

The synthesis and reactions of some *N*-acyl-*N*-aryliminium ions

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Dedicated to Professor Gurnos Jones on the occasion of his 70th birthday

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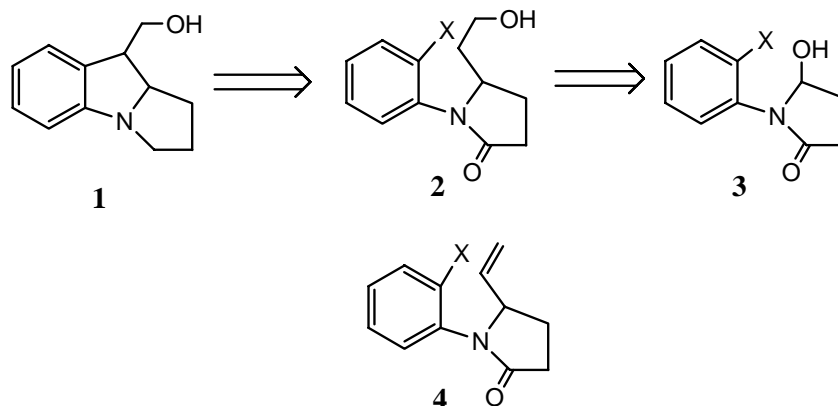
Abstract

The synthesis of the *N*-acyl-*N*-aryliminium ion precursors 6 and 13 is presented and their reactions with vinyl organometallics is explored. The synthesis of *N*-phenyl-5-(prop-2-enyl)pyrrolidin-2-one 16 using *N*-acyliminium ion chemistry is described and its transformation to iodoester 21 is presented.

Keywords: *N*-Acyl-*N*-aryliminium ions, vinyl organometallics, Diels-Alder reaction

Introduction

We have been interested in the synthesis of the pyrrolo[1,2-*a*]indolenine skeleton 1 for some time.¹ It forms the tricyclic core of the mitomycins and has been the subject of a number of synthetic approaches by a wide variety of different strategies. We have disclosed three different syntheses of this ring system employing both radical and carbanion intermediates.² Each of our routes has drawbacks and consequently, we decided to explore the disconnection shown in scheme 1.

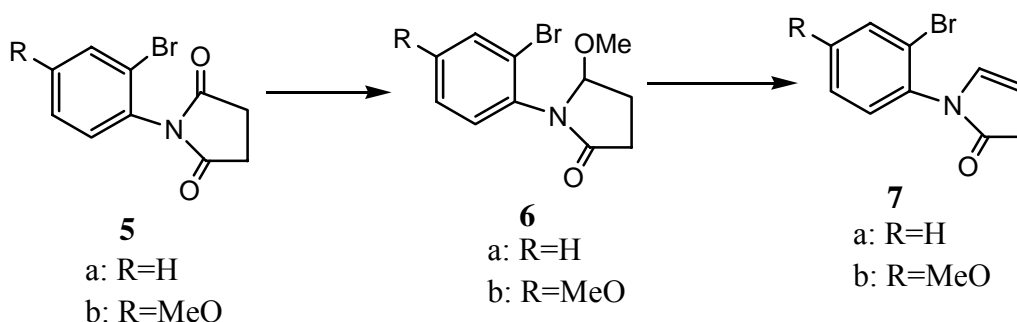


Scheme 1

Disconnection of the C-8a/C-9 bond leads to the 5-substituted-*N*-aryl-2-pyrrolidinone 2 as a key intermediate. The obvious method to prepare such compounds is via *N*-acyliminium ion chemistry utilising the 5-hydroxy-*N*-aryl-2-pyrrolidinone 3 or its methyl ether as the precursor of this reactive intermediate. Although *N*-acyliminium ion chemistry has been investigated extensively by the group of Speckamp in particular,³ *N*-aryl substituted systems have been much less extensively explored.⁴ Our first target became the preparation of the vinyl-substituted pyrrolidinone 4 which should give the pyrrolo[1,2-*a*]indolenine system *via* radical cyclisation.

Results and Discussion

The *N*-(2-bromophenyl)succinimide 5a⁵ was prepared by heating 2-bromoaniline with succinic anhydride in toluene to give the succinamic acid which was cyclised to the imide by heating with acetic anhydride and sodium acetate to give 5a in 80% yield. A one-pot reduction-methylation procedure using lithium triethylborohydride as the reductant⁶ and then acidic methanol gave the 5-methoxy-2-pyrrolidinone 6a in 61% yield after chromatography. The reaction of *N*-acyliminium ions with vinyl magnesium bromide is well precedented.⁷ However, treatment of 6a with vinyl magnesium bromide and boron trifluoride diethyl etherate at -78 °C gave a mixture of compounds containing none of the desired product. The enamine 7a was tentatively identified as the major product. Clearly, rather than act as a nucleophile to the *N*-acyliminium ion, the Grignard reagent has acted as a base leading to deprotonation. Consequently, we explored the use of a cuprate reagent to achieve this transformation but again, all attempts were unsuccessful.

