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FORMATION OF HETEROCYCLIC DERIVATIVES OF α-AMINO ACIDS USING VICINAL TRICARBONYL METHODOLOGY

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Abstract - Monoaldehydes derived from diesters of *N*-protected aspartic and glutamic acids have been reacted with precursors of vicinal tricarbonyl esters to form electrophilic products. These substances were converted to heterocyclic derivatives of the amino acids.

There has been continued recent interest in the synthesis of unnatural amino acids prompted by the biological and toxicological activity observed with members of this group.[1-3] When incorporated into proteins in a site-specific manner, these amino acids offer opportunity for studying structure-function relationships, and for developing new medicinal agents.

In one class of modified α-amino acids, reactive electrophilic units have been incorporated into the amino acid backbone, and these units have been transformed into heterocyclic derivatives offering possibilities for new types of reactivity.[3-5] An entity which has received attention in this connection is the 1,2,3-vicinal tricarbonyl system. This aggregate contains a potent electrophilic site at the central carbonyl group, and, in recent years, vicinal tricarbonyls have been extensively employed[6-9] in the synthesis of varied bioactive products. A generally useful method for forming this building block involves the reaction of carboxylic acids with alkyl triphenylphosphoranilidine acetates, yielding stable diacyl ylides which may readily be converted to tricarbonyl esters by oxidizing agents such as ozone. Recent work by Baldwin[5] has shown how monocarboxylic acid derivatives of protected aspartic and glutamic acids were transformed to tricarbonyl esters by this route. The amino acids activated in this way could then be converted to novel heterocyclic products by reactions with aromatic diamines and other dinucleophiles.

We wish to report related recent studies on the use of tricarbonyl chemistry to introduce heterocyclic systems into α-amino acids making use of monoaldehydes formed from *N*,*N*-di-Boc dimethyl esters of aspartic and glutamic acids by selective reduction. The aldehydes, prepared by the method of Martin and

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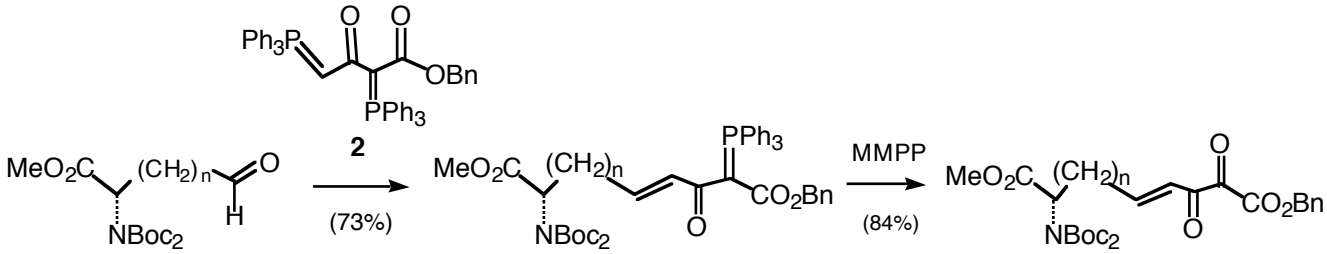
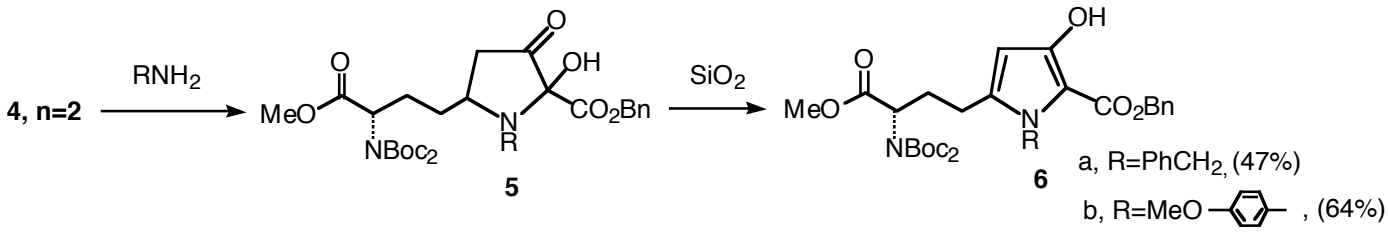
Dedicated to Professor A.I. Meyers in celebration of his 70th birthday, with special appreciation of his creativity, enthusiasm, humanity and infectious sense of humor.

coworkers[10] have now been employed as starting points for forming heterocyclic derivatives of α-amino acids by three different procedures, as described below. In the first phase of our studies, the monoaldehydes were allowed to react with the diylides previously prepared by Chopard.[11] We focused on mono Wittig processes which would generate unsaturated derivatives (**3**). These could then lead to heterocyclic-substituted amino acids through precursors (**4**).



