamic Acid and 3-Alkylglutamates

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We report here a short and efficient synthesis (four steps, 78% overall yield) of dimethyl (2S)-N-(9-phenylfluoren-9-yl)-3,4-didehydroglutamate (1) in enantiomerically pure form from L-glutamic acid. The C–C double bond in 1 was introduced by selective selenenylation–oxidation of dimethyl N-(9-phenylfluoren-9-yl)glutamate. 1 did not undergo loss of enantiomeric purity when stored for several weeks at room temperature, thus demonstrating the ability of the 9-phenylfluoren-9-yl (Pf) group to protect the highly acidic chiral center of 1 from racemization. The α,β-unsaturated carboxyl group of 1 was selectively reduced with DIBAL. Carbamoylation of the resulting alcohol, followed by OsO_4-mediated hydroxylation of the double bond and deprotection afforded (+)-5-O-carbamoylpolyoxamic acid, a component of the polyoxin family of antifungal antibiotics (>40% overall yield from glutamic acid). 1 underwent lithium dimethyl cuprate addition with complete retention of chiral integrity, albeit in a nonstereoselective fashion, to give 3-methylglutamates and 3-methylpyroglutamates.

Introduction

The need to maintain the integrity of preexisting chiral centers during a chirospecific synthesis is becoming more acute as higher enantiomeric purity standards have to be met due to efficiency reasons and biological and pharmaceutical activity considerations. In the particular case of α-amino acid-based chirospecific synthesis, this usually implies that care should be exercised to avoid racemization of the base-sensitive chiral α-center.[1] Recently, Rapoport has introduced the 9-phenylfluoren-9-yl (Pf) group for both nitrogen and chiral center protection in amino acid chemistry.[2] The stereoelectronic hindrance[3] posed by the Pf group to abstraction of the α-hydrogen in amino acid esters has led to the development of elegant and efficient stereoselective preparations of 3-substituted aspartates and 4-substituted glutamates by alkylation of the corresponding amino acid diester enolates.[4,5] Even α-amino aldehydes[2c,d] and ketones[2b] have been turned into chirally stable, useful synthetic intermediates when N-protected with the Pf group.

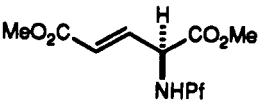

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Figure 1.

We desired to test if the Pf group could impart protection to even more acidic (i.e. more prone to racemization) chiral centers, such as the one present in the didehydroglutamate 1, in which the chiral center is part of a vinylogous malonate system.

Derivatives of 1 in which the C-1 carboxyl group had been reduced to the alcohol oxidation state and protected have been used for the chirospecific synthesis of a number of natural and pharmacologically interesting products.[6,7] In many instances the C-1 group had to be oxidized back to the carboxylate in order to obtain the desired products.[7] This reduction–oxidation protocol (which avoids racemization during the synthesis by greatly reducing the acidity of the chiral center) lengthens the synthesis and in some cases leads to complications during the deprotection and oxidation steps. To avoid these problems we decided to undertake the synthesis of the unsaturated diester 1 and

• Abstract published in *Advance ACS Abstracts*, October 15, 1993.

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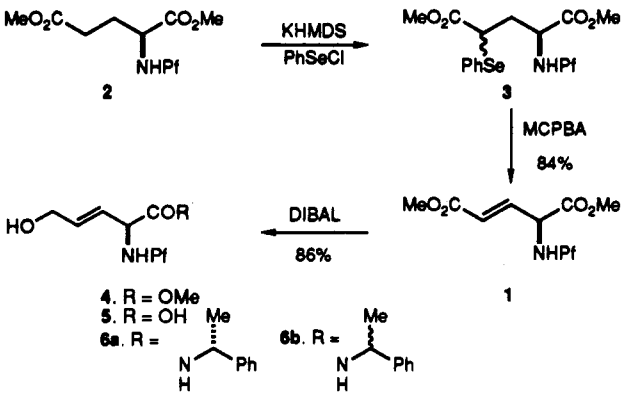
Scheme I



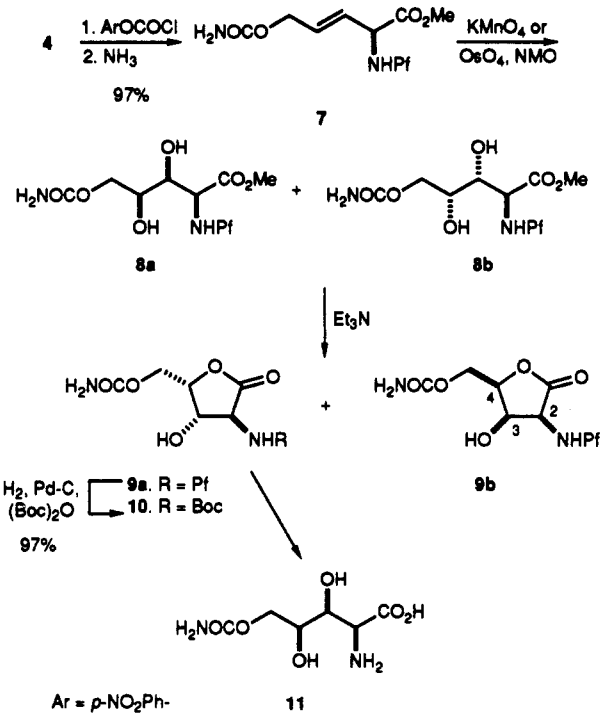
to explore its potential as a chiral, nonracemic, highly functionalized intermediate for asymmetric synthesis. We present herein a short, efficient synthesis of enantiomerically pure 1 from glutamic acid and its application to the chirospecific synthesis of 5-*O*-carbamoylpolyoxamic acid (11) and of 3-alkylglutamates.

