vacuo and flash chromatography of the residue (triethylamine-treated SiO_2, 0.5 × 5 cm, ethyl acetate) afforded **10** (4.1 mg, 6.7 mg theoretical, 61%) as a pale yellow solid: mp 215-218 °C; ^1H NMR ($CDCl_3$, 500 MHz, ppm) 9.19 (s, 1 H, NH), 6.92 (d, 1 H, J = 2.4 Hz, C3'-H), 6.89 (d, 1 H, J = 1.5 Hz, C3-H), 6.77 (s, 1 H, C4'-H), 6.60 (d, 1 H, J = 9.8 Hz, C6-H), 6.45 (dd, 1 H, J = 1.5, 9.8 Hz, C5-H), 4.39 (dd, 1 H, J = 4.9, 10.4 Hz, C1-H), 4.32 (d, 1 H, J = 10.4 Hz, C1-H), 4.07 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 2.65 (m, 1 H, C7a-H), 1.79 (dd, 1 H, J = 4.6, 7.9 Hz, C7-H), 1.50 (t, 1 H, J = 4.9 Hz, C7-H); IR (KBr) ν_{max} 3444, 2936, 1636, 1526, 1492, 1464, 1404, 1364, 1306, 1278, 1230, 1110, 1050, 752 cm^{-1}; UV (methanol), 334 (ε 21 000), 278 nm (13 000); EIMS m/e (relative intensity) 380 (M^+, 22), 234 (100), 146 (91); CIMS (isobutane) m/e 381 (M + H^+, 100); EIHRMS m/e 380.1372 ($C_{21}H_{20}N_2O_5$ requires 380.1372).

Reaction of N-[(5,6,7-Trimethoxyindol-2-yl)carbonyl]-1,2,7,7a-tetrahydrocycloprop[1,2-c]indol-4-one (10) with Hydrochloric Acid. A solution of **10** (2.0 mg, 5.3 μmol) in ethyl acetate (2 mL) at 24 °C under argon was treated with 3 N anhydrous hydrochloric acid in ethyl acetate (0.2 mL, ca. 100 equiv). After the solution was stirred for 20 min (24 °C), the solvent was removed in vacuo. Flash chromatography (0.5 × 3.5 cm SiO_2, 0-20% THF-hexane gradient elution) afforded **9** (1.7 mg, 2.2 mg theoretical, 77%) identical in all respects with authentic **9**.

DNA Binding Studies. Singly 5'-^{32}P-end-labeled double-stranded DNA constituting SV40 DNA fragments (w794, nucleotides no. 5238-138, 144 base pairs; w836, nucleotides no. 5189-91, 145 base pairs; c988, nucleotides no. 4359-4210, 149 base pairs; c820, nucleotides no. 4201-4356, 155 base pairs; c1346, nucleotides no. 1632-1782, 150 base pairs) cloned into the *Sma*I site of M13mp10 were prepared by treatment of single-stranded templates[28] with 5'-^{32}P-end-labeled universal primer [5'-d(GTAAAACGACGGCCAGT)-3'], extension of the primer-template duplex with the Klenow fragment of DNA polymerase I, and subsequent *Eco*R I cleavage of the double-stranded DNA immediately following the inserted DNA.[27] The resultant double-stranded DNA was treated with the agents at 4 °C or 37 °C (24 h) at a range of agent concentrations. Removal of the unreacted agent through ethanol precipitation of the DNA, thermally induced cleavage of a solution of the double-stranded DNA-agent covalent complexes at the sites of covalent alkylation (100 °C, 30 min),[24-27] gel electrophoresis under denaturing conditions of the resultant DNA alongside Sanger dideoxynucleotide sequencing reactions, and subsequent autoradiography revealed the sites of covalent alkylation and their relative intensities.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (D.L.B., Grant No. CA41986) and the Wesley Foundation (P.A.K., Grant No. 8812007). We thank Subas M. Sakya for the preparation of **22**, Dr. K. Takahashi (Kyowa Hakko Kogyo Co., Ltd.) and Dr. T. Shomura (Meiji Seika Kaisha, Ltd.) for providing samples of duocarmycin A (KT) and duocarmycin C_1 and C_2 (KT, TS), and Dr. Y. Takeuchi (Meiji Seika Kaisha Ltd.) for structural parameters (bond lengths, bond angles) for pyrindamycin A (X-ray).

Supplementary Material Available: General experimental details and full experimental details for the preparation of **22**, **24**, and **25**, supporting autofootprinting studies, force field parameters for duocarmycin for use with MacroModel (Version 2.5, AMBER force field), and stereoviews of Figure 7, parts a-b, are provided (19 pages). Ordering information may be found on any current masthead page.

Asymmetric Induction in the Vinylogous Amide Photocycloaddition Reaction. A Formal Synthesis of Vindorosine

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Abstract: The application of the intramolecular vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure sequence to a formal synthesis of vindorosine, **6**, starting from L-tryptophan, is described. The synthesis of **7**, which has been converted to vindorosine by Buchi, in 14 steps (7% overall yield from L-tryptophan) in homochiral form attests to the efficiency of this photochemical approach to the synthesis of the aspidosperma alkaloids, and demonstrates the exceedingly high levels of asymmetric induction which are possible via the intramolecular [2 + 2]photocycloaddition reaction of vinylogous amides.

We have recently introduced a new method for the construction of nitrogen-containing ring systems, **1**-**4** (Scheme I), which has been applied to a synthesis of the alkaloid (±)-mesembrine.[4] Intramolecular photocycloaddition of **1**, followed by retro-Mannich fragmentation of photoadduct **2**, leads to the formation of the keto imine **3**, which can undergo a final Mannich closure to generate the perhydroindole **4**. The effect of substitution on the tether connecting the vinylogous amide chromophore and the reacting alkene, as illustrated in **5**, on the stereochemical outcome of the photocycloaddition has now been examined. We report herein that exceedingly high levels of asymmetric induction are indeed possible and describe the application of this methodology to a formal synthesis of vindorosine, **6**,[5] *in homochiral form*, starting from L-tryptophan.[6]

The retrosynthetic analysis for the application of the vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich

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(2) Fellow of the Medical Scientist Training Program, The University of Chicago.

(3) Author to whom correspondence regarding the X-ray structures of **18** and **22** should be addressed. Full details regarding the crystallographic data will be reported in a separate publication.

