A Thesis Submitted for the Degree of PhD at the University of Warwick

Highly Efficient Synthesis of Heterocycles *via* 5-*Endo* Radical Cyclisation

by

John P. McDonagh

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Department of Chemistry
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To Mam and Dad

"Outside of a dog, a book is man's best friend. Inside of a dog it's too dark to read"

Groucho Marx (1890 - 1977)

Contents

Acknowledgements xvi

Declaration xvii

Abstract xviii

Abbreviations xix

Chapter 1

Introduction

1.1 General Introduction 1

1.2 Carbon Radicals 1

1.2.1 Stability and Structure 2

1.2.2 Reaction Types 3

1.2.3 Abstraction/Atom Transfer Reactions 4

1.2.4 Addition Reactions 5

1.2.4.1 Intermolecular Addition 5

1.2.4.1.1 Electronic Nature of Radicals 6

a) Nucleophilic Radicals 6

b) Electrophilic and Ambiphilic Radicals 8

1.2.4.2 Intramolecular Addition (Cyclisation) 9

1.3 Synthesis of *N*-Heterocycles *via* Radical Cyclisation Methods 12

1.4 Methods Used to Conduct Carbon Radical Reactions 14

1.4.1 Metal Hydride Methods 15

1.4.2 The Thiohydroxamate Method/Barton Method 17

1.4.3 The Fragmentation Method 18

1.4.4 The Atom-Transfer Method 19

1.5 Transition Metal Promoted Radical Cyclisations 21

1.5.1 Introduction 21

(a) Oxidative Process 22

(b) Reductive Process 22

1.5.2 Copper Mediated Radical Cyclisation Reactions 23

1.5.3 Second Generation Copper Catalysts 30

1.5.3.1 *N*-Alkyl-2-pyridylmethanimnes 31

1.5.3.2 *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) 33

1.5.3.3 *N,N,N',N',N",N"*-Hexamethyltriethylenetetramine 34

1.5.4 Contemporary Transition Metal Mediated Radical Cyclisation Reactions 37

Chapter 2

5-*Endo* Radical Cyclisations of Trichloroacetamides Mediated by Copper(I) Amine Complexes

2.1 Introduction 45

2.2 Synthesis of Trichloroacetamide Precursors 47

2.3 Copper(I) Mediated Cyclisation of Trichloroacetamides 49

2.4 Application of this Methodology Towards the Synthesis of L-755,807 59

2.5 Conclusion 63

Chapter 3

5-*Endo* Radical Cyclisations of Monohaloacetamides Mediated by Copper(I)-Amine Complexes

3.1 Introduction 66

3.2 Cyclisation of 3° Monobromoacetamides 66

3.2.1 Precursor Preparation 66

3.2.2 Copper Catalysyed 5-*Endo* Cyclisation 68

3.2.3 Trapping of *N*-Acyliminium Ions after Cyclisation 71

3.2.4 Construction of Tricyclic and Other Frameworks 74

3.3 Cyclisation of 2° monobromoacetamides 81

3.3.1 Method Development and Solvent Effects 81

3.3.2 Tricyclic Systems and Other Frameworks 86

3.3.3 Deprotection of γ-Lactams and Application Towards Natural Product Architectures 90

3.4 Copper(I) Mediated Radical Cyclisations in Ionic Liquids 103

3.4.1 Introduction 103

3.4.2 Copper Mediated Radical Cyclisations in [bmim][PF_6] 104

3.5 Conclusion 107

Chapter 4

5-*Endo* Radical Cyclisation of Enamides Mediated by Ceric Ammonium Nitrate

4.1 Introduction 110

4.2 Ceric Ammonium Nitrate Mediated Cyclisations 111

4.3 Application of Ceric Ammonium Nitrate Mediated Cyclisations Towards the Synthesis of Natural Product Templates 119

4.3.1 Introduction 119

4.3.2 CAN Promoted Production of Methoxy and Hydroxy γ-Lactams 121

4.3.3 Deprotection of γ-Lactams 128

4.3.4 Introducing Diversity in the Side Chain 130

4.3.5 Alternative Approaches to Introducing a Side-Chain for PI-091 132

4.3.6 Other Reactivity of Hydroxylactam (323) 134

4.4 Conclusion 135

Chapter 5. Experimental

Experimental Notes 138

5.1 Experimental for Chapter 2

5.1.1 General procedure for the preparation of substituted imines **139**

Benzyl-cyclopentylidene-amine (362) **139**

Benzyl-cyclohexylidene-amine (102) **140**

Benzyl-cyclooctylidene-amine (363) **140**

4-Methoxy-*N*-benzyl-cyclohexylimine (364) **141**

(1,2-Dimethyl-propylidene)-(4-methoxy-benzyl)-amine (365) **141**

5.1.2 General procedure for the preparation of trichloroacetamide cyclisation precursors **142**

N-Benzyl-2,2,2-trichloro-*N*-cyclopent-1-enyl-acetamide (104) **143**

N-Benzyl-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide (97) and 1-(2-Benzylamino-cyclohex-1-enyl)-2,2,2-trichloro-ethanone (103) **143**

N-Benzyl-2,2,2-trichloro-*N*-cyclooct-1-enyl-acetamide (105) and 1-(2-Benzylamino-cyclooct-1-enyl)-2,2,2-trichloro-ethanone (366) **144**

2,2,2-Trichloro-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-acetamide (106) **145**

2,2,2-Trichloro-*N*-(4-methoxy-benzyl)-*N*-(2-methyl-cyclohex-1-enyl) -acetamide (107) **146**

2,2,2-Trichloro-N-(1-isopropyl-vinyl)-N-(4-methoxy-benzyl) -acetamide (139) **146**

5.1.3 General procedure for the cyclisation of trichloroacetamides **147**

1-Benzyl-3-chloro-1,4,5,6-tetrahydro-indol-2-one (98a) and 1-Benzyl-3,7-dichloro-1,4,5,6-tetrahydro-indol-2-one (111) 147
1-Benzyl-3-chloro-4,5-dihydro-1H-cyclopenta[b]pyrrol-2-one (112) 148
1-Benzyl-3-chloro-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (113) 149
3-Chloro-1-(4-methoxy-benzyl)-1,4,5,6-tetrahydro-indol-2-one (124) and 1-(4-Methoxy-benzyl)-1,4,5,6-tetrahydro-indol-2-one (125) 150
3-Chloro-1-(4-methoxy-benzyl)-3a-methyl-1,3,3a,4,5,6-hexahydro-indol-2-one (126) 151
3-Chloro-5-isopropylidene-1-(4-methoxy-benzyl)-1,5-dihydro-pyrrol-2-one (140) 151

5.1.4 General method for the attempted deprotection of *p*-methoxybenzylamides 152

3-Chloro-5-hydroxy-5-(1-hydroxy-1-methyl-ethyl)-1,5-dihydro-pyrrol-2-one (141) 152

5.2 Experimental for Chapter 3

Benzyl-cycloheptylidene-amine (367) 153
Benzyl-cyclododecylidene-amine (368) 153
Benzyl-(3,4-dihydro-2H-naphthalen-1-ylidene)-amine (369) 154
Benzyl-(3,4-dihydro-naphthalen-2-yl)-amine (370) 154
(2-Cyclohex-1-enyl-ethyl)-cyclohexylidene-amine (371) 155
(2-Bromo-benzyl)-cyclohexylidene-amine (372) 156
Benzyl-indan-1-ylidene-amine (373) 156
2,4-Dimethoxy-*N*-benzyl-cyclohexylimine (374) 157
4-Methoxy-*N*-benzyl-cyclooctylimine (375) 157

(3,4-Dihydro-naphthalen-2-yl)-(4-methoxy-benzyl)-amine (376) 158
Indan-1-ylidene-(4-methoxy-benzyl)-amine (377) 159
Cyclohexylidene-(4-nitro-benzyl)-amine (378) 159

5.2.1 General procedure for the synthesis of tertiary bromoacetamide cyclisation precursors **160**

N-Benzyl-2-bromo-*N*-(cyclopent-1-enyl)-2-methyl-propanamide (146) 160
N-Benzyl-2-bromo-*N*-(cyclohex-1-enyl)-2-methyl-propanamide (145) 161
N-Benzyl-2-bromo-*N*-(cyclohept-1-enyl)-2-methyl-propanamide (147) 161
N-Benzyl-2-bromo-*N*-(cyclooct-1-enyl)-2-methyl-propanamide (148) 162
N-Benzyl-2-bromo-*N*-(cyclododec-1-enyl)-2-methyl-propanamide (149) 162
2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-2-methyl-propionamide (150) 163
2-Bromo-*N*-cyclohex-1-enyl-*N*-(2,4-dimethoxy-benzyl)-2-methyl-propionamide (151) 164
2-Bromo-*N*-cyclohex-1-enyl-*N*-(2-cyclohex-1-enyl-ethyl)-2-methyl-propionamide (162) 164
N-Benzyl-2-bromo-*N*-(3H-inden-1-yl)-2-methyl-propionamide (167) 165
N-Benzyl-2-bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-2-methyl-propionamide (168) 165
N-Benzyl-2-bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-2-methyl-propionamide (169) 166
2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(2-methyl-cyclohex-1-enyl)-propionamide (179a) and 2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(6-methyl-cyclohex-1-enyl)-propionamide (179b) 167
2-Bromo-*N*-(2-bromo-benzyl)-*N*-cyclohex-1-enyl-2-methyl-

propionamide (188) 168

2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (257) 168

2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (272) 169

5.2.2 General procedure for copper mediated cyclisations of tertiary bromoacetamides (catalytic method) **170**

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (152b) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (152a) 170

1-Benzyl-3,3-dimethyl-3,3a,4,5,6,7-hexahydro-1H-cyclohepta[b]pyrrol-2-one (156b) and 1-Benzyl-3,3-dimethyl-3,4,5,6,7,8-hexahydro-1H-cyclohepta[b]pyrrol-2-one (156a) 171

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6,7,8-octahydro-cycloocta[b]pyrrol-2-one (157b) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7,8,9-octahydro-cycloocta[b]pyrrol-2-one (157a) 172

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6,7,8,9,10,11,12-dodecahydro-cyclododeca[b]pyrrol-2-one (158b) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-cyclododeca[b]pyrrol-2-one (158b) 173

1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (159b) and 1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (159a) 174

1-(2,4-Dimethoxy-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (160b) and 1-(2,4-Dimethoxy-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (160a) 175

1-(2-Cyclohex-1-enyl-ethyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (163b) and 1-(2-Cyclohex-1-enyl-ethyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (163a) **176**

1-Benzyl-7a-methoxy-3,3-dimethyl-octahydro-indol-2-one (164) **177**

3-Benzyl-1,1-dimethyl-3,8-dihydro-1H-3-aza-cyclopenta[a]inden-2-one (170) **178**

1-Benzyl-3,3-dimethyl-1,3,4,5-tetrahydro-benzo[g]indol-2-one (171) **179**

1-Benzyl-1'-bromo-3,3-dimethylspiro(azetidine-4,2'-1',2',3',4'-tetrahydronapthalen)-2-one (172) **179**

1-(4-Methoxy-benzyl)-3,3-dimethyl-5-methylene-1-aza-spiro[3.5]nonan-2-one (180) and 1-(4-Methoxy-benzyl)-3,3,7-trimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (181) **180**

1-(4-Methoxy-benzyl)-3,3,3a-trimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (184) and 1-(4-Methoxy-benzyl)-3,3,7-trimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (181) **181**

1-(2-Bromo-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (189) and 1-(2-Bromo-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (190) **182**

1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,3a,4,4a,5,6,7,8,8a-decahydro-benzo[f]indol-2-one (258b) and 1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,4,4a,5,6,7,8,8a,9-decahydro-benzo[f]indol-2-one (258a) **183**

5.2.3 General synthesis of secondary bromoacetamide cyclisation precursors 184

N-Benzyl-2-bromo-*N*-(cyclohex-1-enyl)-propanamide (196) **185**

N-Benzyl-2-bromo-*N*-(cyclooct-1-enyl)-propanamide (202) **185**

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-propionamide (204) **186**

2-Bromo-*N*-cyclooct-1-enyl-N-(4-methoxy-benzyl)-propionamide (205) **186**

N-Benzyl-2-chloro-2-phenyl-*N*-cyclohex-1-enyl-acetamide (203) **187**

2-Chloro-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-2-phenyl-acetamide (206) **188**

1-(4-Methoxy-benzyl)-2,2-diphenyl-1,2,4,5,6,7-hexahydro-indol-3-one (217) **188**

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-acetamide (225) **189**

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-nitro-benzyl)-propionamide (207) **190**

N-Benzyl-2-bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-propionamide (227) **190**

2-Bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-*N*-(4-methoxy-benzyl)-propionamide (228) **191**

2-Bromo-*N*-(3H-inden-1-yl)-*N*-(4-methoxy-benzyl)-propionamide (229) **192**

2-Bromo-*N*-(3,4-dihydro-naphthalen-2-yl)-*N*-(4-methoxy-benzyl)-propionamide (230) **192**

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(2-methyl-cyclohex-1-enyl)-propionamide (235a) and 2-Bromo-N-(4-methoxy-benzyl)-N-(6-methyl-cyclohex-1-enyl)-propionamide (235b) **193**

4-Oxo-piperidine-1-carboxylic acid benzyl ester (239) **194**

4-[(2-Bromo-propionyl)-(4-methoxy-benzyl)-amino]-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (240) **195**

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (255) **195**

2-Bromo-*N*-[17-(1,5-dimethyl-hexyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl]-*N*-(4-methoxy-benzyl)-propionamide (261) **196**

2-Bromo-*N*-[17-(1,5-dimethyl-hexyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl]-*N*-(4-nitro-benzyl)-propionamide (262) 197

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (269) 198

2-Bromo-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-*N*-(4-nitro-benzyl)-propionamide (273) 199

5.2.4 General procedure for cyclisation of secondary bromoacetamides (stoichiometric method) 200

1-Benzyl-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (197) 200

1-Benzyl-3-methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (208) 200

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (210) 201

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (211) and 1-(4-Methoxy-benzyl)-3-methyl-1,3,3a,4,5,6,7,8-octahydro-cycloocta[b]pyrrol-2-one (214) 202

1-Benzyl-3-phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (209) 203

1-(4-Methoxy-benzyl)-3-phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (212) 203

3-Methyl-1-(4-nitro-benzyl)-1,4,5,6,7,7a-hexahydro-indol-2-one (213) 204

1-Benzyl-3-methyl-1,4,5,6-tetrahydro-indol-2-one (218) 205

1-Benzyl-3-methyl-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (219) 205

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6-tetrahydro-indol-2-one (221) 206

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (222) 206

1-Benzyl-3-phenyl-1,4,5,6-tetrahydro-indol-2-one (220) 207

1-(4-Methoxy-benzyl)-3-phenyl-1,4,5,6-tetrahydro-indol-2-one (223) **208**

3-Methyl-1-(4-nitro-benzyl)-1,4,5,6-tetrahydro-indol-2-one (224) **208**

N-Cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-acetamide (226) **209**

1-Benzyl-3-methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (231) **210**

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (232) **210**

3-(4-Methoxy-benzyl)-1-methyl-3a,8-dihydro-3H-3-aza-cyclopenta[a]inden-2-one (233) **211**

3-(4-Methoxy-benzyl)-1-methyl-3,3a,4,5-tetrahydro-benzo[e]indol-2-one (234) **211**

1-(4-Methoxy-benzyl)-3,7-dimethyl-1,4,5,6,7,7a-hexahydro-indol-2-one (236) **212**

1-(4-Methoxy-benzyl)-3-methyl-2-oxo-1,2,4,6,7,7a-hexahydro-pyrrolo[3,2c]pyridine-5-carboxylic acid benzyl ester (241) **213**

1-(4-Methoxy-benzyl)-3-methyl-1,4,4a,5,6,7,8,8a,9,9a-decahydro-benzo[f]indol-2-one (256) **214**

1-(1,5-Dimethyl-hexyl)-7-(4-methoxy-benzyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,6,6a,7,10,10a,10b,11,12,12a-hexadecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (263) **215**

1-(1,5-Dimethyl-hexyl)-7-(4-methoxy-benzyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,7,10,10a,10b,11,12,12a-tetradecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (264) **216**

1-(1,5-Dimethyl-hexyl)-9,10a,12a-trimethyl-7-(4-nitro-benzyl)-2,3,3a,3b,4,5,5a,7,10,10a,10b,11,12,12a-tetradecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (265) **217**

1-(4-Methoxy-benzyl)-3,4a-dimethyl-1,4,4a,5,6,7,8,8a,9,9a-decahydro-benzo[f]indol-2-one (270) 218

1-(4-Methoxy-benzyl)-3,4a-dimethyl-1,4,4a,5,6,7,8,8a-octahydro-benzo [f]indol-2-one (271) 218

3-Methyl-octahydro-indol-2-one (244) 219

5.2.5 General method for the deprotection of p-methoxybenzylamides 220

3-Methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (245) 220

1-(4-Methoxy-benzyl)-3,3-dimethyl-3,3a,4,5-tetrahydro-1H-indole-2,6-dione (246) 221

1-Benzyl-3,3-dimethyl-3,3a,4,5-tetrahydro-1H-indole-2,6-dione (247) 222

3-Methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (248) 222

3-Phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (249) 223

3-Methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (250) 224

1-Methyl-3,3a,4,5-tetrahydro-benzo[e]indol-2-one (251) 224

1-(1,5-Dimethyl-hexyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,6,6a,7,10,10a,10b,11,12,12a-hexadecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (379) 225

5.2.6 General procedure for copper mediated cyclisations of bromoacetamides in the ionic liquid [bmim][PF_6] 226

5.3 Experimental for Chapter 4

5.3.1 General procedure for the preparation of *N*-Acyl Enamines 226

N-Cyclohex-1-enyl-N-(4-methoxy-benzyl)-malonamic acid methyl ester (290) 227

N-(4-Methoxy-benzyl)-N-(6-methyl-cyclohex-1-enyl)-malonamic acid methyl ester (301a) **227**

N-(3,4-Dihydro-naphthalen-1-yl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (303) **228**

N-(3,4-Dihydro-naphthalen-2-yl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (304) **229**

N-(1-Isopropyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (316) and 2-Isopropyl-3-(4-methoxy-benzyl)-6-methoxycarbonylmethyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid methyl ester (318) **229**

N-(1-Isopropyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid ethyl ester (330) and 2-Isopropyl-3-(4-methoxy-benzyl)-6-methoxycarbonylmethyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid ethyl ester (332) **231**

N-(2,4-Dimethoxy-benzyl)-N-(1-isopropyl-vinyl)-malonamic acid ethyl ester (331) and 3-(2,4-Dimethoxy-benzyl)-6-ethoxycarbonylmethyl-2-isopropyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid ethyl ester (333) **232**

N-(2-Cyclohex-1-enyl-ethyl)-N-(1-isopropyl-vinyl)-malonamic acid methyl ester (336) **233**

N-(1-Isopropyl-vinyl)-N-[2-(4-nitro-phenyl)-ethyl]-malonamic acid methyl ester (345) **234**

N-(1-sec-Butyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (339) **235**

N-(1-sec-Butyl-vinyl)-N-[2-(4-nitro-phenyl)-ethyl]-malonamic acid methyl ester (346) **236**

3-(2,4-Dimethoxy-benzyl)-6-heptyl-2-isopropyl-2-methyl-2,3-dihydro-[1,3]oxazin-4-one (358) **237**

5.3.2 General procedure for cyclisations utilising ceric ammonium nitrate **237**

7a-Methoxy-1-(4-methoxy-benzyl)-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester (291) **238**

1-(4-Methoxy-benzyl)-2-oxo-2,4,5,6-tetrahydro-1H-indole-3-carboxylic acid methyl ester (300) **238**

7a-Methoxy-1-(4-methoxy-benzyl)-7-methyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester (302) **239**

3-(Hydroxy-methoxy-methylene)-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[g]indol-2-one (305) **240**

N-(4-Methoxy-benzyl)-N-naphthalen-2-yl-malonamic acid methyl ester (308) **240**

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (317) and 5-Isopropyl-4,5-dimethoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (329) **241**

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (317) **242**

5-Hydroxy-5-isopropyl-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (323) **243**

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (334) **243**

5-Hydroxy-5-isopropyl-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (335) **244**

1-(2-Cyclohex-1-enyl-ethyl)-5-isopropyl-5-methoxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (337) **245**

1-(2-Cyclohex-1-enyl-ethyl)-5-hydroxy-5-isopropyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (338) **246**

5-sec-Butyl-5-hydroxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (340) **247**

5.3.3 General method for the attempted deprotection of *p*-methoxybenzylamides **247**

5-Isopropylidene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (323) **248**

5-sec-Butylidene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (343) **248**

4-Hydroxy-5-isopropylidene-1-(4-methoxy-benzyl)-2-oxo-pyrrolidine-3-carboxylic acid methyl ester (344) **249**

4-[4-Ethoxycarbonyl-2-hydroxy-2-isopropyl-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-1-isopropyl-2-(4-methoxy-benzyl)-3-oxo-6-oxa-2-aza-bicyclo[3.1.0]hexane-4-carboxylic acid ethyl ester (359) **250**

5-Isopropylidene-4-(4-methoxy-benzyl)-3-oxo-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-2-carboxylic acid methyl ester (361) **251**

References **253**

Appendix **265**

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Declaration

The work described in this thesis is the original work of the author, except where acknowledgement has been made to results and ideas previously reported. The work was carried out in the Department of Chemistry, University of Warwick between November 19th 1998 and November 19th 2001 and has not been previously submitted for a degree at any other institution.

Abstract

The principal aim of this project was to synthesise a range of functionalised heterocycles using novel transition metal promoted radical cyclisation reactions as an alternative to the well-established tin hydride method. On achieving this we hoped to successfully apply these methods towards the synthesis of natural product templates.

In chapter two, a series of copper(I)-amine catalysts were employed to mediate the 5-*endo-trig* radical cyclisation of trichloroacetamides, which led to the formation of a variety of highly functionalised bicyclic γ-lactams in good to excellent yield. A variety of cyclisation precursors were examined. This work was also extended towards the synthesis of analogues of the heterocyclic ring fragment of non-peptide bradykinin inhibitor, L-755,807. In chapter 3, the reaction of a series of tertiary bromoacetamides with catalytic copper(I) bromide/*N,N,N',N',N",N"*-hexamethyltriethylenetetramine (Me_6-tren) at room temperature is described. This reaction furnished regioisomeric mixtures of unsaturated pyrrolidinones *via* a highly efficient 5-*endo-trig* radical cyclisation reaction. We also illustrated that a variety of less activated secondary bromoacetamides undergo efficient 5-*endo-trig* radical cyclisation reactions to give α,β-unsaturated monoene lactams under atom transfer conditions mediated by copper(I) bromide and tripyridylamine (TPA) in refluxing toluene. Changing the solvent for this reaction to 1,2-dichloroethane caused α,β-unsaturated diene lactams to be produced instead. This approach was used towards the synthesis of analogues of the sesquiterpenic alkaloid, eremophilene γ-lactam. Chapter 4 describes an alternative route to constrained bicyclic ring systems mediated by ceric ammonium nitrate (CAN). In addition, the first reported 5-*endo-trig* radical cyclisation of β-amido esters to afford functionalised γ-lactams was developed. This methodology was exploited in the production of analogues of the heterocyclic ring fragments of a number of biologically active natural products.

Abbreviations

abs.	Absolute
AIBN	Azobisisobutyronitrile
ap	Apparent
Ar	Aryl
ATRC	Atom transfer radical cyclisation
ATRP	Atom transfer radical polymerisation
Bipy	Bipyridine
Bn	Benzyl
br	Broad
Bu	Butyl
t-Bu	Tertiary butyl
Bz	Benzoyl
CAN	Ceric(IV) ammonium nitrate
Cbz	Benzyloxycarbonyl
CI	Chemical ionisation
d	Doublet
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
dd	Doublet of doublets
d.e.	Diastereomeric excess
DEA	*N,N*-Diethylaniline
DEAD	Diethyl azodicarboxylate
Dmb	2,4-Dimethoxybenzyl

dt	Doublet of triplets
EI	Electron impact
EPHP	1-ethylpiperidine hypophosphite
eq.	Equivalents
Et	Ethyl
g	Grams
HOMO	highest occupied molecular orbital
Hz	Hertz
i	*ipso*
i-Pr	isopropyl
IR	Infra-red
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	*meta*
m	Multiplet
M	Molar
Me	Methyl
Me_6-tren	*N,N,N',N',N'',N''*-hexamethyltriethylenetetramine
mg	Milligrams
mmol	Millimole
mol	Mole
m.p.	Melting point
MS	Mass spectrum
Ms	Mesyl
N.M.R.	Nuclear magnetic resonance
NPMI	*N*-alkyl-2-pyridylmethanimines

n.O.e	Nuclear Overhauser effect
o	*ortho*
p	*para*
PG	Protecting group
Ph	Phenyl
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzyl
PNPE	2-(4-nitrophenyl)ethyl
p.p.m.	Parts per million
PTOC	Pyridine-2-thioneoxycarbonyl
q	Quartet
RT	Room Temperature
s	Singlet
SOMO	Singly occupied molecular orbital
sp	Septet
t	Triplet
TEA	Triethylamine
Tf	Trifluoromethane sulphonate
tlc	Thin layer chromatography
TMEDA	Tetramethyl-ethylenediamine
TMS	Trimethylsilyl
TPA	Tris(pyridyl)-amine
Ts	4-Toluenesulfony

Chapter 1 Introduction

1.1 General Introduction

Free radicals have been defined as species that contain one or more unpaired electrons which, in contrast to ionic species (anions and cations) can react easily with themselves. The formation of carbon-carbon bonds employing free radicals has ushered a new era in the field of synthetic organic chemistry.[1-8] This development, which took place during the last decade, has clearly changed the old notion of free-radical reactions being "notoriously uncontrollable".[2a] Consequently, synthetic organic chemists are now more confident in dealing with these reactions on realisation that they can be carried out in more precise and controlled manner. The pioneering work of the groups of Julia,[1] Beckwith,[2] and Walling[9] have convinced many others to venture into the area of synthesis employing free radicals, and these efforts have culminated in adding a new dimension to the repertoire of synthetic methodology.

The application of their exceptional work was first demonstrated by Hart[5]and Stork,[10] and later by Curran[8] and others. Giese's excellent physical organic work laid the foundation for applications in intermolecular carbon-carbon bond-forming processes.[6] Later advances in this area dealt with the aspect of stereochemistry largely due to the work of Rajanbabu,[11] Curran[12b] and Houk[23] which provided a clear insight into the stereochemical control during intramolecular free-radical cyclisations, and this development has encouraged hectic activity in the area of complex natural products synthesis.[12]

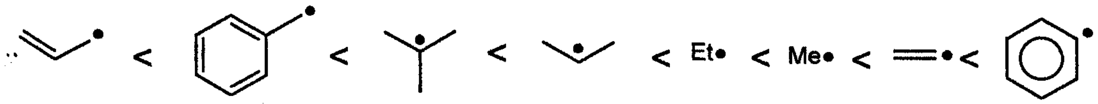
1.2 Carbon Radicals

The principal focus in this area has centred on the creation of C-C bonds using carbon centred radicals. Carbon-centred radicals are highly reactive intermediates which often show high chemoselectivities, regioselectivities and stereoselectivities upon addition to C-C multiple bonds.[8] They also have the distinct advantage in that they can be prepared under essentially neutral conditions, and thus many of the undesired side reactions that are often associated with basic anionic reagents are generally avoided. Neutral carbon centred radicals also have the advantage that they are less sensitive to solvent effects, i.e. aggregation or ion pairing, which makes them particularly suited for conducting reactions at crowded bonds or carrying out transformations in highly hindered frameworks.[13] The tolerance of such functional groups as N-H and O-H to radicals also removes the need for successive protection/deprotection steps, which has the effect of shortening particular synthetic routes. However, protecting groups may still be required for other steps in a synthetic sequence and almost all popular classes of protecting group are tolerated *via* radical reactions.

1.2.1 Stability and Structure

The relative stability of substituted carbon-centred radicals can be estimated by applying a simple rule, the lower the bond dissociation of the carbon-hydrogen bond the more stable the radical.[14] Table 1 shows the relative stability and bond dissociation energies of several carbon centred radicals.[15]

Table 1. C-H bond dissociation energies (kJ mol^{-1}).



Allyl	Benzyl	Tertiary	Secondary	Primary	Me	Vinyl	Aryl
360	368	401	402	418	438	439	464

Carbon centred radicals can adopt either a planar or pyramidal structure. Conjugating substituents favour the planar structure while alkyl, electron withdrawing (e.g. F) and heteroatom substituents can cause pyrimidalisation (fig. 1).[16]

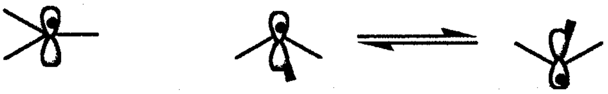


Figure 1. Structure of alkyl radicals.

The barrier to inversion in the pyramidal structure is very low and as a consequence stereochemical information at the prochiral centre is lost.[17] Vinyl radicals are usually thought to be bent and also have a low barrier to inversion.[18] However, inversion can be slowed with the introduction of electronegative substituents.[19-20] Vinyl radicals can either exist in the bent form or the linear form (fig. 2). The latter is preferred with conjugating substituents.[12(b)]

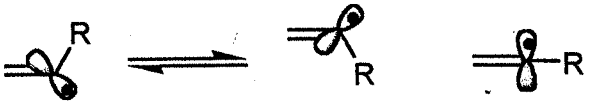


Figure 2. Structure of vinyl radicals.

1.2.2 Reaction Types

Aside from oxidation (yielding cations) and reduction (yielding anions), radicals normally react in one of two ways. The first is by abstracting an atom or group *via* a homolytic substitution reaction (S_H2) and the second is by undergoing addition reactions to unsaturated moieties either inter- or intra-molecularly. The scope that is available from the reactions of radicals comes from the broad range of reactants that participate in these two primary classes.

1.2.3 Abstraction/Atom Transfer Reactions

This is a very broad class of reactions in which radicals can react with saturated organic compounds and halogenated compounds by abstracting a hydrogen or halogen atom. The reaction is very similar to a S_N2 reaction and is often referred to as a S_H2 reaction[13] (Scheme 1).

$$\mathrm{R{-}X} + \mathrm{A}\bullet \rightleftharpoons \mathrm{R}\bullet + \mathrm{XA}$$

Scheme 1. Abstraction reaction

The selectivity of a free radical towards C-H and C-halogen bonds of different types is determined principally by two factors: bond dissociation energy and polar effects. The general rule being, lower bond dissociation energies facilitate H-abstraction, e.g. allylic and benzylic C-H bonds (322 KJ mol^{-1}) are significantly weaker than those in saturated systems, as such they undergo H-abstraction more readily. The reason for this is because the unpaired electron in the resulting radical is delocalised (Scheme 2).

Scheme 2. Delocalisation of an allylic radical

Compounds containing halogens also follow the above rule, e.g. bromotrichloromethane reacts by loss of the bromine atom and C-Br rather than C-Cl cleavage occurs because the former bond is weaker. Secondly, polar factors are operative in many radical reactions. The polarisation of a bond by an electronegative element such as Cl has the effect of decreasing the likelihood of H-abstraction at the α-position; an example of this regioselectivity in abstraction can be seen in butyl chloride (fig. 3).[21]

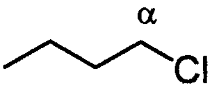


Figure 3. Inductive effects in butyl chloride

These principles apply to electrophilic radicals and the contrary would apply for nucleophilic radicals such as alkyl radicals.

1.2.4 Addition Reactions

One of the most significant classes of radical reactions is considered to be the addition reaction, as it represents one of the mildest and most efficient ways to create carbon-carbon bonds. Free radicals undergo addition reactions to common unsaturated groupings, i.e. double and triple bonds. The most important of these unsaturated groups is the C=C bond, addition to which can show considerable selectivities. The effects of substituents located on both the radical carbon and the multiple bond on the rate and regioselectivity of the reaction has been studied in great depth.[13, 22] Giese found that the rate of addition of nucleophilic radicals to alkenes increases with the electron withdrawing ability of substituents on the alkene partner and with the number of alkyl groups attached to the initial radical.[6]

1.2.4.1 Intermolecular Addition

Carbon centred radicals can undergo intermolecular addition to both carbon-carbon double and triple bonds. The formation of a new σ C-C bond (368 kJ mol^{-1}) is at the expense of a π C=C bond (226 kJ mol^{-1}) and is a highly energetically favourable exothermic process.[17] The rate of addition of the radical, and the rate of trapping of the final radical must be greater than that of termination caused by unwanted side reactions for intermolecular addition processes to be successful. Theoretical studies have shown that carbon radical addition to alkenes is along a preferred tetrahedral trajectory with a long forming bond (fig. 4).[23]

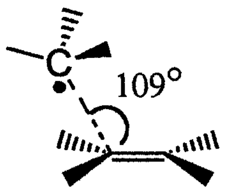


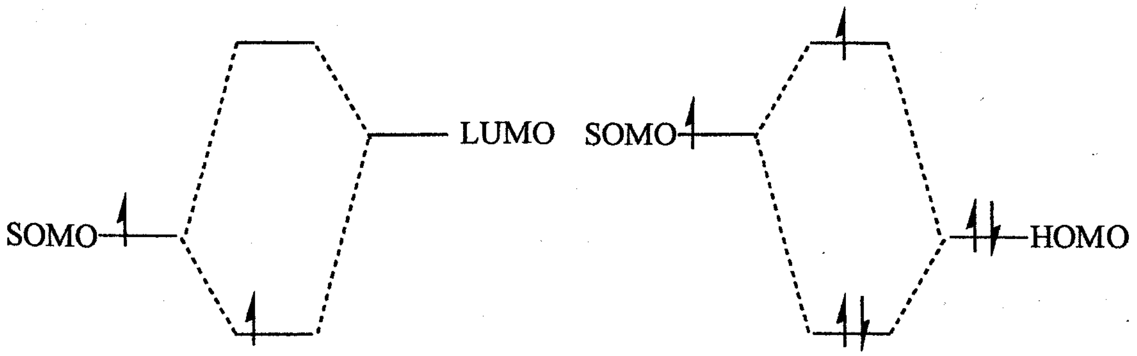
Figure 4. Radical attack on an alkene

1.2.4.1.1 Electronic Nature of Carbon Radicals

All radicals can be classified in accordance with their electronic nature. They fall into three categories: (a) nucleophilic, (b) electrophilic and (c) ambiphilic radicals. The nature of which depend on the substituents attached to the radical. The electronic character of the radical will determine the types of reactions that a particular radical will undergo. Due to the high exothermicity of most additions an early transition state can be postulated for radical addition to alkenes. This allows such reactions to be rationalized using frontier molecular orbital (FMO) theory.[24]

(a) Nucleophilic Radicals

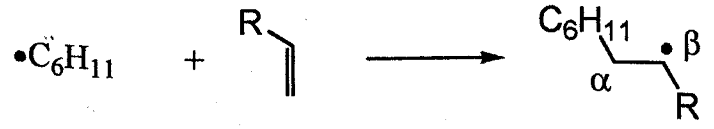
Many radicals are nucleophilic (despite being electron deficient) because they have relatively high lying singly occupied molecular orbitals (SOMO) (e.g. heteroatom-substituted, vinyl, aryl and acyl and most importantly alkyl radicals). The SOMO of the radical can theoretically react with either the lowest unoccupied molecular orbital (LUMO) or the highest occupied molecular orbital (HOMO) of the carbon-carbon multiple bond (fig. 5).[25] Nucleophilic radicals, such as alkyl radicals, react preferentially with electron deficient alkenes which have a relatively low lying LUMO.



Nucleophilic addition to an electron poor alkene Electrophilic addition to an electron rich alkene

Figure 5. Electrophilic and nucleophilic radical orbital interactions

Generally, intermolecular additions of nucleophilic radicals to unactivated alkenes are too slow as to render them synthetically useful. However, the rates of these reactions can be made more efficient by electronic modifications to the alkene partner or the radical itself. The addition of electron donating substituents on the radical centre serves to raise the energy of the SOMO and often gives rise to a small increase in rate, hence the order of reactivity is tertiary>secondary>primary.[26] Conversely, intermolecular additions can be accelerated by as much as a factor of 10^4 by the introduction of an electron withdrawing substituent on the β position of the alkene (Scheme 3).[13] Electron withdrawing substituents introduced in the α position also serve to lower the LUMO but the rate of acceleration is not so marked.



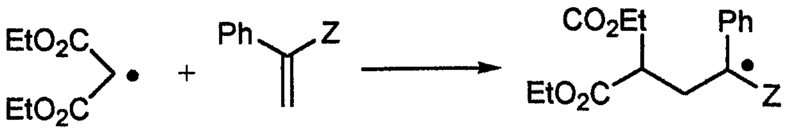
when R = Bu $k_{rel} = 0.004$
R = CN $k_{rel} = 24$

Scheme 3. Rate of addition of nucleophilic carbon radicals to β-substituted alkenes

(b) Electrophilic and (c) Ambiphilic Radicals

Until recently radicals that contained one conjugated electron withdrawing substituent were considered as electrophilic. The notion that ambiphilic radicals exist as intermediates between both electrophilic and nucleophilic radicals is relatively new. The distinction between electrophilic and ambiphilic radicals is not at all clear. Generally radicals with two electron-withdrawing substituents are classed as electrophilic, while those with one electron withdrawing substituent will be classed as ambiphilic.

Electrophilic radicals possess a relatively low-lying SOMO and react preferentially with electron rich alkenes that contain a high energy HOMO. FMO theory predicts that the introduction of electron withdrawing substituents to the radical centre and electron donating substituents on the alkene will have the effect of lowering the SOMO and raising the HOMO respectively, which will increase the rate of such an addition. The introduction of electron donating groups on the alkene only gives rise to modest increases in the rate of addition (Scheme 4).[27]



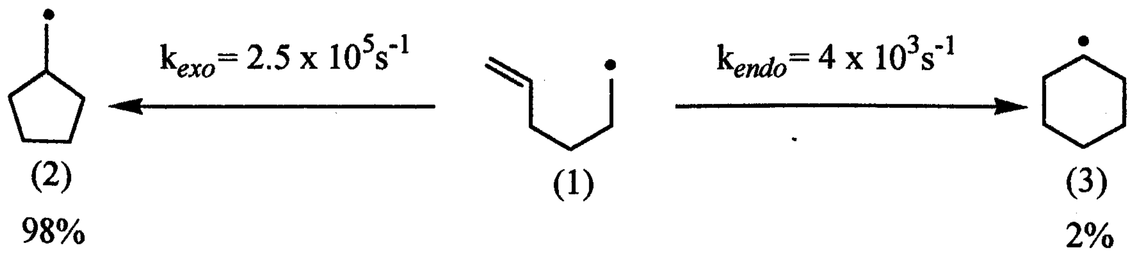
when $Z = CO_2Et$ $k_{rel} = 0.27$
$Z = OMe$ $k_{rel} = 2.1$

Scheme 4. Rate of addition of electrophilic carbon radicals to substituted alkenes

Ambiphilic radicals have SOMO energies that are intermediate between that of nucleophilic and electrophilic radicals. The addition reactions of ambiphilic radicals would be accelerated by introduction of either electron withdrawing or electron donating alkene substituents. This has been confirmed by kinetic studies on such radicals.[27] Both electrophilic and nucleophilic radicals react faster with alkenes than alkynes.[25] This is in direct contrast to nucleophilic anions, as they attack triple bonds faster than double bonds.

1.2.4.2 Intramolecular Addition (Cyclisation)

Intramolecular addition reactions are of particular importance in the construction of ring systems, especially in complex natural products. Radical cyclisations are normally easier to carry out than intermolecular radical additions. This is because most cyclisations proceed at a much faster rate due to the radical donor and acceptor being held within defined molecular architectures.[25]



Scheme 5. Regioselective outcome of a simple hex-5-enyl radical cyclisation

Cyclisation of the simple hex-5-enyl radical (1) at room temperature furnishes both the 5-*exo* (2) and the 6-*endo* (3) products in a ratio of 98:2 (Scheme 5). 5-*Exo* cyclisations are generally favoured over their 6-*endo* counter parts primarily for stereoelectronic reasons (Scheme 5).[28] In fact it has been calculated that the rate of 5-*exo* cyclisation is approximately fifty times faster than the alternative 6-*endo* mode of ring closure.[2c] Hence, the less thermodynamically stable primary cyclopentymethyl radical (2) is formed in preference to the secondary cyclohexenyl radical (3). The Beckwith-Houk transition state model can be used to explain these experimental observations.[28-31]

Efficient orbital overlap in the transition state must be achieved between the SOMO of the radical and the HOMO of the alkene. The model states that this is attained by the adoption of a chair conformation by the hex-5-enyl radical (fig. 6). The strain in accommodating the most favourable arrangement of reactive centres has been calculated as being much greater for the 1,6-transition state than the 1,5-transition state. In addition, the rate of the 5-*exo*-ring closure could be further enhanced by the additional steric effects resulting from 1,3-diaxial interactions in the transition state as well as a more favourable entropy of activation.

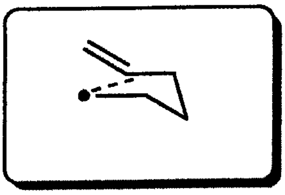


Figure 6. The chair-like 1,5 transition state

The Beckwith-Houk transition state also serves as the basis for the prediction and rationalisation of the diastereoselectivities observed in 5-*exo* hexenyl radical cyclisations.[28-31] As the transition state of a 5-*exo* radical ring closure resembles the chair conformation of a cyclohexane ring, substituents at C-2, C-3 and C-4 would be expected to adopt a pseudo-equatorial position rather than a pseudo-axial position (fig. 7).

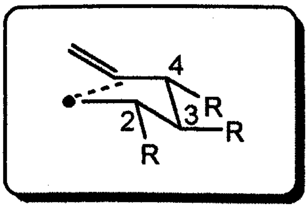
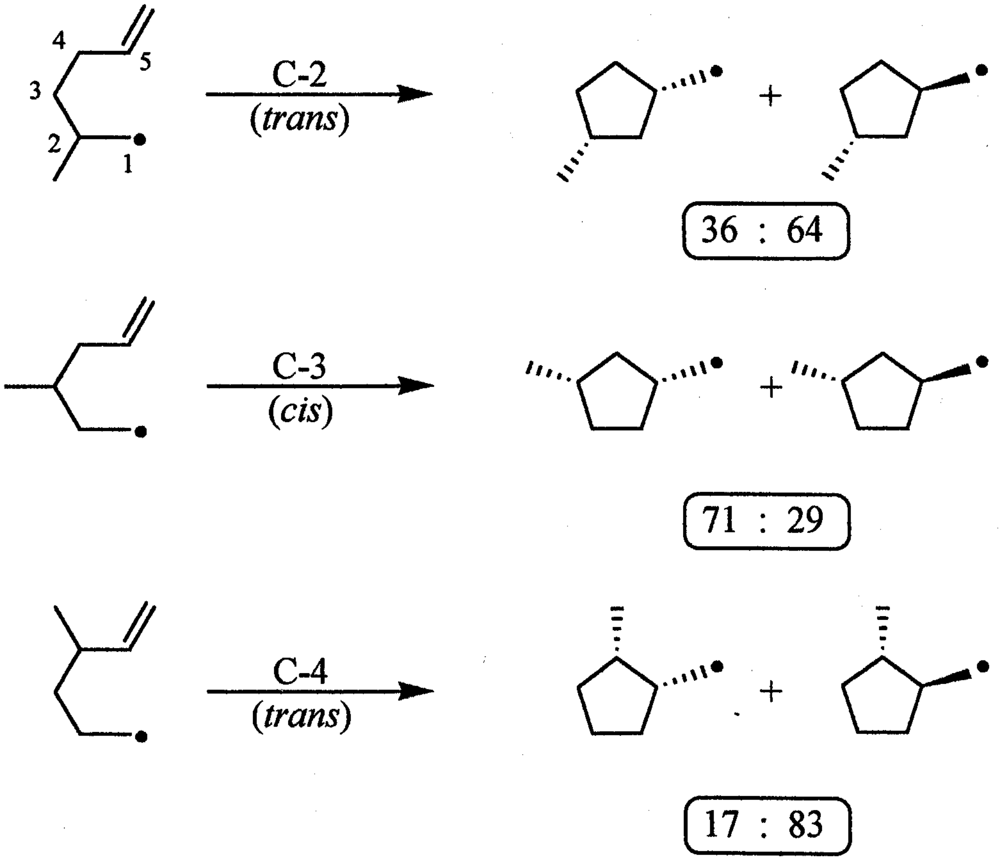


Figure 7. Pseudo-equatorial position of substituents

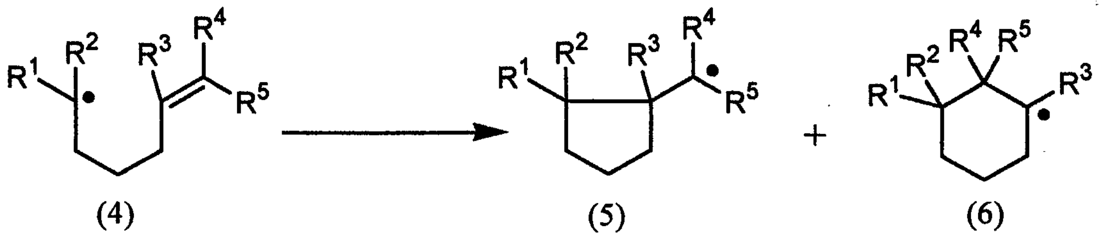
A greater proportion of the equatorial conformer is obtained when 1,3-diaxial steric interactions become stronger due to larger substituents on the ring. It has been shown that substitution at C-1 or C-3 of the hex-5-enyl radical gives preferentially *cis*-

disubstituted cyclopentyl products whereas C-2 or C-4 substitution gives preferentially *trans*-disubstituted cyclopentyl products (Scheme 6).