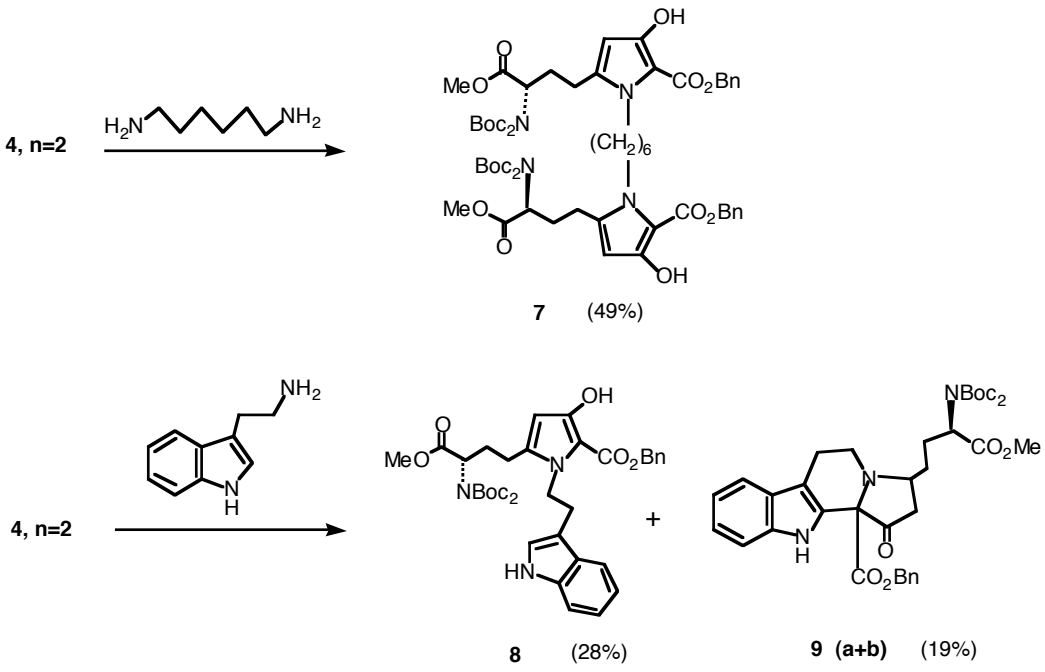
Our reaction sequence began with the aldehyde (**1**, **n=2**) prepared by the reduction of a di-*N*-Boc - protected glutamic acid dimethyl diester.[10] Wittig reaction of **1** with the bis phosphorane (**2**)[11] yielded the α,β-unsaturated keto ylido ester (**3**), which was then oxidized to yield the alkenyl tricarbonyl (**4**). In the course of our studies, we have employed a number of oxidizing agents to cleave the carbon-phosphorous double bond in ylides of this type: ozone,[12a] singlet oxygen,[12b] Oxone® [12c] or dimethyldioxirane (DMDO).[12d] In the present work, we found that mangesium monoperphthalate (MMPP)[13] also gave excellent results.

Along the lines of our synthesis of prodigiosin,[14] the first use of an alkenyl tricarbonyl as a trielectrophile, we treated (**4, n=2**) with primary amines, including benzylamine, *p*-anisidine, 1,6-diaminohexane and tryptamine. As observed in previous studies,[8c] the intermediate labile hydroxy pyrrolidonecarboxylates (**5**) were readily converted to the stable *N*-substituted pyrroles (**6**). Similar reactions carried out using aspartic acid as the starting material and DMDO as the oxidant, yielded *N*-substituted pyrroles (**18**-**20**).[15]

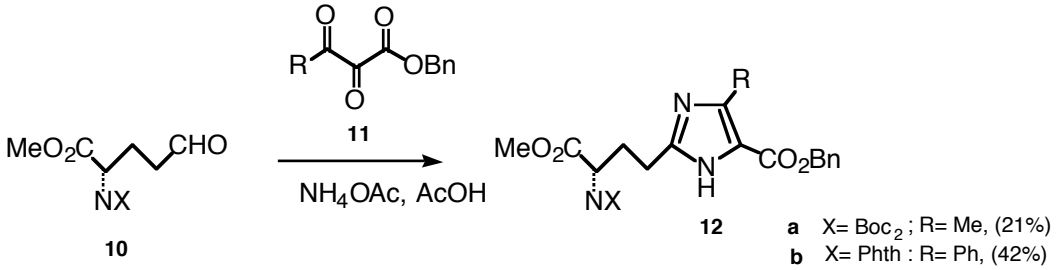


1,6-Diaminohexane underwent bis-addition to the alkenyl tricarbonyl yielding the alkyl-bridged bipyrrole (**7**). With tryptamine, the reaction took place through the typical pyrrole-forming route yielding **8** along with a secondary product, the mixture of diastereomers (**9**) (**a** and **b**), formed *via* intramolecular addition

of the indole ring to an iminium intermediate. The structural assignment to **9** was based on the ^{1}H, ^{13}C NMR and HRMS spectrometry.