(4) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831.

(5) Gorman, M.; Neuss, N.; Biemann, *J. Am. Chem. Soc.* **1962**, *84*, 1058.

(6) For alternative strategies for the synthesis of aspidosperma alkaloids in homochiral form starting from L-tryptophan, see: (a) Vercautren, J.; Bideau, A.; Massiot, G. *Tetrahedron Lett.* **1987**, 1267. (b) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517 and references cited therein.

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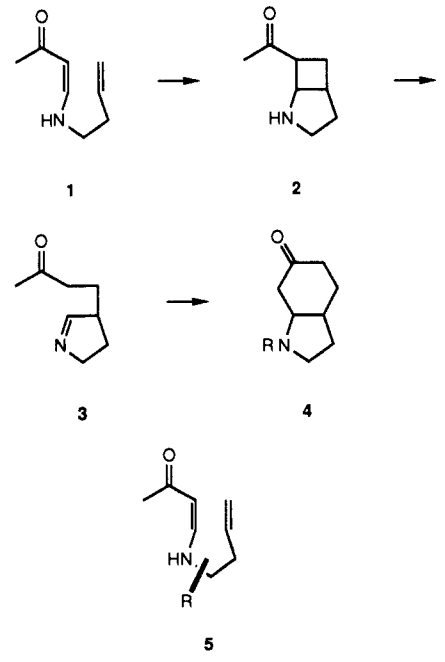
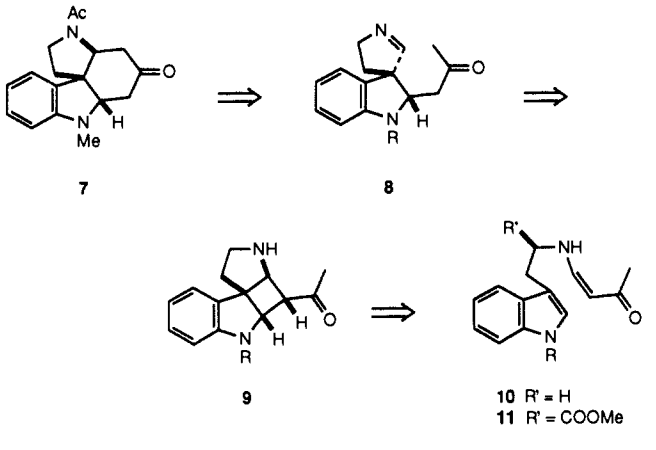
Scheme I

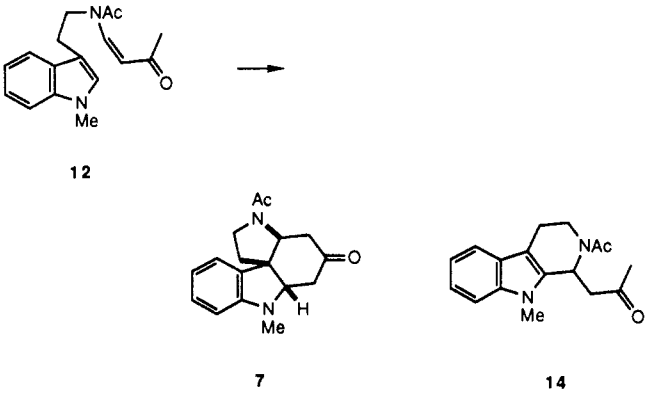


Scheme II

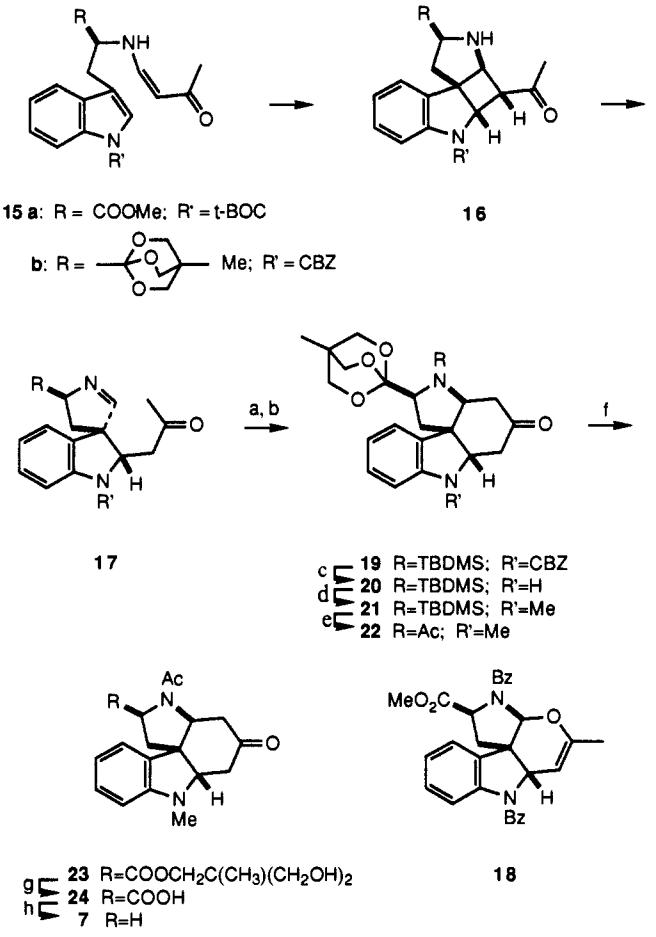


closure sequence to the construction of the tetracyclic ketone **7**, which has been converted to (±)-vindorsine, **6**, by Buchi,[7] is outlined in Scheme II. The tetracyclic ketone **7** could be derived by Mannich closure of **8**, the keto imine derived from retro-Mannich fragmentation of photoadduct **9**, which would in turn be derived from the intramolecular photocycloaddition of a secondary vinylogous amide with the $\Delta^{2,3}$ alkene of an indole, as illustrated in **10**, where R would necessarily be an electron-withdrawing group, based on the work of Ikeda[8] and Julian.[9] As in our recently reported synthesis of (−)-perhydrohistrionicotoxin,[10]

Scheme III



Scheme IV[a]



[a](a) LDA, TBDMSOTf, THF; (b) *n*-Bu_4NF, THF (51% overall from **17b**); (c) H_2/Pd–C, EtOH (92%); (d) CH_2O, $NaCNBH_3$, CH_3CN (77%); (e) CH_3COCl, CH_2Cl_2 (100%); (f) 1.5 equiv of 1 M $NaHSO_4$, dimethoxyethane, 5 min, 0 °C (77%); (g) LiOH, DME (100%); (h) Barton decarboxylation (73%).

we envisioned that both absolute and relative stereochemical control might be achieved via the intramolecular photocycloaddition, starting with a substrate **11**, which could be prepared from a naturally occurring α-amino acid, in this case, L-tryptophan.