Results and Discussion

Preparation of *N*-Pf-3,4-Didehydroglutamate 1. *N*-Pf glutamate 2 was prepared from glutamic acid in two steps (93%) following the procedure of Rapoport and coworkers.[4c,d] Selective selenenylation[8] of 2 was achieved by ω-ester enolate formation with KHMDS and inverse quenching with PhSeCl to give 3 as a 1/1 mixture of epimers at C-4. Oxidation–elimination of selenide 3 proved to be more demanding than anticipated, due to the ease of oxidation of the amine group. After considerable experimentation we found that conversion of crude 3 to 1 was best carried out with MCPBA at −20 °C, using K_3PO_4 as an acid scavenger. Final purification of 1 had to be performed by column chromatography with gravity (70–230 mesh) silica gel, since the use of higher activity silica gel led to substantial losses of material. This protocol provided the *E*-didehydroglutamate 1 ($^3J_{3,4}$ = 15.4 Hz) in 84% yield from 2. 1 was obtained as a pale yellow foam which could not be crystallized, but which was stable for months when stored in a desiccator at rt. Most gratifyingly, 1 showed a non-zero optical rotation, confirming that the Pf group had imparted some protection to the chiral center. In order to check if the synthesis of 1 had proceeded with complete retention of chiral integrity we prepared the diastereomeric α-phenylethyl amides 6. We decided to reduce the ω-carboxylate in order to avoid complications during α-ester hydrolysis and amide formation. Reduction of 1 with DIBAL (−40 °C) took place selectively to afford alcohol 4 (86% yield), which was quantitatively hydrolyzed with LiOH to give acid 5. Coupling of 5 with both (+)- and (±)-α-phenylethylamine under standard conditions (diisopropylcarbodiimide, *N*-hydroxybenzotriazole)[2d] yielded amides **6a** and **6b** (90% yield). ^{1}H-NMR doping experiments on mixtures of **6a** and **6b** showed that acid 5, and thus dehydroglutamate 1, had an enantiomeric ratio (er) > 99.5/0.5.[9]

Synthesis of (+)-5-*O*-Carbamoylpolyoxamic Acid (11). With an efficient preparation of enantiomerically pure 1 in hand we set out to explore its utility in asymmetric synthesis. In this context, 1 was envisioned as an ideal precursor for (+)-5-*O*-carbamoylpolyoxamic acid (11), a component of the polyoxin family of antibiotics,[10,11] which are used as agricultural fungicides[10] and also have inhibitory activity against *Candida albicans*.[11]

Scheme II



Starting from alcohol 4 only two transformations were required to provide a protected derivative of 11: *O*-carbamoylation and *cis*-hydroxylation. Little or no carbamate 7 was obtained when we applied the standard carbamoylation conditions[7g,12] to 4, but slow addition of 4 to a solution of *p*-nitrophenyl chloroformate gave a crude mixed carbonate which yielded the desired 7 (97% overall yield) when treated with aqueous NH_3. Oxidation of 7 with $KMnO_4$ at low temperature gave a mixture of the expected diols **8a** and **8b** together with the lactones **9a** and **9b**.[7g] Since the diols were inseparable by chromatography while the lactones were easily separable by crystallization, we found it more convenient to push the lactonization reaction to completion. Thus, treatment of the crude hydroxylation mixture with Et_3N gave a 2/1 mixture of **9a** and **9b** in 75% combined yield. The diastereomeric ratio of the lactones was the same as that of their parent hydroxy esters and thus no epimerization took place during the lactonization under basic conditions. Since the diastereoselectivity of the hydroxylation was not very high we next studied the OsO_4-catalyzed *cis*-hydroxylation of 7, a reaction that offered the possibility of not only getting asymmetric induction from the C-2 chiral center, but also from external chiral ligands.[13] When the oxidation was carried out in the absence of chiral ligands, a 1/1 mixture of **9a** and **9b** was obtained (90% yield).[14] This lack of selectivity has

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(9) Even samples of 1 that had been stored at rt for 2 months had er > 99.5/0.5.

(10) For a comprehensive review of the polyoxins see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333–351.

(11) Synthetic studies on polyoxamic acid: (a) ref 7g. (b) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307–309, and refs therein. (c) Duréault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 150–155.

(12) Millar, A.; Kim, K. H.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 189–196.

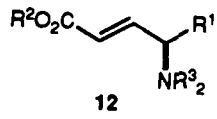

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Figure 2.

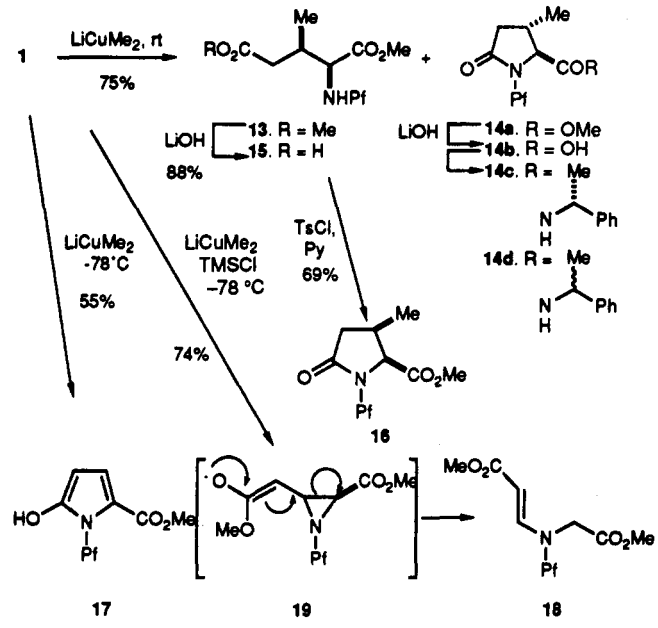
been repeatedly observed in the hydroxylation of allylamines.[7g] We next attempted to improve the stereoselectivity of the reaction using a variety of Sharpless' dihydroquinine (DHQ)- and dihydroquinidine (DHQD)-derived ligands;[13b,c] the best results were achieved by using the 9-*O*-(4′-methyl-2′-quinolyl) ethers (MEQ)[13c] of DHQ and DHQD during the oxidation. In this way the lactones **9a** and **9b** were obtained in 2/1 and 1/2.6 ratios, respectively (90% yield).