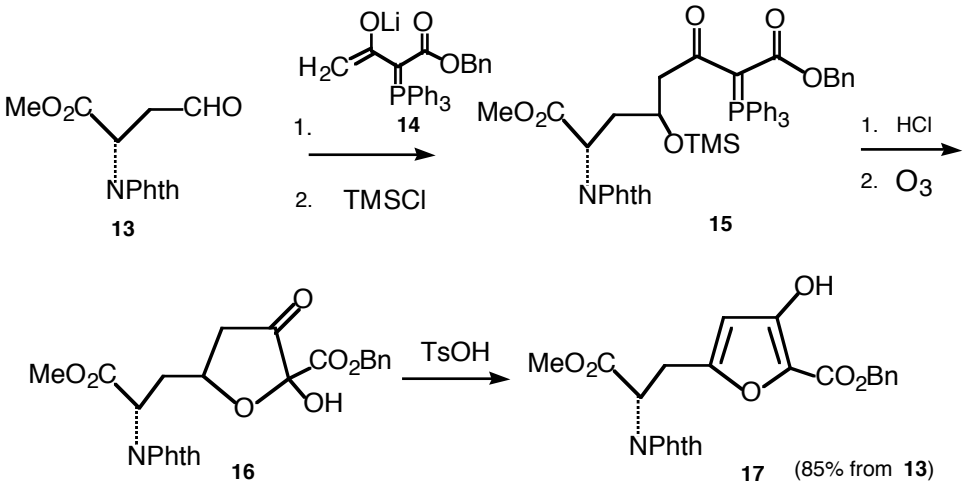


In a second phase of this work, our goal was the preparation of imidazole derivatives from the aldehydo amino acid ester (**1, n=2**). The formation of imidazole carboxylic acids from the reaction of aldehydes with tricarbonyl esters in the presence of ammonium acetate was previously reported by Brackeen.[16] In the present work we allowed (**10**), X=Boc_2 to react with the tricarbonyl ester (**11, R=Me**) in the presence of ammonium acetate forming the imidazole carboxylate (**12a**). Low yields in this transformation may have resulted from side reactions due to the presence of considerable enol in **11** (**R=Me**). With a non-enolizable tricarbonyl (**11, R=Ph**) and an aldehyde ester containing the phthalimide protecting group (**10, X=Phth**) the imidazole product (**12b**) was formed in improved yield.



Based on procedures which we have previously developed,[17] the aldehyde esters could also be employed in the formation of furan derivatives of α-amino acids. Thus, the phthalimide protected aldehyde ester

(**13**) derived from aspartic acid dimethyl ester underwent reaction with the lithiated tricarbonyl derivative (**14**) in the presence of TMSCl to form a diasteromeric mixture of the TMS protected alcohol (**15**). Deprotection of the alcohol (HCl) followed by ozonolysis yielded a tricarbonyl which underwent cyclization to **16**, and then conversion to the furan (**17**) in the presence of TsOH.



EXPERIMENTAL

All solvents and reagents were commercially supplied from Aldrich. NMR spectra were recorded using Bruker 400 and 500 instruments. Chemical shifts are quoted in parts per million (ppm) and are referenced to either residual solvent peaks or to TMS peaks. HRMS spectrometry was performed at the Yale Cancer Center Mass Spectrometry Resource, Yale School of Medicine, Yale University, by electrospray. Flash chromatography was performed using silica gel from Silicycle Chemical Division Inc., with particle size of 230-240 mesh (40-60 nm) as stationary phase. Thin layer chromatography was carried out on glass backed plates commercially provided by Analtech Inc., which were visualized by UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulfuric acid followed by heat.

Unsaturated Ylide (3, n=2). The di-ylide (**2**), formed[11] from the corresponding hydrochloride salt (113 mg, 0. 16mmol), was dissolved in 3 mL of methylene chloride at 0 °C and treated with triethylamine (31 mg, 42 uL, 0.30 mmol). The mixture was stirred at 0 °C for 30 min and at rt for 20 min, and then aldehyde (**1**) (52 mg, 0.15 mmol) in 6 mL of CH_2Cl_2 was added. The solution was stirred for 2.5 h prior to the addition of 0.1 mL of water. After a further 10 min of stirring, the solvent was removed and the oily residue was purified using thin layer chromatography (50 % EtOAc/Hex), yielding compound (**3**) (85 mg, 73%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 6 H), 7.48-7.43 (m, 4 H), 7.39-7.34 (m, 6 H), 7.21-7.14 (m, 2 H), 6.94-6.88 (m, 2 H), 6.60 (dt, 1 H, J = 8.2, 19.2 Hz), 4.89-4.86 (m, 1 H), 4.72 (s, 2 H), 3.69 (s, 3 H), 2.30-2.21 (m, 3 H), 2.05-1.99 (m, 1 H), 1.47 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0 (d, J = 15.6 Hz), 171.1, 167.7 (d, J = 58.0 Hz), 152.3 (2C), 140.3, 136.7, 132.9 (d, J =

38.4 Hz, 6C), 131.5 (2C), 131.4 (2C), 129.4, 128.5 (d, 6C, J = 50.8 Hz), 128.1 (3C, d, J = 40.0 Hz), 127.5, 126.5 (3C, J = 373.0 Hz), 83.0 (2C), 71.8 (d, J = 446.4 Hz), 64.7, 57.9, 52.1, 29.2, 29.2, 28.0 (6C). HRMS Calcd for $C_{45}H_{50}NO_9$ (M + H) 780.3301, Found 780.3295.