Scheme 6. The effects of substituents on the stereochemistry of cyclisation

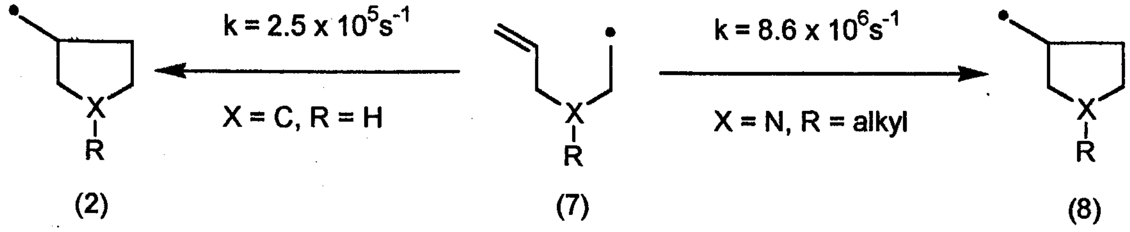
The effects of substituents on the regiochemistry of cyclisation of hex-5-enyl radicals (4) was investigated by Beckwith.[4] Substituents either at the product radical (R^4, R^5) or on the initial radical centre (R^1, R^2) show small effects (Scheme 7). However, the introduction of substituents at the 2-position of the alkene (R^3) greatly retards the rate of the reaction. Furthermore, when a large substituent group (R^3) is present at C-5, the rate of 1,5-cyclisation (5) is lowered to the point where 1,6-cyclisation (6) becomes the preferred pathway. Six-membered rings can also be isolated if the cyclisation is reversible and under thermodynamic control. The initial radical generated must be stabilised in order to allow fragmentation of the cyclic 5-*exo* radical to be faster than other processes such as reduction.



Scheme 7. The effects of substituents on the regiochemistry of cyclisation

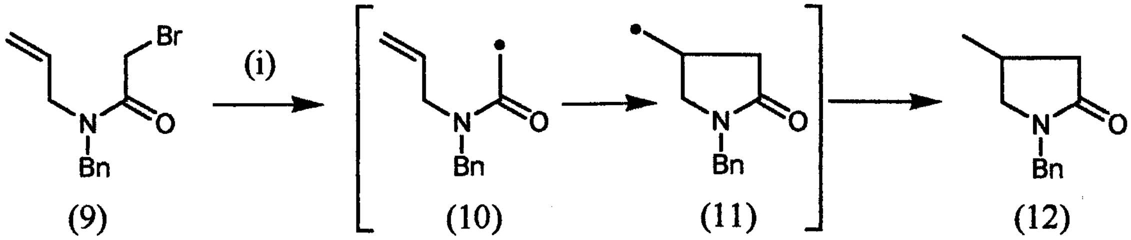
1.3 Synthesis of *N*-Heterocycles *via* Radical Cyclisation Methods

The incorporation of a heteroatom (e.g. N atom) into the hex-5-enyl chain can further augment both the rate and regioselectivity of the 5-*exo* cyclisation. This may be attributed to two effects. Firstly, the C-N-C bond angle (107.8°) is less than the tetrahedral C-C-C angle (109.5°) and secondly the C-N bond length (1.469 Å) is shorter relative to the C-C bond (1.524 Å).[32] Hence, the radical is closer to the internal carbon atom of the alkene in the transition state which reduces the activation energy of the cyclisation reaction. Consequently, the rate of the 5-*exo* cyclisation is observed to increase by at least an order of magnitude. For example, it has been calculated that the 3-aza-hex-5-enyl radical (7) cyclises at a rate of $8.6 \times 10^6\ s^{-1}$ which compares with a rate of $2.5 \times 10^5\ s^{-1}$ for the hex-5-enyl cyclisation of (1) (Scheme 8).



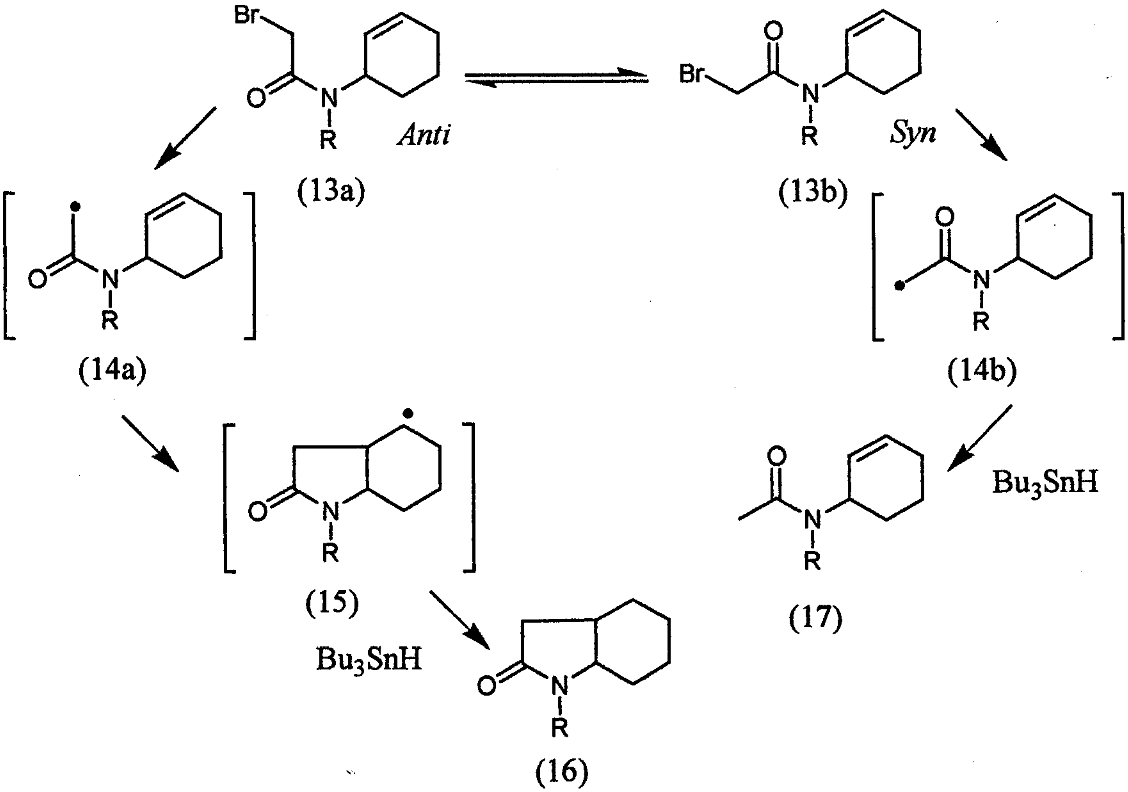
Scheme 8. Comparison of rates of cyclisation

It has been reported that the rate of cyclisation to form the pyrrolidinone system (12) is relatively slower than for the analogous system which does not contain an amide bond (Scheme 9).[33] It was suggested that the decrease in rate was due to rotation about the amide bond and that this effect was temperature dependant. The barrier to rotation[34] about an amide bond is typically between 67-92 kJ mol^{-1}. This is significantly higher than the activation energy of a radical cyclisation reaction (<42 kJ mol^{-1})[2(a)] and the additional activation may be explained in terms of amide conformer effects.



Scheme 9. (i) Bu_3SnH, AIBN, benzene

The C-N bond of the amide functional group contains sufficient double bond character to allow the molecule to exist in either of two conformations. The *anti* conformation is when both the amide carbonyl and nitrogen R group are on the same side (13a) and the *syn* arrangement is when the amide carbonyl and nitrogen R group are opposite to each other (13b) (Scheme 10). A detailed investigation into these amide conformer effects has been carried out by Stork, who investigated the *5-exo* cyclisations of bromoethanamides.[35] When the secondary bromoethanamide (13, R=H) was treated with tributyltin hydride/AIBN in benzene at 80°C, only the reduced compound (17, R=H) was isolated (unreported yield). This result was attributed to the preference of the intermediate α-carbamoylmethyl radical to exist in the *syn* conformation, in which the radical centre and alkene are too far apart for an intramolecular addition to occur. Hence, the initial radical generated is simply quenched by reaction with the reagent. In contrast, the incorporation of a bulky nitrogen protecting group, for example R = Ts, gave the desired lactam (16) *via* (13a) in 85% yield and only 2% of the simple reduced compound (17) was isolated.



Scheme 10. Amide conformer effects in 5-*exo* radical cyclisations

It was therefore concluded that the *syn*:*anti* equilibrium (13a:13b), and hence the ratio of reduced:cyclised (17:16) products is influenced by the steric bulk of the group attached to nitrogen. In general, for amide precursors, elevated reaction temperatures together with a substituent on nitrogen are a prerequisite for efficient cyclisation to occur. These factors are thought to alter the conformer populations and/or the barrier to rotation about the amide bond.

1.4 Methods used to conduct carbon radical reactions

As stated earlier most free radicals are highly reactive species and will undergo reactions with themselves by either combination or disproportionation at rates approaching the diffusion control limit. This means that a low concentration of radicals is required over the course of the reaction. This is usually achieved using radicals formed in chain reactions. The concentration difference between the substrate and radical enables the reactions to be synthetically useful. Addition of the product radical is eliminated by the addition of trapping agents. Trapping may be achieved by hydrogen donors, heteroatom donors, electron donors or intramolecular bond cleavage.[36] The rate of trapping must be faster than polymerisation, but slower than that for trapping the original radical or no addition reaction will take place. Other factors need to be considered for the chain reaction to be successful. To be useful in synthesis the chain reaction must be able to generate the radicals site selectively and the radicals must have a sufficient lifetime to be able to react. However, radicals with too long a lifetime may engage in destructive chain termination steps. The following sections will review the methods which are most commonly employed to conduct radical reactions, with a major emphasis being placed on copper based cyclisations and other metal promoted methods that are relevant to this thesis.

1.4.1 Metal Hydride Methods

The reduction of organic functional groups by organotin hydrides has continued to increase in importance since its discovery in the 1960's.[37] Since its conception it has become the most commonly used method for facilitating radical chain reactions.[38]

Tributyltin hydride and *tris*(trimethylsilyl) silane are the most popular among an increasing collection of reagents for conducting metal hydride radical reactions. The chain for Bu_3SnH[38] mediated reactions is shown in scheme 11 and an analogous chain can be written for $(TMS)_3SiH$.[39] Abstraction of an atom or group X from a precursor by the $Bu_3Sn•$ radical generates the initial radical A• which then undergoes a transformation (inter- or intra-molecularly) to provide a new radical B•. Hydrogen atom transfer then forms the final product B-H and regenerates the tributyltin radical to continue the chain.

$$\mathrm{A{-}X} + \mathrm{Bu_3Sn\bullet} \longrightarrow \mathrm{A\bullet} + \mathrm{Bu_3SnX}$$

$$\mathrm{A\bullet} \longrightarrow \mathrm{B\bullet}$$

$$\mathrm{B\bullet} + \mathrm{Bu_3SnH} \longrightarrow \mathrm{B{-}H} + \mathrm{Bu_3Sn\bullet}$$

Competing reaction

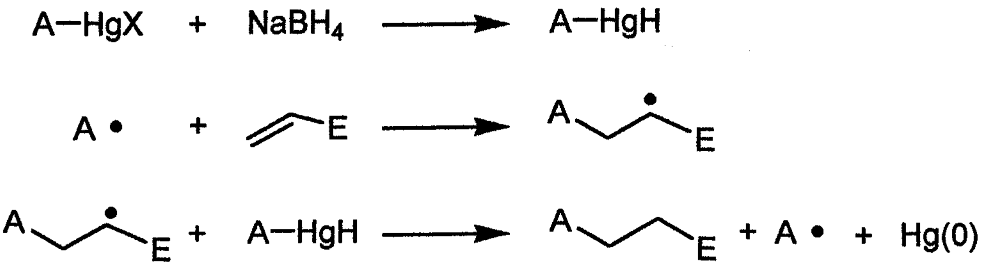
$$\mathrm{A\bullet} + \mathrm{Bu_3SnH} \longrightarrow \mathrm{A{-}H} + \mathrm{Bu_3Sn\bullet}$$

Scheme 11. Chain reaction using tributyltin hydride

The standard problem in both tin and silicon hydride reactions is the premature reduction of A• by the reagent itself. If the rate of conversion of A• to B• is slow, then it is common to use low concentrations of the hydride reagent to reduce the rate of the competing reaction (scheme 11). Syringe pump techniques are often used to maintain a steady, low concentration of this reagent. Other techniques used include polymer bound tin hydrides,[40-42] and the generation of trialkyltin hydrides *in situ* by reaction of a catalytic amount of tin halide with a standard reducing agent ($NaBH_4$ or $NaCNBH_3$).[43-45] The use of $(TMS)_3SiH$ instead of Bu_3SnH is advantageous as $(TMS)_3SiH$ is a poorer hydrogen donor, therefore lower rates of hydrogen transfer are achieved often leading to less premature reduction of A•.[39]

Many radical precursors can be used in both the $(TMS)_3SiH$ and the tin hydride method. Beckwith and Pigou devised a scale of reactivity of various substrates towards reduction by trialkyltin hydride.[46] They found that the order of reactivity towards S_H2 attack by the tributyltin radical is I>Br>PhSe>secondary and tertiary xanthate esters>tertiary nitro>Cl>*p*-CNC_6H_4S>PhS>*p*-MeC_6H_4S>MeS. For the least reactive alkyl chlorides and alkyl phenyl sulfides the rate of abstraction may not be sufficient to propagate a chain even with a rapid intermediate cyclisation. The degree of stabilisation of the initial radical is also an important factor, hence $XCH_2CO_2Et > RCH_2OCH_2X > RCO_2CH_2X > RCH_2X$.[46]

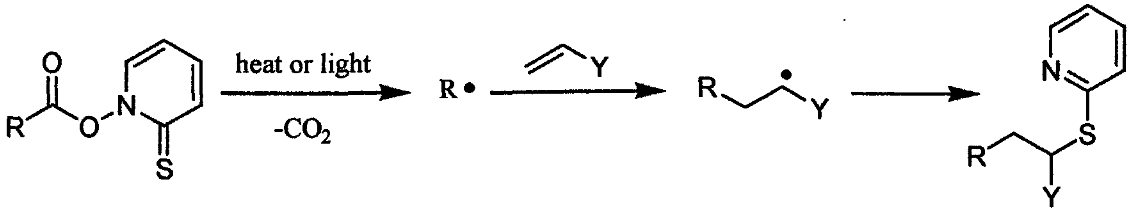
Mercuric hydrides are another example of metal hydride based radical generation.[12b] These reactions have several advantages over their tin counterparts as they are easy to conduct at ambient temperatures, are rapid, clean and easy to purify. However their reduction is fast due to the superior hydrogen transfer from mercuric reagents. This methodology is typically used for the rapid addition of nucleophilic radicals to electron poor alkenes as summarised in scheme 12.[47-48]



Scheme 12. Chain reaction for mercuric chloride

1.4.2 The Thiohydroxamate Method/Barton Method

Barton developed a new methodology towards the generation of radicals via a radical chain reaction based on the chemistry of thiohydroxamic acid esters.[49] The Barton method has one distinct advantage over hydrogen atom donor reagents is that the radical chain is terminated by reduction. Trapping with a heteroatom also enables the introduction of further functionality. This method involves the homolysis of thiohydroxamate esters either photochemically or thermally, to form nucleophilic radicals. (Scheme 13)

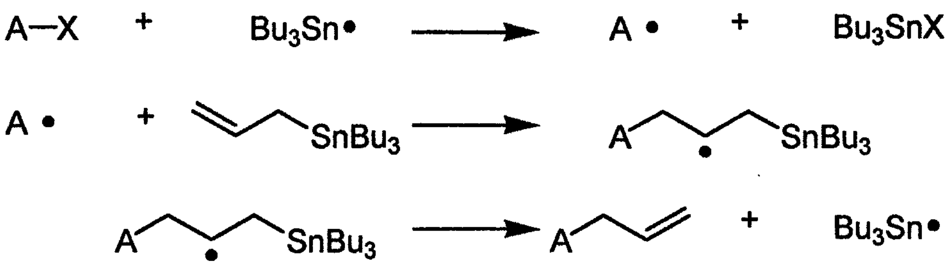


Scheme 13. Overview of the Barton method

To maximise the formation of the addition product an excess of alkene is normally required. Good yields are normally obtained for activated alkenes, alkynes and doubly activated internal alkenes.

1.4.3 The Fragmentation Method

One of the major disadvantages with the R_3SnH method when generating radicals is that the chain transfer reagent $R_3Sn•$ is generated by H-abstraction. This problem can be overcome by generating the chain transfer agent by fragmentation rather than by hydrogen atom abstraction. Instead of obtaining reduced products, substitution products are formed as an alkene is regenerated in the fragmentation step. This method involves the fragmentation of relatively weak bonds such as C-Br, C-Sn or C-SR when they are located β-to a radical (Scheme 14). Allyl stannanes have become the most popular reagents for this method. The accepted chain mechanism for allylation with allyltributylstannane is shown in scheme 14. Abstraction of X (normally a halogen) by the tributyltin radical is followed by the addition of the generated radical A• to allyltributylstannane. Rapid β–fragmentation then provides the allylated product and the regenerated tributyl tin radical.[12b] Vinylations can also be accomplished by this approach.[50]

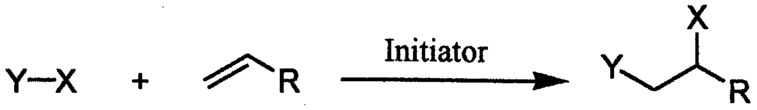


Scheme 14. Chain reaction for allyltributylstanne mediated allylation

This approach has many of the advantages of the tin hydride method without the associated liability of premature trapping of A• by the metal hydride. Since the addition of most radicals to allyltributylstannane is not a particularly fast reaction, it is often possible to conduct one or more reactions in between radical generation and allylation.[51] The power of the method lies in the fact that the β–fragmentation process is rapid and unimolecular. Reactions with allylstannanes are easy to conduct,[52] and a number of related reagents have also been used.[53-54]

1.4.4 The Atom-Transfer Method

The addition of a reagent X-Y across a carbon-carbon double or triple bond is one of the most fundamental reactions of organic free radicals.[55-56] The basic transformation, sometimes called a Kharasch addition,[57] is outlined below in scheme 15.

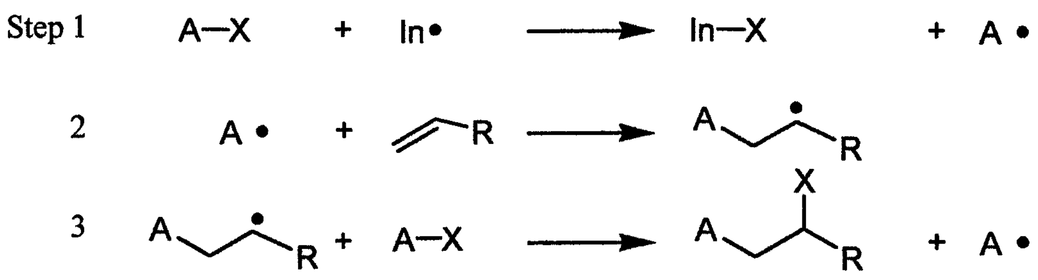


X = H or Halogen
Y = C or Hetroatom

Scheme 15. Illustrative example of a Kharasch addition

A wide variety of heteroatom and carbon groups Y can be added. When Y is a heteroatom, a wide variety of atoms or groups X may be incorporated, due to the weak nature of most interhetroatom bonds.[58] When Y is a carbon, X is usually restricted to a univalent ion atom (H, Cl, Br, I).

A generalised mechanism for this class of reaction is shown in scheme 16. The atom or group X in A-X acts as both the radical precursor and the radical trap.[12b]



Scheme 16. Atom transfer reaction mechanism

The limiting factor is the rate of atom transfer in step 3. If this is too slow then polymerisation can occur. Generally, the more exothermic the atom transfer step the less chance of any telomerisation. This is usually achieved by using reactive iodides as radical precursors.[12b] Julia has studied hydrogen atom transfer cyclisations, but while hydrogen atom transfer reactions are well known they have limited synthetic usefulness.[1a] Halogen atom transfer reactions however have much more scope for synthetic development and this will be discussed in more detail in the following sections.

1.5 Transition Metal Promoted Radical Cyclisations

1.5.1 Introduction

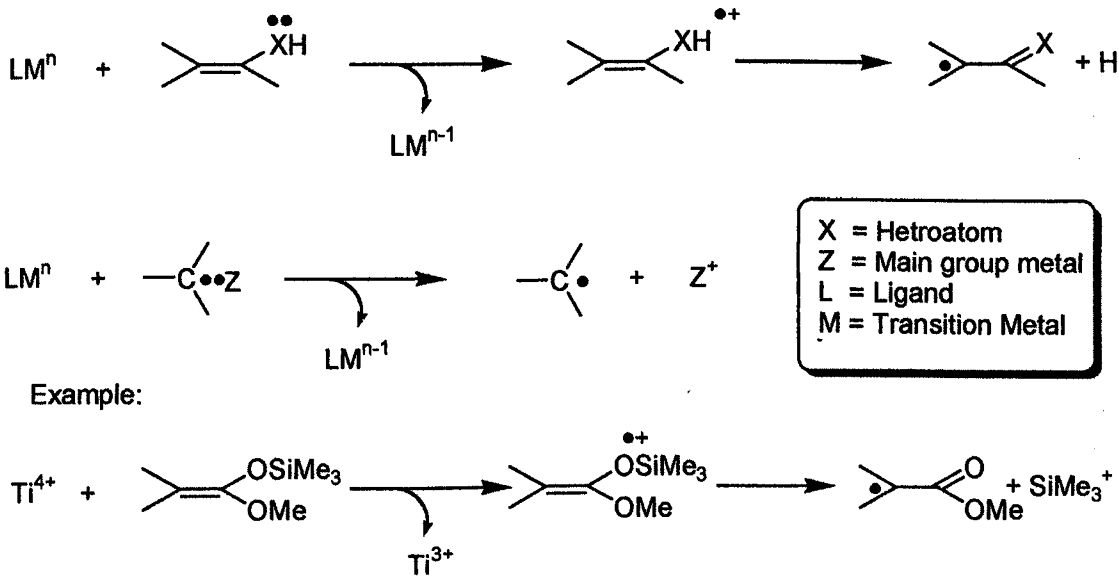
As previously discussed, carbon-centred radicals can be produced by cleaving a C-halogen, C-S or C-OR bond with tributyltin radical generated in *situ* from tributyltin hydride or hexabutylditin. However, among the disadvantages of organotin hydrides are: (a) their toxicity, (b) their cost, (c) the reductive nature of their reactions, and (d) final product purification problems born from the difficulties involved in removing stannanes from the product mixture. These are the primary factors that dissuade pharmaceutical companies from employing them.

The last decade has seen the emergence of transition metal-promoted radical reactions as a useful alternative to the stannane-based radical chemistry largely due to the pioneering efforts of Kharash,[57] Kochi,[59] and Minisci,[60] who showed that carbon-centred radicals may be generated using organometallic reagents. The advantage of transition metal-promoted radical reactions over those employing metal hydrides is that reactions are usually terminated with the introduction of functionality in the product. Transition metal-promoted radical reactions have found widespread use in organic synthesis, and one of the most well-known examples of this application is the conjugate addition reaction of organocopper reagents to enones.[61] The exciting development in this area is beginning to show its potential, as evidenced from the application of this methodology in strategy-level bond formation during the synthesis of complex molecules. The advantage associated with transition metal promoted reactions have led to hectic research activity, and as a result, titanium, manganese, iron, cobalt, copper, and ruthenium-mediated free-radical reactions have emerged as important synthetic methods for new carbon-carbon bond formation.[62]

Transition metal promoted reaction of carbon-centred radicals may be divided into the following two categories: reactions of radicals generated by an oxidative process and reactions of radicals generated by a reductive process.

(a) Oxidative Process

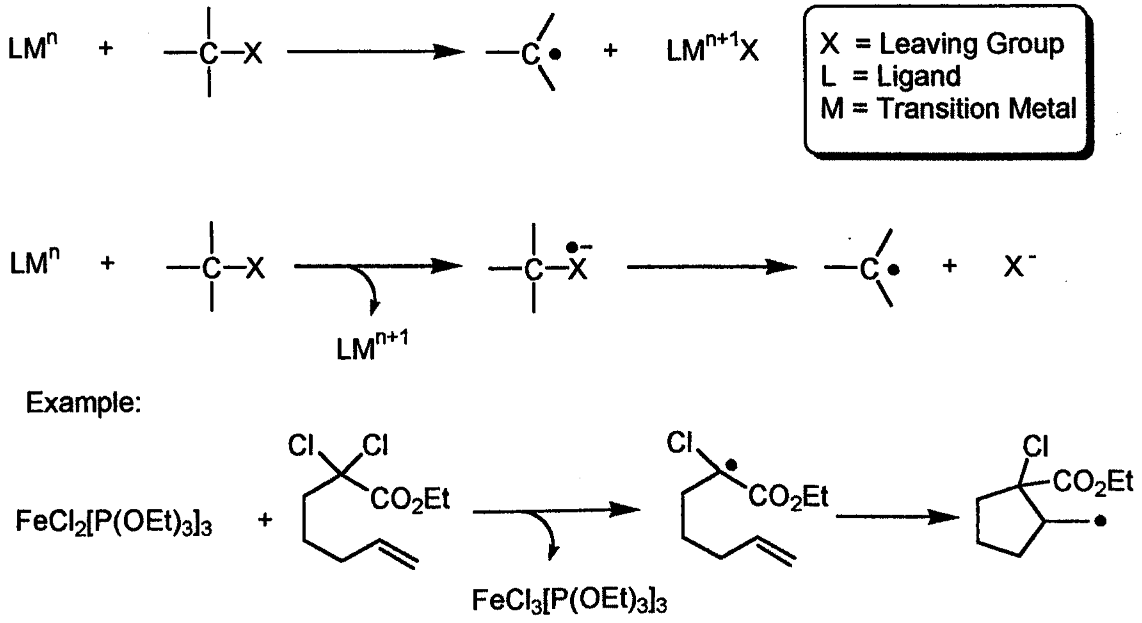
The metal acts as an oxidant in this process, which involves the generation of radicals by an electron transfer from radical precursor to the metal complex. The reactions proceeds via an organometallic reagent, which may lead to a carbon-centred radical on homolytic cleavage of carbon metal bond (Scheme 17).



Scheme 17. Illustrative example of an oxidative process

(b) Reductive Process

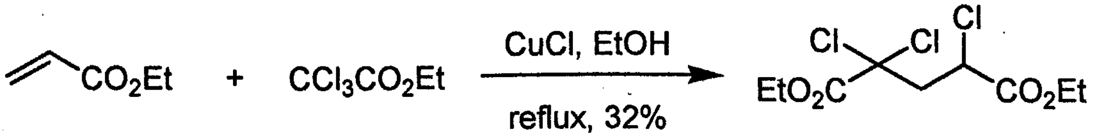
The metal acts as a reductant in this process with the carbon centred radical being generated by an atom transfer or electron transfer from metal complex to the radical precursor. The reaction may proceed via an organometallic reagent that eventually leads to a free radical homolytic cleavage of the metal-carbon bond (Scheme 18).



Scheme 18. Illustrative example of a reductive process

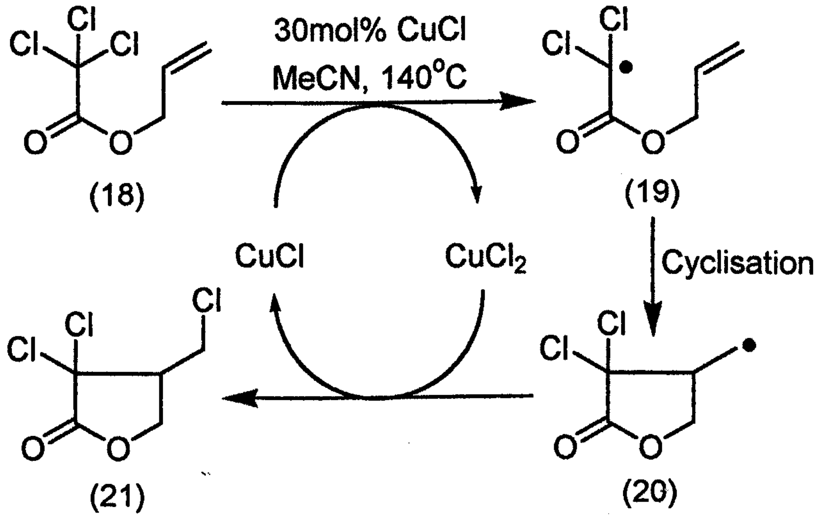
1.5.2 Copper Mediated Radical Cyclisation Reactions

Copper catalysed intermolecular addition of polyhalocarbon derived molecules to alkenes has been known for some time, (Scheme 19).[63] The intramolecular version of this reaction, atom transfer radical cyclisation (ATRC) can provide a convenient method for the construction of various ring systems.



Scheme 19. Intermolecular copper catalysed reaction

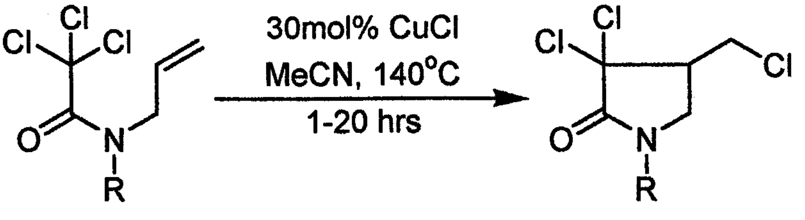
In particular ATRC reactions of 2,2,2-trichlorinated carbonyl compounds have been reported with a range of metal catalysts, *e.g.* $RuCl_2(PPh_3)_3$, and $FeCl_2(P(OEt)_3)_3$.[62] However, by far the most successful catalysts have been those derived from copper(I)-based halogen compounds.[62] These reductive atom transfer cyclisations involve redox reactions between copper(I) and copper(II) complexes. Nagashima has shown that the reaction of an activated trichloroacetate (18) with CuCl in MeCN at 140 °C in a pressure bottle for 1 hour generates the initial radical (19) and $CuCl_2$ (Scheme 20).[64] After cyclisation the newly formed (more reactive) primary radical (20) reacts with $CuCl_2$ to regenerate the CuCl catalyst and furnish the cyclised product (21).



Scheme 20. Oxidative copper(I) mediated atom transfer radical cyclisation

The use of copper complexes in mediating radical cyclisations thus has a number of advantages over alternative reductive methods including; (a) the low cost of copper halides, (b) the ease of work-up of the reactions, and (c) the catalytic nature of the processes.

The use of ATRC mediated by catalytic amounts of CuCl has been utilised to prepare not only γ-lactones but also γ-lactams.[65-66] Nagahisma has shown that heating both the trichloracetamide derivatives (22a-b) with CuCl in MeCN at 140 °C furnished the desired 5-*exo* atom transfer products (23a-b) in 57% and 87% yield respectively, (Scheme 21).[65] No products arising from 6-*endo* cyclisation were detected. Using this protocol it was possible to cyclise both secondary (22a) and tertiary (22b) amides, although the cyclisation of the tertiary amide (22b) was the more efficient of the two.

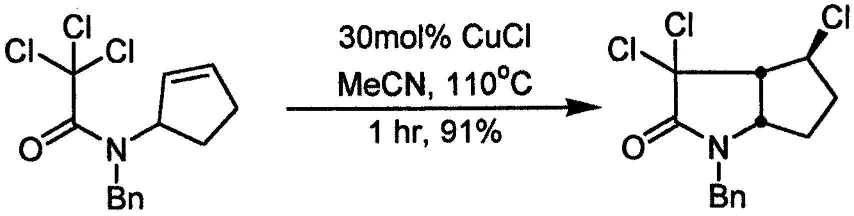


(22a) R = H
(22b) R = allyl

(23a) R = H, 57%
(23b) R = allyl, 87%

Scheme 21.

Using this approach, Nagashima was also able to produce bicyclic lactams providing access to pyrrolidine alkaloid skeletons (Scheme 22). Cyclisation of (24) at 110 °C furnished one diastereoisomer (25) containing the *cis* fused ring junction in 91% yield.[66]

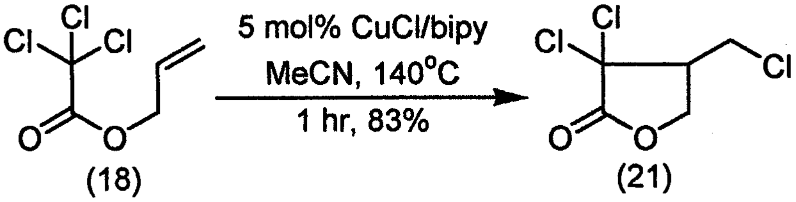


(24)

(25)

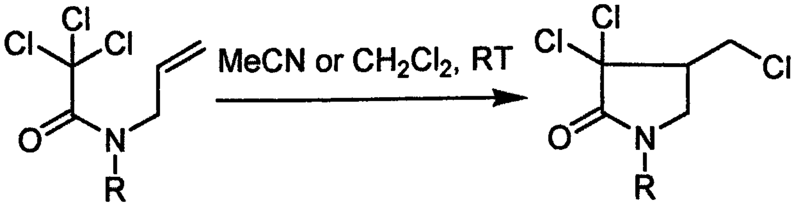
Scheme 22.

Nagashima also showed by screening other copper salts that a range of compounds were effective in mediating the cyclisation of trichloroacetate (18) at elevated temperatures including Cu_2O, $Cu(NO_3)_2.H_2O$, and Cu(CCPh).[67] The concentration of the reactions was also found to be crucial with relative high concentrations leading to telomerisation of the substrate. While a range of solvents were investigated only acetonitrile and alcohols were found to be effective in mediating the cyclisation to lactone (21).[67] However, the addition of an equimolar amount of 2,2'-bipyridine (bipy) to CuCl was found to accelerate the rate of the reaction fourfold (Scheme 23).[67]



Scheme 23. Ligand accelerated ATRC

In general, the addition of either amine or pyridine ligands to atom transfer reactions has been found to cause rapid rate accelerations for a variety of cyclisation and intermolecular addition reactions.



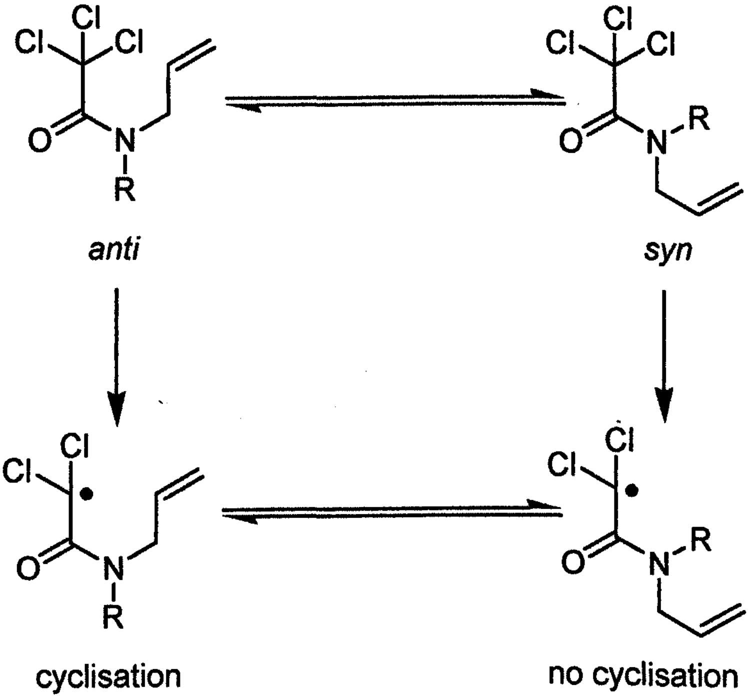
(26a) R = Bn
(26b) R = Ts
(26c) R = Boc

(27a) R = Bn
(27b) R = Ts
(27c) R = Boc

Scheme 24.

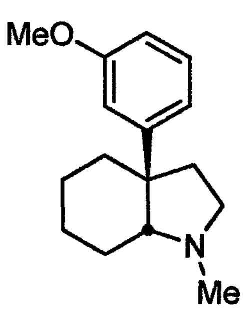
Ligands may act in two ways to accelerate atom transfer processes by either, a) increasing the solubility the CuCl, or b) by altering the redox potential of the catalyst system, (or both). Screening the precursors (26a-c) with various ligand systems indicated that the use of 30 mol% of a 1:1 mixture of CuCl:bipy in CH_2Cl_2 catalysed the cyclisation more rapidly than CuCl in MeCN.[68] Other solvents such as 1,2-dichloroethane and THF were also compatible with the use of CuCl:bipy as a mediator. Thus, with this more activated catalyst system it was possible to cyclise a variety of substrates at room temperature or below. The nature of the *N*-protecting group was found to affect the rate of the cyclisation, for example, electron-withdrawing groups, such as R = Ts (26b), or R = Boc (26c), facilitated the cyclisation by increasing the rate of homolysis of the carbon-chlorine bond as well as by decreasing the barrier to amide rotation.[68]

In general the cyclisation of α-*N*-allyl-carbamoyl radicals, derived from (26), is a difficult process requiring high temperatures, primarily due to the high barrier to rotation that characterises the amide bond. Only one conformer can cyclise (*anti*) and the nature of the *N*-protecting group alters the conformer population, thus bulky or electron withdrawing substituents (26b-c) favour cyclisation by shifting the equilibrium towards the *anti* conformer (scheme 25).[69]

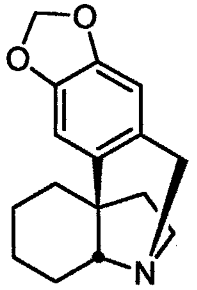


Scheme 25. Conformer equilibria

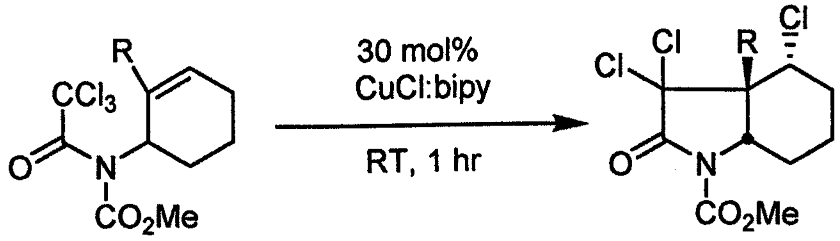
This phenomenon has been used to good effect in the formal total synthesis of both mesembrane (28) and crinane (29).[69] Cyclisation of substrates (30a-b) with 30 mol% CuCl:bipy furnished the products (31a-b) in 78% and 78% yield respectively (Scheme 26). Manipulation of these intermediates to the *dl*-natural products, mesembrane (28) and crinane (29), was then accomplished using standard chemistry.[69] Attempts to mediate the cyclisation of substrates (30) which contained the desired *N*-Me group only produced low yields (20%) of the desired products due to unfavourable conformer populations (e.g. Scheme 25).[69]



(28) *dl*-mesembrane



(29) *dl*-crinane

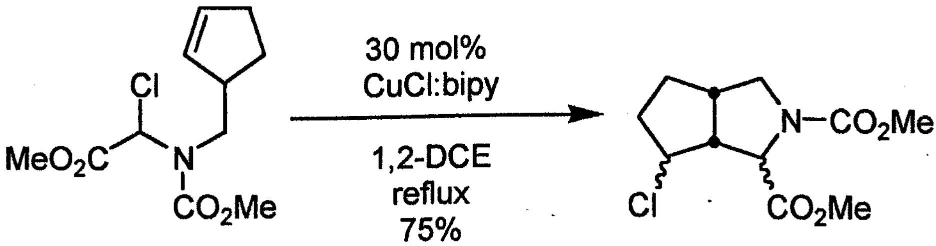


(30a) R = 3,4-dimethoxyphenyl
(30b) R = 3,4-methylenedioxyphenyl

(31a) 78%
(31b) 78%

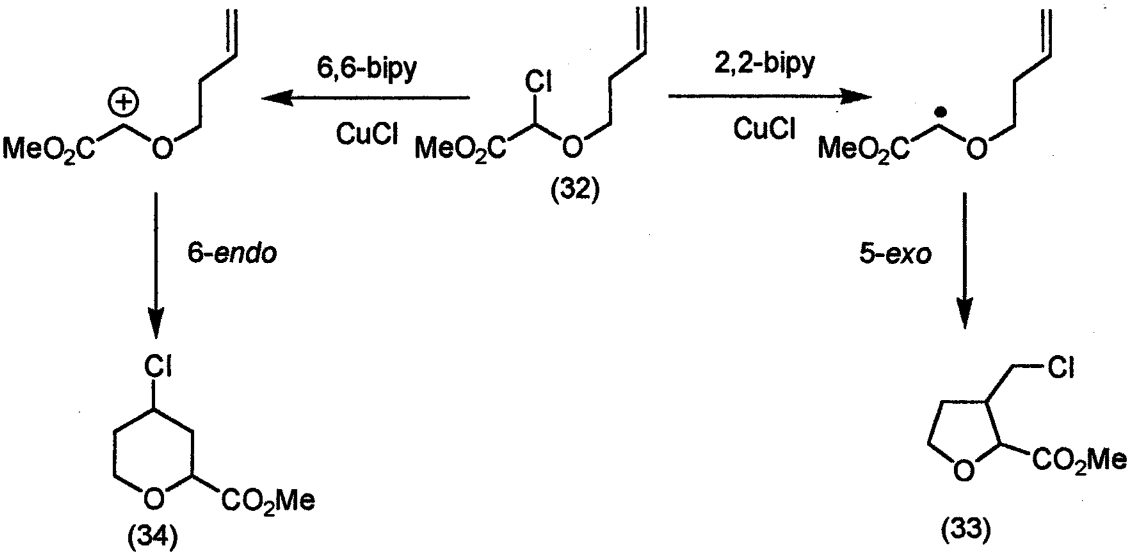
Scheme 26.

The highly activated nature of the CuCl:bipy catalyst system allows the cyclisation of mono-halo substrates at elevated temperatures (80°C). Hence, Speckamp has applied this protocol to the synthesis of cyclic amino acids.[70] Best results were obtained when the reactions were performed at 80 °C for 18 hours, (Scheme 27).



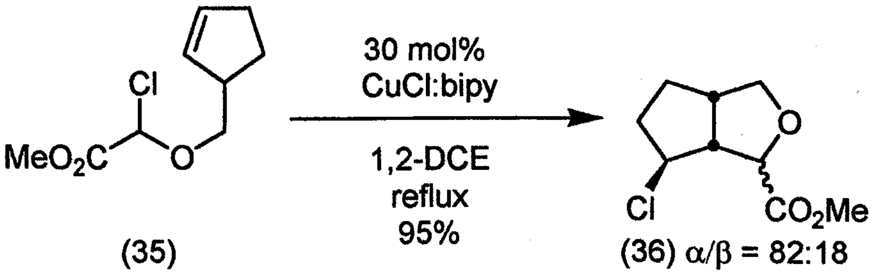
Scheme 27. A novel route to cyclic α- amino-acids

A variety of solvents were found to be compatible with the cyclisation of the glycine derived radicals, however the use of good hydrogen atom donors like THF, dimethoxyethane and acetone led to substantial amounts of reduced cyclisation products. The regioselectivity and stereoselectivity of the cyclisations were found to parallel those obtained from Bu_3SnH mediated cyclisations. In analogous chemistry the cyclisation of radicals derived from 2-(3-alken-1-oxy)-2-chloroacetates was possible, (Scheme 28).[71]



Scheme 28. Reaction regioselectivity

Interestingly the regioselectivity of the reactions was dependant upon the copper complex used. Hence, cyclisation of (32) with CuCl:2,2-bipyridine proceeded as expected to give the 5-*exo* product (33) while the use of 6,6'-bipyridines led exclusively to the 6-*endo* product (34).[71] This was rationalised due to the different ligands promoting either a radical or cationic cyclisation pathway respectively. The use of CuCl:bipy in the cyclisation of a range of 2-(3-alkene-1-oxy)-2-chloroacetates furnished 3-(1-chloroalkyl)-substituted tetrahydrofurans in good yields. Hence, cyclisation of (35) furnished (36) in 95% yield as an 82:18 mixtures of α/β isomers respectively (Scheme 29). The chlorine substituent incorporated in the products could be used to good effect in further chemistry (e.g. lactonisation reactions). The utilisation of this atom transfer/lactonisation protocol allowed for the efficient total synthesis of the natural products avenaciolide and isovenaciolide.[71]



Scheme 29.

1.5.3 Second Generation Copper Catalysts

The discovery that different ligands can alter the reactivity, yield and selectivity of atom transfer reactions has prompted various groups (including our own) to investigate the use of alternative ligand systems in cyclisation reactions. The ability to modify both the solubility and redox potential of the catalysts by varying the ligand has enabled a range of highly activated catalyst systems to be prepared. In addition the choice of ligand used can often modify the product distribution significantly (see Table 2). By far the most useful of the new generation of atom transfer catalysts are those based upon a) *N*-alkyl-2-pyridylmethanimines (NPMI) (37),[72-77] b) *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (38),[78-81] and c) *N,N,N',N',N",N"*-hexamethyltriethylenetetramine (Me_6-tren) (39).[72, 76, 77, 82] Each of these ligand systems will now be covered in more detail as their utilisation forms an integral part of this thesis.