The stereochemistry of lactone **9b** was established by NOE experiments which showed that irradiation of H-2 (δ 2.91 ppm) or H-3 (δ 3.11 ppm) led to enhancement of H-3 and H-4 (δ 4.18 ppm), or H-2 and H-4, respectively. The stereochemical assignment of lactone **9a** was performed by correlation with Boc-lactone **10**, an intermediate in Garner's synthesis of **11**.[7g] Thus, hydrogenolysis of **9a** (10% Pd–C) in the presence of $(Boc)_2O$[4b] gave **10** (97% yield) identical with an authentic sample kindly provided by Prof. Garner.[15] The Boc-lactone **10** can be quantitatively deprotected to give polyoxamic acid **11**.[7g] The overall yield for the synthesis of **10** or **11** from L-glutamic acid is >40% (9 or 10 steps).

Cuprate Additions to Didehydroglutamate 1. Conjugate additions to unsaturated esters of general structure **12** have provided access to a variety of interesting compounds, including kainic acid analogs,[7a] γ-amino acids,[16] and β-hydroxy-γ-amino acids.[17] In order to test if the 9-phenylfluoren-9-yl group could be used to preserve the chiral integrity of **1** under the usually highly basic conditions needed to achieve conjugate addition to unsaturated esters, we have explored the reaction of **1** with $LiCuMe_2$.

The outcome of this reaction was highly dependent on the reaction conditions; thus when the reaction was carried out at low temperature (below 0 °C), pyrrole **17** was isolated as the major product. Reaction at −78 °C in the presence of TMSCl[16] led to enamine **18** as the only product, probably through the intermediacy of aziridine **19**. These results showed that C–C bond formation is a slow process and

Scheme III



that the Pf-protected nitrogen is fairly nucleophilic toward intramolecular electrophiles.

The desired alkylation at C-3 was achieved at temperatures between 0 °C and rt to give a 1/1 mixture of glutamate **13** and *trans*-lactam **14a** (75% combined yield).

NOE experiments showed that the substituents in lactam **14a** were in a *trans* disposition. The stereochemistry of **13** was ascertained after selective hydrolysis of the ω-ester to give acid **15**, followed by cyclization with TsCl in pyridine,[18] to give lactam **16**. A NOE study of **16** showed that the substituents were *cis*.

In order to check if the cuprate addition had proceeded without loss of enantiomeric purity we synthesized the diastereomeric derivatives **14c,d** by ester hydrolysis of **14a** followed by 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT)[19] mediated coupling with (+)- and (±)-α-phenylethylamine. ^{1}H-NMR analysis of mixtures of **14c** and **14d** showed that **14b** had an er > 99.5/0.5 and thus that the cuprate addition had indeed proceeded with complete retention of chiral integrity.

Conclusion

We have developed a short and efficient synthesis (four steps, 78% overall yield) of *N*-Pf-didehydroglutamate **1** from glutamic acid. **1** was used as educt in a short, efficient, stereoselective synthesis of 5-*O*-carbamoylpolyoxamic acid, a component of the polyoxin family of antifungal antibiotics. **1** was also shown to undergo cuprate addition with complete retention of chiral integrity, albeit in a nonstereoselective fashion.

Experimental Section

General. All reactions were carried out under an atmosphere of dry Ar, unless otherwise noted. THF and Et_2O were distilled from Na/benzophenone; dioxane was distilled from Na; CH_2Cl_2, triethylamine, TMSCl and pyridine were distilled from CaH_2; absolute ethanol (reagent grade) was used without further purification. Chromatography was carried out using 230–400

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(14) *N*-Methylmorpholine oxide (NMO) was used as cooxidant in all the cases studied. The use of $K_3Fe(CN)_6$[13d,h] as cooxidant resulted in a very slow reactions.

(15) We thank Prof. Garner for kindly providing us with a sample of **10**.

(16) Reetz, M. T.; Röhrig, D. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1706–1709.

(17) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477–4480.

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mesh silica gel unless otherwise noted. NMR spectra were taken in $CDCl_3$ unless otherwise noted, and are referenced to internal TMS (for $CDCl_3$ solutions) or the appropriate solvent signal (DMSO-d_6). NOE difference experiments were carried out on a Bruker WM-250 or a Bruker AMX-500 spectrometers.

