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THE SYNTHESIS OF A γ-KETO-α-AMINO ACID, A KEY INTERMEDIATE IN THE SYNTHESIS OF MONATIN, A NEW NATURAL SWEETENER

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Abstract: An efficient method was developed for the synthesis of the keto-amino acid **2**, a key intermediate in the synthesis of the novel sweet compound, monatin **1**. Preparation of **2** entails coupling of a suitably protected indole acetate anion to an aspartic acid derivative.

Monatin, (Indol-3-yl)-2-amino-4-carboxy-4-hydroxypentanoic acid **1**, is a sweet tasting α-amino acid isolated by ion chromatography from the roots of the plant *Schlerochiton ilicifolius*[2]. Monatin was evaluated by a taste panel

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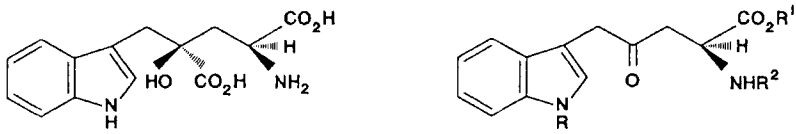
and the relative sweetness established as 1400 and 1200 times that of a 5 and 10% (w/v) sucrose solution, respectively[2]. As a sweetener monatin performs well, the pronounced body giving flavour enhancement, in common with other protein-based sweeteners. Monatin creates highly acceptable blends with other sweeteners such as aspartame in a variety of flavours and with or without carbonation.

Structural and stereochemical analysis established the structure of monatin as the novel γ-hydroxy-γ-indolyl glutamic acid **1**, the published absolute stereochemistry[2] being 2S,4S. The preparation of γ-keto-α-amino acids of high optical purity have been widely explored[3,4]. Baldwin's recent



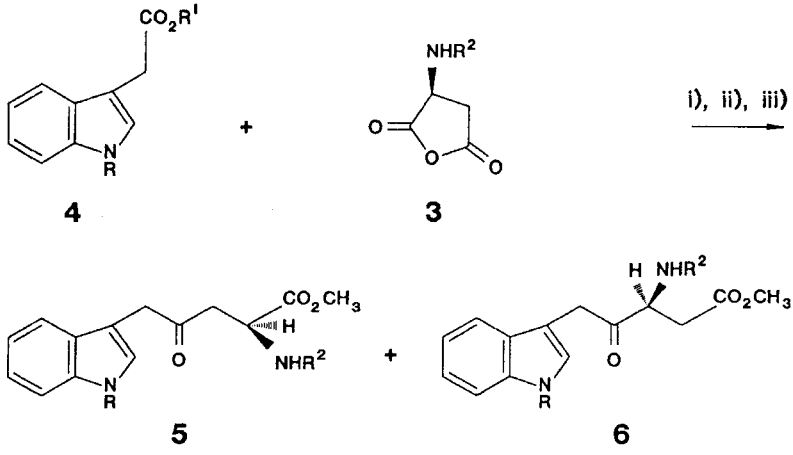
1 **2**

FIG 1

publication[5] of a new and efficient synthesis of γ-keto-α-amino acids from appropriate β-lactams prompts us to describe our own approach to these compounds.

Our approach to the synthesis of monatin involves the intermediary of the γ-keto-α-amino acid derivative of type **2**. We now describe the efficient

synthesis of such compounds from L-aspartic acid. Ketone intermediate **2** was prepared by coupling of a suitably protected L-aspartic anhydride **3**[6] to the N-protected indolyl acetic acid ester **4**. Thus, the LDA generated anion of **7**[7] was reacted with anhydrides **3**, to afford coupling products which were subjected to hydrogenolysis in the presence of Pd/charcoal (affecting removal of the benzyloxycarbonyl group) followed by treatment with diazomethane to furnish the isomeric esters **5** and **6** (scheme 1). The results summarised in table 1 shows that selectivity of attack of the anion on the two carbonyls of the



