Synthesis of a Peptidomimetic Tricyclic Tetrahydrobenzo[*ij*]quinoline as a VLA-4 Antagonist

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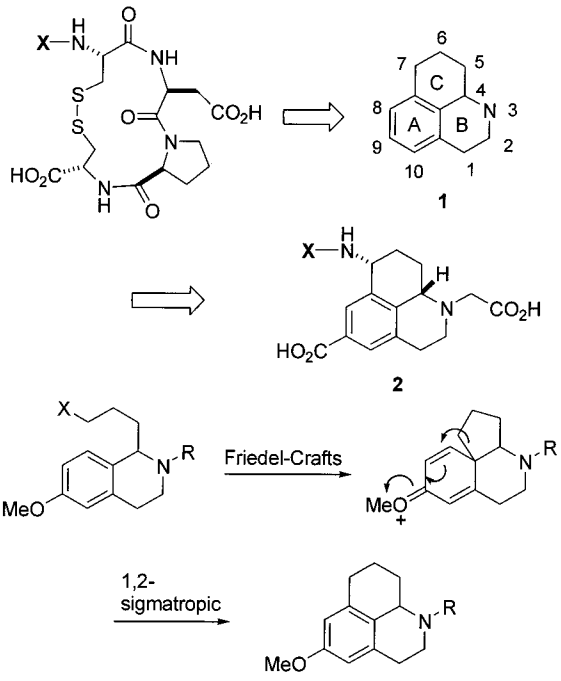
Received July 21, 1999

Development of inhibitors that block leukocyte recruitment by interfering with cell−cell and cell−matrix interactions has been the focus of considerable attention. Multiple molecular targets have been characterized in the process of leukocyte adhesion to endothelial cells and extracellular matrix proteins.[1] Integrin α4β1, very late antigen (VLA-4), expressed in stimulated monocytes and lymphocytes binds to cytokine-activated endothelial cells through recognition of vascular cell adhesion molecule-1 (VCAM-1) as well as to the extracellular matrix protein fibronectin (FN) within the alternatively spliced CS-1 region. This adhesion process has been implicated in the pathogenesis of a variety of diseases. A monoclonal antibody against α4β1 has demonstrated efficacy in a number in vitro and in vivo studies.[2] In addition, several peptide-based VLA-4 antagonists have been reported,[3,4] and some have been evaluated in clinical trials for the treatment of asthma and multiple sclerosis.

Lobl and Cardarelli have reported a cyclic pentapeptide, RC*D(ThioP)C* (the asterisks denote residues bridged by a disulfide bond) to be a potent inhibitor of α4β1-mediated cell adhesion to CS-1 site and VCAM[2] with IC_{50} ranging from 2 to 9 μM in cell adhesion assays. This rigid peptide, which does not inhibit cell adhesion to other extracellular matrix proteins including laminin and vitronectin or trigger platelet aggregation, represents a starting point for the design of nonpeptidic inhibitors. Recently, a similar series of cyclic peptides based on XC*DPC* have been reported to be low nanomolar cell adhesion inhibitors.[5] Also a series of β-turn mimics based on the CS-1 fragment LDV sequence have been synthesized by combinatorial methods and showed low micromolar inhibition.[6]

Scheme 1



Molecular modeling together with NMR analysis of C*DPC* led us to identify a tricyclic framework, 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (**1**),[7] that mimics the cyclic pentapeptide backbone. This *iso*-julolidine template can be found as a part of the aporphine alkaloid structure.[8] The two crucial carboxylic acid moieties presented by the aspartate and C-terminal cystein of XC*DPC* would be mimicked by carboxylates at the 3 and 9 positions of **1.** The amino group corresponding to the N-terminus needs to be placed at the 7 position of **1** in a stereospecific fashion. Here we report the synthesis of the novel molecule **2** via a nonclassical Friedel−Crafts cyclization/1,2-sigmatropic rearrangement tandem reaction (Scheme 1).

The synthesis started with coupling of 3-methoxyphenethylamine (**3**) and 4-pentenoyl chloride (**4**). The resulting amide **5** was cyclized via a Bischler−Napieraski reaction to give the dihydroisoquinoline which, without purification, was reduced with sodium cyanoborohydride to tetrahydroisoquinoline **6** in 87% yield over three steps (Scheme 2). The olefin functional group tethered at the C1 position of **6** will be manipulated for effective closure of the C-ring.

Taylor et al. have demonstrated an effective six-membered ring Friedel−Crafts cyclization of an epoxide for the formation of tetrahydronaphthalene.[9] To follow this protocol, the nitrogen of tetrahydroisoquinoline **6** was protected as a benzyloxycarbanoyl (Cbz) and the resulting

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(1) *Leukocyte Recruitment in Inflammatory Disease*; Peltz, G., Ed.; Chapman & Hall: New York, 1996.

(2) (a) Laberge, S.; Rabb, H.; Issekutz, T. B.; Martin, J. G. *Am. J. Respir. Crit Care Med.* **1995**, *151*, 822. (b) Barbadillo, C.; G-Arroyo, A.; Salas, C.; Mulero, J.; Sanchez-Madrid, F.; Andreu, J. L. *Springer Semin. Immunopathol.* **1995**, *16*, 375. (c) Podalski, D. K. *N. Engl. J. Med.* **1991**, *325*, 928.

(3) Lin, K.-C.; Zimmerman, A. C.; Lee, W.-C.; Hammond, C. E.; Ateeq, H. S.; Hsiung, S. H.; Chong, L. T.; Liao, Y.; Almquist, R. G.; Kalkunte, S.; Adam, S. P. 213th ACS Natioal Meeting, Medicinal Chemistry Division # 315, San Francisco, 1997.

(4) Nowlin, D. M.; Gorcsan, F.; Moscinski, M.; Chiang, S.-L.; Lobl, T. J.; Cardarelli, P. M. *J. Biol. Chem.* **1993**, *268*, 20352.

(5) Jackson, D. Y.; Quan, C.; Artis, D. R.; Rawson, T.; Blackburn, B.; Struble, M.; Fitzgerald, G.; Chan, K.; Mullins, S.; Burnier, J. P.; Fairbrother, W. J.; Clark, K.; Berisini, M.; Chui, H.; Renz, M.; Jones, S.; Fong, S. *J. Med. Chem.* **1997**, *40*, 3359.

(6) Souers, A. J.; Virgilio, A. A.; Schurer, S. S.; Ellman, J. A.; Kogan, T. P.; West, H. E.; Ankener, W.; Vanderslice, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2297.