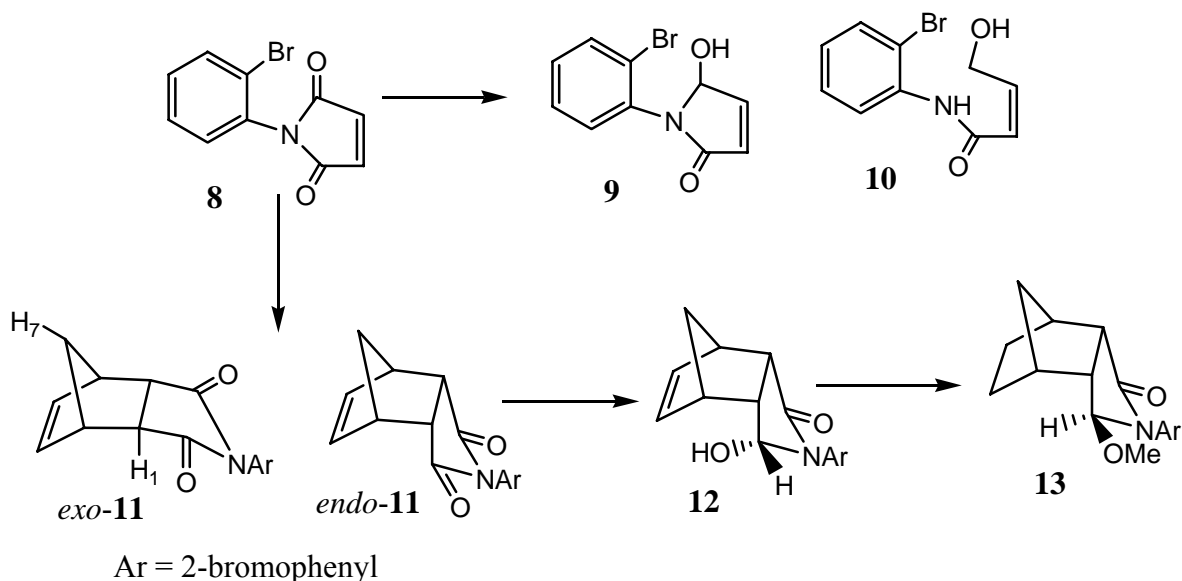


Scheme 2

The ease of elimination from this system caused us to consider whether additional stabilisation of the *N*-acyliminium ion would allow preferential addition. To this end, we prepared the *para*-methoxy substituted series based on the idea that the electron-releasing methoxy group would provide the desired stabilisation. The succinimide 5b was readily prepared in 87% yield as described for 5a. Imide 5b was converted into *N*-acyliminium ion precursor 6b

by reduction and methylation in 57% yield. However, reaction with vinyl magnesium bromide and a Lewis acid again gave enamine 7b as the only identifiable product.

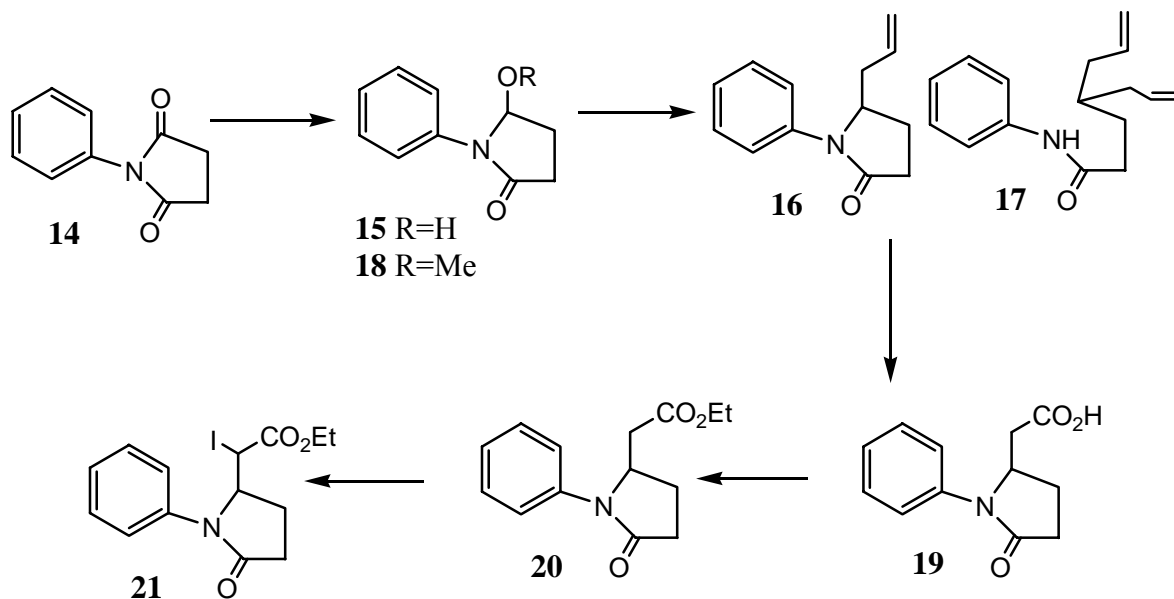
At this juncture, we decided to explore the corresponding reactions of the *N*-arylmaleimide series as the presence of the extra double bond should prevent elimination to form the enamine. The *N*-arylmaleimide 8 was prepared in a similar manner to the succinimides in 89% yield. Lithium triethylborohydride reduction gave rise to a mixture of several products and the required reduction was best achieved using sodium borohydride and cerium(III) chloride⁸ to give the hydroxy compound 9 in 40% yield along with 26% of ring opened product 10. Attempts to make the methyl ether of 9 failed under a variety of conditions and as this must proceed through the iminium ion, it was felt that further exploration of this system would be fruitless. Possibly conjugation with the lactam carbonyl through the double bond destabilises the carbocation significantly and prevents its formation.



Scheme 3

In order to temporarily remove the double bond,⁹ maleimide 8 was reacted with freshly cracked cyclopentadiene to give the Diels-Alder adduct 11 in quantitative yield as a 4:1 mixture of *endo:exo* isomers. This assignment of stereochemistry was based on the fact that in the major isomer, the H1/H6 signals in the proton nmr appeared as a singlet whereas in the minor isomer they appeared as a doublet of doublets with coupling to H2/H5 and to H7 by a long-range coupling. Only in the *exo*-isomer are the H1/H6 and one of the H7 protons in the correct orientation to display a $J=4$ Hz coupling. Reduction of this mixture using lithium triethylborohydride gave a 75% yield of the single diastereoisomer 12. Either the minor *exo*-isomer reacted more slowly or was simply purified out of the mixture on crystallisation. Reduction would be expected to occur on the open face of *endo*-11 and in accord with this the

proton next to the newly-formed hydroxyl group appears as a 7.4 Hz doublet at δ 4.89 indicating a dihedral angle close to zero. Reaction with methanol and *p*-toluenesulfonic acid gave the methyl ether 13 again as a single diastereomer but this time possessing the opposite stereochemistry at the methyl ether centre. Confirmation of this assignment again comes from the proton nmr in which the proton at the methyl ether centre now appears as a singlet at δ 4.74 in good accord with a dihedral angle of 120° . This is entirely expected if reaction proceeds through the iminium ion with attack by methanol on the outer face of the C=N. With the *N*-acyliminium ion precursor in hand, reaction with vinyl magnesium bromide under a variety of conditions involving both addition of copper(I) salts and Lewis acid gave poor yields of compounds assigned ring-opened structures.¹⁰