Dimethyl *N*-(9-Phenylfluoren-9-yl)-3,4-Didehydroglutamate (1). A solution of glutamate **2** (2.150 g, 5.18 mmol) in THF (11 mL) was added dropwise (10 min) to a solution of KHMDS (9.4 mL, 10.36 mmol, 1.1 M in THF) at −78 °C. The resulting pale-yellow solution was stirred for 1.5 h at −78 °C and then transferred via cannula (cooled to −78 °C) onto a solution of PhSeCl (2.182 g, 11.4 mmol, 220 mol %) in THF (9 mL) at −78 °C. THF (5 mL) was added to the flask that contained the enolate solution, cooled to −78, and cannulated to the PhSeCl solution. The reaction mixture was stirred for 2h at −78 °C, HOAc (1.5 mL) was added, and the resulting suspension was allowed to warm up to rt, diluted with EtOAc/hexane (2:1, 100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give **3** as a sticky yellow oil which was dissolved in CH_2Cl_2 (40 mL) and the resulting solution cooled to −20 °C. K_3PO_4 (3.300 g, 15.54 mmol, 300 mol %) was added followed by MCPBA (55% purity, 3.725 g, 12.95 mmol, 250 mol %, in portions over a period of 30 min). Solid $NaHSO_3$ was then added, and the resulting suspension was stirred vigorously and allowed to warm up to rt, filtered and diluted with EtOAc/hexane 3:1 (150 mL), washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Short column chromatography (70–230 mesh silica gel) eluting with EtOAc/hexane 1:6 gave **1** (1.797 g, 4.35 mmol, 84%) as a pale-yellow foam: $[\alpha]^{22}_D = -61.6°$ (c = 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.21 (m, 1 H, H-2), 3.42 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 6.12 (d, J = 15.4 Hz, 1 H, H-4), 6.68 (dd, J = 15.4, 5.2 Hz, 1 H, H-3), 7.16–7.46 (m, 11 H, Ar), 7.63–7.71 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 51.5, (OCH_3), 52.3 (OCH_3), 57.3 (C-2), 72.9 (C-9′), 119.9, 120.0, 122.2, 125.4, 125.8, 126.2, 127.4, 127.7, 128.0, 128.4, 128.5, 128.6, 140.0, 141.2, 144.1, 145.5 (C-3), 148.5, 148.8, 166.6 (C-5), 172.8 (C-1); IR (NaCl) 3300, 3050, 2940, 1730, 1650 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{28}H_{23}NO_4$: 413.1627. Found: 413.1634.

Methyl (2S)-2-[*N*-(9′-Phenylfluoren-9′-yl)amino]-5-hydroxy-3-pentenoate (4). DIBAL (2.32 mL, 2.32 mmol, 1.0 M in hexanes) was added dropwise, over a period of 20 min, to a solution of **1** (320 mg, 0.775 mmol) in THF (25 mL) at −40 °C. The resulting solution was stirred for 2.5 h, quenched at −40 °C with EtOAc (0.5 mL), and allowed to warm up to rt. Solid KH_2PO_4 (0.5 g) was added and the mixture was carefully concentrated under vacuum to 1/2 of the initial volume. The resulting mixture was diluted with $CHCl_3$ (30 mL) and cooled to 0 °C; saturated aqueous $NaHCO_3$ (0.5 mL) was added with vigorous stirring, until a precipitate appeared. Anhydrous Na_2SO_4 was then added and stirring was continued for a few minutes. The resulting mixture was filtered through a Celite pad and concentrated. Flash chromatography of the residue (EtOAc/hexane 2:3) gave **4** (255 mg, 0.660 mmol, 86%) as a white foam: $[\alpha]^{20}_D = -114.6°$ (c = 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.35 (dd, J = 6.3, 0.9 Hz, 1 H, H-2), 3.40 (s, 3 H, OCH_3), 3.91 (dd, J = 5.1, 1.0 Hz, 2 H, H_2C-5), 5.45 (ddt, J = 15.4, 6.3, 1.3 Hz, 1 H, H-3), 5.55 (dtd, J = 15.4, 5.0, 0.8 Hz, 1 H, H-4), 7.18–7.45 (m, 11 H, Ar), 7.64–7.71 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 51.9 (OCH_3), 57.9 (C-2), 62.7 (C-5), 72.8 (C-9′), 119.8, 119.9, 125.6, 125.8, 126.1, 127.3, 127.7, 128.3, 128.4, 128.5, 129.4, 131.5, 140.3, 140.9, 144.4, 148.6, 149.7, 174.1 (CO); IR (NaCl) 3400, 3060, 1730 (CO), 1450 cm^{-1}. Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.89; H, 6.03; N, 3.63. Found: C, 77.89; H, 6.37; N, 3.49.

(2S)-2-[*N*-(9′-Phenylfluoren-9′-yl)amino]-5-hydroxy-3-pentenoic Acid (5). $LiOH{\cdot}H_2O$ (89 mg, 2.10 mmol) was added to a solution of **4** (135 mg, 0.35 mmol) in dioxane/water (2:1, 3 mL) at 0 °C. The solution was stirred for 4 h at 0 °C, poured onto 5% H_3PO_4 (15 mL), and extracted with 5:1 $CHCl_3$/*i*-PrOH (3 × 15 mL). The combined organic phase was dried and concentrated to give pure **5** (130 mg, 0.35 mmol, 100%) as a white solid. $[\alpha]^{20}_D = +76.0°$ (c = 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.10 (d, J = 9.1 Hz, 1 H, H-2), 3.56 (d, J = 3.2 Hz, 2 H, H_2C-5), 4.91 (broad d, J = 15.2 Hz, 1 H, H-4), 5.40 (dd, J = 15.2, 9.1 Hz, 1 H, H-3), 6.97–7.66 (m, 13 H, Ar); ^{13}C NMR ($CDCl_3$) δ 59.9 (C-2), 61.5 (C-5), 73.4 (C-9′), 120.2, 120.5, 124.1, 125.9, 126.2, 127.0, 128.1, 128.4, 128.7, 129.8, 129.9, 136.4, 140.2, 140.6, 141.1, 143.9, 144.5, 171.9 (CO); IR (NaCl) 3400, 1700 (CO), 1460 cm^{-1}.

