The Synthesis of *syn*- and *anti*-2(*S*)-Phthalimidomethyl-2,3,4,4a,7,7a-hexahydro-6-oxo-5*H*-pyrano[2,3-*b*]pyrroles as Rigid β-Bend Peptide-Mimetics [1]

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The synthesis of the *syn*- **14** and *anti*- **13** isomers of 2(*S*)-phthalimidomethyl-2,3,4,4a,7,7a-hexahydro-6-oxo-5*H*-pyrano[2,3-*b*]pyrrole was accomplished starting from sodium 3,4-dihydro-2*H*-pyran-2-carboxylate. The isomers were separated by preparative high performance liquid chromatography. Both isomers can serve as β-bend mimetics and represent three amino acids plus the amino group of the fourth amino acid of a peptide. The lactam nitrogen was alkylated to provide the equivalent of a leucine as the fourth amino acid residue.

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The β-bend is a conformational entity in peptides, and is often mentioned as being a component of the active conformation of various neuropeptides. For example, Veber and coworkers have synthesized cyclic analogs of somatostatin that indicate that the active conformation of somatostatin may involve a type II′ β-bend [2,3]. Other neuropeptides that potentially contain β-bends are LHRH [4], bradykinin [5], oxytocin [6], and the enkephalins [7].

A β-bend involves a reversal in the direction of the peptide backbone. Four amino acid residues are the minimal requirement for a β-bend, and the ϕ,θ angles of the second and third residues of the bend are sufficient to define the bend. The peptide becomes folded and more compact by reversing the chain direction. Frequently, low energy conformations of peptides are represented by such folded conformations, often stabilized by hydrogen bonding. Since a folded conformation can exhibit more structural stability than a linear, freely rotating peptide, it would serve as a better ligand for a receptor site since the binding portions of the peptide are initially held in the proper orientation for receptor interaction. Thus, it is not surprising to see that many neuropeptides already exist in predominantly bent forms to take advantage of this structural stabilization, as in the case of the cyclic peptides oxytocin, somatostatin, and vasopressin. Even linear peptides seem to take advantage of this by their preference for folded conformations.

In order to better understand the importance of the β-bend conformation as a requisite for receptor interaction in biologically active peptides, we have proposed a rigid ring system representing the β-bend portion of the peptide that can be incorporated into an appropriate peptide sequence [8]. Through a study of peptide X-ray crystal structures, various spectroscopic results and molecular models, we have designed the 2-substituted-2(*S*)-2,3,4,4a,-7,7a-hexahydro-6-oxo-5*H*-pyrano[2,3-*b*]pyrrole ring system as one that could provide the necessary spatial characteristics to serve as a rigid β-bend replacement.

Figures 1, 2, and 3 show the synthetic approach that was developed. Commercially available sodium 3,4-dihydro-

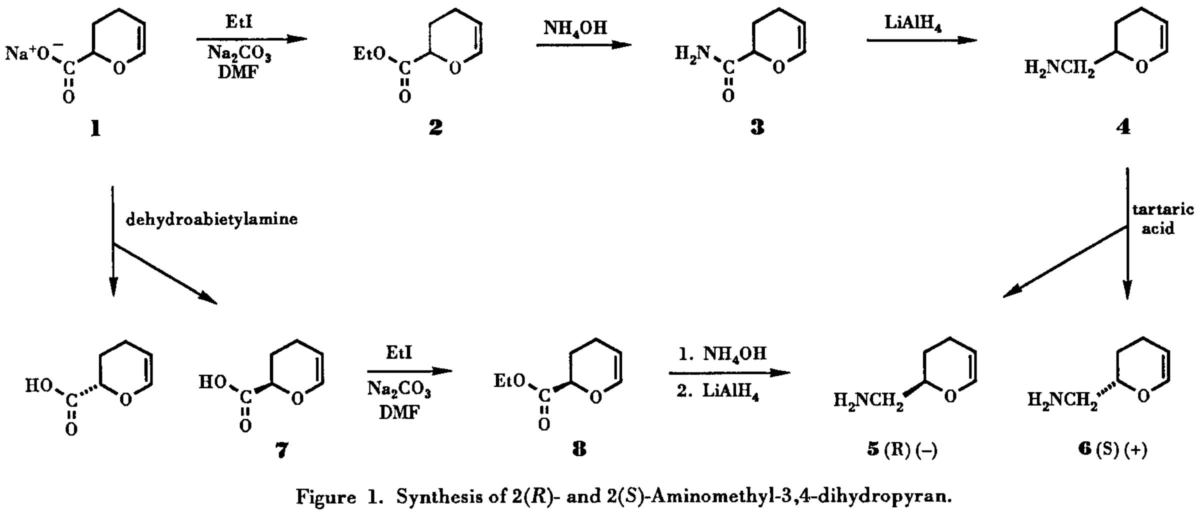

Figure 1. Synthesis of 2(*R*)- and 2(*S*)-Aminomethyl-3,4-dihydropyran.