Scheme 4

With no success in functionalising suitable *N*-aryl systems using vinylic organometals, we decided to switch to the *N*-phenylsuccinimide system and explore the addition of an allyl sidechain *via* *N*-acyliminium ion chemistry. *N*-Phenylsuccinimide 14 was prepared as described for the other succinimides. Reduction with lithium triethylborohydride gave a quantitative yield of the hydroxy compound 15. Reaction of 15 with allyltrimethylsilane using tin(IV) chloride as the Lewis acid gave 5-allyl-2-pyrrolidinone 16 in 42% yield along with some 38% of ring-opened product 17. We felt this low yield could be caused by tin residues in the work up and so we explored the preparation of 16 *via* the methoxy compound 18. Reaction of 15 with methanol and *p*-toluenesulfonic acid overnight gave methyl ether 18 in 93% yield. Treatment with allyltrimethylsilane using boron trifluoride diethyletherate as Lewis acid at -78°C gave 45% of the desired product 16 along with 32% yield of ring-opened product 17. The similarity of these two results indicates that the intermediate *N*-acyl-*N*-phenyliminium ion is not as well-behaved as

N-alkyl analogues and has a propensity for a considerable degree of ring-opening under Lewis acid conditions. Further manipulation of the allyl group to give an appropriate C2 fragment was achieved by ozonolysis at low temperature in methanol followed by an oxidative work up using hydrogen peroxide in 90% formic acid to give the acid 19 in excellent yield. Esterification in acidic ethanol gave the ethyl ester 20 in 66% yield which was converted into the α -iodoester 21 by formation of the enolate with LDA at -78 °C followed by addition of iodine. The yield of this reaction was only 24% and some 31% of starting ester 20 was also recovered. Iodoester 21 was formed as a 2:1 mixture of diastereomers indicating that the stereogenic centre in the enolate derived from 20 exerts only a small effect on the facial selectivity of the reaction.

In summary, we have shown that *N*-acyl-*N*-aryliminium ions do not react with vinyl organometallic reagents to give cyclic products. The parent *N*-phenyl compound does undergo allylation with allylsilanes but in relatively poor yield and the side chain can be manipulated to give a suitable precursor for studying the homolytic substitution reaction as a route to pyrrolo[1,2-*a*]indolenines.¹¹ We hope to be able to report on this reaction in the near future.

Experimental Section

***N*-(2-Bromophenyl)succinimide (5a).** A solution of succinic anhydride (6.9 g, 69.7 mmol) and 2-bromoaniline (10 g, 58.1 mmol) in toluene (120 mL) was heated under reflux for 2.5 h, cooled, and filtered to give crude succinamic acid (15.5 g, 98%). A mixture of this acid (15.5 g, 57.1 mmol), sodium acetate (15.7 g, 188.7 mmol) and acetic anhydride (150 mL) was stirred at 80 °C for 4.5 h. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (100 mL), washed with water (3 x 100 mL) and saturated ammonium chloride solution (100 mL). The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure to give 5a as a white solid (11.8 g, 81%), which was recrystallised from ethyl acetate-hexane; m.p. 112-114 °C (lit.⁵ 112-113 °C); *R*_f(3:7 EtOAc-hexane) 0.13; ν_{\max} /cm⁻¹ 2924, 2854 (w,w, aliphatic C-H), 1709 (s, C=O), 1458 (m, C=C benzene ring); ¹HNMR (360 MHz; CDCl₃) δ 7.70 (1H, dd, *J*=8.0, 1.5 Hz, H-3'), 7.43 (1H, td, *J*=8, 1.5 Hz, H-5'), 7.32 (1H, td, *J*=8, 1.5 Hz, H-4'), 7.20 (1H, dd, *J*=8, 1.5 Hz, H-6'), 2.84-2.99 (4H, m, 2xH-2, 2xH-3); ¹³CNMR (90 MHz; CDCl₃) 175.5 (C=O), 133.6 (C-3'), 131.8 (C-1'), 131.1 (C-5'), 130.0 (C-4'), 128.6 (C-6'), 122.3 (C-2'), 28.8 (C-2, C-3); *m/z* 255 (5%, M⁺,⁸¹Br), 253 (5, M⁺,⁷⁹Br), 174 (100, M⁺-Br) (Found: M⁺ (⁷⁹Br) 252.9739. C₁₀H₈⁷⁹BrNO₂ requires M⁺ 252.9738).

***N*-(2-Bromo-4-methoxyphenyl)succinimide (5b).** A solution of succinic anhydride (1.19 g, 11.9 mmol) and succinimide (2 g, 9.9 mmol) in toluene (20 mL) was heated under reflux for 2.5 h, cooled, and filtered to give crude succinamic acid (2.89 g, 97%). A mixture of this acid (2.89 g, 9.6 mmol), sodium acetate (2.6 g, 31.7 mmol) and acetic anhydride (20 mL) was stirred at 80 °C for 4.5 h. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (100 mL) and washed with water (3'100 mL) and saturated ammonium chloride solution (100 mL). The organic layer was dried (MgSO₄), filtered and

evaporated under reduced pressure to give 5b as a beige solid (2.44 g, 87%), which was recrystallised from ethyl acetate-hexane. mp 122-124 °C; R_f (1:1 EtOAc-hexane) 0.16; $\nu_{\max}/\text{cm}^{-1}$ 3045 (w, aromatic C-H), 2943 (w, aliphatic C-H), 1720 (s, C=O), 1601 (m, benzene ring), 1039 (s, C-O-C symmetric stretching); $^1\text{H NMR}$ (360 MHz; CDCl_3) δ 7.23 (1H, d, $J=2.7$ Hz, H-3'), 7.11 (1H, d, $J=8.7$ Hz, H-6'), 6.95 (1H, dd, $J=8.7, 2.7$ Hz, H-5'), 3.81 (3H, s, OCH_3), 2.99-2.85 (4H, m, 2xH-2, 2xH-3); $^{13}\text{C NMR}$ (90 MHz; CDCl_3) 175.0 (C=O), 160.8 (C-4'), 130.3 (C-1'), 124.1 (C-6'), 122.8 (C-3'), 118.7 (C-2'), 114.5 (C-5'), 55.9 (OCH_3), 28.6 (2x CH_2); m/z 285 (8, M^+ , ^{81}Br), 283 (8%, M^+ , ^{79}Br), 204 (100, M^+ -Br) (Found: M^+ (^{79}Br) 282.9860. $\text{C}_{11}\text{H}_{10}\text{BrNO}_3$ requires M^+ 282.9864).

