CCH_3), 1.30 (s, 3 H, CCH_3); IR (KBr) 3300 (OH), 1735 (C=O) cm^{-1}.

Product **13** was converted to the tetraphenylborate salt:[12] mp 116–118 °C.

Anal. Calcd for $C_{33}H_{40}NO_3B$: C, 77.79; H, 7.91; N, 2.75. Found: C, 77.55; H, 7.94; N, 2.73.

Ethyl 3-Cyano-3-hydroxybutanoate (19). To a stirred solution of acetoacetic ester (10.0 g, 76.8 mmol) and trimethylsilyl cyanide (8.02 g, 76.8 mmol) was added approximately 5 mg each of KCN and 18-crown-6. The mixture became warm and was allowed to cool to room temperature. IR analysis at this point showed that the ketone carbonyl was completely gone. To the mixture was added 40 mL of ether, the solution was cooled in an ice bath, 40 mL of 15% HCl was added, and this was stirred vigorously for 15 min. The ether layer was separated, washed with 40 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 10.2 g (73.0%) of **19** as a pale orange oil. This was distilled to provide a colorless oil: bp 68–70 °C (0.2 mm) [lit.[19] bp 133 °C (23 mm)].

Ethyl 4-Amino-3-hydroxy-3-methylbutanoate, Hydrochloride (20). A mixture of cyanohydrin **19** (1.0 g, 0.64 mol), 50 mL of EtOH, 0.15 g of PtO_2, and 1.0 mL of concentrated HCl was hydrogenated on a Parr shaker at 50 psi overnight. The mixture was filtered and concentrated in vacuo to provide 1.1 g (86%) of crude **20** as an oil. The product was used in this form without further purification: ^1H NMR (D_2O) δ 4.35–3.95 (q, 2 H, OCH_2CH_3), 3.15 (s, 2 H, NCH_2), 2.7 (s, 2 H, CH_2CO_2Et), 1.4–0.8 (m, 6 H, CCH_3 and OCH_2CH_3); IR (liquid film) 3600–2600 (OH, $^+NH_3$), 1715 (C=O) cm^{-1}.

Ethyl 4-(Dimethylamino)-3-hydroxy-3-methylbutanoate (21). A solution of **20** (1.0 g, 5.1 mmol), 30 mL of water, 37% formaldehyde (0.82 g, 10 mmol), and 0.80 g of 10% Pd–C was hydrogenated on a Parr shaker at 50 psi overnight. The mixture was filtered, the filtrate was adjusted to pH 10.5 with granular Na_2CO_3, and the solution was extracted with $CHCl_3$ (4 × 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to provide 0.45 g (47%) of **21** as an oil. The analytical sample was obtained by chromatography of a portion of the crude product on alumina (80% $CHCl_3/Et_2O$, R_f 0.80): ^1H NMR ($CDCl_3$) δ 4.35–3.9 (q, 2 H, OCH_2CH_3), 3.8–3.5 (br s, 1 H, OH), 2.55–2.4 (m, 2 H, NCH_2), 2.3 (m, 8 H, $N(CH_3)_2$ and CH_2CO_2Et), 1.4–1.15 (t, 3 H, OCH_2CH_3), 1.2 (s, 3 H, CCH_3); IR (liquid film) 3400 (OH), 1690 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.02; H, 10.17; N, 7.29.

Registry No. **2**, 96935-73-8; **3**, 97374-60-2; **4**, 97374-61-3; **5**, 97374-62-4; **5**·tetraphenylborate salt, 97374-64-6; **6**, 97374-65-7; **6**·tetraphenylborate salt, 97374-67-9; **7**, 97374-68-0; **8**, 97374-69-1; **9**, 97374-70-4; **10**, 97374-71-5; **11**, 97374-72-6; **12**, 97374-73-7; **13**, 97374-74-8; **13**·tetraphenylborate salt, 97374-76-0; **14**, 141-97-9; **15**, 97374-77-1; **16**, 97374-78-2; **17**, 97374-79-3; **18**, 97374-80-6; **18**·tetraphenylborate salt, 97374-82-8; **19**, 6330-37-6; **20**, 97374-83-9; **21**, 97374-84-0; **22**, 97374-85-1; **23**, 97374-86-2; **23**·teteraphenylborate salt, 97374-88-4; 3-(dimethylamino)-2-butanone, 10524-60-4; diethyl carbonate, 105-58-8; formaldehyde, 50-00-0.

