Application of Arene−Ruthenium Chemistry to a Formal Total Synthesis of OF 4949 III

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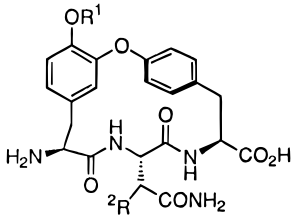
Received May 24, 1996[⊗]

A convergent formal total synthesis of OF 4949 III is described. Arene−ruthenium chemistry was used in the construction of the diaryl ether linkage in high yield, and cycloamidation under high dilution conditions (0.005 M) was achieved using DPPA as coupling reagent. SmI_2 was used to reductively remove the 2-iodoethyl ester protecting group in the presence of DMPU or HMPA.

Introduction

OF 4949 I−IV were isolated from Ehrlich ascites carcinoma cells of *Penicilliun rugulosum*.[1] These agents have exhibited potential aminopeptidase B inhibitory activity, immunopotentiating activity and confirmed antitumor activity without appreciable cytotoxicity. They may constitute a new class of potentially useful antitumor agents that can act as toxicity-free immunopotentiators. Their structures were elucidated based on spectroscopic and chemical degradative studies, the characteristic feature being the isodityrosine subunit connected by a diaryl ether linkage. The first total synthesis of OF 4949 III was reported by Yamamura's group,[2] based on a biomimetic, oxidative thallium trinitrate (TTN)-promoted two-step phenolic coupling methodology. In Schmidt's and Evans' approaches,[3,4] CuO was used as the mediator of the modified Ullmann reaction, while $CuBr{\cdot}SMe_2$ was used in Boger's approach.[5]



R^1	R^2	
CH_3	OH	OF 4949 I
H	OH	OF 4949 II
CH_3	H	OF 4949 III
H	H	OF 4949 IV

Other methods to set in place a diaryl ether linkage have also been developed. The S_NAr reaction was employed by Zhu[6] and Hamilton[7] in the synthesis of several structurally related compounds, while Still has used a similar method to prepare aryl thioether analogs.[8] Brown used the reactivity of aryliodonium salts toward the phenoxide of tyrosine to give related aryl ether derivatives without racemization.[9] Jung and Starkey reported a two-step preparation of *O*-(aryloxy)phenols via cyclohexenone oxides,[10] and a new route was introduced by Rao's group featuring a bromoquinone substitution reaction.[11] Very recently, a Diels−Alder reaction was employed by Olsen for the synthesis of (*S*,*S*)-isodityrosinol.[12]

A novel approach has been developed in our laboratory to synthesize diaryl ether or triaryl diethers by using transition metals.[13] Chloroarenes are activated toward nucleophilic substitution via complexation with MCp (M = Fe, Ru) or $Mn(CO)_3$, allowing the construction of the diaryl ethers from amino acid derivatives with little or no racemization. Ru is superior to Mn and Fe because the attachment of chloroarene derivatives to cyclopentadienyl ruthenium can be effected under very mild conditions that are compatible with the racemization prone amino acid functionalities. Ruthenium chemistry has been successfully used in the synthesis of K-13 and a model of Teicoplanin A.[13e,f,h] We report herein a formal total synthesis of OF 4949 III (**1**) which again demonstrates the application of this chemistry.

Results and Discussion

Our strategy to synthesize OF 4949 III is illustrated in Scheme 1. To suppress competitive succinimide or iminosuccinic anhydride formation, macrocyclization was chosen to be effected at the $C^{11}-N^{10}$ amide bond.[5] According to this retrosynthetic analysis, two intermediates **4** and **5** were required.

The synthesis of intermediate **4** (Scheme 2) started from **6** (prepared from commercially available 3-hydroxy-4-methoxybenzaldehyde). The carboxylic acid was selectively protected as its benzyl ester in the presence of the phenolic group with BnBr/DBU. Subsequent protection of the phenolic group with TBDMSCl was ac-

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1996.

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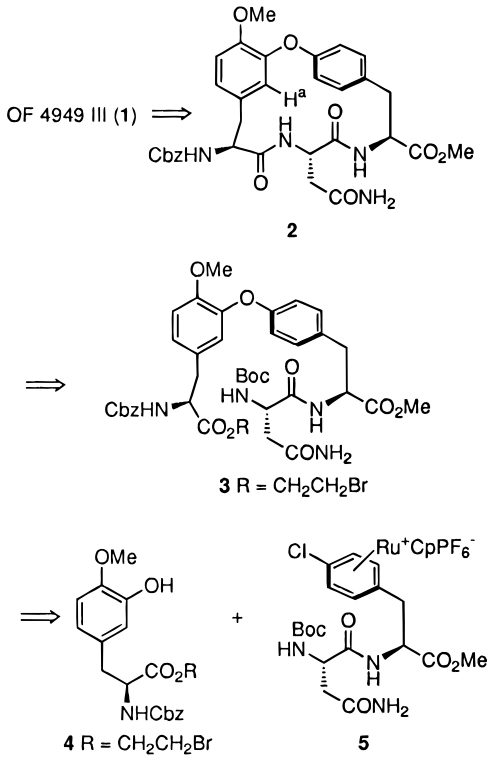
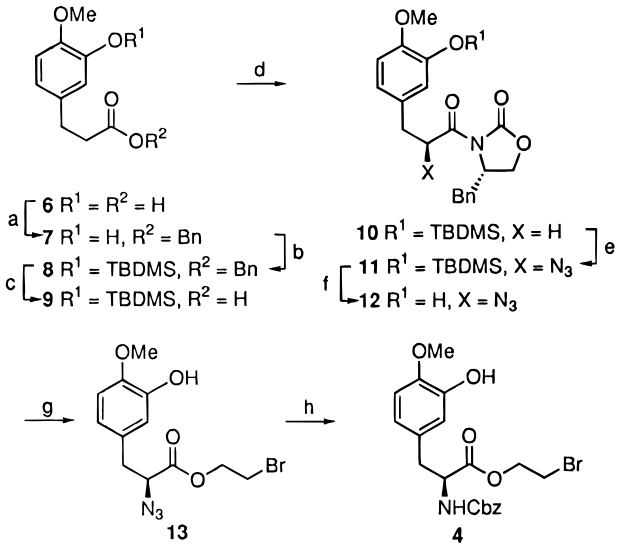
S0022-3263(96)00956-5 CCC: $12.00