***N*-(2-Bromophenyl)-5-methoxypyrrolidin-2-one (6a).** To a solution of 5a (2 g, 7.87 mmol) in THF (60 mL) was added Super Hydride[®] (1 M in THF, 9.5 mL, 9.45 mmol) dropwise at -78 °C under argon. The reaction was stirred at this temperature for 40 minutes and quenched with saturated sodium bicarbonate solution (20 mL). The resulting solution was allowed to stand until the temperature reached 0 °C, then 50 drops of hydrogen peroxide (33% w/v) were added and the mixture stirred for 20 minutes. The aqueous layer was extracted with dichloromethane (3x40 mL), the combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure. The crude product was dissolved in methanol (25 mL) and *p*-toluenesulfonic acid (0.15 g, 0.8 mmol) was added and the resulting solution stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL). After removal of methanol under reduced pressure, the aqueous layer was extracted with ether (3x20 mL), the combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure. The resulting residue was purified by column chromatography (1:1 EtOAc-hexane) to give 6a as a pale yellow oil (1.28 g, 61%); R_f (3:7 EtOAc-hexane) 0.16; $\nu_{\max}/\text{cm}^{-1}$ 3064 (w, aromatic C-H), 2936, 2828 (m,m, aliphatic C-H), 1715 (C=O), 1478 (benzene ring); $^1\text{H NMR}$ (360 MHz; CDCl_3) δ 7.65 (1H, dd $J=8, 1.3$ Hz, H-3'), 7.34-7.40 (2H, m, H-5'+ H-6'), 7.23 (1H, td, $J=8.0, 1.4$ Hz, H-4'), 5.20 (1H, dd, $J=6.0, 1.3$ Hz, H-5), 3.23 (3H, s, OCH_3), 2.77-2.65 (1H, m, H-3 or H-4), 2.53-2.38 (2H, m, 2x (H-3 or H-4)), 2.21-2.12 (1H, m, H-3 or H-4); $^{13}\text{C NMR}$ (90 MHz; CDCl_3) 174.8 (C=O), 136.2 (C-1'), 133.9 (C-3'), 131.2 (C-5'), 129.8 (C-4'), 128.4 (C-6'), 122.4 (C-2'), 92.4 (C-5), 55.4 (OCH_3), 28.9 (CH_2), 25.6 (CH_2); m/z 271 (2%, M^+ , ^{81}Br), 269 (2, M^+ , ^{79}Br), 240 (22, M^+ (^{81}Br)- CH_3O), 238 (20, M^+ (^{79}Br)- CH_3O), 190 (100, M^+ -Br) (Found: M^+ (^{79}Br) 269.0037. $\text{C}_{11}\text{H}_{12}^{79}\text{BrNO}_2$ requires M^+ 269.0051).

***N*-(2-Bromo-4-methoxyphenyl)-5-methoxypyrrolidin-2-one (6b).** To a solution of 5b (0.15 g, 0.528 mmol) in THF (10 mL) was added Super Hydride[®] (1 M in THF, 0.62 mL, 0.623 mmol) dropwise at -78 °C under argon. The reaction was stirred at this temperature for 40 minutes and quenched with saturated sodium bicarbonate solution (5 mL). The resulting solution was allowed to stand until the temperature reached 0 °C, then 5 drops of hydrogen peroxide (33% w/v) were added and the mixture stirred for 20 minutes. The aqueous layer was extracted with dichloromethane (3x10 mL), the combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure. The crude product was dissolved in methanol (10 mL) and *p*-toluenesulfonic acid (10 mg, 0.053 mmol) was added and the resulting solution stirred at room

temperature for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL). After removal of the methanol under reduced pressure, the aqueous layer was extracted with ether (3x10 mL), the combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give 6b as a colourless oil (90 mg, 57%) which required no further purification; R_f (EtOAc) 0.37; $\nu_{\text{max}}/\text{cm}^{-1}$ 3045 (w, aromatic C-H), 2948 (w, aliphatic C-H), 1712 (s, C=O), 1052 (s, C-O-C symmetric stretching); $^1\text{HNMR}$ (360 MHz; CDCl_3) δ 7.24 (1H, d, $J=8.7$ Hz, H-6'), 7.18 (1H, d, $J=2.8$ Hz, H-3'), 6.90 (1H, dd, $J=8.7, 2.8$ Hz, H-5'), 5.13 (1H, dd, $J=6.0, 1.5$ Hz, H-4), 3.80 (3H, s, aromatic OCH_3), 3.24 (3H, s, OCH_3), 2.75-2.62 (1H, m, H-3 or H-4), 2.52-2.36 (2H, m, H-3 or H-4), 2.11-2.19 (1H, m, H-3 or H-4); $^{13}\text{CNMR}$ (90 MHz; CDCl_3) 175.07 (C=O), 159.8 (C-4'), 131.53 (C-1'), 128.7 (C-6'), 122.8 (C-3'), 118.4 (C-2'), 114.2 (C-5'), 92.5 (C-5), 55.7 (OCH_3), 55.4 (OCH_3), 28.8 (C-3 or C-4), 25.5 (C-3 or C-4); m/z 301 (12%, M^+ , ^{81}Br), 299 (12, M^+ , ^{79}Br) 220 (100, M^+ -Br) (Found: M^+ (^{79}Br) 299.0180. $\text{C}_{12}\text{H}_{14}^{79}\text{BrNO}_3$ requires M^+ 299.0157).