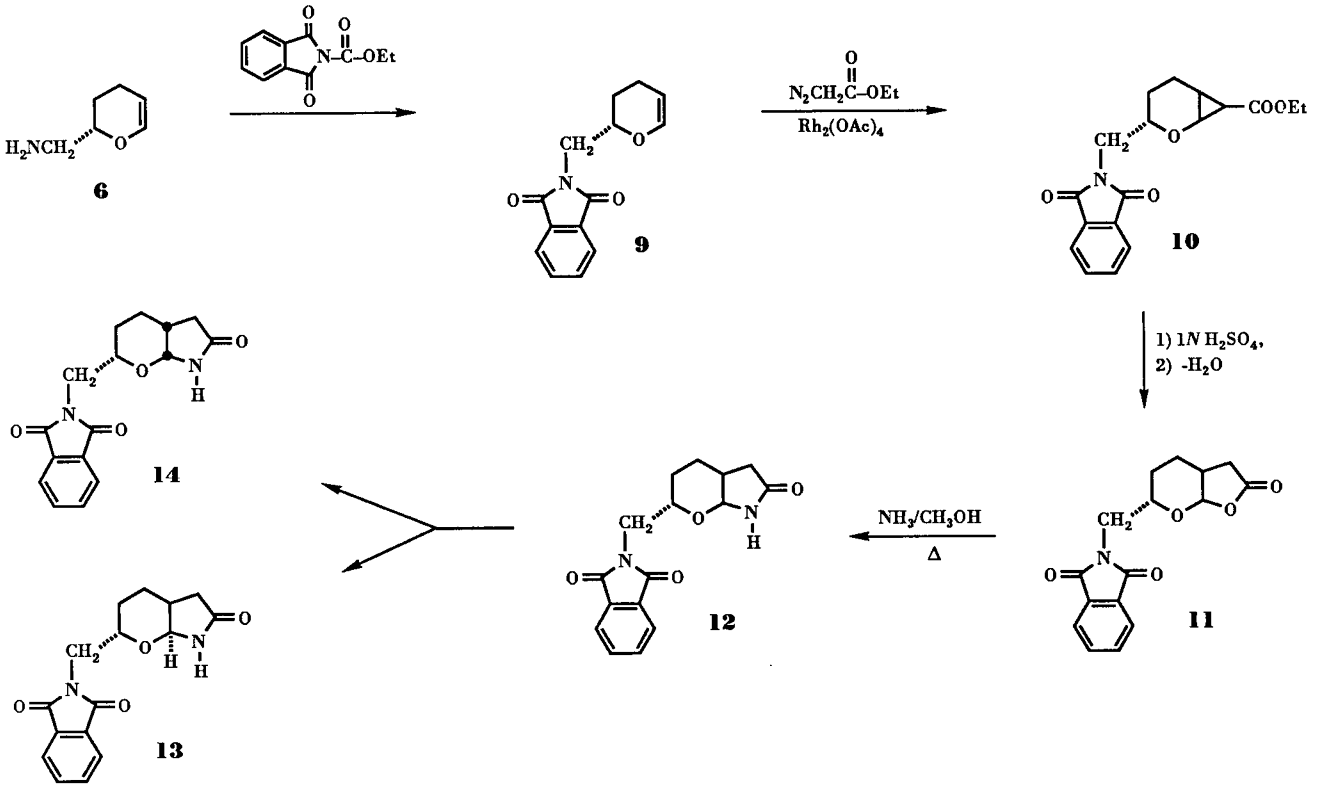

Figure 2. Synthesis of *syn*- and *anti*-2(*S*)-Phthalimidomethyl-2,3,4,4a,7,7a-hexahydro-6-oxo-5*H*-pyrano[2,3-*b*]pyrroles.