Unsaturated Tricarbonyl Ester (4, n=2). Powdered magnesium monoperoxyphthalate hexahydrate (170 mg, 0.34 mmol) was mixed with 82 μL of water. Stirring was maintained until a paste was formed (*ca.* 3 min). Compound (**3**) in 5 mL of methylene chloride was then added to the paste and stirred for 8 h. The mixture was then filtered and the solvent evaporated. The residue was chromatographed (25% EtOAc/Hex) to give **4** (150 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5 H), 7.15 (dt, 1 H, J = 15.8, 5.6 Hz), 6.26 (dd, 1 H, J = 0.7, 15.8 Hz), 5.25 (s, 2H), 4.83 (dd, 1H, J = 4.2, 9.2 Hz), 3.72 (s, 3 H), 2.45-2.22 (m, 4 H), 2.09-1.97 (m, 1H), 1.50 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) 190.5, 170.8, 162.9, 152.4, 152.1, 134.3, 128.9, 128.8 (2 C), 128.6, 128.3 (2C), 122.9, 92.0, 83.6 (2 C), 68.7, 57.4, 52.3, 29.7, 28.1, 28.0 (6 C); HRMS Calcd for $C_{27}H_{35}NO_{10}$ (M + Na) 574.2264, Found 574.2264.

General Procedure for the Preparation of Pyrrole Derivatives from Alkenyl Vicinal Tricarbonyls (4). To compound (**4, n=2**) in 5 mL of methylene chloride at 0 °C was added the amine (1 eq) in methylene chloride. The reaction was stirred at 0 °C for 1 h, then warmed to rt and stirred for a further 1.5 h prior to the addition of 0.3 g of silica gel. The reaction mixture was then stirred for 15 h at rt, 4 h at 60 °C, and then cooled to rt. After the solvent was evaporated, the residue was chromatographed as described below.

Pyrrole (6a). According to the general procedure described above, the reaction of **4** (**n=2**) (61 mg, 0.11 mmol) with benzylamine (13 mg, 0.12 mmol) gave a yellow oil that was purified by chromatography (15% EtOAc/Hex) to give 32 mg (47%) of **6a** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-6.79 (m, 10 H), 5.74 (s, 1 H), 5.33 (br s, 2H), 5.18 (br s, 2 H), 4.84 (dd, 1 H, J = 5.4, 8.6 Hz), 3.68 (s, 3 H), 2.58-2.42 (m, 3 H), 2.15-2.06 (m, 1 H), 1.43 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 152.0 (2 C), 140.1, 138.3, 135.8 (2 C), 128.5 (br s, 2 C), 128.2 (br s), 128.1 (2 C), 127.0, 125.4 (br s, 2C), 105.3, 96.3, 83.6 (2C), 65.6, 57.5, 52.3, 48.1, 29.1, 27.9 (6 C), 23.5. HRMS Calcd for $C_{34}H_{42}N_2O_9$ (M + Na) 645.2788 , Found: 645.2786.

Pyrrole (6b). According to the general procedure described above, the reaction of **4** (67 mg, 0.126 mmol) with *p*-anisidine (15.6 mg, 0.126 mmol) gave a yellow solid that was purified by chromatography (35% EtOAc/Hex) to give 51 mg (64%) of **6b** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (br s, 1 H), 7.25-7.20 (m, 5 H), 7.09-6.85 (m, 4 H), 5.78 (s, 1 H), 5.03 (br s, 2 H), 4.79-4.76 (m, 1H), 3.80 (s, 3 H), 3.68 (s, 3 H), 2.37-2.33 (m, 2 H), 1.42 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.3 (2 C), 151.8, 140.8, 135.6, 131.3, 129.4, 129.3, 128.2 (2 C), 127.8, 127.6 (2 C), 113.9, 113.8, 107.2, 96.2,

83.2 (2 C), 65.3, 57.5, 55.6, 52.2, 28.9, 27.9 (6 C), 23.8; HRMS Calcd for $C_{34}H_{42}N_2O_{10}$ (M + Na) 661.2731, Found 661.2733.