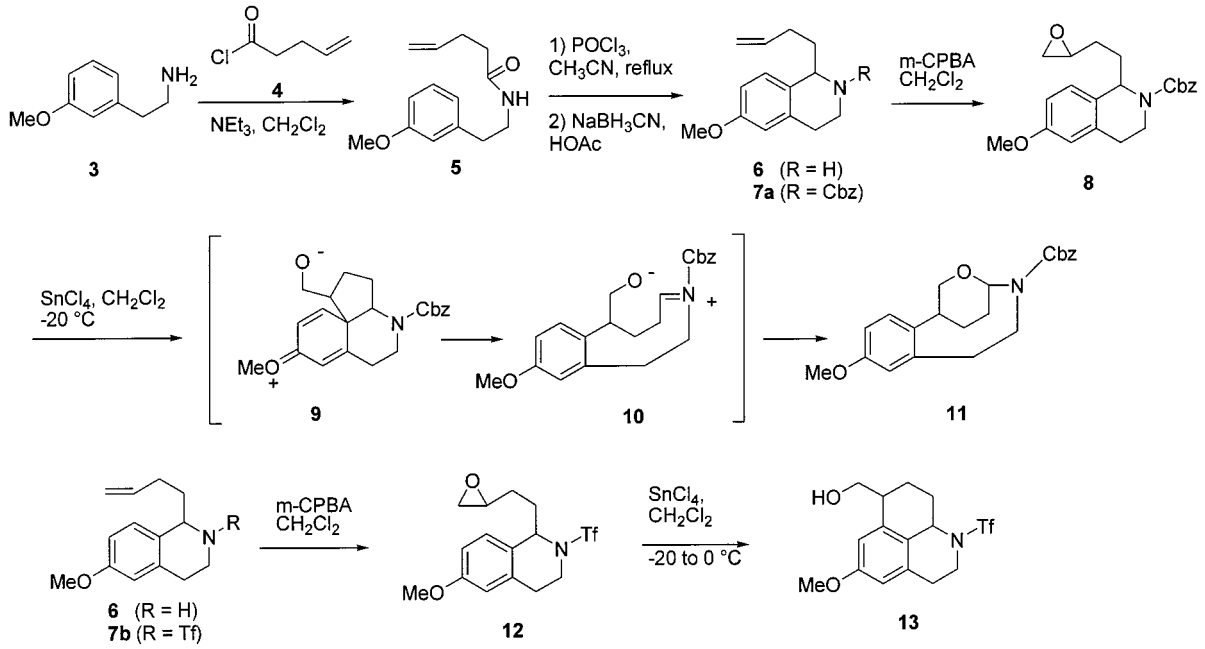
(7) Numbering system of **1** is based on its close analogue, julolidine, 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine. For a review of the chemistry of julolidine, see: *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New Yorks, 1977; Vol. 3, pp 494−515.

(8) For aporphine review, see: *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1977; Vol. 3, pp 1−272.

(9) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449.

10.1021/jo991162k CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/13/2000

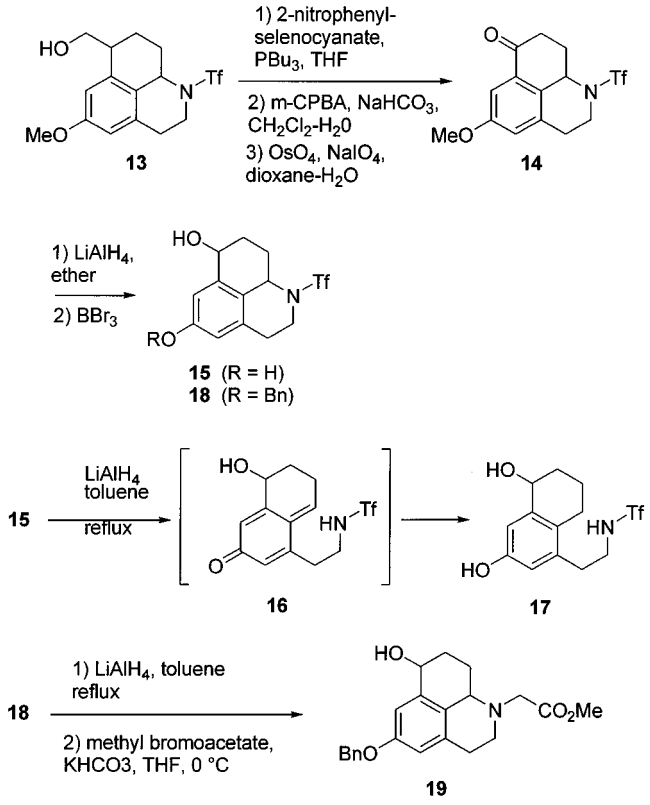
Scheme 2



7a was oxidized by *m*-CPBA to give epoxide **8** as a mixture of two diastereomers. Taylor's condition ($SnCl_4$, 1 equiv, −20 °C) was employed to effect the cyclization of the C-ring. This reaction, however, led to several products with the predominant one being the pyranose **11** (Scheme 2).[10] A possible mechanism for its formation involves electrophilic cyclization to the intermediate **9**, which then rearranges to iminium salt **10**. Cyclization via a nucleophilic attack of the hydroxyl group accounts for the formation of **11**.This process is not unprecedented; a similar observation has been reported by Harcourt et al.[11]

We reasoned that a more strongly electron-withdrawing group on nitrogen should disfavor formation of the iminium salt **10**. Thus, the amino group of **6** was protected as its triflate (**7b)** and, upon oxidation, the resulting epoxide **12** was subjected to stannic chloride-mediated ($SnCl_4$, −78 °C) cyclization. As anticipated, the desired tricyclic product **13** was obtained in around 10% yield along with starting material (50% recovery). To optimize the reaction, a study varying reaction conditions was carried out. Among Lewis-acid catalysts studied stannic chloride promoted the cyclization with the best yield, proving superior to $TiCl_4$ and $BF_3{\cdot}Et_2O$. Comparable yields were obtained whether one or two equivalents of stannic chloride were used, and the optimum reaction temperature was −20 to 0 °C. Lower temperatures resulted in lower product yield and more recovered starting material. Thus, under optimized condition (1 equiv of $SnCl_4$, −20 to 0 °C in CH_2Cl_2) epoxide **12** was cyclized to give the tricyclic ring of **13** in 75% yield as a mixture of two diastereomers.[12] Having the core template constructed, remaining tasks involved the functional group transformations of hydroxymethyl to amino at position 7 and methoxy to carboxylic acid at position 9, the incorporation of the acetate group at 3 position, and separation of the diastereomers.