	4a	4b	3a	3b	3c	5a/6a	5b/6b	6c
R	t-Boc	benzyl	-	-	-	t-Boc	benzyl	t-Boc
R^1	benzyl	t-butyl	-	-	-	-	-	-
R^2	-	-	t-Boc	Cbz	acetyl	t-Boc	Cbz	acetyl

i) LDA , -78°C , THF ; ii) H_2/Pd charcoal (5a, 6a, 6c) ; p-toluenesulfonic acid , benzene (5b , 6b) ; iii) CH_2N_2

scheme 1

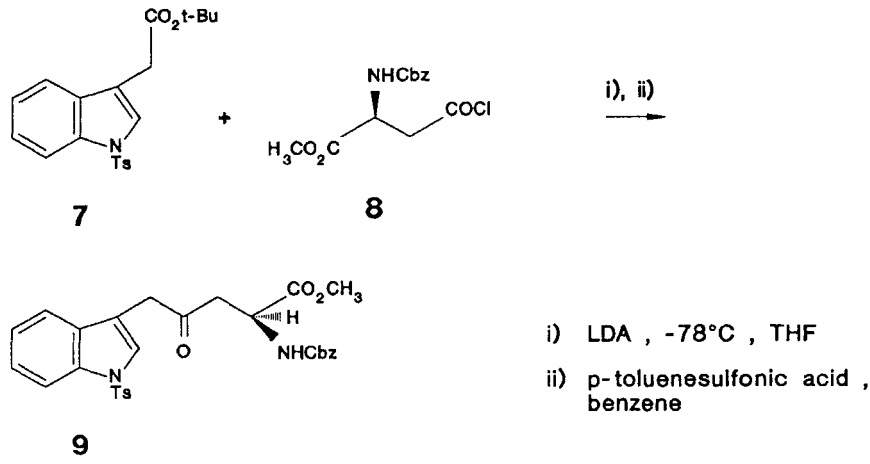
Table. The effect of anhydride protecting groups on the ratio of compounds **5** and **6**.

Protecting group	Ratio (**5**/**6**)*	Yield (%)
t-Boc	50:50	70
Cbz	35:65	60
Acetyl	<5:>95	62

* Determined by chromatographic isolation.

anhydride is influenced by the nature of the protecting group (vz. N-acetyl, N-Cbz, N-t-Boc) on the anhydride. All three protecting groups have an electron withdrawing effect on the amine, increasing the electrophilicity of the carbonyl group and therefore its susceptibility to attack by the anion. This is exemplified by the N-acetyl protecting group where the ratio of **5**/**6** is <5:>95 (**5c** was not fully characterised). However, the bulkier N-t-Boc protecting group directs more of the attack of the anion to the less hindered side of the anhydride resulting in a ratio of **5**/**6** of 50:50. Compound **5a** was prepared in an overall yield of 35% from the N-t-Boc anhydride.

A more efficient synthesis of **2** involved coupling of the anion of t-butyl 1-p-toluenesulfonylindole-3-acetate **7** to the acid chloride generated from α-methyl N-carbobenzoxy-L-aspartate **8**[8]. p-Toluenesulfonic acid catalysed deprotection of the t-butyl ester was followed by spontaneous decarboxylation of the acid to afford the required γ-keto-α-amino acid **9** in good yield (scheme 2).



scheme 2

The formation of the γ-keto-α-amino acid derivative may proceed via the *in situ* formation of the β-lactam. No evidence for the intermediacy of a β-lactam

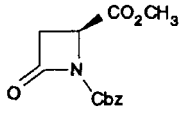


FIG 2

(FIG 2) could be obtained. Direct coupling to the acid chloride or reaction via a ketene intermediate cannot be excluded. In this regard we found[9] that the reaction of the anion of **7** with protected β-lactams did furnish the γ-keto-α-amino acid as expected, but in considerable lower yield than the corresponding reaction with the acid chloride. Nevertheless these results indicate Baldwin's γ-keto-α-amino acid synthesis can be applied to nucleophiles other than sulfone stabilised carbon nucleophiles.