Photosubstrate **10** differs only in the substituents on nitrogen from **12** (Scheme III), the substrate employed by Buchi in his synthesis of (±)-vindorosine, in which the ground-state cyclization of **12** on treatment with BF_3–Et_2O led to the formation of both **7** and **14**, which result from the addition of the β- and α-carbon of the indole, respectively, to the vinylogous imide.[7] We reasoned that the photocycloaddition approach outlined retrosynthetically in Scheme II could solve the regiochemical problems encountered in these earlier studies by Buchi.

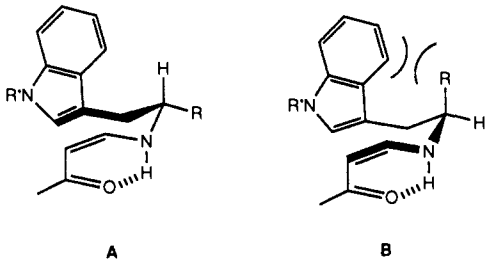
(7) Buchi, G.; Matsumoto, K.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880.

(8) Ikeda, M.; Ohno, K.; Mohri, S.; Takahashi, M.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 405 and references cited therein.

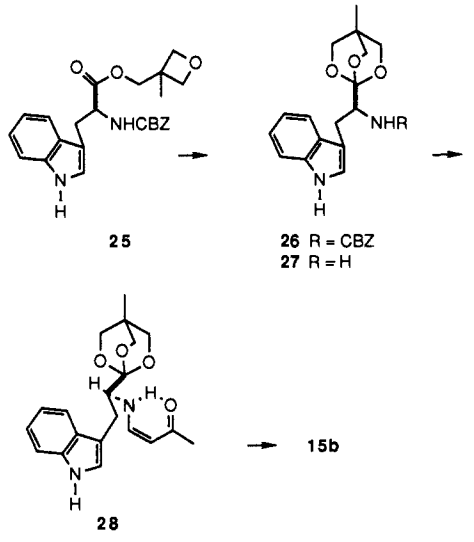
(9) Julian, D.; Foster, R. *J. Chem. Soc., Chem. Comm.* **1973**, 311.

(10) Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, 5177. Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.

Chart I



Scheme V



The application of the vinylogous amide photocycloaddition to the construction of the tetracyclic ketone **7** is outlined in Scheme IV. We first examined the photocycloaddition of **15a** (R = COOMe) for two reasons: first, as stated above, the photosubstrate could be prepared from the naturally occurring amino acid, L-tryptophan, and, second, the R group could be removed after the photocycloaddition reaction by Barton decarboxylation.[11] In the event, irradiation of **15a**[12] through Pyrex in acetonitrile at 25 °C led to the formation of a mixture of two diastereomeric keto imines in a 3:1 ratio, which increased to 5:1 when the reaction was carried out at −40 °C. The ratio of diastereomers obtained in the photocycloaddition was not sensitive to the irradiation solvent, i.e., comparable results were obtained in methanol, acetone, and benzene. The relative stereochemical relationships of the major diastereomer, **17a**, obtained in the photocycloaddition/retro-Mannich sequence, were established by single-crystal X-ray analysis of **18**, which was produced from **17a** by treatment with an excess of benzoyl chloride and triethylamine in methylene chloride.[13]

The observed stereoselectivity can be rationalized by examination of the two orientations, **A** and **B** (Chart I) of photosubstrate **15**. The unfavorable interaction of the aromatic ring and the amino acid carboxyl (R = COOMe) shown in **B** should favor the approach of the vinylogous amide from the α-face of the indole, i.e., **A**, leading, on photoaddition and retro-Mannich fragmentation, to the predominant formation of keto imine **17**.

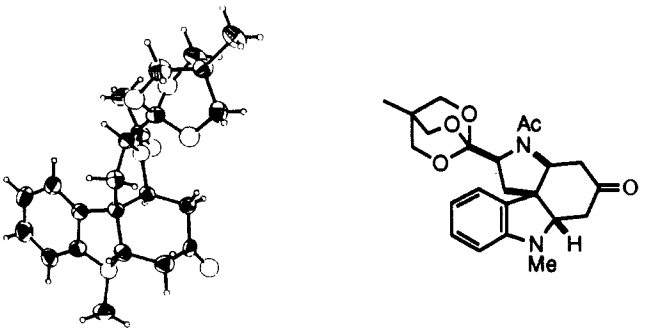


Figure 1.

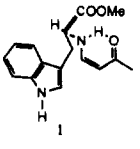
In an effort to increase the stereoselectivity of the photocycloaddition, the effective size of the amino acid carboxyl was increased by its conversion to an OBO ortho ester.[14] The requisite photosubstrate **15b** was prepared as shown in Scheme V. Esterification of L-*N*-Cbz-tryptophan with 3-(hydroxymethyl)-3-methyloxetane (DCC, DMAP, Et_2O, 25 °C, 84%) gave **25**, which on acid rearrangement (BF_3–Et_2O, CH_2Cl_2, −4 °C, 84%) gave the corresponding ortho ester **26**. Removal of the benzyloxycarbonyl protecting group (1 atm H_2, Pd–C, ethanol, 96%) gave amine **27**, which on condensation with 4-chloro-3-buten-2-one (triethylamine, tetrahydrofuran, 88%) gave the vinylogous amide, **28**. Protection of the indole nitrogen (*n*-butyllithium, benzyl chloroformate, tetrahydrofuran, −78 °C, 81%) provided the requisite photosubstrate, **15b**.