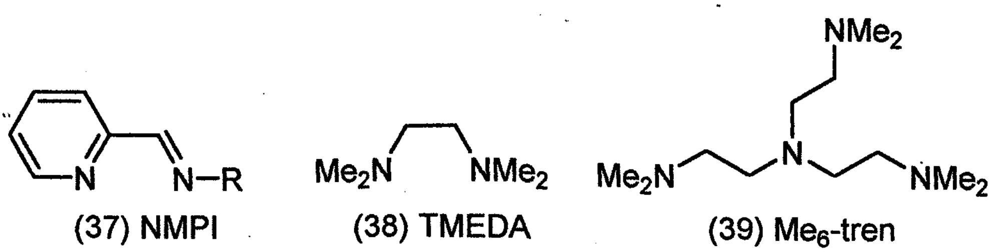
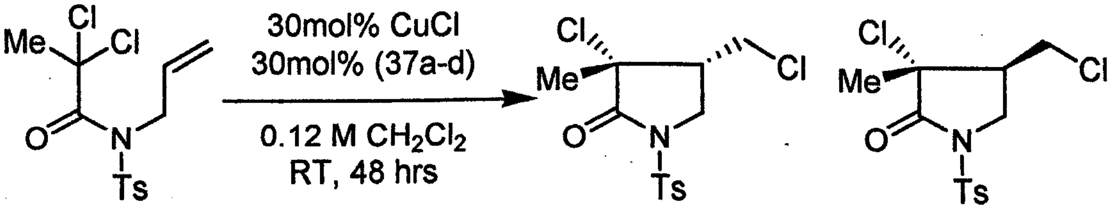


Figure 8. Second generation copper ligands

1.5.3.1 *N*-Alkyl-2-pyridylmethanimines (NPMI's)

In systems where copper halides are used in conjunction with bipy, the bipy is thought to primarily serve to solubilise the copper halide as [Cu(I)(bipy)$_2$]X. In addition, the low-lying LUMO π^* orbital, present in the conjugated π-system of bipy, is able to accept electron density from the metal and hence serve to stabilise the Cu(I) oxidation state. Clark and co-workers reported that the structurally similar NPMI ligands solubilise Cu(I) halides and also have low lying π^* orbitals.[73] However, the relative ease of preparation of these ligands (easily prepared by reaction of commercially available amines with pyridine carboxaldehydes in the presence of $MgSO_4$) has allowed a whole range of catalysts with different solublities, steric and electronic properties to be prepared.[74] Structure activity relationships have indicated that the nature of the imine substituent is crucial in controlling the rate and selectivity of the cyclisation reaction. Hence, cyclisation of precursor (40) with the range of ligands shown indicate that bulky substituents retarded the rate of cyclisation significantly, (table 2).[74] In addition the diastereoselectivity of the process was also affected by the nature of the *N*-alkyl group. The optimum ratio of ligand to copper halide was found to be 2:1.[73-74]



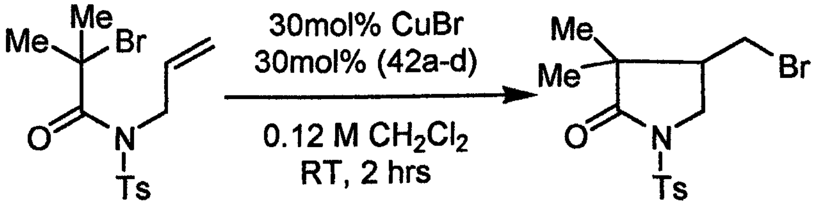
(40)

Ligand	R-group	Relative rate	diast. ratio
(37a)	*n*-Bu	45	18:82
(37b)	*i*-Bu	28	28:72
(37c)	*s*-Bu	3	32:68
(37d)	*t*-Bu	1	51:49

Relative rate with respect to the reaction of ligand (37a)

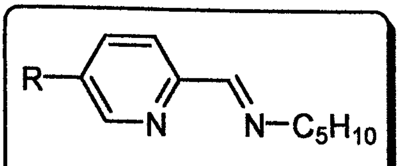
Table 2. Effect of *N*-alkyl group on cyclisation

Clark also showed that solubility of the complexes could be altered by tailoring the length of the *N*-alkyl substituent, e.g. (37e) R = *n*-Pr -the catalyst was soluble in water at room temperature and insoluble in toluene at room temperature but soluble in toluene at 110 °C. The active nature of the catalyst (37f), R = *n*-pentyl allowed for the cyclisation of mono-halosubstrates such as (41) at room temperature (Table 3).[74] Screening of a range of electronically modified ligands (42a-d) in the cyclisation of (41) indicated that the order of reactivity was 42b>42a>42c>42d. This suggests that inductive effects onto the pyridine nitrogen are the dominant features for this class of ligands in cyclisation reactions.[75] The ligand (42b) which contained a mildly inductive electron donating group (which causes an increase in the energy of the ligand LUMO and thus a decrease in the relative stability of the Cu(I) oxidation state) showed a rate enhancement, whereas those with electron withdrawing inductive groups caused a decrease in the rate of reaction. Thus the rates of ATRC reactions may well parallel the basicity of the ligands themselves.[75] This fits in with the observation that the more basic sp_3 hybridised ligands TMEDA, and Me_6-tren are more active catalysts in ATRC reactions.[72, 78]



(41) (43)

Ligand	R-group	Ratio 41:43
(42a)	H	41:69
(42b)	Me	34:66
(42c)	OMe	73:27
(42d)	NO_2	>98:2

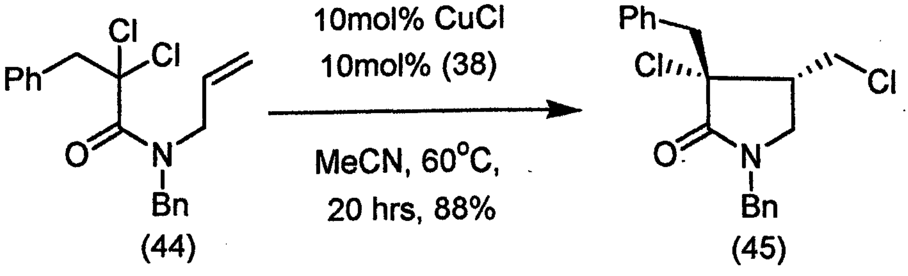


(42a-d) NMPI

Table 3. Effect of the pyridyl group on the cyclisation of precursor (41)

1.5.3.2 *N,N,N',N'*-Tetramethylethylenediamine (TMEDA)

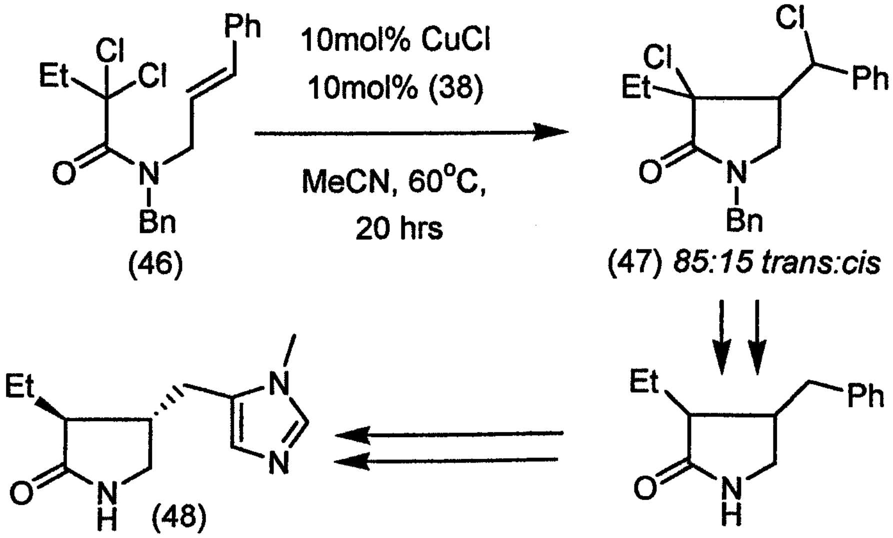
One of the major disadvantages of the CuCl:bipy reagent system is that substantial amounts of catalyst (normally 30 mol%) of this relatively expensive reagent are required for efficient catalysis. The use of the more reactive CuCl:TMEDA reagent combination furnishes a catalyst system that gives better yields at lower catalyst loading in simple ATRC reactions. In addition, cyclisations can often be carried at out at lower temperatures than when compared to CuCl:bipy. An added advantage is the relative inexpense and commercial availability of the TMEDA additive. As in the case of the bidentate NMPI ligands, the optimum ratio of the bidentate TMEDA ligand to CuCl was found to be 2:1.[78] Thus CuCl:$(TMEDA)_2$ complex can mediate efficient 5-*exo* cyclisations of a range of trichloro- and dichloro-acetamide derivatives. Ghelfi and co-workers reported that the cyclisation of (44) with 10 mol% CuCl:$(TMEDA)_2$ in acetonitrile for 20 hours at 60 °C furnished the product (45) as one diastereomer in 88% yield, (Scheme 30).[78] Interestingly, attempts to cyclise this substrate with CuCl:bipy failed, indicating the importance in utilising the correct choice of ligand for a given cyclisation.



Scheme 30.

Both Parsons and Ghelfi have shown the influence of the *N*-benzylic protection in the CuCl:$(TMEDA)_2$ catalysed 5-*exo* cyclisation of a range of chiral substrates.[79-80] The steric nature of the *N*-substituent was not found to influence the stereoselectivity of the cyclisations to any significant extent.[79] The synthetic utility of CuCl:$(TMEDA)_2$

promoted cyclisation has been explored by application to the formal total synthesis of pilolactam (48)[79] and in the synthesis of 3-benzylimino-2-pyrrolidinones.[81]

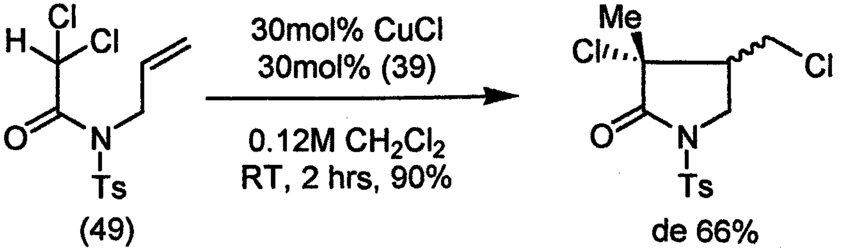


Scheme 31. Application of ATRC in the total synthesis of pilolactam

1.5.3.3 *N,N,N',N',N",N"*-Hexamethyltriethylenetetramine (Me_6-tren)

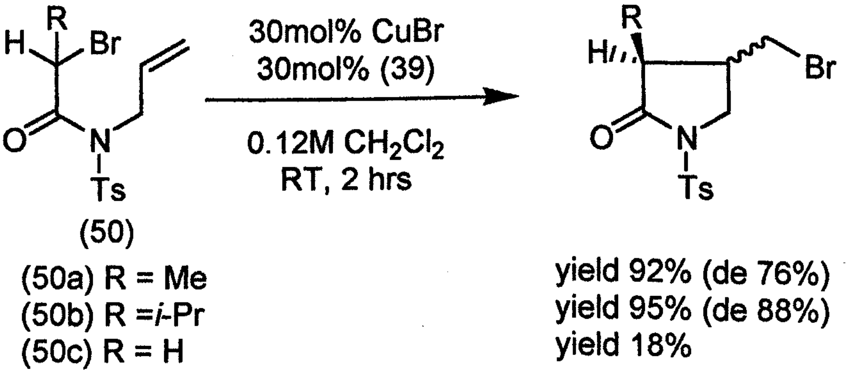
The origin of the reported improvement in the activity of $CuCl(TMEDA)_2$ relative to CuCl(bipy) has been speculated to arise due to the fact that simple copper(amine) complexes have lower redox potentials than copper(pyridine) complexes. Ghelfi and co-workers reported that the optimum ratio for copper halide:TMEDA was 1:2 indicating that two equivalents of bidentate ligand are required to make the active catalyst.[78] As a consequence of this observation a range of other multidentate amine ligands have also been screened in ATRC reactions. Clark and co-workers reported that the most active polydentate amine ligand to date was found to be the tetradentate Me_6-tren ligand (39).[72, 82] The use of a 1:1 ratio of copper halide:(39) in various solvents was found to produce a catalyst far more active than either bipyridine, NMPI or TMEDA. Thus cyclisation of precursor (49) proceeded only slowly at room temperature with NMPI (42a) (72hrs, 15% conversion) but rapidly (less than 2 hours, yield 90%) with Me_6-tren

(39). The more activated nature of the catalyst allowed cyclisation to take place with lower catalyst loadings, thus cyclisation of precursor (40) was accomplished with only 5 mol% catalyst at room temperature in 24 hours (Scheme 32).[72, 82] While it was possible to use even lower catalysts loadings at room temperature (e.g. 0.5 mol%) the reaction only proceeded to give a 33% conversion in the same 24 hour period.



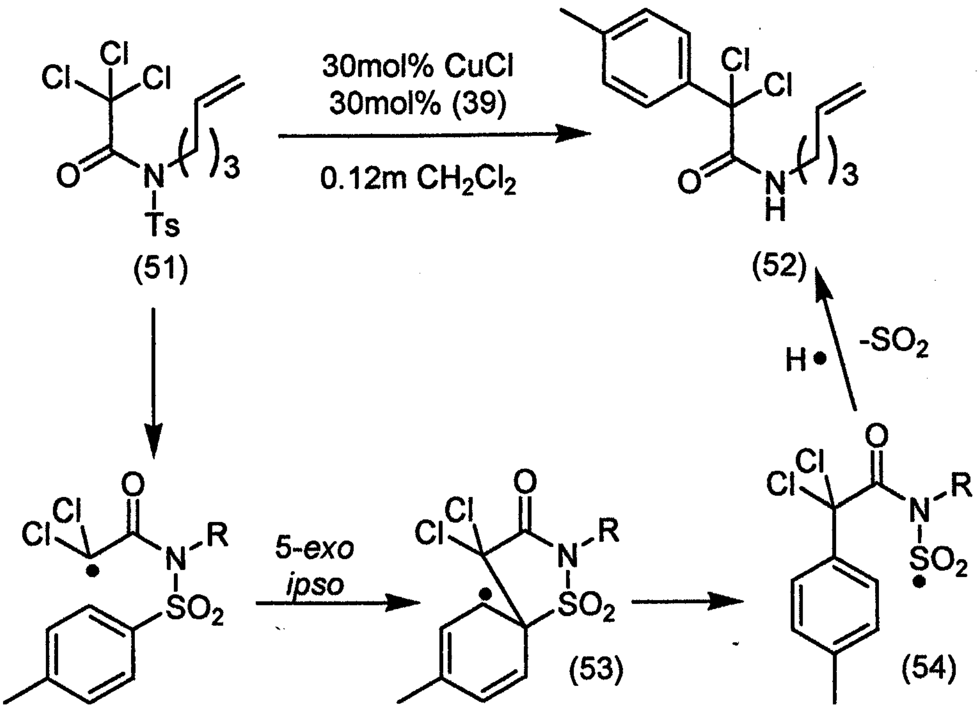
Scheme 32.

Cyclisation of a range of monohalosubstrates (50a-b) was possible at room temperature. Cyclisation of the primary bromide (50c) was possible albeit at elevated temperature. The product was obtained in low yield due to competing amide cleavage (Scheme 33).[72]



Scheme 33.

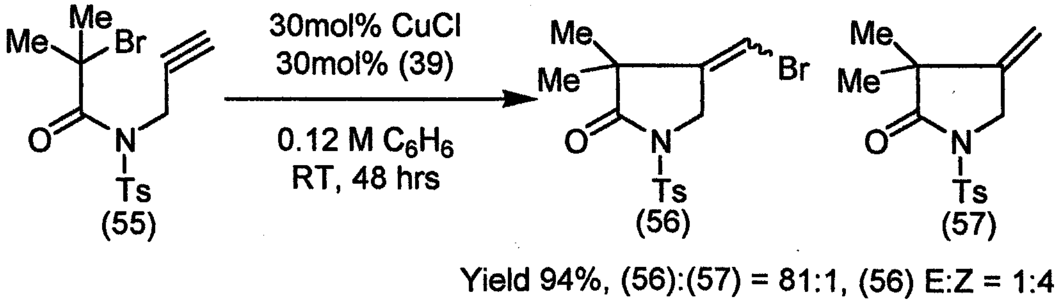
Using this protocol it was not necessary to use vigorously dried glassware or solvents. In addition work-up of the reactions was facile, as the crude reaction mixture was passed through a small silica plug and the solvent removed to furnish the atom transfer products directly. Attempts to mediate *8-endo* macrocyclisations of *N*-tosylamide (51) using this ligand system failed, with the main products being the rearranged compound (52) as well as unreacted starting material (53).[72] The rearranged product (52) was postulated to arise *via* a competing 5-*exo ipso* aromatic radical substitution to give (53) followed by re-aromatisation followed by C-S bond cleavage to give (54), loss of SO_2 and reduction of the resulting amide radical (Scheme 34).



Scheme 34. Postulated rearrangement mechanism under ATRC conditions

Clark and co-workers have recently published the use of the CuBr:(39) system in the 5-*exo* ATRC of 1-halo-*N*-propargylacetamides.[76] Cyclisation of the mono-bromo precursor (55) gave both the expected atom transfer product (56) plus the reduced product (57) arising from the abstraction of a hydrogen atom by the intermediate vinyl radical (Scheme 35). The ratio of these compounds was dependent on both the solvent and ligand employed.

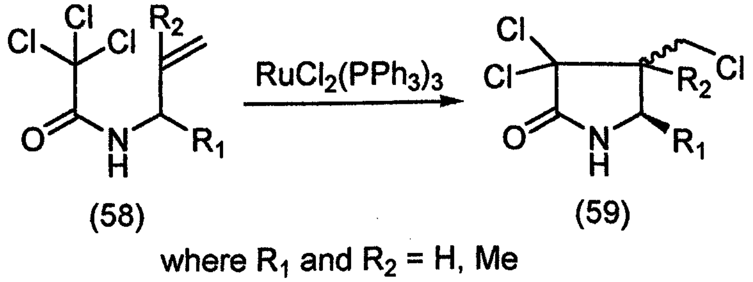
The copper catalysts born from the ligands discussed above have also been exploited in the area of atom transfer radical polymerisation ATRP[83] and the solid phase polymer chemistry of methyl methacrylate.[84]



Scheme 35.

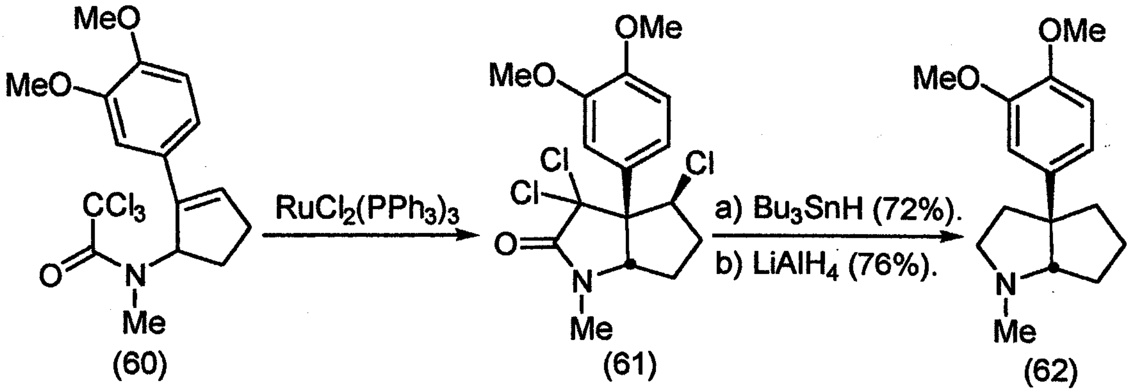
1.5.4 Contemporary transition metal mediated radical cyclisation reactions

The use of ruthenium complexes to mediate the formation of carbon-carbon bonds in free-radical reactions is well know.[62] Matsumoto and co-workers have reported that $RuCl_2(PPh_3)_3$ catalysed the addition of α-chloroesters to alkenes.[85] Itoh then developed this complex in the preparation of γ-lactams as an alternative to the conventional method of cyclisation *via* acyl-nitrogen bond formation. Itoh showed that secondary amides (58) underwent 5-*exo* cyclisation in modest yields (Scheme 36).[65]



Scheme 36.

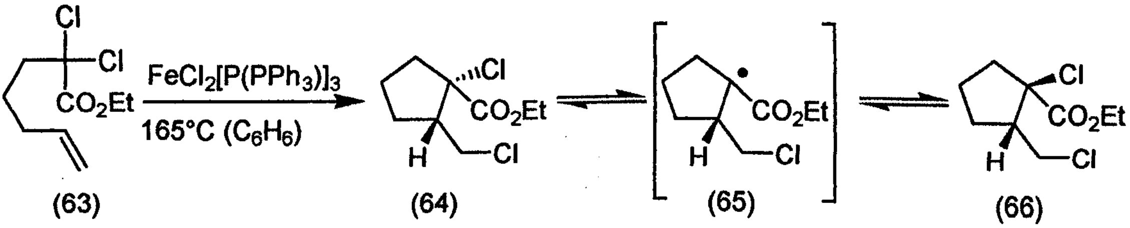
$RuCl_2(PPh_3)_3$ was used to cyclise *N*-allyl-trichloroacetamides with cyclohexenyl or cyclopentenyl (60) groups that were appropriately substituted to form the corresponding *cis* fused trichlorinated γ-lactams (Scheme 37).[66] Furthermore, reductive dechlorination by Bu_3SnH followed by reduction with $LiAlH_4$ gave pyrrolidine alkaloid mesembrine (62) in a yield of over 70% in both steps.[66]



Scheme 37.

Bergbreiter developed an excellent bi-phasic polymer-bound ruthenium (II) catalyst and showed its application to intramolecular addition of trichloroalkenes.[86] Comparison with the unsupported catalyst proved favourable.

Iron (II) complexes act as good catalysts in promoting the Kharasch reaction with various halocarbons and alkenes.[87-90] Iron (II) complexes generate radicals *via* reductive processes which are terminated by halogen atom transfer. Weinreb has utilized iron (II) in the form of $FeCl_2[P(PPh_3)_3]$ in the intramolecular addition of unsaturated α,α-dichloroesters (63) (Scheme 38).[91]



Scheme 38. Iron mediated intramolecular addition of α,α-dichloroesters

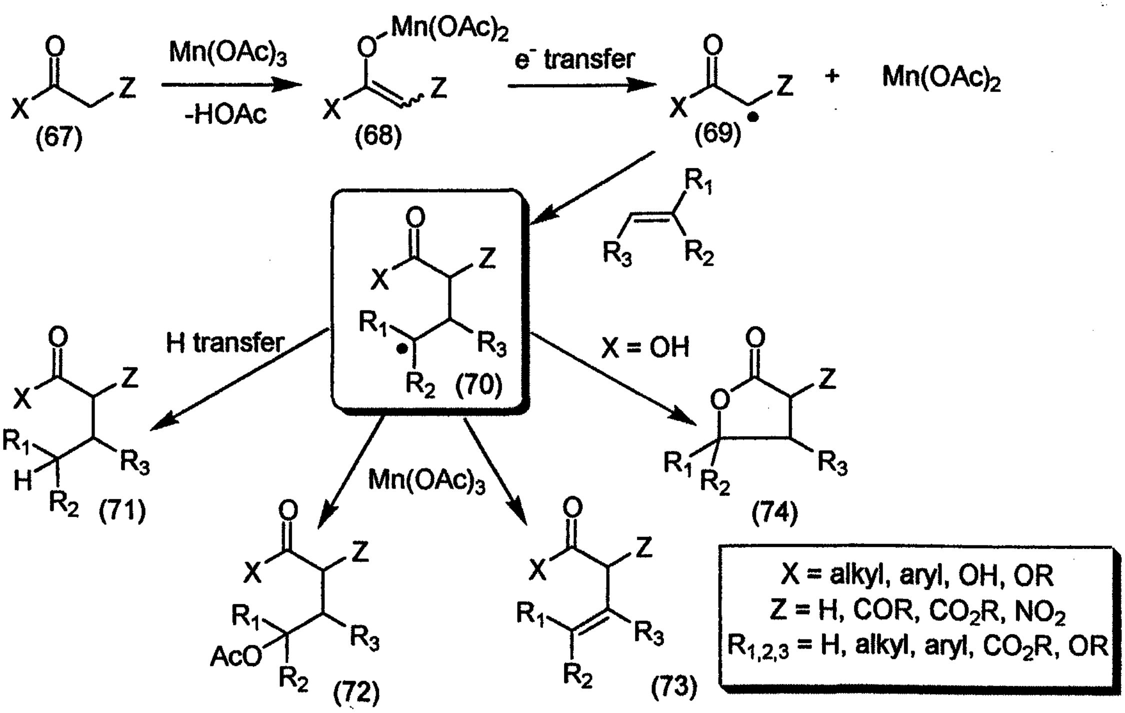
The ratio of diastereoisomers (64/66) was found to be dependent upon catalyst concentration and the reaction time. These variances were attributed to isomerisation *via* reversible α-chlorine abstraction and recombination *via* the planar radical (65). The scope of this methodology was extended to encompass less activated α-chloroesters with a high degree of success.[92] Fe-$FeCl_3$ has been shown to promote the cyclisation of

N-allyl-*N*-benzyl-2,2-dichloroacetamides although in poor yields.[78] Very recently Verlhac has reported the utilisation Fe (II) *tris*-pyridine-2-ylmethyl-amine in the synthesis of various lactones.[93]

Ban and co-workers have reported the ATRC of *N*-allyl iodoacetamides using the palladium complex $Pd(PPh_3)_4$ as the transition metal catalyst, albeit in low yields.[94]

The most widely employed reagent for conducting oxidative free-radical cyclisations is manganese(III) acetate, which can be prepared quite easily from potassium permanganate and manganese(II) acetate in acetic acid.[95] The groups of Heiba and Dessau[96] and also Bush and Finkbeiner[97] have reported the oxidative addition of acetic acid to alkenes using the one-electron oxidant manganese(III) acetate. This provided the basis for a general approach to oxidative free-radical cyclisation that has considerable synthetic potential. In addition to the ease of product purification the approach allows highly functionalised products to be prepared from simple precursors. The oxidative cyclisation of unsaturated β-keto esters was subsequently reported by Corey and Snider.[98-99]

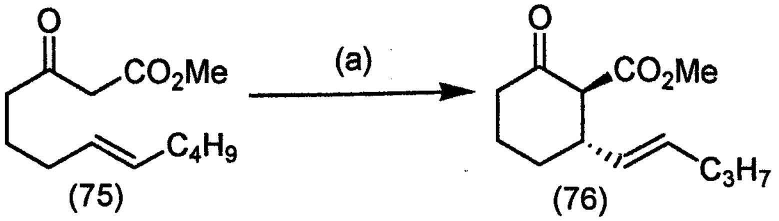
The mechanism of oxidation of monocarbonyl substrates with manganese(III) acetate has been extensively studied. Fristad and Peterson showed that the rate of radical generation with manganese(III) acetate, which is actually an oxo-centred triangle of Mn(III) with bridging acetates, correlates with the enolisability and C-H acidity of the precursors (67) (Scheme 39).[100-102] The broad variety of suitable radical precursors include carboxylic acids, ketones, malonates, β-keto esters, 1,3-diketones and β-nitro esters.[103] In the initial step of the reaction, the manganese(III) enolate (68) is believed to be formed and this undergoes fast electron transfer to afford radical (69). Due to the electron-withdrawing substituents, such radicals exhibit electrophilic character and add readily to electron-rich alkyl- and aryl-substituted alkenes.



Scheme 39. Radical generation using Mn(OAc)$_3$

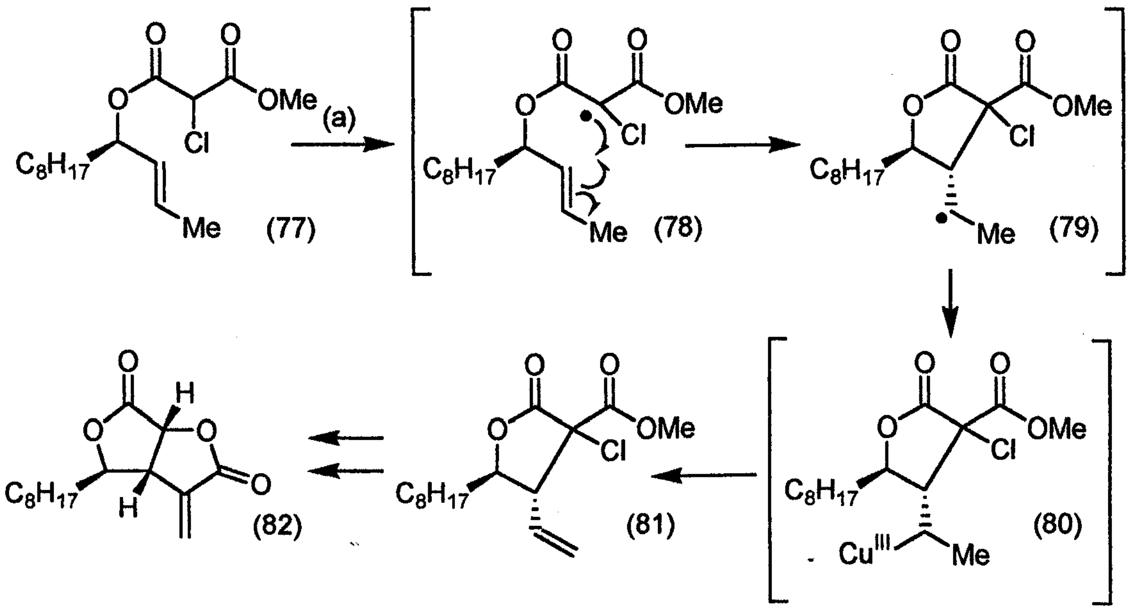
The product distribution of manganese(III)-mediated C-C bond formations depends strongly upon the substitution pattern of the adduct radical (70) and the reaction conditions. Low concentrations of manganese(III) acetate favour hydrogen atom abstraction from the solvent or starting material to afford the saturated product (71). In competing reactions, an excess of oxidant results in the formation of acetates (72) and alkene (73), which becomes the predominant process especially for tertiary radicals. Finally, lactones (74) are obtained as the major products by Mn(III)-mediated additions of carboxylic acids (X = OH) to double bonds. Whether the first steps proceed within the ligand sphere of the metal or if free-radicals are involved is still a matter of debate. Acetic acid is most commonly employed as the reaction medium for manganese(III) acetate reactions. Alternative solvents include DMSO, ethanol, methanol and acetonitrile although higher reaction temperatures are required and lower yields of products are sometimes obtained. Manganese(III) acetate is involved in the termination step and rapidly oxidises tertiary radicals to cations that lose a proton to give an alkene or react with acetic acid to give acetates. However, manganese(III) acetate oxidises primary or secondary radicals slowly so that hydrogen atom abstraction from solvent or the starting material becomes the predominant process.[104] Heiba and Dessau found that copper(II) acetate oxidises secondary radicals 350 times faster than manganese(III) acetate does and that the two reagents can be used together.[105]

Manganese(III) mediated cyclisations are mainly based on the pioneering and extensive studies of Snider which were recently reviewed.[105] The potential of this methodology for the construction of five- and six-membered ring is exemplified by the sequence shown in Scheme 40.[106] The reaction of β-keto ester (75) with manganese(III) acetate and copper(II) acetate affords the cyclohexanone (76), regio- and stereoselectively in 75% yield. Thus, the radical is generated at the more acidic position and *6-exo* cyclisation is favoured over the *7-endo* mode.



Scheme 40. (a) 2 eq. $Mn(OAc)_3$, 1 eq. $Cu(OAc)_2$, AcOH, 60°C, 75%

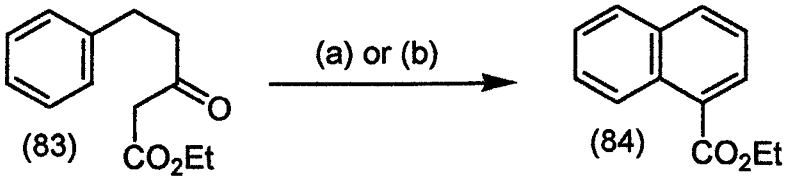
Furthermore, Snider has reported the synthesis of avenaciolide (82) from the α-chloro diester (77) (Scheme 41).[107] The initial *5-exo* cyclisation gives rise to the secondary radical (79) which can be oxidised by an equivalent of copper(II) acetate to produce an organocopper(III) intermediate (80). This can undergo an oxidative elimination to form the less substituted alkene (81). The stereochemistry at C-4 is controlled by the octyl substituent at C-5 and steric interactions ensure that these groups are *trans* to each other. Further radical generation was prevented by the α-chloro substituent in (81). Elaboration to avenaciolide (82) involved displacement of the chlorine substituent to form the second lactone ring.



Scheme 41. (a) 2 eq. $Mn(OAc)_3$, 1 eq. $Cu(OAc)_2$, AcOH, 82%

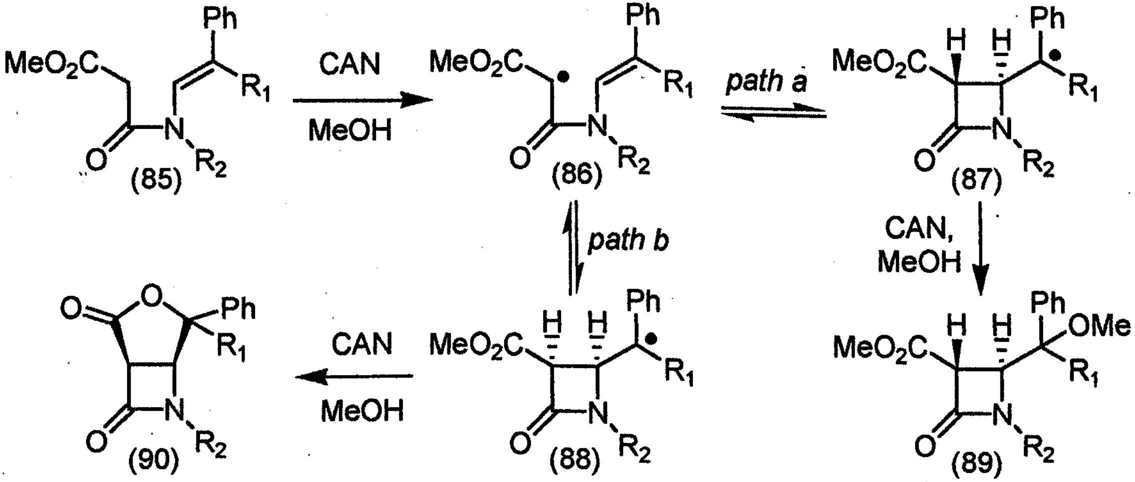
Manganese(III) acetate also represents a powerful and versatile reagent for mediating tandem radical cyclisations. Recent advances in this area have been made by Parsons and co-workers who have utilised manganese(III) acetate in boiling methanol to prepare functionalised pyrolidinones *via* 5-*endo* radical cyclisations,[108] this will be covered in more detail in the following chapters. Although not particularly expensive or difficult to handle on a laboratory scale, the use of more than one equivalent of $Mn(OAc)_3$ reagent is usually required therefore its use on an industrial scale could be problematic.

Cerium(IV) compounds represent the most notable oxidants among lanthanide reagents.[109] In particular, cerium(IV) ammonium nitrate (CAN) has been utilised extensively for a variety of oxidative transformations. A number of studies have recently been conducted to compare the reactivity of manganese(III) acetate with CAN and these indicate that the cerium(IV) reagent is superior to manganese(III) acetate in the oxidative addition of 1,3-dicarbonyl compounds to unactivated alkenes.[110-111] Unfortunately, there has been little investigation into the employment of CAN in intramolecular reactions. One example, shown in Scheme 41, shows the formation of (84) in either 62% or 24% yield using CAN or manganese(III) acetate, respectively (Scheme 42).[112]



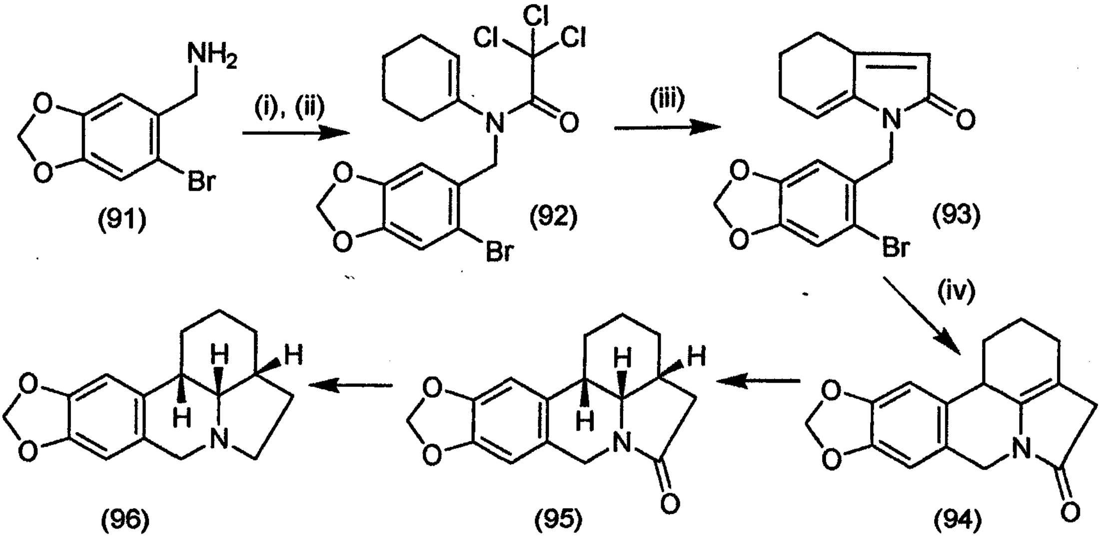
Scheme 42. (a) 4 eq. CAN, MeOH, 10°C, 62%; (b) 4 eq. $Mn(OAc)_3$, AcOH, 50°C, 24%

D' Annibale and co-workers have reported that CAN in methanol promotes the 4-*exo-trig* cyclisation of enamides to give highly functionalised *trans* β-lactams in moderate yields (Scheme 43).[113] The radical (86) generated by CAN oxidation of enamide (85), cyclises in a 4-*exo-trig* mode affording radicals (87) (path a) and (88) (path b), with *trans* and *cis* stereochemistry respectively, these are further oxidised by another equivalent of CAN to final products (89) and (90).



Scheme 43. Ceric(IV) ammonium nitrate (CAN) promoted radical cyclisation

Zard and co-workers have described a nickel powder and acetic acid promoted radical cyclisation of *N*-alkenyl trichloroacetamides.[114-115] This reductive non-atom transfer approach has been applied to 4-*exo-trig* cyclisations leading to the formation of β-lactams and even in some cases disfavoured 5-*endo* ring closures, more of which will be discussed in the following chapters. Recently, this methodology has been extended towards the asymmetric synthesis of (-)-γ-lycorane (96) using a key 5-*endo* radical cyclisation (Scheme 44).[116]



(i) cyclohexanone, toluene, reflux; (ii) $Cl_3CC(O)Cl$, Et_3N, toluene, 73%, (iii) Ni, AcOH, AcONa, 2-propanol, reflux, 60%; (iv) Bu_3SnH, AIBN, toluene, reflux; (v) $Na(CN)BH_3$, AcOH, 65% from (93); $LiAlH_4$, THF, reflux, 88%

Scheme 44.

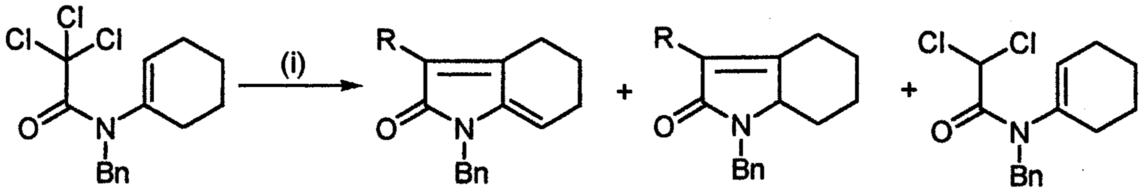
The trichloroacetamide (92) was treated with 30 equivalents of nickel powder, acetic acid and sodium acetate in refluxing 2-propanol to afford the tetrahydroindolone (93) in 60% yield. This was subsequently reacted with tributyltin hydride and (94) was furnished *via* a 6-*endo* radical cyclisation. Subsequent reductions using $Na(CN)BH_3$ and then $LiAlH_4$ afforded (-)-γ-lycorane (96) to give an overall yield of 25% from starting material 6-bromopiperonylamine (91).

Chapter 2: 5-*Endo* Radical Cyclisations of Trichloroacetamides Mediated by Copper(I) Amine Complexes

2.1 Introduction

In the previous chapter we described the recent fervent interest in transition metal atom transfer processes.[62] We also mentioned that one of the driving forces behind this development is the design of new efficient methods for conducting radical reactions, which replace the use of Bu_3SnH as a mediator.[117] This reagent, which is relatively expensive, significantly toxic and often difficult to remove from crude product mixtures also leads to reductive cyclisations. To circumvent some of these problems atom transfer radical cyclisation reactions (ATRC) of 2,2,2-trichlorinated carbonyl compounds have been reported for a range of metal catalysts.[62] By far the most popular methods to mediate atom transfer cyclisations have been those utilising $RuCl_2(PPh_3)_3$ (see Section 1.5.4), CuCl(bipy) (Section 1.5.2) or $CuCl(TMEDA)_2$ (Section 1.5.3.2). As illustrated in sections 1.5.2-4 in the previous chapter, the majority of published atom transfer radical cyclisation reactions have primarily involved the 5-*exo-trig* cyclisation of trichloro- or dichloro-acetamides and acetates at elevated temperatures. While there are a number of reported Bu_3SnH mediated 5-*endo* cyclisations in the literature[118] there are very few reports of cyclisations under atom transfer conditions proceeding in the 5-*endo-trig* mode. Zard has recently reported that by using Ni powder in refluxing AcOH and *i*PrOH (typical atom transfer conditions) trichloroacetamides (97) can undergo an unexpected 5-*endo-trig* cyclisation followed by double elimination of HCl, (Scheme 45). This approach was used to synthesise the

Erythrina and *Armaryllidaceae* alkaloid skeletons with the later culminating in an extremely efficient synthesis of (-)-γ-lycorane (96).[116] However among the disadvantages of these approaches were the large quantity of Ni powder required, (up to 30 equivalents), and elevated reaction temperatures in AcOH / 2-propanol. Very recently, the use of $Cu(OAc)_2$ as a co-oxidant additive in this procedure has been shown to lead to different product outcomes with increased efficiency under milder conditions.[119]



(97)

(98a) R = Cl, 18%
(98b) R = H, 18%

(99a) R = Cl, 18%
(99b) R = H, 22%

(100) 9%

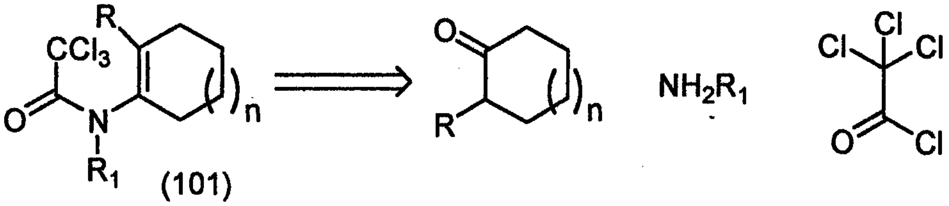
(i) 30 eq. Ni powder, AcOH, 2-propanol, N_2, reflux

Scheme 45. Ni/AcOH promoted 5-*endo* radical cyclisations

The use of $Mn(OAc)_3$ has also been described to mediate oxidative *5-endo* cyclisations, however the yields were often poor and required up to 4 equivalents of $Mn(OAc)_3$ for reaction.[120] We have recently reported that copper catalysts (42a) and (39) will mediate a range of 5-*exo-trig* atom transfer processes of monohaloacetamides at room temperature often proceeding with greater selectivity than for related catalysts (see Section 1.5.3).[72-77] As a consequence of this work, the main aim of this study was to investigate the efficiency of a range of copper complexes (used within our group) in mediating 5-*endo-trig* radical cyclisations. In particular, we hoped that this approach would allow rapid and efficient access to a range of alkaloid skeletons allowing for the synthesis of derivatives of a number of important biologically active natural products, such as those derived from the *Erythrina* and *Amaryllidaceae* family.[121]

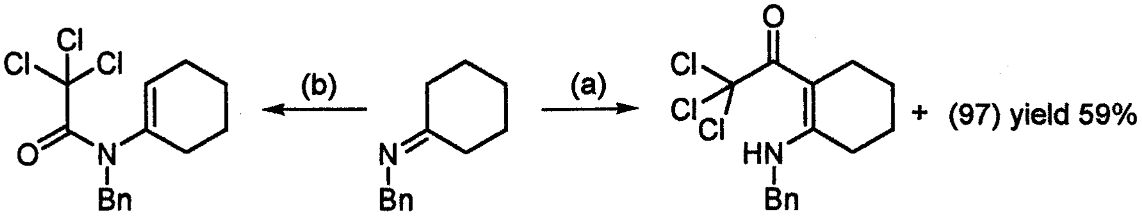
2.2 Synthesis of Trichloroacetamide Precursors

We initially decided to investigate the copper mediated 5-*endo-trig* cyclisation of the known trichloroacetamide (97)[114] and its derivatives, in order to compare the efficiency of cyclisation with those reported for Zard's Ni mediated[114-116] and Ikeda's Bu_3SnH mediated processes.[118] Disconnection of compounds of type (101) reveal that they can be easily synthesised from commercially available cyclic ketones, primary amines and acyl halides (Scheme 45).



Scheme 46.