***N*-(2-Bromophenyl)maleimide (8).** 2-Bromoaniline (2 g, 11.63 mmol) in toluene (30 mL) was added dropwise to a solution of maleic anhydride (1.37 g, 13.95 mmol) in toluene (15 mL) at 35 °C. After addition was complete the reaction was allowed to stir for 16 h at room temperature. The crude acid was cooled and filtered under vacuum. This acid (2.88 g, 10.7 mmol) was then dissolved in acetic anhydride (30 mL), sodium acetate (2.9 g, 35.33 mmol) was added and the reaction heated at 80 °C for 5 h. The reaction mixture was poured onto water (50 mL) and extracted with dichloromethane (3x50 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give 8 as a biege solid (2.58 g, 89%), which was recrystallised from ethyl acetate-hexane; mp 70-74 °C; R_f (1:1 EtOAc-hexane) 0.38; $\nu_{\text{max}}/\text{cm}^{-1}$ 3101 (w, aromatic C-H), 2985 (w, aliphatic C-H), 1719 (s, C=O), 1585 (m, C=C ring stretching); $^1\text{HNMR}$ (360 MHz; CDCl_3) δ 7.71 (1H, dd, $J=7.6, 1.5$ Hz, H-3'), 7.42 (1H, td, $J=7.6, 1.5$ Hz, H-5'), 7.33 (1H, td, $J=7.6, 1.7$ Hz, H-4'), 7.26 (1H, dd, $J=7.6, 1.7$ Hz, H-6'), 6.88 (2H, s, H-3, H-4); $^{13}\text{CNMR}$ (90 MHz; CDCl_3) 168.9 (C=O), 134.6 (C-3 + C-4), 133.7 (C-3'), 131.1 (C-5'), 131.0 (C-4'), 130.8 (C-1'), 128.5 (C-6'), 123.3 (C-2'); m/z 253 (30%, M^+ , ^{81}Br), 251 (30, M^+ , ^{79}Br), 172 (100, M^+ -Br) (Found M^+ (^{79}Br) 250.9591. $\text{C}_{10}\text{H}_6\text{BrNO}_2$ requires M^+ 250.9582).

***N*-(2-Bromophenyl)-5-hydroxy-3,4-dehydropyrrolidin-2-one (9).** To a solution of 8 (1 g, 3.97 mmol) in methanol (10 mL) at 0 °C was added cerium trichloride heptahydrate (1.8 g, 4.76 mmol) followed by sodium borohydride (0.18 g, 4.76 mmol). The reaction was allowed to stir for 30 minutes after which time the reaction mixture was poured onto water (20 mL) and extracted with ethyl acetate (3x20 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give a white solid (0.97 g) which was purified by chromatography (2:3 ethyl acetate-hexane) to give 9 as a white solid (0.4 g, 40%), which was recrystallised from dichloromethane; mp 84-86 °C; R_f (50% EtOAc-hexane) 0.32; $\nu_{\text{max}}/\text{cm}^{-1}$; 3377 (m, O-H), 3053 (m, aromatic C-H), 2966 (m, aliphatic C-H), 1711 (s, C=O), 1586 (m, benzene ring); $^1\text{HNMR}$ (360 MHz; CDCl_3) δ 7.69 (1H, dd, $J=7.9, 1.5$ Hz, H-3'), 7.39 (1H, td, $J=7.8, 1.5$ Hz, H-5'), 7.29 (2H, m, H-4', H-6'), 7.08 (1H, dd, $J=6.0, 1.7$ Hz, H-4), 6.30 (1H, dd, $J=6.0, 1.0$ Hz, H-3), 5.85 (1H, m, H-5), 2.75 (1H, brs, OH); $^{13}\text{CNMR}$ (90MHz; CDCl_3) 168.6 (C=O),

146.1, 134.6, 133.6, 131.6, 130.1, 128.6, 128.5, 123.9, 84.9 (C-5); m/z 174 (100%, M^+ -Br) (Found: M^+ -Br 174.0561. $C_{10}H_8NO_2$ requires 174.0555).

4-(2-Bromophenyl)-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (11). To a solution of 8 (2 g, 7.94 mmol) in toluene (20 mL) was added freshly cracked cyclopentadiene (4 mL, 47.6 mmol). The reaction was allowed to stir at room temperature for 4 h, after which time the solvent was removed under reduced pressure to give 11 as a white solid (2.5 g, 99%) mp 158-160 °C; R_f (1:1 EtOAc-hexane) 0.53; ν_{max}/cm^{-1} 3058 (w, aromatic C-H), 2982 (w, aliphatic C-H), 1709 (s, C=O), 1479 (m, ring stretching); 1H NMR (360 MHz; $CDCl_3$) δ 7.67 (1H, dd, $J=8.0, 1.5$ Hz), 7.36 (1H, td, $J=8, 1.5$ Hz), 7.29 (1H, td, $J=8, 1.5$ Hz), 7.08 (0.2H, dd, $J=8, 1.5$ Hz), 6.98 (0.8H, dd, $J=8, 1.5$ Hz), 6.34 (0.4H, t, $J=1.7$ Hz), 6.30 (1.6H, s), 3.50 (3.6H, brs), 3.47 (0.4H, dd, $J=2.9, 1.7$), 1.80 (1H, dd, $J=8.4, 3.3$), 1.62 (1H, dd, $J=8.4, 5.0$); ^{13}C NMR (90 MHz; $CDCl_3$) 175.9 (C=O major), 175.7 (C=O minor), 135.3 (minor), 134.7 (major), 133.9 (minor), 133.5 (major), 131.7, 130.8 (major), 130.6 (minor), 130.2 (minor), 129.8 (major), 128.3, 122.4 (major), 122.0 (minor), 52.7 (minor), 52.4 (major), 46.9 (minor), 46.0 (major), 45.4 (major), 45.3 (minor); m/z 319 (10%, M^+ , ^{81}Br), 317 (10, M^+ , ^{79}Br), 238 (80, M^+ -Br), 172 (100) (Found: M^+ (^{79}Br) 317.0036. $C_{15}H_{12}BrNO_2$ requires M^+ 317.0051).