Scheme 1



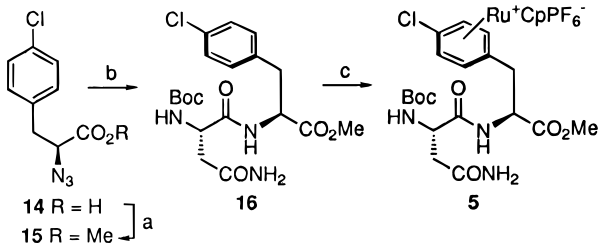
Scheme 2[a]



[a] Reaction conditions, reagents and yields: (a) BnBr (1.0 equiv), DBU, benzene, reflux, 7 h, 65%; (b) TBDMSCl (1.2 equiv), DMAP (0.08 equiv), Et_3N (1.3 equiv), CH_2Cl_2, rt, 20 h, 86%; (c) H_2, Pd−C (10%), THF, rt, 3.5 h, 99%; (d) Et_3N (1.3 equiv), pivaloyl chloride (1.1 equiv) then (4*S*)-4-(phenylmethyl)-2-oxazolidinone/n-BuLi (0.95 equiv), THF, −78 °C to rt, 12 h, 87%; (e) KHMDS (1.3 equiv), trisyl azide (1.1 equiv), THF, −78 °C, 2 min, 75%; (f) TBAF (1.0 equiv), THF, 0 °C, 1 h, 62%; (g) LiOH (2 equiv), H_2O_2 (6 equiv), THF, 0 °C, 1.5 h, then 2-bromoethanol (1.2 equiv), DCC (1.1 equiv), CH_2Cl_2, 0 °C, 12 h, 87%; (h) H_2, Pd−C (10%), 5 N HCl (3 equiv), THF, rt, 1.5 h, then CbzCl (1.1 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2/H_2O, 0 °C to rt, 5 h, 84%.

complished by employing the standard procedure to give **8**,[14] which was selectively deprotected to give acid **9** under hydrogenolysis conditions employing Pd−C (10%)/H_2 (1 atm). Attachment of the chiral auxiliary [(4*S*)-4-(phenylmethyl)-2-oxazolidinone] was effected by standard methods, and the product **10** was treated with trisyl azide under Evans's azidation conditions to afford the α-azido compound **11**. The diastereomer ratio was determined to be 97:3 by HPLC. Deprotection of **11** with TBAF (1.0 M in THF) gave disappointingly low yield (30−40%). We also tried deprotection with HF/Py, but the product was obtained in only 23% yield. Acceptable yield (>60%) was achieved by using anhydrous TBAF (azeotropically dried with benzene).[15] Removal of the chiral auxiliary with LiOH/H_2O_2, followed by ester formation with DCC/2-bromoethanol gave **13** in high yield, which was then subjected to hydrogenolysis conditions to give the amine hydrochloride, and this was reacted with CbzCl/$NaHCO_3$ to afford the Cbz protected compound **4** in 83% yield.

Scheme 3[a]



[a] Reaction conditions, reagents and yields: (a) PTSA (2.0 equiv), MeOH, reflux, 12 h, 95%; (b) H_2, Pd−C (10%), 5 N HCl (3.0 equiv), THF, rt, 4 h, then Boc-Asn, HOBt·H_2O (1.5 equiv), EDC (1.2 equiv), $^iPr_2NEt$ (1.0 equiv), THF/DMF (1:1), 0 °C to rt , 24 h, 81%; (c) $(CH_3CN)_3RuCpPF_6$ (1.2 equiv), 1,2-dichloroethane, reflux, 5 h, 100%.

The chloroarene ruthenium complex **5** was synthesized from **14** (Scheme 3), which was also prepared by Evans's azidation methodology.[4] Acid-catalyzed esterification under reflux conditions gave **15** in 95% yield. Hydrogenolysis of **15** with Pd−C (10%)/H_2 (1 atm) in THF/MeOH (1:1) suffered from serious problems with dechlorination. The same problem was encountered when THF alone was used as the solvent. It was presumed that the newly formed amino group coordinates with Pd and enhances the catalytic activity of the metal which can now cleave the C−Cl bond easily. The dechlorination problem was solved by adding 3 equiv of HCl to the reaction mixture, in anticipation that the HCl would remove NH_2 from the catalytic center immediately after its formation. The resulting amine hydrochloride was used in subsequent peptide formation under standard reaction conditions with N-Boc-Asn, HOBt·H_2O, EDC and *N*-methylmorpholine as base to give the dipeptide, but with complete epimerization at one center (identity is unknown). $^iPr_2NEt$ was then used as the base to give the desired dipeptide **16** with less than 5% epimerization. The minor epimer was removed by recrystallization in THF/hexane, and the pure dipeptide was obtained in 81% yield. Complexation of **16** with $[(CH_3CN)_3RuCp]PF_6$ under the usual conditions[13f] gave the intermediate **5** in essentially quantitative yield.