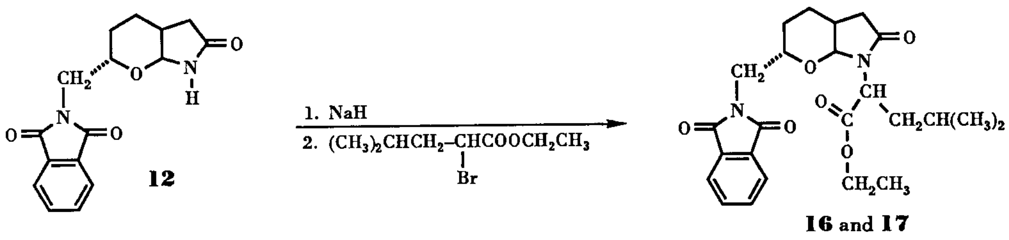

Figure 3. *N*-Alkylation of the lactam to complete the rigid β-bend analog.

2*H*-pyranyl-2-carboxylate (**1**) was esterified by the method of Hashimoto and Sumitomo [10]. The ester **2** was subsequently converted to the amide **3** in 62% yield from **1** and reduced to the corresponding amine **4** with lithium aluminum hydride [11]. The amine was resolved by fractional crystallization of the (+)-tartrate salt to provide the 2(*S*) isomer **6** in 39% yield. The amine was then converted to the phthalimido derivative **9** by the method of McArthur [12] in 73% yield. The (2)*R*-carboxylate **7** was prepared according to Hashimoto and Sumitomo [10] by fractional crystallization of the dehydroabiethylammonium salt, and then **7** was converted into the amine **5** and the corresponding phthalimido derivative by the route described above. The amine **6** and phthalimido derivative **9** were both dextrorotatory, while the amine **5** and phthalimido derivative were both levorotatory, establishing the 2(*S*) configuration for **6**.

The protected (2)*S*-amine **9** was then treated with ethyl diazoacetate in the presence of rhodium tetraacetate according to the method of Hubert [13,14] to provide the cyclopropane ester **10**. Acid hydrolysis of **10** followed by azeotropic removal of water was accomplished by an adaptation of the method of Canonica *et al.* [15] to provide **11** in 28% yield from **9**. Lactone **11** was subsequently converted to the corresponding lactam **12** with methanolic ammonia in 26% (Figure 1).

The separation of the *syn*- and *anti*-isomers of **12** was accomplished by hplc on a methyl phenyl derivatized silica gel column that functioned as a preparative reverse-phase partition column. The faster eluting isomer was assigned as the *anti*-isomer **13** and the slower eluting isomer was assigned as the *syn*-isomer **14** based on the nmr spectra. Lactam **12** was also alkylated with ethyl 2-bromo-4-methylpentanoate and the *syn*- (17% yield) and *anti*- (12% yield) isomers of the alkylated product were also separated by preparative hplc. The resolution of amine **4** into the *R* and *S* isomers made possible the separation of **13** and **14** and **16** and **17** as diastereomeric pairs.

The 0.5 δ anisotropic shift of the 7a proton by the C-C bond of the pyran ring of the *syn*-isomer **14** provided a convenient means of establishing the identity of the respective isomers. The structure of all compounds was confirmed by ir, nmr, mass spectra and elemental analyses.

EXPERIMENTAL

Sodium 3,4-dihydro-2*H*-pyran-2-carboxylate, ethyl iodide, lithium aluminum hydride, dehydroabietylamine, rhodium(II) tetraacetate, ethyl 2-bromo-4-methylpentanoate, dichloromethylphenylsilane, hexamethyldisilazane, and trimethylsilyl chloride were purchased from Aldrich Chemical Company. All solvents and other reagents used were either of hplc or of analytical reagent grade and were used without further purification. All melting points reported were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined using a Perkin-Elmer model 241 polarimeter with a cell having a path length of 1.0001 dm. A Varian T-60A NMR spectrometer equipped with a TT 7 fourier transform accessory was used for the 60 MHz nmr spectra that are reported. A Nicolet MX-1 FT IR was used for obtaining the infrared spectra. Mass spectra were obtained from a Hitachi Perkin-Elmer RMU-6D spectrometer. High-performance liquid chromatography (hplc) was performed on a system that consisted of a Waters M-6000A pump, a Waters 440 absorbance detector, a Rheodyne 7125 injector and a Sargent-Welch SRG chart recorder. Elemental analyses were performed by Microtech Laboratories, Inc., Skokie, Illinois.

