for $C_{20}H_{18}N_2O_3$ 334.1317, found 334.1317. Anal. Calcd for $C_{20}H_{18}N_2O_3 \cdot H_2SO_4 \cdot {}^1/_2H_2O$: C, 54.42; H, 4.79; N, 6.35. Found: C, 54.68; H, 4.38; N, 6.17.

Ethyl 6-Chlorobenzo[*c*]phenanthridine-12-carboxylate (18a). A mixture of **10d** (50 mg, 0.122 mmol) and $POCl_3$ (1 mL) was stirred for 3 h at 60 °C, cooled to 0 °C, diluted with ice/water (5 mL), treated with NH_4OH, and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was washed with H_2O (1 × 15 mL) and dried (Na_2SO_4). Evaporation in vacuo afforded imine **18a** (40 mg, 97% yield): mp 145–146 °C (hexane); ^1H NMR δ 9.43–9.39 (m, 1 H, ArH), 9.22 (s, 1 H, H_{11}), 8.99–8.95 (m, 1 H, ArH), 8.75 (d, J = 8.3 Hz, 1 H, ArH), 8.59 (d, J = 8.3 Hz, 1 H, ArH), 8.04–7.97 (m, 1 H, ArH), 7.87–7.79 (m, 3 H, ArH), 4.61 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.58 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 167.50, 152.86, 142.68, 135.00, 132.13, 131.62, 130.90, 128.89, 128.51, 127.92, 127.75, 127.47, 125.85, 125.59, 125.34, 124.52, 122.72, 119.48, 61.55, 14.44; IR (film) 1720, 1605 (mild) cm^{-1}; UV (EtOH) λ_{max} 226, 268, 332, 336, 352, 370 nm; LRMS m/z 335 (100), 307 (17), 290 (60), 227 (53); HRMS calcd for $C_{20}H_{14}NO_2Cl$ 335.0713, found 335.0711. Anal. Calcd for $C_{20}H_{14}NO_2Cl$: C, 71.54; H, 4.20; N, 4.17. Found: C, 71.18; H, 4.09; N, 4.23.

Ethyl Benzo[*c*]phenanthridine-12-carboxylate (18b). To a solution of **18a** (35 mg, 0.104 mmol) in 1:1 benzene/ethanol (4 mL) was added 10% Pd/C (4 mg) and NaOAc (10 mg, 0.122 mmol). Air was removed from the reaction flask and replaced with hydrogen using a balloon, and the mixture was stirred for 3 h at rt and then filtered over Celite. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (1 × 15 mL). The organic phase was dried over Na_2SO_4, concentrated, and chromatographed on a silica gel column (4:1 CH_2Cl_2/hexane) to afford **18b** (25 mg, 80% yield) as a white solid: mp 95–97° C; ^1H NMR δ 9.52 (s, 1 H, ArH), 9.51–9.48 (m, 1 H, ArH), 9.25 (s, 1 H, ArH), 8.99–8.95 (m, 1 H, ArH), 8.72 (d, J = 8.2 Hz, 1 H, ArH), 8.17–8.14 (m, 1 H, ArH), 7.97–7.90 (m, 1 H, ArH), 7.84–7.73 (m, 3 H, ArH), 4.60 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.56 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 167.69, 154.09, 143.52, 133.02, 132.53, 131.44, 130.64, 128.92, 128.43, 127.62, 127.33, 127.20, 127.02, 125.84, 125.17, 124.95, 122.19, 119.40, 61.42, 14.42; IR (film) 2920, 1715, 1620 cm^{-1}; UV (EtOH) λ_{max} 224, 268, 334, 368 nm; LRMS m/z 301 (100), 273 (22), 256 (55), 228 (42), 201 (39); HRMS calcd for $C_{20}H_{15}NO_2$ 301.1108, found 301.1077. Anal. Calcd for $C_{20}H_{15}NO_2 \cdot {}^1/_3H_2O$: C, 78.16; H, 5.14; N, 4.56. Found: C, 78.54; H, 4.88; N, 4.59.

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Registry No. 2b, 6872-57-7; **3a**, 143370-25-6; **3b**, 548-31-2; **5a**, 462-80-6; **5b**, 70429-31-1; **6c**, 38973-42-1; **6d**, 21640-31-3; **7b**, 78363-90-3; **7c**, 128637-93-4; **7d**, 143370-33-6; **8a**, 143370-26-7; **8b**, 143370-34-7; **9a**, 78379-92-7; **9b**, 143370-35-8; **9c**, 128637-90-1; **9d**, 143370-36-9; **10a**, 128637-89-8; **10b**, 128637-92-3; **10c**, 143370-38-1; **10d**, 143370-42-7; **10e**, 143370-39-2; **10f**, 143370-40-5; **11**, 143370-27-8; **12**, 143370-28-9; **13**, 143370-30-3; **14a**, 118-92-3; **14b**, 20332-16-5; **15a**, 1608-42-0; **15b**, 143370-43-8; **16**, 143370-31-4; **17a**, 128637-91-2; **17b**, 143370-37-0; **18a**, 143370-32-5; **18b**, 143370-41-6; $Me_2NCH{=}C(NHCOPh)COOMe$, 56952-04-6; $NCCH_2CO_2Et$, 105-56-6.