Using the method reported by Zard for (97),[114] cyclohexanone was treated with benzylamine under typical "Dean-Stark" conditions to produce an intermediate imine, which was subsequently *N*-acylated with trichloroacetyl chloride and triethylamine (TEA) at 0°C to produce the required product (97) in 59 % yield (Scheme 47). Formation of the amide bond was indicated by the characteristic carbonyl bond absorption of the amide at 1677 cm^{-1} in the infra-red spectrum. The alkene proton was unexpectedly observed as a broad singlet at δ 5.57 ppm in the ^1H nmr spectrum. Normally a triplet would be expected from the coupling with the adjacent ring protons, however due to peak broadening, a broad singlet was observed. This was also true for the benzylic protons for which a pair of AB doublets would normally be expected. Instead, in their place two very broad peaks at δ 5.05 ppm and δ 4.20 ppm were observed, which coupled strongly in the COSY spectra. These broadening effects are most likely due to hindered rotation around the amide bond caused by the bulky acyl and benzyl groups. We also found using this procedure that a large amount of competitive C-acylated product (103) was being formed, which was not previously reported by Zard[114] or others (Scheme 47).[118]

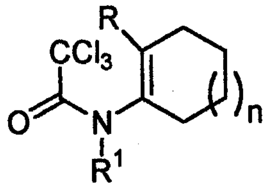


(97) yield 81% (102) (103) yield 20%

(a) (i) CCl_3COCl, toluene, 1hr, 0 °C; (ii) TEA, 2 hrs; (iii) sat. $NaHCO_3$, 3 hrs
(b) CCl_3COCl, DEA, toluene, 2hrs, 0 °C

Scheme 47. N-acylation *versus* C-acylation

This side reaction significantly lowered the yields of product (97). We observed that changing TEA to the less basic *N,N*-diethylaniline (DEA) led to this competitive reaction being eliminated completely, which had a marked improvement on reaction time and yields. It should be noted that these reactions may be carried in out "one-pot" rather than in two steps, although in most cases a small amount of the imine intermediate was isolated and purified. This was carried out due to the lack of recent ^1H and ^{13}C nmr data available for imines in the literature. The precursors synthesised for this study are presented in table 4, the influence that ring size (n=0,1,3), alkene substituents (R) and protecting groups (R^1) have on the cyclisation reaction was also examined.



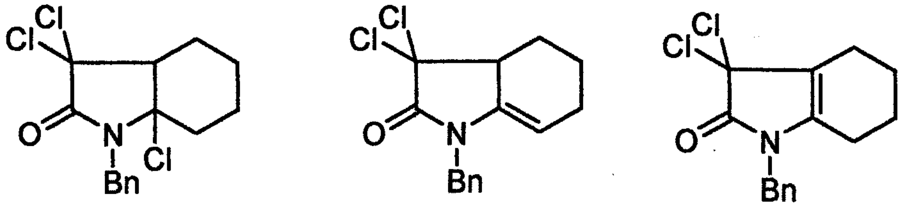
Compound	n	R	R1	Method/Yield
(104)	0	H	Bn	(a) 51%
(97)	1	H	Bn	(a) 59%, (b) 81%
(105)	3	H	Bn	(a) 52%, (b) 87%
(106)	1	H	PMB	(b) 79%
(107)	1	Me	PMB	(b) 74%

(a) (i) CCl_3COCl, toluene, 1hr, 0°C; (ii) TEA, 2 hrs; (iii) sat. $NaHCO_3$, 3 hrs
(b) CCl_3COCl, DEA, toluene, 2hrs, 0°C

Table 4. Trichloroacetamide precursors

2.3 Copper(I) Mediated Cyclisation of Trichloroacetamides

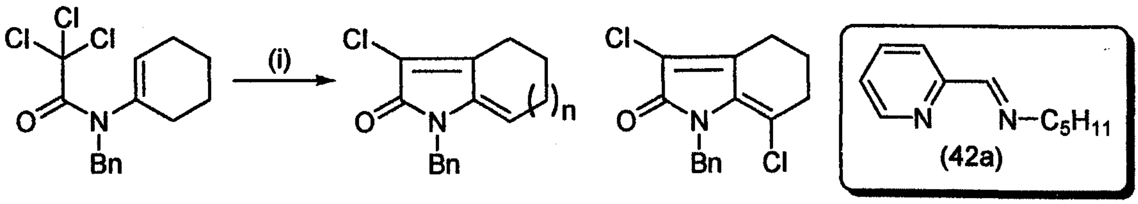
As stated earlier, we have recently shown that copper(I) halide complexes of Me_6-tren ligand (39) were more reactive than bipyridine as catalysts in 5-*exo* cyclisations.[72-77] Therefore, we initially examined the reaction of enamide (97) with this catalyst system. Before this reaction was carried out, and based on the results achieved for previous 5-*exo-trig* ATRCs, it was proposed that the unstable bicyclic lactam (108) would be formed (Figure 9). It was then likely that elimination of hydrogen chloride would result in the formation of one or both of the regioisomers (109) or (110). Furthermore, both compounds would contain a relatively weak C-Cl bond and would therefore be susceptible to further radical generation.



(108) (109) (110)

Figure 9.

Typically, we found that the optimum conditions for our 5-*exo-trig* ATRCs involved 0.12 M of substrate in dichloromethane catalysed with a catalytic amount (0.3 equivalents) of CuCl:Me$_6$-tren(39).[72, 82] When we attempted the cyclisation of precursor (97) using these conditions, a highly complex mixture of products was formed (seconds after initiation of the reaction *via* the addition of copper(I) chloride). We concluded from this that the reaction may be proceeding so rapidly that further production of radicals after initial cyclisation maybe be causing the production of complex polymers or telomers, although we could not obtain any evidence of this by GCMS or flash chromatography. Carrying out this reaction at lower temperatures (-78 to 0°C) had absolutely no effect on the complex mixture that was formed. However, reaction with 30 mol% of the less activated catalyst CuCl:(42a) at room temperature resulted in the formation of diene (98a) in 10% yield together with some unreacted starting material (65%). Subsequent optimisation of this promising reaction resulted in the use of 1 equivalent of catalyst at 40°C for 48 hrs to yield (98a) and (111) in 70% and 7% yield respectively (Scheme 48). The structure of diene (98a) was confirmed by nmr and mass spectroscopy, the evidence of which matched those previously published in the literature.[114, 120b]



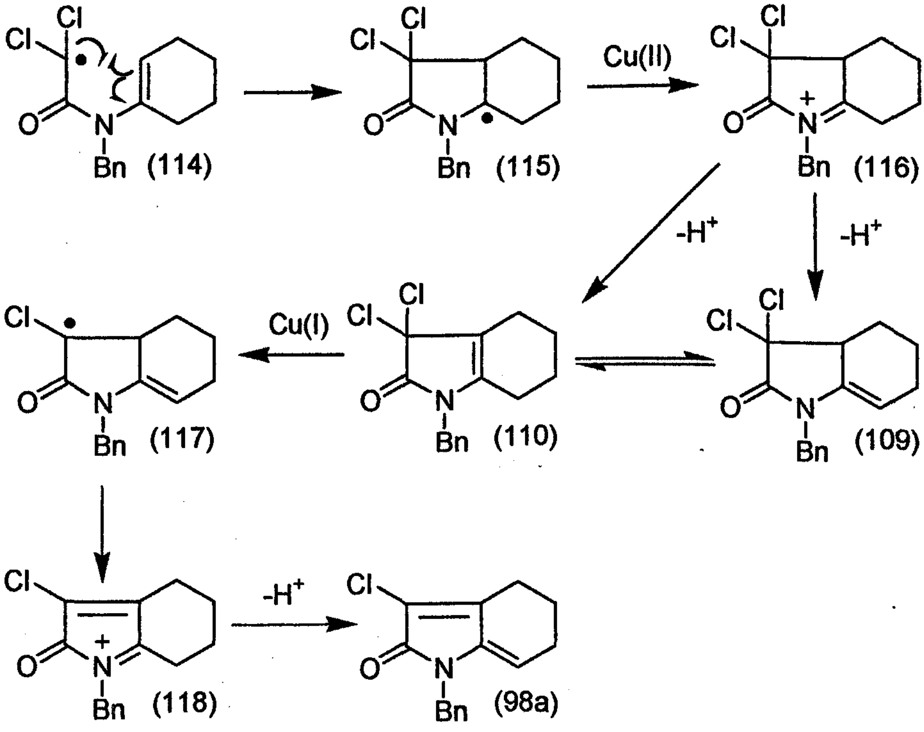
(104) n = 0
(97) n = 1
(105) n = 3

(112) n = 0, 61%
(98a) n = 1, 70%
(113) n = 3, 65%

(111) 7%

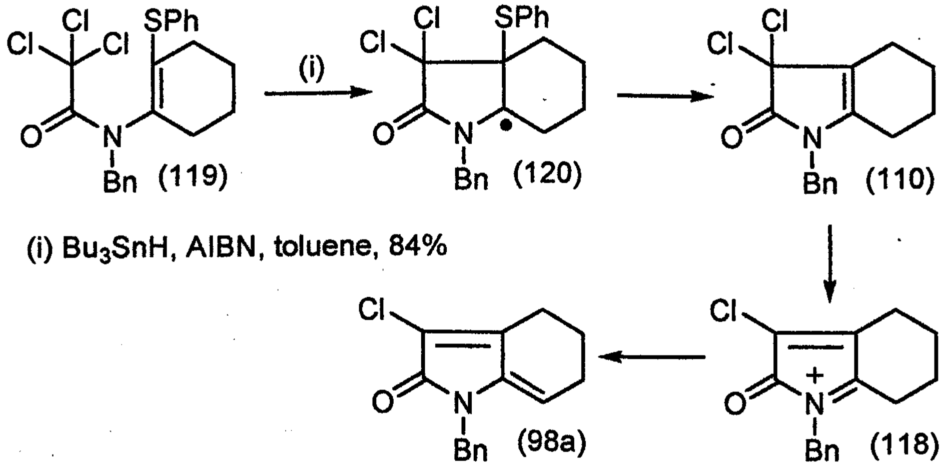
Scheme 48. (i) 1 eq. CuCl:(42a), DCM, 40°C, 48 hrs

Subsequent cyclisation of 5-membered (104) and 8-membered (105) ring enamides using the same conditions furnished dienes (112) and (113) respectively, although no analogous compound to (111) was formed (Scheme 48). The effect of ring size had no obvious effect on the reaction.



Scheme 49. Proposed mechanism for radical-polar cross over reaction

The construction of these dienes can be rationalised by initial 5-*endo* cyclisation of carbamoylmethyl radical (114) mediated by CuCl:(42a) followed by oxidation of the 3° radical (115) to the acyl iminium ion (116) by $CuCl_2$:(42a) produced in the cyclisation step. This was observed in related Mn(III)[120] and Ni[114] cyclisation reactions which have indicated that these type of 3° radicals (115) are very susceptible to oxidation *via* electron transfer. Elimination of a proton would furnish both regioisomers (110) and HCl. Generation of a secondary radical from chlorine abstraction from (109) or (110) furnishes the allylic radical (117) which again undergoes a second oxidation and elimination to furnish the observed products (Scheme 49). This sequence requires only a catalytic amount of the copper(I) complex as the copper(II), formed on the generation of (114), is reduced back to copper(I) on reaction with 3° radical (115). It is not clear why more than 0.3 equivalents of copper(I) complex is required although the formation of (98a) requires the double elimination of HCl and this may disrupt the redox cycle. This use of a large amounts of cyclisation catalyst has been observed with similar reactions in the literature.[122] This mechanism is now widely accepted and is referred to as a radical-polar cross over reaction.[77, 114, 122]

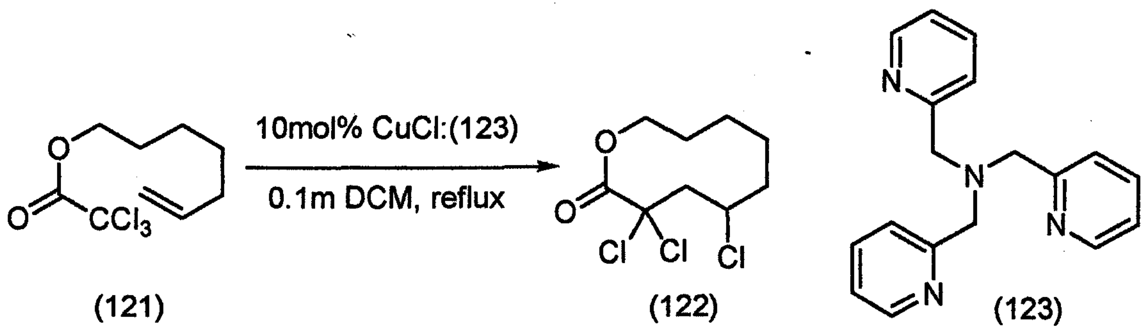


(i) Bu_3SnH, AIBN, toluene, 84%

Scheme 50.

Interestingly, the diene (98a) has also been isolated from a related tin hydride mediated cyclisation by Ikeda and co-workers (Scheme 50).[123] They also postulated a similar mechanism to the one described in scheme 49. The tertiary radical (120) is formed after the 5-*endo-trig* cyclisation of the carbamoylmethyl radical of type (114). This step is then followed by elimination of a benzenethiyl radical to give the hexahydroindolone (110). The formation of the diene (98a) was then postulated to have occurred *via* the generation of acyliminium ion (118) and elimination of HCl.

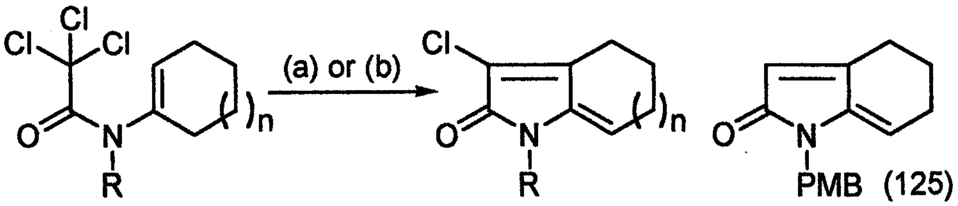
During the course of this work a report detailing the 5-*endo-trig* cyclisation of comparable trichloroacetamide substrates was published. This work centred on their cyclisation at elevated temperatures (refluxing in toluene, ~110°C) using 0.5 equivalents of CuCl:bipy.[122] The products obtained from these reactions were identical to the diene compounds formed in our reactions. The reaction times and yields of both of these catalytic systems compared favourably, the main differences being the use of higher temperatures (110°C) and lower catalyst loadings (0.5 eq.) for the CuCl:bipy system. Also, a requirement of the CuCl:bipy system was the use of dried toluene for a successful reaction, whereas using dry solvent with our catalyst system had no beneficial effects on the reaction time, yield or products. One of the benefits of both copper catalysts is the fact that cyclisation of trichloroacetamide precursor (97) affords a single diene product whereas cyclisation using the Ni/AcOH system gave a mixture of 4 different products in a combined yield of 71% (Scheme 45), which limits its synthetic utility. Optimisation of this reaction has recently been published by Zard and co-workers, they found that the addition of $Cu(OAc)_2$ as a co-oxidant in the Ni/AcOH system allowed control over the oxidation level of the products.[119] Using this revised procedure the 5-*endo* cyclisation of substrate (97) resulted in the production of the analogous diene (98a) in 60% yield. Other than minor differences in yields and reaction times, the copper catalysed methods have a number of practical advantages over the Ni/AcOH acid method. In order to carry out the latter reactions 30 equivalents of Ni and 22 equvalents of AcOH acid are required, whereas only 0.5 to 1 equivalent of the copper catalysts suffices. Also, in the work-up copper residues are removed easily by passing the reaction mixture through a silica bung whereas the Ni method requires removal of excess Ni through celite followed by neutralisation with aqueous base and liquid-liquid extraction. However, regardless of these slight practical differences these metal promoted radical reactions represent important protocols for the facile production of γ-lactams, which are valuable synthetic intermediates to many natural products systems.



Scheme 51. An example of 8-*endo* cyclisation using CuCl:TPA (123)

Recently, Verhlac and co-workers published a report detailing the highly efficient 8- and 10-*endo* ATRCs of trichloroacetates.[93,124] The ligands used were highly activated multidentate pyridine ligands (Scheme 51). Of these ligands the tris(pyridyl)-amine (TPA) (123) interested us the most, indeed in a collaborative effort between Verlhac's group and ours, a range of crown-ethers and δ-lactams were produced using these copper catalysts.[72]

Since we had already devised efficient reaction conditions using the TPA ligand (123) for the copper mediated 5-*endo-trig* radical cyclisations of deactivated monobromoacetamides (detailed in chapter 3),[125] we decided to try and utilise these conditions for the cyclisation of our trichloroacetamide precursors. Reaction of (97) with a 30mol% CuCl:(123) at reflux in toluene gave the diene compound (98a) in 36% yield after 48 hrs. In an effort to improve this yield we tried this same reaction in both dichloromethane and 1,2-dichloroethane, in which the catalyst system is more soluble. The reactions were initially carried out at room temperature with no reaction, then at reflux, the result of which was an inseparable, unidentifiable, mixture of complex compounds. We thought that these solvents may be causing the production of polymers or telomers, hence with this in mind we returned to the use of toluene as the reaction solvent and increased the catalyst loading to 1 equivalent of CuCl:(123). After only two hours using this method the diene (98a) was produced in excellent yield (89%). It should be noted that when these reaction conditions were applied to the CuCl:(42a) catalyst the reaction did not proceed and the starting material was recovered quantitatively. This suggests that the type of solvent used accommodates the catalyst system in some way that is not yet fully understood.

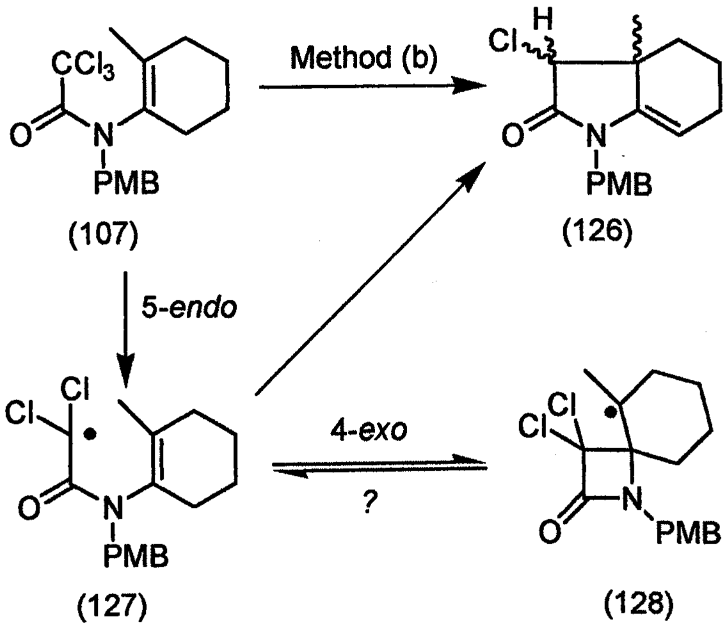


Precursor	n	R	Product	Method (a)	Method (b)
(104)	0	Bn	(112)	61%	83%
(97)	1	Bn	(98a)	70%	89%
(105)	3	Bn	(113)	65%	94%
(106)	1	PMB	(124)	-	73%

Method (a) CuCl:(42a), dichloromethane, 40°C, 48 hrs
Method (b) CuCl:(123), toluene, 110°C, 2 hrs

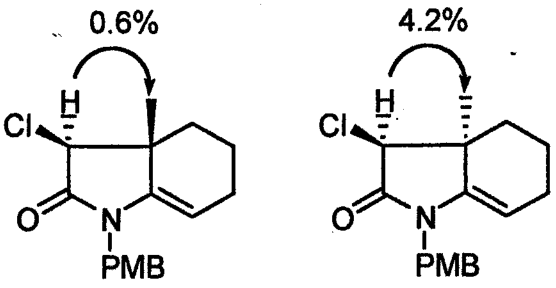
Table 5. Comparison of cyclisation results

The *p*-methoxybenzyl protected compound (106) was cyclised under these conditions to afford dienes (124) and (125) in 73% and 14% yield respectively. It is suspected that diene (124) undergoes a further reduction, elimination of HCl to give the diene (125). On the basis of these results we applied these conditions to all the substrates in the table 4, the results of which are shown in table 5. On the basis of these results we can conclude that the CuCl:(123) catalyst system produces γ-lactams in greater yields and reduced reaction times when compared to the CuCl:(42a) system. When using this protocol it is not necessary to use vigorously dried glassware or solvents. In addition the work-up is facile, as the crude mixture is passed through a small silica bung and in some cases no further chromatography is required.



Scheme 52.

Based on these results, we decided to examine the effect a methyl substituent on the double bond would have on ring closure. Thus, the cyclisation of compound (107), prepared from 2-methylcyclohexanone following the general procedure, afforded an inseparable mixture of bicyclic diastereomers (126) in a combined yield of 96% (Scheme 52). The mechanism for this reaction was thought to proceed in the same manner as (97), shown in scheme 49. From ^{1}H nmr evidence it was possible to calculate that the ratio of the major and minor isomer was 6:1, although n.O.e evidence would be required in order to assign these ratios their exact stereochemistry. The n.O.e effect is useful in determining which protons in a molecule are in close proximity to each other. If two protons are within 3.5 Angstroms of each other then irradiation of one will result in the enhancement of the other. The increase in the intensity of the signal can be as much as 50% but is typically less than 5%. The effect is normally viewed by obtaining a n.O.e difference spectrum. A conventional ^{1}H spectrum is recorded, followed by a spectrum in which a specific signal is irradiated. Subtraction of the conventional ^1H spectrum from the irradiated spectrum gives the n.O.e difference spectrum, which only exhibits the enhanced portions of the spectrum, i.e. the protons that are close in space. This type of experiment requires the chemical shifts of the protons to be well separated from other peaks (which in this case they were) or they cannot be effectively irradiated. Therefore the C<u>H</u>Cl proton and the methyl protons were irradiated for each isomer. The results from this experiment show that the major compound (126a) is *trans* as the n.O.e effect is small between the C<u>H</u>Cl proton and the methyl protons. The opposite is true for minor compound (126b), it shows a large n.O.e effect between the same protons, therefore we can assign this as the *cis* isomer (fig.10).



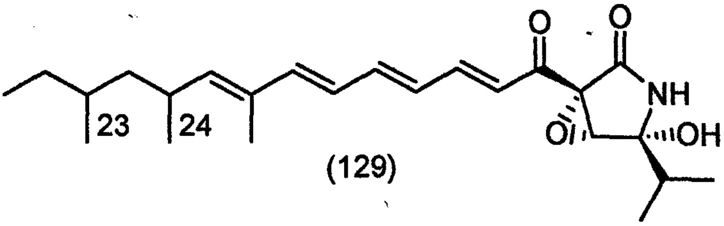
(126a) Major   *trans:cis* 6:1   (126b) Minor

Figure 10. n.O.e evidence for isomers of (126)

Introduction of a methyl group on the double bond should have reduced the rate of 5-*endo* cyclisation, but it seems under these conditions 5-*endo* attack is still preferred over 4-*exo* cyclisation. Moreover, even if 4-*exo* cyclisation occurs the radical produced (128) may not be trapped easily and ring re-opening is the most probable outcome (Scheme 52). By contrast, 5-*endo* cyclised radical (127) is readily oxidised, as previously mentioned, giving a cation that affords γ-lactam (126). Zard has observed similar results for his Ni/AcOH mediated systems.[114]

2.4 Application of this Methodology Towards the Synthesis of L-755,807

In 1996 a new non-peptide bradykinin antagonist, L-755,807 (129) was isolated by Lam and co-workers[126] from *Microspaerropsis* sp. MF6057. In biological tests using ^{3}H-bradykinin binding to a cloned human B_2 receptor expressed in Chinese hamster ovary cells, L-755,807 only showed a IC_{50} of 71 μM which is relatively weak when compared to the other known non-peptide bradykinin antagonist WIN 64338[127] which has an IC_{50} of 61 nM.

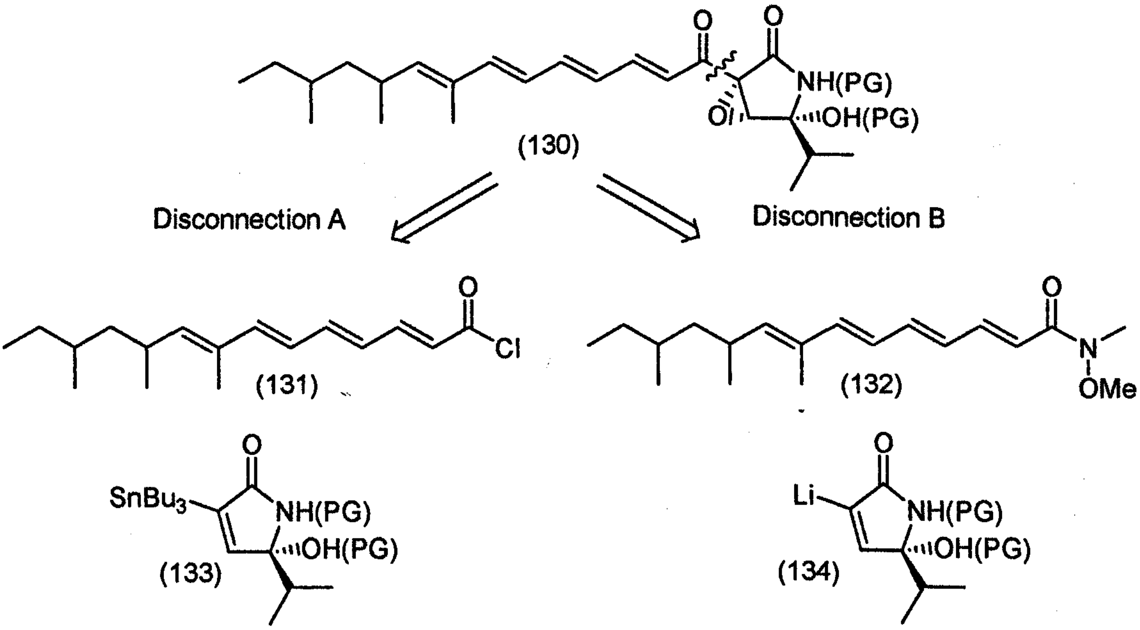


(129)

Figure 11. L-755,807

They elucidated the structure by detailed spectroscopic studies. However they were only able to determine that the relative stereochemistry of the epoxide and hydroxyl group about the lactam ring was *syn*. The stereochemistry of the methyl groups (C23 and C24) was not determined.

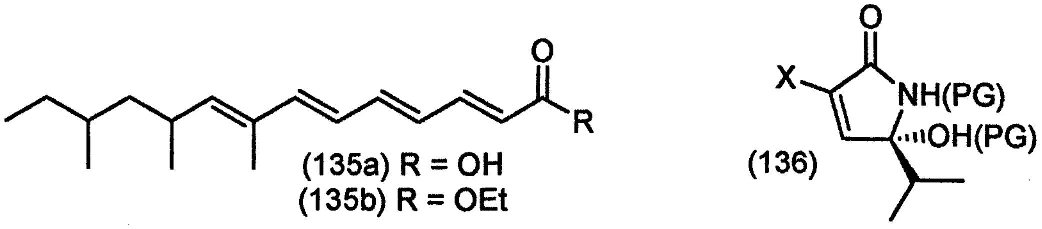
This natural product is of great interest to our group and we have recently published a report detailing the synthesis of both diastereomers of the C9-C25 side chain fragment (135b) which provided evidence for the relative configuration of these groups as being *syn* (fig. 12).[128] A number of strategies towards the synthesis of the heterocyclic ring fragment of L-755,807 were carried out.[128-129] One of these strategies proposed a convergent approach towards the synthesis of (129) (Scheme 53). The obvious place to disconnect (130) is between the ring moiety and the side chain carbonyl group as these disconnections bring the greatest degree of simplicity to the synthons.



Scheme 53. A convergent approach towards the synthesis of L-755,807

Disconnection A requires the use of a palladium mediated Stille type coupling reaction between acid chloride (131) and a ring system containing the vinyl stannane group (133). The major benefit of this approach is that such palladium coupling reactions usually proceed under mild reaction conditions. Disconnection B requires the use of anionic chemistry between a side chain fragment containing a Weinreb amide (132) and the vinyl lithium ring fragment (134).

Both of these approaches require common intermediates. The acid chloride (131) and Weinreb amide (132) side-chain units would be derived from the tetraene carboxylic acid (135a) while the vinyl stannane lactam (133) and the vinyl lithium lactam (134) would require the vinyl halide (136) (fig.12). Another member of our group carried out most of this methodology including the synthesis of the tetraene ester (135b).[128-129]

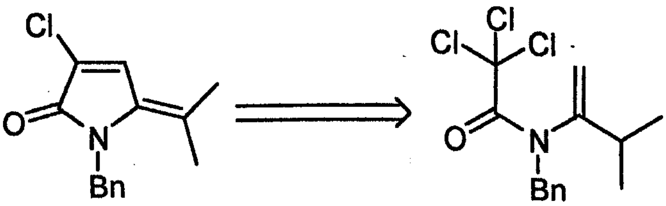


(135a) R = OH
(135b) R = OEt

(136)

Figure 12. Propsed synthons for the ring system and the side chain

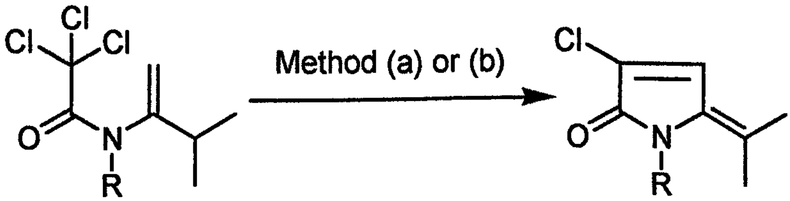
Based on these strategies, we were interested in applying our *5-endo-trig* methodology (detailed in Section 2.2) towards a racemic approach to ring fragment (136). With this in mind we can now place some synthetic equivalent atoms on synthon (136), i.e X = Cl and PG = Bn. If we also remove the hydroxyl group from ring system (136) it forms a new double bond outside of the ring forming a new conjugated lactam (137). We can now disconnect this again to a potential cyclisation substrate (138) (Scheme 54).



(137) (138)

Scheme 54.

Trichloroacetamide (138) was prepared by condensation of 3-methyl-2-butanone with benzylamine (with the azeotropic removal of H_2O) followed by *N*-acylation of the imine intermediate with trichloroacetyl chloride. The subsequent cyclisation using the CuCl:(42a) catalyst system gave the required diene (137) in 22% yield (Scheme 55).[77] Another group member carried out further manipulation of this compound towards the synthesis of ring fragment (136). One of the problems that they encountered was the suitability of the benzyl group towards deprotection. The low yield obtained from the use of the CuCl:(42a) catalyst system also proved problematic as a large amount of product (137) is required for further structural elucidation. Therefore, we decided to change the amide protecting group to one more activated towards removal, in this case the *p*-methoxybenzyl group was used. The substrate (139) was synthesised in the same manner as (138) using *p*-methoxybenzylamine in place of benzylamine. Consequent cyclisation of (139) using both catalyst systems (a) and (b) (Scheme 55) gave the required γ-lactam (140) in 60% yield and 89% yield respectively.



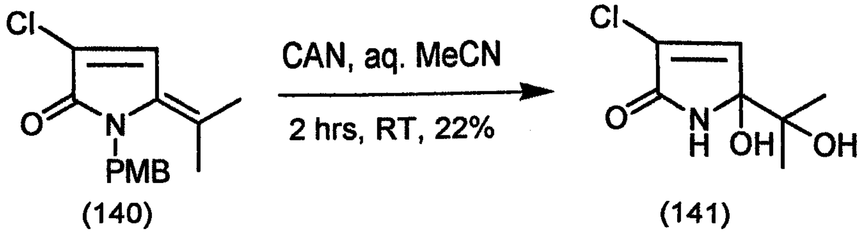
(138), R = Bn, 54%
(139), R = PMB, 81%

(137), R = Bn, (a) 22%
(140), R = PMB, (a) 60%, (b) 89%

Method (a) CuCl:(42a), dichloromethane, 40°C, 48 hrs
Method (b) CuCl:(123), toluene, 110°C, 2 hrs

Scheme 55.

The deprotection of (140) proved more difficult than we originally expected. Deprotection using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[130] in dichloromethane and water resulted in no reaction after 48 hours and returned (140) in quantitative yield. Treatment of (140) in trifluoroacetic acid (TFA)[131] at both room temperature and reflux gave an inseparable, unidentifiable mixture of compounds. However, oxidative removal of the PMB group with ceric ammonium nitrate (CAN)[132] in aqueous acetonitrile gave deprotected γ-lactam (141) in 22% yield after two hours (Scheme 56). It is not clear whether the hydrolysis of the double-bond in (141) occurred in the reaction media of the deprotection step or on the silica used for flash chromatography that followed. These cyclisation and deprotection methods are currently being investigated and developed within our group for the synthesis of ring systems such as (136), which can provide access to a wide range of natural product skeletons.



Scheme 56. CAN deprotection

2.5 Conclusion

Two highly efficient copper(I)-based cyclisation procedures have been examined, both of which lead to the formation of a variety of highly functionalised γ-lactams. The use of one equivalent of CuCl:(42a) in refluxing dichloromethane for 48 hrs was found to be the optimum conditions for this catalyst system. Under these conditions a variety of functionalised dienes were furnished in good yields 60-70%. The second catalyst system involved the use of 1 equivalent of CuCl:(123) in refluxing toluene for 2hrs. A variety of analogous dienes were produced using this method in excellent yield 89-94%. The reaction conditions of this catalyst system (toluene, 110°C) were very different when compared to the CuCl:(42a) system (dichloromethane, 40°C) indicating that the solvent may have a crucial role to play in controlling the reactions presumably by affecting the solubility of the complex. Also, the use of CuCl:(123) system reduced reaction times and improved yields, which increased the overall efficacy these cyclisations when compared to the CuCl:(42a) system and other methods. In theory both of these reactions should only require catalytic amounts (0.3 equivalents) of reagent and the reason for the lower yields when this was employed are not straightforward. However, the formation of (98a) involves the overall loss of two equivalents of hydrogen chloride that may disrupt the redox cycle (Scheme 49). A variety of cyclisation precursors were examined; the effect of ring size or protecting group was observed to have no obvious effect on the reaction times, yields or product ratios. The cyclisation of methyl substituted precursor (107) using the CuCl:(123) system afforded a 6:1 ratio of *cis:trans* isomers of lactam (126) in 96% yield.

This methodology was also successfully applied towards the synthesis of a heterocyclic ring template (141) for the use in the total synthesis of non-petide bradykinin inhibitor, L-755,807. Although the molecule produced lacked the full functionality required, a synthetic route to produce more complex analogues is currently being developed.

To further build on this work, potential follow up studies may include the an investigation into formation of chlorinated products from dichloro- and mono-chloroacetamides and also the application of this methodology towards the synthesis of highly functionalised asymmetric β- and γ-lactams. In conclusion, the scope and variety of copper(I) reactions together with the high yield of products mean that this method could potentially replace the tin hydride method in many cyclisation reactions. Product purification is simple and the products retain functionality that has the potential to be exploited through a variety of synthetic manipulations.

Chapter 3: 5-*Endo* Radical Cyclisations of Monohaloacetamides Mediated by Copper(I) Amine Complexes

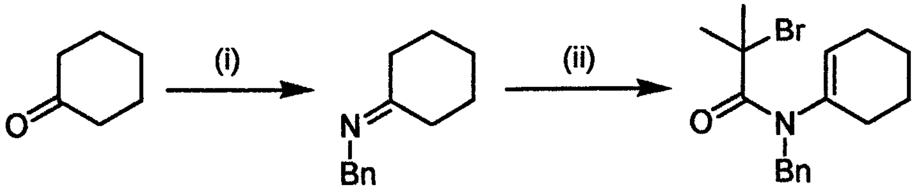
3.1 Introduction

In chapter 2 we reported that copper catalysts CuCl:(42a) and CuCl:(123) efficiently mediated the 5-*endo-trig* radical cyclisation of trichloroacetamides at elevated temperatures. While most atom transfer radical reactions utilising $RuCl_2(PPh_3)_3$,[66] CuCl(bipy),[68] Ni/AcOH,[114] and $Mn(OAc)_3$[62] also exploit these highly activated precursors, we have recently reported that tertiary, secondary and primary monohaloacetamides undergo efficient 5-*exo-trig* ATRC at room temperature catalysed by copper(I) amine complexes.[74, 82, 133] As a consequence of this we decided to investigate if these catalysts would mediate the 5-*endo-trig* cyclisation of a series of diverse monohaloacetamide precursors. We also hoped that the development of this chemistry would give us access to some important β- or γ-lactam templates that we could use for the synthesis of some related natural products.

3.2 Cyclisation of 3° Monobromoacetamides

3.2.1 Precursor Preparation

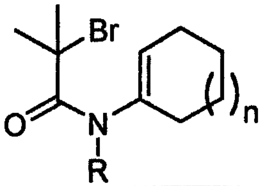
The tertiary monobromoacetamide precursor (145) was produced in 69% overall yield using the procedure outlined in Chapter 2 (Scheme 57). Cyclohexanone was treated with benzylamine under typical "Dean and Stark" conditions in toluene to produce an intermediate imine that could be isolated or used directly for the next step. Subsequent, *N*-acylation of the imine (102) with 2-bromoisobutyryl-bromide at 0°C furnished the required enamide (145) (Scheme 57). No competitive C-acylation was observed. Formation of this compound was indicated by the characteristic carbonyl bond absorption for the amide carbonyl at 1627 cm^{-1} in the IR and also the appearance of the enamide double bond C-H at δ 5.58 ppm in the ^1H nmr spectra, which was observed as a broad singlet rather than a triplet due broadening caused by hindered rotation around the amide bond. This broadening effect was observed in the ^1H spectra for all compounds of this class.



(102) (145) 81%

Scheme 57. (i) $BnNH_2$, Dean-Stark, toluene, reflux; (ii) $BrCOCBrMe_2$, DEA, 0°C

The precursors synthesised for this study are presented in table 6, the influence that ring size (n=0,1,2..) and protecting groups (R) have on the cyclisation reaction was also examined (PMB = 4-methoxybenzyl, Dmb = 2,4-dimethoxybenzyl).

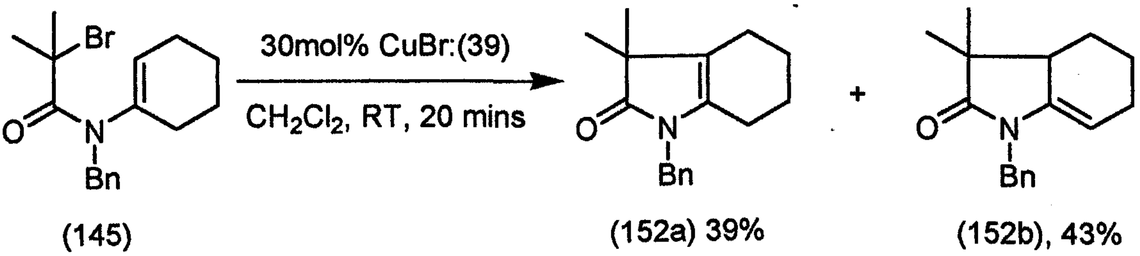


Compound	n	R	Yield
(146)	0	Bn	60%
(145)	1	Bn	69%
(147)	2	Bn	71%
(148)	3	Bn	95%
(149)	7	Bn	78%
(150)	1	PMB	78%
(151)	1	Dmb	84%

Table 6. Tertiary monobromoacetamide precursors

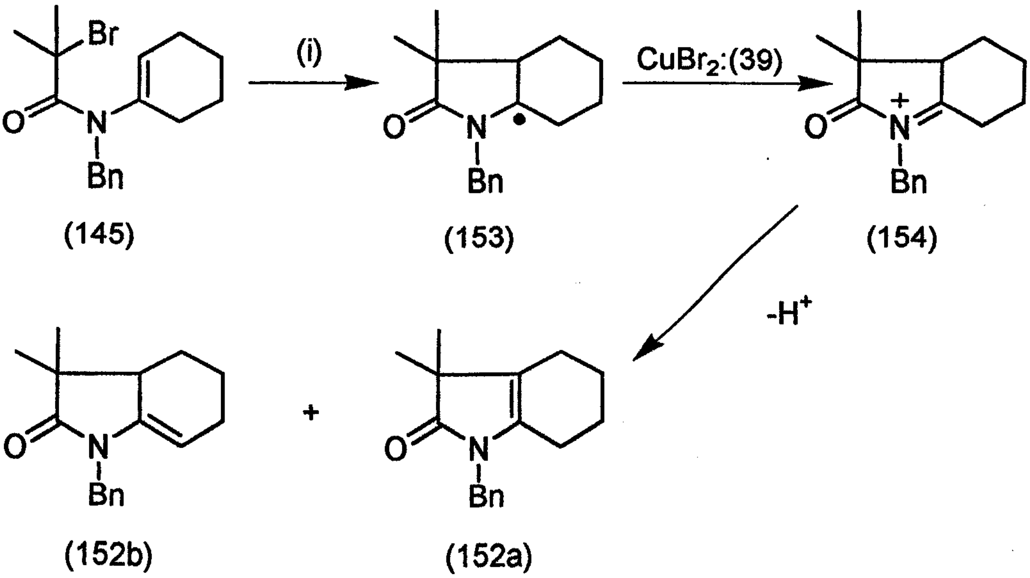
3.2.2 Copper Catalysed 5-*Endo* Cyclisation

We have previously reported that 5-*exo-trig* ATRC of tertiary monohaloacetamide (41) occurs rapidly at room temperature using a series of multi-dentate ligands (see section 1.5.3.1).[82] The most active ligand in this study was found to be the tetradentate amine ligand, Me_6-tren (39), therefore based on these results we decided to utilise these established conditions on precursor (145). Hence, to precursor (145) in dichloromethane at room temperature was added 30 mol% of Cu(I)Br and 30 mol% of Me_6-tren ligand (39). In contrast to its trichloroacetamide analogue (97), cyclisation of monobromoacetamide (145) proceeded rapidly and was complete after just 20 minutes at room temperature producing a 1:1 mixture of alkene regioisomers (152a) and (152b) in 82% overall yield (Scheme 58).[77]



Scheme 58. Regioisomeric alkene products

Presumably initial radical formation and 5-*endo* cyclisation is followed by rapid oxidation of the heteroatom stabilised radical (153) to a cation by the Cu(II)Br_2:(39) formed in the initial step.[114] Elimination of H^+ from the intermediate acyliminium ion (154) can then furnish the observed alkene products (Scheme 59). Interestingly the overall process represents a formal "Heck type" cyclisation albeit using substrates that would not normally undergo a palladium mediated Heck process.



(i) 30mol% CuBr:(39), CH_2Cl_2, RT, 20 mins

Scheme 59. Proposed mechanism for 5-*endo* cyclisation of monobromoacetamide (154)

These isomers could be separated by flash chromatography on silica but underwent equilibration in $CDCl_3$ to give a 1:1 mixture in 1-2 hours. Due to this effect all nmr spectra for related compounds were carried out in C_6D_6. Confirmation of the formation of these regioisomers was obtained by ^{13}C nmr, with the disappearance of the $\underline{C}BrMe_2$ quaternary carbon at δ 58.3 ppm from (145) and appearance of the new $\underline{C}Me_2$ quaternary carbon at δ 46.1 ppm and δ 42.9 ppm for isomers (152a) and (152b) respectively. A Mass spectrum of the isomers also showed that there was no bromine present in these bicyclic products.

The cyclisation of precursor (145) could also be mediated by 30 mol% of solid support ligand (142) (fig. 13) and CuBr, however the reaction took much longer and now required heating in 1,2-dichloroethane for 24 hours. The relative decrease in the activity of solid support catalyst CuBr:(142) is consistent with that observed for 5-*exo-trig* cyclisations.[133] However, attempts to mediate this cyclisation with ligands (143) and (144) gave no reaction at various temperatures (RT to reflux) and in a variety of solvents (MeCN, DCM, DCE, MeOH, toluene and acetone).

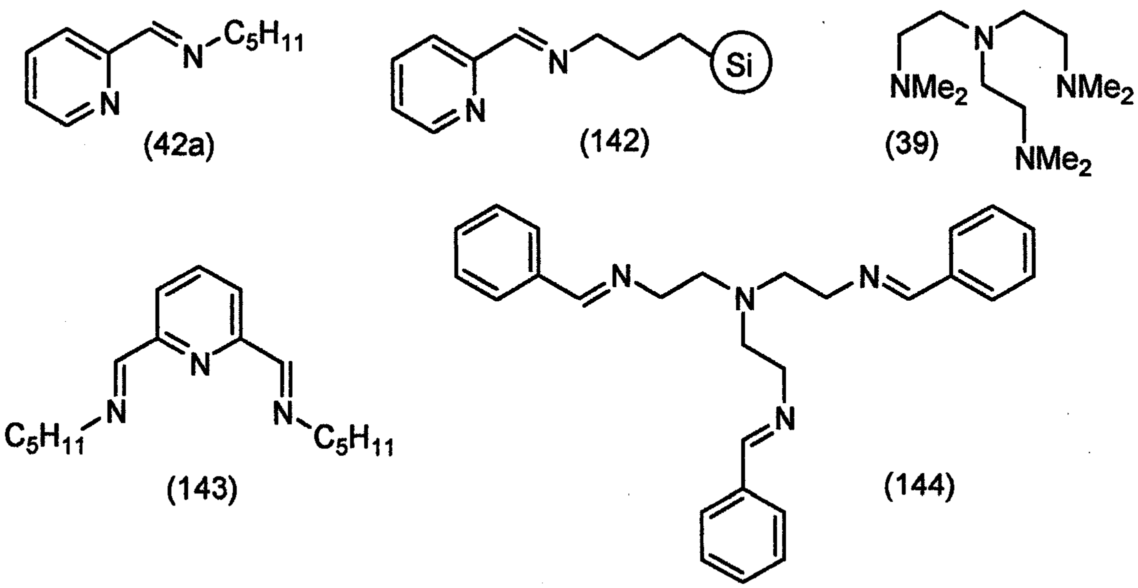
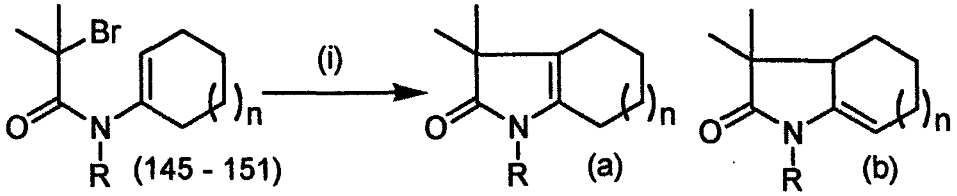


Figure 13.