(2S)-*N*-[(1′*R*)-1′-Phenylethyl)]-2-[*N*-(9″-phenylfluoren-9″-yl)amino]-5-hydroxy-3-pentenamide and (2S)-*N*-[(1′*R*,*S*)-1′-Phenylethyl)-2-[*N*-(9″-phenylfluoren-9″-yl)amino]-5-hydroxy-3-pentenamide (6a and 6b). Diisopropylcarbodiimide (54 μL, 45 mg, 0.35 mmol), HOBT·H_2O (24 mg, 0.18 mmol), and (+)- or (±)-phenylethylamine (23 μL, 21 mg, 0.18 mmol) were added to a solution of **5** (53 mg, 0.14 mmol) in THF (0.3 mL) at 0 °C. After stirring for 2 h at 0 °C, the mixture was hydrolyzed with a few drops of 5% HCl solution, diluted with ether (5 mL), filtered through a Celite pad, and concentrated. The optical purity studies were carried out with the unpurified material. For characterization, the residue was purified by preparative TLC to give the amide **6a** (foam, 62 mg, 91%). **6b** was obtained in 85% yield. **6a**: ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 6.9 Hz, 3 H, H_3C-3′), 3.0 (br s, 1 H, NH), 3.16 (d, J = 7.8 Hz, 1 H, H-2), 3.78 (d, J = 4.7 Hz, 2 H, H_2C-5), 4.95 (quint., J = 7.0 Hz, 1 H, H-1′), 5.15 (dt, J = 15.5, 5.3 Hz, 1 H, H-4), 5.38 (dd, J = 15.5, 7.8 Hz, 1 H, H-3), 7.17–7.37 (m, 16 H, Ar), 7.67 (d, J = 6.6 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.8 (C-2′), 48.6 (C-1′), 59.3 (C-2), 62.5 (C-5), 72.9 (C-9″), 119.9, 120.1, 125.3, 125.6, 125.9, 126.0, 127.3, 127.4, 127.5, 128.0, 128.4, 128.5, 128.7 (2C), 129.6, 132.7, 140.4, 140.7, 143.1, 143.9, 148.1, 149.5, 171.2 (CO); IR ($CHCl_3$) 3000, 1660 (CO), 1510 cm^{-1}. Anal. Calcd for $C_{32}H_{30}N_2O_2{\cdot}H_2O$: C, 78.02; H, 6.54; N, 5.68. Found: C, 78.11; H, 6.37; N, 5.87.

Methyl (2S)-2-[*N*-(9′-Phenylfluoren-9′-yl)amino]-5-(carbamoyloxy)-3-pentenoate (7). Pyridine (2 mL) was added to a suspension of *p*-nitrophenyl chloroformate (851 mg, 2.4 mmol) in CH_2Cl_2 (8 mL) at 0 °C. A solution of **4** (265 mg, 0.68 mmol) in CH_2Cl_2 (7 mL) was then added over a period of 30–45 min. The reaction mixture was diluted with EtOAc/hexane 3:1 (50 mL), washed successively with 0.5 M H_2SO_4 (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (25 mL), dried, and concentrated to a pale-yellow solid. The residue was dissolved in THF (7 mL), cooled to 0 °C, and treated with aqueous ammonia (1.5 mL). After stirring for 30 min, the mixture was diluted with EtOAc/hexane 3:1 (50 mL), washed with saturated aqueous $NaHCO_3$ (3 × 25 mL), dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1.25:1) to give **7** (281 mg, 0.65 mmol, 97%): $[\alpha]^{20}_D = -96.6°$ (c = 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.30 (d, J = 4.71 Hz, 1 H, H-2), 3.38 (s, 3 H, OCH_3), 4.42 (d, J = 5.5 Hz, 2 H, H_2C-5), 4.65 (broad s, 2 H, NH_2), 5.56 (dd, J = 16.0, 5.6 Hz, 1 H, H-3), 5.67 (dt, J = 15.5, 5.6 Hz, 1 H, H-4), 7.18–7.70 (m, 13 H, Ar); ^{13}C NMR ($CDCl_3$) δ 52.5 (OCH_3), 58.3 (C-2), 65.3 (C-5), 73.6 (C-9′), 120.5, 120.6, 126.1, 126.6, 126.9, 127.2, 128.0, 128.3, 128.5, 129.0, 129.1, 129.2, 132.6, 140.9, 141.7, 145.1, 149.5, 149.9, 157.1 (NCO_2), 174.7 (CO); IR (NaCl) 3490, 3320, 3060, 1730 (CO), 1600 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.66; N, 6.53. Found: C, 72.48; H, 5.72; N, 6.35.

Hydroxylation of 7 with $KMnO_4$ (9a and 9b). A solution of $KMnO_4$ (114 mg, 0.84 mmol) in H_2O (4 mL) was added dropwise to a solution of **7** (180 mg, 0.42 mmol) in absolute EtOH (6 mL) at −25 °C. The resulting mixture was stirred for 1 h at −25 °C and allowed to warm up to −10 °C for 30 min. Solid $NaHSO_3$ (350 mg) was added and the resulting suspension was allowed to warm up to rt. The mixture was poured onto H_2O (15 mL), extracted with CH_2Cl_2/*i*-PrOH 5:1 (3 × 15 mL), dried, and concentrated. The residue was dissolved in acetone (5 mL), Et_3N (0.288 mL, 212 mg, 2.10 mmol) was added, and the resulting solution was stirred for 16 h, poured onto 0.5 M H_2SO_4 (15 mL), and extracted with 5:1 CH_2Cl_2/*i*-PrOH (2 × 20 mL). The combined organic layers were washed with 0.5 M H_2SO_4 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried, and concentrated to give the mixture of lactones as a white solid. Flash chromatography (1:1 EtOAc/hexane) gave **9b** (40 mg) and **9a** (96 mg) (75% combined yield). **9b**: mp > 250 °C (from trituration with ether); $[\alpha]^{20}_D = -174.5°$ (c = 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.91 (d, J = 4.5 Hz, 1 H, H-2), 3.11 (dd, J = 2.6, 4.4 Hz, 1 H, H-3), 4.18 (m, 1 H, H-4), 4.20 (m, 1 H, H-5), 4.43 (m, 1 H, H-5), 4.62 (broad s, 2 H, NH_2), 7.20–7.76 (m, 13 H, Ar); ^{13}C NMR (DMSO-d_6) δ 57.6, 62.6, 68.6, 72.7, 78.8, 120.5, 120.6, 125.1, 125.4, 126.2, 127.4, 128.1, 128.3, 128.5, 128.8, 139.8, 140.4, 144.8, 149.1, 149.7, 156.5 (NCO_2), 176.25 (CO); IR (KBr) 3500, 3450, 3380, 1790, 1740, 1610 cm^{-1}. Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.75; H, 5.16;