Synthesis of Genotoxic Heterocyclic Amines Trp-P-1 and Trp-P-2

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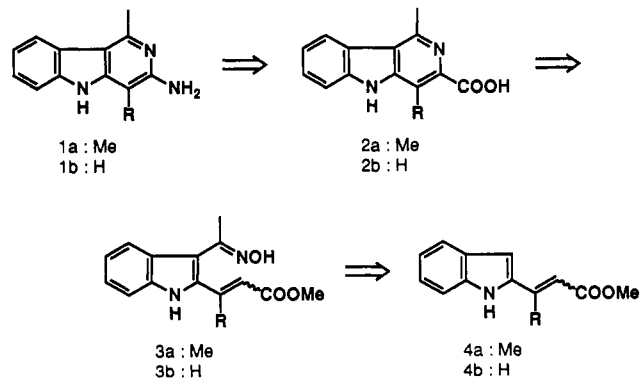
Trp-P-1 (**1a**) and Trp-P-2 (**1b**) possessing a pyrido[4,3-*b*]indole system have been newly synthesized. The key reaction step in the synthetic sequence has been the thermal electrocyclic reaction of the 1-azahexa-1,3,5-triene system **3** involving the indole [*b*] bond derived from 2-vinylindoles **4**. 2-Vinylindole **4a** has been derived from *N*-(benzenesulfonyl)indole (**5**) in a four-step sequence. 2-Vinylindole **4b** has been synthesized by two routes using either ethoxymethylidene Meldrum's acid (**6b**) or diethyl ethoxymethylidenemalonate (**10**) as Michael acceptors to the 2-lithio-*N*-(benzenesulfonyl)indole.

A variety of genotoxic heterocyclic amines are known to be formed when amino acids are pyrolyzed or protein-containing foods are cooked at high temperature.[1-4] Among these amines, Trp-P-1 (**1a**) and Trp-P-2 (**1b**) were isolated from tryptophan pyrolysate,[5] whose structures were determined by X-ray analysis and spectroscopic evidence as 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (**1a**) and 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (**1b**).[6] Synthetic routes to Trp-P-2 (**1b**) have been reported simultaneously by the Takeda[7] and Akimoto[8] groups, the latter of whom have also completed a synthesis of Trp-P-1 (**1a**).[8]

Scheme I



We are currently interested in the synthesis of condensed heterocyclic compounds, especially fused pyridine

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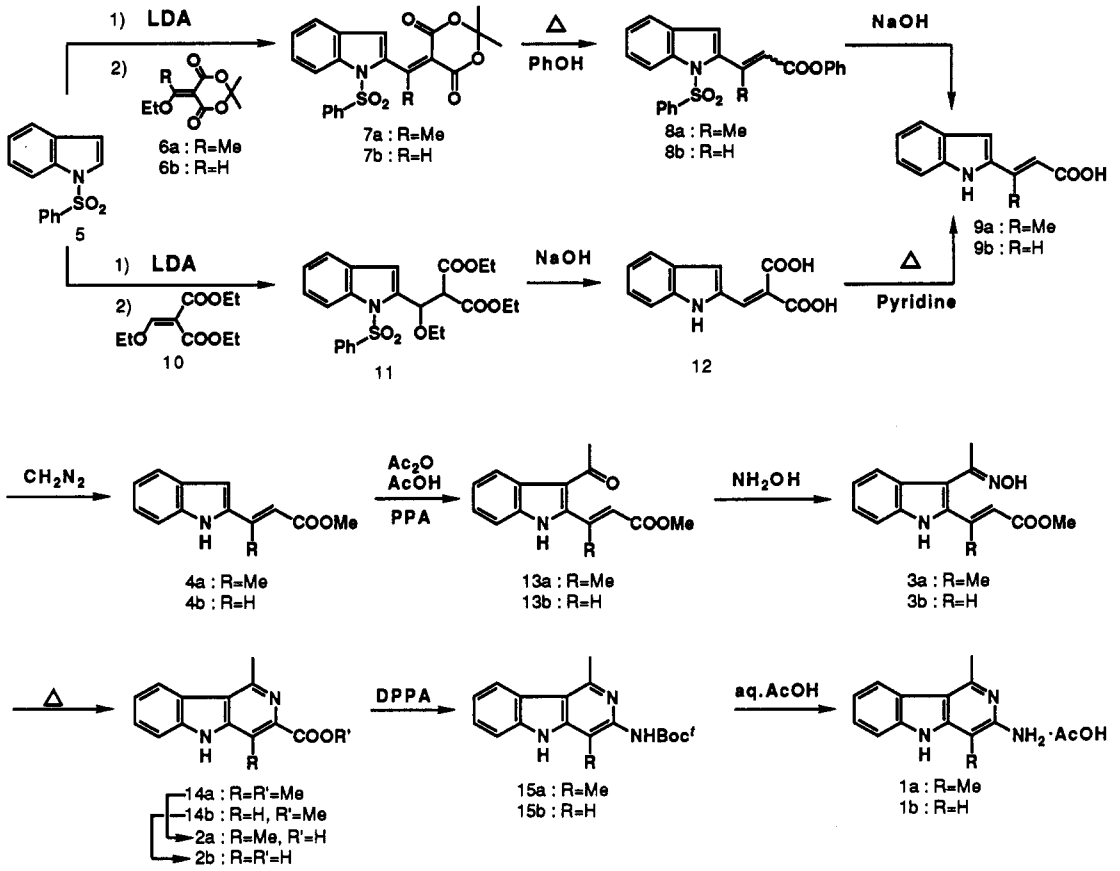
0022-3263/92/1957-5917$03.00/0