Synthesis of γ-Lactam-Constrained Tryptophyllysine Derivatives

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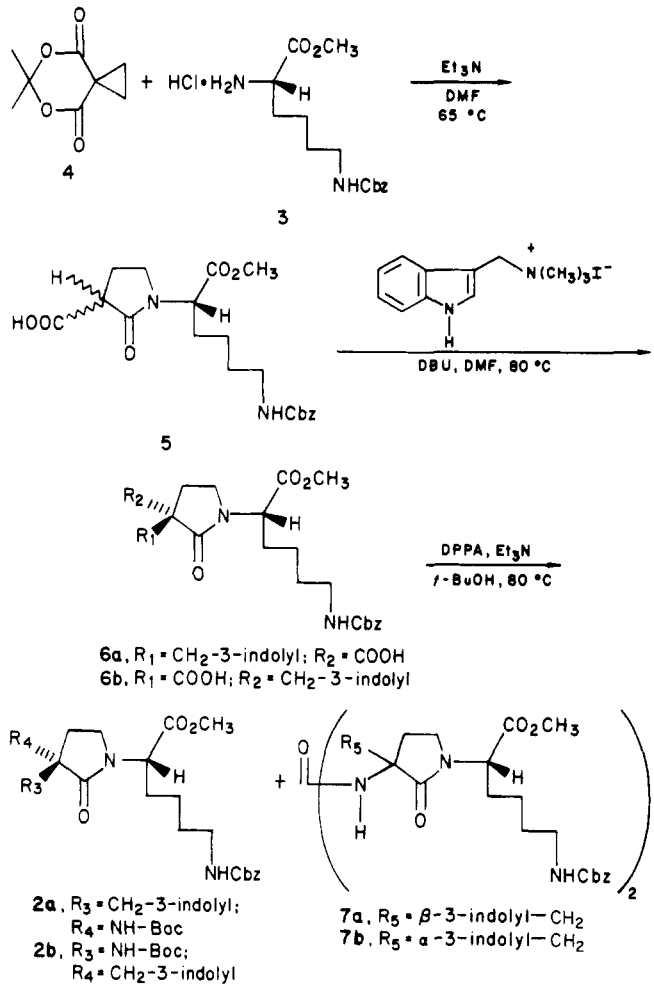
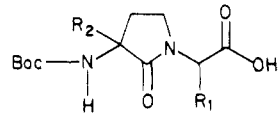
Received February 5, 1985

We previously reported the synthesis of γ-lactam-constrained dipeptides for use in conformation–activity studies of biologically active peptides.[1] Such lactams serve as analogues of glycyl dipeptides restricted to turn conformations. It is of general interest to similarly constrain dipeptide units not containing glycine. A specific example is the tryptophyllysine unit of somatostatin. The published synthesis utilized the cyclization of methylsulfonium salts of Boc-Met-X-OCH_3, where X was any of several α-amino acids, and provided ready access to lactam dipeptides such as **1a**. Extension of this synthetic route to prepare the Trp-Lys derivative **1b**, however, was not straightforward. We now describe the synthesis of the methyl ester of **1b** (**2**) by a novel approach that has potential generality for a variety of γ-lactam-constrained dipeptides.