Irradiation of **15b** (0.01 M in CH_3CN, 450-W medium pressure Hg lamp with Pyrex filter) gave, after retro-Mannich fragmentation of the photoadduct, a 91% yield of **17b** (Scheme IV) as a unique diastereomer. The single stereogenic center in the photosubstrate has led to complete stereochemical control in the formation of **17b**, which contains two new stereogenic centers. Treatment of **17b** with lithium diisopropylamide, followed by an excess of *tert*-butyldimethylsilyl triflate and reaction of the crude product with tetrabutylammonium fluoride, led to the formation of the desired tetracyclic product **19** in 51% yield. Removal of the benzyloxycarbonyl protecting group, reductive methylation of the dihydroindole nitrogen, and acetylation of the pyrrolidine nitrogen provided **22** in 71% overall yield from **19**. The relative stereochemical relationships indicated in **22**, confirmed by single-crystal X-ray analysis (see Figure 1),[15] were in accord with the results obtained in the photocycloaddition of **15a**. Hydrolysis of the ortho ester, followed by saponification and Barton decarboxylation,[11] provided (+)-**7** in >97% optical purity.[16] The synthetic (+)-**7** was identical by ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectra with an authentic sample of racemic **7** provided by Professor Buchi.

The synthesis of **7** in homochiral form in 14 steps (7% overall yield from L-tryptophan) attests to the efficiency of this photochemical approach to the synthesis of the aspidosperma alkaloids and demonstrates the exceedingly high levels of stereochemical control which are possible by using the intramolecular [2 + 2]-photocycloaddition reaction of vinylogous amides. The extension of the vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure sequence to the synthesis of other nitrogen-containing ring systems is currently in progress in our

(11) Barton, D.; Motherwell, W.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1983**, 939.

(12) Photosubstrate **15a** was prepared by the condensation of tryptophan methyl ester hydrochloride with 4-chloro-3-buten-2-one to give vinylogous amide, **i**, followed by reaction with *tert*-butyl cyanoformate. Details are given in the Experimental Section.



1

(13) The tetracyclic enol ether aminal **18** crystallized in the centrosymmetric, monoclinic space group $P2_1/c$. The unit cell parameters were determined to be a = 9.404 (3) Å, b = 20.485 (8) Å, c = 14.055 (6) Å, and β = 112.02 (4)°; R = 0.040, R_w = 0.046.

(14) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, 5571.

(15) The tetracyclic ketone **22** crystallized in the noncentrosymmetric, orthorhombic space group $P2_12_12_1$. The unit cell parameters were determined to be a = 9.436 (2) Å, b = 10.301 (2) Å, and c = 23.286 (4) Å; R = 0.046, R_w = 0.057.

(16) The optical purity of **7** (prepared from L-tryptophan) was determined by ketalization with (−)-2,3-butanediol. Comparison by HPLC (reverse phase [C_{18}], mobile phase: 65% 1:1 CH_3CN:CH_3OH/35% H_2O) with the diastereomeric ketals prepared from (−)-2,3-butanediol and the racemic **7** supplied by Professor Büchi indicated that our sample was at least 97% optically pure.

laboratory and will be reported in due course.[17]

Experimental Section

General Procedures. ^1H NMR were recorded at 500 MHz in $CDCl_3$. ^{13}C NMR were recorded on a GE QE-300 spectrometer. The pH 7 buffer (3 M KH_2PO_4) which was used in many of the workups was prepared from 205 g of KH_2PO_4 and 35 g of NaOH in 1 L of water. *n*-BuLi was titrated against diphenylacetic acid.

Photosubstrate 15a. To a stirring solution of vinylogous amide **i** (350 mg, 1.22 mmol) in 7 mL of dry THF at −78 °C under N_2 atmosphere was added dropwise 1.02 mL *n*-BuLi (2.45 M) over 2 min. After 30 min, *tert*-butyl cyanoformate (freshly distilled, 155 mg, 1.22 mmol) was added dropwise over 1 min. TLC analysis (5% methanol/chloroform) indicated that the reaction was complete after 20 min. The solution was then partitioned between pH 7 buffer and diethyl ether, dried with Na_2SO_4, filtered, and concentrated to give 570 mg of a crude viscous oil. The residue was chromatographed on 60 g of silica gel by using gradient elution (0–5% methanol/chloroform) to provide 316 mg (67%) of vinylogous amide **15a**: ^1H NMR 1.66 (s, 9 H), 2.03 (s, 3 H), 3.08 (dd, 1 H, J = 8, 16 Hz), 3.30 (dd, 1 H, J = 6, 16 Hz), 3.73 (s, 3 H), 4.05 (m, 1 H), 4.93 (d, 1 H, J = 8 Hz), 6.32 (dd, 1 H, J = 8, 13 Hz), 7.22 (t, 1 H), 7.30 (t, 1 H), 7.40 (t, 1 H), 7.49 (d, 1 H), 8.10 (br d, 1 H), 12.2 (m, 1 H, NH); IR (cm^{-1}, $CDCl_3$) 1732, 1643, 1569, 1452, 1380, 1370; exact mass calculated for $C_{21}H_{26}N_2O_5$ 386.1842, found 386.1844; $[\alpha]_D$ = −98.3° (*c* 7.8, CH_2Cl_2).

Photosubstrate 15b. *n*-Butyllithium (3.42 mmol, 0.490 mL, in hexane) was added dropwise to **28** (1.160 g, 3.26 mmol) in 32 mL of dry THF at −78 °C under N_2 atmosphere. After 10 min, benzyl chloroformate (3.42 mmol, 0.490 mL) was added dropwise over ca. 15 min. The reaction was complete in 30 min (TLC: 5% $CH_3OH/CHCl_3$) and was partitioned between 10% K_2CO_3 and diethyl ether. The separated organic layer was dried with Na_2SO_4, filtered, and concentrated to give a light yellow foam. Chromatography on 50 g of silica gel pretreated with 2% Et_3N, using gradient elution (50–75% chloroform/petroleum ether), provided 1.30 g of **15b** (81%): ^1H NMR 9.75 (m, 1 H, NH), 8.17 (br s, 1 H), 7.50 (d, 1 H), 7.42 (d, 2 H), 7.34–7.38 (m, 4 H), 7.26 (t, 1 H), 7.20 (t, 1 H), 6.14 (dd, 1 H, J = 7, 13 Hz), 5.38 (br s, 2 H), 4.71 (d, 1 H, J = 7 Hz), 3.94 (s, 6 H), 3.31 (dt, 1 H, J = 3, 9 Hz), 3.25 (dd, 1 H, J = 3, 16 Hz), 2.74 (dd, 1 H, J = 9, 16 Hz), 1.96 (s, 3 H), 0.82 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 2880, 1730, 1641, 1565, 1456, 1197; exact mass calculated for $C_{28}H_{30}N_2O_6$ 490.2104, found 490.2098; $[\alpha]_D$ = −229° (*c* 0.0026, $CHCl_3$).