Scheme II



ring systems, by the thermal electrocyclic reaction of monoazahexa-1,3,5-triene systems including one double bond of the aromatic or heteroaromatic.[9] In 1984, we reported a new synthesis of pyrido[4,3-*b*]indoles by the electrocyclic reaction of the 1-azahexa-1,3,5-triene system involving the indole [*b*] bond.[9g] We now describe here the synthesis of Trp-P-1 (**1a**) and Trp-P-2 (**1b**) by an application of this methodology to the γ-carboline framework.

In our retrosynthetic analysis (Scheme I), we envisioned that the amino group at the C-3 position of **1** could be derived from a carboxylic acid at this position of the γ-carbolines **2** at first. Next, we felt that the 2-alkenyl-3-iminoindoles **3** might be derived from the cleavage of the 2,3-bond of γ-carbolines **2**. Therefore, the desired 1-azahexa-1,3,5-triene system involving the indole [*b*] bond would be prepared from methyl 3-(2-indolyl)-2-butenoate (**4a**) and methyl 3-(2-indolyl)propenoate (**4b**).

Thus, we initially required the 2-vinylindoles **4**. Although a preparation of methyl 3-(2-indolyl)propenoate (**4b**) from indole-2-carboxaldehyde by a Wittig reaction has been reported by Pindur and co-workers,[10] the application of this method to the other vinylindole **4a** was not explored. We therefore sought to develop a new route to 2-vinylindoles **4** using Meldrum's acid derivatives **2**[11] as Michael-type acceptors depicted in Scheme II. Namely, treatment of *N*-(benzenesulfonyl)indole (**5**)[12] with lithium diisopropylamide (LDA) followed by addition of ethoxyethylidene or ethoxymethylidene Meldrum's acid **6a** or **6b**[13] gave the desired Michael adducts **7a** and **7b** in 32% and 34% yields, respectively, with some unreacted starting material.[14] The thermal decomposition of the Meldrum's acid derivatives **7** in phenol[15] at reflux temperature afforded the α,β-unsaturated phenyl esters **8**, from which the *N*-benzenesulfonyl group were removed together with ester hydrolysis by alkaline medium to give α,β-unsaturated carboxylic acids **9** from **7** in good yields (**9a**, 98%, and **9b**, 97%).[16] Subsequent esterification of the acids **9** with diazomethane gave the α,β-unsaturated methyl esters (**4a**, 77%, and **4b**,[10] 86%).

On the other hand, another route to the methyl ester **4b** was tried. In this instance, treatment of **5** with LDA followed by addition of diethyl ethoxymethylidenemalonate (**10**) gave the adduct **11**, which eliminated ethanol during hydrolysis by sodium hydroxide to give the dicarboxylic acid **12**. Heating of **12** in pyridine at reflux afforded the α,β-unsaturated carboxylic acid **9b**, which also provided the methyl ester **4b** in 26.8% overall yield upon

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(14) The purity of ethoxyethylidene Meldrum's acid **6a** was not able to be determined because it was very sensitive to moisture and immediately changed to the known acetyl Meldrum's acid. cf. Sato, M.; Ogasawara, H.; Yoshizumi, E.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1902.

(15) These Meldrum's acid were not decomposed by low-boiling solvents such as methanol and ethanol.

(16) This procedure was done in order to introduce an appropriate substituent to the C-3 position of indoles at a later stage.

treatment with diazomethane.