3,4-Dihydro-2*H*-pyran-2-carboxamide (**3**).

A mixture containing sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (**1**) (150.1 g, 1.00 mole), anhydrous sodium carbonate (17.2 g, 0.16 mole), ethyl iodide (123 ml, 239.8 g, 1.54 moles), a trace amount of hydroquinone, and dimethylformamide (495 ml) was heated with stirring for 4.5 hours on a steam bath. Upon cooling to room temperature, benzene (950 ml) and water (430 ml) were added. After mixing and allowing the layers to separate, the aqueous layer was discarded, and the organic layer was washed with water (3 x 430 ml), dried (sodium sulfate) and evaporated. Ester **2** was stirred on a steam bath with concentrated ammonium hydroxide (600 ml) until the mixture became homogenous (approximately 45 minutes). The solution was allowed to cool to room temperature and then refrigerated. Crystalline **3** was collected by filtration and washed with small amounts of ice water, air dried and then further dried over phosphorous pentoxide in a vacuum dessicator, yield 79.3 g (62%), mp 95-96°; ^{1}H nmr (deuteriochloroform): δ 1.63-2.60 (m, 4H $[-CH_2-CH_2-]$), 4.25-4.59 (m, 1H $[H_2NCOCH=]$), 4.72-5.01 (m, 1H $[-CH_2CH=CH-]$), 5.38-6.24 (broad s, 2H $[H_2N-]$), 6.38 (d of t, J = 5.9 Hz, 1H $[-CH=CHO-]$); ir (chloroform): ν 3290, 3210 (N-H), 1677 (C=O, C=C overlap), 1434 (C-N), 1224, 1052 (C-O-C) cm^{-1}.

Anal. Calcd. for $C_6H_9NO_2$ (127.1): C, 56.68; H, 7.14; N, 11.02. Found: C, 56.52; H, 7.09; N, 10.89.

(+)-(2*S*)-3,4-Dihydro-2*H*-pyran-2-methanamine Tartrate (**6**).

To an ice-bath cooled slurry of lithium aluminum hydride (25.0 g, 197 mmoles) in anhydrous ether (500 ml) was added **3** (25.0 g, 197 mmoles) in portions. The flask was fitted with a condenser and drying tube and stirred at room temperature overnight. The mixture was again cooled with an ice-bath and water (25 ml), then 15% sodium hydroxide (25 ml), and water again (75 ml), were carefully added. The mixture was allowed to stand at room temperature for 1 hour and then filtered. The white precipitate was washed with ether (300 ml), and the combined ether filtrates were dried (sodium sulfate) and evaporated *in vacuo* leaving the amine **4** as a colorless liquid. This amine in methanol (25 ml) was carefully added to a boiling solution of (+)-tartaric acid (29.6 g, 197 mmoles) in methanol (150 ml), and the solution was allowed to crystallize overnight at 0°. The partially resolved amine tartrate salt which crystallized was collected by filtration, air-dried, and repeatedly recrystallized from methanol until a constant optical rotation was obtained for the salt, approximately eight recrystallizations, yield 10.0 g (39%), mp 115-118°; $[\alpha]_D^{24}$ + 59.1 (c 1.00, water); ^{1}H nmr (deuteriomethanol): δ 1.23-2.28 (m, 4H $[-CH_2-CH_2-]$), 3.82-4.57 (m, 3H $[H_2NCH_2CHO-]$), 4.70-5.00 (m, 1H $[-CH=CHO-]$), 6.39 (d of t, $J_{5,6}$ = 6.1 Hz, $J_{4,6}$ = 0.9 Hz, 1H $[-CH=CHO-]$).

Anal. Calcd. for $C_{10}H_{17}NO_7 \cdot 0.5H_2O$ (272.2): C, 44.12; H, 6.66; N, 5.14. Found: C, 43.77; H, 6.61; N, 5.01.

(+)-(2*S*)-2-Phthalimidomethyl)-3,4-dihydro-2*H*-pyran (**9**).