Bis-pyrrole Derivative (7). To a solution of tricarbonyl compound (**4, n=2**) in 10 mL of methylene chloride at 0 ^oC (552 mg, 0.97 mmol) was added 1,6-diaminohexane (42 mg, 0.354 mmol). The reaction mixture was stirred at 0 ^oC for 1.5 h at rt for 1.3 h prior to the addition of 0.44 g of silica gel. The reaction mixture was stirred for a further 11 h at rt, followed by heating for 4.5 h at 65 ^oC. The solution was then cooled to rt, the silica gel was removed by filtration and the liquid concentrated and chromatographed on silica gel (17% EtOAc/Hex), yielding **7** as a pale yellow oil (99 mg, 24%). For **7**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 10 H), 5.62 (s, 2 H), 5.29 (s, 4 H), 4.89 (dd, 2 H, J = 5.4, 8.2 Hz), 3.92 (br s, 4H), 3.53 (s, 6H), 2.65-2.42 (m, 6 H), 2.14-2.06 (m, 2 H), 1.54 -1.42 (m, 8 H), 1.49 (s, 2 H, OH), 1.47 (s, 36 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1 (2 C), 171.2 (4 C), 169.0 (2 C), 152.4 (2 C), 136.3 (2 C), 129.1 (4 C), 129.0 (2 C), 128.8 (2 C), 128.6 (4 C), 105.0 (2 C), 95.9 (2 C), 83.8 (4 C), 66.0 (2 C), 57.9 (2 C), 52.7 (2 C), 45.4 (2 C), 31.9 (2 C), 29.5 (2 C), 28.4 (12 C), 26.8 (2 C), 23.8 (2 C). HRMS Calcd for $C_{60}H_{82}N_4O_{18}$ (M + Na) 1169.5522 , Found: 1169.5495.

Indolopyrrole (8), and Tetracyclic Indole Derivatives (9a) and (9b). According to the general procedure described above, the reaction of **4** (**n=2**) (85 mg, 0.16 mmol) with tryptamine (26 mg, 0.16 mmol) gave a yellow oil that was purified by chromatography (15% EtOAc/Hex) to give 20 mg (19 %) of **9**, a pale yellow oil, as a mixture of diastereomers and 30 mg of **8** (28%) as a pale yellow oil: For **8**: ^1H NMR (500 MHz $CDCl_3$) δ 7.95 (br s, 1 H), 7.50-7.47 (m, 1 H), 7.41-7.31 (m, 6H), 7.18-7.15 (m, 1 H), 7.10-7.05 (m, 1 H), 5.59 (s, 1 H), 5.33 (br s, 2H), 5.30 (s, 1 H), 4.73 (dd, 1 H, J = 5.2, .8.5 Hz), 4.36-4.27 (br s, OH), 3.69 (s, 3 H), 3.02 (br t, 2 H, J = 7.1 Hz), 2.42-2.26 (m, 4 H), 2.05-1.97 (m, 2 H), 1.44 (s, 18 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 170.8, 152.0 (2 C), 140.0, 136.1, 136.0, 128.7 (2 C), 128.6, 128.5 (2 C), 128.4, 127.3, 122.2, 122.0, 119.6, 118.6, 112.4, 111.1, 104.6, 95.5, 83.4 (2 C), 65.7, 57.3, 52.2, 45.9, 28.9, 28.3 (6 C), 27.2, 23.2. HRMS Calcd for $C_{37}H_{45}N_3O_9$ (M + Na) 698.3054, Found 698.3041. For (**9a**): ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 7.50 (d, 1 H, J = 8.7 Hz), 7.37-7.29 (m, 6 H), 7.20-7.17 (m, 1 H), 7.10-7.07 (m, 1 H), 5.26 (d, 1 H, J = 12.6 Hz), 4.91 (dd, 1 H, J = 5.1, 8.9 Hz), 3.71 (s, 3 H), 3.51 (dd, 1 H, J = 5.2, 14.7 Hz), 3.35-3.31 (m, 1 H), 3.27-3.19 (m, 1 H), 3.02-2.95 (m, 1 H), 2.61-2.59 (m, 1 H), 2.57-2.55 (m, 1 H), 2.37 (dd, 1 H, J = 10.7, 17.7 Hz), 2.17-1.96 (m, 3 H), 1.63-1.58 (m, 1 H), 1.50 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 171.1, 167.2, 152.2 (2 C), 136.5, 135.4, 128.6 (2C),128.3, 127.7 (2 C), 126.3, 124.6, 122.8, 119.6, 118.6, 111.3, 111.0, 82.3 (2 C), 73.6, 67.7, 57.8, 53.5, 52.3, 42.3, 40.3, 29.7, 28.0 (6C), 25.8, 15.6. HRMS Calcd for $C_{37}H_{45}N_3O_9$ (M + H) 676.3234 , Found: 676.3238. For **9b**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.49 (d, 1 H, J = 7.8 Hz), 7.38-7.31 (m, 6 H), 7.20-7.17 (m, 1 H), 7.10-7.07 (m, 1 H), 5.26 (d, 1 H, J = 12.6 Hz), 5.19 (d, 1 H, J = 12.6 Hz), 4.88 (dd, 1 H, J =

5.8, 8.5 Hz), 3.72 (s, 3 H), 3.53 (dd, 1 H, J = 5.1, 14.8 Hz), 3.33-3.20 (m, 2 H), 2.59-2.58 (m, 1 H), 2.57-2.55 (m, 1 H), 2.45 (dd, 1 H, J = 10.7, 17.7 Hz), 2.30-2.25 (m, 1 H), 1.97-1.91 (m, 1 H), 1.88-1.81 (m, 1 H), 1.78-1.69 (m, 1 H), 1.48 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 171.0, 167.8 152.2 (2 C), 136.5, 135.5, 128.6 (2 C), 128.3, 127.7 (2 C), 126.3, 124.7, 122.8, 119.5, 118.5, 111.3, 111.0, 82.3 (2 C), 73.6, 67.7, 58.1, 53.7, 52.3, 42.3, 40.3, 29.8, 28.0 (6 C), 25.9, 15.6. HRMS Calcd for $C_{37}H_{45}N_3O_9$ (M + H) 676.3234 , found: 676.3233.