The completion of the monatin synthesis requires the addition of a carboxylic acid group to the ketone moiety. The conversion of ketone intermediate **2** to the corresponding protected cyanohydrin and subsequent hydrolysis to monatin will be described in a following paper.

EXPERIMENTAL

General. ^{1}H and ^{13}C N.m.r. spectra were recorded on a Bruker WM-500 or AM-300 spectrometer. IR spectra were recorded on a Perkin-Elmer 883 spectrometer. Mass spectra were taken on a Finnigan MAT 90 double focussing mass spectrometer. Optical rotations refer to solutions in chloroform and were recorded on a Perkin-Elmer 241 polarimeter. M.p.'s were recorded

on a Kofler hot-stage and are uncorrected. Merck silica gel 60 was used for column chromatography.

Synthesis of benzyl 1-t-butyloxycarbonylindole-3-acetate (4a)

A solution of benzyl indole-3-acetate[10] (2.0 g, 7.5 mmol), di-t-butyl dicarbonate (1.7 g, 8.3 mmol) and N,N-dimethylaminopyridine (DMAP) (10 mg) was stirred at room temperature in 10 ml dry acetonitrile for 3 hours. The solvent was removed *in vacuo* and the product extracted with diethyl ether, washed with dilute hydrochloric acid followed by a saturated sodium bicarbonate solution. The ether layer was dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to afford **4a** (2.8 g, 100%) as a slightly yellow oil: ν_{max} 2950-3050, 1750-1715; ^{1}H N.m.r. ($CDCl_3$) δ 1.67 (s, 9H, t-Boc), 3.73 (s, 2H, Ind-C$\underline{H}_2$), 5.15 (s, 2H, O-C$\underline{H}_2$), 6.85-8.20 (m, 9H, aromatic).

Synthesis of t-butyl 1-benzylindole-3-acetate (4b)

A solution of 1-benzylindole-3-acetic acid[11] (10.0 g, 37.7 mmol), t-butanol (10.6 ml, 0.11 mol) and DMAP (0.5 g) dissolved in 100 ml dry dichloromethane, was stirred at 0°C. Dicyclohexylcarbodiimide (8.6 g, 41.6 mmol) was added over a period of 5 minutes from a solid addition funnel, the ice bath was removed and the reaction mixture stirred for 3 hours at room

temperature. The precipitated dicyclohexylurea was removed by filtration and the filtrate washed with dilute hydrochloric acid and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The product was isolated by column chromatography (ethyl acetate-hexane) and crystallized from ethyl acetate-hexane to afford **4b** (4.3 g) as yellow crystals, m.p. 59°-60°C; ^{1}H N.m.r. ($CDCl_3$) δ 1.44 (s, 9H, t-Butyl), 3.67 (s, 2H, Ind-C$\underline{H}_2$), 5.27 (s, 2H, N-C$\underline{H}_2$), 7.09-7.62 (m, 9H, aromatic); ^{13}C N.m.r. ($CDCl_3$) δ 28.07 (t-butyl), 32.61 (C$\underline{H}_2$), 49.96 (C$\underline{H}_2$), 80.57 (C$\underline{(CH_3)_3}$), 108.32-137.57 (aromatic), 171.34 ($\underline{C}$O); Calcd for $C_{21}H_{23}NO_2$: C, 78.50; H, 7.16; N, 4.36. Found C, 78.03; H, 7.89; N, 4.62.