N, 6.50. Found: C, 69.73; H, 5.15; N, 6.45. **9a**: (oil) $[\alpha]^{20}_D$ = −144.8° (*c* = 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.09 (d, *J* = 8.0 Hz, 1 H, H-2), 4.00 (dd, *J* = 12.4, 4.1 Hz, 1 H, H-5), 4.15 (dd, 1 H, *J* = 12.4, 3.0 Hz, H-5), 4.31 (t, 2 H, *J* = 7.7 Hz, H-3, OH), 4.49–4.55 (m, 1 H, H-4), 7.23–8.04 (m, 13 H, Ar); ^{13}C NMR (DMSO-d_6) δ 61.2, 62.4, 72.2, 72.8, 80.3, 120.1, 120.3, 125.2, 125.6, 126.1, 127.0, 127.7, 127.8, 128.1, 128.3, 128.4, 139.8, 140.0, 144.9, 148.8, 149.5, 156.4 (NCO_2), 175.7 (CO); IR (KBr) 3500, 3450, 3380, 1790, 1740, 1610 cm^{-1}. Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.75; H, 5.16; N, 6.50. Found: C, 69.70; H, 5.18; N, 6.35.

Hydroxylation of 7 with OsO_4 (9a and 9b). DABCO (30 mg, 0.26 mmol), *N*-methylmorpholine oxide (76 mg, 0.65 mmol), and OsO_4 (0.025 mmol, 0.5 mL, 0.05 M in *t*-BuOH) were successively added to a solution of **7** (225 mg, 0.52 mmol) in 1:1 acetone–H_2O (4 mL). The reaction was stirred at rt until complete consumption of the starting material (6–12 h). After this period, solid $NaHSO_3$ (300 mg) and triethylamine (344 μL, 250 mg, 2.47 mmol) were added and the resulting suspension was stirred for 4 h. The resulting mixture was poured onto H_2O (20 mL) and extracted with 5:1 CH_2Cl_2/*i*-PrOH (2 × 20 mL). The combined organic layers were washed with 0.5 M H_2SO_4 (10 mL) and saturated aqueous $NaHCO_3$ (10mL), dried, and concentrated to give the mixture of lactones as a white solid. Flash chromatography eluting with 1:1 EtOAc/hexane gave 89 mg of **9b** and 111 mg of **9a** (90% combined yield). An alternative and highly efficient method for the separation of these lactones was found and is based in their different solubility in ether: lactone **9b** is almost insoluble in ether, while lactone **9a** is quite soluble; therefore trituration of the crude mixture with ether left pure lactone **9b** as white, well-formed crystals. The mother liquors were concentrated to a foam from which pure **9a** was obtained as an oil after treatment with EtOAc–hexanes.

Hydroxylation of 7 with OsO_4 in the Presence of DHQD–MEQ[13c] and DHQ–MEQ.[13c] The same procedure as above was used except that the appropriate chiral ligand (20 mol %) was used instead of DABCO. When dihydroquinine–MEQ[13c] was used, a 2/1 ratio of **9a** and **9b** (90% combined yield) was obtained. When dihydroquinidine–MEQ[13c] was used a 1/2.6 ratio of **9a** and **9b** (90% combined yield) was obtained.

(2*S*,3*S*,4*S*)-2-[*N*-[(1′,1′-dimethylethoxy)carbonyl]amino]-4-(carbamoyloxy)-3-hydroxy-γ-butyrolactone (10). A suspension of **9a** (84 mg, 0.196 mmol), Boc_2O (107 mg, 0.49 mmol), and 10% Pd/C (25 mg) in dioxane (4 mL) was hydrogenated at 50 psi for 5 days. After this period, the resulting suspension was filtered through a Celite pad and concentrated. The residue was subjected to flash chromatography with EtOAc/hexane 2:1 as eluant to give **10** (55 mg, 97%) as a white solid.

Reaction of 1 with Me_2CuLi (13, 14a). MeLi (3.4 mmol, 1.7 mL, 2.0 M solution in Et_2O) was added dropwise to a suspension of Cu_2I_2 (323 mg, 1.7 mmol) in Et_2O (3.5 mL) at 0 °C. The resulting colorless solution was allowed to warm up to rt and treated with **1** (130 mg, 0.31 mmol) in THF (3.5 mL). The reaction mixture was stirred for 20 min. A solution of NH_3/NH_4Cl adjusted to pH 8 (20 mL) was added, and the resulting suspension was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography (EtOAc/hexane 1:6) to give **13** (R_f 0.35, 130 mg, 0.30 mmol, 36%) and then with 1:1 EtOAc/hexane to give **14a** (130 mg, 0.33 mmol, 39%). **13**: mp 101–103 °C (EtOAc/hexane); $[\alpha]^{20}_D$ = −227.5° (*c* = 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.94–2.11 (m, 2 H, H-3, H-4), 2.23 (dd, *J* = 15.7, 5.9 Hz, 1 H, H-4), 2.47 (br s, 1 H, H-2), 2.89 (broad s, 1 H, NH), 3.18 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 7.18–7.70 (m, 11 H, Ar), 7.59 (t, *J* = 8.2 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 34.0 (C-3), 37.9 (C-4), 51.2 (OCH_3), 51.3 (OCH_3), 58.3 (C-2), 72.8 (C-9′), 119.9, 125.7, 126.1, 126.7, 127.2, 127.3, 127.9, 128.3, 140.2, 141.3, 144.7, 148.3, 148.8, 173.0 (CO), 175.7 (CO); IR ($CHCl_3$) 3000, 2950, 1730 (CO) cm^{-1}. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.49; H, 6.35; N, 3.26. Found: C, 75.13; H, 6.08; N, 3.34. **14a**: mp 209–211 °C (CH_2Cl_2/hexane); $[\alpha]^{20}_D$ = +29.0° (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.92 (dd, *J* = 16.3, 1.1 Hz, 1 H, H-4), 2.14 (quint, *J* = 7.4 Hz, 1 H, H-3), 2.85 (dd, *J* = 16.3, 7.9 Hz, 1 H, H-4), 3.30 (d, *J* = 1.0 Hz, 1 H, H-2), 3.34 (s, 3 H, OCH_3), 7.10–7.69 (m, 13 H, Ar); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 32.1(C-3), 39.1 (C-4), 51.8 (CH_3O), 67.5 (C-2), 73.3 (C-9′), 119.8, 125.3, 126.9, 127.0, 127.6, 127.7, 128.3, 128.5, 128.9, 129.2, 139.6, 140.2, 141.0, 146.7, 147.0, 172.9 (CO), 175.9 (CO); IR ($CHCl_3$) 3000, 1740 (CO), 1690 (CO) cm^{-1}. Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.56; H, 5.84; N, 3.52. Found: C, 78.18; H, 5.90; N, 3.63.