Scheme I





The synthesis of **2** is outlined in Scheme I. ε-(Benzyloxycarbonyl)-L-lysine methyl ester hydrochloride **3** was warmed with electrophilic cyclopropane derivative **4**[2] in dimethylformamide (DMF) to produce the α-carboxy lactam **5** as a mixture of diastereomers. This reaction presumably occurs by initial attack of the lysine amino group at a cyclopropane methylene to open the three-membered ring. The intermediate then cyclizes on one of the lactone carbonyls to expel acetone and produce **5**.

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0022-3263/85/1950-3631$01.50/0

Danishefsky had previously observed this reaction with aniline.[3] A byproduct isolated from this step was N^{ϵ}-(benzyloxycarbonyl)-N^{α}-formyllysine methyl ester, which presumably arises from reaction of **3** with DMF. This compound also forms under similar conditions in the absence of cyclopropane **4**.

The indolylmethyl side chain was next introduced by alkylation of crude **5** with gramine methiodide in DMF in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The product **6** is a 1:1 mixture of diasteromers which is readily separated by silica gel chromatography. The more mobile diastereomer (**6a**) was tentatively assigned the configuration corresponding to L-tryptophan, and the less mobile compound (**6b**) was assigned the D-tryptophan configuration. These assignments are based on analogy of the chemical shifts of the γ-methylene protons of the lysine side chains of **6a** and **6b** in methanol with the corresponding shifts of L- and D-Trp-Lys in water. These signals for L- and D-Trp-Lys are found at 1.25 and 0.5 ppm, respectively, while those of **6a** occur at >1.3 ppm and those of **6b** are at 0.67 and 0.86 ppm. Previous studies of dipeptides with one aromatic and one aliphatic side chain have consistently shown upfield shifts of side chain aliphatic protons to be more pronounced for D,L than L,L compounds.[4] The yield of purified diastereomers from starting lysine derivative **3** was 25%.

The acids **6a** and **6b** were converted stereospecifically to target compounds **2a** and **2b** in 66% yield by the modified Curtius rearrangment with diphenylphosphoryl azide (DPPA) in *tert*-butyl alcohol.[5] The γ-methylene protons of Lys in **2a** and **2b** show chemical shifts analogous to those of **6a** and **6b**, respectively. Byproducts of these reactions are the ureas **7** (12%), which presumably arise from the presence of traces of water reacting with the intermediate isocyanate.[6] The lactams **2** are in protected form suitable for use in peptide synthesis, and their incorporation into somatostatin analogues will be described in a forthcoming publication.

The route used to prepare **2** is potentially applicable to the synthesis of protected, lactam-constrained dipeptides **1** containing a variety of R_1 and R_2 side chains. The availability of a broader range of dipeptide lactam structures will extend the versatility of lactams in conformation–activity studies of biologically active peptides.