Synthesis of keto-amino acids (5a-b, 6a-c). General procedure

A solution of diisopropylamine (1.1 mmol, 0.15 ml) in 5 ml dry THF was stirred under nitrogen at -78°C. n-Butyllithium (1.1 mmol, of a 1.5 N solution in hexane) was added by syringe and the solution stirred for 10 minutes at -78°C. LDA formation was allowed to proceed for 30 minutes at room temperature. The LDA solution was cooled to -78°C and the protected indole acetate (1 mmol), dissolved in 2 ml dry THF, added by syringe. The solution was stirred for 30 minutes at -78°C followed by addition by syringe of the corresponding protected anhydride (0.5 mmol) in 2 ml dry THF. After stirring of the solution at -78°C for 2 hours, 1N HCl was added and the pH

adjusted to 3. THF was removed *in vacuo* and the aqueous phase extracted with ethyl acetate, the combined organic layers dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The product was isolated by column chromatography, dissolved in 15 ml methanol and 25 mg palladium/charcoal added. The mixture was hydrogenated for 1 hour at 1 atmosphere pressure. The mixture was filtered, and the solution treated with diazomethane. The product was isolated by column chromatography.

The following derivatives were prepared by this method.

Methyl 2-(t-butyloxycarbonylamino)-5-(N-t-butyloxycarbonylindolyl-3')-4-oxopentanoate (5a) and methyl 3-(t-butyloxycarbonylamino)-5-(N-t-butyloxycarbonyl-3')-4-oxopentanoate (6a)

Reaction with 1.41 g N-t-butyloxycarbonyl-L-aspartic anhydride[6a] and 4.80 g benzyl 1-t-butyloxycarbonylindole-3-acetate, afforded i) compound **5a** in 30 % yield (oil): $[\alpha]^{25}_{D}$ +27.9 (c, 0.39); ^{1}H N.m.r. ($CDCl_3$) δ 1.38 (s, 9H, t-Boc), 1.64 (s, 9H, t-Boc), 2.99 (dd, 1H, J=18.1 Hz, J=4.3 Hz, C$\underline{H}_2$-CH), 3.19 (dd, 1H, J=18.1 Hz, J=4.3 Hz, C$\underline{H}_2$-CH), 3.62 (s, 3H, O-C$\underline{H}_3$), 3.74 (s, 2H, Ind-C$\underline{H}_2$), 4.46 (m, 1H, CH_2-C$\underline{H}$), 5.44 (d, 1H, NH), 7.19-8.11 (m, 5H, indole); ^{13}C N.m.r. ($CDCl_3$) δ 28.15, 39.55 (t-Boc), 43.55 (C$\underline{H}_2$-CH), 49.48 (CH_2-C$\underline{H}$), 52.47 (O-C$\underline{H}_3$), 80.00, 83.70 (C$\underline{C}$[CH_3]$_3$), 112.57-135.42 (indole), 149.47, 155.43 (N-C$\underline{O}$), 171.70 (C$\underline{O}$-OCH_3), 206.00 (ketone); Calcd accurate mass for $C_{24}H_{32}N_2O_7$: 460.2209,

Found: 460.2187, and

ii) compound **6a** in 30% yield, m.p. 88°-89° C (ethyl acetate-hexane); $[\alpha]^{25}_D$ -39.6 (c, 0.44); ^{1}H N.m.r. ($CDCl_3$) δ 1.45, 1.64 (s, 9H, t-Boc), 2.77 (dd, 1H, J=17.1 Hz, J=4.9 Hz, C$\underline{H}_2$-CH), 2.98 (dd, 1H, J=17.1 Hz, J=4.9 Hz, C$\underline{H}_2$-CH), 3.64 (s, 3H, O-C$\underline{H}_3$), 3.94 (d, 1H, J=17.3 Hz, Ind-C$\underline{H}_2$), 4.00 (d, 1H, J=17.3 Hz, Ind-C$\underline{H}_2$), 4.58 (m, 1H, CH_2-C$\underline{H}$), 5.66 (d, 1H, NH), 7.18-8.11 (Indole); ^{13}C N.m.r. ($CDCl_3$) δ 28.16, 35.61 (t-Boc), 51.98 (O-$\underline{C}H_3$), 55.41 (CH_2-$\underline{C}H$), 80.43, 83.54 ($\underline{C}[CH_3]_3$), 112.59-135.38 (Indole), 149.53, 155.36 (N-$\underline{C}O$), 171.96 ($\underline{C}O$-OCH_3), 205.30 (ketone); Anal Calcd for $C_{26}H_{32}N_2O_7$: C, 62.60; H, 6.95; N, 6.08. Found C, 61.97; H, 6.82; N, 6.13.