(4*S*,5*S*)-5-Carboxy-4-methyl-1-(9′-phenylfluoren-9′-yl)-2-pyrrolidone (14b). $LiOH·H_2O$ (277 mg, 6.6 mmol) was added to a solution of **14a** (86 mg, 0.22 mmol) in 2:1 dioxane/H_2O (5 mL) at 0 °C. The reaction mixture was allowed to warm up to rt, stirred for 6 h, poured onto 5% HCl solution (10 mL), extracted with CH_2Cl_2 (2 × 15 mL), dried, and concentrated. The residue was purified by flash chromatography to give **14b** (74 mg, 0.19 mmol, 88%) as a foam, that was recrystallized from EtOAc to give white crystals: mp 255 °C dec; $[\alpha]^{20}_D$ = +165.8° (*c* = 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.99 (d, *J* = 16.5 Hz, 1 H), 2.28 (quint, *J* = 7.1 Hz, 1 H), 2.89 (dd, *J* = 7.8, 16.5 Hz, 1 H), 3.27 (d, *J* = 0.73 Hz, 1 H, H-2), 7.09–7.78 (m, 13 H, Ar); ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 32.7 (C-3), 39.0 (C-4), 67.4 (C-2), 73.5 (C-9′), 119.8, 119.9, 125.3, 126.8, 127.0, 127.3, 127.8, 128.3, 128.6, 129.1, 129.3, 139.7, 140.3, 140.6, 146.2, 147.0, 176.78 (CO), 176.81 (CO). IR ($CHCl_3$) 3000, 1720 (CO), 1700 (CO), 1450, 1380. Anal. Calcd for $C_{25}H_{21}NO_3·0.75\ H_2O$: C, 75.64; H, 5.66; N, 3.52. Found: C, 75.61; H, 5.48; N, 3.53.

(4*S*,5*S*)-4-Methyl-5-[[(1′*S*)-phenylethyl]carbamoyl]-1-(9″-phenylfluoren-9″-yl)-2-pyrrolidone and (4*S*,5*S*)-4-Methyl-5-[[(1′*R*,*S*)-phenylethyl]carbamoyl]-1-(9″-phenylfluoren-9″-yl)-2-pyrrolidone (14c and 14d). Methyl triflate (25 mg, 0.15 mmol) was added to a solution of CDI (13 mg, 0.075 mmol) in THF (0.3 mL) and stirred for 15 min. A solution of **14b** (24 mg, 0.062 mmol) in THF (0.3 mL) was added to the resulting solution, stirred for 15 min, and treated with (+)- or (±)-phenylethylamine (10 μL, 9 mg, 0.075 mmol). After stirring for 30 min, the mixture was diluted with EtOAc (20 mL), washed with 1 M H_3PO_4 (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:2) to give **14c** or **14d** (18 mg, 0.037 mmol, 60%) as a white foam. **14c**: ^1H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.12 (d, *J* = 7.0 Hz, 3 H, NCHC*H*$_3$), 1.94 (dd, *J* = 16.8, 1.6 Hz, 1 H, H-4), 2.21 (quint, *J* = 7.5 Hz, 1 H, H-3), 2.73 (dd, *J* = 16.8, 8.6 Hz, 1 H, H-4), 3.59 (d, *J* = 1.0 Hz, 1 H, H-2), 4.63 (quint, *J* = 7.2 Hz, 1 H, NCH), 5.63 (d, *J* = 7.7 Hz, 1 H, NH), 6.89–7.28 (m, 14 H, Ar), 7.45 (t, *J* = 8.3 Hz, 2 H, Ar), 7.54 (d, *J* = 7.6 Hz, 1 H, Ar), 7.80 (d, *J* = 7.7 Hz, 1 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3), 21.9 (CH_3), 33.5 (C-4), 39.2 (C-3), 48.7 (NCH), 70.3 (C-5), 73.0 (C-9″), 120.0, 120.1, 124.8, 125.7, 126.1, 127.0, 127.2, 127.5, 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 129.1, 129.2, 139.6, 140.3, 141.6, 142.2, 146.0, 147.5, 170.2 (CO), 176.3 (CO); IR ($CHCl_3$) 3000, 1690, 1510 cm^{-1}.

(3*R*,4*S*)-4-(Methoxycarbonyl)-3-methyl-4-[*N*-(9′-phenylfluoren-9′-yl)amino]butanoic Acid (15). $LiOH·H_2O$ (64 mg, 1.5 mmol) was added to a solution of **13** (65 mg, 0.15 mmol) in 1:1 dioxane/H_2O (2.5 mL) at 0 °C. The reaction mixture was allowed to warm up to rt, stirred for 4 h, poured onto 5% HCl, extracted with CH_2Cl_2 (2 × 15 mL), dried, and concentrated to give **15** (63 mg, 100%) as a foam, which was used directly for the next step: ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.01–2.19 (m, 2 H), 2.38 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.60 (d, *J* = 4.2 Hz, 1 H), 3.27 (s, 3 H, OCH_3), 7.18–7.70 (m, 11 H, Ar), 7.59 (t, *J* = 8.2 Hz, 2 H, Ar).