Scheme 3



Scheme 3 illustrates these subsequent functional group transformations. Alcohol **13** was converted to ketone **14** via a three-step reaction sequence, where the hydroxyl was first converted to the seleno ether according to the Grieco's procedure,[13] followed by *m*-CPBA mediated

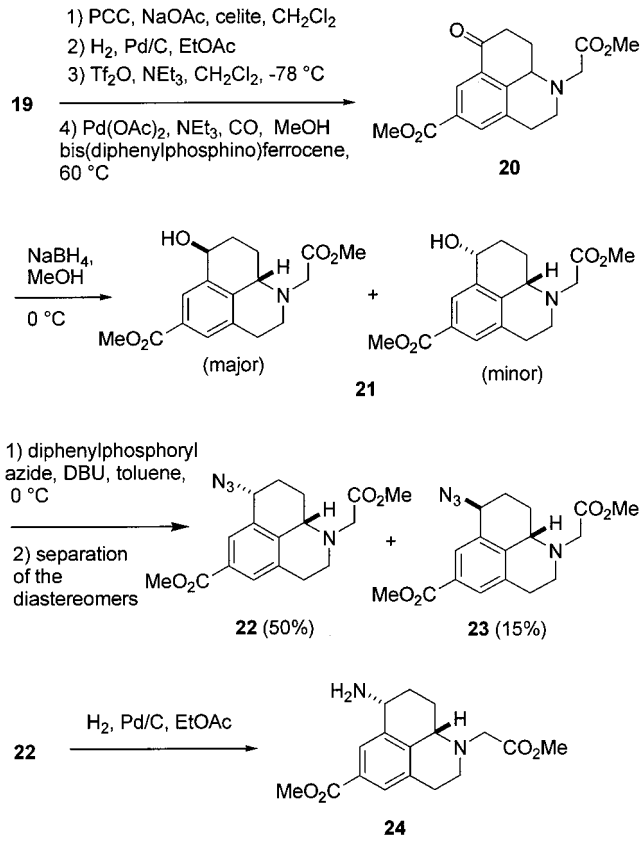
(10) The proton NMR spectrum of **11** (available in the Supporting Information section) indicated the disappearance of the benzylic proton, and its mass spectrum ($m/e^+ = 367$) was consistent with the molecular formula.

(11) Harcourt, D. N.; Hussain, F.; Taylor, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1329.

(12) Attempted cyclization of olefin **7b** using phenylselenenyl chloride or NBS were unsuccessful, resulting in starting material.

(13) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

Scheme 4

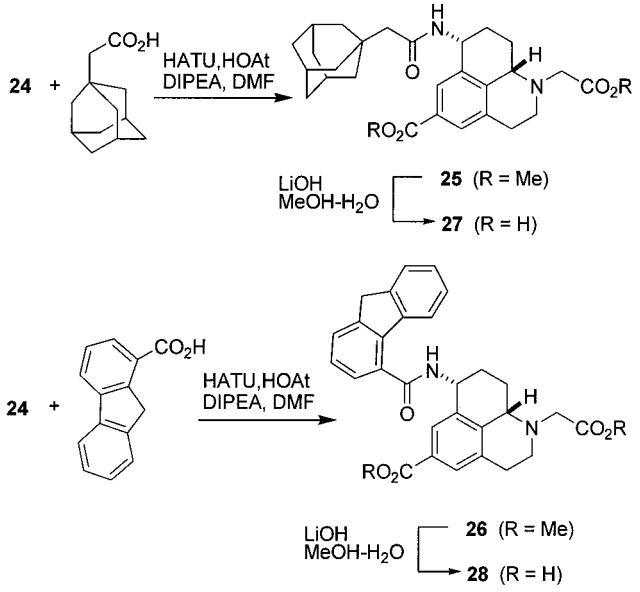


oxidative deselenation. The resulting olefin was further oxidized by OsO_4 and $NaIO_4$ to give tetralone **14**. We were unable to demethylate **14** using boron tribromide, trimethylsilyl iodide,[14] potassium iodide,[15] and PhSNa;[16] mostly, decomposition was observed. The carbonyl group of **14** was, therefore, reduced to benzylic hydroxyl group and subjected to boron tribromide treatment. It was found that desired phenol **15** was obtained in a good yield in the presence of the benzyl alcohol functional group.

To remove the triflate protecting group, **15** was then treated with $LiAlH_4$ under the refluxing toluene conditions and, surprisingly, only resulted in ring opening of tetrahydroisoquinoline, yielding **17** quantitatively where the triflate remained intact. The reaction may take place via methaquinone intermediate **16** since trifluoromethanesulfonamide is a good leaving group and the presence of a *p*-hydroxy group would allow the formation of **16**. Accordingly, phenol of **15** was protected as its benzyl ether, and the resulting **18** was reduced under the same conditions ($LiAlH_4$, refluxing toluene condition) to successfully unmask the secondary amine in an excellent yield. The amine intermediate was then coupled with methyl bromoacetate to provide **19**.

The next task was the introduction of the carboxy group into the aromatic ring. As shown in Scheme 4, **19** was converted to **20** through a sequence of reactions, in which the benzylic alcohol was oxidized to the ketone, benzyl ether was deprotected, and the resulting phenol was converted to the triflate. This compound was subjected to palladium-mediated carboxylation[17] to anchor the second carboxy group at the C9 position.

Scheme 5



Ketone **20** was then reduced to **21**.[18] Proton NMR showed a diastereomeric ratio of 4.5:1 in favor of the equatorial alcohol. This assignment was confirmed by the ^{13}C NMR spectrum in which two distinct peaks at 69.4 and 66.7 ppm, corresponding to carbons bearing equatorial alcohol and axial alcohol,[19] respectively, were observed in an intensity ratio of ca. 5:1. The diastereomeric mixtures of **21**, upon treatment with diphenylphosphoryl azide,[20] was converted to azides **22** and **23** as two readily separable diastereomers with 50% and 15% yield, respectively, after chromatography. Modeling reveals that C-ring of **22** and **23** possesses a half-chair conformation with pseudoaxial and pseudoequatorial substituents at the C7 position. The ^1H NMR spectrum of **22** shows that the benzylic proton at the C7 position is a triplet having a coupling constant of 4.2 Hz, whereas the corresponding proton of **23** is doublet of doublet (dd) having coupling constants of 8.2 and 5.9 Hz. This observation confirms that the azide group of **22** is in the pseudoaxial position. Having azide **22** with the desired stereochemistry in hand, it was reduced to amine **24** via hydrogenation to yield the desired tricyclic template with desired functional groups and correct stereochemistry. Amine **24** was not purified. Instead, it was characterized as **25** and **26** after coupling with 1-adamantane acetic acid and 1-fluorenecarboxylic acid, respectively. Subsequent base hydrolysis afforded the final products **27** and **28** (Scheme 5).