Methyl 2-(benzyloxycarbonylamino)-5-(N-benzylindolyl-3')-4-oxopentanoate (5b) and methyl 3-(benzyloxycarbonylamino)-5-(N-benzylindolyl-3')-4-oxo-pentanoate (6b)

Reaction with 0.77 g N-carbobenzoxy-L-aspartic anhydride[6b] and 2 g t-butyl 1-benzylindole-3-acetate, afforded the coupled products in an overall yield of 56 %. Deprotection of the t-butyl ester with p-toluenesulfonic acid in refluxing benzene, was followed by esterification with diazomethane as previously described, to give

i) **5b** in 19 % yield (oil): $[\alpha]^{22}_D$ +12.8 (c, 0.28); ^{1}H N.m.r. ($CDCl_3$) δ 2.99 (dd, 1H, J=18.3 Hz, J=4.0 Hz, C$\underline{H}_2$-CH), 3.23 (dd, 1H, J=18.3 Hz, J=4.0

Hz, C$\underline{H}_2$-CH), 3.59 (s, 3H, O-C$\underline{H}_3$), 3.79 (s, 2H, Ind-C$\underline{H}_2$), 4.52 (m, 1H, CH_2-C$\underline{H}$), 5.05 (s, 2H, O-C$\underline{H}_2$), 5.26 (s, 2H, C$\underline{H}_2$-phenyl), 7.04 - 7.49 (m, 15H, aromatic); 13C N.m.r. ($CDCl_3$) δ 39.86 (C$\underline{H}_2$-CH), 40.94 (Ind-C$\underline{H}_2$), 49.95 (O-C$\underline{H}_3$), 52.46 (O-C$\underline{H}_2$), 52.65 (CH_2-C$\underline{H}$), 69.79 (C$\underline{H}_2$-phenyl), 116.75 - 139.66 (aromatic), 155.98 (C$\underline{O}$-CH_2-phenyl), 171.46 (C$\underline{O}$-OCH_3), 207.02 (ketone); Calcd accurate mass for $C_{29}H_{28}N_2O_5$: 484.1998, Found: 484.1970, and

ii) **6b** in 37% yield (oil): $[\alpha]^{22}_D$ +0.00 (c, 0.16); ^{1}H N.m.r. ($CDCl_3$) δ 2.77 (dd, 1H, J=16.9 Hz, J=4.7 Hz, C$\underline{H}_2$-CH), 2.96 (dd, 1H, J=16.9 Hz, J=4.5 Hz, C$\underline{H}_2$-CH), 3.58 (s, 3H, O-C$\underline{H}_3$), 4.00 (s, 2H, C$\underline{H}_2$-phenyl), 4.66 (m, 1H, CH_2-C$\underline{H}$), 5.06 (d, 1H, J=13.0 Hz, Ind-C$\underline{H}_2$), 5.10 (d, 1H, J=13.0 Hz, Ind-C$\underline{H}_2$), 5.25 (s, 2H, O-C$\underline{H}_2$), 7.04 - 7.51 (m, 15H, aromatic); ^{13}C N.m.r. ($CDCl_3$) δ 35.65 (C$\underline{H}_2$-CH), 36.14 (Ind-C$\underline{H}_2$), 50.05 (O-C$\underline{H}_3$), 51.97 (C$\underline{H}_2$-phenyl), 55.47 (CH_2-C$\underline{H}$), 109.81 - 137.37 (aromatic), 156.50 (C$\underline{O}$-CH_2), 171.80 (C$\underline{O}$-OCH_3), 205.31 (ketone); Calcd accurate mass for $C_{29}H_{28}N_2O_5$: 484.1998, Found: 484.1970.