The stereochemistries of the α,β-unsaturated esters **4** were determined by ^1H NMR spectra to possess the *E*-configuration. Although we initially assumed that a mixture of *E* and *Z* isomers was produced,[9a] we herein revise that assignment and report that **4a** is obtained exclusively in the *E*-configuration on the basis of ^1H–^1H decoupling experiments which displays a doublet (J = 1.02 Hz) due to the methyl protons at δ 2.64 and a doublet (J = 1.02 Hz) due to the vinyl proton at δ 6.16. The orientation of the compound **9a** was also assigned as the *E*-form by a similar allylic coupling (J = 1.00 Hz). Although the orientation of the esters **8** was not established, since they were directly hydrolyzed, it is suggested that it too exists as the *E*-form. The compound **4b** derived from either route was confirmed as the same compound by spectral data, which was easily assigned as trans (J = 18 Hz). Consequently, it is assumed that the conversion of **7** into **8** involves a nucleophilic addition of phenol to a methyleneketene carbonyl group produced by thermal decomposition of the Meldrum's acids **7** to give an enolate type ion, which goes back to a carbonyl group followed by trapping of a proton in a direction of thermodynamically stable *E*-form by a ketene double bond to provide *E*-compounds **8** and **9**.

At the next stage, the key compounds **3** were prepared as follows. The acylations to the C-3 position of the indole derivatives **4** were carried out by the method of Murakami and co-workers[17] to give the 2-alkenyl-3-acylindoles (**13a**, 94%, and **13b**, 86%). Although we examined the acylation protocol of Gribble,[18] we were unsuccessful in this case. Subsequent treatment of the ketones **13** with hydroxylamine then afforded the desired keto oximes (**3a**, 87%, and **3b**, 65%), thus constituting the desired 1-azahexa-1,3,5-triene system.

Finally, the electrocyclic reactions[9] of **3** were carried out by heating in xylene to provide (after loss of water) the expected γ-carbolines (**14a**, 55%, and **14b**, 51%). Hydrolysis of the ester functions gave the known γ-carboline carboxylic acids **2**[8b] quantitatively. The modified Curtius rearrangement by diphenylphosphoryl azide (DPPA)[19] of **2** in 2-methyl-2-propanol afforded *N*-*t*-Boc-Trp-P-1 (**15a**) and *N*-*t*-Boc-Trp-P-2 (**15b**) in 82 and 98% yields, respectively. Subsequent hydrolysis of **15** with aqueous acetic acid gave Trp-P-1 (**1a**) and Trp-P-2 (**1b**) as their acetates, whose structures were identical with authentic samples by direct comparison.

Thus, the new synthetic routes to Trp-P-1 (**1a**) and Trp-P-2 (**1b**) possessing the γ-carboline nucleus have been provided by using the thermal electrocyclic reaction of the 1-azahexa-1,3,5-triene system involving the indole [*b*] bond.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded by a Shimadzu IR-408 spectrophotometer. Proton nuclear magnetic resonance (^1H-NMR) spectra were taken with JEOL PMX 60Si and JEOL GX-400 instruments using tetramethylsilane as an internal standard. The measurement solvent used was $CDCl_3$ unless otherwise stated. Mass spectra were measured by Shimadzu GC-MS 6020 and 9020DF instruments at 70-eV chamber voltage on a direct inlet system. Silica gel (60–100 mesh, Merck Art 7734) or Iatrobeads (Iatron Chem. Prod.) were used for column chromatography.

5-(1-Ethoxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6a). A solution of Meldrum's acid (10 g, 69.4 mmol) and triethyl orthoacetate (20 mL, 9.2 mmol) in pyridine (10 mL) was heated at 80 °C for 20 min. The solution was cooled quickly to room temperature, and the solvent was removed under reduced pressure at temperatures below 45 °C. The residue was extracted with ligroin several times under heating at reflux, and the combined extracts were concentrated to give the title compound **6a** (4.8 g, 32%) as yellow crystals. This compound was immediately used for the next reaction because of its sensitivity to moisture. Further purification of this compound could not be achieved:[14] ^1H NMR δ 1.50 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.68 (6 H, s, $CH_3 \times 2$), 2.69 (3 H, s, CH_3), 4.37 (2 H, q, J = 7 Hz, OCH_2CH_3); mass spectrum m/z 214 (M^+).