We also found after similar experimentation that 30 mol% of CuBr:(42a) catalyses this reaction only in refluxing 1,2-dichlorethane after 48 hours. This was also true for the CuBr:TPA (123) catalyst, except in this case the reaction only proceeded after 48 hours in refluxing toluene. A similar solvent effect was also observed when these two catalysts were utilised for the cyclisation of cyclic trichloroacetamide precursors in chapter 2 indicating that the choice of solvent may play a crucial role in the activity and solubility of the complex.



Compound	n	R	Ratio a:b*	Yield (a+b)
(155)	0	Bn	-	-
(152)	1	Bn	1:1	82%
(156)	2	Bn	1:5	62%
(157)	3	Bn	1:3	81%
(158)	7	Bn	5:1	70%
(159)	1	PMB	1:1	83%
(160)	1	Dmb	1:2	90%

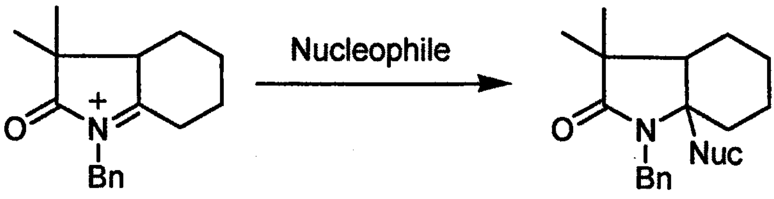
(i) 30mol% CuBr:(39), CH_2Cl_2, RT, 20 mins.
*Calculated from ^{1}H nmr of mixtures

Table 7. CuBr:(39) catalysed 5-*endo* cyclisation of substrates (145-151)

Cyclisation of the analogous precursors (145-151) proceeded smoothly under the same conditions as (145) to give similar mixtures of regioisomers in excellent yield (Table 7). However, 5-membered cyclic precursor (155) afforded a complex mixture of unidentifiable products that could not be purified or identified by GCMS. The results shown in table 7, suggest that the variations in ring and benzyl group have no obvious effects on the reaction.

3.2.3 Trapping of *N*-Acyliminium Ions after Cyclisation

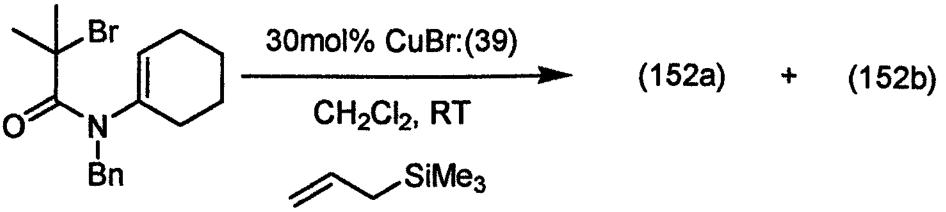
Mechanistically we[77] and others[111, 122] have proposed that the described cyclisation reactions involve an intermediate acyliminium ion (154) (i.e. they are radical-polar crossover reactions). If this is the case then it should be possible to expand the scope of the methodology by sequencing the initial cyclisation reaction by a second intermolecular or intramolecular nucleophilic triggered reaction to give (161) (Scheme 60).



(154) (161)

Scheme 60. Generalised trapping reaction

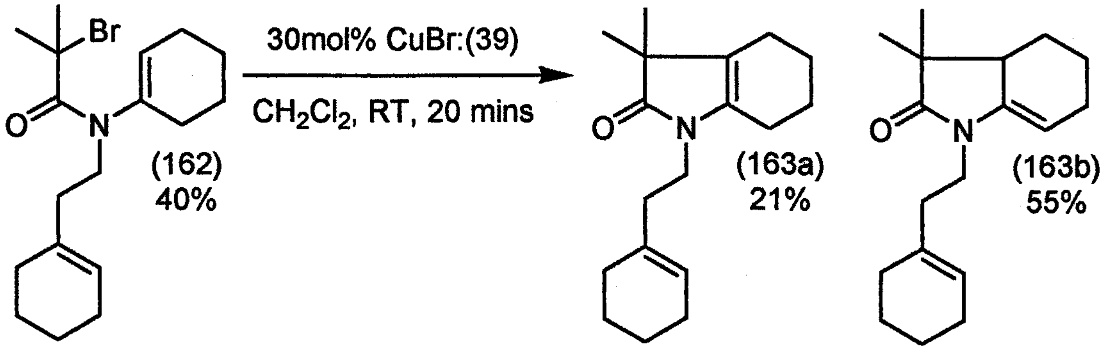
In order to test this hypothesis we initially examined the CuBr:(39) mediated cyclisation of (145) in the presence of 10 equivalents of allyltrimethylsilane at room temperature. Although the reaction took much longer than usual to go to completion under these conditions no intermolecular trapping of the acyliminium ion was detected, instead only the products arising from elimination of H$^+$ were isolated (152a-b) (Scheme 61).



(145)

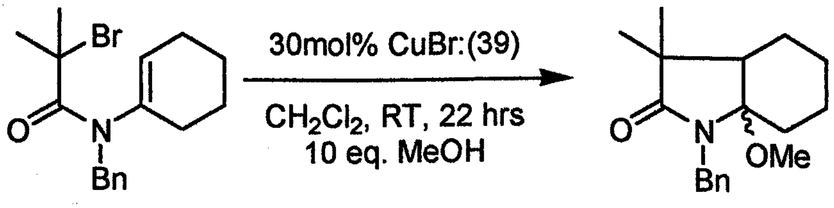
Scheme 61.

Attempts to mediate an intramolecular trapping using a tethered alkene (162) also failed. Cyclisation of this compound only furnished a mixture of regioisomeric non-trapped products (163a) and (163b) (Scheme 62).



Scheme 62.

However, when we cyclised (145) with a catalytic amount of CuBr:(39) in the presence of 10 equivalents of methanol it was possible to isolate the methoxy compound (164) in 36% yield after 22 hours (Scheme 63). In addition to (164) the two alkene products (152a) and (152b) were isolated (yields 19% and 26%). This methoxy compound however proved to be unstable and slowly eliminate to furnish a 1:1 mixture of (152a) and (152b) in $CDCl_3$ at room temperature. A similar decomposition effect was observed after storage for 1 week at -20°C.

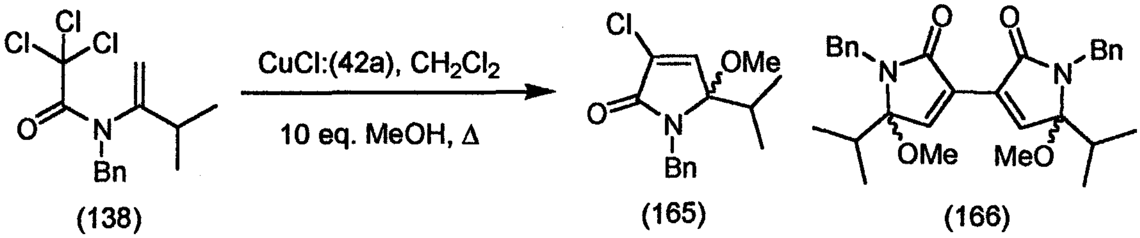


(145) (164)

Scheme 63.

After the discovery of this trapping methodology we thought that it could provide a possible route to the introduction of the desired tertiary hydroxy group present in the ring system of L-755, 807 (129) which we covered in section 2.3. Therefore, trichloroacetamide

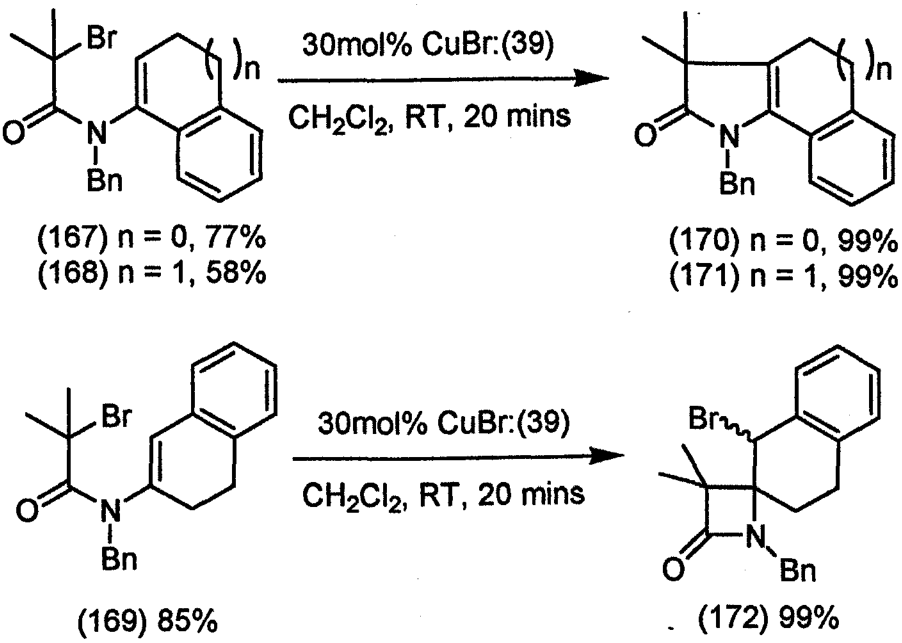
(138) was reacted with 1 equivalent of CuCl:(42a) and refluxed in dichloromethane in the presence of 10 equivalents of methanol (Scheme 64). The desired methoxy compound (165) was isolated in 10% yield along with 1% of a compound tentatively assigned as the diene (166).[129] Interestingly the methoxy compound (165) appears to be relatively stable with no decomposition observed at –20°C after 6 months.



Scheme 64.

3.2.4 Construction of Tricyclic and Other Frameworks

Having established that simple enamides (145-151) underwent highly efficient 5-*endo* oxidative cyclisation using catalytic quantities of CuBr:(39) at room temperature to give bicyclic alkene regioisomers, we next wanted to investigate if the cyclisation of the precursors (167-169) would furnish tricyclic skeletons upon cyclisation. Hence, acylation of *N*-benzylimines derived from 1-indanone and 1- and 2-tetralone gave the required cyclisation precursors (167-169). Reaction of (167-168) with 30 mol% CuBr:(39) in dichloromethane at room temperature for 20 minutes furnished high yields of the expected tricyclic conjugated alkenes (170-171) (Scheme 65). Unlike the reactions of (145-151) where elimination of H^+ leads to two possible regioisomers, elimination from the intermediate *N*-acyliminium ion generated in the reactions of (167-168) can only occur in one direction leading to high yields of single products (170-171). These high yields are also due to the fact that further purification by column chromatography is not required after the reaction mix is purged of copper residues by passing it through a silica bung.



(167) n = 0, 77%
(168) n = 1, 58%

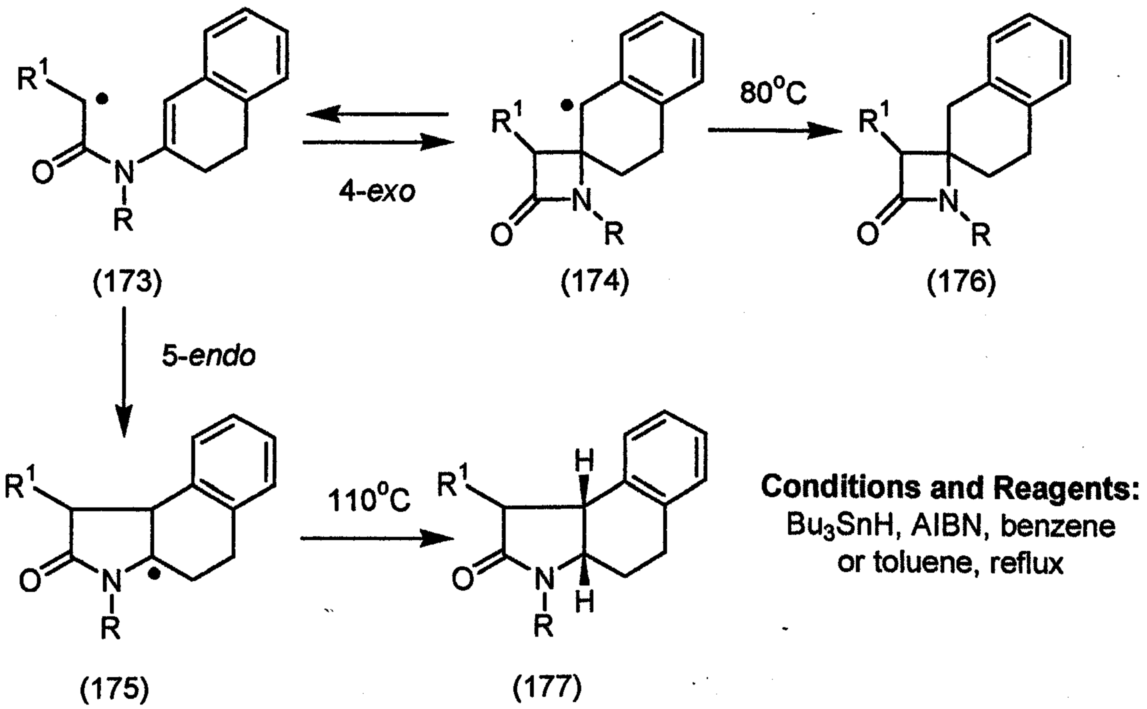
(170) n = 0, 99%
(171) n = 1, 99%

(169) 85%

(172) 99%

Scheme 65.

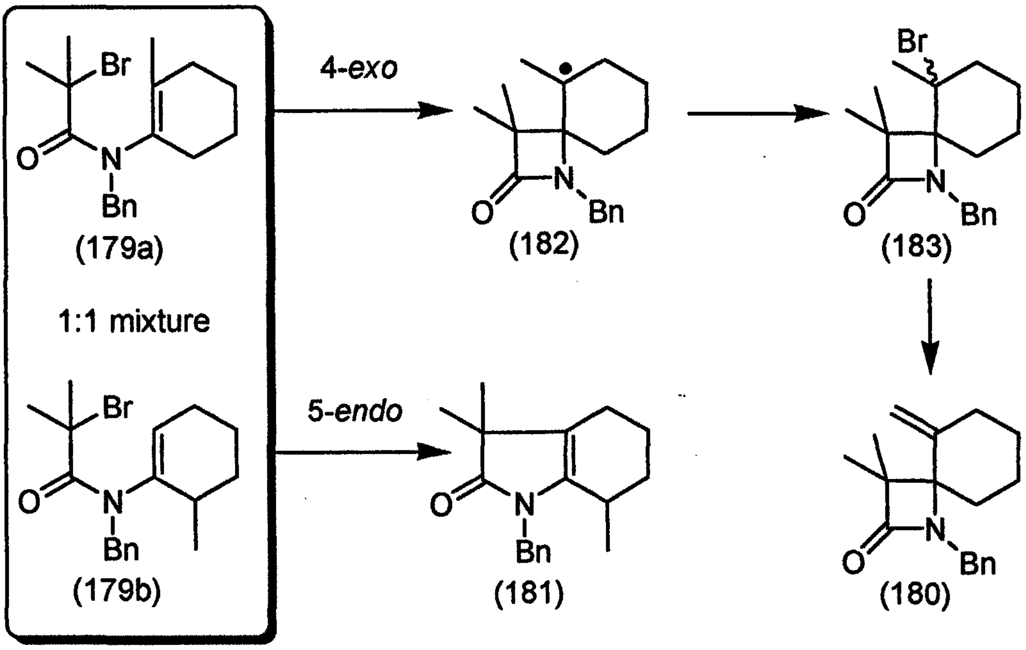
Cyclisation of β–tetralone derivative (169) under the usual conditions however proceeded in a 4-*exo-trig* fashion to give atom transfer product (172) as a 1:1 mixture of diastereomers (Scheme 65). Recently Ikeda and co-workers reported that the regiochemistry of cyclisation (4-*exo-trig* versus 5-*endo-trig*) of 2-halo-*N*-(3,4-dihydro-2-napthyl)acetamides similar to (169) were temperature dependent, with lower temperatures (<80°C) producing β-lactams predominantly while higher temperature (>80°C) favoured γ-lactams. Their hypothesis was based on the consideration of the reversibility of the 4-*exo-trig* cyclisation and ring opening between (173) and (174). Their results indicate that the 4-*exo* cyclisation is a kinetically favoured process in refluxing benzene, whereas at higher temperatures (in refluxing toluene), the ring opening of radicals (174) formed by 4-*exo* cyclisation rapidly occurs and the resulting radicals cyclise in a 5-*endo* fashion to give thermodynamically stable radicals (175) (Scheme 66).[118a]



Scheme 66. 4-*exo-trig* cyclisation versus 5-*endo-trig* cyclisation

Presumably, in our example, 4-*exo* cyclisation takes place at room temperature to give initially a stabilised benzylic radical, similar to (174), that is trapped under atom transfer conditions to give the observed brominated β-lactam (172). Attempts to provide evidence for Ikeda's hypothesis by conducting the atom transfer cyclisation of (169) in refluxing 1,2-dichloroethane (~80°C) and toluene (~110°C) or re-subjection of the initially formed (172) to these same reaction conditions met with failure and only complex mixtures of unidentified products were obtained in each case.

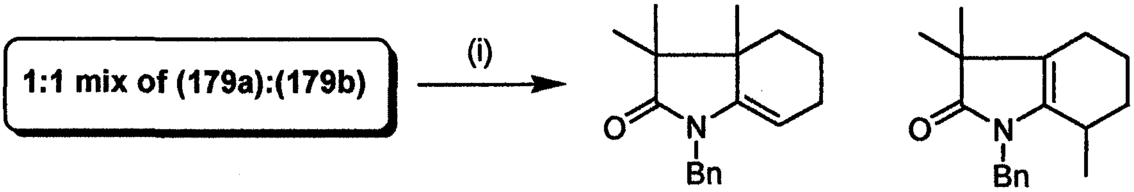
Based on the above results we decided to investigate whether the introduction of a methyl group on the 4-position of the alkene would induce 4-*exo* cyclisation over 5-*endo* cyclisation at room temperature.



Conditions: 30mol% CuBr:(39), CH_2Cl_2, RT, 18 hrs

Scheme 67.

The precursor (179) was synthesised in the normal manner from 2-methylcyclohexanone to give an inseparable 1:1 mixture of regioisomeric compounds (179a) and (179b) in 85% overall yield. Subsequent cyclisation of (179a-b) with 30 mol% CuBr:(39) at room temperature afforded a 1:1 mixture of 4-*exo* cyclised product (180) and 5-*endo* cyclised product (181) in 88% overall yield. Presumably, cyclisation of regioisomer (179b) proceeds as normal yielding the 5-*endo* product (181). However, the alkene substituted regioisomer (179a) forms the kinetically favourable 4-*exo* product by initial cyclisation to from tertiary radical (182) followed by bromine atom transfer (183) with subsequent elimination to (180) (Scheme 67). Interestingly, when we carried out this procedure at higher temperature (110°C in toluene) using a catalytic amount of CuBr:(123) we found that regioisomer (179a) now formed the thermodynamic 5-*endo* product (184) whilst regioisomer (179b) formed the same 5-*endo* product (181) as the initial reaction (Scheme 68). These products were isolated in 85% overall yield and in a 3:1 ratio of (184):(181) respectively, therefore the initial 1:1 ratio of starting regioisomers (179a):(179b) may have also been altered at high temperature. These results contribute adequate evidence towards Ikeda's hypothesis regarding 4-*exo* versus 5-*endo* cyclisations explained above, although more research into this area will need to be carried out in order to back up our initial findings.



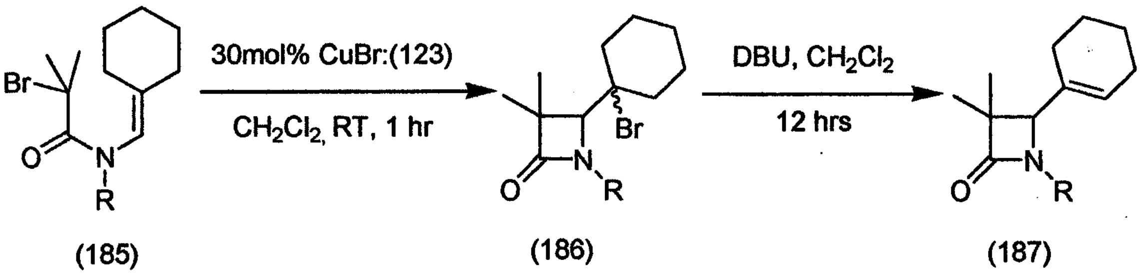
(i) 30mol% CuBr:(123), toluene, Δ, 1 hr

(184) 64%

(181) 21%

Scheme 68.

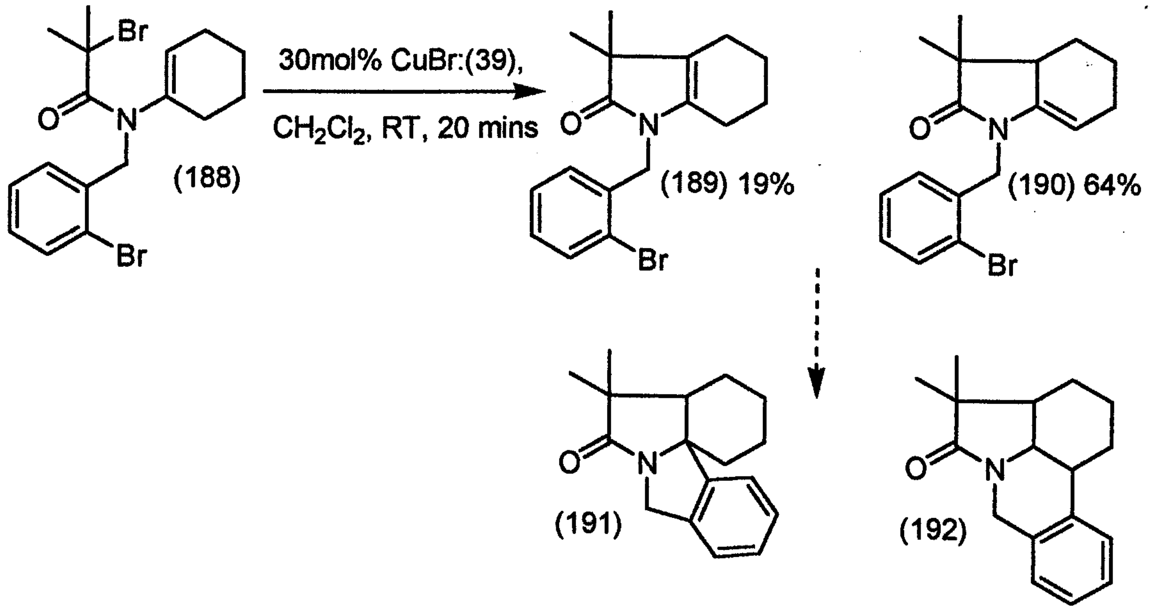
We also recently reported that tripyridylamine (123) copper(I) halide complexes mediate the ATRC of monobromoacetamides to give β-lactams exclusively with no formation of γ-lactam.[134] Initial products (186) arose from 4-*exo* bromine atom transfer but elimination can be readily achieved by reaction with DBU to furnish alkenes (187) in high yields (92-98%) (Scheme 69). Interestingly, it was found that even at 110°C in toluene, these compounds furnished the 4-*exo* products exclusively highlighting the efficient nature of the atom transfer catalyst used in trapping out the intermediate cyclised radical. Steric hindrance at the terminal carbon is thought to be responsible for the absence of 5-*endo* cyclisation observed.



R = Bn, PMB, *i*-Bu, *o*-BrBn

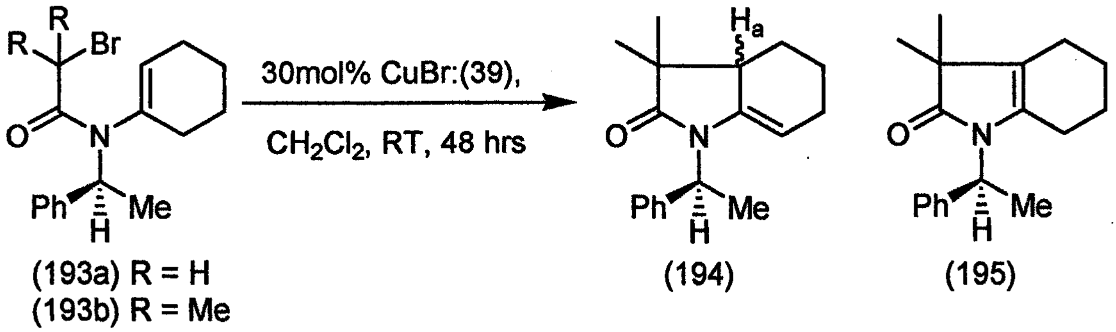
Scheme 69. β-lactam synthesis *via* 4-*exo* ATRC

Next we investigated the cyclisation of the dibromo precursor (188) in order to determine if the aryl bromide substituent would be tolerated under these conditions. Hence, reaction of (188) under the same reaction conditions as above furnished the two regioisomeric alkenes (189-190) as a 1:3 ratio in 83% combined yield (Scheme 70). Recently, Zard showed that structures related to (188) undergo 6-*endo* cyclisation using conventional organostannane radical chemistry leading to an efficient synthesis of lycorane analogues.[116] Further research regarding non-tin hydride methods (e.g. palladium) of coupling (189) and (190) to give poly cyclic compounds akin to (191) and (192) is currently being carried out within our group through a series of analogous compounds to precursor (188). By achieving this we hope to apply this chemistry towards the synthesis of *Amaryllidacae* and *erythirina* alkaloid templates.



Scheme 70.

In addition Ikeda and co-workers recently reported the asymmetric synthesis of (-)-γ-lycorane (96) *via* 5-*endo* Bu_3SnH mediated cyclisation of chiral amide derivative (193a).[135] As a consequence we briefly examined the cyclisation of the related (193b) at room temperature under our atom transfer conditions.[77] Cyclisation was slow relative to the previous reactions already described in this chapter (48 hours) and gave two regioisomeric products (194-195) as expected (Scheme 71). Although chiral induction from the remote chiral auxiliary to the ring junction proton H_a in (194) was modest (2:1) it was marginally better than that reported for Bu_3SnH cyclisation of (193a) at 110°C (3:2).[135] The relative decrease in the rate of cyclisation of *N*-α-methylbenzyl derivative (193b) compared to *N*-benzyl derivative (145) is similar to that reported by Ghelfi and co-workers for 5-*exo* atom transfer cyclisation reactions of trichloroacetamides and is likely to be due to conformational effects.[79]

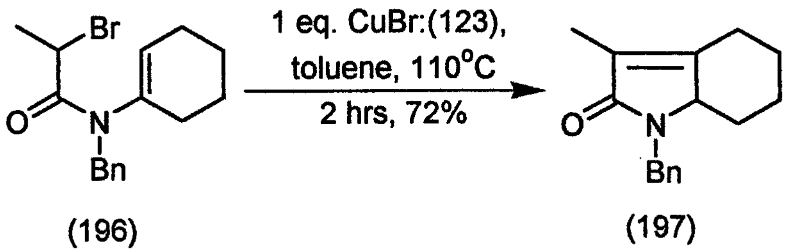


Scheme 71.

3.3 Cyclisation of 2° Monobromoacetamides

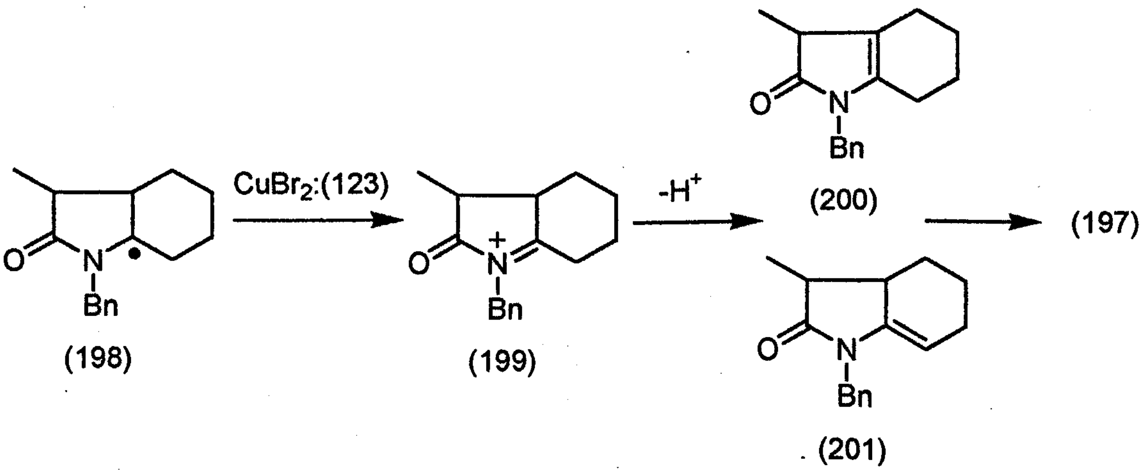
3.3.1 Method Development and Solvent Effects

We have shown above that 3° bromoacetamides of type (145) undergo rapid radical polar crossover reactions to furnish unsaturated pyrrolidinones derivatives at room temperature with activated copper complex derived from CuBr and (39). As a consequence of this we decided to investigate whether this copper complex would mediate the cyclisation of a 2° bromoacetamide precursor, which is less activated as a radical precursor. Preliminary studies investigated the cyclisation of precursor (196), which was synthesised using the standard method discussed in section 3.2.1 using 2-bromopropionyl-bromide in place of 2-bromoisobutyryl-bromide. All attempts to cyclise (196) using CuBr:(39) (as well as all the ligands shown in figure 13) failed at various temperatures, solvent and catalyst loading. In most of these cases the starting material (196) was recovered in quantitative yield. However, when we carried out this reaction using copper(I) bromide and the more activated TPA ligand (123) in refluxing toluene the bicyclic γ-lactam (197) was generated after 2 hours in 72% yield (Scheme 72).[125]



Scheme 72.

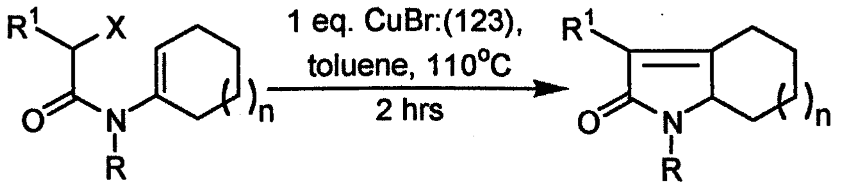
Mechanistically, it is likely that the observed products arise *via* a 5-*endo* cyclisation of the initially generated radical to give tertiary radical (198) which upon oxidation to cation (199) by Cu(II) (generated in the initial step) gives initially the alkenes (200) and (201) which undergo isomerisation to the more stable α,β-unsaturated ketone (197) under the reaction conditions (Scheme 73).



Scheme 73. Postulated radical-polar crossover mechanism

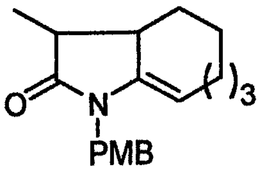
We then probed the generality of the reaction by investigating the cyclisation of a variety of precursors (202-207) (Table 8). In all cases the corresponding α,β-unsaturated products were obtained in good yields. Evidence for the intermediacy of alkenes such as (200) and

(201) was obtained by the isolation of 7% of the regioisomeric alkene (214) during the cyclisation of (205).



Precursor	X	R	R1	n	Product (%)
(196)	Br	Bn	Me	1	(197) 72
(202)	Br	Bn	Me	3	(208) 78
(203)	Cl	Bn	Ph	1	(209) 59
(204)	Br	PMB	Me	1	(210) 86
(205)	Br	PMB	Me	3	(211) 82*
(206)	Cl	PMB	Ph	1	(212) 87
(207)	Br	PNB	Me	1	(213) 65

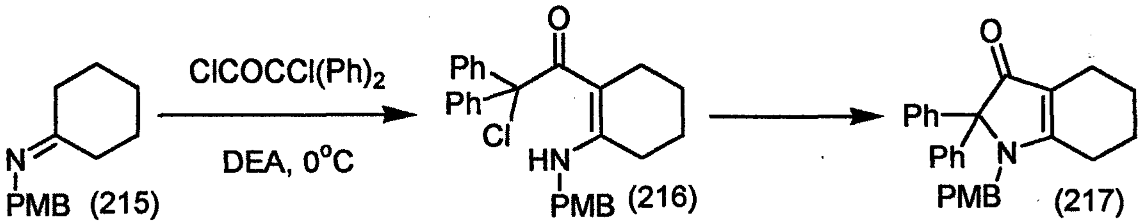
* 7% of (214) was isolated



(214)

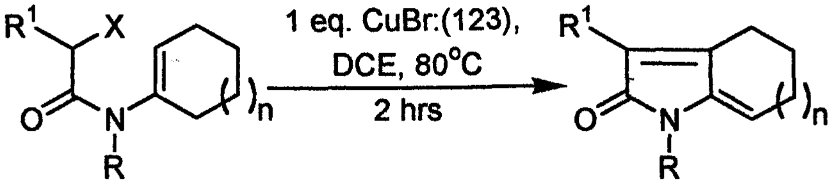
Table 8. Cyclisation of halo-acetamides

Table 8 also shows that the cyclisation of chloro-acetamides (203) and (206) efficiently yield α,β-unsaturated lactams (209) and (212), by alternatively using CuCl:(123) rather than CuBr:(123) under the same reaction conditions as (196). Interestingly, when we attempted to make a diphenyl version of precursor (206) by acylation of the appropriate imine (215) with chloro-diphenyl-acetyl chloride, we acquired the C-acylated product (216) only, which promptly cyclised under the work-up conditions to yield bicyclic compound (217) in 80% yield (Scheme 74).



Scheme 74.

During the course of this work an interesting solvent effect was uncovered. If the cyclisation reactions were repeated using 1,2-dichloroethane as the solvent (at 80°C), then instead of the monoenes (196, 202-207), the corresponding dienes (218-224) arising from further oxidation were isolated (Table 9).

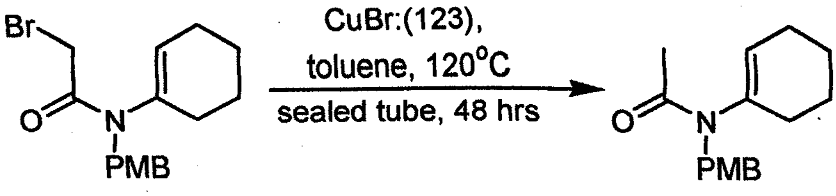


Precursor	X	R	R1	n	Product (%)
(196)	Br	Bn	Me	1	(218) 42
(202)	Br	Bn	Me	3	(219) 57
(203)	Cl	Bn	Ph	1	(220) 64
(204)	Br	PMB	Me	1	(221) 71
(205)	Br	PMB	Me	3	(222) 86
(206)	Cl	PMB	Ph	1	(223) 74
(207)	Br	PNB	Me	1	(224) 64

Table 9. Cyclisation of halo-acetamides in 1,2-dichloroethane

Mechanistically, it is uncertain how this further oxidation takes place. Presumably under the reaction conditions further oxidation of the tertiary position to generate another acyliminium ion is facile thus leading to the observed dienes. Whether radicals derived from decomposition of the chlorinated solvent under the reaction conditions are responsible for this oxidation or whether the solvent modifies the redox potential of the catalyst facilitating oxidation is unclear. However, a reaction using acetonitrile and methanol as solvents furnished the diene (albeit in low yield), suggest the latter may be important. However, re-submitting the pure monoene (212) to the reaction conditions of CuBr and ligand (123) in refluxing 1,2-dichloroethane for 2 hours furnished the diene (223) in 77% yield, indicating that the monoenes are precursors to the formation of the dienes under these conditions.

Our next action was to distinguish whether the conditions above could be utilised for the cyclisation of the less activated 1° bromoacetamide precursor (225). However, after reaction of (225) with CuBr:(123) in 1,2-dichloroethane/toluene under the conditions outlined above, no cyclisation was observed and the precursor was returned quantitatively. Successive reactions using CuBr and the ligands in figure 13, under similar reaction conditions yielded analogous results. We next attempted to force the cyclisation using the Cu(I)Br:(123) catalyst in toluene under sealed tube conditions at 120°C for 48 hours. This reaction was followed closely by TLC and seemed to be proceeding, but on final work up we found that these harsh reaction conditions afforded reduction product (226) in 17% yield and also re-isolation of precursor (225) (Scheme 74).

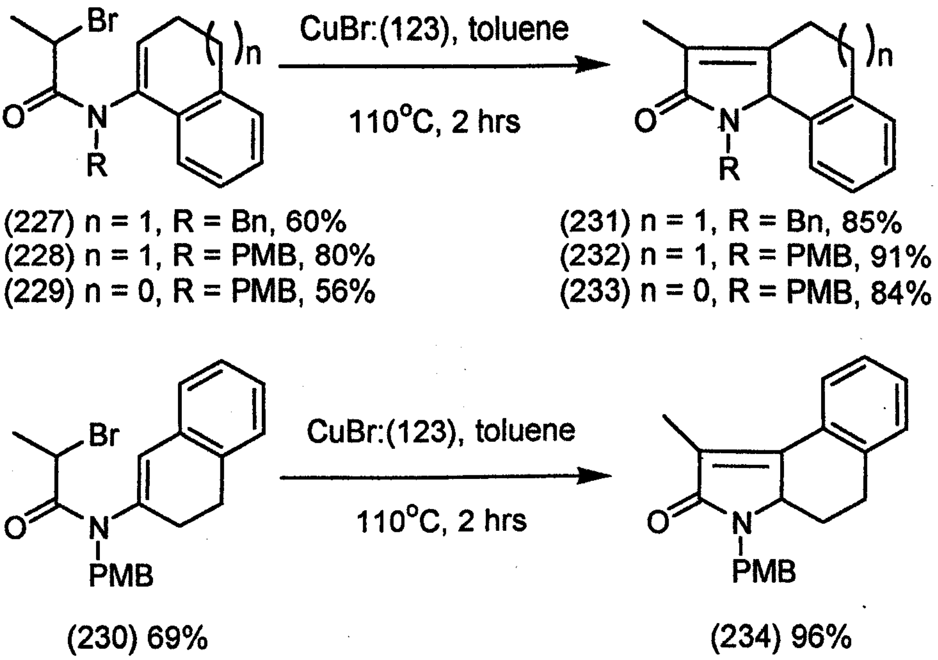


(225) 62% (226) 17%

Scheme 74.

3.3.2 Tricyclic Systems and Other Frameworks

Having developed the methodology required to cyclise simple 2° haloacetamides of type (196) using 1 equivalent of CuBr:(123) in either refluxing 1,2-dichloroethane or toluene, we thought we should now investigate whether this methodology could mediate the cyclisation of precursors (227-230) to afford tricyclic systems similar to those revealed in section 3.2.4. We were also interested to see if precursor (230) would carry out a 4-*exo* cyclisation comparable to (169) under these conditions. Consequently, acylation of the appropriate *N*-benzyl imines derived from 1-inadanone and 1- and 2-tetralone gave the desired cyclisation precursors (227-230). Reaction of (227-230) with 1 equivalent of CuBr:(123) in toluene at 110°C furnished the expected tricyclic α,β-unsaturated systems (231-234) in high yield (Scheme 75).



(227) n = 1, R = Bn, 60%
(228) n = 1, R = PMB, 80%
(229) n = 0, R = PMB, 56%

(231) n = 1, R = Bn, 85%
(232) n = 1, R = PMB, 91%
(233) n = 0, R = PMB, 84%

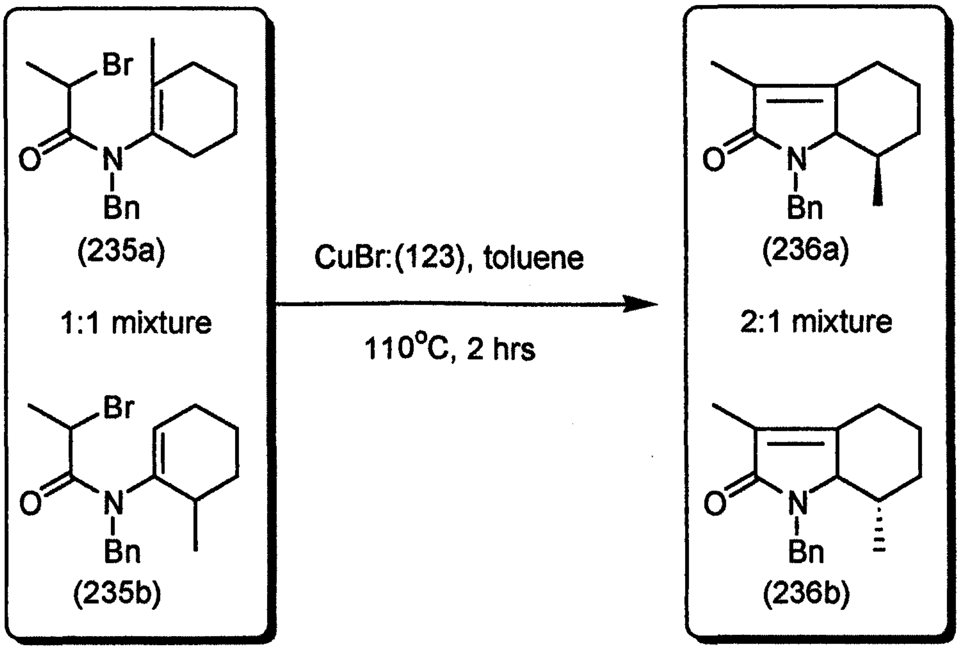
(230) 69%

(234) 96%

Scheme 75.

However, using this method we found that the cyclisation of (230) proceeded by the 5-*endo-trig* mode only. As we have mentioned in section 3.2.4, Ikeda postulated that 5-*endo-trig* cyclisation of compound (230) is thermodynamically favoured at this temperature, he also proved by experiment that cyclisation of (230) by 4-*exo-trig* mode would only occur at the lower temperature of 80°C in refluxing benzene using Bu_3SnH.[118a] Based on these results we decided to see if we could provide similar evidence for (230) using our copper mediated method, therefore the reaction was carried out in refluxing benzene, disappointingly only a complex mixture of unidentifiable products was obtained. A similar result was achieved when the reaction was carried out in 1,2-dichloroethane (which has a similar boiling point, ~80°C) and since we found that this reaction would not progress in any other typical cyclisation solvent our attempts to provide evidence for this hypothesis met with failure.

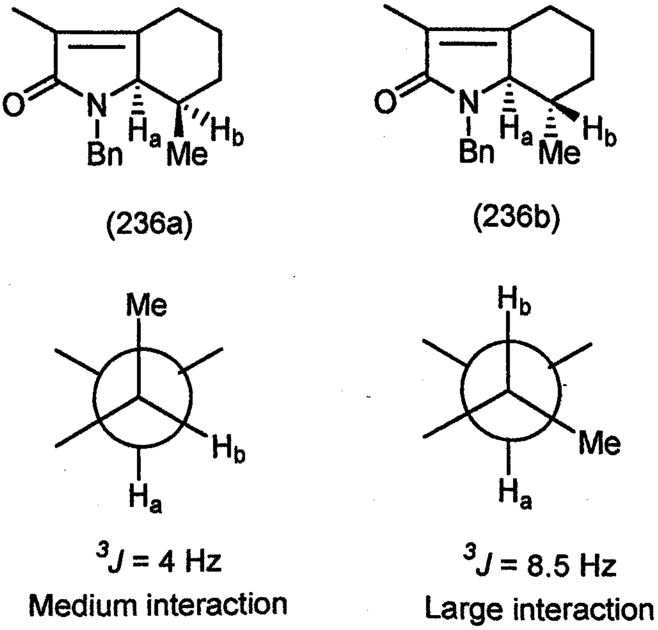
For our next step we decided to investigate whether the introduction of a methyl group on the alkene would induce a 4-*exo* cyclisation analogous to that shown for (179) in section 3.2.4. The appropriate precursor was synthesised according to the standard procedure to afford a 1:1 mixture of inseparable regioisomers (235a) and (235b) in 60% yield. This mixture of regioisomers was then treated with Cu(I)Br:(123) in toluene at 110°C to give a 2:1 mix of diastereomers (236a) and (236b) in 88% overall yield (Scheme 76).



Scheme 76.

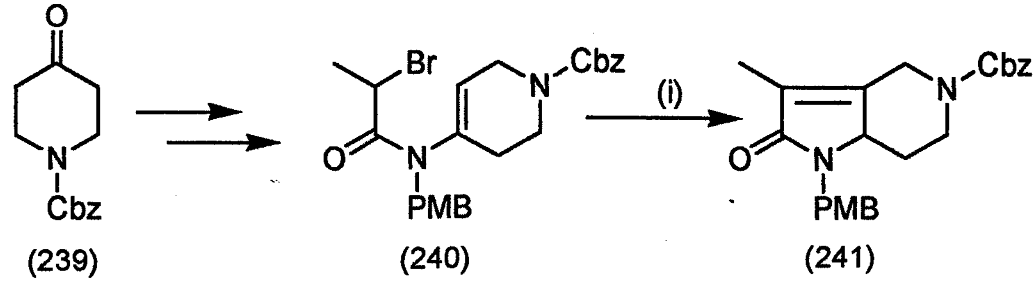
This unpredicted result might arise from initial isomerisation of the presumably more thermodynamically stable tetra-substituted alkene (235a) to give its corresponding regioisomer (235b) followed by 5-*endo* cyclisation. This is in fact the exact opposite to what we observed for (179) in section 3.2.4, scheme 68. However, Stork and co-workers have observed in unsymmetrical enamines (derived from 2-methylcyclohexanone), that the formation of the least substituted enamine is favoured over that of the tetrasubstituted one.[136] The explanation given for this unexpected selectivity is that there is a need for the enamine to have a high degree of σ-π orbital overlap, between the nitrogen lone pair electrons and the double bond. For this to occur the system must be planar and this is difficult with enamines formed from α-substituted ketones, such as 2-methylcyclohexanone. This hypothesis would certainly go some way to explain the results shown in scheme 76, although why the exact opposite happens for (179) in scheme 68 is not obvious.