In summary, the use of a Bischler−Napieraski reaction and Friedel−Crafts cyclization via an epoxide allows the construction of a novel tricyclic ring system **25** intended to mimic the cyclic pentapeptide backbone of XC*DPC*. The diacids **27** and **28** were only weakly active in our jurkat cell adhesion assay (IC_{50} = 0.5 mM). This activity

(14) Jung, M. E.; Lyster, M. A., *J. Org. Chem*. **1977**, *42*, 3761.
(15) Harrison, I. T., *J. Chem. Soc., Chem. Commun*. **1969**, 616.
(16) Feutrill, G. I.; Mirrington, R. N., *Tetrahedron Lett*. **1970**, 1327.
(17) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1986**, *27*, 3931.
(18) This reaction was accompanied with 22% yield of the over-reduced product due to the reduction of acetate functional group.
(19) Gunther, H. NMR Spectroscopy, 2nd ed.; John Wiley & Sons: England, 1995; p 501.
(20) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem*. **1993**, *58*, 5886.

did, however, seem to be due to VLA-4 antagonism rather than to nonspecific toxicity since the compounds were inactive in cell adhesion assays that did not involve this ligand.

Experimental Section

General Methods. All the reactions were carried out under a nitrogen atmosphere. All solvents and reagents were obtained from commercial sources and were used without further purification except where noted. Flash chromatography purification was performed on silica gel 60 (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and the chemical shifts were expressed in parts per million downfield from tetramethylsilane. Melting points are uncorrected. Infrared (IR) was recorded on a FT-IR spectrometer using KBr disks or as neat liquids.

***N*-(4-Pentenoyl) 3-Methoxyphenethylcarboxamide (5).** A solution of oxalyl chloride (2 M in CH_2Cl_2) (150 mL, 0.3 mol) was added slowly to pentenoic acid (30.0 g, 0.3 mol) at 0 °C. The solution was stirred at 0 °C for 1 h and then at room temperature until gas evolution ceased. The mixture was concentrated at <10 °C at reduced pressure. The volatile acid chloride, after being taken up in CH_2Cl_2 (400 mL), was added slowly to a solution of 3-(methoxy)phenylethylamine (**3**) (45.4 g, 0.3 mol) and triethylamine (45.5 g, 0.45 mol) in CH_2Cl_2 (600 mL) at 0 °C. After being stirred overnight (18 h) at 0 °C to room temperature, the mixture was concentrated and partitioned between EtOAc and 1 N HCl solution. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was evaporated to give vinyl amide **5** (63.0 g, 0.27 mol) as a brown oil in 90% yield. This product was used for the next reaction without purification. An analytical sample was obtained by vacuum distillation (200 °C, 0.5 Torr): ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 4 H, Ph), 6.78 (m, 2 H), 5.77 (m, 1H), 5.52 (br s, 1 H), 5.05 (m, 2 H), 3.80 (s, 3 H), 3.52 (dd, J = 12.9, 6.8 Hz, 2 H), 2.78 (t, J = 6.8 Hz, 2 H), 2.37 (m, 2 H), 2.22 (m, 2 H); IR 3385−3236, 2957, 1678, 1633, 1539 cm^{-1}; MS 233 (M^+), 134. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.67; H, 8.31; N, 6.12.

1-(3-Butenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6). To a solution of vinyl amide **5** (35.0 g, 0.15 mol) in anhydrous CH_3CN (800 mL) was added freshly distilled $POCl_3$ (100 mL, 1.06 mol) in N_2 atmosphere at room temperature. The mixture was refluxed for 1.5 h. After being cooled to room temperature, it was carefully poured into aqueous K_2CO_3 at 0 °C (pH 9−10). The product was extracted into EtOAc. The organic layer was dried over K_2CO_3. Solvent was removed to give the imine intermediate (32.8 g). This intermediate, after being taken up with glacial acetic acid (700 mL), was treated with $NaBCNH_3$ (8.95 g, 0.14 mol) in portions at 0 °C. The mixture was stirred at room temperature for 2 h and quenched with H_2O (500 mL). Most of the solvent was removed on a rotovapor at ca. 50 °C. The residue was basified at 0 °C with 5 N NaOH solution to pH = 10. The product was extracted into EtOAc. The combined organic layers were washed with brine, dried over K_2CO_3, filtered, and concentrated to give a crude residue. It was triturated in EtOAc (100 mL) at 0 °C. Undissolved solid was filtered off, and the filtrate was concentrated to get the tetrahydro-isoquinoline **6** (31.6 g, 0.145 mol) in 97% yield as a brown syrup. This product was used for the next reaction without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.267.04 (d, J = 8.5 Hz, 1 H), 6.72 (dd, J = 8.5, 2.8 Hz, 1 H), 6.61 (d, J = 2.7 Hz, 1 H), 5.87 (m, 1 H), 5.1−4.85 (m, 2 H), 3.93 (dd, J = 9.0, 3.5 Hz), 3.78 (s, 3 H), 3.21 (m, 1 H), 2.97 (m, 1 H), 2.88−2.67 (m, 2 H), 2.21 (m, 2 H), 1.96−1.72 (m, 2 H).

1-(3-Butenyl)-2-(*N*-trifluoromethanesulfonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (7b). To a solution of tetrahydroquinoline **6** (25.0 g, 0.12 mol) in anhydrous CH_2Cl_2 (245 mL) at −78 °C were added dropwise triflic anhydride (35.7 g, 0.13 mol) and triethylamine (12.8 g, 0.13 mol). The mixture was stirred at − 78 °C for 2 h and concentrated. The residue was partitioned between EtOAc and 0.5 N HCl. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product. It was purified by flash chromatography over silica gel (3/1 hexanes−EtOAc) to give a syrupy product **7b** (30.3 g, 0.09 mol) in 76% yield: ^{1}H NMR (MHz, $CDCl_3$) δ 6.97−6.66 (m, 3 H), 5.83 (m, 1 H), 5.11−5.05 (m, 2 H), 4.85 (d, J = 8.8, 5.5 Hz, 1 H), 4.02 (m, 1 H), 3.78 (s, 3 H), 3.61 (m, 1 H), 3.08 (m, 1 H), 2.80 (m, 1 H), 2.22 (m, 2 H), 2.01−1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 137.1, 133.0, 127.9, 122.0, 117.7, 115.5, 113.8, 112.9, 57.5, 55.3, 40.0, 36.6, 30.3, 27.6; IR 2941, 1614, 1504, 1466, 1327, 1277, 1248 cm^{-1}; MS 349 (M^+), 294, 161.