The amine tartrate **6** (107.0 g, 407 mmoles) was added to 4 *N* sodium hydroxide (310 ml) and extracted with ether (3 x 100 ml). The ether extract was dried (sodium sulfate) and evaporated *in vacuo*. The resulting amine ($[\alpha]_D^{24}$ +74.8 (c 1.09, chloroform)) was dissolved in tetrahydrofuran (450 ml). *N*-Carboethoxyphthalimide (89.60 g, 409 mmoles) (prepared by the method of Worster *et al.* [9]) was added to the solution with stirring, and the mixture was refluxed overnight and then evaporated *in vacuo*. The residue was taken up into benzene (660 ml) and water (180 ml). The layers were separated and the organic layer was washed with water (180 ml), 5% sodium hydroxide (180 ml), water (2 x 180 ml), and brine (180 ml). The organic layer was dried (sodium sulfate) and evaporated *in vacuo* leaving **9** (97.0 g) as a white solid which was recrystallized from ether-petroleum ether (1:1), yield 72.64 g (73%), mp 87-88°; $[\alpha]_D^{26}$ +42.1 (c 1.00, chloroform); ^{1}H nmr (deuteriochloroform): δ 1.49-2.20 (m, 4H $[-CH_2CH_2-]$), 3.51-4.32 (m, 3H $[PhtCH_2CH-]$), 4.52-4.80 (m, 1H $[-CH=CHO-]$), 6.30 (d of t, $J_{5,6}$ = 6.1 Hz, 1H $[-CH=CHO-]$), 7.54-8.05 (m, 4H $[ArH]$); ir (chloroform): ν 1773, 1713 (C=O), 1651 (C=C), 1425, 1393 (C-N), 1240, 1070 (C-O-C) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.3): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.18; H, 5.36; N, 5.66.

(+)-(2*R*)-Ethyl-3,4-dihydro-2*H*-pyranyl-2-carboxylate (**8**).

According to the method of Hashimoto and Sumitomo [10] sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (51.14 g, 0.342 moles) was added to 6 *N* hydrochloric acid (60 ml) and the resultant mixture was extracted with ether (300 ml, then 2 x 100 ml). The combined ether extracts were added to an ice-cooled solution of dehydroabietylamine (96.76 g, 0.339 mole) in ether (500 ml). Upon standing at room temperature, a copious white precipitate, dehydroabietylammonium 3,4-dihydro-2*H*-pyran-2-carboxylate, was obtained which was then recrystallized three times from methanol, yield 17.32 g (24%), mp 175-177°; $[\alpha]_D^{24}$ +14.8 (c 1.00, ethanol) (lit [10] mp 173-176°); $[\alpha]_D^{23}$ + 11.9 (c 1.0, ethanol). The resulting salt (17.22 g, 41.8 mmoles) was stirred in ether (10 ml) and 1.4 *M* sodium hydroxide (30 ml) until all of the solids were dissolved. The ether layer was removed and the aqueous layer was washed with ether (2 x 15 ml). The aqueous layer was evaporated *in vacuo* leaving the resolved sodium salt, which was dried in a desiccator over phosphorous pentoxide. This salt was converted to the ester according to the procedure for **3**. Crude **8** was distilled, bp 80-83°/3 mm Hg, yield 5.86 g (90%), $[\alpha]_D^{25}$ -64.3 (c 1.04, ethanol) (lit [10] $[\alpha]_D^{25}$ -68.9 (c 1.0, ethanol).

(-)-(2*R*)-2-(Phthalimidomethyl)-3,4-dihydro-2*H*-pyran (**15**).

The ester **8** (2.74 g, 17.5 mmoles) was converted to the amide by the procedure used for **6**, yield 0.87 g (39%) mp 95-96°; $[\alpha]_D^{26}$ + 21.4 (c 1.00, ethanol) (lit [10] mp 94-95°; $[\alpha]_D^{25}$ +20.8 (c 1.0, ethanol). The amide (0.82 g, 6.4 mmoles) was converted to amine **5** by the method used for **6**, yield 0.69 g (95%); $[\alpha]_D^{26}$ -53.3 (c 1.04, chloroform). The resulting amine **5** (0.90 g, 8.0 mmoles) was then converted to the phthalimide by the procedure used for **9**, yield 0.20 g (10%), mp 87-89°; $[\alpha]_D^{24}$ -29.4 (c 1.00, chloroform); ^{1}H nmr (deuteriochloroform): δ 1.32-2.35 (m, 4H [-CH_2CH_2-]), 3.60-4.53 (m, 3H [PhtCH_2CHO-]), 4.53-4.94 (m, 1H (-CH=CHO-]), 6.30 (d, J = 6.4 Hz, 1H [-CH=CHO-]), 7.50-8.00 (m, 4H [ArH]).