4-(2-Bromophenyl)-5-hydroxy-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (12). To a solution of 11 (2 g, 6.29 mmol) in THF (20 mL) was added Super Hydride[®] (1 M in THF, 7.5 mL, 7.55 mmol) dropwise at -78 °C under argon. The reaction was stirred at this temperature for 40 minutes then quenched with saturated sodium bicarbonate solution (10 mL). The resulting solution was allowed to stand until the temperature reached 0 °C, then 50 drops of hydrogen peroxide (33% w/v) were added and the mixture stirred for 20 minutes. The aqueous layer was extracted with dichloromethane (3x20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 12 as a white solid (1.58 g, 75%) which was recrystallised from dichloromethane; mp 126-128 °C; R_f (1:1 EtOAc-hexane) 0.11; ν_{max}/cm^{-1} 3388 (br, O-H), 3060 (w, aromatic C-H), 2977 (w, aliphatic C-H), 1712 (s, C=O); 1H NMR (360 MHz; $CDCl_3$) δ 7.60 (1H, dd, $J=8.0, 1.4$ Hz), 7.30 (1H, td, $J=8, 1.4$ Hz), 7.18 (1H, td, $J=8, 1.4$ Hz), 7.12 (1H, dd, $J=8, 1.4$ Hz), 6.27-6.22 (2H, m), 4.89 (1H, d, $J=7.4$ Hz), 3.61 (1H, brd, $J=7.1$ Hz), 3.25 (2H, s), 3.22 (1H, s, OH), 2.77 (1H, m), 1.62 (1H, d, $J=8.5$ Hz), 1.42 (1H, d, $J=8.5$ Hz); m/z 321 (14%, M^+ , ^{81}Br), 319 (14, M^+ , ^{79}Br), 174 (100) (Found: M^+ 319.0212. $C_{15}H_{14}^{79}BrNO_2$ requires M^+ 319.0208).

4-(2-Bromophenyl)-5-methoxy-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (13). To a solution of 12 (1.5 g, 4.69 mmol) in methanol (20 mL) was added *p*-toluenesulfonic acid (89 mg, 0.469 mmol), the reaction was allowed to stir at room temperature for 16 h. The reaction mixture was then quenched with saturated sodium bicarbonate solution (5 mL). After removal of the methanol under reduced pressure, the aqueous layer was extracted with ether (3x20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by column chromatography (1:9 - 3:7 EtOAc-hexane) to give 13 as a viscous yellow oil (0.82 g, 52%); R_f (1:1 EtOAc-hexane) 0.32; ν_{max}/cm^{-1} 3059 (w, aromatic C-H), 2979 (w, aliphatic C-H), 1703 (s, C=O), 1084 (s, C-O-C stretching); 1H NMR (360 MHz;

CDCl_3) δ 7.62 (1H, dd, $J=8$, 1.4 Hz), 7.32 (1H, td, $J=8$, 1.4 Hz), 7.18 (1H, d, $J=8$ Hz), 7.15 (1H, td, $J=8$, 1.4 Hz), 6.32 (1H, dd, $J=5.6$, 2.8 Hz), 6.28 (1H, dd, $J=5.6$, 2.0 Hz), 4.74 (1H, s), 3.36 (1H, s), 3.34 (1H, s), 3.24 (1H, brs), 3.17 (3H, s, OCH_3), 2.87 (1H, ddd, $J=8.5$, 4.4, 1.3 Hz), 1.66 (1H, d, $J=8.5$ Hz), 1.49 (1H, d, $J=8.5$ Hz); $^{13}\text{CNMR}$ (CDCl_3) 174.8 (C=O), 136.8, 134.2, 133.7, 129.4, 128.2, 55.8 (OCH_3), 51.7 (CH_2), 49.0, 45.4, 45.1, 45.0 (neither quaternary aromatic carbon was observed and it appears there is a coincidence of 2 CH signals); m/z 335 (40%, M^+ , ^{81}Br), 333 (40%, M^+ , ^{79}Br), 188 (100) (Found: M^+ (^{79}Br) 334.0348. $\text{C}_{16}\text{H}_{16}^{79}\text{BrNO}_2$ requires M^+ 334.0364).

N-Phenylsuccinimide (14). A solution of succinic anhydride (8.4 g, 83.9 mmol) and aniline (6.5 g, 69.9 mmol) in toluene (100 mL) was heated under reflux for 2.5 h, cooled, and filtered to give crude succinamic acid (13.1 g, 98%). A mixture of this acid (13.1 g, 68.2 mmol), sodium acetate (18.5 g, 0.225 mol) and acetic anhydride (150 mL) was stirred at 80 °C for 4.5 h. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (100 mL), washed with water (3x100 mL) and saturated ammonium chloride (100 mL). The organic layer was dried (MgSO_4), filtered and evaporated under reduced pressure to give 14 as a white solid (11.5 g, 94%), which was recrystallised from ethyl acetate-hexane; mp 154-158 °C (lit.⁴ 153-154 °C); R_f (50% EtOAc-hexane) 0.21; $\nu_{\text{max}}/\text{cm}^{-1}$ 3055 (w, aromatic C-H), 2980 (w, aliphatic C-H), 1712 (s, C=O); $^1\text{HNMR}$ (360 MHz; CDCl_3) δ 7.46 (2H, t, $J=7.2$ Hz, H-3', H-5'), 7.38 (1H, t, $J=7.2$ Hz, H-4'), 7.26 (2H, d, $J=7.2$ Hz, H-2', H-6'), 2.84 (4H, s, H-3, H-4); $^{13}\text{CNMR}$ (90 MHz; CDCl_3) 176.3 (C=O), 131.9 (C-1'), 129.2 (C-3', C-5'), 128.6 (C-4'), 126.5 (C-2', C-6'), 28.4 (C-3, C-4); m/z 175 (100%, M^+), 119 (70) (Found: M^+ 175.0629. $\text{C}_{10}\text{H}_9\text{NO}_2$ requires M^+ 175.0633).