Imidazole Derivative (12a). To a solution containing tricarbonyl compound (**11**, **R= Me**) (247 mg, 0.6 mmol) and aldehyde (**1, n=2**) (331 mg, 0.5 mmol) in 1.5 mL of glacial acetic acid was added NH_4OAc (430 mg, 5.5 mmol). The mixture was heated at 65 ºC for 1 h prior to the removal of solvent under high vacuum. The residue was dissolved in 200 mL of EtOAc and then was washed with two portions of saturated $NaHCO_3$ (25 mL x2) and brine (20 mL). The organic layer was then dried with Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography (35-70% EtOAc/Hex), yielding **12a** (53 mg, 21%) as an oil. ^{1}H NMR (500 MHz, 75 ºC, C_6D_6) δ 7.28-7.27 (m, 2 H), 7.15-7.12 (m, 2 H), 7.09-7.07 (m, 1 H), 5.48 (dd, 1 H, J = 6.2 Hz, 7.9 Hz), 5.21 (d, 1H, J = 12.5 Hz), 5.18 (d, 1 H, J = 12.5 Hz), 3.53 (dd, 1 H, J = 6.2, 15.6 Hz), 3.38 (dd, 1 H, J = 8.0, 15.7 Hz), 3.35 (s, 3H), 2.52 (s, 3 H), 1.37 (s, 18 H) NH proton missing; ^{13}C NMR (125 MHz, 75 ºC, C_6D_6) δ 170.8, 161.4, 152.9 (2 C), 146.7, 137.4, 128.9 (2 C), 128.7 (2 C), 128.6, 128.4 , 128.2, 83.5 (2 C), 66.1, 57.7, 52.2, 30.6, 28.4 (br s), 28.3 (6 C). HRMS Calcd for $C_{26}H_{35}N_3O_8$ (M + H) 518.2502, Found 518.2497.

Imidazole Derivative (12b). To a solution containing (**11, R=Ph**) (109 mg, 0.52 mmol) and aldehyde (**10**) (X=Phth) (130 mg, 0.47 mmol) in 1.5 mL of glacial acetic acid was added NH_4OAc (406 mg, 5.27 mmol). The mixture was heated at 65 ºC for 45 min prior to the removal of solvent under vacuum. The residue was dissolved in 200 mL of EtOAc and then washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was subjected to silica gel chromatography (35-70% EtOAc/Hex), yielding compound (**12b**) (88 mg, 42%). ^{1}H NMR (400MHz, 78 ºC, C_6D_6) δ 9.56 (br s, 1 H), 8.31 (d, 2 H, J = 7.0 Hz), 7.58-7.53 (m, 2 H), 7.37-7.23 (m, 3 H), 7.07-7.05 (m, 2 H), 5.16 (br dd, 1 H, J = 5.5, 9.0 Hz), 3.57 (s, 3 H), 3.42 (s, 3 H), 2.90-2.82 (m, 2 H), 2.70-2.59 (m, 2 H); ^{13}C NMR (100 MHz, 78 ºC, C_6D_6): δ 165.7, 164.4, 158.5, 147.0, 145.9, 132.9, 131.8, 130.5 (2 C), 127.8, 126.4, 126.3, 125.9 (2 C), 121.4 (2 C), 115.8, 50.3, 50.2, 48.9, 25.6, 23.7. HRMS Calcd for $C_{24}H_{21}N_3O_6$ (M + H) 448.1508, (M+Na) 470.1328, Found 448.1507, 470.1323 respectively.

Protected Aldehyde Ester (13). To a solution of dimethyl aspartate (4.0 g, 24.8 mmol) in THF (30 mL) was added *N*-carbethoxyphthalimide (5.44 g, 24.8 mmol). The solution was stirred at rt for 24 h before removal of the solvent. The residue was chromatographed (35% EtOAc/Hex) to give 6.14 g (85%) of the phthalimide-protected dimethyl ester. ^{1}H NMR δ 7.86-7.77 (m, 4 H) 5.41 (dd, 1 H, J = 5.5, 9.0 Hz, CH)

3.71 (s, 3 H) 3.28 (m, 2 H). The diester was converted to the monoaldehyde (**13**) using the DIBAL reduction procedure reported by Martin.[10] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1 H), 7.82-7.67 (m, 4 H), 5.45 (dd, 1 H, J = 5.0, 8.5 Hz), 3.70 (s, 3 H), 3.38 (m, 2 H).