Experimental Section

6-[(Benzyloxycarbonyl)amino]-2(*S*)-(3-carboxy-2-oxo-1-pyrrolidinyl)hexanoic Acid Methyl Ester (5). N^{ϵ}-(Benzyloxycarbonyl)-L-lysine methyl ester hydrochloride (Bachem) (43.3 g, 0.13 mol), triethylamine (18.2 mL, 0.13 mol), and isopropylidene cyclopropane-1,1-dicarboxylate (Fluka) (22.2 g, 0.13 mol) were mixed in 330 mL of freshly degassed DMF and heated at 65 °C. After 1 h, solid sodium bicarbonate (11 g, 0.13 mmol) was added and heating was continued. Additional increments of cyclopropane reagent (4.3 g, 25 mmol, and 4.8 g, 28 mmol) were added after 49 and 55.5 h, respectively. Heating was stopped after a total of 98 h. The DMF was removed in vacuo, and the brown residue was dissolved in 500 mL of methylene chloride. This solution was washed successively with 1 N HCl (3 × 200 mL), H_2O (2 × 200 mL), and saturated aqueous sodium chloride (200 mL) and dried (Na_2SO_4). Filtration and concn. in vacuo gave 65 g of a brown oil. A sample was purified by HPLC (Waters C-18 semiprep, 1:1000 trifluoroacetic acid/H_2O buffer–acetonitrile gradient), giving **5** as a mixture of diastereomers and N^{ϵ}-(benzyloxycarbonyl)-N^{α}-formyllysine methyl ester in the ratio of 5:1. ^{1}H NMR data for **5** is as follows: (CD_3OD) δ 1.30 (m, 2 H), 1.53 (m, 2 H), 1.82 (m, 1 H), 1.96 (m, 1 H), 2.33 (m, 2 H), 3.12 (2 overlapping t due to 2 diastereomers, 2 H, $J \sim 7$ Hz), 3.46 (t, 2 H, $J = 7$ Hz), 3.55 (m, 1 H), 3.65 (2 s separated by ~2 Hz, 3 H, due to 2 diastereomers), 4.69 (2 overlapping t due to 2 diastereomers, 1 H, $J = 11$ Hz), 5.07 (s, 2 H), 7.35 and 7.37 (2 s due to 2 diastereomers 5 H). Spectral data for N^{ϵ}-(benzyloxycarbonyl)-N^{α}-formyllysine methyl ester is as follows: ^{1}H NMR (CD_3OD) δ 1.37 (m, 2 H), 1.51 (m, 2 H), 1.72 (m, 1 H), 1.83 (m, 1 H), 3.11 (t, 2 H, $J = 7$ Hz), 3.72 (s, 3 H), 4.48 (m, 1 H), 5.06 (s, 2 H), 7.34 (m, 5 H), 8.08 (s, 1 H); FAB mass spectrum, m/e 323 (M + H).

6-[(Benzyloxycarbonyl)amino]-2(*S*)-(3-carboxy-3-(indol-3-ylmethyl)-2-oxo-1-pyrrolidinyl)hexanoic Acid Methyl Ester (6). The crude acid **5** (63 g, 0.13 mol, based on starting lysine derivative) was dissolved in 630 mL of degassed DMF, and DBU (23 mL, 0.15 mol) and gramine methiodide (58.8 g, 0.19 mol) were added. The mixture was heated under nitrogen at 80 °C for 45 min. Additional amounts of gramine methiodide (58.8 g, 0.19 mol, and 12 g, 0.04 mol) were added after 45 min and 2 h, respectively. The mixture was cooled to room temperature after 135 min and poured into 2 L of methylene chloride. This mixture was washed with 1 N HCl (3 × 750 mL), H_2O (2 × 750 mL), and saturated aqueous sodium chloride (750 mL) and dried (Na_2SO_4). Filtration and concentration in vacuo gave 80.3 g of brown oil. A 40-g portion of this material was chromatographed on 2.5 kg of E. Merck Silica Gel 60 (230–400 mesh), eluting with 95:5:5:0.5:0.1 $CHCl_3$–MeOH–H_2O–HOAc. There was obtained 5.0 g of the more mobile diastereomer and 4.8 g of the less mobile diastereomer along with 0.3 g of mixed fractions. Spectral data for more mobile diastereomer is as follows: IR ($CHCl_3$) 3400, 2920, 1700 cm^{-1} (br shoulders at 1740 and 1710 cm^{-1}); ^{1}H NMR (CD_3OD) δ 1.30 (m, 2 H), 1.49 (m, 2 H), 1.75 (m, 1 H), 1.86 (m, 1 H), 2.14 (m, 1 H), 2.34 (m, 1 H), 3.01 (m, 1 H), 3.08 (t, 2 H, $J = 5$ Hz), 3.36 (s, 2 H), 3.53 (s, 3 H), 4.65 (d of d, 1 H, $J_1 = 5$ Hz, $J_2 = 10$ Hz), 5.06 (s, 2 H), 7.0–7.1 (m, 3 H), 7.32 (m, 1 H), 7.34 (2 s, 5 H), 7.60 (d, 1 H, $J = 7$ Hz); $[\alpha]^{24}_D$ +18.08 (c 0.6, MeOH); FAB mass spectrum, m/e 536 (M + H). Spectral data for less mobile diastereomer is as follows: IR ($CHCl_3$) 3400, 3300, 2900, 1710 (br) cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.69 (m, 1 H), 0.87 (m, 1 H), 1.30 (m, 2 H), 1.56 and 1.62 (m, 2 H), 2.18 (m, 1 H), 2.45 (m, 1 H), 2.77 (m, 1 H), 2.97 (m, 2 H), 3.2–3.6 (m, ~4 H), 4.54 (d of d, 1 H, $J_1 = 5$ Hz, $J_2 = 10$ Hz), 5.09 (s, 2 H), 7–7.7 (m, 10 H); $[\alpha]^{24}_D$ −76.76 (c 0.7, MeOH); FAB mass spectrum, m/e 536 (M + H).