(4*R*,5*S*)-5-(Methoxycarbonyl)-4-methyl-1-(9′-phenylfluoren-9′-yl)-2-pyrrolidone (16). TsCl (114 mg, 0.6 mmol) was added to a solution of **15** (63 mg, 1.5 mmol) in pyridine (0.5 mL). The resulting solution was stirred for 90 min at rt, poured onto 5:1 Et_2O/hexane (30 mL), washed with 5% H_2SO_4 (3 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:1) to give **16** (40 mg, 0.10 mmol, 69%) as a solid. Recrystallization from CH_2Cl_2/hexane gave white crystals: mp 218–220 °C; $[\alpha]^{20}_D$ = −28.5° (*c* = 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.37–2.41 (m, 2 H), 2.47–2.64 (m, 1 H), 3.30 (s, 3 H, OCH_3), 3.79 (d, *J* = 8.2 Hz, 1 H, H-2), 7.18–7.66 (m, 13 H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 31.7 (C-3), 38.7 (C-4), 51.4 (OCH_3), 65.2 (C-5), 73.2 (C-9′), 119.6, 119.8, 125.0, 126.7, 126.8, 127.7, 127.8, 128.2, 128.3, 128.9, 129.1, 139.9, 140.0, 140.9, 146.7, 147.0, 171.4 (CO), 176.2 (CO); IR

($CHCl_3$) 3000, 1740 (CO), 1690 (CO) cm^{-1}. Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.56; H, 5.84; N, 3.52. Found: C, 78.27; H, 5.93; N, 3.55.

2-Hydroxy-5-(methoxycarbonyl)-1-(9′-phenylfluoren-9′-yl)pyrrole (17). MeLi (0.78 mmol, 0.56 mL, 1.4 M solution in Et_2O) was added dropwise to a suspension of Cu_2I_2 (74 mg, 0.96 mmol) in Et_2O (0.3 mL) at 0 °C. The resulting colorless solution was cooled to −78 °C and treated with a solution of **1** (40 mg, 0.10 mmol) in Et_2O (0.3 mL). The reaction mixture was stirred for 4 h while the temperature raised from −78 °C to 0 °C. A solution of NH_3/NH_4Cl adjusted to pH 8 (10 mL) was added at 0 °C and the mixture was allowed to warm up to rt and extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography (EtOAc/hexane 1:3) to give **17** (21 mg, 55%) as a pale-yellow foam. Recrystallization from EtOAc/hexane gave white crystals: mp 193–197 °C; ^1H NMR ($CDCl_3$) δ 3.21 (s, 3 H, OCH_3), 5.68 (d, J = 3.3 Hz, 1 H, H-3), 6.48 (d, J = 3.3 Hz, 1 H, H-4), 7.14–7.72 (m, 13 H, Ar), 9.27 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 50.2 (OCH_3), 77.3 (C-9′), 96.2 (C-3), 106.5, 120.1, 120.3, 124.8, 125.3, 125.5, 126.2, 127.2, 128.2, 128.4, 128.5, 128.9, 129.0, 129.1, 139.8, 143.7, 147.7, 159.1, 163.4 (CO); IR (NaCl) 3060, 1720, 1640, 1550, 1450 cm^{-1}. Anal. Calcd for $C_{25}H_{19}NO_3 \cdot 2H_2O$: C, 71.92; H, 5.56; N, 3.35. Found: C, 71.65; H, 5.42; N, 3.37.

Methyl [[*N*-[2-(Methoxycarbonyl)ethenyl]-*N*-(9′-phenylfluoren-9′-yl)amino]ethanoate (18). MeLi (1.93 mmol, 1.38 mL, 1.4 M solution in Et_2O) was added dropwise to a suspension of Cu_2I_2 (183 mg, 0.96 mmol) in THF (1.6 mL) at 0 °C. The resulting colorless solution was cooled to −78 °C and treated with a mixture (centrifuged and decanted under argon) of TMSCl (40 mg, 0.36 mmol), Et_3N (8 mg, 0.07 mmol), and THF (0.15 mL). **1** (100 mg, 0.24 mmol) in THF (0.5 mL) was added immediately and the reaction mixture was stirred for 20 min, when TLC (EtOAc/hexane 1:5) showed the formation of a product (R_f = 0.20) at the expense of **1** (R_f = 0.45). A solution of NH_3/NH_4Cl adjusted to pH 8 (10 mL) was added at −78 °C, the mixture was allowed to warm up to rt, and then it was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography (EtOAc/hexane 1:3) to give **18** (74 mg, 0.18 mmol, 74%) as a pale-yellow foam. Recrystallization from EtOAc/hexane gave white needles: mp 180–181 °C; ^1H NMR ($CDCl_3$) δ 3.47 (s, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 4.61 (d, J = 13.4 Hz, 1 H), 7.25–7.69 (m, 13 H, Ar), 7.94 (d, J = 13.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.9 (CH_2), 50.5 (OCH_3), 52.1 (OCH_3), 79.0 (C-9′), 90.2 (N-CH), 120.4, 125.5, 127.3, 128.2, 128.3, 129.0, 129.3, 139.9, 141.2, 146.2, 150.1, 168.9 (CO), 169.5 (CO); IR ($CHCl_3$) 3000, 1750, 1730, 1690 cm^{-1}. Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.52; H, 5.62; N, 3.39. Found: C, 75.24; H, 5.66; N, 3.35.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of **1**, **5**, and **14c** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.