Protected Alcohol Ylide (15). To a solution of the tricarbonyl ylide (**11**) (2.5 g, 5.75 mmol) in THF (20mL) was added BuLi (2.18 mL of 2.5 M in hexanes, 5.45 mmol) at 0 ºC. The resulting solution was stirred at 0 ºC for 1 h before cooling to –78 ºC. At this temperature, triethylamine (6.41 mL, 46.0 mmol) and trimethylsilyl chloride (5.84 mL, 46.0 mmol) were added in succession. The mixture was stirred for a further 30 min at this temperature before the addition of **13** (1.08 g, 4.12 mmol) in THF (5 mL). The reaction was stirred for a further 6 h at rt before evaporation of the volatiles. The residue was chromatographed (35% EtOAc/Hex) to give the product (**15**) (2.2 g, 75%). ^{1}H NMR δ 7.82-6.82 (m, 24 H), 5.20 (dd, 1 H, J = 7, 17 Hz), 4.41 (m, 2 H), 3.85 (s, 3 H), 3.24 (m, 1 H), 2.30 (m, 2 H): ^{13}C NMR δ 197.0, 196.8, 170.9, 170.5, 168.1, 167.9, 136.8, 134.4, 134.2, 133.4, 133.3, 133.2, 132.2, 129.0, 128.6, 128.6, 128.5, 128.0, 123.8, 72.8, 72.7, 71.9, 71.8, 67.91, 65.2, 53.0, 50.2, 49.6, 47.0, 46.6, 36.2, 35.5. HRMS Calcd for $C_{42}H_{36}NO_8P.H^+$ 714.2206, Found 741.2256.

Hydroxy Furanone Carboxylate (16). A solution of **15** (250 mg, 0.35mmol) in EtOAc (2.0 mL) was treated with 1N HCl (2.0 mL) and the mixture stirred for 20 min at rt. Extraction of the reaction mixture with further EtOAc (20 mL) and evaporation gave the corresponding alcohol. The alcohol was redissolved in CH_2Cl_2 (10 mL) and cooled to –78 ºC before ozone was passed through the solution for 3 min. The reaction was stirred at that temperature for a further 5 min before the excess ozone was removed by a stream of dry nitrogen. The solution was stirred to rt and the solvent removed. The residue was chromatographed (50% EtOAc/Hex) to give **16** (204 mg, 86%). ^{1}H NMR δ 7.89-7.02 (m, 9 H), 5.30-5.02 (m, 2 H), 4.41 (br, 2 H), 3.83 (s, 3 H), 2.51 (m, 2 H): ^{13}C NMR δ 205.1, 169.4, 169.3, 169.1, 167.7, 167.6, 167.5, 167.4, 134.4, 134.3, 134.2, 131.8, 131.7, 131.6, 129.7, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 123.7, 123.6, 123.5, 95.3, 95.1, 74.4, 68.7, 68.6, 68.5, 53.0, 48.9, 48.7, 48.4, 40.8, 40.4, 39.8, 36.2, 35.2, 35.0, 34.5.

Furan (17). To a solution of **16** (68 mg, 0.14 mmol) in benzene (10 mL) was added *p*-TsOH.H_2O (4 mg, 0.15 eq.) and the mixture refluxed for 10 h. The reaction was cooled, washed with saturated $NaHCO_3$(aq.), and the organic layer separated and dried before evaporation of the solvent. The ^{1}H NMR of the reaction mixture showed the presence of the furane but it proved unstable to chromatography. Accordingly, this product was not isolated but after evaporation, the residue was redissolved and treated with 2,6-lutidine (8.5 μL, 7.0 mmol) and TBSOTf (64.4 μL, 0.28 mmol) at 0 ºC. The reaction was then quenched with 1N HCl (1 mL) and extracted with CH_2Cl_2. Evaporation and chromatographic purification (35% EtOAc/Hex) gave **17** (67.1 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.70 (m, 4 H), 7.43 (m, 5

H), 5.87 (s, 1 H), 5.24 (m, 1 H), 3.83 (s, 3 H), 3.52 (m, 2 H), 0.78 (s, 9 H), 0.10 (s, 6 H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.5, 158.7, 154.3, 150.9, 136.4, 134.6, 131.9, 131.0, 128.9, 128.8, 128.4, 124.0, 106.5, 66.0, 53.5, 50.6, 30.1, 28.8, 26.0, 25.7, 18.5, -4.6. HRMS Calcd for $C_{24}H_{19}NO_8H^+$ 450.1173, Found 450.1188.

Unsaturated Ylide (3, n = 1), Derived from Aspartic Acid. A solution of monoaldehyde (**1**, **n = 1**) (3.96 g, 12.0 mmol) and ylide (**2**) (7.75 g, 10.9 mmol) in CH_2Cl_2 (50 mL) was refluxed for 12 h. The reaction was cooled to rt and the solvent removed. The residue was chromatographed (50% EtOAc/Hex) to give **3** (**n = 1**) (7.4 g, 89%). ^{1}H NMR δ 7.61-7.20 (m, 20 H), 6.91 (dd, 1 H, J = 1, 15 Hz), 6.57 (dd, 1 H, J = 6, 16 Hz), 5.05 (dd, 1 H, J = 5, 9 Hz), 4.73 (m, 2 H), 3.78 (s, 3 H), 2.87 (m, 2 H), 1.39 (s, 18 H); ^{13}C NMR δ 185.7, 170.7, 167.7, 167.0, 151.4, 136.6, 133.2, 132.9, 132.8, 132.5, 131.5, 131.4, 131.3, 128.5, 128.4, 128.1, 127.4, 127.0, 126.0, 82.9, 72.1, 70.9, 64.5, 57.8, 52.1, 33.2, 28.0 (6 C). HRMS Calcd for $C_{44}H_{48}NO_9PH^+$ 766.3128, Found 766.3144.