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.3): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.73; H, 5.22; N, 5.76.

(6*S*)-2-Oxo-6-(phthalimidomethyl)-3a,5,6,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran (**11**).

A solution of **9** (64.55 g, 266 mmoles), rhodium(II) tetraacetate [13,14] (1.53 g, 3.46 mmoles), and anhydrous ether (275 ml) was stirred at room temperature for 20 minutes. Ethyl diazoacetate (39.93 g, 350 mmoles) in ether (80 ml) was added dropwise over 18 hours. The reaction mixture was then passed through a 60 mm diameter x 60 mm alumina column followed by ether (500 ml). The combined ether eluant was evaporated leaving a golden oil. This oil was triturated with petroleum ether (5 x 50 ml). The remaining oil was crude **10**. The combined petroleum ether fractions were evaporated and the yellow liquid residue was placed on a 60 mm diameter x 60 mm alumina column and eluted with petroleum ether-ethyl acetate (9:1) (400 ml) followed by ethyl acetate (300 ml). The first 350 ml of eluant contained primarily the by products of the reaction, diethyl maleate and diethyl fumarate and was discarded. The next 150 ml fraction was collected and evaporated *in vacuo* leaving additional **10**. The combined fractions of cyclopropane ester **10** were dissolved in dioxane (150 ml) and 1 *N* sulfuric acid (100 ml). This solution was mechanically stirred and refluxed for three days. Powdered barium hydroxide dihydrate (9.47 g, 50.0 mmoles) was added to the solution which was stirred for another hour. The mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. The brown residue was azeotroped with benzene (400 ml) for two days. After evaporation *in vacuo*, the dark brown residue was eluted through a 90 mm diameter x 90 mm silica gel column with chloroform. The eluant was evaporated *in vacuo* leaving 80.10 g of an orange oil. This oil was dissolved in methanol (80 ml) and was allowed to stand at room temperature. Lactone **11** crystallized and was collected by filtration, washed with methanol and dried, yield 21.94 g (28%), mp 186-189°; $[\alpha]_D^{26}$ +8.3 (c 1.00, chloroform); ^{1}H nmr (deuteriochloroform): δ 1.02-2.78 (m, 7H [=CHCH_2CH_2CHCH_2CO-]), 3.41-4.60 (m, 3H [PhtCH_2CHO-]), 5.77 (d, J = 3.6 Hz, 1H [-OCHO-]), 7.62-8.03 (m, 4H [ArH]); ir (chloroform): ν 1775, 1717 (C=O), 1159 (C-CO-O) cm^{-1}; ms: (150°, 70 eV) (m/z) M$^+$ 301 (6), 242 (11), 161 (42), 160 (59), 148 (10), 141 (57), 130 (11), 110 (11), 104 (18), 97 (47), 95 (14), 77 (19), 76 (20), 73 (17), 67 (15).

Anal. Calcd. for $C_{16}H_{15}NO_5$ (301.3): C, 63.78; H, 5.02; N, 4.65. Found: C, 63.62; H, 5.18; N, 4.57.

(2*S*)-5*H*-2,3,4,4a,7,7a-Hexahydro-6-oxo-2-(phthalimidomethyl)-pyrano[2,3-*b*]pyrrole (**12**).