Methyl 3-(acetylamino)-5-(N-t-butyloxycarbonylindolyl-3')-4-oxopentanoate (6c)

Reaction with 1 g N-acetyl-L-aspartic anhydride[6c] and 4.64 g benzyl 1-t-butyloxycarbonylindole-3-acetate, afforded compound **6c** in 25 % yield (oil):

$[\alpha]^{22}_D$ -18.0 (c, 0.2); ^{1}H N.m.r. ($CDCl_3$) δ 1.63 (s, 9H, t-Boc), 2.03 (s, 3H, N-acetyl), 2.79 (dd, 1H, J=15.0 Hz, J=4.9 Hz, C$\underline{H}_2$-CH), 2.97 (dd, 1H, J=15.0 Hz, J=4.5 Hz, C$\underline{H}_2$-CH), 3.64 (s, 3H, O-C$\underline{H}_3$), 3.89 (d, 1H, J=17.1 Hz, Ind-C$\underline{H}_2$), 3.95 (d, 1H, J=17.1 Hz, Ind-C$\underline{H}_2$), 4.89 (m, 1H, CH_2-C$\underline{H}$), 6.70 (s, 1H, NH), 7.17 - 8.13 (m, 5H, indole); ^{13}C N.m.r. ($CDCl_3$) δ 28.16 (t-Boc), 35.16 (C$\underline{H}_2$-CH), 35.63 (Ind-C$\underline{H}_2$), 52.08 (CH_2-C$\underline{H}$), 54.14 (O-C$\underline{H}_3$), 83.70 (C-[CH_3]$_3$), 112.35 - 136.49 (Indole).

Synthesis of t-butyl 1-p-toluenesulfonylindole-3-acetate (7)

A solution of 1-p-toluenesulfonylindole-3-acetic acid[12] (7.2 g, 22.1 mmol), phosphoric acid (1.0 g) and boron trifluoride/etherate (1.3 ml) was stirred in 140 ml dry dichloromethane at room temperature. Isobutylene gas was bubbled through the solution in small bursts for two hours and the solution stirred for a further two hours at room temperature. The reaction mixture was poured into an aqueous sodium bicarbonate solution, the organic layer was separated and the solvent and polyisobutylene removed *in vacuo*. The brown residue was purified by column chromatography (toluene-ethyl acetate) and the product recrystallized from toluene-hexane to afford 6.7 g **7** as pale yellow crystals, m.p. 80-81°C; ^{1}H N.m.r. ($CDCl_3$) δ 1.42 (s, 9H, t-butyl), 2.31 (s, 3H, Tosyl), 3.59 (s, 2H, Ind-C$\underline{H}_2$), 7.17-8.00 (9H, m, aromatic); ^{13}C N.m.r. ($CDCl_3$, δ 21.44 (Tosyl), 27.94 (t-butyl), 32.37 (Ind-C$\underline{H}_2$), 81.15 (C(CH_3)$_3$), 113.64-144.98 (aromatic), 169.60 (C$\underline{O}$); M^+ 385

(Calcd for $C_{21}H_{23}NO_4S$: M, 385); Anal Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found C, 65.67; H, 6.03; N, 3.72.

Synthesis of α-methyl N-Carbobenzoxy-L-aspartic acid chloride (8)