5-Hydroxy-N-phenylpyrrolidin-2-one (15). To a solution of 14 (2 g, 6.29 mmol) in THF (20 mL) was added Super Hydride[®] (1 M in THF, 7.5 mL, 7.55 mmol) dropwise at -78 °C under argon. The reaction was stirred at this temperature for 40 minutes and quenched with saturated sodium bicarbonate solution (10 mL). The resulting solution was allowed to stand until the temperature reached 0 °C, then 50 drops of hydrogen peroxide (33% w/v) were added and the mixture stirred for 20 minutes. The aqueous layer was extracted with dichloromethane (3x20 mL), the combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give 15 as a white solid (2.1 g, 100%) which was recrystallised from dichloromethane; mp 114-116 °C; R_f (1:1 EtOAc-hexane) 0.11; $\nu_{\text{max}}/\text{cm}^{-1}$ 3348 (br, O-H), 1678 (s, C=O), 1598 (m, benzene ring); $^1\text{HNMR}$ (360 MHz; CDCl_3) δ 7.47 (2H, d, $J=7$ Hz, H-2', H-6'), 7.34 (2H, t, $J=7$ Hz, H-3', H-5'), 7.25 (1H, t, $J=7$ Hz, H-4'), 5.54 (1H, dd, $J=6.2$, 1.7 Hz, H-5), 2.73-2.62 (1H, m, H-3 or H-4), 2.43-2.22 (2H, m, H-3 or H-4), 2.21-1.65 (1H, m, H-3 or H-4); $^{13}\text{CNMR}$ (90 MHz; CDCl_3) 174.6 (C=O), 137.2 (C-1'), 129.0 (C-3', C-5'), 126.1 (C-4'), 123.5 (C-2', C-6'), 85.2 (C-5), 29.7 (C-3), 28.2 (C-4); m/z 177 (98%, M^+), 93 (100) (Found M^+ 177.0796. $\text{C}_{10}\text{H}_{11}\text{NO}_2$ requires M^+ 177.0790).

N-Phenyl-5-(prop-2-enyl)-pyrrolidin-2-one (16). To a solution of 15 (1 g, 5.65 mol) in dichloromethane (15 mL) at -78 °C under argon was added a solution of tin(IV)chloride (0.99 mL, 8.47 mmol) in dichloromethane (8 mL) dropwise. After 15 minutes allyltrimethylsilane

(2.7 mL, 17.0 mmol) was added dropwise, the reaction mixture was placed in a freezer for 16 h (-22 °C). After this time the reaction was allowed to warm to room temperature, the solvent was removed under reduced pressure and the residue redissolved in ethyl acetate. This solution was washed with sodium bicarbonate (3x100 mL) (separation was difficult due to the formation of a thick emulsion) and brine (100 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give 16 as a yellow oil (1.09 g) which was purified by column chromatography (1:4 - 2:3 ethyl acetate-hexane) to give a yellow oil (0.48 g, 42%); R_f (1:1 EtOAc-hexane) 0.32; $\nu_{\max}/\text{cm}^{-1}$ 3073 (w, aromatic C-H), 2928 (w, aliphatic C-H), 1694 (s, C=O), 1597 (m, benzene ring); ¹HNMR (360 MHz; CDCl₃) 7.39 (4H, m, aryl-H), 7.20 (1H, m, aryl-H), 5.67 (1H, ddt, $J=17.0, 10.3, 7.0$ Hz, CH=CH₂), 5.11 (1H, dq, $J=10.3, 1.0$ Hz, CH=CH₂*cis*), 5.06 (1H, dq, $J=17.0, 1$ Hz, CH=CH₂*trans*), 4.33-4.26 (1H, m, H-5), 2.67-2.47 (2H, m), 2.40-2.17 (3H, m), 1.95-1.86 (1H, m); ¹³CNMR (90 MHz; CDCl₃) δ 174.4 (C=O), 137.4, 132.5, 129.1, 125.9, 124.1, 118.9 (alkene CH₂), 59.0 (C-5), 37.5, 31.2, 23.0; m/z 201 (2%, M⁺), 160 (100, M⁺-C₃H₅) (Found: M⁺ 201.1160. C₁₃H₁₅NO requires M⁺ 201.1154).

5-Methoxy-N-phenylpyrrolidin-2-one (18). To a solution of 15 (20 g, 0.11 mol) in methanol (100 mL) was added *p*-toluenesulfonic acid (2.15 g, 11.3 mmol), the reaction was then allowed to stir at room temperature for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (50 mL). After removal of the methanol under reduced pressure, the aqueous layer was extracted with ether (3x60 mL), the combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give 18 as a yellow oil (20 g, 93%); R_f (1:1 EtOAc-hexane) 0.1; $\nu_{\max}/\text{cm}^{-1}$ 3059 (w, aromatic C-H), 2950 (w, aromatic C-H), 1697 (s, C=O), 1597 (m, benzene ring); ¹HNMR (360 MHz; CDCl₃) δ 7.51 (2H, dd, $J=7.7, 0.9$ Hz, H-2', H-6'), 7.38 (2H, t, $J=7.7$ Hz, H-3', H-5'), 7.23 (1H, td, $J=7.7, 0.9$ Hz, H-4'), 5.34 (1H, m, H-4), 3.29 (3H, s, OCH₃), 2.82-2.72 (1H, m, H-3 or H-4), 2.54-2.46 (1H, m, H-3 or H-4), 2.45-2.24 (1H, m, H-3 or H-4), 2.18-2.12 (1H, m, H-3 or H-4); ¹³CNMR (90 MHz; CDCl₃) 174.4 (C=O), 128.9 (C-3', C-5'), 125.9 (C-4'), 123.4 (C-2', C-6'), 85.1 (C-5), 53.6 (OCH₃), 29.9 (C-3), 24.5 (C-4); m/z 91 (100%, M⁺-C₅H₈O₂).

N-Phenyl-5-(prop-2-enyl)pyrrolidin-2-one (16) from (18). To a solution of 18 (20 g, 0.1 mol) in dichloromethane (150 mL) at -78 °C under argon was added boron trifluoride diethyl etherate (18 mL, 0.147 mol) dropwise. After 15 minutes allyltrimethylsilane (25 mL, 0.157 mol) was added dropwise. The reaction mixture was placed in a freezer for 16 h (-22 °C) and allowed to warm to room temperature before being washed with saturated sodium bicarbonate solution (3x100 mL) and brine (100 mL). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give a yellow oil (20.8 g) which was purified by column chromatography (1:4 - 2:3 ethyl acetate-hexane) to give a yellow oil (9.5 g, 45%). The experimental data was identical to that previously described for 16.