The coupling reaction was first conducted according to the standard protocol developed in our laboratory (Scheme 4). Compound **4** was treated with sodium 2,6-di-*tert*-butyl phenoxide and then allowed to react with the dipeptide complex **5** in THF. The mixture was stirred at −78 °C for 1 h and then at rt for 3 h. After filtering

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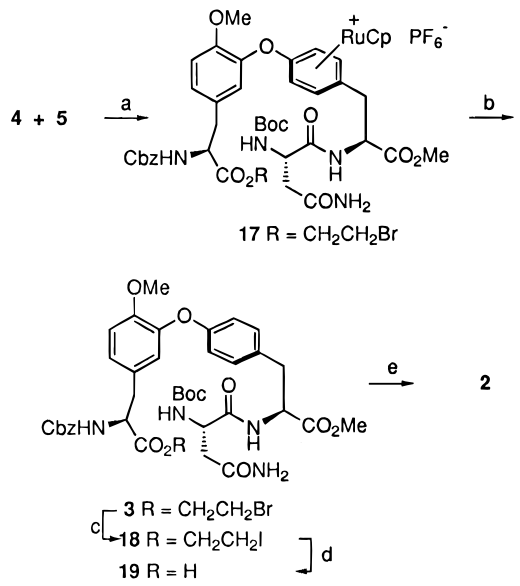
Scheme 4[a]



[a] Reaction conditions, reagents and yields: (a) Sodium 2,6-di-*tert*-butylphenoxide (1.1 equiv), acetone, −30 °C then to rt; (b) sunlamp (300 W), CH_3CN rt, 24 h, two times, 77% two steps; (c) NaI (7 equiv), acetone, reflux, 5 h, 98%; (d) SmI_2 (7 equiv), DMPU (42 equiv), THF, 0 °C, 10 min, rt, 3 h, 61%; (e) 30% TFA/CH_2Cl_2, thioanisole (20 equiv), 0 °C, 1.5 h then DPPA (1.5 equiv), $NaHCO_3$ (5 equiv), DMF, 0 °C, 3 d, 52%.

through a Celite pad and removal of the solvent, complex **17** was obtained in 87% yield. Demetalation (two cycles) was achieved in CH_3CN with a sun lamp (300W, GE) in a quartz tube to give compound **3** in 34% yield. The metal was recovered in the form of $(CH_3CN)_3RuCpPF_6$ in more than 80% yield. To optimize this reaction, acetone was employed as the solvent in the coupling step, which was performed at −30 °C and allowed to warm to rt.[13g] Demetalation gave **3** in 77% yield (two steps). It should be noted that in the NMR spectrum the CO_2Me group gave two peaks in about 1:1 ratio, which we attributed to restricted rotation about a C−N bond (amide resonance). NMR at 90 °C in CD_3NO_2 led to partial coalescence to a singlet, and the peak doubling reappeared when cooling to rt. Similar phenomena have been observed previously in our laboratory.[13f]

To complete the synthesis, we needed to remove the carboxylic acid protecting group. The 2-bromoethyl ester was chosen as the carboxylic acid protecting group because it has been found to give better yield in both coupling and demetalation reactions.[13e] Finkelstein reaction (7 equiv of NaI, acetone, reflux) gave the 2-iodoethyl ester in 98% yield. Halogen exchange was confirmed by upfield shift of methylene group next to the halogen atom from ∼3.6 ppm to ∼3.2 ppm in the ^1H NMR spectrum. The 2-iodoethyl ester was reductively deprotected with SmI_2 using DMPU as an additive (7 equiv of SmI_2, SmI_2:DMPU 1:6). The reaction proceeded very well at 0 °C to rt, and the stability of Boc and Cbz group under these very mild neutral conditions was remarkable.[16] The acid **19** was obtained in 61% yield, with ∼15% starting material recovered. The polarity of the deprotected acid was comparable to that of DMPU, so in order to overcome difficulties in separating the product, HMPA was used as an alternate additive that could readily be removed by washing with 0.1 N HCl, giving comparable yield (59%). After the Boc protecting group was removed with 30% TFA/CH_2Cl_2 in the presence of thioanisole, DPPA-promoted cycloamidation was accomplished by slow addition of **19** into a DPPA/$NaHCO_3$/DMF mixture over 3 h via a syringe pump (final concentration: 0.005 M), and stirring for a further period of 3 days at 0 °C furnished **2** as a white solid in 53% yield, mp 181−183 °C (lit. 179−182 °C), $[\alpha]^{23}_D$ −73° (*c* 0.35, CH_3OH) (lit. −74°, *c* 0.1, CH_3OH).[5] ^1H NMR spectroscopy of compound **2** provided evidence for the cycloamidation: the aromatic proton H^a (see structure) stood out clearly in the higher field region (∼6.0 ppm), compared with between 7.7−6.7 ppm for all other aromatic Hs. This is a known feature for this series of compounds.[17] Intermediate **2** was used by Boger to synthesize OF 4949 III,[5] so our results constitute a formal total synthesis of this target.

Conclusions

Chloroarene−ruthenium chemistry was used for construction of the aryl ether linkage in the development of a convergent total synthesis of OF 4949 III. The dipeptide **16** with polar substituents can be metalated selectively under the usual complexation conditions in quantitative yield. Deprotection of a 2-iodoethyl ester was effected by using SmI_2 in the presence of DMPU or HMPA in satisfactory yield, and both Boc and Cbz were stable under these mild conditions.

Experimental Section

General. Genral procedures are as described elsewhere.[16]

3-(3-Hydroxy-4-methoxyphenyl)propionic Acid Benzyl Ester (7). To a stirred solution of 3-(3-hydroxy-4-methoxyphenyl)propionic acid (**6**) (4.90 g, 25.0 mmol) in 50 mL of dry benzene were added DBU (3.73 mL, 1.0 equiv), and benzyl bromide (3.56 mL, 1.0 equiv), and the resulting mixture was heated to reflux for 7 h under Ar. The reaction mixture was cooled to rt, washed with water, saturated $NaHCO_3$, and brine, and dried with $MgSO_4$. Removal of solvent under reduced pressure gave a pale yellow residue, which was purified by flash chromatography to afford 4.44 g (65%) of **7** as a pale yellow solid: mp 52.5−54.0 °C; R_f 0.47 (6:4 hex/EtOAc); IR (KBr) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.25 (m, 5H), 6.77−6.64 (m, 3H), 5.58 (s, 1H), 5.11 (s, 2H), 3.85 (s, 3H), 2.88 (t, 2H, J = 7.8 Hz), 2.64 (t, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 145.5, 145.0, 135.0, 133.7, 128.5, 128.2, 119.6, 114.5, 110.6, 66.2, 55.9, 36.0, 30.3; HRMS calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1210.