The stereochemistry for diastereomers (236a) and (236b) were tentatively assigned from the ^{1}H nmr which clearly showed the vicinal coupling between H_a and H_b (Scheme 77). The vicinal coupling constant (^3J) for (236a) was found to be 4.0 Hz, which indicates by the Karplus equation that there is a medium interaction between H_a and H_b.[137] For this interaction to occur H_b would need to be equatorial, thus the methyl group would be axial (237) (Scheme 77). For diastereomer (236b) the vicinal coupling constant between H_a and H_b was 8.5 Hz. This indicates a large interaction according to Karplus, therefore for this to occur H_b would need to be axial (approximately 180° from H_a), thus the methyl group would be equatorial (238). Unfortunately all attempts to reinforce this information by n.O.e spectra proved unsuccessful, due to ineffective irradiation of non-elucidated peaks.



Scheme 77. Illustrative example of the stereochemistry of (236) *via* Newman projections

In order to probe further the generality of this catalyst system, we decided to insert a heteroatom into the cyclic ring to see whether it would influence cyclisation. Initially, protection of 4-piperidone was carried out using benzyl chloroformate to generate ketone (239) in 83% yield, followed by the standard imination and *N*-acylation to afford (240) in 35%. Subsequent cyclisation of (240) proceeded normally in toluene with CuBr:(123) to produce monoene (241) in 42% yield (Scheme 78). However, when we carried out this reaction in 1,2-dichloroethane to produce the corresponding diene a complex mixture of inseparable products was produced.



(i) CuBr:(123), toluene, 110°C, 2 hrs

Scheme 78.

3.3.3 Deprotection of γ-Lactams and Application Towards Natural Product Architectures

Having established that a number of structurally diverse bicyclic and tricyclic γ-lactams can be synthesised using our highly efficient copper(I) mediated radical cyclisation reaction, we next decided to extend this methodology by evaluating whether these catalysts could be employed towards the synthesis of natural products templates. A sesquiterpenic alkaloid, eremophilene γ-lactam (242) was isolated from the rhizomes of *Pestasites hybridus* by Jizba and co-workers.[138] The total synthesis of this compound (242) has to our knowledge not been previously reported, although the total synthesis of its corresponding lactone (243) has been cited by a number of authors (Fig. 14).[139]

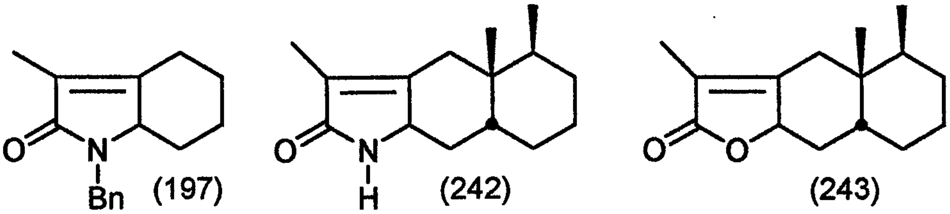
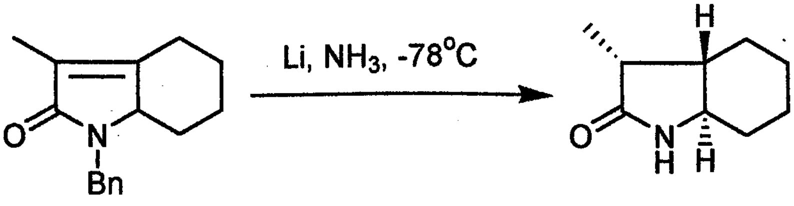

(197) (242) (243)

Figure 14. Comparison of γ-lactam (197) with natural analogues (242) and (243)

Compound (197) contains two of the three rings found in the skeleton of sesquiterpenic alkaloid (242), therefore we decided to attempt and integrate our cyclisation techniques into the manufacture of alkaloid (242). However any strategy towards the synthesis of this alkaloid would need to address the removal of the *N*-benzyl protecting group to furnish the unsubstituted lactam. Our initial attempts to remove the *N*-benzyl protecting groups from (197) using a variety of standard protocols[140] such as hydrogenation failed.[141] However, deprotection of the amide (197) was possible using lithium in liquid ammonia[142] but the unsaturated alkene also underwent reduction to give one stereoisomer of the bicyclic lactam (244) in 95% yield (Scheme 79). The stereochemistry of this lactam was not rigorously assigned but its spectral details matched that for the known compound (244) reported in the literature.[143]

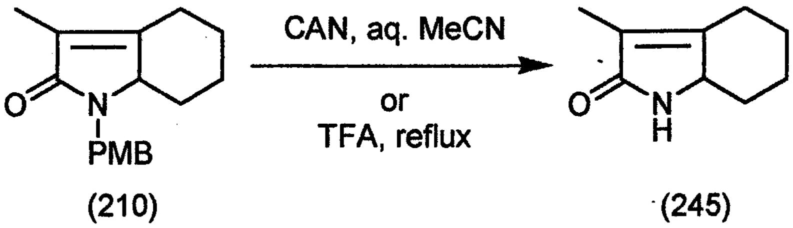


(197) (244)

Scheme 79.

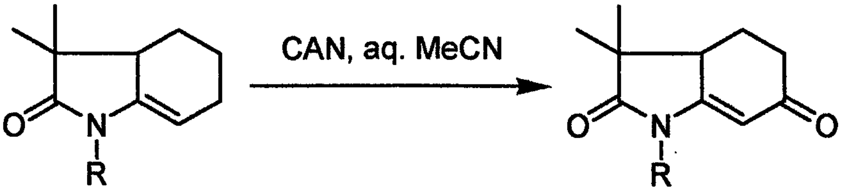
In order to facilitate this key cyclisation/deprotection sequence we have already incorporated a series of diverse *N*-benzyl groups into the lactam architecture as the chemical methods employed for their removal are reported to be more tolerant of highly functionalised systems.[140]

To our gratification deprotection of *p*-methoxy protected lactam (210) proceeded smoothly using ceric(IV) ammonium nitrate in aqueous acetonitrile after 2 hours.[132] The required lactam (245) was isolated in excellent yield (96%). We also carried out a number of other deprotection techniques on (210), most of which failed.[140] We did however manage to deprotect (210) in refluxing trifluroacetic acid in 2 hours to give (245) in 83% yield (Scheme 80).[131]



Scheme 80.

Deprotection of bicyclic regioisomer (159b) using the ceric ammonium nitrate method to our surprise gave the unusual oxidation product (246), this suggest that the oxidation of the allylic methylene group is favoured over that of the benzylic position (Scheme 81). Oxidations of this type have been reported in the literature for cyclic olefins, but they have been found to be extremely solvent dependent.[144] An identical oxidation was observed for benzyl derivative (152b).

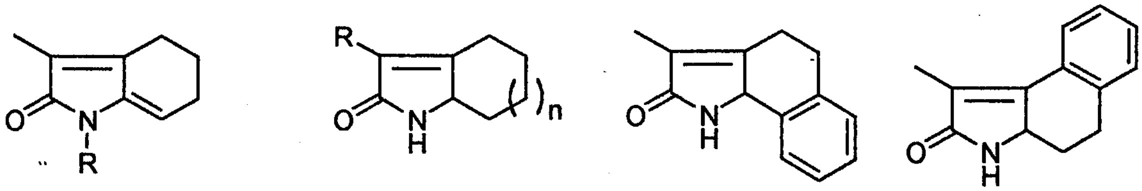


(159b), R = PMB
(152b), R = Bn

(246), R = PMB, 74%
(247), R = Bn, 68%

Scheme 81.

Unfortunately, each of the literature methods[140] employed to deprotect *p*-methoxybenzyl lactams of type (159a-b) and (221) (fig. 15) met with failure. Deprotection of diene (221) (Table 9) *via* ceric ammonium nitrate did not show any similar oxidation products analogous to those observed in scheme 81 and an unidentifiable complex mixture was obtained. Deprotection of *p*-nitrobenzyl monoene (213) and diene (224) *via* palladium catalysed hydrogenation were also unsuccessful and the starting material was re-isolated in quantitative yield in both cases. However, the ceric ammonium nitrate method proved to be versatile in the deprotection of a number of our bicyclic and tricyclic lactams with bicyclic compounds (211) and (212) and tricyclic compounds (232) and (234) all yielding their corresponding deprotected analogues (248-251) in excellent yield (fig. 15).



(221) R = PMB
(224) R = PNB

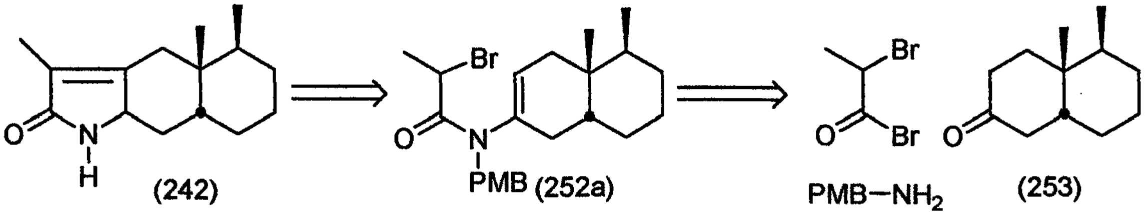
(248) R = Me, n = 3, 86%
(249) R = Ph, n = 1, 84%

(250) 86%

(251) 79%

Figure 15.

Having achieved this important deprotection step for γ-lactams of type (210), our next step was to incorporate these cyclisation/deprotection methodologies into a synthetic strategy for the total synthesis of sesquiterpenic alkaloid (242). The complex monobromoacetamide (252a) could be prepared in several steps, incorporating the imination and *N*-acylation steps detailed previously. Eremophilene (242) could then be obtained after treatment of enamide (252a) with copper(I) bromide:(123) followed by deprotection of the cyclised product with ceric ammonium nitrate (Scheme 82).



Scheme 82.

Before addressing the synthesis of *cis*-decalone (253) an important issue concerning the formation of enamide (252a) needed to be considered. The *cis*-decalone used to construct precursor (253) is now unsymmetrical in comparison to the cyclohexanone-type precursors we have studied previously, this brings in the question of regioisomerism. We now have the possibility two different types of regioisomers (252a) and (252b) (fig. 16). Since we know we require regioisomer (252a), we envisaged that some model systems should be synthesised before the application of this chemistry to alkaloid (242).

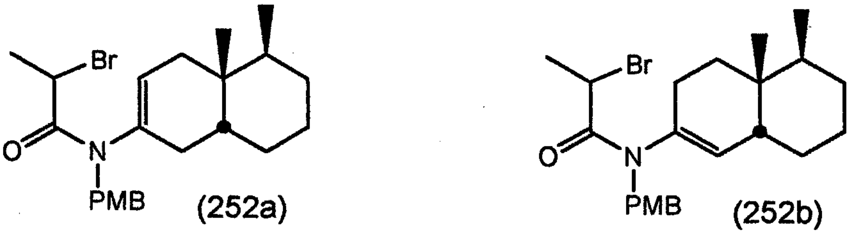
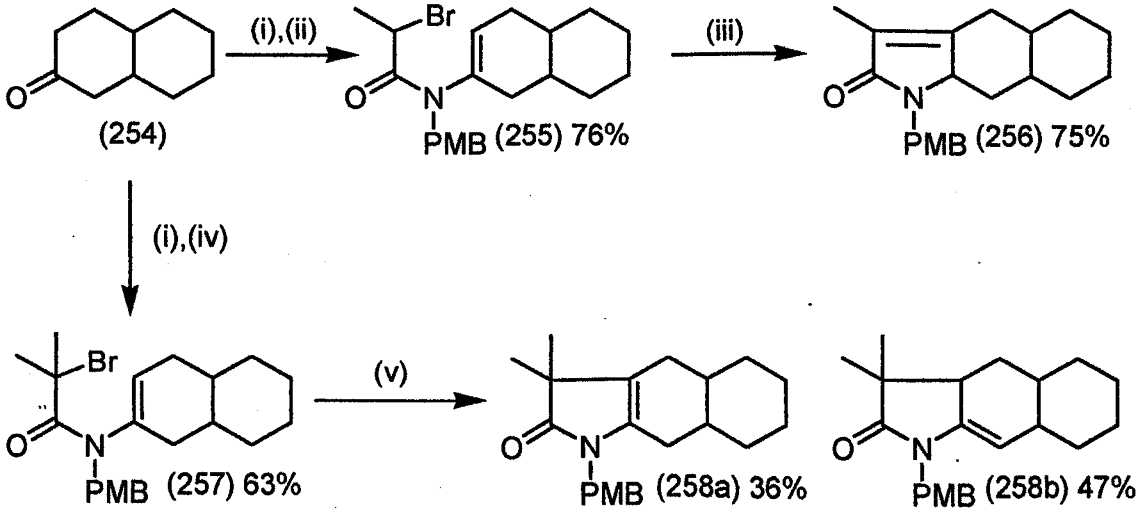


Figure 16. Regioisomers of enamide (252)

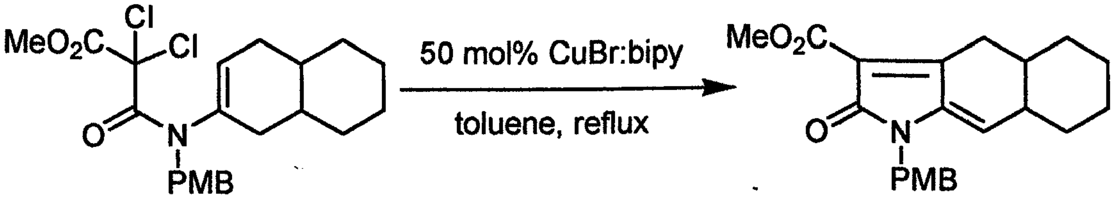
2-Decalone (254) was treated with *p*-methoxybenzylamine and 2-bromopropionyl-bromide to afford enamide (255) in good overall yield (76%). The ^{13}C nmr spectrum confirmed that only one regioisomer was present, although it was not obvious from the complex 2D spectra which one was present. Therefore, we attempted to solve the structure from the cyclised product, treatment of the enamide (255) with 1 equivalent of CuBr:(123) in toluene resulted in the formation of the monoene (256) (Scheme 83). Again, the ^{13}C nmr spectrum clearly showed that only one product was obtained, although due to the complexity of the ^{1}H and 2D nmr spectra the regiochemistry of the structure could not be fully assigned. The employment of n.O.e. on precursor (255) and cyclised product (256) was ineffective as irradiation of a clearly resolved peak proved impossible. In addition, the products (258a) and (258b) from the cyclisation of tertiary bromoenamide (257) using 30 mol% of copper(I) bromide and Me_6-tren (39) at room temperature, provided no further structural information.



(i) $PMBNH_2$, Dean-Stark, toluene, reflux; (ii) MeBrHCC(O)Br, DEA, 0°C; (iii) CuBr:(123), toluene, reflux; (iv) $Me_2BrCC(O)Br$, DEA, 0°C; (v) CuBr:(39), DCM, RT

Scheme 83.

Around the time that this work was being carried out, Parsons and co-workers published the use of a structurally similar dichloroacetamide (259), which was also based on 2-decalone (254). This compound was being used to manufacture diene (260) *via* CuCl:bipy radical cyclisations (Scheme 84).[122b] When we compared the ^1H and ^{13}C nmr spectroscopic data for the ring structure of bromoenamide (255), we established that it was similar to the data published for Parson's chloroenamide (259), with the alkenic proton signal observed at δ 5.36 ppm and its corresponding carbon signal at δ 134.4 ppm.

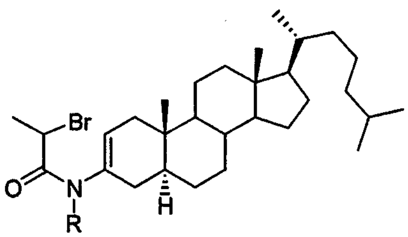


(259)

(260)

Scheme 84.

We decided that we needed further evidence to solve this regioisomer problem, therefore for our next study the preparation of precursors (261) and (262) was examined (fig. 17). The intention was that these precursors would be sufficiently crystalline to provide us with an X-ray structure, thus determining the correct position of the alkene by measurement of the appropriate bond lengths. Imination of α-cholesterone with the appropriately substituted benzylamines, followed by the standard *N*-acylation gave precursors (261) and (262) in 89% and 72% yield respectively. The crystals produced from *p*-methoxybenzyl derivative (261) were not of the quality required for X-ray crystallography, however the crystals grown from the *p*-nitrobenzyl derivative (262) produced the X-ray structure shown in figure 17 and detailed in the appendix.



(261) R = PMB, 89%
(262) R = PNB, 72%

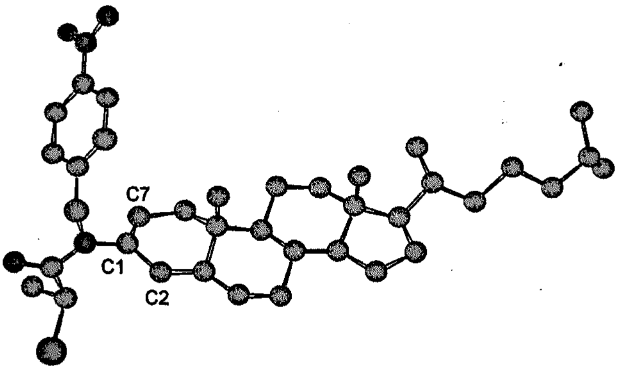
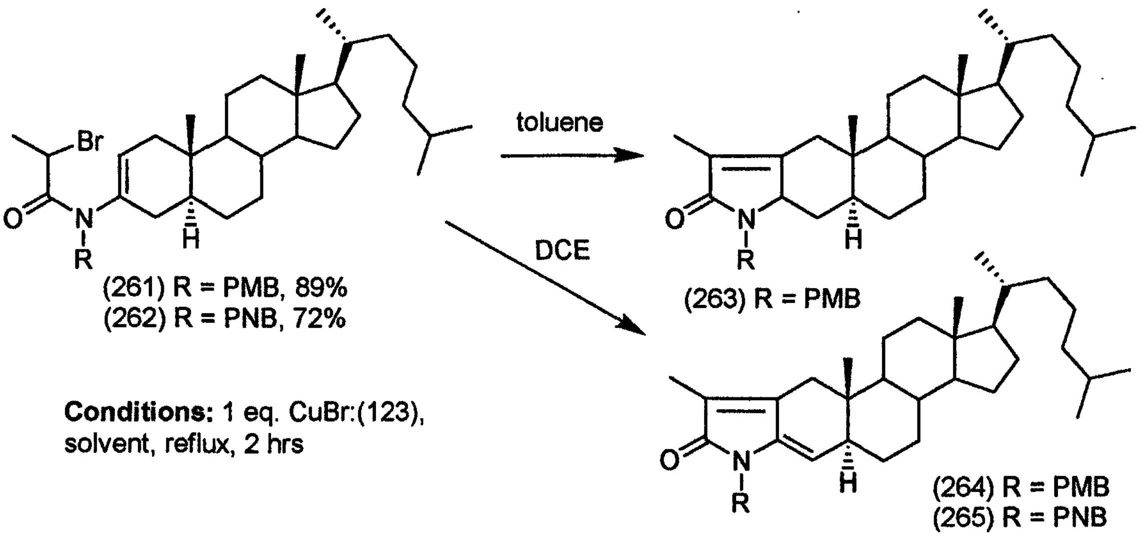


Figure 17. Ball and stick representation of the crystal structure of (262)

Typically, bond lengths for sp^3 carbon-carbon bonds are quoted in the literature as 1.54 Å, while those for sp^2 C=C bonds are 1.34 Å.[145] From the x-ray structure of precursor (262) we discovered that the bond length between C1 and C2 was 1.50 Å which indicates the presence of a sp^3 carbon-carbon bond. The bond length between C1 and C7 was 1.32 Å indicating the presence and position of the alkene double bond. We also found that the position of the alkene in the ^{1}H and ^{13}C nmr spectra was comparable to that of precursors (255) and (259). Using the evidence obtained from the X-ray structure coupled with the ^{1}H and ^{13}C nmr evidence we have unambiguously assigned the structure of (262) as the regioisomer of interest (Scheme 85). Cyclisation of *p*-methoxybenzyl (261) using 1 equivalent of CuBr:(123) in toluene gave the multi-cyclic monoene (263) in 69% yield, its respective diene (264) was also produced in 79% yield by changing the solvent system to 1,2-dichloroethane.[125] The *p*-nitrobenzyl derivative (262) however, unexpectedly produced the diene (265) in both toluene and 1,2-dichloroethane in 76% and 59% yield respectively (Scheme 85). The initial formation of the monoene was not observed under either of these conditions. Subsequent CAN deprotection of monoene compound (263) progressed efficiently and in excellent yield (81%), however deprotection of dienes (264) and (265) failed using both CAN and TFA procedures.



(261) R = PMB, 89%
(262) R = PNB, 72%

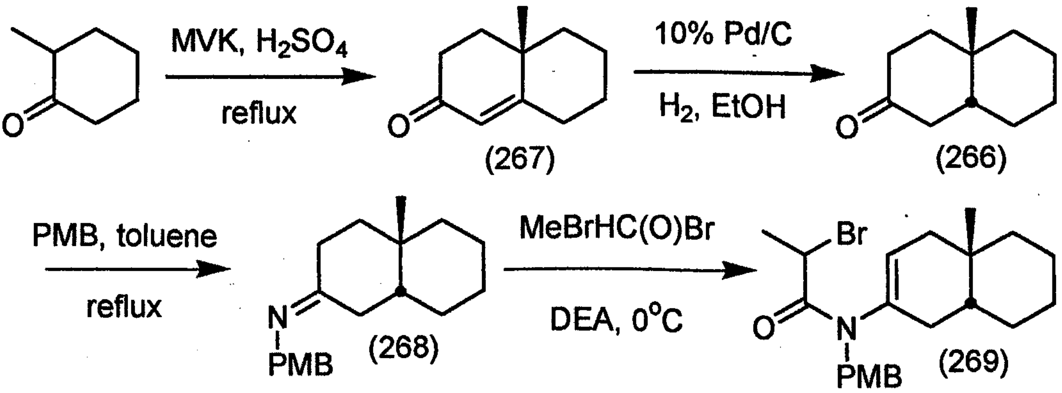
(263) R = PMB

(264) R = PMB
(265) R = PNB

Conditions: 1 eq. CuBr:(123), solvent, reflux, 2 hrs

Scheme 85.

Next we prepared the methyl substituted cyclohexenone (266) from 2-methylcyclohexanone and methyl vinyl ketone (MVK) *via* the acid catalysed Robinson annulation reported by McMurry.[146] Hydrogenation of enone (267) to give bicyclic ketone (266)[147] was followed by treatment with *p*-methoxy benzylamine and acylation with 2-bromopropionyl-bromide to give the cyclisation precursor (269) in 84% yield (Scheme 86).



(267)

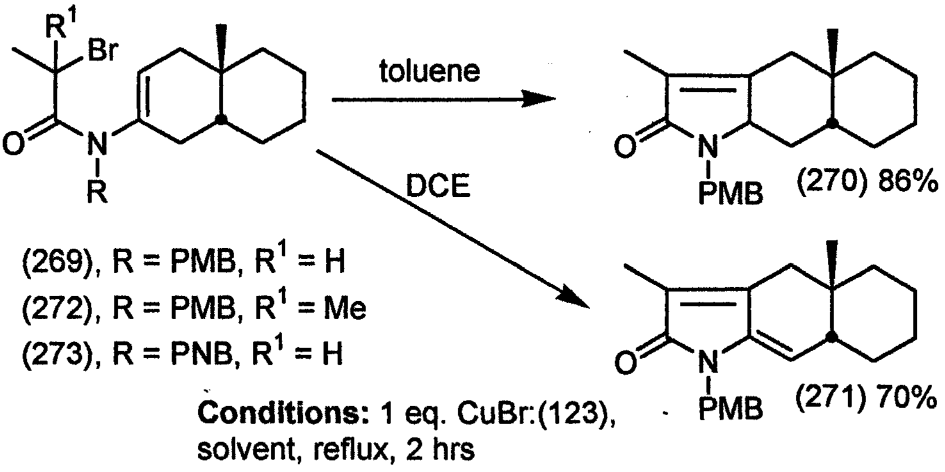
(266)

(268)

(269)

Scheme 86.

Employing the usual CuBr:(123) catalyst in toluene, precursor (269) cyclised to afford monoene (270) in 66% yield, and when 1,2-dichloromethane was used as the solvent the diene (271) was formed in 70% yield (Scheme 87). Unfortunately, cyclisation of tertiary bromoacetamide derivative (272) and also the *p*-nitrobenzyl derivative (273) failed and in all cases the starting material was recovered quantitatively (Scheme 87).

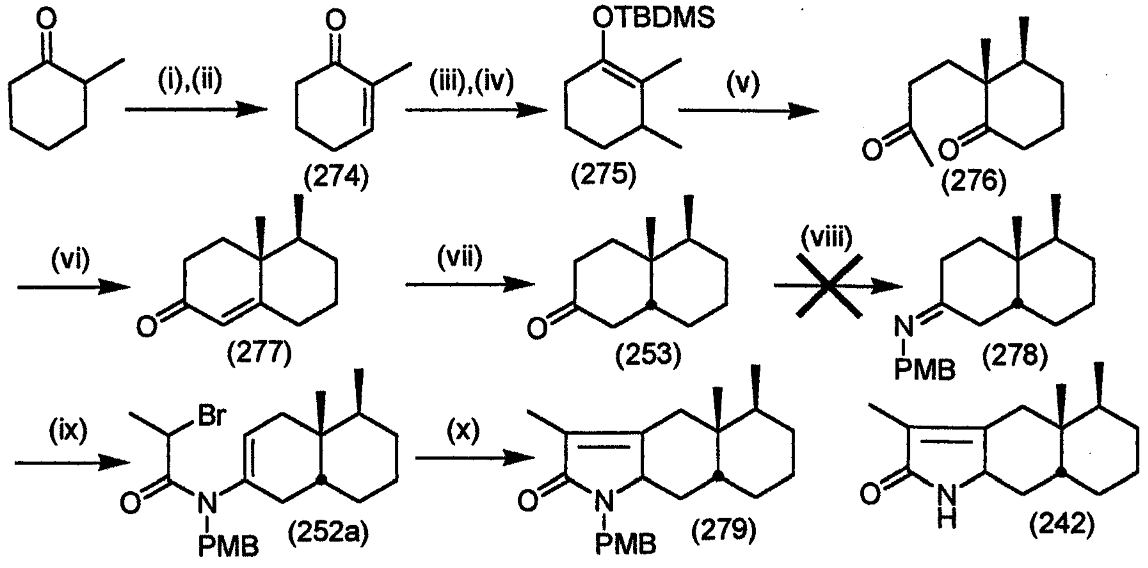


(269), R = PMB, R^1 = H
(272), R = PMB, R^1 = Me
(273), R = PNB, R^1 = H

Conditions: 1 eq. CuBr:(123), solvent, reflux, 2 hrs

Scheme 87.

We have previously shown (Scheme 82) that the initial building block required for the construction of eremophilene γ-lactam (242) was *cis*-decalone (253). Duhamel and co-workers have reported the diasteroselective synthesis of *cis*-decalone (253) in 4-steps from 2-methylcyclohexenone (274) (Scheme 88).[148] The enone (274) was produced from 2-methylcyclohexanone *via* a dehydrohalogenation reaction using *N*-bromosuccinimide and lithium bromide.[149] Regiocontrolled synthesis of tetrasubstituted silyl enol ether (275) was achieved through addition of dimethyl cuprate to 2-methylcyclohexenone (274), followed by trapping intermediate enolate using *tert*-butyldimetylsilyltriflate (TBDMSOTf). Stereocontrol of diketone formation (276) was achieved *via* Michael addition of the electrophile on the less hindered side of the double bond.[148] Aldol condensation using dilute sodium methoxide afforded bicyclic enone (277) and subsequent hydrogenation[150] gave the required *cis*-decalone in 78% yield overall (Scheme 88).



(i) NBS, CCl$_4$; (ii) LiCO$_3$, LiBr; (iii) Me$_2$CuLi, HMPA; (iv) TBDMSOTf; (v) MVK, AcOH, BF$_3$Et$_2$O; (vi) NaOMe; (vii) 10% Pd/C, H$_2$, EtONa; (viii) PMB, toluene; (ix) MeBrHC(O)Br, DEA; (x) CuBr:(123), toluene; (xi) CAN, aq. MeCN

Scheme 88.

At this point all that was required was to synthesise the imine (278), then precursor (252a), followed by copper(I) mediated cyclisation to (279). However, when we carried out the standard condensation reaction between *p*-methoxybenzylamine and ketone (253) (with azeotropic removal of water on a Dean and Stark trap), we discovered no reaction had occurred and the starting material was recovered quantitatively. The removal of forming water is necessary to complete this reversible reaction, therefore we attempted to use methods that facilitate this process from the literature.[151] These included the use of organic acids (e.g. tosic acid),[151a] Lewis acids (e.g. TiCl$_4$)[151b] to aid condensation and also the use of different solvents that form azeotropes with water at both higher and lower temperature than toluene.[151c] We also tried the technique of substituting *p*-methoxybenzylamine (PMB) with trimethylsilyl (TMS) groups in order to aid the leaving group ability of the oxonium ion by the formation of TMS ether.[152]

Initially we thought that the steric bulk of the PMB group was hindering the Bürgi-Dunitz trajectory of 109° that the nucleophile requires in order to attack the carbonyl group, but when we carried out the same reaction using both benzylamine and also the less bulky methylamine it resulted in no reaction.[153] It is not clear why the structurally similar compound (266) can form the required imine and *cis*-decalone (253) cannot, especially when the only clear difference between them is one methyl group (Figure 18).

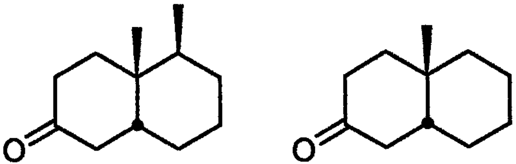
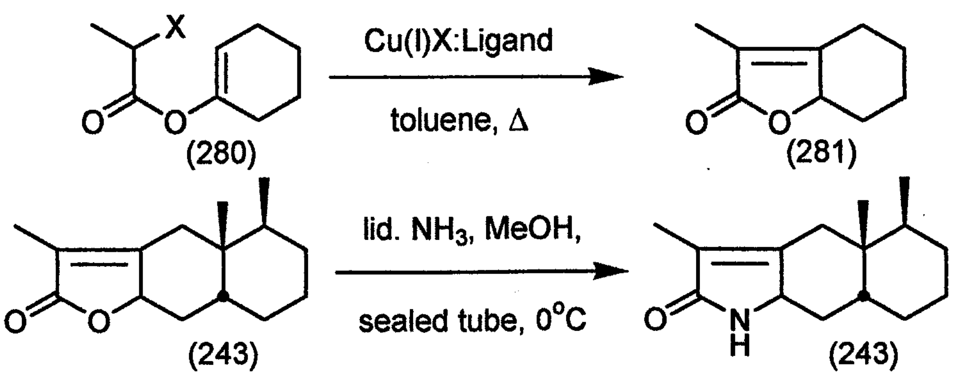

(253) (266)

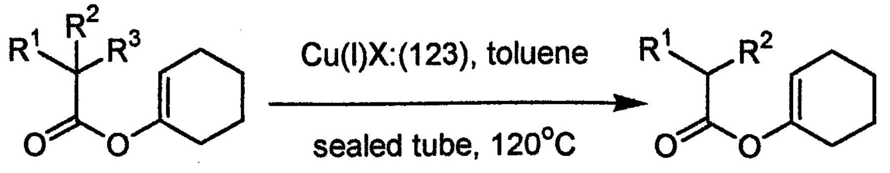
Figure 18.

Unknown conformational effects caused by the additional methyl group may be attributed to these results, but we could compile no evidence to support this assumption. Unfortunately, due to this problem we were unable to complete the synthesis of alkaloid (242) using this pathway. Next, we decided to attempt a different pathway to the alkaloid (242). Cyclisation of a haloacetate (280) using our copper(I)-amine complexes could give the bicyclic lactone (281). The idea behind this was that if this cyclisation proceeded it may give us access to the lactone derivative (243), which can be readily converted to the lactam using standard chemistry, for example liquid ammonia and methanol in a sealed tube at 0°C has been reported for similar compounds.[154] (Scheme 89).



Scheme 89.

Cyclisation precursors (282-283) were synthesised by treatment of cyclohexanone with the appropriate haloacetic anhydride in the presence of dicyclohexylcarbodiimide (DCC) according to literature procedure.[155] The ^{1}H and ^{13}C nmr data matched that quoted in the literature. Reaction of precursors (282-283) using 30-100 mol% of CuCl or CuBr:(123) respectively, in both refluxing toluene and 1,2-dichloroethane resulted in no cyclisation and quantitative recovery of starting material. We then repeated these reactions under sealed tube conditions, but unfortunately this led only to production of the reduced compounds (284-285) (Scheme 90). The nmr spectra for these compounds also matched those quoted in the literature.[156] At this point we resigned to the fact that copper(I) mediated cyclisation of these haloacetates would not proceed using our catalyst systems or reaction conditions, therefore we were unable to use these methods to gain access to eremophilene alkaloid (242).



(282) $R^{1,2,3}$ = Cl, 54% (284) $R^{1,2,}$ = Cl, 78%

(283) R^1 = Me, R^2 = H, R^3 = Br, 60% (285) R^1 = Me, R^2 = H, 91%

Scheme 90.

During the course of this investigation we have shown that the synthesis of a number of complex multi-cyclic alkaloid templates can be synthesised using our copper(I) radical cyclisation chemistry and future work may involve the application of this chemistry towards the manufacture of other medicinally important natural product architectures.

3.4 Copper(I) Mediated Radical Cyclisations in Ionic Liquids

3.4.1 Introduction

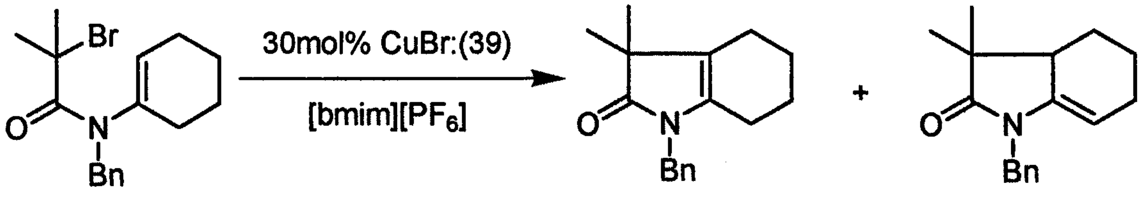
The applications of environmentally benign reaction media are becoming very important factors in today's environmentally conscious society. In connection with this, ionic liquids have attracted considerable interest. Ionic liquids are salts that are liquid at low temperature (<100°C) and represent a new class of solvents with nonmolecular, ionic character. Even though the first representative of this class has been known since 1914,[157] ionic liquids have only been investigated as solvents for transition metal mediated reactions in the past ten years.[157-159] Publications to date have shown that replacing an organic solvent by an ionic liquid can lead to remarkable improvements in yields and stereochemistry of well-known processes.[158] Ionic liquids form biphasic systems with many organic product mixtures. This gives rise to the possibility of a multi-phase reaction procedure with easy isolation and recovery of homogenous catalysts. In addition ionic liquids have practically no vapour pressure which facilitates product separation by distillation.[158] There are also indications that switching from a normal solvent to an ionic liquid can lead to novel and unusual chemical reactivity.[157] Room temperature ionic liquids have been used to great effect as solvents for a number of reactions, for example, Heck reactions,[160] Friedel-Crafts reactions,[161] isomerisations of fatty acid derivatives,[162] dimerisation reactions of alkenes,[163] Diels-Alder reactions,[164] and hydrogenation reactions[165] to name a few. Ionic liquids such as 1-butyl-3-methylimidazolium hexaflurophosphate[157] ([bmim][PF_6]) have a particularly useful set of properties, being virtually insoluble in water and alkanes but readily dissolving many transition metal catalysts. This ionic liquid and its analogues [bmim][X] are shown in figure 19.

X = PF_6^-, SbF_6^-, BF_4^-, OTf^-

Figure 19.

3.4.2 Copper Mediated Radical Cyclisations in [bmim][PF_6]

Our initial interest in this area was to investigate whether we could carry out a copper(I) mediated 5-*endo* radical cyclisation of a tertiary bromoacetamide (145) in the ionic liquid [bmim][PF_6]. Since we have already established that the cyclisation of (145) takes place at room temperature using a catalytic amount of CuBr:(39) (section 3.2.2), all that was necessary was to replace the organic solvent (DCM) with [bmim][PF_6]. The standard procedure for catalyst removal on completion of these DCM reactions was to pass the reaction mix through a silica bung. This rendered catalyst recycling impractical. However, if the final products can be removed from an ionic liquid by extraction using an immiscible organic solvent (such as toluene), the catalyst may be recycled and used again for another reaction. Cyclisation of (145) in [bmim][PF_6] using the standard conditions proceeded rapidly (20 minutes) (Table 10). Subsequent extraction of the dark green coloured ionic liquid/catalyst with toluene afforded a 3:1 mixture of regisomeric products (152a) and (152b) in 99% yield. It should be noted that the yield for the reactions carried out in the ionic liquids are markedly improved on those utilising organic solvents and the initial reaction times for both compare favourably. Leaching of CuBr:Me$_6$-tren catalyst into the extracted products was not observed in the ^{1}H or ^{13}C nmr of the products, nor was this observed in the mass spectrum.



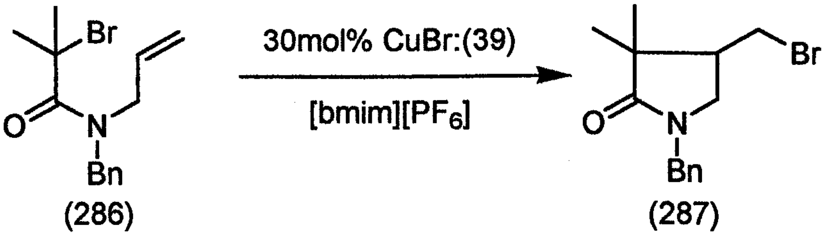
(145) (152a) (152b)

Reaction	Time	Yield	Ratio a:b
1	20 mins	99%	3:1
2	1 hrs	99%	3:1
3	2.5 hrs	74%	3:1
4	6 hrs	20%	2:1
5	12 hrs	no rxn	-
"	24 hrs	no rxn*	-
"	48 hrs	no rxn	-

* Addition of 1 equivalent of copper(0)

Table 10. Catalyst recycling results for 5-*endo* cyclisations

Next, we reused the same ionic liquid/catalyst system to carry out another cyclisation of (145), on this occasion the reaction took significantly longer to reach completion (1 hour). This trend continued after recycling the catalyst system a number of times, the results of which are shown in table 10. After the 5th time of recycling no reaction occurred after 48 hours. We thought that the catalyst system maybe exhausted (i.e. totally oxidised to Cu(II)), therefore we added 1 equivalent of copper(0) after 24 hours, in an attempt to reactivate the catalyst *via* reduction to copper(I). This procedure was thought to have failed as no further reaction was observed. We also carried out an analogous experiment on *N*-allyl-*N*-benzylbromoacetamide (286)[166] which we found undergoes an instantaneous 5-*exo-trig* atom transfer radical cyclisation in dichloromethane using CuBr:(39) to afford cyclic product (287).



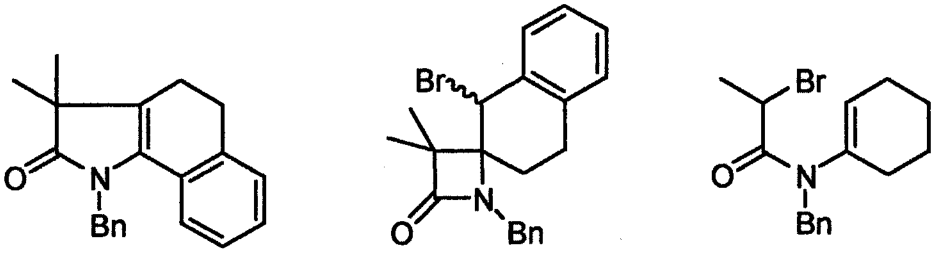
Reaction	Time	Yield
1	50 mins	99%
2	2 hrs	99%
3	6 hrs	90%
4	12 hrs	no rxn
"	24 hrs	no rxn*
"	48 hrs	no rxn

* Addition of 1 equivalent of copper(0)

Table 11. Catalyst recycling results for 5-*exo* cyclisations

This experiment showed a similar trend with the catalyst becoming inactive after the 4th time of recycling. Also, catalyst reactivation was not observed after the addition of copper(0) (Table 11). Although, the initial cyclisation of (286) in the ionic liquid took significantly longer to complete (50 minutes) compared to DCM (<20 seconds), it should be noted that cyclisation only proceeded to give 9% of (287) in toluene, 14% in 1,2-dichloroethane and resulted in no reaction in methanol, pentane and acetonitrile.

We have also successfully carried out a number of other 5-*endo* cyclisation reactions in [bmim][PF$_6$], including the cyclisation of bicyclic precursors (167-169) to form tricyclic compounds (170-172) in excellent yield (99%) (fig.20).



(170) 99% (172) 99% (196)

Figure 20.

Cyclisation of less activated secondary bromoacetamide (196) unsurprisingly did not proceed at room temperature *via* the CuBr:(123) catalyst system. When we heated the reaction at 90°C in [bmim][PF$_6$] it produced a complex mixture of unidentifiable products. Further work in this area may entail the use of ionic liquids with different cationic and anionic fragments (e.g. Figure 19), as others have reported that simply changing the counter ion has been reported to have enormous effects on reactivity and selectivity of processes.[157-158]

3.5 Conclusion

In this chapter we have demonstrated a number of highly efficient radical cyclisations reactions mediated *via* copper(I) amine complexes. We have shown that the reaction of tertiary bromoacetamides (146-151) with catalytic CuBr:Me$_6$-tren(39) at room temperature produces regioisomeric mixtures of γ-lactams (152, 155-160) in a highly efficient manner *via* an initial 5-*endo-trig* cyclisation followed by oxidation and elimination of H$^+$. We have also demonstrated that it was possible to trap the intermediate acyliminium ion (154) *via* intermolecular nucleophilic addition of methanol, although the trapped product is unstable and eliminates slowly after a short time. This chemistry has also been applied to the cyclisation of tricyclic lactams. We discovered that α-substituted bromoacetamides (167-168) furnished γ-lactams (170-171) *via* a 5-*endo* cyclisation pathway whereas the respective β-substituted derivative (169) furnished the β-lactam (172) *via* a 4-*exo* cyclisation pathway. Several potential tandem cyclisation reactions were examined, however, after initial cyclisation to give regioisomeric products, no tandem cyclisations occurred.

A variety of less activated secondary haloacetamides (196, 202-207) were shown to undergo efficient 5-*endo-trig* radical cyclisations to give α,β-unsaturated monoene lactams (197, 208-213) mediated by CuBr:TPA (123) in refluxing toluene. Changing the solvent to refluxing 1,2-dichloroethane furnished the corresponding α,β-unsaturated diene lactams (218-219). These reactions also proceed by a radical-polar crossover mechanism of the type described above. Primary bromoacetamide (225) did not undergo cyclisation under any of the conditions applied to it, and instead when heated in a sealed tube its reduction product (226) was isolated. A series of multi-cyclic compounds were also produced using this method and their subsequent deprotection led towards the attempted synthesis of the sesquiterpenic alkaloid, eremophilene γ-lactam. We have also demonstrated that it is possible to effectively synthesise a series of γ-lactams *via* 5-*endo* radical cyclisation in the ionic liquid [bmim][PF_6] at room temperature. The 5-*exo* ATRC of *N*-allyl-*N*-benzylbromoacetamide (286) to form (287) was also established. Using this method the catalyst system was shown to be easily recyclable for further reaction. Overall a wide variety of cyclisation precursors were examined with most providing a high yield of product. All successfully deprotected γ-lactams have been sent for biological testing for antibacterial activity in *pseudomonads*.

Chapter 4: 5-*Endo* Radical Cyclisation of Enamides Mediated by Ceric Ammonium Nitrate

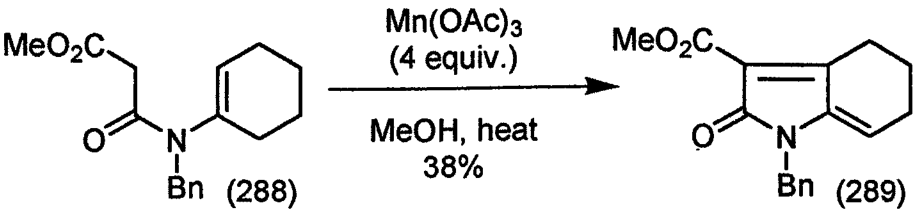
4.1 Introduction

In chapter one it was shown that one of the most important methods for preparing 5-membered nitrogen heterocycles is the radical cyclisation of unsaturated organohalides. Cyclisations proceeding by a 5-*exo-trig* pathway have been shown to provide a mild and flexible approach to a variety of pyrrolidinones (Chapter 1, section 1.5). It has been demonstrated, however, in the preceding chapters and also in the literature, that an alternative approach to pyrrolidinones which centres on the 5-*endo-trig* radical cyclisation of halo-enamides is also possible.[77, 125, 118, 120] This cyclisation is unusual in that the initial carbamoylmethyl radical reacts to form a 5- rather than a 4-membered (or β-lactam) ring. The 4-*exo-trig* cyclisation, to form a β-lactam, is generally observed when radical-stabilising (aromatic) groups are introduced on the enamide C=C bond.[167] These 5-*endo* cyclisations, which can be mediated by copper or tributyltin hydride, have been shown, for example, to provide efficient approaches to substituted pyroglutamates.[168] However, the use of tributyltin hydride is far from ideal as tin-containing by-products are often difficult to remove and the cyclisation leads to the reduction of two functional groups (i.e. the C-halogen and C=C bonds). With a view to developing a more straightforward and versatile approach to functionalised pyrrolidinones, this chapter describes the use of ceric ammonium nitrate (CAN) as an initiator for 5-*endo-trig* radical cyclisations. The results of which will be compared to the previously discussed copper(I)-amine reagents in the last two chapters. Both methods have a number of advantages over the use of tributyltin hydride. Hence, the reagents are cheaper, the metal by-products are more easily removed and, importantly, a functional group (generally a double bond or halogen atom) is introduced into the product after cyclisation.