N-Phenylpyrrolidin-2-one-5-ethanoic acid (19). To a solution of 16 (2 g, 9.95 mmol) in methanol (15 mL) was passed a steady stream of ozone until a blue colouration appeared (45 minutes), ozone was then passed for a further hour. After this time the methanol was removed under reduced pressure and the resultant oil was redissolved in a 90% solution of formic acid

(15 mL). To this solution was added hydrogen peroxide (30% w/v, 7 mL) and the mixture was heated gradually to reflux and maintained under reflux for 1 h. After cooling, the solvent was removed under reduced pressure, the resultant residue was suspended in water and basified using saturated sodium bicarbonate solution. The solution was then washed with dichloromethane (3x20 mL). The aqueous layer was acidified using conc. HCl, then extracted into dichloromethane (3x20 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give 19 as a beige solid (2.15 g, 99%). m.p. 142-150 °C; $\nu_{\max}/\text{cm}^{-1}$ 3054 (w, aromatic C-H), 2986 (w, aliphatic C-H) 2950 (br, acid O-H), 1712 (s, dimeric acid C=O) 1629 (s, lactam C=O), 1265 (s, dimeric acid C-O); ¹HNMR (360 MHz; CDCl₃); δ 7.42-7.34 (4H, m, aryl-H), 7.26-7.21 (1H, m, aryl-H), 4.62-4.55 (1H, m, H-5), 2.75-2.48 (4H, m), 2.39 (1H, dd, J =16.0, 9.5 Hz), 1.98-1.89 (1H, m); ¹³CNMR (90 MHz; CDCl₃) 174.7 (C=O), 174.4 (C=O), 136.9, 129.3, 126.6, 124.4, 56.8 (C-5), 38.1, 30.8, 24.5; m/z 219 (45%, M⁺), 160 (100, M⁺-C₂H₃O₂) (Found M⁺ 219.0887. C¹²H₁₃NO₃ requires M⁺ 219.0895).

Ethyl N-phenylpyrrolidin-2-one-5-ethanoate (20). To a solution of 19 (2 g, 9.13 mmol) in ethanol (15 mL) was added *p*-toluenesulfonic acid (0.17 g, 0.913 mmol), the solution was then heated under reflux for 16 h. After cooling, the solvent was removed under reduced pressure and the resulting residue redissolved in ethyl acetate. The solution was washed with water (3x20 mL), dried (MgSO₄) and evaporated under reduced pressure to give a brown oil (2.2 g) which was purified by column chromatography (2:3 ethyl acetate-hexane) to give 20 as a dark yellow oil (1.48 g, 66%); R_f (2:3 EtOAc-hexane) 0.16; $\nu_{\max}/\text{cm}^{-1}$ 3059 (w, aromatic C-H), 2982 (w, aliphatic C-H), 1729 (s, ester C=O), 1698 (s, lactam C=O), 1597 (m, benzene ring); ¹HNMR (360 MHz; CDCl₃); δ 7.42-7.28 (4H, m, aryl-H), 7.25-7.20 (1H, m, aryl-H), 4.69-4.58 (1H, m, H-5), 4.11 (2H, q, J =7.2 Hz, OCH₂), 2.71-2.42 (4H, m), 2.37 (1H, dd, J =15.7, 9.2 Hz), 1.98-1.86 (1H, m), 1.25 (3H, t, J =7.1 Hz, CH₃); ¹³CNMR(90 MHz; CDCl₃) 174.1 (C=O, amide), 170.5 (C=O, ester), 136.9, 129.2, 126.3, 124.3, 60.8 (OCH₂), 56.6 (C-5), 38.6, 30.8, 24.4, 14.1 (CH₃); m/z 247 (30%, M⁺), 160 (100, M⁺-C₄H₇O₂) (Found M⁺ 247.1203. C₁₄H₁₇NO₃ requires M⁺ 247.1208).

Ethyl N-phenylpyrrolidin-2-one-5-(2-iodoethanoate) (21). A solution of 20 (1 g, 4.05 mmol) in THF (2 mL) was added to a freshly prepared solution of LDA (0.48 g, 4.45 mmol) at -78 °C under argon. The reaction was allowed to stir for 30 minutes at this temperature after which time a solution of iodine (1.03 g, 4.05 mmol) in THF (10 mL) was added dropwise. The resulting solution was allowed to warm to room temperature then stirred for a further hour, the reaction had turned dark brown after this time. The reaction mixture was poured onto cold HCl (1 M, 10 mL) and extracted into ethyl acetate (3x20 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give a dark brown gum (0.96 g) which was purified by column chromatography (1:4 ethyl acetate-hexane) to give a dark yellow oil 21 as a 7:3 mixture of diastereoisomers (0.36 g, 24%); R_f (1:1 EtOAc-hexane) 0.34; $\nu_{\max}/\text{cm}^{-1}$ 2983, 2930 (w, w, aliphatic C-H), 1728 (s, ester C=O), 1701 (s, lactam C=O); ¹HNMR(360 MHz; CDCl₃); δ 7.48-7.36 (3H, m, aryl-H), 7.33-7.25 (2H, m, aryl-H), 4.89-4.82 (0.3H, m, H-5 minor), 4.77 (0.3H, dd, J =8.8, 3.6 Hz, CHI minor), 4.73 (0.7H, dd, J =7.1, 2.3 Hz, CHI major), 4.62-4.54

(0.7H, m, H-5 major), 4.09 (0.6H, q, $J=7.1$ Hz, OCH₂ minor), 4.06 (1.4H, q, $J=7.1$ Hz, OCH₂ major) 3.18 (0.6H, m, CH₂ minor), 2.92 (0.6H, m, CH₂ minor), 2.83-2.71 (1.4H, m, CH₂), 2.48-2.35 (1.4H, m, CH₂), 1.22 (0.9H, t, $J=7.1$ Hz, CH₃ minor), 1.19 (2.1H, t, $J=7.1$ Hz, CH₃ major); ¹³CNMR(90 MHz; CDCl₃) δ 170 (C=O amide), 152 (C=O ester), 137.0, 129.4, 129.3, 127.2, 126.8, 124.9, 124.0, 61.0 (OCH₂), 56.1 (C-5 minor), 55.3 (C-5 major), 38.3 (minor), 37.7 (major), 36.5 (minor), 35.8 (major), 18.2, 15.5 (CH₃ minor), 14.1 (CH₃ major); m/z 373 (40%, M⁺), 77 (100, M⁺-C₈H₁₁NIO₃) (Found: M⁺ 373.0163. C₁₄H₁₆NIO₃ requires M⁺ 373.0173).

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