3-[4-Methoxy-3-(*tert*-butyldimethylsilyloxy)phenyl]-propionic Acid Benzyl Ester (8). To a stirred solution of the benzyl ester **7** (4.36 g, 15.3 mmol) and TBDMSCl (2.75 g, 1.2 equiv) in 50 mL of CH_2Cl_2 were added DMAP (0.149 g, 0.08 equiv) and Et_3N (2.76 mL, 1.30 equiv), and the resulting mixture was stirred for 17 h under Ar. The reaction mixture was washed with water, saturated NH_4Cl, and brine and dried with $MgSO_4$. The solvent was removed to give crude product, which was purified by flash chromatography to provide 5.22 g (86%) of **8** as a colorless oil: R_f 0.49 (7:3 hex/EtOAc); ^1H NMR ($CDCl_3$) δ 7.36−7.32 (m, 5H), 6.78 (d, 1H, J = 8.2 Hz), 6.75 (d, 1H, J = 2.0 Hz), 6.71 (dd, 1h, J = 8.2, 2.0 Hz), 5.09 (s, 2H), 3.77 (s, 3H), 2.85 (t, 2H, J = 7.7 Hz), 2.63 (t, 2H, J = 7.7 Hz), 1.00 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.8, 149.4, 144.9, 135.9, 133.0, 128.5, 128.2, 121.2, 121.0, 112.2, 66.2, 55.5, 36.1, 30.2, 25.7, 18.4, −4.6; HRMS calcd for $C_{23}H_{32}O_4Si$ 400.2070, found 400.2074.

3-[4-Methoxy-3-(*tert*-butyldimethylsilyloxy)phenyl]-propionic Acid (9). TBDMS-protected phenylpropionic acid

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(18) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

benzyl ester **(8)** (5.19 g 13.0 mmol) was added into a slurry of Pd−C (10%) (~530 mg) in 60 mL of THF. The mixture was stirred for 3.5 h at rt under hydrogen atmosphere (1 atm). The solid catalyst was filtered off, and the filter cake was washed with 20 mL of THF. The solvent was removed *in vacuo* to give a white solid, which was dried further under high vacuum to provide pure product **9** (3.95 g, 99%): mp 75.5−77.5 °C; R_f 0.47 (6:4 hex/EtOAc); IR 3400−2500 (br), 1702 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.79 (d, 1H, J = 8.2 Hz), 6.76 (d, 1H, J = 2.0 Hz), 6.71 (dd, 1H, J = 8.2, 2.0 Hz), 3.76 (s, 3H), 2.83 (t, 2H, J = 7.7 Hz), 2.62 (t, 2H, J = 7.7 Hz), 0.98 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (CD_2Cl_2) δ 179.3, 149.9, 145.2, 133.3, 121.5, 121.3, 112.5, 55.8, 36.1, 30.1, 15.8, 18.7, -4.6; HRMS calcd for $C_{16}H_{26}O_4$ Si 310.1600, found 310.1600.

(4*S*)-3-[3-[4-Methoxy-3-(*tert*-butyldimethylsilyloxy)-phenyl]-1-oxopropionyl]-4-(phenylmethyl)-2-oxazolidinone (10). To a stirred, precooled solution (−78 °C) of the TBDMS protected phenylpropionic acid **9** (1.99 g, 6.49 mmol) in 60 mL of THF under N_2 were added by syringe 1.18 mL (1.3 equiv) of freshly distilled Et_3N followed by 0.88 mL (1.1 equiv) of distilled pivaloyl chloride. The resulting slurry was stirred at −78 °C for 25 min and 0 °C for 50 min and then cooled again to −78 °C under N_2. In a separate flask, 1.07 g (1.0 equiv) of (4*S*)-4-(phenylmethyl)-2-oxazolidinone was dissolved in 40 mL of THF and cooled to −78 °C, to this solution was added by syringe 4.06 mL of n-BuLi (1.6 M in hexane), and the resulting solution was stirred at −78 °C for 25 min under N_2. This metalated oxazolidinone solution was transferred to the above slurry *via* cannula, and the resulting mixture was stirred for 30 min at −78 °C and then overnight at rt. The reaction was quenched with 40 mL of 1.0 N $NaHSO_4$, and the volatile was removed *in vacuo*. The product was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a pale yellow oily residue. Flash chromatography provided **10** (2.50 g, 87%) as a colorless oil: R_f 0.32 (7:3 hex/EtOAc); $[\alpha]^{23}_D$ +36.8° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 3695, 3610, 1786, 1706, 1611 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.35−7.16 (m, 5H), 6.83−6.78 (m, 3H), 4.69−4,62 (m, 1H), 4.21−4.11(m, 2H), 3.76 (s, 3H), 3.29−3.09 (m, 3H), 2.92−2.77 (m, 3H), 1.00 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (CD_2Cl_2) δ 172.6, 153.8, 149.8, 145.2, 135.9, 133.7, 129.8, 129.2, 127.2, 121.8. 121.6, 112.5, 66.6, 55.8, 55.3, 38.3, 37.7, 29.8, 25.9, 18.7, −4.6; HRMS calcd for $C_{26}H_{33}NO_5$ Si 469.2284, found 469.2296.