Keto Imines 17a and 17a′. Vinylogous amide **15a** (466 mg, 1.21 mmol) in 100 mL of acetonitrile was irradiated through Pyrex at 25 °C for 3 h. Evaporation of the solvent left 442 mg of crude solid which by ^1H NMR was a mixture of diastereomeric cyclobutane photoadducts. Chromatography of the residue on 50 g of silica gel using gradient elution (5–10% ethyl acetate/chloroform) gave 340 mg (77%) of an inseparable mixture of two diastereomeric imino ketones, **17** and **17′**, in a ratio of 3:1. To a solution of this mixture of keto imines in 2 mL of CH_2Cl_2 was added 2 mL of trifluoroacetic acid. TLC analysis (60% ethyl acetate/petroleum ether) indicated that the reaction was complete after 20 min at 25 °C. The reaction mixture was then neutralized with sodium bicarbonate, extracted into chloroform, dried, and concentrated to give 239 mg of a crude oil. Chromatography of the residue on 40 g of silica gel using gradient elution (45–100% ethyl acetate/petroleum ether) provided 116 mg (40%) of the less polar, major diastereomer and 62 mg (21%) of the more polar, minor diastereomer.

Major Diastereomer 17 (R = COOMe; R′= H). ^1H NMR 2.13 (dd, 1 H, J = 7, 14 Hz, CCH_2CH), 2.21 (s, 3 H, $COCH_3$), 2.64 (dd, 1 H, J = 9, 14 Hz, CCH_2CH), 2.73 (dd, 1 H, J = 11, 18 Hz, CH_2COCH_3), 2.90 (dd, 1 H, J = 1, 18 Hz, CH_2COCH_3), 3.81 (s, 3 H, CO_2CH_3), 4.13 (d, 1 H, J = 11 Hz, NHC*H*), 4.61 (br s, 1 H, NH), 4.94 (ddd, 1 H, J = 2, 7, 9 Hz, $CH_2CHN{=}CH$), 6.65 (d, 1 H), 6.73 (t, 1 H), 6.87 (d, 1 H), 7.06 (t, 1 H), 7.47 (d, 1 H, J = 2 Hz, $CHN{=}CH$); IR (cm^{-1}, $CDCl_3$) 3395, 1739, 1715, 1623, 1605, 1482, 1465; exact mass calculated for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1323; $[\alpha]_D$ = +312° (*c* 4.7, CH_2Cl_2).

Minor Diastereomer 17′ (R = COOMe; R′ = H). ^1H NMR 2.19 (s, 3 H, $COCH_3$), 2.21 (dd, 1 H, J = 9, 15 Hz, CCH_2CH), 2.58 (dd, 1 H, J = 2, 19 Hz, CH_2COCH_3), 2.64 (dd, 1 H, J = 8, 15 Hz, CCH_2CH), 2.74 (dd, 1 H, J = 11, 19 Hz, CH_2COCH_3), 3.83 (s, 3 H, CO_2CH_3), 4.13 (dd, 1 H, J = 2, 11 Hz, NHC*H*), 4.55 (br s, 1 H, NH), 4.82 (ddd, 1 H, J = 2, 8, 9 Hz, $CH_2CHN{=}CH$), 6.65 (d, 1 H), 6.75 (t, 1 H), 7.03 (d, 1 H), 7.07 (t, 1 H), 7.42 (d, 1 H, J = 2 Hz, $CHN{=}CH$); IR (cm^{-1}, $CDCl_3$) 3395, 1739, 1715, 1623, 1605, 1482, 1465; exact mass calculated for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1305; $[\alpha]_D$ = −104° (*c* 2.1, CH_2Cl_2).

Keto Imine 17b. Photosubstrate **15b** (235 mg, 0.479 mmol) was dissolved in 100 mL of acetonitrile, degassed for 30 mins, cooled to ca. 10 °C, and irradiated through Pyrex until the reaction was complete (ca. 65 min, TLC: 5% $CH_3OH/CHCl_3$). Concentration and chromatography on 25 g of silica gel pretreated with Et_3N using gradient elution (50–80% chloroform/petroleum ether) provided 215 mg (91%) of imino ketone **17b**: ^1H NMR 7.42 (d, 1 H, J = 2 Hz), 7.30–7.40 (m, 6 H), 7.19 (t, 1 H), 6.96 (t, 1 H), 6.83 (d, 1 H), 5.23 (ab, 2 H), 4.82 (t, 1 H, J = 7 Hz), 4.41 (ddd, 1 H, J = 2, 6, 8 Hz), 3.94 (s, 6 H), 2.89 (dd, 1 H, J = 7, 16 Hz), 2.78 (dd, 1 H, J = 7, 16 Hz), 2.39 (dd, 1 H, J = 6, 14 Hz), 2.11 (dd, 1 H, J = 8, 14 Hz), 2.06 (br s, 3 H), 0.82 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 2950, 1709 (br), 1482, 1399; exact mass calculated for $C_{28}H_{30}N_2O_6$ 490.2104, found 490.2098; $[\alpha]_D$ = +160° (*c* 1.9, $CHCl_3$).

Tetracyclic Aminal 18. To keto imine **17a** (major diastereomer) (249 mg, 0.87 mmol) and triethylamine (0.36 mL, 2.60 mmol) in 18 mL of CH_2Cl_2 at 25 °C was added a solution of benzoyl chloride (747 mg, 5.31 mmol) in 2 mL of CH_2Cl_2. TLC analysis (20% ethyl acetate/petroleum ether) indicated that the reaction was complete after 20 mins. The reaction mixture was then partitioned between pH 7 buffer and CH_2Cl_2, dried, filter, and concentrated to give 740 mg of crude product. Chromatography of the residue on 50 g of silica gel using gradient elution (15–80% ethyl acetate/petroleum ether) provided 301 mg (70%) of the bis-benzoylated tetracyclic enol ether aminal **18**: ^1H NMR 1.86 (s, 3 H), 2.38 (dd, 1 H, J = 9, 15 Hz), 2.73 (dd, 1 H, J = 9, 15 Hz), 3.81 (s, 3 H), 4.76 (m, 1 H), 4.80 (br s, 1, H, NC*H*O), 5.22 (m, 1 H), 5.37 (t, 1 H, J = 9 Hz), 6.31 (m, 1 H), 6.90 (m, 2 H), 6.98 (m, 1 H), 7.34–7.53 (m, 8 H), 7.77 (d, 2 H); IR (cm^{-1}, $CDCl_3$) 1759, 1735, 1684, 1647, 1602, 1593, 1580, 1481, 1396, 1354; exact mass calculated for $C_{30}H_{26}N_2O_5$ 494.1842, found 494.1768; $[\alpha]_D$ = +81.0° (*c* 8.6, CH_2Cl_2).