6-[(Benzyloxycarbonyl)amino]-2(*S*)-[3(*S*)-((*tert*-butyloxycarbonyl)amino)-3-(indol-3-ylmethyl)-2-oxo-1-pyrrolidinyl]hexanoic Acid Methyl Ester (2b). Acid **5b** (4.5 g, 8.4 mmol) was dissolved in 127 mL of dry *tert*-butyl alcohol, and DPPA (2.0 mL, 9.3 mmol) and Et_3N (1.3 mL, 9.3 mmol) were added. The solution was heated at reflux under nitrogen for 48 h. The solution was concentrated in vacuo. The residue was dissolved in 150 mL of methylene chloride, and this solution was washed with 0.5 M citric acid (2 × 150 mL), 1 N $NaHCO_3$ (3 × 150 mL), and H_2O (150 mL) and dried (Na_2SO_4). Filtration and concentration in vacuo gave 4.6 g of a yellow-brown foam. This material was chromatographed on E. Merck Silica Gel 60 (230–400 mesh) eluting with 98:2:0.1 $CHCl_3$–MeOH–H_2O to give 3.36 g (66%) of a white foam. Spectral data is as follows: IR ($CHCl_3$) 3400, 2900, 1695 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.69 (m, 1 H), 0.85 (m, 1 H), 1.2–1.6 (m, 4 H), 1.43 (s, 9 H), 2.44 (m, 2 H), 2.96 (m, 2 H), 3.11 (d, 1 H, $J = 14$ Hz), 3.18 (d, 1 H, $J = 14$ Hz), 3.1–3.2 (m, 2 H), 3.64 (s, 3 H), 4.30 (t, 1 H, $J = 7$ Hz), 5.07 (s, 2 H), 6.60 (m, <1 H), 6.89 (m, <1 H), 7.00 (t, 1 H, $J = 6$ Hz), 7.10 (t, 1 H, $J = 6$ Hz), 7.16 (s, 1 H), 7.36 (s, buried d, 6 H), 7.59 (d, 1 H, $J = 8$ Hz); FAB mass spectrum, m/e 607 (M + H); $[\alpha]^{24}_D$ −33.20° (c 0.4, MeOH).

Isolated as a minor product from this reaction was **7b**, 0.59 g (12%), as a white foam: IR ($CHCl_3$) 1700, 1650, 1500 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.71 and 0.85 (m, 4 H), 1.24 (m, 6 H), 1.35 (m, 2 H), 2.44 (m, 1 H), 2.50 (m, 3 H), 2.97 (m, 4 H), 3.18 (d, 2 H, $J = 14$ Hz), 3.23 (d, 2 H, $J = 14$ Hz), 3.2–3.3 (m, 4 H), 3.64 (s, 6 H), 4.30 (t, 2 H, $J = 7$ Hz), 5.06 (s, 4 H), 6.99 (t, 2 H, $J = 7.5$ Hz), 7.07 (t, 2 H, $J = 7.5$ Hz), 7.17 (s, 2 H), 7.25–7.4 (s, 10 H), 7.59 (d, 2 H, $J = 8$ Hz); FAB mass spectrum m/e 1039 (M + H); $[\alpha]^{24}_D$ −32.20 (c 0.5, MeOH).