(4*S*,2*S*)-3-[2-Azido-3-[4-methoxy-3-(*tert*-butyldimethylsilyloxy)phenyl]-1-oxopropionyl]-4-(phenylmethyl)-2-oxazolidinone (11). To a stirred solution of the chiral auxiliary adduct **10** (476 mg, 1.04 equiv) in 20 mL of THF at −78 °C was added rapidly, by syringe, 2.71 mL (0.5 M in toluene, 1.3 equiv) of KHMDS, and the resulting solution was stirred for 20 min at −78 °C under Ar. To this solution was transferred, via cannula over 30 s, a precooled (−78 °C) solution of 354.5 mg (1.1 equiv) of trisyl azide in 10 mL of THF. The resulting solution was stirred for 5 min at −78 °C and quenched by rapid addition of 149.0 μL (2.5 equiv) of glacial acetic acid followed by immediate warming to 35 °C with a water bath. The white slurry was stirred for 3 h at rt, diluted with 50 mL of CH_2Cl_2, and separated. The organic layer was washed with a mixture of brine and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography of the crude product gave 399 mg (75%) of **11** as a colorless oil: R_f 0.36 (CH_2Cl_2); $[\alpha]^{23}_D$ +70.4° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 1785, 1711 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.39−7.22 (m, 5H), 6.89−6.81 (m, 3H), 5.17 (dd, 1H, J = 9.2, 5.2 Hz) 4.67−4.61 (m, 1H), 4.23−4.14 (m, 2H), 3.78 (s, 3H), 3.28 (dd, 1H, J = 13.5, 3.2 Hz), 3.12, dd, 1H, J = 13.8, 5.2 Hz), 2.96−2.85 (m, 2H), 1.00 (s, 9H), 0.166 (s, 3H), 0.161 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 170.8, 153.2, 150.7, 145.3, 135.4, 129.8, 128.7, 127.7, 122.7, 122.2, 112.5, 67.1, 62.1, 55.8, 37.1, 25.8, 18.7, −4.59, −4.63; HRMS calcd for $C_{25}H_{34}N_2O_5Si$ $(M - N_2)^+$ 482.2237, found 482.2256.

(4*S*,2*S*)-3-[2-Azido-3-(3-hydroxy-4-methoxyphenyl)-1-oxopropionyl]-4-(phenylmethyl)-2-oxazolidinone (12). The α-azido adduct **11** (815.6 mg, 1.60 mmol) in 20 mL of THF was cooled to 0 °C with an ice bath. To this was added anhydrous TBAF solution, and the resulting mixture was stirred for 1 h at 0 °C and then diluted with 50 mL of CH_2Cl_2. The solution was washed with brine and the aqueous layer was again extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography gave **12** (377 mg, 62%) as a pale yellow solid: mp 153−155 °C; R_f 0.34 (1:1, hex/EtOAc); $[\alpha]^{23}_D$ +79.3° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3546 1787, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.20 (m, 5H), 6.88−6.80 (m, 3H), 5.63 (s, 1H), 5.22 (dd, 1H, J = 9.0, 5.4 Hz), 4.65−4.60 (m, 1H), 4.21−4.10 (m, 2H), 3.85 (s, 3H), 3.32 (dd, 1H, J = 13.4, 3.1 Hz), 3.13 (dd, 1H, J=13.7, 5.4 Hz), 2.95 (dd, 1H, J = 13.7, 9.0 Hz), 2.82, dd, 1H, J = 13.4, 9.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 152.7, 145.8, 145.6, 134.7, 129.4, 129.0, 128.7, 127.5, 120.9, 115.3, 110.7, 66.5, 61.4, 55.9, 55.4, 37.5, 37.0; HRMS calcd for $C_{20}H_{20}N_4O_5$ 396.1434, found 396.1424.

(2*S*)-2-Azido-3-(3-hydroxy-4-methoxyphenyl)propionic Acid 2-Bromoethyl Ester (13). Into a solution of **12** (655 mg, 1.68 mmol, 1 equiv) in 15 mL of THF and 5 mL of H_2O, cooled to 0 °C, were added H_2O_2 (30%, 1.04 mL, 6 equiv) and LiOH (0.5 M, 6.8 mL, 2 equiv). The mixture was stirred for 1.5 h and quenched by addition of Na_2SO_3 (1.5 M, 9.0 mL). After removal of THF, the aqueous residue was acidified with 6 N HCl and extracted with EtOAc. The extracts were dried over Na_2SO_4 and evaporated to give 374 mg acid, which was then subjected to the next reaction directly. To a precooled solution (0 °C) of the acid (374 mg, 1.58 mmol) in 25 mL CH_2Cl_2 were added DMAP (9 mg, 0.08 equiv), 2-bromoethanol (236 μL, 2 equiv), and then DCC (359 mg, 1.1 equiv). The resulting mixture was stirred overnight (0 °C to rt) and filtered. The solvent was evaporated, and the slightly brown residue was separated on a flash column to give 472 mg (87%) product as a pale yellow oil: R_f 0.41 (3:2 hex/EtOAc); $[\alpha]^{24}_D$ −24.1° (*c* 1.95, $CHCl_3$); IR ($CHCl_3$) 3549, 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80−6.60 (m, 3H), 5.65 (s, 1H), 4.42 (t, 2H, J = 6.1 Hz), 4.00 (dd, 1H, J = 8.5, 5.6 Hz), 3.83 (s, 3H), 3.46 (t, 2H, J = 6.1 Hz), 3.07 (dd, 1H, J = 14.0, 5.6 Hz), 2.90 (dd, 1H, J = 14.0, 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 145.8, 145.6, 128.7, 120.8, 115.2, 110.7, 64.8, 63.1, 55.9, 37.0, 28.0; HRMS calcd for $C_{12}H_{14}N_3O_4Br$ 343.0168, found 343.0170.