***N*-Silyl Keto Amine 19.** To lithium diisopropylamide (1.84 mmol) in 7.8 mL of dry THF at −78 °C under N_2 atmosphere was added a solution of **17b** (759 mg, 1.55 mmol) in 2 mL of dry THF over 5 min. After 15 min, the enolate generated was cannulated rapidly into a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.064 g, 4.03 mmol, 0.917 mL) in 5 mL of dry THF at −78 °C under N_2 atmosphere. The reaction was complete in 20 min (TLC: 25% ethyl acetate/petroleum ether for **19**, 5% methanol/chloroform for **17b**). The solution was partitioned between cold 5% aqueous K_2CO_3 and CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to give 1.2 g of a mixture of mono- and disilylated products in a 2:3 ratio. The mixture was dissolved in 16 mL of dry THF and treated with *n*-Bu_4NF (1.0 mmol, 1.0 mL of a THF solution) at room temperature. Workup as above and chromatography on 20 g of silica gel pretreated with Et_3N using gradient elution (5–30% ethyl acetate/petroleum ether) gave 476 mg (51%) of the desired N-silylated **19**: ^1H NMR 7.31–7.39 (m, 7 H), 7.18 (m, 2 H), 6.96 (t, 1 H), 5.24 (ab quartet, 2 H), 4.47 (br d, 1 H, J = 7 Hz), 3.81 (s, 6 H), 3.76–3.84 (m, 2 H), 2.90 (br d, 1 H, J = 10 Hz), 2.81 (dd, 1 H, J = 7, 10 Hz), 2.51 (dd, 1 H, J = 4, 18 Hz), 2.38 (dd, 1 H, J = 6, 8 Hz), 2.19 (m, 2 H), 0.92 (s, 9 H), 0.78 (s, 3 H), 0.24 (s, 3 H), 0.15 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 2931, 2880, 1708 (br), 1482, 1405, 1260; *m/e* (CI) = 605; *m/e* (EI, M − *t*-Bu) = 547; exact mass calculated for $C_{30}H_{35}N_2O_6Si$ 547.2264, found 547.2255; $[\alpha]_D$ = +63.3° (*c* 1.2, CH_2Cl_2).

Keto Amine 20. Compound **19** (157 mg, 0.26 mmol) and Pd–C (16 mg, 0.015 mmol) were stirred in 2.6 mL of ethanol under 1 atm of hydrogen for 40 min. Filtration and concentration provided 112 mg (92%) of the deprotected dihydroindole **20**: ^1H NMR 7.00 (t, 1 H), 6.93 (d, 1 H), 6.71 (t, 1 H), 6.61 (d, 1 H), 4.15 (m, 1 H), 3.99 (t, 1 H, J = 8 Hz), 3.87 (s, 6 H), 3.79 (m, 1 H), 3.33 (dd, 1 H, J = 7, 10 Hz), 3.14 (dd, 1 H, J = 10, 16 Hz), 2.68 (dd, 1 H, J = 7, 16 Hz), 2.39–2.46 (m, 3 H), 2.29 (dd, 1 H, J = 8, 16 Hz), 0.81 (s, 3 H), 0.79 (s, 9 H), 0.19 (s, 3 H), −0.37 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 2945, 2868, 1717, 1270; *m/e* = 470, 413 (M − *t*-Bu); exact mass calculated for $C_{22}H_{29}N_2O_4Si$ 413.1896, found 413.1911; $[\alpha]_D$ = +38.0° (*c* 1.5, CH_2Cl_2).

***N*-Methyl Keto Amine 21.** Dihydroindole **20** (138 mg, 0.293 mmol), formaldehyde (37% in H_2O, 120 mg, 1.46 mmol, 0.111 mL), and sodium cyanoborohydride (29 mg, 0.47 mmol) were stirred in 1.2 mL of acetonitrile for 15 min at 25 °C and then treated with 17 μL of acetic acid. TLC analysis (30% ethyl acetate/petroleum ether) of an aliquot, which had been partitioned between 5% aqueous K_2CO_3 and dichloromethane, indicated complete reaction 10 min after the addition of the acetic acid. The reaction mixture was partitioned between 5% aqueous K_2CO_3 and dichloromethane and chromatographed on 8 g of silica gel, pretreated with triethylamine, using 20% ethyl acetate/petroleum ether to give 110 mg (77%) of the N-methylated **21**: ^1H NMR 7.09 (t, 1), 6.90 (d, 1), 6.71 (t, 1), 6.53 (d, 1), 4.02 (t, 1), 3.98 (s, 6), 3.49 (m, 1), 3.17–3.28 (m, 2), 2.68 (s, 3), 2.60–2.70 (m, 2), 2.40–2.50 (m, 2), 2.26 (dd, 1), 0.83 (s, 3), 0.78 (s, 9), 0.20 (s, 3), −0.41 (s, 3); IR (cm^{-1}, $CDCl_3$) 2930, 1710, 1480, 1287; *m/e* = 484, 427 (M − *t*-Bu); exact mass calculated for $C_{23}H_{31}$-

(17) For the recent extension of this methodology to the photocycloaddition of tertiary vinylogous amides, see: Winkler, J. D.; Haddad, N.; Ogilvie, R. *Tetrahedron Lett.* **1989**, 5703.

N_2O_4Si 427.2053, found 427.2066; $[\alpha]_D$ = +42.5° (*c* 1.6, CH_2Cl_2).