Unsaturated Tricarbonyl Derivative (4, n = 1), Derived from Aspartic Acid Dimethyl Ester. Alkenyl ylide (**3, n = 1**) (2.20 g, 2.88 mmol) was dissolved in acetone (20 mL) and cooled to –30 °C. A solution of DMDO in acetone (3.6 mL, 0.8 M, 2 eq.) was added and the solution stirred at rt over a period of 1 h. The solvent was removed and the residue chromatographed (EtOAc/Hex) to give the tricarbonyl compound (**4, n = 1**) as a clear oil (1.49 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5 H), 7.12 (dt, 1 H, J = 6, 16 Hz), 6.41 (dd, 1 H, J = 1, 16 Hz), 5.20 (s, 2 H), 4.91 (dd, 1 H, J = 4, 9 Hz), 3.70 (s, 3 H), 2.80 (m, 2 H), 1.48 (s, 18 H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 170.0, 169.0, 151.6, 148.5, 134.4, 133.9, 128.8, 128.6, 128.5, 128.2, 125.6, 124.8, 92.2, 83.8, 68.4, 68.3, 56.7, 56.5, 33.7, 28.0 (6 C). Pyrroles (**18**-**20**) were prepared by the method used in the conversion of **4** (**n = 2**) to pyrroles (**6**).

***N*-Benzylpyrrole Derivative (18)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-6.82 7.32-6.82 (m, 10 H), 5.78 (s, 1 H), 5.45 (s, 2 H), 5.20 (br s, 2 H), 5.18 (dd, 1 H, J = 5.5, 8.5 Hz), 3.68 (s, 3 H), 3.28 (m, 2 H), 1.42 (s, 18 H). ^{13} C NMR (125 MHz, $CDCl_3$) δ 170.2, 152.7, 139.9, 139.14, 129.0, 128.9, 128.7, 128.6, 127.9, 127. 7, 126.0, 106.3 105.5, 96.7, 83.1, 82.9, 65.6, 58.04, 52.0, 49.5, 29.3, 27.8 (6 C). HRMS Calcd for $C_{33}H_{40}N_2O_9H^+$ 609.2802, Found 609.2812.

***N*-3-Hydroxypropylpyrrole Derivative (19).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5 H), 5.57 (s, 1 H), 5.40 (s, 2 H), 5.17 (dd, 1 H, J = 5.5, 8.5 Hz), 3.78 (m, 2 H), 3.70 (s, 3 H), 3.41 (m, 2H), 3.30 (m, 2 H), 2.08 (m, 2 H), 1.42 (s, 18 H). ^{13} C NMR (125 MHz, $CDCl_3$) δ 170.6, 152.2, 139.9, 129.0, 128.8, 128.3, 128.2, 127.1, 106.0, 98.5, 96.4, 83.9, 83.7, 66.0, 65.2, 57.8, 57.7, 52.8, 52.7, 49.6, 28.2, 27.7 (6 C). HRMS Calcd. for $C_{29}H_{40}N_2O_{10}Na^+$ 599.2548, Found 599.2562.

***N*-3-Bromopropylpyrrole Derivative (20)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5 H), 5.60 (s, 1 H), 5.39 (s, 2 H), 5.20 (dd, 1 H, J = 5.5, 8.5 Hz), 4.01 (m, 2 H), 3.70 (s, 3 H), 3.48 (m, 2 H), 2.12 (m, 2 H), 1.42 (s, 18 H). ^{13} C NMR (125 MHz, $CDCl_3$) δ 172.3, 152.5, 134.9, 129.2, 129.4, 128.7, 128.6, 127.1, 108.2, 97.2, 94.2, 84.4, 84.2, 68.8, 58.52, 55.12, 55.0, 53.2, 53.0, 38.6, 35.7, 28.4 (6 C). HRMS Calcd. for $C_{29}H_{39}N_2O_9BrH^+$ 639.1902, Found 639.1917.

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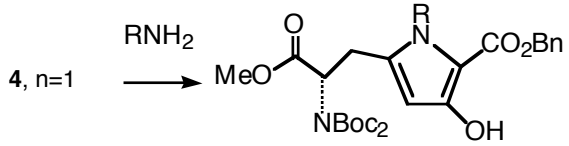
15. Reactions of the aldehydo ester derived from aspartic acid with amines yielded pyrroles as shown:



18, R= CH_2Ph, (72%)
19, R=$(CH_2)_3OH$, (68%)
20, R=$(CH_2)_3Br$, (75%)

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