1-(3,4-Epoxybutyl)-2-(*N*-trifluoromethanesulfonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (12). *m*-CPBA (57−86%) (30.0 g) was added portionwise to a solution of olefin **7b** (30.0 g, 86.0 mmol) in CH_2Cl_2 (500 mL) at room temperature. The mixture was stirred for 18 h. Solid was filtered off, and the filtrate was concentrated. The residue was partitioned between EtOAc and 7% K_2CO_3 aqueous solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude residue. This was purified by flash chromatography over silica gel (3/1 hexanes−EtOAc) to afford the epoxide **12** (25.2 g, 69.0 mmol) in 80% yield. (This product is a 1:1 diastereomeric mixture judged by the proton NMR spectrum): mp 70.2−74.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (m, 1 H), 6.78−6.66 (m, 2 H), 4.87 (m, 1 H), 4.02 (m, 1 H), 3.79 (s, 3 H), 3.61 (m, 1 H), 3.14−2.74 (m, 4 H), 2.53 (m, 1 H), 2.0−1.4 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 158.8, 135.9, 132.9, 127.9, 127.8, 127.6, 121.3, 117.9, 113.8, 113.0, 57.8, 57.4, 55.3, 51.7, 51.4, 47.0, 46.9, 39.9, 33.6, 29.3, 29.0, 27.5; IR 2953, 1614, 1504, 1387, 1279, 1248, 1224, 1188, 1153 cm^{-1}; MS 365 (M^+), 294, 232, 161. Anal. Calcd for $C_{15}H_{18}NO_4F_3$: C, 49.31; H, 4.96; N, 3.83. Found: C, 49.45; H, 4.95; N, 3.89.

3-(*N*-Trifluoromethanesulfonyl)-7-hydroxymethyl-9-methoxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (13). Tin tetrachloride (1 M in CH_2Cl_2) (100 mL, 100 mmol) was added dropwise to a solution of epoxide **12** (23.5 g, 64.4 mmol) in anhydrous CH_2Cl_2 (700 mL) at −20 °C. After completion of the addition (ca. 30 min), the mixture was stirred at −20 °C for 1.5 h and then at 0 °C for 2 h. It was carefully quenched with water (500 mL) at 0 °C, and the resulting mixture was vigorously stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution, brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (2/1 hexanes−EtOAc) to give **13** (17.0 g, 46.6 mmol) as an oil in 73% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 2.9 Hz, 0.5 H), 6.74 (d, J = 2.5 Hz, 0.5 H), 6.59 (m, 1 H), 4.67 (br s, 1 H), 4.13 (m, 1 H), 4.01 (dd, J = 10.8, 5.1 Hz, 0.5 H), 3.91 (dd, J = 10.8, 6.0 Hz, 0.5 H), 3.80 (s, 1.5 H), 3.79 (s, 1.5 H), 3.74 (m, 1 H), 3.30−2.95 (m, 2 H), 2.72 (m, 2 H), 2.37 (m, 1 H), 2.12 (m, 1 H), 1.95−1.46 (m, 2 H); IR 3404, 2943, 1610, 1593, 1477, 1387, 1327, 1280, 1224, 1188, 1151 cm^{-1}; MS 365 (M^+), 320, 294, 232, 214.

3-(*N*-Trifluoromethanesulfonyl)-7-oxo-9-methoxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (14). To a solution of alcohol **13** (21.0 g, 57.5 mmol) in anhydrous THF (225 mL) at room temperature was added 2-nitrophenylselenocyanate (16.8 g, 74.0 mmol) and tri-*tert*-butylphosphine (19 mL, 75.8 mmol). The mixture was stirred for 1 h at room temperature and concentrated. The residue was subjected to silica gel chromatography (3.5/1 hexanes−EtOAc) to give the selenide (28.1 g). It was taken up with CH_2Cl_2 (1 L) and saturated $NaHCO_3$ (330 mL) aqueous solution and to which *m*-CPBA (57−86%) (12.5 g) was added portionwise at 0 °C with strong mechanical stirring. After being vigorously stirred for 5 min at 0 °C and for 1 h at room temperature, the two phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution, brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (5/1 hexanes−EtOAc) to give the olefin intermediate (12.0 g, 34.7 mmol) as a pale yellow solid in 60% yield. An analytical sample was obtained by triturating the product in hexanes followed by filtration: mp 113.0−113.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 2.6 Hz, 1 H), 6.64 (d, J = 2.5 Hz, 1 H), 5.51 (br s, 1 H), 5.07 (br s, 1 H), 4.65 (br m, 1 H), 4.10 (m, 1 H), 3.82 (s, 3 H), 3.23 (m, 1 H), 3.01 (m, 1 H), 2.75−2.70 (m, 3 H), 2.34 (m, 1 H), 1.89−1.79 (m, 1 H); IR 1601, 1471, 1377, 1363, 1261, 1224, 1190, 1149, 1138 cm^{-1}; MS 347 (M^+), 294, 214, 185. Anal. Calcd for

$C_{15}H_{16}NO_3F_3S$: C, 51.87; H, 4.64; N, 4.03. Found: C, 52.09; H, 4.67; N, 4.13.