Cerium (IV) compounds represent the most notable oxidants among lanthanide reagents. In particular, CAN has been utilised extensively for a variety of oxidative transformations.[144] As might be expected for very powerful one-electron oxidants, the chemistry of Ce(IV) oxidations of organic molecules is dominated by radical and radical cation chemistry, this area has been extensively reviewed by Molander.[109]

4.2 Ceric Ammonium Nitrate Mediated Cyclisations

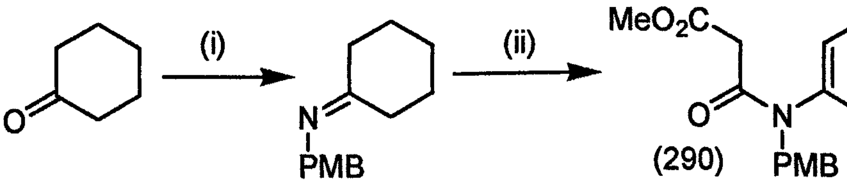
Parsons has recently reported that the β-amido ester (288) undergoes a 5-*endo-trig* radical cyclisation to form bicyclic diene (289) in 38% yield. This cyclisation reaction was mediated using 4 equivalents of manganese(III) acetate ($Mn(OAc)_3$) in boiling methanol (Scheme 91).[122]



Scheme 91.

Nair and co-workers have recently carried out a number of studies to compare the reactivity of $Mn(OAc)_3$ with CAN, the results of which indicated that the cerium(IV) reagent is superior to the manganese(III) reagent in the oxidative addition of 1,3-dicarbonyl compounds to unactivated alkenes (Chapter 1, Scheme 42).[110-112] With this in mind, we decided to investigate whether CAN could be used to mediate a 5-*endo-trig* cyclisation of β-amido ester (290), as to our knowledge this type of process had not been reported. In chapter one we also specified that CAN was used to promote the 4-*exo-trig* cyclisation of enamides to give highly functionalised β-lactams in moderate yield (Scheme 43).[113] The conditions used to carry out these reactions were the addition of 2 equivalents of CAN to a solution of the appropriate precursor in stirring methanol at room temperature. Therefore, we decided to use this procedure as the starting point of our study.

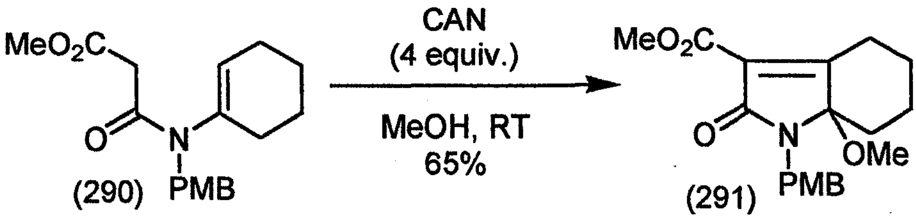
The β-amido ester precursor (290) was prepared by *N*-acylation of the imine derived from cyclohexanone and *p*-methoxybenzylamine, with methyl malonyl chloride (Scheme 92). The spectral data compiled for (290) compared favourably to that reported for analogue (288) in the literature.[122]



(i) $PMBNH_2$, Dean-Stark, toluene, reflux;
(ii) MeO_2CCH_2COCl, toluene, 0°C, 57%

Scheme 92.

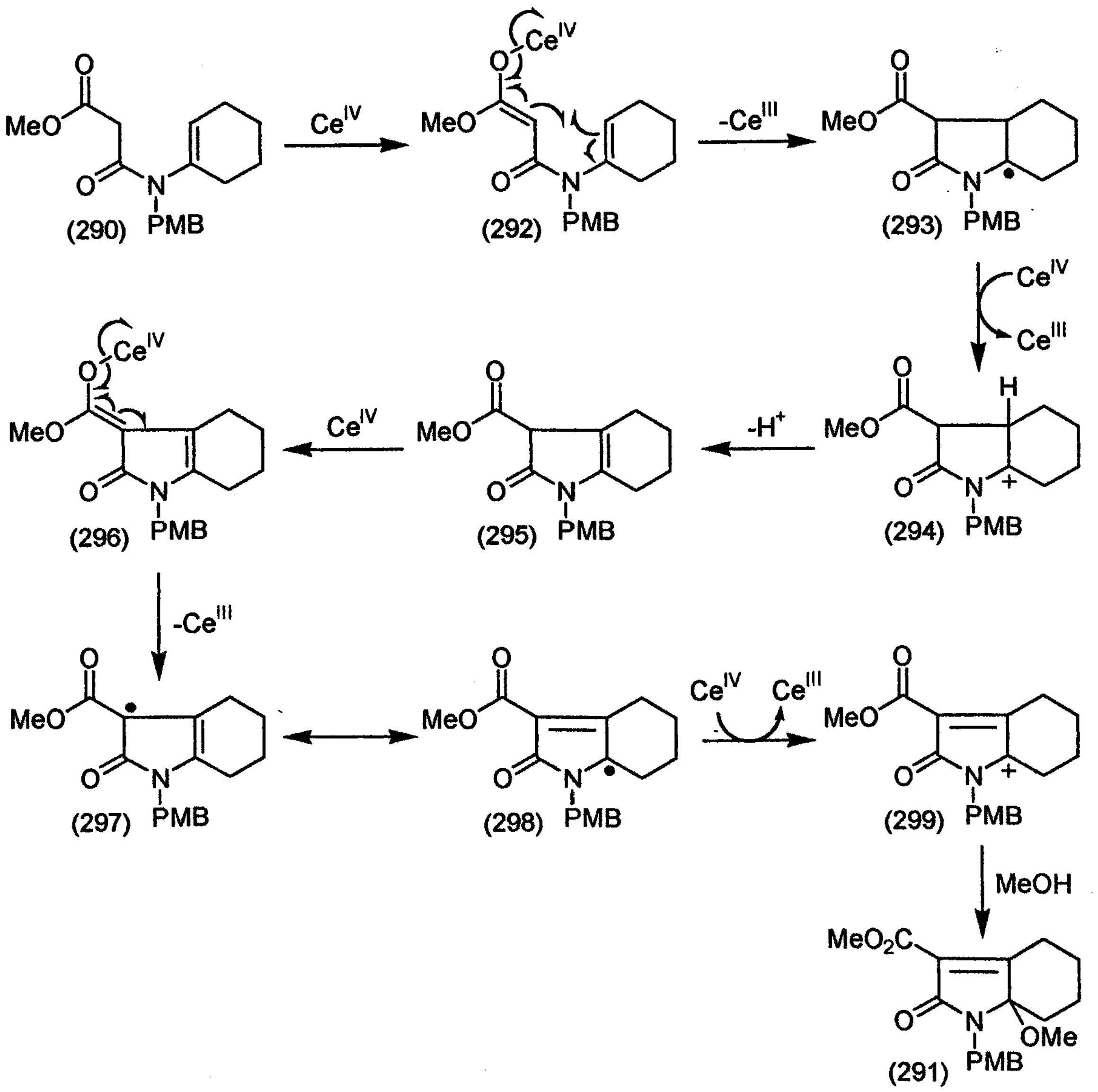
Initial reactions of (290) with 2 equivalents of CAN in methanol at room temperature gave the bicyclic lactam (291) in 28% yield. However, the yield of this reaction was found to improve from 28% to 65% when 4 equivalents of CAN were employed, whereas addition of >4 equivalents was found to have a detrimental effect on the product yield. (Scheme 93).



Scheme 93.

Interestingly under these conditions no deprotection of the PMB group was observed. A review of the literature suggested that there is no conclusive reaction mechanism for CAN mediated processes, although the nature of the initiation and termination processes is thought to be similar to that of $Mn(OAc)_2$.[104, 122] However, we propose a mechanism consistent with the experimental data obtained in scheme 94.

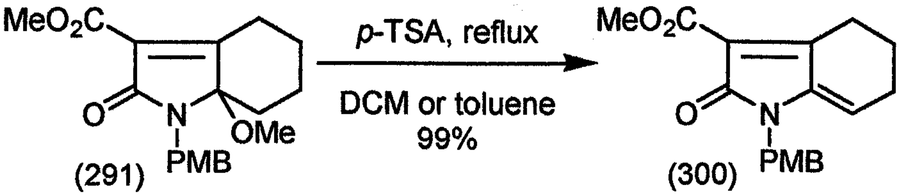
It is suggested that the cerium enolate (292) is formed *via* loss of a proton from precursor (290) upon treatment with CAN. This could then cyclise in a 5-*endo* fashion to produce the bicyclic intermediate radical (293). We have already observed for our Cu(I) cyclisations that tertiary radicals such as (293) are particularly susceptible to oxidation and formation of cation (294) could occur using another equivalent of CAN. Following the loss of a proton, the alkene (295) could be obtained. However, the proton adjacent to the ester is still relatively acidic and a secondary cerium enolate (296) could be formed. The radical (297) derived from enolate (296) is likely to be oxidized to cation (299), which is in turn trapped *via* nucleophilic addition of methanol (291) (Scheme 94). It should be noted that the use of traditional radical traps, (e.g. diphenyl selenide and diphenyl sulphide), were ineffective in these processes and the methoxy trapped product was afforded in all cases.



Scheme 94. Proposed mechanism for the cyclisation of (290)

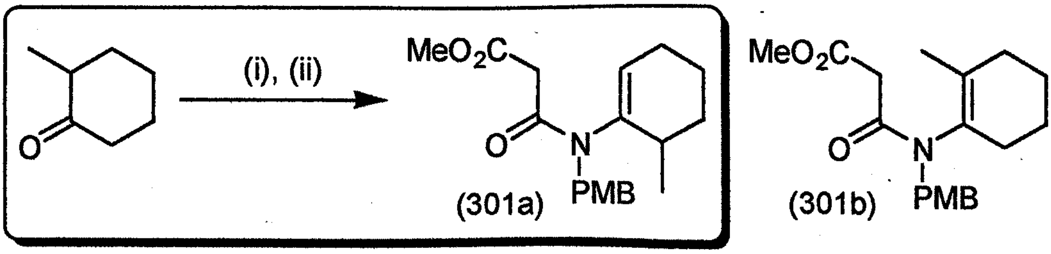
The fact that the best yield of (291) was obtained using 4 equivalents of CAN could therefore be explained by the two radical generation and oxidation sequences. This methoxy trapped compound proved to be very stable, unlike the copper(I) cyclised derivative (164) (section 3.2.3). However, we did discover that refluxing (291) in DCM or toluene with a catalytic amount of tosic acid (*p*-TSA) afforded the corresponding diene

(300) in quantitative yield (Scheme 95). We also discovered during the course of this work that cyclisation of (290) will not proceed in solvents such as dichloromethane, 1,2-dichloroethane, benzene and toluene at room temperature or higher because of solubility problems with CAN. Precursor (290) was recovered quantitatively from these reactions, although we did find that reaction in water or acetonitrile facilitated the solvation of CAN, but unfortunately these reactions yielded unidentifiable complex mixtures.



Scheme 95.

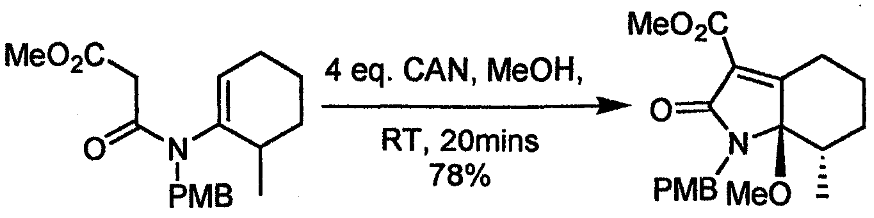
Efforts were focused on modifying the structure of the precursor to examine the effect on the ring closure. The methyl-substituted precursor (301a) was produced on treatment of 2-methylcyclohexanone with *p*-methoxybenzylamine and methyl malonyl chloride under the standard conditions. Interestingly, this reaction gave only one product (301a), its corresponding regioisomer (301b) was not observed by ^{1}H, ^{13}C or 2D nmr spectroscopy (Scheme 96).



(i) PMBNH$_2$, Dean-Stark, toluene, reflux; (ii) MeO$_2$CCH$_2$COCl, toluene, 0°C, 69%

Scheme 96.

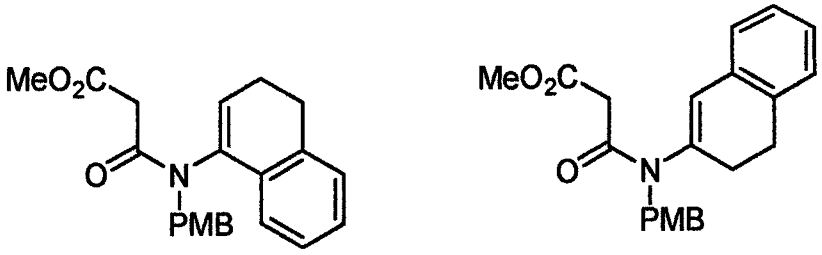
Methyl-substituted precursor (301a) was treated with 4-equivalents of CAN in methanol, the result of which gave the bicyclic methoxy derivative (302) in 78% yield as a single diastereomer (Scheme 97).



(301a) (302)

Scheme 97.

The synthesis of some tricyclic systems was then investigated. The enamide precursors (303) and (304) were prepared from α-tetralone and β-tetralone in 66% and 69% yield respectively, using the standard preparation (Figure 21).

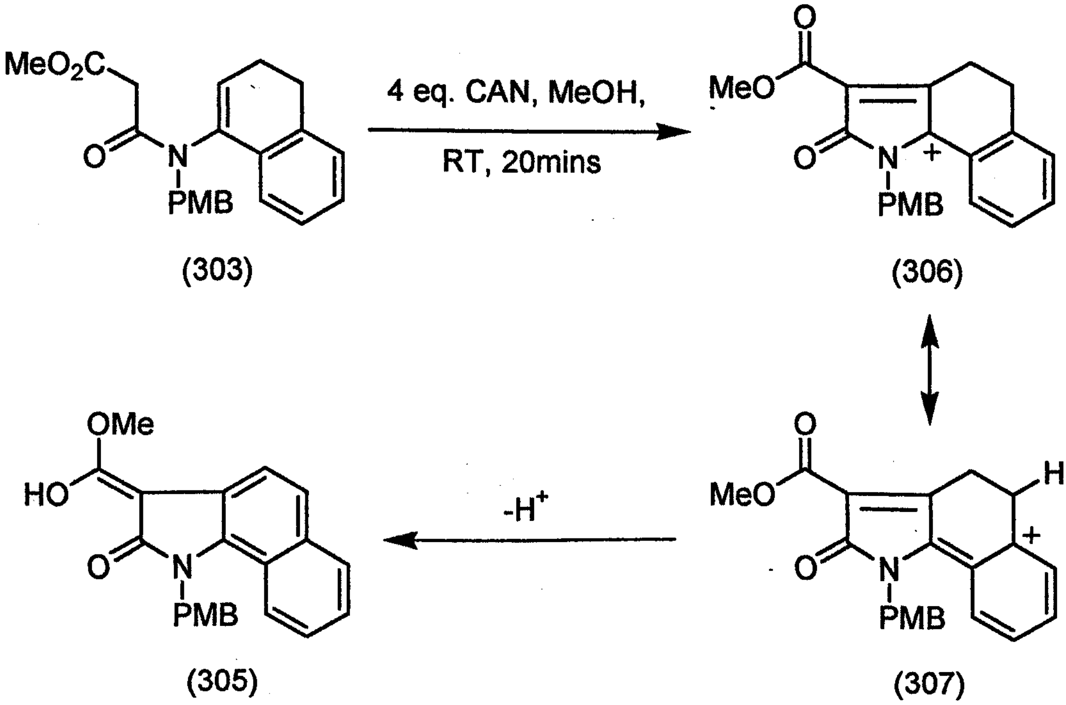


(303) 66% (304) 69%

Figure 21.

It should be noted that the ^{1}H nmr spectra observed for each of these compounds was quite different. In the ^{1}H spectra for α-substituted derivative (303) the alkenic proton was observed as a sharp triplet at δ 6.81 ppm and the benzylic protons were observed as a sharp set of AB doublets at δ 5.47 and 3.80 ppm, which suggests that they are in different chemical environments. However, the alkenic and benzylic protons for β-substituted derivative (304) were observed as broad singlets at δ 6.18 and 4.73 ppm respectively. The ^1H evidence suggested that α-substituted derivative (303) was a single rotamer held in position *via* restricted rotation around the amide bond. The broadness found in the ^1H spectra for β-substituted derivative (304) and the fact that its alkenic and benzylic protons are observed as broad singlets suggest that there is less hindered or slow rotation around its amide bond.

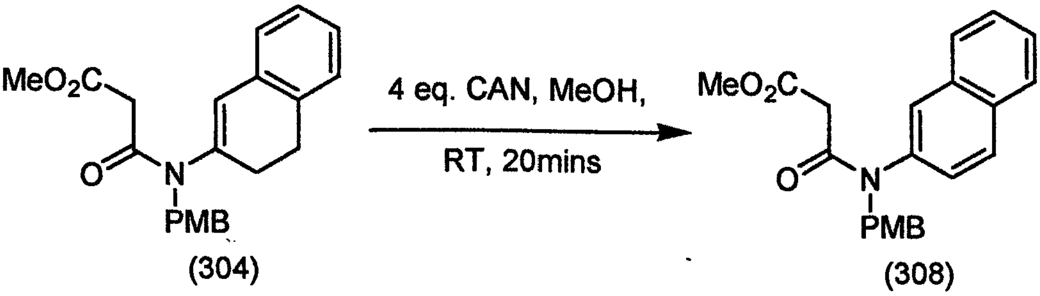
Cyclisation of α-substituted derivative (303) using 4 equivalents of CAN in methanol at room temperature gave the tricyclic compound (305) in 47% yield (Scheme 98).



Scheme 98.

The mechanism for this cyclisation was thought to proceed *via* a 5-*endo-trig* cyclisation similar to that shown in scheme 98, with four equivalents of CAN being used for two radical generation sequences and two oxidation sequences to furnish cationic intermediate (306). Finally, production of the aromatic middle ring may involve elimination of a proton from cationic intermediate (307) to afford the indolone (305).

However, when we tried to cyclise the β-substituted derivative (304) with CAN using the same procedure we found that no cyclisation took place and the tetralone ring portion of (304) fully oxidised to give the naphthalene based aromatic system (308) in 45% yield (Scheme 99).



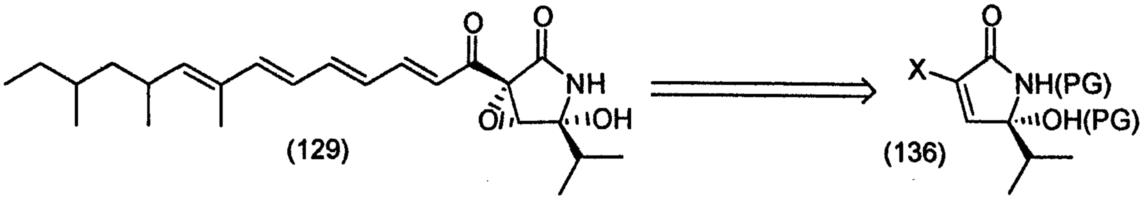
Scheme 99.

These results suggest that the restricted rotation around the amide bond in α-substituted precursor (303) confine the radical donor and acceptor in a position that is beneficial towards cyclisation, i.e. the initial carbomoyl radical can react faster with its alkene electron acceptor than aromatisation can occur. With the β-substituted precursor (304) however, the aromaisation occurs faster than cyclisation. It should be noted that no 4-*exo* or 5-*endo* cyclisation products (analogous to those observed using copper) were isolated for the cyclisation of (304). In fact no such products were detected when the reaction was run at lower (-10°C - 0°C) or higher temperatures (refluxing methanol) using varying concentrations of CAN (1-8 equivalents). We also discovered while probing the reaction conditions for the cyclisation of (303) and (304), that using 4 equivalents of CAN in acetonitrile (rather than methanol) gave the desired products (305) and (308) in higher yield (72% and 77% respectively), although the exact reason for this is not clear.

4.3 Applications of Ceric Ammonium Nitrate Mediated Cyclisations Towards the Synthesis of Natural Product Templates

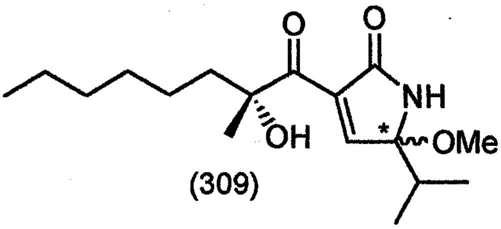
4.3.1 Introduction

In chapter one (section 2.3) we described the application of copper(I) mediated 5-*endo-trig* radical cyclisations towards the synthesis of the heterocyclic ring portion of non-peptide bradykinin inhibitor L-755,807 (129). We also described two convergent approaches towards the racemic synthesis of this ring portion (Scheme 53) both of which resulted in the proposal of synthon (136) as a target molecule (Scheme 100).



Scheme 100.

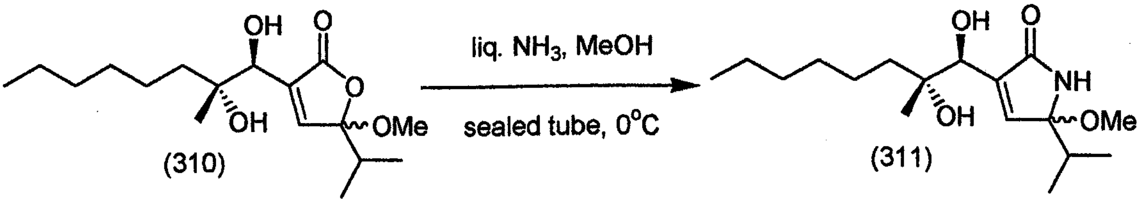
A number of biologically active and structurally similar molecules to synthon (136) and L-755,807 (129) have been reported in the literature, which we will now describe briefly. Although PI-091 (309), a platelet aggregation inhibitor isolated from *Paecilomyces* sp. F-3430,[169] contains no epoxide, it does contain the basic hydroxylactam ring system that is present in both (129) and (136). In this case the compound exists as a 1:1 diastereomeric mixture at the quaternary carbon atom (*) in the lactam ring (fig. 22).



(309)

Figure 22.

To date two syntheses of PI-091 have been reported. One by Iwasawa and Maeyama[170] which uses a carbene approach towards the ring system while the second synthesis reported by Tadano and co-workers was achieved *via* the lactone (310).[154] Treatment of (310) with liquid ammonia (Scheme 101) furnished lactam (311) which was oxidised to complete the synthesis of PI-091 (309).



(310)

(311)

Scheme 101.

Other natural products which have a similar heterocyclic ring structures include: Fusacarin C (312), a mutagenic produced by *Fusarium moniliforme*;[171] (+)-Cerulenin (313), an antibiotic[172] and lipid synthesis inhibitor[173] which was isolated from *Cephalosporium caerulens*;[174] (+)-Epolactaene (314), a neuritogenic agent isolated from *Penicillium* sp.

BM1689-P;[175] and also Quinolactacin C (315), a novel quinolone antibiotic which was isolated from the fermentation broth of *Penicillium* sp. EPF-6 (fig. 23).[176]

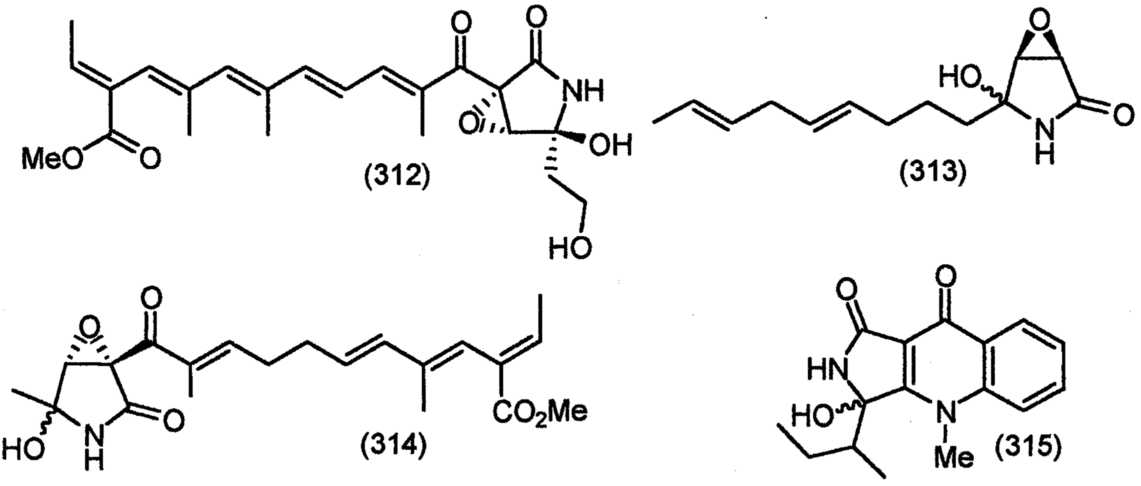

(312) (313) (314) (315)

Figure 23. Natural products with a related heterocyclic ring structure

Since we had already established that the cyclisation of (290) using 4-equivalents of ceric ammonium nitrate in methanol afforded the methoxylactam (291) (Scheme 93), we decided to investigate whether these conditions could be used effectively towards the synthesis of the heterocycles of both synthon (136) and methoxylactam PI-091 (309) (fig. 24).

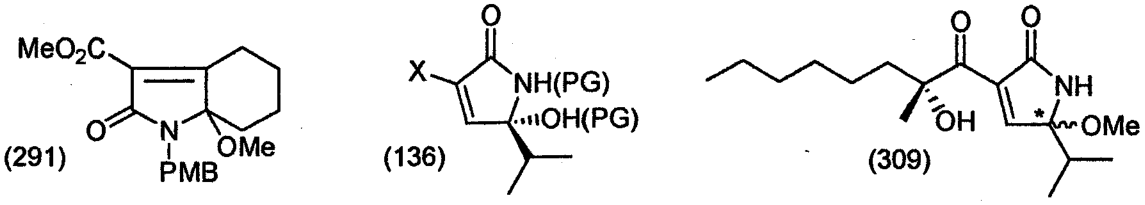
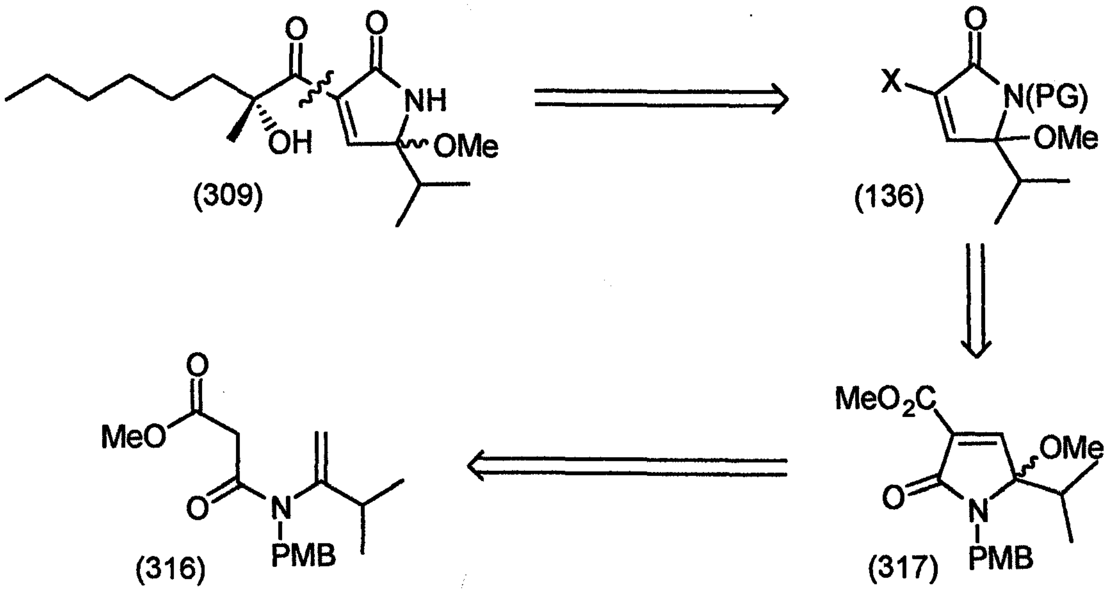

(291) (136) (309)

Figure 24.

4.3.2 CAN Promoted Production of Methoxy and Hydroxy γ-Lactams

For our initial disconnection of PI-091 we removed the side chain to give familiar synthon (136). We can now place some synthetic equivalent atoms on synthon (136), i.e. X =

COOCH$_3$, PG = PMB, and disconnect again to give potential cyclisation precursor (316) (Scheme 102).



Scheme 102.

Enamide (316) was prepared in "one-pot" *via* condensation of 3-methyl-2-butanone with *p*-methoxybenzylamine on a Dean-Stark water trap followed by *N*-acylation of the intermediate imine with methyl malonyl chloride. Subsequent flash column chromatography revealed that two compounds were obtained, the first being the required precursor (316) (33% yield) while the second compound was revealed to be the 1,3-oxazin-4-one (318) (36% yield) (fig. 25). There is very little reported about these class of compounds in the literature and their synthesis has only been reported in a few of cases.[177] They are however, closely related to the medicinally important glyceryl trinitrates (319)[178] such as ITF 296 (320). Such compounds have shown preferential action on large coronary vessels along with good oral bioavailability (fig. 25).[179]

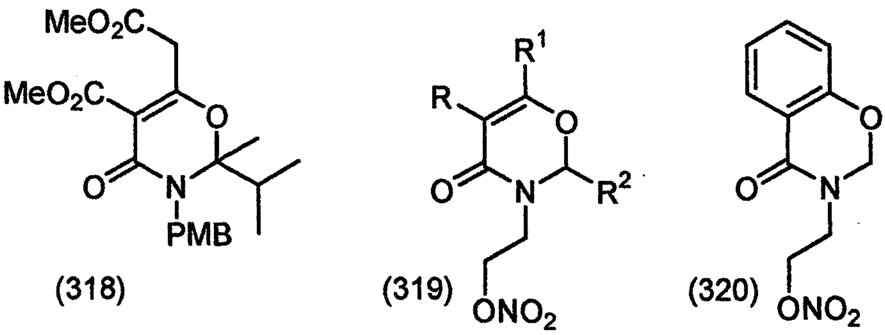
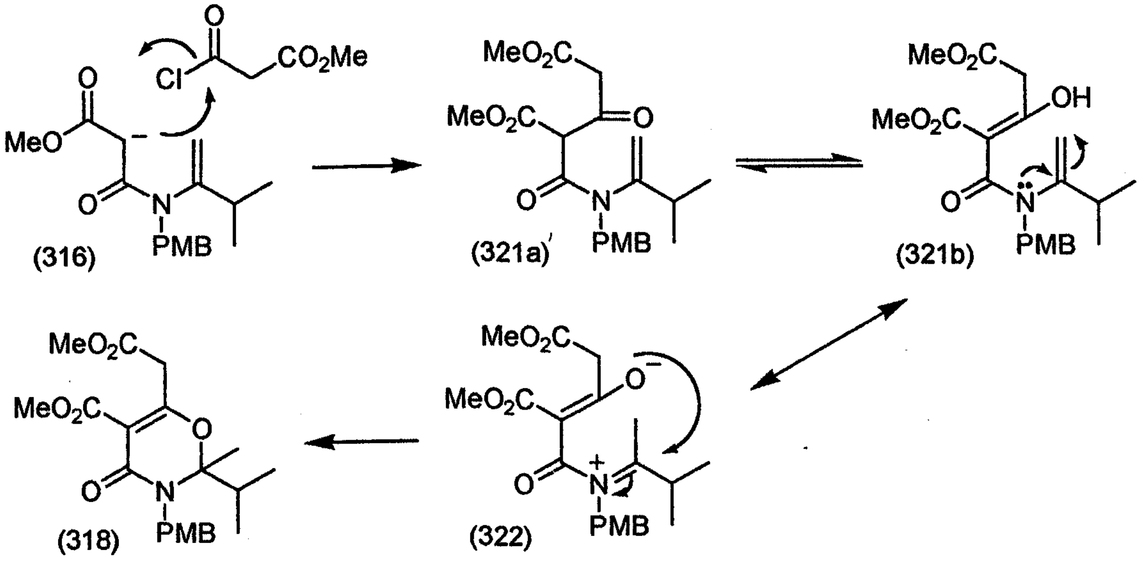

(318) (319) (320)

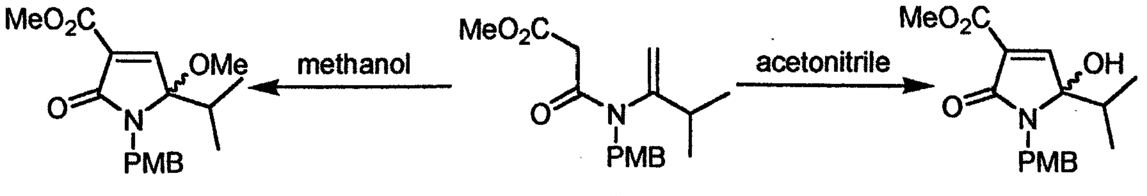
Figure 25.

The construction of 1,3-oxazin-4-one (318) can be rationalised by initial base deprotonation of precursor (316) followed by nucleophilic attack on another molecule of methyl malonyl chloride affording tautomers (321a-b), subsequent nucleophilic attack of the hydroxyl group on the acyliminium ion in (322) furnishes the 1,3-oxazin-4-one (318) (Scheme 103).


(316) (321a) (321b) (318) (322)

Scheme 103.

Treatment of precursor (316) with 4 equivalents of ceric ammonium nitrate in methanol at room temperature furnished the expected methoxylactam (317) in 67%. However, by simply changing the solvent to acetonitrile the hydroxylactam (323) was produced in excellent yield (95%) (Scheme 104).



(317) 67% (316) (323) 95%

Conditions: 4 equivalents of CAN, solvent, RT, 20 mins

Scheme 104.

The mechanism for these reactions are thought to proceed in the same manner as that for (290), shown in scheme 94, the main difference being the trapping of the hydroxylactam by water present in the solvent. However, when we carried out this reaction in various aqueous acetonitrile solutions (i.e. added water) we found that competitive PMB deprotection took precedence over radical cyclisation and no cyclisation products were obtained. Isolation and purification of these deprotected systems proved difficult, therefore the only evidence we could obtain for their existence was the isolation of *p*-methoxybenzaldehyde, which is the known by-product when CAN is used to remove PMB groups from amides.[132] It should be noted that while the purification of methoxylactam (317) required careful column chromatography, the synthesis of hydroxylactam (323) was very clean and no further purification was necessary leading to higher yields. In the interest of comparison, we also attempted to mediate the cyclisation of (316) using 4 equivalents of $Mn(OAc)_3$ in boiling methanol, as reported by Parsons,[122] although after 48 hours no reaction took place and the starting material was recovered quantitatively.

We also discovered that when the CAN mediated cyclisation and oxidation of precursor (316) was carried out in refluxing methanol that the Michael addition product (329) as well

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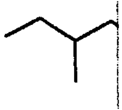

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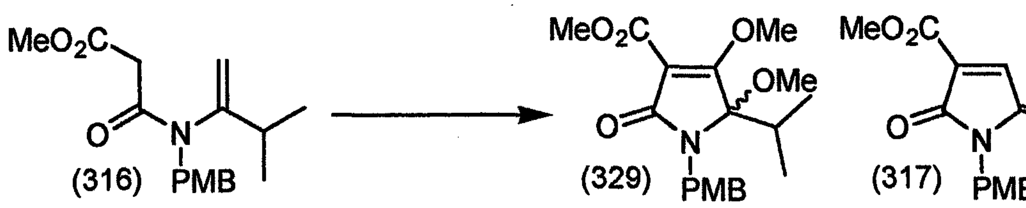
as the methoxylactam (317) were isolated in 23% and 29% yield respectively (

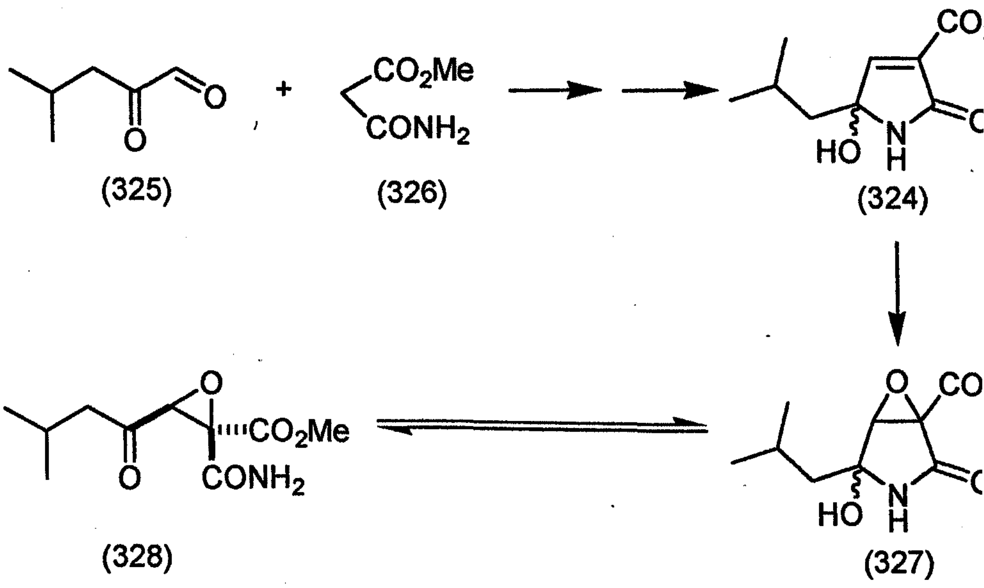
105).



Conditions: 4 equivalents of CAN, methanol, Δ, 2 hrs

Scheme 105.

During studies to prove the configuration of the antibiotic flavipucine, Girotra and carried out the synthesis of a structurally similar hydroxylactam (324).[180] The synth accomplished *via* condensation between 4-methyl-2-oxopentanal (325) and malonamidic ester (326) followed by conversion to the structurally similar hydro (324) (Scheme 106).



Scheme 106.

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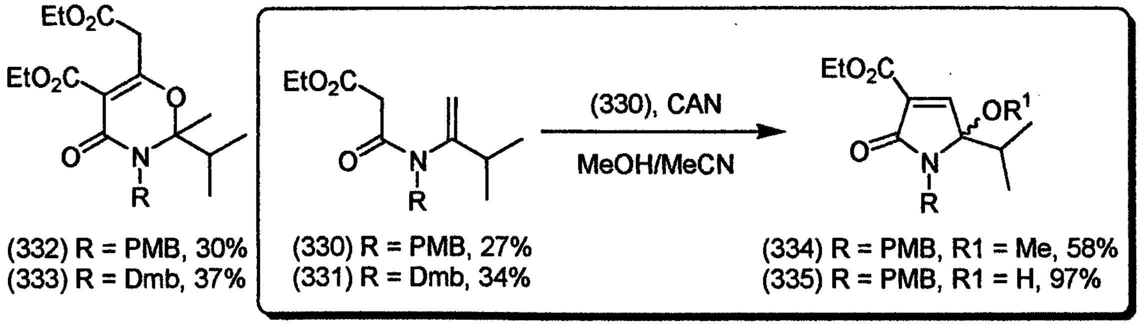
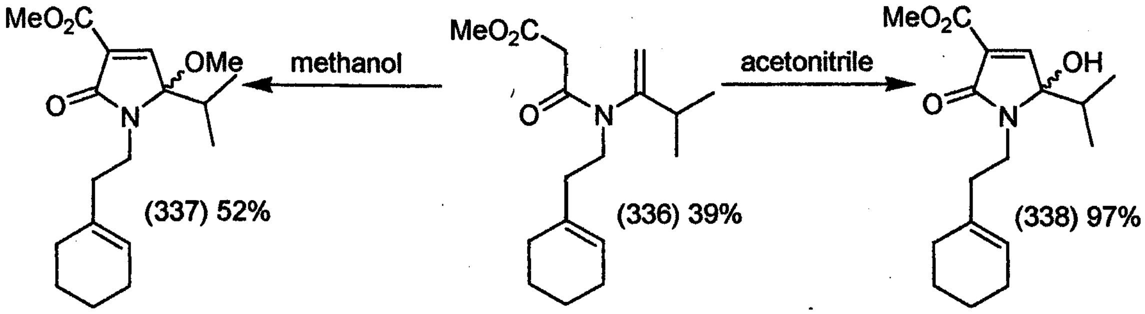
compiled for this deprotection process was the isolation of 2,4-dimethoxybenzaldehyde (the main by-product of this CAN deprotections).



Scheme 107.

We also attempted to mediate an intramolecular trapping of the postulated cationic intermediate produced in the cyclisation step *via* a tethered alkene (336). However, on reaction only (337) and (338) were isolated where the cation was preferably trapped intermolecularly by either methanol or water (Scheme 108).

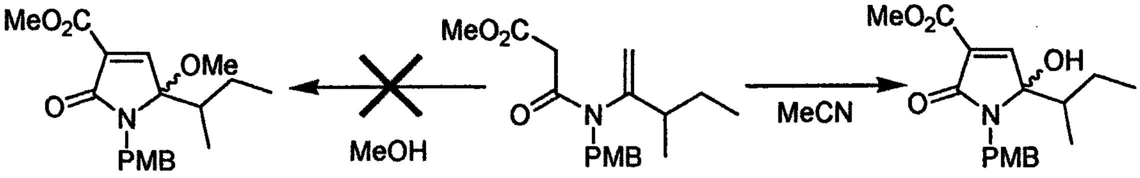


Conditions: 4 equivalents of CAN, solvent, RT, 20 mins

Scheme 108.

We next investigated the effect of the alkyl chain enamide substituent upon cyclisation. Thus, precursor (339), (which was prepared from 3-methylpentanone using the standard procedure) produced γ-lactams (340) as a mixture of diastereomers in 84% yield (Scheme

109). However, attempts to prepare the methoxylactam (341) *via* CAN cyclisation of (339) in methanol proved impossible. Reaction at both room temperature and reflux failed, with quantitative recovery of the starting material in both cases.



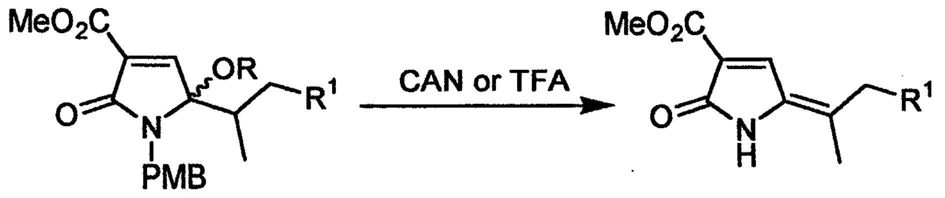
(341) (339) 41% (340) 84%

Conditions: 4 equivalents of CAN, solvent, RT, 20 mins

Scheme 109.

4.3.3 Deprotection of γ-Lactams

At this stage we had achieved our goal of producing protected methoxylactams (317) and hydroxylactams (323) and (340) that represent the heterocyclic ring portions of PI-091 (309), L-755,807 (129) and quinolactacin C (315) respectively. For our next step we hoped to successfully remove the PMB protecting group from these γ-lactams using some of the methods employed in the previous chapters. Oxidative removal of the PMB group from methoxylactam (317) with a further 4 equivalents of CAN in aqueous acetonitrile furnished the deprotected elimination product (342) in excellent yield. Whether the elimination step occurred before or after deprotection was uncertain. Unfortunately, the unwanted elimination product (342) was again produced when the hydroxylactam (323) was deprotected in the same manner. Varying the temperature (-78°C to 0°C) had no effect on the product outcome. Analogous results were also achieved when (317) and (323) were refluxed in trifluoroacetic acid (Scheme 110).

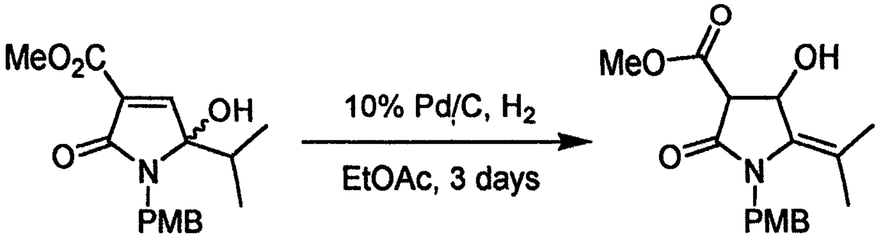


(317), R = Me, R^1 = H
(323), R = H, R^1 = H
(340), R = H, R^1 = Me

(342), R^1 = H, 86-95%
(343), R^1 = Me, 93-97%

Scheme 110.

Subsequent reaction of the quinolactacin C template (340) using both the CAN and TFA techniques also afforded the conjugate diene (343) in a 1:1 ratio of *cis:trans* isomers (Scheme 110). An interesting result was also obtained when we attempted to deprotect hydroxylactam (323) using standard hydrogenation conditions (Scheme 111). While the removal of the PMB group failed, the starting material was not re-isolated, instead the Michael addition product (344) was obtained in 97% yield. It is not clear whether the addition of the hydroxyl group to the 1,4-enone occurs inter- or intra-molecularly.