5-[[2-[1-(Benzenesulfonyl)indolyl]]ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-diones (7a). A solution of *N*-(benzenesulfonyl)indole (**5**) (20 g, 77.7 mmol) in anhyd THF (100 mL) was added to the stirred solution of LDA [prepared from diisopropylamine (12 mL, 85.6 mmol) and BuLi (1.57 M hexane solution; 54 mL, 85.6 mmol)] with cooling (ice) under N_2 atmosphere. After being stirred for 30 min at the same temperature, a solution of the Meldrum's acid derivative **6a** (18.4 g, 86 mmol) in anhyd THF (100 mL) was added gradually and the stirring was continued for 1 h. The mixture was then quenched with an aqueous NH_4Cl solution and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 200 g) using 5–20% EtOAc/hexane as eluent to give the title compound **7a** [10.6 g, 32% (80% on the basis of recovered **5**)] as pale yellow crystals, mp 163–164.5 °C (benzene/hexane): IR (KBr) 1741 cm^{-1} (cyclic ester C=O); ^1H NMR δ 1.80 (6 H, s, $CH_3 \times 2$), 2.79 (3 H, s, CH_3), 6.67 (1 H, s, C_3-H), 7.08–7.84 (9 H, m, aromatic protons); mass spectrum m/z 425 (M^+). Anal. Calcd for $C_{22}H_{19}NO_6S$: C, 62.10; H, 4.50; N, 3.29. Found: C, 62.29; H, 4.71; N, 3.40.

5-[[2-[1-(Benzenesulfonyl)indolyl]]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (7b). The same procedure as above gave the title compound **7b** [34% (57% on the basis of recovered **5**)], mp 123–124 °C (benzene/hexane): IR (KBr) 1740 cm^{-1} (cyclic ester C=O); ^1H NMR δ 1.81 (6 H, s, $CH_3 \times 2$), 7.00–8.15 (9 H, m, aromatic protons), 8.21 (1 H, s, C_3-H), 9.04 (1 H, s, –CH=); mass spectrum m/z 411 (M^+). Anal. Calcd for $C_{21}H_{17}NO_6S$: C, 61.30; H, 4.17; N, 3.40. Found: C, 61.25; H, 3.92; N, 3.21.

3-(2-Indolyl)-2-butenoic Acid (9a). A mixture of the Meldrum's acid derivative **7a** (4.3 g, 10.1 mmol) in phenol (40 mL) was heated at 180 °C for 1.5 h. After the mixture was cooled to room temperature, benzene (100 mL) was added. The benzene layer was washed with 0.5 N NaOH solution (30 mL × 10 times) and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was refluxed for 12 h in aqueous 20% NaOH (50 mL) and EtOH (50 mL). After removal of solvent, the mixture was acidified with concd HCl. The resulting precipitate was filtered and recrystallized from Et_2O to give the carboxylic acid **9a** (2.0 g, 98%) as pale yellow needles, mp 182.5–185 °C: ^1H NMR (400 MHz) δ 2.57 (3 H, d, J = 1.0 Hz, CH_3), 3.33 (1 H, br s, COOH), 6.20 (1 H, d, J = 1.0 Hz, –CH=), 6.88 (1 H, s, indole C_3-H), 6.99–7.61 (4 H, m, aromatic protons), 9.85 (1 H, br s, NH); mass spectrum m/z 201 (M^+). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.52; H, 5.66; N, 6.92.

3-(2-Indolyl)-2-propenoic Acid (9b). The same procedure as above gave the carboxylic acid **9b** (97%), mp 181–183 °C (Et_2O): ^1H NMR δ 6.52 (1 H, d, J = 16.5 Hz, –CH=), 6.75–7.58 (5 H, m, aromatic protons), 7.62 (1 H, d, J = 16.5 Hz, –CH=); mass spectrum m/z 187 (M^+). Anal. Calcd for $C_{11}H_9NO$: C, 70.58; H, 4.87; N, 7.48. Found: C, 70.43; H, 4.98; N, 7.43.

The Reaction of *N*-(Benzenesulfonyl)indole (5) with Diethyl Ethoxymethylidenemalonate (10). A solution of *N*-(benzenesulfonyl)indole (**5**) in anhyd THF (100 mL) was added dropwise to an ice-cooled solution of LDA [prepared from diisopropylamine (12 mL, 85.6 mmol) and BuLi (1.6 M hexane solution, 52.5 mL, 85 mmol) in anhyd THF (50 mL)] under N_2 atmosphere. After the mixture was stirred for 30 min at the same temperature, a solution of diethyl malonate **10** (18.5 g, 85.5 mmol) in anhyd THF (100 mL) was added slowly. The stirring was continued for 14 h at 0 °C and the mixture allowed to warm to room temperature. After the addition of aqueous NH_4Cl solution,

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the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography with 1% EtOAc/hexane as eluent to give the starting material **5** (7.28 g). Increasing the solvent polarity to 10% EtOAc from 1% EtOAc/hexane gave the diester **11** [14.8 g, 40% (63% on the basis of recovered **5**)] as a viscous oil: ^1H NMR δ 0.86–1.44 (9 H, m, $CH_3 \times 3$), 3.42 (2 H, q, $J = 8$ Hz, OCH_2CH_3), 3.94–4.35 (5 H, m, $OCH_2- \times 2$, $CH(COOC_2H_5)_2$), 5.69 (1 H, d, $J = 6$ Hz, $-CHOC_2H_5$), 6.73 (1 H, indole C_3-H), 6.90–8.26 (9 H, m, aromatic protons); mass spectrum m/z 473 (M^+); exact mass calcd for $C_{24}H_{17}NO_7S$ 473.1507, found 473.1447.