(2*S*)-2-[*N*-[(Phenylmethoxy)carbonyl]amino]-3-(3-hydroxy-4-methoxyphenyl)propionic Acid 2-Bromoethyl Ester (4). To a preactivated (with H_2, 30 min) slurry of Pd−C (10%, 5.5 mg) in 5 mL of THF/MeOH (1:1) were added 55.4 mg (0.16 mmol) of azido compound **13** and 5 N HCl (100 μL, 3 equiv). After stirring under 1 atm H_2 for 1.5 h, the mixture was filtered through Celite and solvent was removed under reduced pressure. The residue was dried *in vacuo* and then redissolved in 10 mL of CH_2Cl_2 and 5 mL of H_2O. The solution was cooled to 0 °C, $NaHCO_3$ (27.1 mg, 2 equiv) and 27 μL of CbzCl (1.1 equiv) were added, and the mixture was stirred at for 1.5 h at 0 °C and 2 h at rt. Extraction with CH_2Cl_2 and evaporation of solvent provided 80 mg of crude product. Flash chromatography (4:1 hex/EtOAc) gave 61.5 mg (84%) of product **4** as a colorless oil. R_f 0.27 (6:4 hex/EtOAc); $[\alpha]^{24}_D$ −22.7° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3695, 3550, 3445 1733, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (b, 5H), 6.80−6.50 (m, 3H), 5.64 (s, 1H), 5.21 (d, 1H, J = 7.7Hz), 5.10 (s, 2H), 4.62 (dd, 1H, J = 7.7, 5.5 Hz), 4.40 (t, 2H, J = 5.8 Hz), 3.85 (s, 3H), 3.46(t, 2H, J = 5.8 Hz), 3.03 (d, 2H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 155.6, 145.8, 145.7, 136.1, 128.5, 128.2, 128,1, 120.8, 115.4, 110.8, 67.0, 64.5, 55.9, 54.8, 37.4, 28.1; HRMS calcd for $C_{20}H_{22}NO_6Br$ 451.0630, found 451.0635.

(2*S*)-2-Azido-3-(4-chlorophenyl)propionic Acid Methyl Ester (15). A solution of the acid **14** (970 mg, 4.3 mmol) and *p*-toluenesulfonic acid (818 mg, 1 equiv) in 30 mL of anhydrous CH_3OH was refluxed for 8 h. After cooling to rt, the mixture was adjusted to basic with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and flash chromatographed to give 994 mg (95%) of the methyl ester **15** as a colorless oil: R_f 0.41 (4:1 hex/EtOAc); $[\alpha]^{24}_D$ −50.7° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (d, 2H), 7.16 (d, 2H), 4.06 (dd, 1H, J = 8.6, 5.3 Hz), 3.78 (s, 3H), 3.14 (dd, 1H, J = 14.0, 5.3 Hz), 2.97 (dd, 1H, J = 14.0, 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.1, 134.3, 133.2, 130.5, 128.8, 63.0, 59.1, 52.7, 36.9; HRMS calcd for $C_{10}H_{10}N_3O_2Cl$ 239.0461, found 239.0461.

***N*-[*N*-[(1,1-Dimethylethoxy)carbonyl-L-asparaginyl]-L-(*p*-chlorophenyl)alanine Methyl Ester (16).** A slurry of Pd/C (10%, 80 mg) in 20 mL of THF was purged with H_2 for 30 min. To the slurry was added (2*S*)-2-azido-3-(4-chlorophenyl)propionic acid methyl ester (**15**) (800 mg, 3.33 mmol) and 5 N HCl (2 mL, 3 equiv). The mixture was stirred at rt under 1 atm of H_2 for 4 h and then filtered through Celite. After removing solvent the solid was redissolved in a mixture of 25 mL of THF and 15 mL of DMF and was cooled to 0 °C. Into the solution were added N-Boc-asparagine (930 mg, 1.2 equiv), HOBt·H_2O (678 mg, 1.5 equiv), $^iPr_2NEt$ (580 μL, 430 mg, 1 equiv), and EDC (770 mg, 1.2 equiv). The mixture was stirred for 24 h (0 °C to rt). THF was then removed, the residue was diluted with 150 mL CH_2Cl_2 and washed with 1 N $NaHSO_4$, 1 N $NaHCO_3$, and saturated brine, and the organic layer was separated and dried over Na_2SO_4. After removing the solvent, recrystallization with THF/hexane gave 1.14 g (81%) desired dipeptide (two crops) as a white solid: mp 209−211 °C. $[\alpha]^{23}_D$ −5.1° (*c* 0.04, CH_3OH); IR ($CHCl_3$) 3387, 3345, 1745, 1676, 1626 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.60 (bs, 1 H), 7.38 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.6 Hz), 7.05 (bs, 1H), 6.46 (bs, 2H), 4.74 (dd, 1H, *J* = 12.9, 6.7 Hz), 4.46 (br, 1H), 3.72 (s, 3H), 3.20 (dd, 1H, *J* = 13.9, 6.7 Hz), 3.10 (dd, 1H, *J* = 13.9, 6.7 Hz), 2.80 (dd, 1H, *J* = 15.9, 5.5 Hz), 2.65 (dd, 1H, *J* = 15.9, 6.1 Hz), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.3, 171.5, 170.9, 135.9, 130.7, 129.3, 128.6, 127.1, 80.1, 53.6, 52.1, 51.1, 38.0, 36.9, 28.2; HRMS calcd for $C_{19}H_{26}N_3O_6Cl$ 427.1510, found 427.1526.

[η^6-[(2*S*)-[4-Chloro-1-[2-[[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]amino]-2-(methoxycarbonyl)ethyl]-benzene]](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (5). A mixture of the dipeptide **16** (85.6 mg, 0.2 mmol, 1 equiv) and $[(CH_3CN)_3RuCp]PF_6$ (104 mg, 1.2 equiv) in 12 mL of 1,2-dichloroethane was purged with Ar for 20 min and then refluxed for 5 h. After filtration through Celite, the solvent was removed to give 189 mg (100%) of the dipeptide complex as a brown solid: ^1H NMR (CD_3CN) δ 7.34 (d, *J* = 6.7 Hz), 6.46 (dd, 2H, *J* = 8.0, 6.5 Hz), 6.25 (d, 1H, *J* = 6.5 Hz), 6.22 (bs, 1H), 6.09 (d, 1H, *J* = 8.0 Hz), 6.00 (bs, 1H), 5.74 (bs, 1H), 4.62 (dd, 1H, *J* = 8.7, 4.7 Hz), 4.28 (dd, 1H, *J* = 5.7, 5.5 Hz), 3.70 (s, 3H), 3.01 (dd, 1H, *J* = 14.1, 4.7 Hz), 2.79 (dd, 1H, *J* = 14.1, 8.7 Hz), 2.62 (dd, 1H, *J* =16.2, 5.7 Hz), 2.50 (dd, 1H, *J* = 16.2, 5.5 Hz), 1.41 (s, 9H); ^{13}C NMR (CD_3CN) δ 173.6, 172.6, 171.4, 155.3, 105.8, 101.8, 88.3, 88.2, 88.0, 83.8, 80.4, 54.0, 53.4, 52.2, 45.6, 36.8, 36.3, 28.6.