Acetylated Keto Amine 22. Keto amine **21** (65 mg, 0.134 mmol) was treated with acetyl chloride (15.8 mg, 0.201 mmol, 0.014 mL) in 0.67 mL of CH_2Cl_2. TLC analysis (75% ethyl acetate/petroleum ether) indicated complete conversion to a single product after 1.25 h. Partitioning between saturated aqueous sodium bicarbonate and dichloromethane provided 58 mg (quantitative yield) of a white foam which was used in the next step without purification. A sample was recrystallized from methanol for X-ray analysis: ^{1}H NMR 7.09 (t, 1 H), 6.77 (d, 1 H), 6.67 (t, 1 H), 6.49 (d, 1 H), 4.60–4.70 (br s, 1 H), 3.92 (s, 6 H), 3.58 (t, 1 H, *J* = 5 Hz), 3.46 (d, 2 H, *J* = 3 Hz), 3.10–3.20 (br s, 1 H), 2.70 (s, 3 H), 2.65–2.72 (m, 2 H), 2.57 (m, 1 H), 2.44 (dd, 1 H, *J* = 9, 14 Hz), 2.05 (br s, 3 H, $-NCOCH_3$), 0.83 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 2967, 2882, 1720, 1653, 1635, 1482; exact mass calculated for $C_{23}H_{28}N_2O_5$ 412.1998, found 412.2027; $[\alpha]_D$ = +49.1° (*c* 1.0, CH_2Cl_2); mp = 149–151 °C.

Diol Ester 23. Ortho ester **22** (55 mg, 0.133 mmol) was treated with 1 M $NaHSO_4$ (0.266 mmol, 0.27 mL) in 1 mL of 1,2-dimethoxyethane at 0 °C for 2 min. TLC analysis (5% methanol/chloroform) showed complete conversion to the diol ester. The reaction mixture was partitioned between saturated sodium bicarbonate and dichloromethane, and the organic residue was chromatographed on 3 g of silica gel using gradient elution (1–5% methanol/chloroform) to give 44 mg (77%) of **23** as a flaky white foam: ^{1}H NMR 7.18 (t, 1), 6.91 (d, 1), 6.74 (t, 1), 6.55 (d, 1), 4.89 (t, 1), 4.59 (d, 1), 4.02 (d, 1), 3.95 (dd, 1), 3.57–3.68 (cm, 5), 3.52 (dd, 1), 2.87–2.98 (cm, 2), 2.74 (s, 3), 2.63–2.81 (cm, 2), 2.43 (dd, 1), 1.98 (s, 3), 0.87 (s, 3); IR (cm^{-1}, $CDCl_3$) 1727, 1652, 1482; exact mass calculated for $C_{23}H_{30}N_2O_6$ 430.2104, found 430.2073; $[\alpha]_D$ = +78.2° (*c* 1.1, CH_2Cl_2).

Acid 24. Diol ester **23** (64 mg, 0.149 mmol) was stirred with 1 M LiOH (0.298 mmol, 0.298 mL) in 1 mL of dimethoxyethane at 25 °C. TLC analysis (10% methanol/ethyl acetate containing 1% acetic acid) indicated complete saponification in 20 min. The solution was acidified to pH = 2–3 with 3 N HCl and then partitioned between saturated aqueous NH_4Cl and dichloromethane, and the organic layer was dried and concentrated to give 49 mg (100%) of **24**: ^{1}H NMR 7.16 (t, 1 H), 6.87 (d, 1 H), 6.75 (t, 1 H), 6.57 (d, 1 H), 5.00 (t, 1 H, *J* = 8 Hz), 3.92 (m, 1 H), 3.64 (t, 1 H, *J* = 6 Hz), 2.73 (s, 3 H), 2.72–2.81 (m, 6 H), 2.00 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 1753, 1726, 1652, 1605, 1482; exact mass calculated 328.1404, found 328.1423; $[\alpha]_D$ = −46.6° (*c* 0.30, CH_2Cl_2).

Büchi Ketone 7. To acid **24** (49 mg, 0.149 mmol) and *N*-methylmorpholine (15.5 mg, 0.150 mmol, 0.016 mL) in 0.7 mL of dry tetrahydrofuran at −15 °C under N_2 was added isobutyl chloroformate (20.5 mg, 0.150 mmol, 0.019 mL). After 5 min, triethylamine (0.150 mmol, 0.021 mL) and *N*-hydroxypyridinethione (19.5 mg, 0.150 mmol) were added sequentially and stirred for 15 min. *tert*-Butylthiol (135 mg, 1.5 mmol, 0.17 mL) was added, and the mixture was irradiated with a sun lamp at room temperature for 12 min at which time liberation of CO_2 ceased. TLC analysis (5% methanol/ethyl acetate) indicated complete conversion to material which co-eluted with the authentic sample of **7** supplied by Professor Büchi. Partitioning between saturated aqueous sodium bicarbonate and dichloromethane and evaporation of the organic phase gave 65 mg of a crude oil which was chromatographed on 6 g of silica gel using gradient elution (0–4% methanol/ethyl acetate) to give 30 mg (73%) of product as a colorless oil: ^{1}H NMR 7.16 (t, 1 H), 7.01 (d, 1 H), 6.98 (amide bond conformer), 6.74 (t, 1 H), 6.69 (amide bond conformer), 6.50 (d, 1 H), 4.15 (m, 1 H), 3.80 (m, 1 H), 3.69 (m, 1 H), 3.60 (m, 1 H), 3.02 (dd, 1 H, *J* = 7, 17 Hz), 2.70–2.74 (m, 2 H), 2.70 (s, 3 H), 2.55 (m, 2 H), 2.12 (m, 1 H), 2.09 (s, 3 H); IR (cm^{-1}, $CDCl_3$) 1717, 1645, 1606, 1487, 1407; exact mass calculated for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1546; $[\alpha]_D$ = +19.0° (*c* 3.0, CH_2Cl_2).