Lactone **11** (20.0 g, 66.0 mmoles) was placed in a pressure vessel with methanolic ammonia (saturated at 0°) (600 ml). The mixture was stirred at room temperature for 1 hour, then placed in an oil bath at 110° overnight. Upon cooling, the vessel was opened and the methanolic ammonia evaporated *in vacuo*. The residue was eluted on a 60 mm diameter x 50 mm silica gel column with chloroform (200 ml) followed by chloroform-acetone (1:1) (1000 ml). The eluant was evaporated *in vacuo* and the residue dissolved in chloroform-acetone (4 ml). Ether (100 ml) was added to the mixture and after three days 2.45 g of **12** was deposited as crystals. The careful addition of petroleum ether to the filtrate gave an additional 3.10 g of **12**, yield 5.65 g (26%), mp 229-232°; $[\alpha]_D^{24}$ +35.8 (c 1.00, chloroform); ^{1}H nmr (deuteriochloroform): δ 0.95-3.00 (m, 7H [-CH_2CH_2CHCH_2CO-]), 3.12-4.69 (m, 3H [PhtCH_2CH-]), 4.90 (d, $w_{1/2}$ = 7 Hz, 0.5H [-OCHN=]), 5.40 (d, J = 4.7 Hz, 0.5H [-OCHN=]), 7.04 (broad, 1H NH), 7.68-8.11 (m, 4H [ArH]); ms: (160°, 70 eV) (m/z) 300 (2), 244 (4), 187 (3), 186 (3), 160 (20), 141 (18), 140 (100), 104 (13), 97 (25), 96 (93), 83 (18), 77 (12), 76 (16), 69 (13).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$ (300.3): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.72; H, 5.36; N, 9.43.

7-(1-Carboethoxy-3-methylbutyl)-(2*S*)-5*H*-2,3,4,4a,7,7a-hexahydro-6-oxo-2-(phthalimidomethyl)pyrano[2,3-*b*]pyrrole (**16** and **17**).

The protected lactam **12** (1.60 g, 5.33 mmoles) and sodium hydride (264 mg, 11 mmoles) were refluxed together in dry toluene (30 ml) for 2 hours. Ethyl 2-bromo-4-methylpentanoate (2.45 g, 11 mmoles) was then added and the mixture refluxed overnight, filtered and the filtrate evaporated to dryness *in vacuo*. The residue was passed through a short column of silica gel (45 mm diameter x 30 mm) which was eluted with chloroform. Evaporation of the yellow eluate provided the diasteromeric mixture of products. Preparative separation of these diastereomers was accomplished by high-performance liquid chromatography. The mobile phase was 40% acetonitrile in water on a 3/8" diameter x 3' methylphenyl reverse-phase column. Three major fractions were obtained. Fraction 1, **17**, was obtained as a colorless oil, yield 292 mg (12%), $[\alpha]_D^{27}$ + 16.5 (c 0.98, chloroform) determined by nmr to be a diastereomeric mixture at the carbon attached to N-7 of the *anti*-isomer; ^{1}H nmr (deuteriochloroform): δ 1.20 (d, J = 6.9 Hz, 6H [-CH(CH_3)$_2$]), 1.27 (t, J = 7.0 Hz, 3H [-OCH$_2$CH_3]), 0.60-2.76 (m, 10H [-CH_2CH(CH$_3$)$_2$ and -CH_2CH_2-CH-CH_2CO-]), 4.16 (q, J = 4.2 Hz, 2H [-OCH_2CH$_3$]), 3.38-4.40 (m, 4H (Pht-CH_2CHO- and =N-CHCO-]), 5.28 and 5.33 (d, J = 5.6 and 5.1 Hz, 1H [-OCH-N=]), 7.69-7.91 (m, 4H [ArH]); ms: (m/z) M$^+$ 442.

Anal. Calcd. for $C_{24}H_{30}N_2O_6 \cdot 0.75H_2O$ (442.5+13.5): C, 63.21; H, 6.96; N, 6.14. Found: C, 63.10; H, 7.04; N, 5.42 [16].

Fraction 2, **16**, was also obtained as a colorless oil, yield 269 mg (11%), $[\alpha]_D^{27}$ -37.5 (c 1.11, chloroform) determined by nmr to be a diasteromeric mixture at the carbon attached to N-7 of the *syn*-isomer; ^{1}H nmr (deuteriochloroform): δ 1.20 (d, J = 7.2 Hz, 6H $[-CH(C\mathit{H}_3)_2]$), 1.24 (t, J = 6.9 Hz, 3H $[-OCH_2C\mathit{H}_3]$), 0.74-2.68 (m, 10H $[-C\mathit{H}_2C\mathit{H}(CH_3)_2$ and $-C\mathit{H}_2C\mathit{H}_2C\mathit{H}-C\mathit{H}_2CO-]$), 3.46-3.95 (m, 3H $[Pht-C\mathit{H}_2C\mathit{H}O-]$), 4.09 and 4.12 (q, J = 7.1 and 7.1 Hz, 2H $[-OC\mathit{H}_2CH_3]$), 4.46 and 4.78 (t, J = 7.8 and 7.4 Hz, 1H $[=NC\mathit{H}-CO-]$), 4.89 and 5.15 (d, J = 3.8 and 3.5 Hz, 1H $[-OC\mathit{H}N=]$), 7.68 and 7.90 (m, 4H $[Ar\mathit{H}]$); ms: (m/z) M^+ 442.