[η^6-[4-[(*S*)-5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-[(2-bromoethoxy)carbonyl]ethyl]-2-methoxyphenoxy]-1-[2-(methoxycarbonyl)-2-[*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]amino]ethyl]benzene]] (η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (17). Method A: To a pre-cooled (0 °C) solution of phenol **4** (90.5 mg, 0.2 mmol, 1 equiv) in 8 mL of THF was added a stock solution of sodium 2,6-di-*tert*-butylphenoxide (as prepared in method B) (3.3 mL, 1.1 equiv). The mixture was stirred for 25 min at 0 °C and for 5 min at rt under Ar and then transferred via cannula into a precooled solution (−78 °C) of the complex **5** (148 mg, 1 equiv) in 5 mL of THF. After stirring at −78 °C for 1 h and rt for 3 h, the solvent was removed and the residue was redissolved in ∼2 mL of CH_3CN and precipitated with 100 mL of Et_2O. The precipitate was dissolved in 15 mL of CH_3CN and filtered through neutral alumina (1 × 5 cm) to give complex **17** as a brown solid. No further purification was performed, and the product was used in the next reaction directly: ^1H NMR ($CDCl_3$) δ 7.50−7.10 (m, 8H), 6.5−5.7 (m, 9H), 5.25 (s, 5H), 5.02 (s, 2H), 4.70−4.20 (m, 5H), 3.81 (s, 3H), 3.70 (s, 3H), 3.58 (dd, 2H, *J* = 5.5, 5.5 Hz), 3.30−2.40 (m, 6H, 1.41 (s, 9H). **Method B**: A basic stock solution was first prepared from 53.5 mg of NaH and 276 mg of 2,6-di-*tert*-butylphenol in 20 mL of THF at rt for 30 min. THF was then removed, and the yellow residue was dissolved in 20 mL of freshly distilled acetone. A 1.65 mL (1.1 equiv) amount of this new stock solution was quickly added to a precooled solution (−30 °C) of the phenol **4** (50 mg, 1.1 equiv) in 3 mL of dry acetone. After stirring for 20 min, the solution was transferred via cannula to a precooled solution of **5** (73.5 mg, 1 equiv) in 3 mL of acetone. The mixture was stirred at −30 °C and allowed to warm to rt over a period of 4−5 h. Similar workup as in method A gave **17** as a brown solid which gave identical analytical data.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-[(2-bromoethoxy)carbonyl]ethyl]-2-methoxyphenyl]-*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (3). A solution of complex **17** in ∼15 mL of freshly distilled CH_3CN in a quartz tube was purged with N_2 for 20 min and then irradiated with a sunlamp for 24 h. The solvent was removed, and ∼1.5 mL of CH_3CN was added. The unreacted complex was precipitated by the addition of 100 mL of Et_2O. The ether solution was decanted and set aside, and the residue was subjected to the photoreaction conditions again. The combined ether solution was dried and flash chromatographed to give (34%, method A), 65 mg (77% overall yield, method B) of the tripeptide **3** as a white solid: R_f 0.31 (EtOAc), 0.51 (THF/$CHCl_3$, 1/1); $[\alpha]^{24}_D$ +24.6° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3513, 1737, 1717, 1693 cm^{-1}; ^1H NMR (CD_3NO_2) δ 7.80−7.40 (bs, 5H), 7.10−6.60 (m, 8H), 6.10−5.30 (bs, 4H), 5.04 (s, 2H), 4.80−4.20 (m, 5H), 3.78 (s, 3H), 3.66 (s, 3H), 3.37 (dd, 2H, *J* = 5.7, 5.7 Hz), 3.40−3.20 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (CD_3NO_2) δ 173.2, 171.5, 171.2, 170.8, 156.7, 155.6, 150.4, 145.9, 136.2, 130.7, 130.6, 130.5, 130.3, 130.1, 128.7, 128.6, 128.2, 128.1, 125.4, 121.6, 117.6, 112.9, 80.4, 68.0, 67.0, 64.7, 56.0, 54.9, 53.6, 53.4, 52.3, 51.0, 50.9, 37.2, 28.3, 25.6; HRMS (FAB) calculated for $C_{39}H_{48}N_4O_{12}Br$ $(M + H)^+$ 843.2452, found 843.2435.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-[(2-iodoethoxy)carbonyl]ethyl]-2-methoxyphenyl]-*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (18). To a solution of **3** (65.0 mg, 0.077 mmol) in 3 mL of anhydrous acetone was added NaI (64.0 mg, 7 equiv). The mixture was refluxed under Ar for 6 h. The solvent was removed, and the residue was purified by flash chromatography (EtOAc) to give 67.0 mg (98%) of iodoethyl ester **18** as a white solid: R_f 0.31 (EtOAc); $[\alpha]^{24}_D$ +20.0° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 1745, 1719, 1685 cm^{-1}; ^1H NMR (CD_3NO_2) δ 7.45−7.30 (m, 5H), 7.29−7.10 (m, 4H), 7.07 (s, 1H), 6.95−6.79 (m, 3H) 6.19 (bs, 1H), 6.00 (bt, 1H, *J* = 10 Hz), 5.81 (bt, 1H, *J* = 10 Hz), 5.72 (b, 1H), 5.07 (b, 2H), 4.70 (m, 1H), 4.52 (m, 1H), 4.45−4.25 (m, 3H), 3.80 (s, 3H), 3.72 and 3.70 (two singlets, 3H), 3.34 (t, 2H, *J* = 6.0 Hz), 3.25−2.90 (m, 4H), 2.85−2.50 (m, 2H),1.41 (s, 9H); ^{13}C NMR (CD_3NO_2) parentheses denote shifts for amide resonance conformer: δ 174.54 (174.48), 173.3, 172.7, 172.6, 158.61 (158.53), 157.33 (157.06), 152.13 (152.06), 145.33 (145.66), 138.0, 132.48 (132.42), 132.0, 131.0, 129.9, 129.4, 129.1, 127.53 (127.46), 123.87 (123.80), 117.77 (117.92), 114.5, 81.2, 67.8, 66.8, 56.63 (56.76), 55.0, 53.1, 52.5, 37.90 (38.01), 28.7, 1.5; HRMS (FAB) calcd for $C_{39}H_{48}N_4O_{12}I$ $(M + H)^+$ 891.2314, found 891.2289.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-carboxyethyl]-2-methoxyphenyl]-*N*-[*N*-[(1,1-dimethylethoxy)-carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (19). To a stirred 0 °C solution of iodoethyl ester **18** (33 mg, 0.037 mmol) in 4 mL of THF was added DMPU (190 μL, 42 equiv) by syringe. To the resulting solution was added SmI_2 (2.6 mL, 0.1 M in THF, 7 equiv). After stirring at 0 °C for 10 min and then at rt for 3 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2 and treated with 15 mL of 0.1 N HCl. The organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with 0.2 M $Na_2S_2O_3$ and brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and the pale yellow oil was purified on a small silica gel column (EtOAc and then 5% HOAc in EtOAc). The fractions containing the product were diluted with benzene and evaporated under reduced pressure with the bath temperature below 10 °C. The product **19** (16 mg, 61%) was obtained as a white powder. This compound was not further purified, but was carried forward to the cycloamidation: R_f 0.42 (5% HOAc/EtOAc); ^1H NMR (CD_3OD) δ 7.25 (bs, 5H), 7.20−6.70 (m, 7H), 5.02 (d, 1H, *J* = 14.0 Hz), 4.96 (d, 1H, *J* = 14.0 Hz), 4.60 (m, 1H), 4.52 (m, 1H), 4.20 (m, 3H), 3.71 (s, 3H), 3.68 and 3.66 (two singlets, 3H), 3.25−2.80 (m, 4H), 2.65−2.35 (m, 2H),1.40 (s, 9H); ^{13}C NMR (CD_3OD) parentheses denote shifts for amide resonance conformer δ 175.5, 173.5, 172.8 (172.9), 158.8, 157.9 (158.0), 157.2,