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6-[(Benzyloxycarbonyl)amino]-2(*S*)-[3(*R*)-((*tert*-butyloxycarbonyl)amino)-3-(indol-3-ylmethyl)-2-oxo-1-pyrrolidinyl]hexanoic Acid Methyl Ester (2a). The compound was prepared from **5a** according to the method described for **2b**. Spectral data is as follows: IR ($CHCl_3$) 3400, 2900, 1700 cm^{-1}; ^1H NMR (CD_3OD) δ 1.30, 1.54, and 1.75 (m, 6 H), 1.39 (s, 9 H), 2.39 (br t, 2 H, J = 8 Hz), 2.79 (m, 1 H), 3.05 (d, 1 H, J = 14 Hz), 3.15 (d, 1 H, J = 14 Hz), 3.05–3.3 (m, 3 H), 3.50 (s, 3 H), 4.64 (d of d, 1 H, J_1 = 6 Hz, J_2 = 11 Hz), 5.07 (s, 2 H), 7.03 (t, 1 H, J = 8 Hz), 7.13 (t, 1 H, J = 8 Hz), 7.14 (s, 1 H), 7.36 (m, 5 H), 7.61 (d, 1 H, J = 8 Hz); FAB mass spectrum, m/e 607 (M + H); $[\alpha]^{24}_D$ −1.69° (c 0.4, MeOH).

Isolated as a minor product from this reaction was **7a**: IR ($CHCl_3$) 1700, 1510, 1430 cm^{-1}; ^1H NMR (CD_3OD) δ 1.25–1.55 (m, 8 H), 1.73 (m, 4 H), 2.29 (m, 2 H), 2.43 (m, 2 H), 2.82 (m, 2 H), 3.05 (d, 2 H, J = 14 Hz), 3.15 (d, 2 H, J = 8 Hz), 3–3.2 (m, 6 H), 3.52 (s, 6 H), 4.62 (m, 2 H), 4.99 (s, 4 H), 7.00 (t, 2 H, J = 7 Hz), 7.09 (t, 2 H, J = 8 Hz), 7.15 (s, 2 H), 7.2–7.35 (m, 10 H), 7.56 (d, 2 H, J = 8 Hz); FAB mass spectrum, m/e 1039 (M + H); $[\alpha]^{24}_D$ −11.74° (c 0.28, MeOH).

Acknowledgment. I thank Dr. B. Arison, Dr. D. Cochran, and J. Murphy for NMR spectra, J. Smith for FAB mass spectra, C. Homnick for HPLC support, Y. Lee for optical rotations, and C. Colton for technical assistance. I also thank M. Banker for typing the manuscript and Drs. D. Veber and P. Anderson for their support of this work.

Registry No. **2a**, 97569-97-6; **2b**, 97569-98-7; **3**, 27894-50-4; **4**, 5617-70-9; **5** (isomer 1), 97551-29-6; **5** (isomer 2), 97551-30-9; **6a**, 97569-99-8; **6b**, 97551-31-0; **7a**, 97570-00-8; **7b**, 97643-01-1; N^{ϵ}-(benzyloxycarbonyl)-N^2-formyllysine methyl ester, 53917-46-7; gramine methiodide, 5457-31-8.