To a suspension of the olefin intermediate (11.3 g, 32.6 mmol) in dioxane (110 mL) and H_2O (35 mL) at room temperature was added OsO_4 solid. The color of the mixture became dark brown after being stirred for 5 min. $NaIO_4$ solid was added in portions at such a rate that the temperature of the mixture maintained at 24−26 °C. The tan-colored slurry was stirred at room temperature for an additional 3 h. The mixture was partitioned between ether and H_2O. The aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (5/1 to 3/1 hexanes−EtOAc) to give **14** (6.0 g, 17.2 mmol) as a white solid in 53% yield: mp 108.5−111.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 2.8 Hz, 1 H), 6.95 (d, J = 2.7 Hz, 1 H), 4.95 (br m, 1 H), 4.20−4.15 (m, 1 H), 3.85 (s, 3 H), 3.19 (m, 1 H), 3.04 (m, 1 H), 2.9−2.5 (m, 4 H), 2.25 (ddd, J = 17.5, 12.4, 5.0 Hz, 1 H); ^{13}NMR (300 MHz, $CDCl_3$) δ 195.3, 159.0, 135.7, 133.5, 129.6, 121.0, 110.2, 55.6, 54.8, 42.8, 37.5, 31.7, 30.3; IR 1686, 1606, 1475, 1389, 1346, 1296, 1282, 1224, 1188, 1151 cm^{-1}; MS 349 (M^+), 293, 216, 215, 188, 160. Anal. Calcd for $C_{14}H_{14}NO_4F_3S$: C, 48.14; H, 4.04; N, 4.01. Found: C, 48.00; H, 4.05; N, 3.96.

3-(*N*-Trifluoromethanesulfonyl)-7,9-dihydroxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (15). To a solution of **14** (5.1 g, 14.6 mmol) in anhydrous ether (150 mL) was added $LiAlH_4$ solution (1 M in THF) (14.3 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and then quenched with 1 N NaOH at 0 °C. The product was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was evaporated to give the alcohol intermediate (5.1 g) in quantitative yield: MS 351 (M^+), 333, 323, 200, 190. To a solution of this intermediate (5.0 g, 14.2 mmol) in anhydrous CH_2Cl_2 (200 mL) at −78 °C was added BBr_3 solution (1 M in CH_2Cl_2) (130 mL). The mixture was stirred at −78 °C for 30 min, at −20 to −10 °C for 2 h, and at room temperature for additional 2 h. After being cooled to −20 °C, the mixture was quenched carefully with excess ether, warmed to room temperature, stirred for 30 min, and concentrated. The residue was taken up with 200 mL of H_2O followed by the addition of THF so as to make the mixture becoming a clear solution. The resulting mixture was stirred at room temperature for 18 h. $AgNO_3$ solid (excess) was added and, after 30 min of stirring, was filtered off. The product was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (1/1 EtOAc−hexanes) to afford **15** (2.8 g, 8.2 mmol) as a gummy solid in 58% yield. (two diastereomers): ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 2.4 Hz, 0.5 H), 6.75 (d, J = 2.5 Hz, 0.5 H), 6.58 (d, J = 2.3 Hz, 1 H), 5.15 (m, 0.5 H), 4.79−4.36 (m, 1.5 H), 4.05 (m, 1 H), 3.20 (m, 1 H), 2.97 (m, 1 H), 2.70 (m, 1 H), 2.48−2.24 (m, 2 H), 1.80−1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.1, 154.8, 142.2, 140.4, 134.2, 122.4, 115.1, 114.1, 113.5, 110.3, 69.4, 66.3, 60.5, 53.1, 52.7, 42.4, 41.9, 29.7, 29.4; IR: 3416, 2945, 1618, 1471, 1385, 1280, 1224, 1190, 1149 cm^{-1}; MS 337 (M^+), 319, 309, 186, 149.

3-(*N*-Trifluoromethanesulfonyl)-7-hydroxy-9-benzyloxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (18). Benzyl bromide (1.1 g, 6.5 mmol) was added to a mixture of phenol **15** (2.2 g, 6.5 mmol) and K_2CO_3 (4.5 g, 32.6 mmol) in anhydrous DMSO (20 mL) at room temperature. After being stirred for 20 h, the mixture was partitioned between H_2O and ether. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography over silica gel (3/1 hexanes−EtOAc) to give **18** (1.6 g, 3.7 mmol) in 57% yield (two diastereomers): ^{1}H NMR ($CDCl_3$) δ 7.45−7.31 (m, 5 H), 7.10 (d, J = 2.4 Hz, 0.5 H), 6.91 (d, J = 2.5 Hz, 0.5 H), 6.72 (m, 1 H), 5.17 (m, 0.5 H), 5.08 (s, 1 H), 5.06 (s, 1 H), 4.84 (t, J = 4.9 Hz, 0.5 H), 4.70 (m, 1 H), 4.13−4.06 (m, 1 H), 3.22 (m, 1 H), 3.07 (m, 1 H), 2.72 (m, 1 H), 2.49 (m, 1 H), 2.32 (m, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H); IR 3379, 2939, 1610, 1595, 1497, 1454, 1385, 1279, 1223, 1188, 1149 cm^{-1}; MS 427 (M^+), 409, 276, 91.

3-[*N*-(Methoxycarbonyl)methyl]-7-hydroxy-9-benzyloxy-2,3,6,7-tetrahydro-1H,5H-benzo[ij]quinoline (19). $LiAlH_4$ solution (1 M in THF) (20 mL) was added slowly to a solution of triflate **18** (1.55 g, 3.63 mmol) in anhydrous toluene (45 mL) at room temperature. The mixture was refluxed for 4 h and quenched at 0 °C successively with H_2O (0.8 mL), 1 N NaOH (2.8 mL), and H_2O (0.2 mL). The resulting mixture was stirred at 0 °C for 30 min to precipitate the inorganic salt and then diluted with EtOAc (200 mL). The solid was filtered off and rinsed with EtOAc. The filtrate, after drying over $MgSO_4$, was concentrated, and the residue was triturated with EtOAc. Once again, the solid was filtered off and the filtrate was concentrated to give the amine intermediate (0.99 g, 3.35 mmol) as a white solid in 92% yield: MS 295 (M^+).

To a mixture of the amine (0.97 g, 3.29 mmol) and $KHCO_3$ (0.43 g, 4.30 mmol) in anhydrous THF (20 mL) at 0 °C was added dropwise methyl bromoacetate (0.65 g, 4.22 mmol). After being stirred at 0 °C for 30 min and at room temperature for 2.5 h, the mixture was partitioned between ether and half- saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $NaSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography over silica gel (EtOAc) to give **19** (0.92 g, 2.49 mmol) as a gummy product in 76% yield (two diastereomers): ^{1}H NMR ($CDCl_3$) δ 7.45−7.31 (m, 5 H), 6.98 (d, J = 2.6 Hz, 0.5 H), 6.86 (d, J = 2.6 Hz, 0.5 H), 6.67 (d, J = 2.6 Hz, 0.5 H), 6.40 (d, J = 2.6 Hz, 0.5 H), 5.04 (s, 2 H), 4.78−4.67 (m, 1 H), 5.04 (s, 3 H), 3.62−3.46 (m, 3 H), 3.17−2.91 (m, 3 H), 2.72 (m, 1 H), 2.4−2.1 (m, 1 H), 2.03 (m, 2 H), 1.70 (m, 1 H); IR 3426, 2947, 1743, 1606, 1466, 1273, 1194, 1159, 1026 cm^{-1}; MS 366 ($M - H)^+$, 349, 339, 308, 294, 280, 266, 248, 91.