151.7 (151.9), 145.2 (145.4), 138.4, 132.2, 132.0, 131.3, 189.3, 128.8, 128.6, 127.4 (127.3), 124.0 (123.6), 117.5, 114.2, 80.7, 67.2, 62.3, 56.5, 55.1, 52.8, 28.7.

Methyl (9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-[[(phenylmethoxy)carbonyl]amino]-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[5.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylate (2). To a precooled solution (0 °C) of the acid **19** (11.0 mg, 0.022 mmol) in 4 mL of CH_2Cl_2 was added by syringe 37.5 μL of thioanisole (20 equiv) and 2 mL of TFA. The resulting mixture was stirred at 0 °C for 1.5 h. The solvent was evaporated, and the residue was dried *in vacuo* to give a pale yellow oil. The oil was redissolved in 2 mL of DMF and was added by syringe pump over a period of 3 h to a precooled (0 °C) solution of $NaHCO_3$ (6.5 mg, 5 equiv) and DPPA (5 μL, 1.5 equiv) in ~1.5 mL of DMF. After stirring at 0 °C for 3 days, DMF was removed under reduced pressure. TLC separation (silica gel, EtOAc) gave 4.8 mg (52%) of cyclized product **2** as a white solid: mp 181−183 °C (lit.[5] 179−182 °C); $[\alpha]^{23}_D$ −73° (*c* 0.35, CH_3OH) (lit.[5] −74°, *c* 0.1, CH_3OH); R_f 0.13 (EtOAc); IR ($CHCl_3$) 3438, 1736, 1718, 1693, 1685, 1600 cm^{-1}; ^1H NMR (CD_3OD) δ 7.70−7.54 (m, 7H), 7.36 (dd, 1H, J = 8.0, 1.9 Hz), 7.23 (dd, 1H, J = 8.0, 1.9 Hz), 7.10 (dd, 1H, J = 8.0, 1.9 Hz), 6.75 (dd, 1H, J = 8.0, 1.9 Hz), 6.05 (s, 1H), 5.24 (d, 1H, J = 12.4 Hz), 5.12 (d, 1H, J = 12.4 Hz), 4.90 (m, 1H), 4.81 (m, 1H), 4.56 (m, 1H), 3.88 (s, 3H), 3,80 (s, 1H), 3.36 (dd, 1H, J = 13.5, 2.5 Hz), 2.97 (dd, 1H, J = 13.5, 3.1 Hz), 2.76 (dd, 1H, J = 14.0, 3.3 Hz), 2.97 (m, 2H), 2.45 (dd, 1H, J = 14.0, 4.7 Hz); ^{13}C NMR (CD_3OD) δ 174.4, 173.0, 171.9, 171.3, 157.3, 155.3, 150.6, 149.3, 138.1, 135.2, 133.2, 131.6, 130.4, 130.2, 129.7, 129.5, 129.3, 129.1, 127.9, 124.9, 123.4, 122.9, 117.3, 113.1, 67.6, 56.6, 55.1, 54.9, 42.1, 40.1, 39.4, 38.2, 35.9; HRMS calcd for $C_{32}H_{34}N_4O_9$ 618.2326, found 618.2331.

Acknowledgment. Financial support from the National Institutes of Health (GM 36925) is gratefully acknowledged.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all compounds reported (33 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.

JO960956L