Oxetane Ester 25. To L-*N*-Cbz-tryptophan (9.0 g, 26.6 mmol), 3-(hydroxymethyl)-3-methyloxetane (2.96 g, 29 mmol), and (dimethylamino)pyridine (0.317 g, 2.6 mmol) in 133 mL of diethyl ether at 25 °C was added dicyclohexylcarbodiimide (5.97 g, 29 mmol). TLC analysis (40% ethyl acetate/petroleum ether) indicated that the reaction was complete after 15 min. After filtration and concentration, the resulting viscous oil (14 g) was chromatographed on 100 g of silica gel using gradient elution (25–50% EA/PE) to yield 9.4 g of product (84%): ^{1}H NMR 8.02 (br s, 1), 7.50 (d, 1), 7.25–7.35 (cm, 5), 7.15 (t, 1), 7.07 (t, 1), 6.98 (d, 1), 5.30 (d, 1, NH), 5.0–5.1 (ab quartet, 2), 4.72 (dd, 1), 4.18–4.30 (cm, 4), 4.04–4.14 (ab quartet, 2), 3.25–3.35 (cm, 2), 1.15 (s, 3); IR (cm^{-1}, $CDCl_3$) 3478, 1720, 1506; exact mass calculated for $C_{24}H_{26}N_2O_5$ 422.1842, found 422.1855; $[\alpha]_D$ = +19.0° (*c* 4.2, $CHCl_3$).

Ortho Ester 26. To oxetane ester **25** (1.912 g, 4.53 mmol) in 4.5 mL of dry dichloromethane at −4 °C under N_2 atmosphere was added BF_3–Et_2O (0.161 g, 1.13 mmol, 0.140 mL). After 2 h, the reaction mixture was treated with 1 equiv of triethylamine (Et_3N), concentrated, and chromatographed on 40 mL of basic alumina using $CHCl_3$ as eluent to give 1.611 g of product (84%): ^{1}H NMR 7.87 (br s, 1), 7.58 (d, 1), 7.23–7.30 (m, 4), 7.18 (m, 1), 7.14 (t, 1), 7.06 (t, 1), 6.98 (br s, 1), 4.97 (ab quartet, 2), 4.90 (br d, 1), 4.26 (dd, 1), 3.90 (s, 6), 3.23 (dd, 1), 2.81 (dd, 1), 0.82 (s, 3); IR (cm^{-1}, $CDCl_3$) 3481, 2881, 1718, 1519, 1457; exact mass calculated for $C_{24}H_{26}N_2O_5$ 422.1842, found 422.1820; $[\alpha]_D$ = −52.2° (*c* 2.0, $CHCl_3$).

Ortho Ester Amine 27. Carbamate **26** (800 mg, 1.89 mmol) and Pd–C (160 mg, 0.15 mmol) were stirred in 2 mL of ethanol under 1 atm of H_2 at room temperature for 7 h. Filtration and concentration provided 526 mg (96%) of amine **27**: ^{1}H NMR 7.93 (br s, 1), 7.63 (d, 1), 7.31 (d, 1), 7.15 (t, 1), 7.06 (t, 1), 7.04 (t, 1), 3.96 (s, 6), 3.23 (cm, 2), 2.63 (dd, 1), 0.84 (s, 3); IR (cm^{-1}, $CDCl_3$) 3480, 2880, 1456, 1052; exact mass calculated for $C_{16}H_{20}N_2O_3$ 288.1474, found 288.1478; $[\alpha]_D$ = −16.0° (*c* 4.5, $CHCl_3$).

Vinylogous Amide 28. To ortho ester **27** (3.317 g, 11.5 mmol) and triethylamine (6.97 g, 69 mmol) in 115 mL of dry tetrahydrofuran at 25 °C under N_2 atmosphere was added 1 equiv of 4-chloro-3-buten-2-one (1.19 g, 11.5 mmol). The temperature was raised to 50 °C, and the resulting mixture was treated with 1 additional equiv of 4-chloro-3-buten-2-one after 4 h and 1 more equiv after 8 h (3 equiv total of 4-chloro-3-buten-2-one). After 11 h total reaction time, the reaction mixture was filtered, concentrated, and chromatographed on 100 g of silica gel pretreated with Et_3N, using gradient elution (40–80% chloroform/petroleum ether) to provide 3.60 g of **28** (88%): ^{1}H NMR 9.76 (m, 1 H, NH), 7.97 (br s, 1 H), 7.56 (d, 1 H), 7.30 (d, 1 H), 7.13 (t, 1 H), 7.06 (t, 1 H), 6.93 (d, 1 H), 6.11 (dd, 1 H, *J* = 7, 14 Hz), 4.68 (d, 1 H, *J* = 7 Hz), 3.94 (s, 6 H), 3.31–3.37 (m, 2 H), 2.78 (dd, 1 H, *J* = 9, 17 Hz), 1.98 (s, 3 H), 0.83 (s, 3 H); IR cm^{-1}, $CDCl_3$) 3472, 2880, 1640, 1559, 1196; exact mass calculated for $C_{20}H_{24}N_2O_4$ 356.1736, found 356.1742; $[\alpha]_D$ = −263° (*c* 3.0, $CHCl_3$).

Vinylogous Amide i. To a suspension of tryptophan methyl ester hydrochloride (recrystallized, 298 mg, 1.17 mmol) and triethylamine (236 mg, 2.34 mmol) in 10 mL of dry THF under N_2 atmosphere was added dropwise, with stirring, 4-chloro-3-buten-2-one (132 mg, 1.28 mmol) in 0.8 mL of dry THF. TLC analysis (10% $CH_3OH/CHCl_3$) indicated that the reaction was complete after 60 h. The mixture was filtered and concentrated to provide 343 mg of a viscous oil, which was chromatographed on 20 g of silica gel using gradient elution (0–1% $CH_3OH/CHCl_3$) to give 250 mg of vinylogous amide i (75%): ^{1}H NMR 2.04 (s, 3 H, $COCH_3$), 3.19 (dd, 1 H, *J* = 8, 16 Hz), 3.35 (dd, 1 H, *J* = 6, 16 Hz), 3.68 (s, 3 H, CO_2CH_3), 4.10 (m, 1 H, amino acid methine), 4.92 (d, 1 H, *J* = 8 Hz, α-enone), 6.32 (dd, 1 H, *J* = 8, 13 Hz, β-enone), 7.03 (d, 1 H), 7.09 (t, 1 H), 7.15 (t, 1 H), 7.31 (d, 1 H), 7.52 (d, 1 H), 10.1 (m, 1 H, NH); IR (cm^{-1}, $CDCl_3$) 3478, 1743, 1642, 1565, 1468; exact mass calculated for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1349; $[\alpha]_D$ = −104° (*c* 4.6, CH_2Cl_2).

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