Anal. Calcd. for $C_{24}H_{30}N_2O_6 \cdot H_2O$ (442.5 + 18): C, 62.59; H, 7.00; N, 6.08. Found: C, 62.14; H, 7.28; N, 4.70 [16].

Fraction 3, **16**, was obtained as a white crystalline solid, yield 134 mg (6%) after recrystallization from ethanol, mp 120-121°; $[\alpha]_D^{27}$ -24.1 (c 1.06, chloroform) determined by nmr to be a single diastereomer at the carbon attached to N-7 (but not established as *R* or *S*) of the *syn*-isomer; ^{1}H nmr (deuteriochloroform): δ 0.41-2.90 (m, 19H $[-C\mathit{H}_2C\mathit{H}-(C\mathit{H}_3)_2$, $-C\mathit{H}_2C\mathit{H}_2C\mathit{H}C\mathit{H}_2CO-$ and $-OCH_2C\mathit{H}_3]$), 3.27-5.00 (m, 6H $[Pht-C\mathit{H}_2C\mathit{H}-$, $-C\mathit{H}_2CH_3$, and $=NC\mathit{H}CO-]$), 5.15 (d, J = 3.9 Hz, 1H $[-OC\mathit{H}N=]$), 7.68-7.90 (m, 4H $[Ar\mathit{H}]$); ms: (m/z) M^+ 442.

Anal. Calcd. for $C_{24}H_{30}N_2O_6$ (442.5): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.84; N, 6.27.

Methylphenyl Reverse-phase Column Preparation.

Kieselgel 60 (240-400 mesh) (40 g) was refluxed with stirring in 2 *N* hydrochloric acid (300 ml) for 2 hours. Upon cooling, the liquid was decanted and the silica gel was washed with water (5 x 300 ml) until the washings were neutral to *p*H paper. The silica gel was suspended in methanol (200 ml), collected by filtration, washed with methanol (3 x 100 ml), and dried in an oven at 76° overnight. The washed silica gel was mechanically stirred in freshly distilled xylene (200 ml) (bp 137.5-139°). The mixture was flushed with argon then brought to reflux. Dichloromethylphenylsilane (13.0 ml, 15.3 g) was added dropwise over 25 minutes, after which the mixture was refluxed for another 3 hours [17]. Upon cooling, the xylene was decanted off and the silica gel was washed with methylene chloride (300 ml) and collected by filtration. The gel was washed with methylene chloride (3 x 150 ml) and absolute methanol (2 x 150 ml) and dried overnight in an oven at 78°. To a stirred slurry of the above gel (35.9 g) in pyridine (160 ml) was added hexamethyldisilazane (32 ml) and trimethylsilyl chloride (16 ml) [18]. This mixture was stirred at 70° for 3 hours, then at 100° for another 2 hours. Upon cooling, the mixture was filtered, the gel was washed with methylene chloride (300 ml), water (400 ml), and methanol (300 ml), then dried in a vacuum dessicator: yield 38.8 g of dried methylphenyl reverse-phase silica gel. A 3/8" O.D. x 3' stainless steel column was dry packed using vibration with this reverse-phase gel (26.5 g). Column void volume after packing = 16.2 ml.

Separation of *Syn*- and *Anti*-Isomers, **14** and **13**.

The reverse-phase column prepared as described above was utilized to preparatively separate the *syn*-, **14**, and *anti*-, **13**, isomers of **12**. This was accomplished with a mobile phase of 25% acetonitrile in water at a flow rate of 4.0 ml/min. The sample load of 0.4-0.5 g was introduced with a 2.0 ml injection loop. Fractions were collected according to the peaks observed with the uv detector. The faster eluting isomer was determined to be the *anti*-isomer, **13**, and the slower eluting isomer was determined to be the *syn*-isomer, **14**. These assignments were based on the 0.5 δ upfield shift of the 7a H for the *syn*-isomer due to the anisotropic effect of the C-C bond in the pyran ring on the 7a H. All of the other signals were quite similar for each of the isomers.

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