3-(2-Indolyl)-2-propenoic Acid (9b) from 11. A stirred mixture of the diester **11** (14.35 g, 30.3 mmol) and 20% aqueous NaOH (150 mL) in EtOH (150 mL) was refluxed for 14 h. After the mixture was cooled, the solvent was removed under reduced pressure. The residue was acidified by concd HCl, and the resulting precipitates were filtered off to give the crude dicarboxylic acid **12**. A stirred mixture of the crude acid **12** (7 g, 30.3 mmol) in pyridine was heated at reflux for 12 h. After the removal of solvent, the residue was dissolved in 10% aqueous NaOH solution (200 mL). The aqueous solution was washed with EtOAc (100 mL × 2) and was acidified by concd HCl. The resulting precipitates were filtered off to give the carboxylic acid **9b** (3.4 g, 60%). This product was identical with authentic samples.

Methyl 3-(2-Indolyl)-2-butenoate (4a). A solution of diazomethane (1.5 g, 35.7 mmol) in Et_2O (100 mL) [prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonylamide (10.7 g, 50 mmol) and KOH (3 g, 53.5 mmol)] was added to an ice-cooled solution of **9a** (1.64 g, 8.15 mmol) in MeOH/$CHCl_3$ (5:95 v/v, 50 mL) under stirring. After 10 min, the solvent was removed. The residue was purified by column chromatography (silica gel, 30 g) using 5% EtOAc/hexane as an eluent to give the methyl ester **4a** (1.25 g, 77%), mp 134.5–135.5 °C (EtOAc/hexane) as pale yellow needles: ^1H NMR (400 MHz) δ 2.64 (3 H, d, $J = 1.02$ Hz, CH_3), 3.79 (3 H, s, OCH_3), 6.16 (1 H, d, $J = 1.02$ Hz, –CH=), 6.80–7.65 (5 H, m, aromatic protons), 8.25 (1 H, br s, NH); mass spectrum m/z 215 (M^+). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.51; H, 6.11; N, 6.54.

Methyl 3-(2-Indolyl)-2-propenoate (4b). Same procedure as above gave the methyl ester **4b** (86%), mp 191–193 °C (lit.[10] mp 194 °C): ^1H NMR δ 3.79 (3 H, s, OCH_3), 6.25 (1 H, d, $J =$ 16.5 Hz, –CH=), 6.83 (1 H, s, indole C_3-H), 7.07–7.64 (4 H, m, aromatic protons), 7.69 (1 H, d, $J = 16.5$ Hz, –CH=), 8.55 (1 H, br s, NH); mass spectrum m/z 201 (M^+).

Methyl 3-[2-(3-Acetylindolyl)]-2-butenoate (13a). A solution of the ester **3a** (1.15 g, 5.35 mmol) in CH_3CN (10 mL) was added to a stirred solution of Ac_2O (3.2 g, 31.4 mmol), AcOH (1.5 g, 31.3 mmol), and PPA (polyphosphoric acid) (1.2 g) in CH_3CN (10 mL) under N_2 atmosphere. The solution was stirred at room temperature for 12 h, quenched with brine (100 mL), and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using 1% MeOH/$CHCl_3$ as an eluent to give the acetylindole **13a** (1.3 g, 94%), mp 118–123 °C ($CHCl_3$/hexane): ^1H NMR δ 2.54 (3 H, s, $COCH_3$), 2.64 (3 H, s, CH_3), 3.70 (3 H, s, $COOCH_3$), 6.07 (1 H, s, –CH=), 7.23–8.17 (4 H, m, aromatic protons); mass spectrum m/z 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.21; H, 5.84; N, 5.47.

Methyl 3-[2-(3-Acetylindolyl)]-2-propenoate (13b). The same procedure as above gave the acetylindole **13b** (86%), mp 245–246 °C ($CHCl_3$/hexane): ^1H NMR δ 2.76 (3 H, s, $COCH_3$), 3.79 (3 H, s, CH_3), 6.51 (1 H, d, $J = 16.5$ Hz, –CH=), 6.87–8.00 (4 H, m, aromatic protons), 8.34 (1 H, d, $J = 16.5$ Hz, –CH=); mass spectrum m/z 231 (M^+). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.67; H, 5.66; N, 5.92.