Enantioselective Synthesis of the Depsipeptide Unsaturated Acid Portion of Madumycin II

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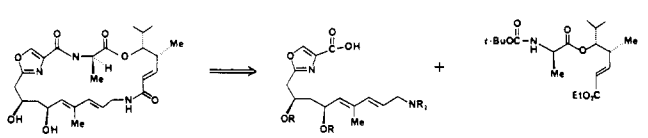
Received February 26, 1985

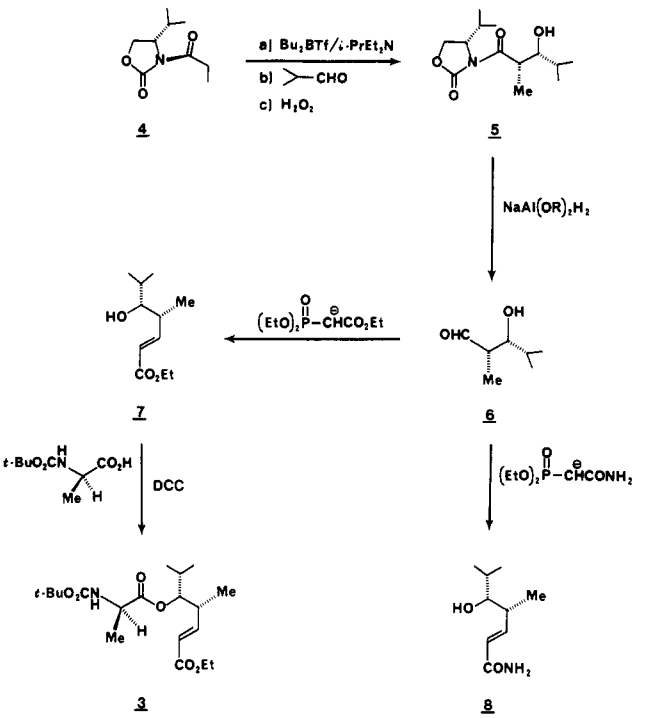
In our efforts directed toward the synthesis of the group A streptogramin antibiotics,[1] griseoviridin,[2] and madumycin II (1), we required an enantioselective route to the depsipeptide unsaturated ester **3**. Our strategy called for coupling **3** to the oxazole moiety **2**[3] to reach madumycin II.



(+)1 (+)2 (+)-3

We describe herein an efficient approach to (+)-**3** which further demonstrates the utility of the oxazolidone-mediated asymmetric synthesis developed by Evans.[4]

Treatment of the *N*-propionyl imide **4** with di-*n*-butyl boron triflate in the presence of Hunig's base produced the *Z*-enolate and addition of isobutyraldehyde at −78 °C gave the β-hydroxy imide **5**, in 71% yield, after oxidative



4 5 7 6 3 8

workup. The diastereomeric ratio of **5** (523:1) was determined via gas chromatography on the *O*-silyl ether with the syn diastereomer predominating. Methanolysis of **5** to its methyl ester and comparison of the optical rotation with the known material indicated that the enantioselectivity was greater than 99%. A single recrystallization gave **5** free of any epimeric material. Reduction with sodium bis(methoxyethoxy) aluminum hydride (Red-Al) produced the β-hydroxy aldehyde **6** which proved to be unstable when isolation was attempted (distillation or chromatography). Therefore, **6** was treated in crude form directly with the potassium salt of triethyl phosphonoacetate at −78 °C and, after workup and purification via chromatography, gave the unsaturated ester **7** in 45% overall yield from **5**. Similarly, reaction of the hydroxy aldehyde **6** with the potassium salt of diethyl phosphonoacetamide gave the unsaturated amide **8** in 32% purified yield.

Ganem[5] has reported an enantioselective synthesis of **7** starting with (*Z*)-β-isopropylallyl alcohol and, after a Sharpless asymmetric epoxidation, followed by seven synthetic steps, furnished the product in 66% ee. More significant in the Ganem work, however, was the confirmation of the absolute stereochemistry in these antibiotics (e.g., virginiamycin M and madumycin) by conversion of **7** into the known lactone degradation product [(2*R*,3*R*)-**9**].

9 10

Our analytical determination of **7** (HPLC) indicated it was now a 96:4 mixture of syn and anti material, with a trace (~2%) of (*Z*)-olefin. Apparently a small amount of epimerization took place at the α-carbon during the Red-Al

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