3-[*N*-(Methoxycarbonyl)methyl]-7-oxo-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (20). To a mixture of alcohol **19** (30 mg, 0.08 mmol), powdered NaOAc, and Celite in anhydrous CH_2Cl_2 (1 mL) at 0 °C was added pyridium chlorochromate (PCC) (31 mg, 0.10 mmol). The mixture was stirred for 2 h and diluted with 2 mL of ether. EtOAc (20 mL) was added, and the solid was filtered off through a pad of Celite. The filtrate was concentrated, and the residue was purified by preparative TLC (2/1 EtOAc/hexanes) to give the gummy tetralone (16 mg, 0.044 mmol) in 54% yield: ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 2.7 Hz, 1 H), 7.44−7.32 (m, 5 H), 6.97 (d, J = 2.7 Hz, 1 H), 5.09 (s, 2 H), 3.88 (d, J = 13.8, 5.2 Hz, 1 H), 3.75 (s, 3 H), 3.60 (dd, AB, J = 11.3, 6.9 Hz, 2 H), 3.21−3.05 (m, 3 H), 2.79 (m, 2 H), 2.56 (m, 1 H), 2.40 (m, 1 H), 1.92−1.76 (m, 1 H); IR: 2964, 1736, 1682, 1604, 1464, 1379, 1352, 1317, 1292, 1201, 1165 cm^{-1}; MS 365 (M^+), 364, 306, 292, 274.

A mixture of tetralone (410 mg, 1.12 mmol) and Pd/C (10%) in EtOAc (10 mL) was stirred under H_2 atmosphere (balloon pressure) for 2 h. Catalyst was filtered off through a pad of Celite, and the filtrate was concentrated to give the phenol intermediate (295 mg). This intermediate was dissolved in anhydrous CH_2Cl_2 (10 mL) and treated at −78 °C with triflic anhydride (364 mg, 1.29 mmol) and triethylamine (141 mg, 1.39 mmol). After being stirred for 3 h at −78 °C, the mixture was partitioned between EtOAc and saturated $NaHCO_3$ aqueous solution. The two phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by preparative TLC (2/1 EtOAc/hexanes) to give the triflate intermediate (262 mg, 0.64 mmol). This intermediate, after being taken up with anhydrous DMF (2 mL), was treated with NEt_3 (130 mg, 1.28 mmol), $Pd(OAc)_2$ (9 mg, 0.039 mmol), bis-(diphenylphosphino)ferrocene (45 mg, 0.081 mmol), and MeOH (0.52 mL). The resulting mixture was purged with CO for 5 min and heated to 60 °C under CO atmosphere (balloon pressure) for 3 h. After being cooled to room temperature, the mixture was quenched with half saturated $NaHCO_3$ aqueous solution. The product was extracted to EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (2/1 EtOAc−hexanes) to give diester **20** (180 mg, 0.56 mmol) (51% in three steps): ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 1.8 Hz, 1 H), 7.99 (d, J = 1.5 Hz, 1 H), 4.02 (dd, J = 12.1, 3.6 Hz, 1 H), 3.92 (s, 3 H), 3.76 (s, 3 H), 3.65 (s, 2 H), 3.24−3.20 (m, 3 H), 2.84 (m, 2 H), 2.67−2.44 (m, 2 H), 1.87 (m, 1 H); IR 2953, 1724, 1690, 1606, 1435, 1317, 1248, 1209, 1149 cm^{-1}; MS 317 (M^+), 316, 286, 261, 258, 244.

3-[*N*-(Methoxycarbonyl)methyl]-7-hydroxy-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (21).

To a solution of **20** (150 mg, 0.51 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (93 mg, 2.46 mmol). After being stirred at 0 °C for 10 min and at room temperature for 1 h, the mixture was quenched with H_2O (10 mL) and allowed to stir for 30 min. The product was extracted to EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by preparative TLC (5:1 EtOAc−hexanes) to give **21** (85 mg, 0.27 mmol, 53% yield) as a diastereomeric mixture of 4.5 to 1 ratio in favor of the (4*S*,7*S*) isomer. A side product, in which one of the ester groups was reduced, was also isolated (33 mg): ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1 H), 7.68 (s, 1 H), 4.83 (br t, J = 7.0 Hz, 1 H), 3.89 (s, 3 H), 3.86 (dd, J = 11.1, 4.1 Hz, 1 H), 3.74 (s, 3 H), 3.53 (dd, J = 13.8, 6.8 Hz, AB, 2 H), 3.19−3.05 (m, 3 H), 2.82 (m, 1 H), 2.4−2.2 (m, 2 H), 1.72 (m, 1 H), 1.53 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 167.1, 139.8, 138.8, 134.5, 129.0, 128.5, 126.2, 69.4, 59.0, 54.3, 52.0, 51.7, 51.1, 31.5, 28.4, 26.4; IR: 3406, 2951, 1720, 1435, 1302, 1203, 1161 cm^{-1}; MS 319 (M^+), 301, 291, 260, 246, 232, 218; HRMS calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1343.