Methyl 3-[2-[3-[1-(Hydroxyimino)ethyl]indolyl]]-2-butenoate (3a). A stirred mixture of the acetylindole **13a** (1 g, 4.67 mmol), NH_2OH·HCl (10 g, 144 mmol), and NaOAc (11.8 g, 144 mmol) in EtOH (50 mL) was refluxed for 1 h. After removal of solvent, water was added. The resulting precipitates were filtered off, and the product was recrystallized from Et_2O/hexane to give the oxime **3a** (0.92 g, 87%), mp 144–147 °C: ^1H NMR δ 2.77 (3 H, s, CH_3), 2.56 (3 H, s, CH_3), 3.66 (3 H, s, $COOCH_3$), 6.06 (1 H, s, –CH=), 7.33–7.67 (4 H, m, aromatic protons), 8.77 (1 H, br s, NH); mass spectrum m/z 272 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.26; H, 5.96; N, 10.36.

Methyl 3-[2-[3-[1-(Hydroxyimino)ethyl]indolyl]]-2-propenoate (3b). The same procedure as above gave the oxime **3b** (77%), mp 203–205 °C: ^1H NMR δ 2.38 (3 H, s, CH_3), 3.73 (3 H, s, $COOCH_3$), 6.31 (1 H, d, $J = 16.5$ Hz, –CH=), 6.91–7.63 (4 H, m, aromatic protons), 8.00 (1 H, d, $J = 16.5$ Hz, –CH=); mass spectrum m/z 246 (M^+). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.53; H, 5.78; N, 11.30.

Methyl 1,4-Dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (14a). A stirred mixture of the oxime **3a** (100 mg, 0.368 mmol) in xylene (10 mL) was refluxed for 24 h. After removal of solvent, the residue was purified by coluumn chromatography (silica gel, 20 g) using $CHCl_3$ as an eluent to give the γ-carboline **14a** (51.4 mg, 55%), mp 273–277 °C (EtOH): ^1H NMR δ 2.77 (3 H, s, CH_3), 3.05 (3 H, s, CH_3), 3.94 (3 H, s, $COOCH_3$), 7.21–8.19 (4 H, m, aromatic protons), 9.23 (1 H, br s, NH); mass spectrum m/z 254 (M^+). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.92; H, 5.62; N, 11.01.

Methyl 1-Methyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (14b). The same procedure as above gave the γ-carboline **14b** (51%), mp 268–272 °C (EtOH): ^1H NMR ($CDCl_3/CD_3OD$) δ 3.09 (3 H, s, CH_3), 4.02 (3 H, s, $COOCH_3$), 7.10–7.63 (4 H, m, aromatic protons), 8.11 (1 H, s, C_4-H); mass spectrum m/z 228 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.31; H, 5.47; N, 12.31.

1,4-Dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylic Acid (2a). A stirred mixture of the ester **14a** (90.9 mg, 0.368 mmol) and 10% aqueous NaOH (2 mL) in EtOH (2 mL) was refluxed for 1 h. After removal of solvent, the residue was neutralized with concd HCl. The resulting precipitates were filtered off and washed with water to give the analytically pure carboxylic acid **2a** (77.3 mg, 90%), mp 284–286 °C (water) (lit.[8b] mp 283.5–284.5 °C); mass spectrum m/z 240 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.04; N, 11.66. Found: C, 69.83; H, 5.11; N, 11.60.

1-Methyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylic Acid (2b). The same procedure as above gave the carboxylic acid **2b** (95%), mp 276–278 °C (water) (lit.[8b] mp 275–277 °C); mass spectrum m/z 226 (M^+). Anal. Calcd for $C_{13}H_{10}N_2O_2$: 69.01; H, 4.46; N, 12.38. Found: C, 69.86; H, 4.68; N, 12.31.

***t*-Boc-Trp-P-1 (15a).** A stirred solution of the carboxylic acid **2a** (28 mg, 0.117 mmol), DPPA (700 mg, 2.54 mmol), and triethylamine (5 mL) in *t*-BuOH (5 mL) was heated at 80 °C for 30 min. After removal of solvent, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with 5% aqueous AcOH, aqueous $NaHCO_3$, and brine, which was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (Iatrobeads, 20 g) using 1% MeOH/$CHCl_3$ as an eluent to give *t*-Boc-Trp-P-1 (**15a**) (29.8 mg, 82%), mp 189–192 °C (MeOH/Et_2O): ^1H NMR (CD_3OD, 400 MHz) δ 1.60 (9 H, s, $CH_3 \times 3$), 2.54 (3 H, s, CH_3), 3.15 (3 H, s, CH_3), 7.00–7.72 (3 H, m, aromatic protons), 8.23 (1 H, d, $J = 8$ Hz, C_5-H); mass spectrum m/z 311 (M^+). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.30; H, 6.89; N, 13.30.