α-Methyl N-Carbobenzoxy-L-aspartate[8] (0.05 g, 0.17 mmol) was dissolved in 10 ml dry THF and stirred under nitrogen at 0°C. Thionyl chloride (0.1 ml, 0.9 mmol) was added by syringe at 0°C and the solution refluxed for one hour. The solvent was removed *in vacuo* and the product **8** crystallized, m.p. 56°-59°C; ^{1}H N.m.r. ($CDCl_3$) δ 3.48 (dd, 1H, J=18.5 Hz, J=3.7 Hz, CH-C$\underline{H}_2$), 3.56 (dd, 1H, J=18.5 Hz, J=3.7 Hz, CH-C$\underline{H}_2$), 3.74 (s, 3H, O-C$\underline{H}_3$), 4.58 (m, 1H, C$\underline{H}$-CH_2), 5.10 (s, 2H, O-C$\underline{H}_2$), 5.72 (d, 1H, NH), 7.30-7.35 (m, 5H, aromatic); ^{13}C N.m.r. ($CDCl_3$) δ 48.75 ($\underline{C}H_2$-CH), 50.56 (CH_2-$\underline{C}$H), 53.10 (O-$\underline{C}H_3$), 67.33 (O-$\underline{C}H_2$), 127.99-135.75 (aromatic), 155.67 (N-$\underline{C}$O), 169.70 ($\underline{C}$O-Cl), 171.86 ($\underline{C}$O-CH_3); Anal. Calcd for $C_{13}H_{14}ClNO_5$: C, 52.08; H, 4.67; N, 4.67. Found C, 52.76; H, 4.96; N, 5.10.

Synthesis of methyl 2-(benzyloxycarbonylamino)-5-(p-toluenesulfonyl-indolyl-3')-4-oxopentanoate (9)

A solution of diisopropylamine (1.3 g, 13.0 mmol) in 10 ml dry THF was stirred under nitrogen at -78°C. n-Butyllithium (13.0 mmol, 8.1 ml, of a 1.6 N solution in hexane) was added by syringe and the solution stirred for

10 minutes at -78°C. After 30 minutes at room temperature the LDA solution was cooled to -78°C and t-butyl N-p-toluenesulfonyl indole-3-acetate (5.0 g, 13.0 mmol), dissolved in 5 ml dry THF, added by syringe. The solution was stirred for 30 minutes at -78°C and α-methyl N-Carbobenzoxy-L-aspartic acid chloride (1.8 g, 6.2 mmol), dissolved in 10 ml dry THF, added slowly by syringe. After stirring of the solution at -78°C for 2 hours, 1N HCl was added and the pH adjusted to 3. THF was removed *in vacuo* and the aqueous phase extracted with ethyl acetate, the combined organic layers dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The product was isolated by column chromatography, affording 1.8 g of the coupling product as an oil. This product (1.8 g, 2.8 mmol) was dissolved in 10 ml dry toluene, p-toluenesulfonic acid (34 mg, 0.2 mmol) added, and the mixture refluxed for 6 hours under nitrogen. Removal of the solvent *in vacuo* was followed by column chromatography to afford **9** in 55 % yield (based on the acid chloride) as a colourless oil: ^{1}H N.m.r. ($CDCl_3$) δ 2.30 (s, 3H, Tosyl), 2.96 (dd, 1H, J=18.0 Hz, J=4.2 Hz, C$\underline{H}_2$-CH), 3.18 (dd, 1H, J=18.0 Hz, J=4.2 Hz, C$\underline{H}_2$-CH), 3.59 (s, 3H, O-CH_3), 3.71 (s, 2H, Ind-C$\underline{H}_2$), 4.53 (m, 1H, CH_2-C$\underline{H}$), 5.06 (s, 2H, O-C$\underline{H}_2$), 5.70 (d, 1H, NH), 7.17-7.97 (m, 14H, aromatic); ^{13}C N.m.r. ($CDCl_3$) δ 21.47 (Tosyl), 36.65 ($\underline{C}H_2$-CH), 39.24 (Ind-$\underline{C}H_2$), 49.89 (CH_2-$\underline{C}$H), 52.57 (O-$\underline{C}H_3$), 64.94 (O-$\underline{C}H_2$), 113.71-144.97 (aromatic), 155.93 ($\underline{C}$O-CH_2-phenyl), 171.21 ($\underline{C}$O-OCH_3), 205.12 (ketone); M^+ 548 (Calcd for $C_{29}H_{28}N_2O_7S$: M, 548).

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