3-[*N*-(Methoxycarbonyl)methyl]-7-azido-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline ((4*S*,7*R*)-22 and (4*S*,7*S*)-23). To a solution of **21** (70 mg, 0.22 mmol) in anhydrous toluene (2 mL) at 0 °C was added diphenylphosphoryl azide (DPPA) (73 mg, 0.26 mmol) followed by DBU (40 mg, 0.26 mmol) dropwise. After being stirred at 0 °C for 2 h and at room temperature for 18 h, the mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by preparative TLC (1/1 hexanes/EtOAc) to obtain two products, **22** (38 mg, 0.11 mmol, 50% yield) and **23** (11 mg, 0.03 mmol, 15% yield). For **22**: ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1 H), 7.75 (s, 1 H), 4.61 (t, J = 4.2 Hz, 1 H), 3.91 (s, 3 H), 3.79 (m, 1 H), 3.74 (s, 3 H), 3.57 (dd, J = 22.2, 17.2 Hz, AB, 2 H), 3.15 (m, 3 H), 2.85 (m, 1 H), 2.11 (m, 3 H), 1.75 (m, 1 H); IR 2951, 2098, 1720, 1435, 1327, 1296, 1215, 1153,cm^{-1}; MS 344 (M^+), 313, 285, 271, 261, 243, 228, 196; HRMS calcd for $C_{17}H_{20}N_4O_4$ 344.1485, found 344.1473. For **23**: ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1 H), 7.74 (s, 1 H), 4.62 (dd, J = 8.2, 5.9 Hz, 1 H), 3.91 (s, 3 H), 3.87 (m, 1 H), 3.75 (s, 3 H), 3.55 (dd, J = 21.1, 16.8 Hz, AB, 2 H), 3.21−3.03 (m, 3 H), 2.82 (m, 1 H), 2.31 (m, 2 H), 2.03 (m, 1 H).

(4*S*,7*R*)-3-[*N*-(Methoxycarbonyl)methyl]-7-amino-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (24). A mixture of **22** (14 mg, 0.04 mmol) and Pd/C (10%) in 1 mL of EtOAc was stirred vigorously under H_2 atmosphere (balloon pressure) at room temperature for 6 h. Catalyst was filtered off through a pad of Celite and rinsed with MeOH. The filtrate was concentrated to give **24** (11 mg, 0.035 mmol) in 84% yield. This material was used directly for the next coupling reaction.

(4*S*,7*R*)-3-[*N*-(Methoxycarbonyl)methyl]-7-(1-admantanylacetamido)-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (25). To a solution of **24** (10 mg, 0.031 mmol) and 1-adamantaneacetic acid (25 mg, 0.125 mmol) in anhydrous DMF (0.5 mL) at room temperature were added *O*-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate (HATU) (48 mg, 0.125 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (17 mg, 0.125 mmol), and diisopropylethylamine (24 mg, 0.188 mmol). After being stirred at room temperature for 18 h, the mixture was quenched with saturated $NaHCO_3$ aqueous solution. The product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by preparative TLC (1.5/1 hexanes−EtOAc) to give **25** (12 mg, 0.024 mmol) in 75% yield: ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 7.70 (s, 1 H), 5.59 (br d, J = 8.1 Hz, 1 H), 5.19 (m, 1 H), 3.88 (s, 3 H), 3.73 (s, 3 H), 3.71−3.51 (m, 3 H), 3.20−2.80 (m, 4 H), 2.18 (m, 1 H), 2.03−1.62 (m, 20 H); IR 2905, 1720, 1643, 1527, 1437, 1294, 1215, 1153 cm^{-1}; MS 494 (M^+), 463, 435, 421, 301, 289, 242; HRMS calcd for $C_{29}H_{38}N_2O_5$ 494.2781, found 494.2772.

(4*S*,7*R*)-3-[*N*-(Methoxycarbonyl)methyl]-7-[1-fluorenecarbonyl)amino]-9-methoxycarbonyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (26). The same procedure as described for **25** affords **26** (18 mg, 0.035 mmol, 80% yield) from **24** (14 mg, 0.044 mmol) and 1-fluorenecarboxylic acid (46 mg, 0.221 mmol): ^{1}H NMR ($CDCl_3$) δ 7.91−7.73 (m, 4 H), 7.60−7.34 (m, 5 H), 6.35 (br d, J = 7.3 Hz, 1 H), 5.41 (m, 1 H), 4.25 (s, 2 H), 3.86 (s, 3 H), 3.76 (s, 3 H), 3.70 (m, 1 H), 3.62 (dd, J = 31.0, 16.9 Hz, AB, 2 H), 3.25−3.16 (m, 3 H), 2.92 (m, 1 H), 2.20 (m, 3 H), 1.61 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 167.0, 166.7, 143.6, 143.3, 143.0, 140.3, 135.7, 134.7, 131.3, 129.1, 128.8, 127.3, 127.1, 126.7, 125.0, 124.4, 122.4, 119.9, 59.0, 54.8, 52.0, 51.7, 51.1, 46.8, 37.6, 28.8, 27.8, 23.2; IR 3431, 3287, 2951, 1755, 1724, 1628, 1520, 1439, 1296, 1213, 1138 cm^{-1}; MS 510 (M^+), 451, 437, 301, 289, 242; HRMS calcd for $C_{31}H_{30}N_2O_5$ 510.2155, found 510.2154.

(4*S*,7*R*)-3-(*N*-Carboxymethyl)-7-(1-admantanylacetamido)-9-carboxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinoline (27). A mixture of **25** (10 mg, 0.02 mmol) and $LiOH\cdot H_2O$ (3.4 mg, 0.08 mmol) in 0.6 mL of (1/1) MeOH−H_2O was stirred at room temperature for 15 h. The diacid product was precipitated after the addition of 0.1 mL of acetic acid. The solid was collected and rinsed with small amount of H_2O. It was dried under vacuum to give **27** as a white solid (5.0 mg, 0.01 mmol) in 50% yield: ^{1}H NMR (CD_3OD−$CDCl_3$) δ 7.91 (s, 1 H), 7.82 (s, 1 H), 5.17 (m, 1 H), 4.47 (m, 1 H), 3.78−3.52 (m, 5 H), 3.23 (m, 2 H), 2.27 (m, 1 H), 2.1−1.6 (m, 20 H); MS (FAB) 467 $(M + 1)^+$, 426, 370, 309, 277, 229, 219; HRMS (FAB) calcd for $C_{27}H_{35}N_2O_5$ $(M + 1)^+$ 467.5884 found 467.2545.

(4*S*,7*R*)-3-(*N*-Carboxymethyl)-7-[(1-fluorenecarbonyl)-amino]-9-carboxymethyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo-[*ij*]quinoline (28). The same procedure described for **27** affords **28** (5 mg, 0.01 mmol, 38% yield) from **26** (14 mg, 0.027 mmol): IR 3433, 2930, 1705, 1639, 1520, 1454, 1396, 1284 cm^{-1}; MS (FAB) 483 $(M + 1)^+$; HRMS (FAB) calcd for $C_{29}H_{27}N_2O_5$ 483.5482, found 483.1920.

Supporting Information Available: ^{1}H NMR spectra of **5**, **6**, **7b**, **11**−**14**, **14** precursor, **15**, **18**, **19**, **20** precursor, **21**−**23**, and **25**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991162K