***t*-Boc-Trp-P-2 (15b).** The same procedure as above gave the *t*-Boc-Trp-P-2 (**15b**) (98%), mp 216–221 °C (MeOH/EtOAc): ^1H NMR (CD_3OD, 400 MHz) δ 1.60 (9 H, s, $CH_3 \times 3$), 3.12 (3 H, s, CH_3), 7.02–7.60 (4 H, m, aromatic protons), 8.18 (1 H, d, $J = 8$ Hz, C_5-H); mass spectrum m/z 297 (M^+). Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.46; H, 6.54; N, 14.30.

Trp-P-1 (1a) Acetate. A stirred mixture of *t*-Boc-Trp-P-1 (**15a**) (20 mg, 0.0643 mmol), AcOH (2 mL), and water (5 mL) was heated at 80 °C for 1 h. After removal of solvent under reduced pressure, the residue was purified by column chromatography (Iatrobeads, 10 g) using 2% MeOH/$CHCl_3$ as an eluent to give Trp-P-1 (**1a**) as its acetate (11 mg, 81%), mp 250–260 °C (EtOAc) (lit.[5,6] mp 252–262 °C): ^1H NMR (CD_3OD, 400 MHz) δ 1.93 (3 H, s, CH_3COOH), 2.32 (3 H, s, CH_3), 2.89 (3 H, s, CH_3), 7.25–7.48 (3 H, m, aromatic protons), 7.98 (1 H, d, $J = 8$ Hz, C_5-H); mass spectrum m/z 211 (M^+). Anal. Calcd for $C_{13}H_{13}N_3 \cdot CH_3COOH$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.37; H, 6.42; N, 15.20.

Trp-P-2 (1b) Acetate. The same procedure as above gave the Trp-P-2 (**1b**) as its acetate (81%), mp 242–247 °C (lit.[5,6] mp 248–250 °C): ^1H NMR (CD_3OD, 400 MHz) δ 1.93 (3 H, s, CH_3COOH), 2.90 (3 H, s, CH_3), 7.15–7.41 (4 H, m, aromatic

protons), 7.97 (1 H, d, J = 8 Hz, C_5-H); mass spectrum m/z 197 (M^+). Anal. Calcd for CH_3COOH: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.13; H, 5.71; N, 16.25.

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The Stereoselective Preparation of Mono- and Bis-β-lactams by the 1,4-Diaza 1,3-Diene–Acid Chloride Condensation: Scope and Synthetic Applications[1]

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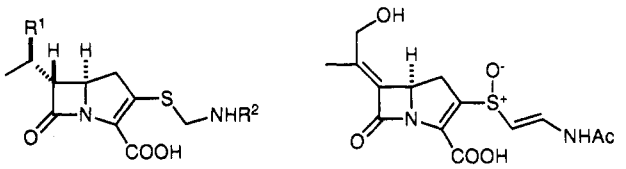
The dehydrochlorination of a variety of acid chlorides with triethylamine in the presence of 1,4-diaza 1,3-dienes gives in fair to excellent yields, with total stereoselectivity, *cis*-4-imino β-lactams **2**, *cis*-4-formyl β-lactams **3**, or C4,C4′-bis-β-lactams **4**, depending on the reaction conditions. The reaction tolerates a wide variety of substituents, including alkoxy, thiophenoxy, amino, aryl, alkyl, alkylidene, and halogen groups, at the ketene moiety. The synthetic versatility of compounds **3** has been demonstrated by their conversion to intermediates in the synthesis of carbapenems PS-5 and PS-6. Base-induced isomerization of compounds **4** to novel bis-γ-lactams **5**, which in turn are aza analogs of glycaric acids, occurred with total retention of the configuration. This process is formally the elongation of glyoxal in four carbons bearing four contiguous stereocenters with total stereoselectivity in only three or four synthetic steps.

Introduction

In spite of the fact that relatively few basic structures are to be found among the clinically important β-lactam antibiotics,[3] there is an upgrowing interest in the chemical synthesis of these compounds. Extensive efforts during recent years have led to many methods to prepare the 2-azetidinone ring, a structural feature which is characteristic of this family of antibiotics.[13] The main approaches to the β-lactam system imply cyclization of β-functionalized acids and their derivatives;[4] cyclization of ester enolates and imines[5] (which strictly speaking could be included in the first route since usually a β-amino ester is formed as the first reaction intermediate); and, finally, the ketene imine synthetic pathway[6] to β-lactams, the venerable Staüdinger reaction.[7] The above approaches have several advantages and some shortcomings, the ketene imine route being the most general when versatility and stereocontrol are taken into account.[8] Furthermore, the introduction of chromium carbene (Fischer) complexes, which upon irradiation act as ketene precursors, has widened the scope of those routes to the 2-azetidinone ring.[9]

Chart I



PS-5 R^1 = H, R^2 = Ac
PS-6 R^1 = Me, R^2 = Ac
Thienamycin R^1 = OH, R^2 = H

Asparenomycin A

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