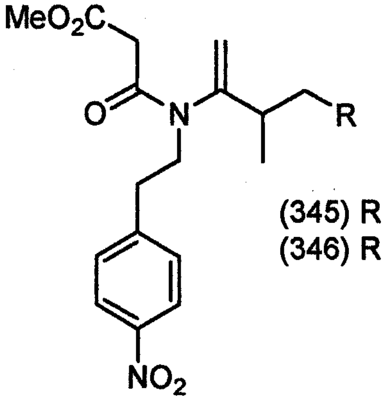


(323)

(344), 97%

Scheme 111.

As attempts to deprotect the hydroxy and methoxy lactams under neutral (hydrogenation) and acidic (TFA) conditions led to elimination of H_2O and methanol respectively, we thought that it might be possible to deprotect these compounds under basic conditions. As a consequence, we examined the *p*-nitrophenylethyl protecting group (fig. 27). It was hoped that treatment with a strong base (i.e. NaH) would facilitate deprotonation at the benzylic position followed by rapid elimination to the amide anion. This protecting group has been reported before for the protection of pyrole and subsequent deprotection was carried out using DBU.[181] However, when we tried to cyclise these compounds with CAN under the normal conditions we found that no reaction took place and the starting material was recovered quantitatively. Re-examination of this reaction at reflux in both acetonitrile and methanol lead to production of unidentifiable polymeric compounds that were insoluble in common nmr solvents. The reason why the cyclisation procedure failed for this class of compounds is unclear.

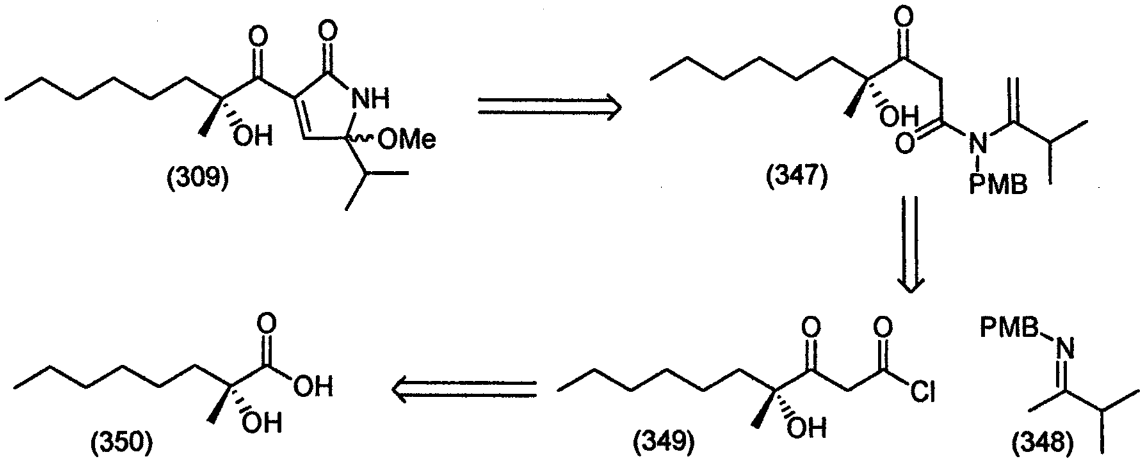


(345) R = H, 42%
(346) R = CH_3, 44%

Figure 27.

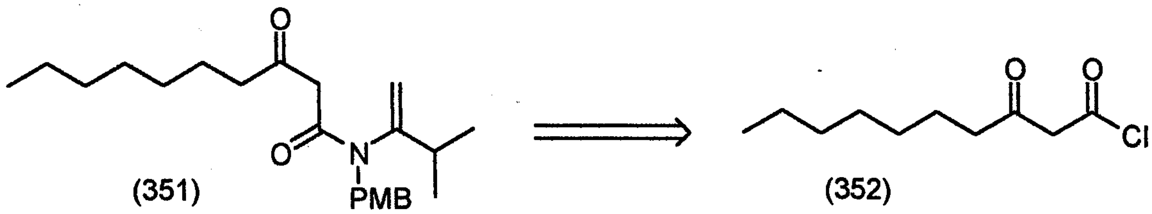
4.3.4 Introducing Diversity in the Side Chain

As an approach towards the synthesis of PI-091 we decided that it may be possible to include the side chain in the initial cyclisation step (i.e. replace the ester with a ketonic side chain). (Scheme 112). Retrosynthetic analysis of PI-091 shows that we could disconnect back to the potential cyclisation precursor (347), further disconnections brings us back to the recognisable imine (348). Disconnection of side chain (349) gives the α-hydroxycarboxylic acid side chain fragment (350), the synthesis of which has been already been published by Kusumi and Yubuchi *via* treatment of 2-octanone with tribromomethane and potassium hydroxide in water.[182]



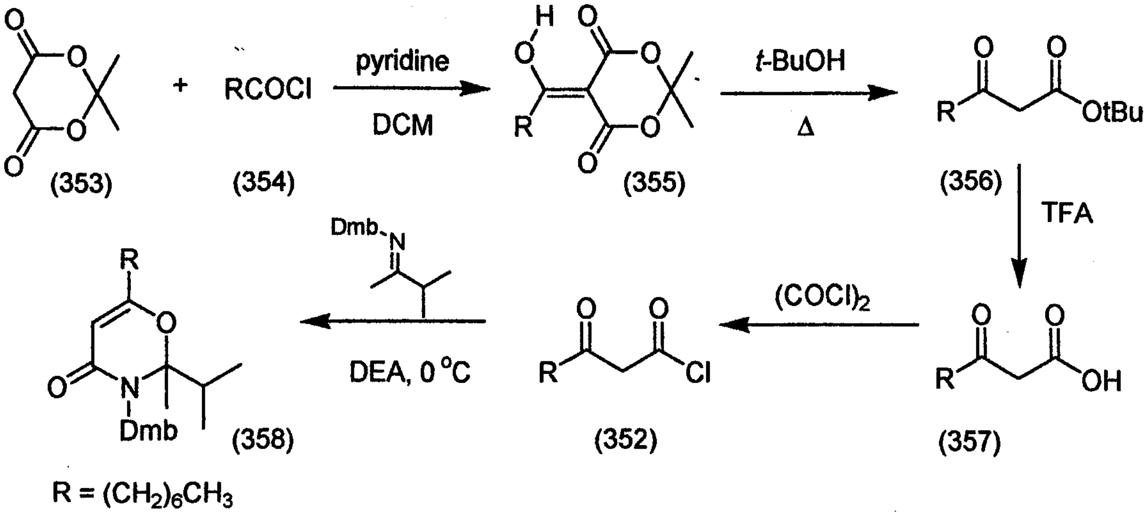
Scheme 112.

Before setting out to synthesise side chain (349), followed by precursor (347) we thought it prudent to carry out the synthesis of a model precursor (351) in order to investigate whether a ketone of this type could firstly be prepared and secondly would undergo cyclisation under our standard conditions (Scheme. 113).



Scheme 113.

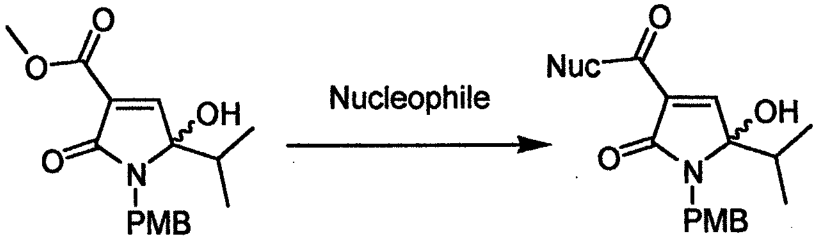
The synthesis of side chain (352) was carried out by the use of standard chemistry. Acylation of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (353) with octanoyl chloride (354) gave the corresponding acyl Meldrum's acid (355), which readily under goes alcoholysis in refluxing *t*-butanol to give the β-keto ester (356).[183] Subsequent, removal of the *t*-butyl group with TFA gave the corresponding carboxylic acid (357),[184] which promptly was chlorinated with oxalyl chloride[185] and used directly for the next step. Unfortunately, acylation of 2,4-dimethoxybenzyl protected imine with (352) using our standard conditions exclusively afforded the 1,3-oxazin-4-one (358) in an overall yield of 59% (Scheme 114). Due to this result of none of the desired cyclisation precursor (351) was detected and the problems we encountered trying to successfully repeat Kusumi and Yubuchi's synthesis of side chain fragment (350) (Scheme 112) we decided not investigate this proposed pathway any further.



Scheme 114.

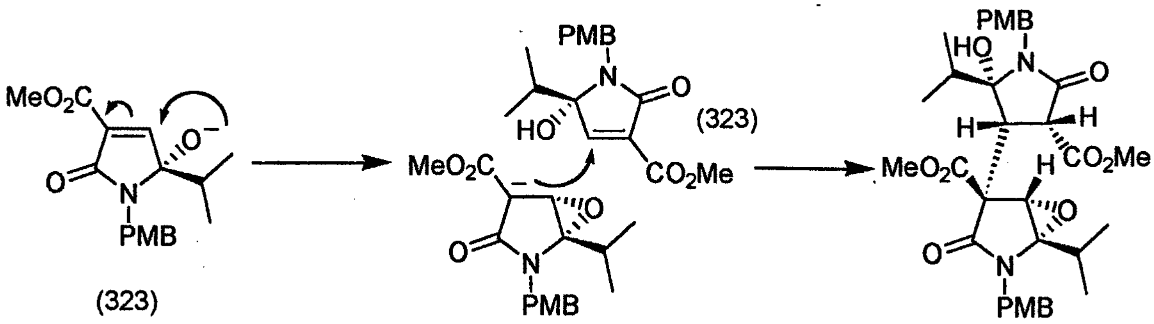
4.3.5 Alternative Approaches to Introducing a Side-Chain for PI-091

Another approach towards the synthesis of the side chain of PI-091 was to investigate whether it was possible to insert the side chain functionality onto the ester portion of (323) *via* a nucleophilic substitution (Scheme 115).



Scheme 115.

Therefore, as a model reaction we decided to carry out this procedure using methyl lithium as the nucleophile. Hence, hydroxylactam (323) was treated with an excess of methyl lithium at -78°C for 1 hour and allowed to warm to room temperature, and upon work-up the unusual dimer (359) was isolated as a single diastereomer in 37% yield (Scheme 116). The tentatively assigned stereochemistry (shown in Scheme 116) was based on the following argument, initial deprotonation of the hydroxylactam (323) by MeLi was followed by an intramolecular Michael addition on the opposite side to the *iso*-propyl group to give anion (360). This anion can in turn perform an intermolecular Michael addition onto the enone portion of another molecule of (323) (on the opposite side of the *iso*-propyl group) to give (359). This reaction was repeated and quenched at temperatures ranging from -78°C to room temperature with no change in the product outcome, hence we decided not to investigate this method any further.



(323)

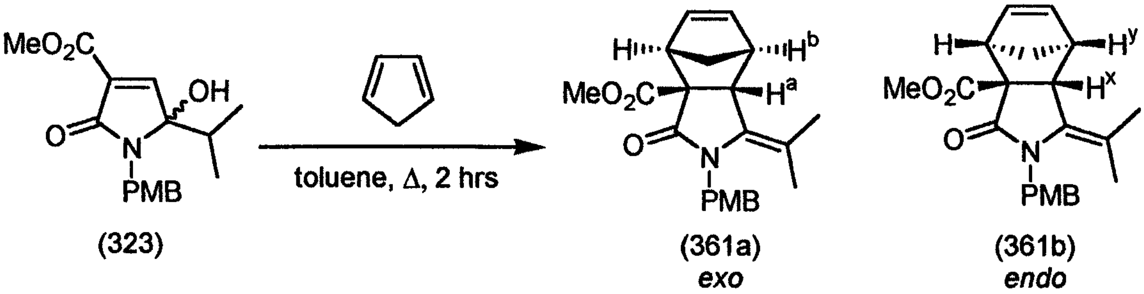
(360)

(359)

Scheme 116.

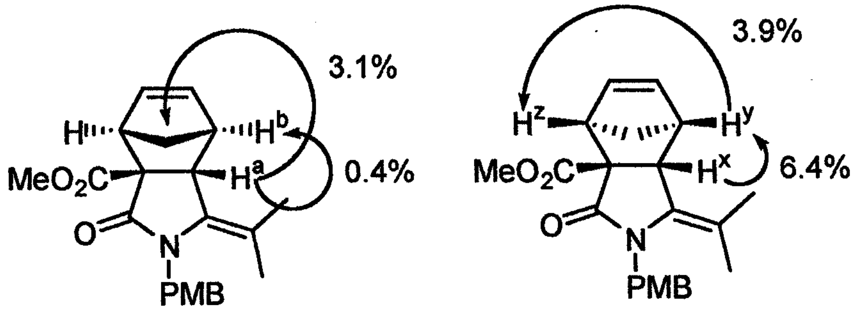
4.3.6 Other Reactivity of Hydroxylactam (323)

In order to further study the reactions of the hydroxylactam (323) we decided investigate whether its enone portion would act as a classic dienophile in a Diels-Alder reaction. Hence, reaction of (323) with 2 equivalents of cyclopentadiene in refluxing toluene for two hours gave the Diels-Alder *exo* (361a) and *endo* (361b) products in a 1:1 ratio (80% overall yield) (Scheme 117).



Scheme 117.

The structure of the isomers (361a-b) were elucidated firstly by proton nmr and then using n.O.e evidence. The nmr for *exo* product (361a) showed no ${}^3J$ coupling between the protons labeled H^a and H^b, subsequent modeling of this structure showed that the angle between these adjacent protons approaches 90°, hence, according to the Karplus equation the coupling constant (${}^3J$) approaches zero.[137] However, by the same design, modeling of *endo* product (361b) showed that the angle between the protons H^x and H^y approaches 30°, which should have a significant ${}^3J$ coupling according to Karplus. The nmr evidence for (361b) supported this hypothesis with a ${}^3J$ coupling constant of 3.5 Hz between the protons H^x and H^y. The n.O.e evidence compiled for these compounds also supports the above hypothesis, with large n.O.e between protons H^x and H^y and a small n.O.e between protons H^a and H^b. The percentage enhancements shown (fig. 28) are large enough to infer with a reasonable degree of accuracy that (361a) and (361b) are the *exo* and *endo* products respectively.



(361a)
exo

(361b)
endo

Figure 28. n.O.e evidence for *exo* (361a) and *endo* (361b) products

4.4 Conclusion

In this chapter we have shown that β-amido esters undergo a highly efficient room temperature *5-endo-trig* radical cyclisations mediated by ceric ammonium nitrate to afford functionalised γ-lactams. The use of 4 equivalents of CAN at room temperature in methanol was found to give the highest yields for these reactions and we have postulated that this can be explained by the two radical and oxidation sequences required in the mechanism (Scheme 94). Also, during these studies we discovered that the solvent (MeOH or MeCN) was required to trap the out the final product and that the use of traditional radical traps such as diphenyl selenide and diphenyl sulphide were ineffective. The fact that these CAN mediated reactions were restricted to a solvent that participated in the production of the final product limits the reaction considerably and due to the methoxy trapped product being quite stable, a secondary step was required for its removal. Whereas a variety of precursors could be efficiently cyclised using our copper(I)-amine chemistry, reactions using CAN were less predictable and proved to be very sensitive towards the nature of the substrate. An example of this was the cyclisation of the precursors derived from β-tetralone for both the copper(I) and CAN methods. The copper(I)-amine mediated cyclisation of precursors (169) and (230) gave 4-*exo-trig* (172) and 5-*endo-trig* (234) products respectively, depending on the ligand used (sections 3.2.4 and 3.3.2 respectively), whereas cyclisation of precursor (304) did not proceed and competing oxidation reaction proceeded to yield (308). Trapping out of the final products with the solvent did become particularly useful in the synthesis of the heterocyclic ring portions of natural products, L-755,807 (129), PI-091 (309) and quinolactacin C (315), especially when we discovered that precursor (316) cyclised in both methanol and acetonitrile to furnish both methoxylactam (317) and hydroxylactam (323) respectively. The CAN method of producing these compounds had distinct advantages over the copper(I)-amine based efforts. The copper(I) method required refluxing the precursor (139) in toluene (section 2.3) and trapping out of the intermediate acyliminium ion with methanol, which was disfavoured over the formation of the diene (140) under these conditions, thus furnishing the methoxylactam (165) in low yield (105) (section 3.2.3). Whereas the CAN promoted version of this reaction gave excellent yields of both the hydroxy- and methoxy-lactams at room temperature for a wide variety of precursors.

The removal of the *p*-methoxybenzyl protecting group from these methoxy- and hydroxy-lactams was carried out successfully, however elimination of the methoxy- and hydroxy-groups also resulted under these conditions. Further studies into a more suitable protecting strategy will be required. Also, the conjugated dienes resulting from these deprotections reactions have been sent for biological testing and identified as potential lead antibiotic compounds (details not reported in this thesis). To further build on this work, potential follow up studies may include investigation into the use of a co-oxidant with CAN in order decrease the amount of equivalents required for cyclisation and also the use of alternative cerium(IV) reagents such as $Ce(OTf)_4$ and $Ce(OMs)_3$ which have shown to be more soluble in organic solvents than CAN could be studied.[109]

CHAPTER 5: Experimental

Experimental Notes

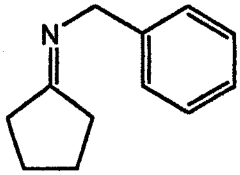
Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Accurate Mass determinations were performed either on a Kratos MS80 spectrometer or a Micromass Autospec spectrometer at the University of Warwick. Only molecular ions (M^+ or MH^+) and major peaks are reported and the intensities of these peaks are quoted as a percentage of the base peak. Microanalysis was recorded on a Leeman Labs Inc. CE440 Elemental Analyser. Infra-red spectra were recorded in a solution cell, as KBr discs or neat, as stated in the text on a Perkin-Elmer 1720X Fourier transform spectrometer, with only selected absorbances (ν_{max}) being reported. ^{1}H N.M.R. spectra were recorded at either 250 MHz, 300 MHz, 400 MHz or 500 MHz on a Bruker ACF250, Bruker DPX300, Bruker ACP400, Bruker DPX400 or Bruker DPX500 instrument respectively. ^{13}C N.M.R. spectra were recorded at 62.9 Mhz, 75 MHz, 100.6 MHz or 128.5MHz. Chemical shifts (δ) are quoted in parts per million (ppm) with residual solvent as an internal standard. Coupling constants (J) are quoted in Hertz (Hz). Chemicals used in the experimental were obtained from either Lancaster or Sigma-Aldrich at the highest grade available. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when needed, by literature methods.[186] Flash Chromatography was carried out on silica gel (Merck Kieselgel $60F_{254}$, 230-400 mesh). TLC was carried out using aluminium backed plates pre-coated with silica (0.2mm, $60F_{254}$). The TLC plates were developed using one or more of the following agents: U.V. fluorescence (254nm), potassium permanganate or phosphomolybdic acid. All reactions were conducted under nitrogen unless otherwise stated.

5.1 Experimental for Chapter 2

5.1.1 General procedure for the preparation of substituted imines.[151]

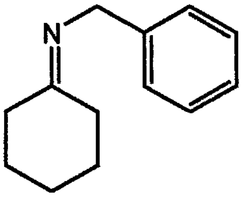
A solution of ketone (30 mmol) and the appropriate benzylamine (30 mmol) in toluene (20 ml) was stirred under reflux in a Dean Stark apparatus for 4-8 hrs. The solvent was removed *in vacuo* to give the crude compounds that were either used crude, purified by distillation or by column chromatography. The imines that were successfully purified have been reported below. In some cases a catalytic amount of tosic acid or $TiCl_3$ was added in order to drive the reaction to completion.[151]

Benzyl-cyclopentylidene-amine (362)



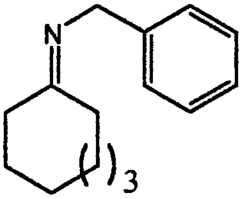
Cyclopentanone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (362): yield (82%); yellow oil; IR ($CHCl_3$, cm^{-1}) 1676, 1617; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32-7.22 (5H, m, Ar-H), 4.42 (2H, s, NCH$_2$), 2.40, (2H, t, J = 6.6 Hz, CH$_2$), 2.27 (2H, t, J = 6.6 Hz, CH$_2$), 1.88-1.70 (4H, m, CH$_2$ x 2); ^{13}C (75 MHz, $CDCl_3$) δ 181.8 (s), 140.7 (s), 128.9 (d x 2), 128.8 (d x 2), 127.4 (d), 58.1 (t), 38.7 (t), 29.7 (t), 25.4 (t), 24.7 (t); EI-MS *m/z* 173 (M$^+$ 13), 144 (26), 91 (100); Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.01; H, 8.70; N, 7.95.

Benzyl-cyclohexylidene-amine (102)



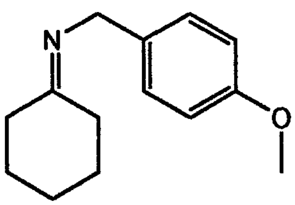
Cyclohexanone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (102): yield (91%); yellow oil; IR ($CHCl_3$, cm^{-1}) 1657, 1603; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31-7.29 (5H, m, Ar-H), 4.53 (2H, s, NCH$_2$), 2.36 (4H, m, CH$_2$ x 2), 1.72 (2H, m, CH$_2$), 1.64 (4H, m, CH$_2$ x 2); ^{13}C (75 MHz, $CDCl_3$) δ 174.7 (s), 140.9 (s), 129.4 (d x 2), 128.8 (d x 2), 127.7 (d), 54.5 (t), 40.7 (t), 29.6 (t), 29.0 (t), 27.4 (t), 26.4 (t); CI-MS *m/z* 188 (MH^+ 75), 107 (80), 91 (100); Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.10; H, 8.88; N, 7.55.

Benzyl-cyclooctylidene-amine (363)



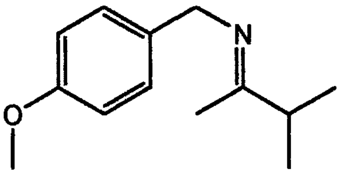
Cyclooctanone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (363): yield (68%); yellow oil; IR (neat, m^{-1}) 1642, 1603; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.19 (5H, m, Ar-H), 4.53 (2H, s, NCH$_2$), 2.42-1.37 (14H, m, CH$_2$ x 7); ^{13}C (75 MHz, $CDCl_3$) δ 177.9 (s), 141.1 (s), 128.7 (d x 2), 128.2 (d x 2), 126.8 (d), 54.8 (t), 42.3 (t), 40.8 (t), 30.4 (t), 27.8 (t), 27.2 (t), 26.0 (t), 25.8 (t); EI-MS *m/z* 215 (M^+, 18), 187 (21), 91 (100); HRMS Calcd for $C_{15}H_{21}N$ 215.1674, found 215.1672.

4-Methoxy-*N*-benzyl-cyclohexylimine (364)



Cyclohexanone and *p*-methoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (364): yield (90%); yellow oil; IR (neat, cm^{-1}) 1661, 736; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, C$\underline{H}$CHCOCH$_3$), 6.88 (2H, d, *J* = 8.7 Hz, C$\underline{H}$=COCH$_3$), 4.50 (2H, s, NC$\underline{H}_2$), 3.81 (3H, s, OC$\underline{H}_3$), 2.40-2.36 (4H, m, C$\underline{H}_2$ x 2), 2.05-2.00 (2H, m, C$\underline{H}_2$), 1.70-1.67 (4H, m, C$\underline{H}_2$ x 2); ^{13}C (75 MHz, CDCl$_3$) δ 174.1 (s), 158.7 (s), 133.2 (s), 129.6 (d x 2), 114.2 (d x 2), 56.3 (q), 53.5 (t), 40.5 (t), 29.1 (t), 27.8 (t), 27.4 (t), 26.5 (t); EI-MS *m/z* 217 (M$^+$, 13), 136 (17), 121 (100); HRMS Calcd for $C_{17}H_{17}N$ 217.1465, found 217.1466.

(1,2-Dimethyl-propylidene)-(4-methoxy-benzyl)-amine (365)



3-methyl-2-butanone and *p*-methoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (365): yield (97%); yellow oil; IR (neat, cm^{-1}) 1643, 1607; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.22 (1H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.85 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.40 (2H, s, NC$\underline{H}_2$), 3.77 (3H, s, OC$\underline{H}_3$), 2.55 (1H, sp, *J* = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.83 (3H, s, OC$\underline{H}_3$), 1.10 (6H, d, *J* = 7.0 Hz, CH(C$\underline{H}_3$)$_2$); ^{13}C (75 MHz, CDCl$_3$) δ 175.4 (s), 158.9 (s), 133.3 (s), 128.9 (d x 2), 114.2 (d x 2), 55.3 (q), 54.4 (t), 40.6 (t), 20.3 (q x 2), 15.3 (q); EI-MS *m/z* 205 (M^+, 50), 136 (37), 121 (100), 78 (40); HRMS Calcd for $C_{13}H_{19}NO$ 205.1468, found 205.1466.

5.1.2 General procedure for the preparation of trichloroacetamide cyclisation precursors

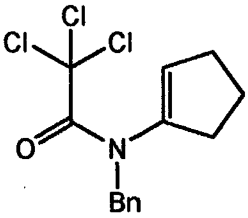
Method A:[114]

The appropriate imine (8 mmol) was dissolved in dry toluene (4 ml) and added dropwise to a stirred ice-cold solution of trichloroacetyl chloride (1.1 eq, 8.8 mmol) in dry toluene (24 ml) under N_2. After stirring for 1hr at 20°C, the mixture was cooled to 0°C and triethylamine (3.0 eq, 24 mmol) in dry toluene (4 ml) was added slowly. The stirring was continued for a further 2 hrs at room temperature and the resulting mixture was then added to a solution of saturated aqueous Na_2CO_3. After stirring for 3 hrs at 20°C, the mixture was extracted with ether (3 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl actetate (9:1).

Method B:

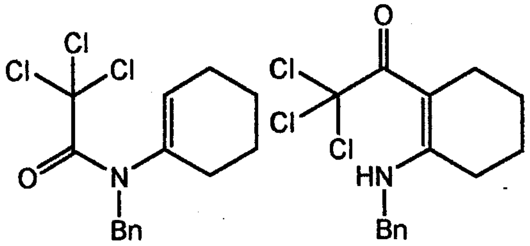
The appropriate imine (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. Trichloroacetyl chloride (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was then stirred for 2hrs at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (9:1).

N-Benzyl-2,2,2-trichloro-N-cyclopent-1-enyl-acetamide (104)



Imine (362) was reacted under the conditions described in the general procedure 5.1.2 (Method A) to give the following compound (104): yield (51%); yellow oil; IR (neat, cm^{-1}) 1673, 1617, 1577; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.26 (5H, m, Ar-H), 5.63 (1H, br, C<u>H</u>=C), 4.71 (2H, s, C<u>H</u>$_2$N), 2.43 (2H, m, C<u>H</u>$_2$), 2.29 (2H, m, C<u>H</u>$_2$), 1.89 (2H, m, C<u>H</u>$_2$); ^{13}C (75 MHz; $CDCl_3$) δ 161.3 (s), 140.6 (s), 136.5 (s), 133.3 (d, br), 128.8 (d x 2), 128.6 (d x 2), 128.1 (d), 90.3 (s), 53.4 (t), 30.6 (t), 29.9 (t), 22.4 (t); EI-MS *m/z* 317 (M^+, 15), 282 (15), 247 (10), 216 (30), 91 (100); HRMS Calcd for $C_{14}H_{14}Cl_3NO$ 317.0141, found 317.0144.

N-Benzyl-2,2,2-trichloro-N-cyclohex-1-enyl-acetamide (97) and 1-(2-Benzylamino-cyclohex-1-enyl)-2,2,2-trichloro-ethanone (103)

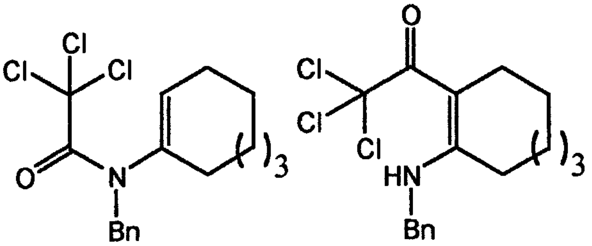


Imine (102) was reacted under the conditions described in the general procedure 5.1.2 to give the following compound (97): yield (Method A 59%); (Method B 81%); yellow oil; IR (neat, cm^{-1}) 1677, 1650, 1569; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (5H, m, Ar-H), 5.57 (1H, br, C<u>H</u>=C), 5.05 (1H, br, C<u>H</u>HN), 4.20 (1H, br, CH<u>H</u>N), 2.20 (2H, m, C<u>H</u>$_2$), 2.00 (2H, m, C<u>H</u>$_2$), 1.68 (2H, m, C<u>H</u>$_2$), 1.58 (2H, m, C<u>H</u>$_2$); ^{13}C (75 MHz; $CDCl_3$)

δ 160.8 (s), 136.1 (s), 131.5 (d, br), 131.1 (d), 128.8 (d x 2), 128.4 (d x 2), 127.7 (d), 93.2 (s), 53.3 (t), 27.6 (t), 24.7 (t), 22.3 (t), 21.1 (t); EI-MS *m/z* 331 (M^+, 10), 296 (65), 261 (28), 226 (27), 125 (50), 91 (100); Anal. Calcd for $C_{15}H_{16}Cl_3NO$: C, 54.16; H, 4.85; N, 4.21; Found: C, 54.18; H, 4.89; N, 4.19.

Data for (103): yield (Method A 20%); yellow crystals; mp 62°C, IR (neat, cm^{-1}) 2944, 1683, 1571; ^1H NMR (250 MHz, $CDCl_3$) δ 12.11 (1H, s, br, N$\underline{H}$), 7.28-7.24 (5H, m, Ar-H), 4.55 (2H, d, J = 6.0 Hz C$\underline{H_2}$N), 2.75 (2H, m, C$\underline{H_2}$), 2.00 (4H, m, C$\underline{H_2}$ x 2), 1.43 (4H, m, C$\underline{H_2}$); ^{13}C (75 MHz; $CDCl_3$) δ 178.8 (s), 173.6 (s), 136.2 (s), 129.4 (d x 2), 128.2 (d), 127.3 (d x 2), 99.6 (s), 47.9 (t), 44.1 (s), 32.6 (t), 28.3 (t), 28.0 (t), 26.1 (t); EI-MS *m/z* 331 (M^+, 55), 324 (36), 108 (27) 91 (100); HRMS Calcd for $C_{15}H_{16}Cl_3NO$ 331.0298, found 331.0297.

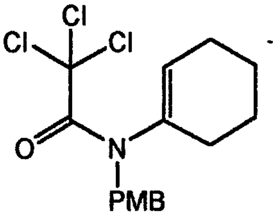
N-Benzyl-2,2,2-trichloro-N-cyclooct-1-enyl-acetamide (105) and 1-(2-Benzylamino-cyclooct-1-enyl)-2,2,2-trichloro-ethanone (366)



Imine (363) was reacted under the conditions described in the general procedure 5.1.2 to give the following compound (105): yield (Method A 52%); (Method B 87%); yellow oil; IR (neat, cm^{-1}) 1700, 1654, 1570; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.25 (5H, m, Ar-H), 5.58 (1H, br, C$\underline{H}$=C), 5.15 (1H, br, C$\underline{H}$HN), 4.27 (1H, br, CH$\underline{H}$N), 2.85 (2H, m, C$\underline{H_2}$), 1.91 (2H, m, C$\underline{H_2}$), 1.71-1.40 (8H, m, C$\underline{H_2}$ x 4); ^{13}C (75 MHz; $CDCl_3$) δ 160.3 (s), 149.1 (s), 135.3 (s), 129.7 (d), 129.0 (d x 2), 128.8 (d x 2), 128.0 (d), 93.1 (s), 54.4 (t), 29.2 (t), 28.7 (t), 26.9 (t), 26.4 (t), 26.2 (t), 24.4 (t); EI-MS *m/z* 360 (M^+, 90), 333 (60), 243 (90), 214 (82), 91 (100); HRMS Calcd for $C_{17}H_{20}Cl_3NO$ 360.0688, found 360.0684.

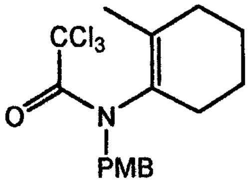
Data for (366): yield (Method A 15%); yellow crystals; IR (neat, cm^{-1}) 2927, 1689, 1560; ^1H NMR (250 MHz, $CDCl_3$) δ 12.09 (1H, s, br, N<u>H</u>), 7.35-7.25 (5H, m, Ar-H), 4.58 (2H, d, *J* = 6.1Hz C<u>H</u>$_2$N), 2.85 (2H, m, C<u>H</u>$_2$), 2.68 (2H, m, C<u>H</u>$_2$), 1.71 (4H, m, C<u>H</u>$_2$ x 2), 1.52 (4H, m, C<u>H</u>$_2$ x 2); ^{13}C (75 MHz; $CDCl_3$) δ 178.2 (s), 173.8 (s), 137.4 (s), 129.4 (d x 2), 128.3 (d), 127.5 (d x 2), 99.4 (s), 48.0 (t), 44.2 (s), 32.6 (t), 28.4 (t), 27.6 (t), 27.0 (t x 2), 26.6 (t); EI-MS *m/z* 359 (M^+, 100), 331 (60), 324 (45), 108 (70); HRMS Calcd for $C_{17}H_{20}Cl_3NO$ 359.0610, found 359.0627.

2,2,2-Trichloro-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-acetamide (106)



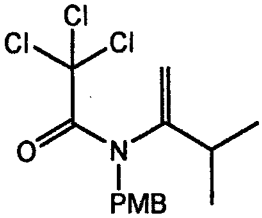
Imine (364) was reacted under the conditions described in the general procedure 5.1.2 (Method B) to give the following compound (106): yield (79%); yellow oil; IR (neat, cm^{-1}) 1680; ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.5 Hz, C<u>H</u>CHCOCH$_3$), 6.79 (2H, d, *J* = 8.5 Hz, C<u>H</u>=COCH$_3$), 5.50 (1H, m, C<u>H</u>=C), 5.00 (1H, br m, C<u>H</u>HN), 4.10 (1H, br m, CH<u>H</u>N), 3.75 (3H, s, OCH$_3$), 2.18 (2H, m, C<u>H</u>$_2$), 1.99 (2H, m, C<u>H</u>$_2$), 1.66 (2H, m, C<u>H</u>$_2$), 1.50 (2H, m, C<u>H</u>$_2$); ^{13}C (75 MHz; $CDCl_3$) δ 159.5 (s), 141.8 (s), 136.1 (s), 132.0 (d), 130.7 (d x 2), 128.7 (s), 114.0 (d x 2), 93.7 (s), 55.6 (q), 52.9 (t), 27.4 (t), 26.8 (t), 24.6 (t), 23.0 (t); EI-MS *m/z* 361 (M^+, 40), 121 (100); HRMS Calcd for $C_{16}H_{18}Cl_3NO_2$:361.0403, found 361.0406.

2,2,2-Trichloro-*N*-(4-methoxy-benzyl)-*N*-(2-methyl-cyclohex-1-enyl)-acetamide (107)



The imine derived from the condensation of *p*-methoxybenzylamine and 2-methylcyclohexanone was reacted under the conditions described in the general procedure 5.1.2 (Method B) to give the following compound (107): yield (74%); clear green oil; IR (neat, cm^{-1}) 1678, 1653; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20 (2H, m, C<u>H</u>CHCOCH$_3$), 6.75 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.12 (1H, br m, C<u>H</u>HN), 4.54 (1H, br s, CH<u>H</u>N), 3.71 (3H, s, OCH$_3$), 2.20 (1H, m, C<u>H</u>H), 1.96 (3H, m, CH<u>H</u>, C<u>H</u>$_2$), 1.51 (4H, m, C<u>H</u>$_2$), 0.96 (3H, m, C<u>H</u>$_3$); ^{13}C (75 MHz; $CDCl_3$) δ 159.7 (s), 135.5 (s), 132.2 (s), 131.3 (q x 2), 128.3 (s), 114.7 (d x 2), 93.4 (s), 55.5 (q), 54.7 (t), 53.9 (s), 31.1 (t), 30.1 (t), 23.4 (t), 22.5 (t), 20.8 (q); EI-MS *m/z* 375 (M$^+$, 80), 121 (100), 83 (45); HRMS Calcd for $C_{17}H_{20}Cl_3NO_2$: 375.0560, found 375.0557.

2,2,2-Trichloro-N-(1-isopropyl-vinyl)-N-(4-methoxy-benzyl)-acetamide (139)



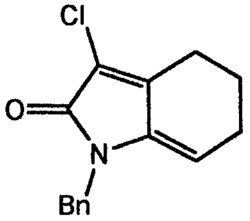
Imine (365) was reacted under the conditions described in the general procedure 5.1.2 (Method B) to give the following compound (139): yield (81%); clear yellow oil; IR (neat, cm^{-1}) 1674, 1454; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.82 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.08 (1H, s, C<u>H</u>H=C), 4.89 (2H, br s, C$\underline{H}_2$N), 4.84 (1H, s, CH$\underline{H}$=C), 3.77 (3H, s, OC$\underline{H}_3$), 2.47 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.03 (6H, d, J = 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$); ^{13}C (75 MHz; CDCl$_3$) δ 160.8 (s), 159.6 (s), 152.7 (s), 130.4 (d x 2), 128.0 (s), 114.5 (d x 2), 114.1 (br t), 93.8 (s), 55.6 (q), 54.5 (t), 32.6 (d), 21.8 (q x 2); EI-MS m/z 350 (M$^+$ 25), 280 (44), 246 (70), 121 (100); HRMS Calcd for $C_{15}H_{18}Cl_3NO$: 350.0481, found 350.0480.

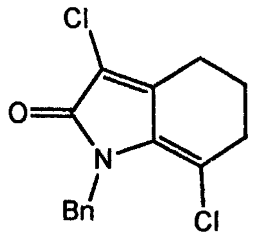
5.1.3 General procedure for the cyclisation of trichloroacetamides

Method A: Cu(I)Cl (29.7 mg, 0.3 mmol) was added to solution of the appropriate precursor (0.3mmol) and pentylimine ligand (42a) (53 mg, 0.3 mmol) in DCM (2.5 ml). The resulting solution was refluxed with stirring for 48 hrs under an inert atmosphere. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness *in vacuo* and purified by flash chromatography (1:2 petroleum ether : ethyl acetate).

Method B: Cu(I)Cl (29.7 mg, 0.3 mmol) was added to solution of the appropriate precursor (0.3 mmol) and TPA (123) (87 mg, 0.3mmol) in toulene (2.5 ml). The resulting solution was refluxed with stirring for 2 hrs under an inert atmosphere. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness *in vacuo* and purified by flash chromatography (9:1 petroleum ether : ethyl acetate).

1-Benzyl-3-chloro-1,4,5,6-tetrahydro-indol-2-one (98a) and 1-Benzyl-3,7-dichloro-1,4,5,6-tetrahydro-indol-2-one (111)



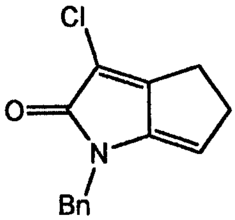


Precursor (97) was cyclised using the general procedure 5.1.3 (Method A) to furnish the following bicyclic systems. Data for (98a): yield (70%); clear yellow oil; IR (neat, cm^{-1}) 1658, 1621; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.23-7.14 (5H, m, Ar-H), 5.57 (1H, t, J = 4.7 Hz, CH=C), 4.78 (2H, s, CH$_2$N), 2.60 (2H, t, *J* = 6.1 Hz, CH$_2$), 2.27 (2H, q, *J* = 6.1 Hz, CH$_2$), 1.80 (2H, quint, *J* = 6.1 Hz, CH$_2$), ^{13}C (75 MHz; CDCl$_3$) δ 165.1 (s), 140.4 (s), 137.5 (s), 137.4 (s), 129.2 (d x 2), 128.2 (d), 127.5 (d x 2), 119.6 (s), 112.2 (d), 43.8 (t), 24.7 (t), 22.6 (t), 22.4 (t); EI-MS m/z 260 (M$^+$ 55), 231 (20), 182 (15), 91 (100); HRMS Calcd for $C_{15}H_{14}ClNO$: 260.0842, found 260.0839.

Data for (111): yield (7%); clear yellow oil; IR (neat, cm^{-1}) 1712, 1646; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19-7.14 (5H, m, Ar-H), 5.21 (1H, s, CH$_2$N), 2.60 (4H, m, CH$_2$ x 2), 1.96-1.86 (4H, m, CH$_2$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 165.6 (s), 141.7 (s), 137.8 (s), 132.3 (s); 129.0 (s), 128.1 (d x 2), 127.2 (d), 126.6 (d x 2), 119.6 (s), 118.9 (s), 44.9 (t), 34.9 (t), 23.1 (t), 22.0 (t); EI-MS m/z 293 (M$^+$, 18), 258 (20), 91 (100); HRMS Calcd for $C_{15}H_{13}Cl_2NO$: 293.0374, found 293.0369.

Precursor (97) was cyclised using the general procedure 5.1.3 method B, which exclusively furnished compound (111) in 89% yield. The spectral details matched those cited above.

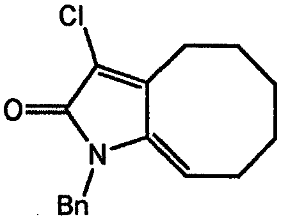
1-Benzyl-3-chloro-4,5-dihydro-1H-cyclopenta[b]pyrrol-2-one (112)



Precursor (104) was cyclised using the general procedure 5.1.3 to furnish the following bicyclic system (112): yield (Method A 61%), (Method B 83%); clear oil; IR (neat, cm$^-$

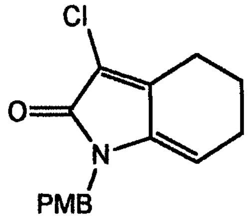
^{1}) 1707, 1650; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.10 (5H, m, Ar-H), 5.40 (1H, t, J = 2.5 Hz, CH=C); 4.79 (2H, s, CH_2N), 2.80 (2H, m, CH_2), 2.77 (2H, m, CH_2); ^{13}C (75 MHz; $CDCl_3$) δ 165.3 (s), 153.6, 143.4, 136.6, 129.0 (d x 2), 128.1 (d x 2), 127.4 (d), 114.8 (s), 101.2 (d), 45.7 (t), 35.0 (t), 23.6 (t); EI-MS m/z 245 (M^+ 12), 167 (19), 149 (62), 91 (100); HRMS Calcd for $C_{14}H_{12}ClNO$: 245.0607, found 245.0615; Anal. Calcd for $C_{14}H_{12}ClNO$: C, 67.99; H, 4.89; N, 5.65. Found C, 68.44; H, 4.92; N, 5.70.

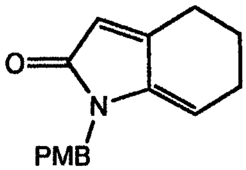
1-Benzyl-3-chloro-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (113)



Precursor (105) was cyclised using the general procedure 5.1.3 to furnish the following bicyclic system (113): yield (Method A 65%), (Method B 94%); clear yellow oil; IR (neat, cm^{-1}) 1667, 1619; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m, Ar-H), 5.55 (1H, t, *J* = 5.0 Hz, CH=C), 4.61 (2H, s, CH_2N), 2.63 (2H, t, *J* = 6.0 Hz, CH_2), 2.30 (4H, m, CH_2 x 2), 1.80 (4H, m CH_2 x 2), ^{13}C (75 MHz; $CDCl_3$) δ 166.1 (s), 140.3 (s), 138.0 (s), 137.4 (s), 129.3 (d x 2), 128.2 (d), 127.8 (d x 2), 119.1 (s), 112.6 (d), 44.2 (t), 25.8 (t), 24.7 (t), 23.1 (t), 22.2 (t), 21.5 (t); EI-MS m/z 287 (M^+ 25), 251 (56), 210 (46), 91 (100); HRMS Calcd for $C_{17}H_{18}ClNO$: 287.1077, found 287.1068.

3-Chloro-1-(4-methoxy-benzyl)-1,4,5,6-tetrahydro-indol-2-one (124) and 1-(4-Methoxy-benzyl)-1,4,5,6-tetrahydro-indol-2-one (125)

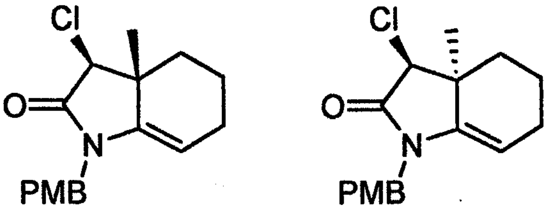




Precursor (106) was cyclised using the general procedure 5.1.3 (method B) to furnish the following bicyclic systems. Data for (124): yield (73%); clear yellow oil; IR (neat, cm^{-1}) 1657, 1613; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (2H, d, J = 8.6 Hz, CHCHCOCH$_3$), 6.75 (2H, d, J = 8.6 Hz, CH=COCH$_3$), 5.62 (1H, t, J = 4.6 Hz, CH=C), 4.74 (2H, s, CH$_2$N), 3.79 (3H, s, OCH$_3$), 2.61 (2H, t, J = 6.6 Hz, CH$_2$), 2.30 (2H, d, J = 5.7 Hz, CH$_2$), 1.80 (2H, quint, J = 6.2 Hz, CH$_2$), ^{13}C (75 MHz; CDCl$_3$) δ 165.1 (s), 159.3 (s), 140.3 (s), 137.4 (s), 129.6 (s), 129.0 (d x 2), 119.6 (s), 114.4 (d x 2), 112.2 (d), 55.6 (q), 43.3 (t), 24.7 (t), 22.9 (t), 22.6 (t); EI-MS m/z 289 (M$^+$ 40), 121 (100), 77 (20); HRMS Calcd for C$_{16}$H$_{16}$ClNO$_2$: 289.0870, found 289.0866.

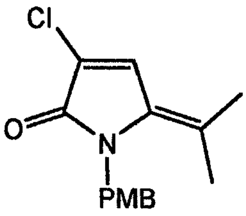
Data for (125): yield (14%); clear yellow oil; IR (neat, cm^{-1}) 1677, 1622; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10 (2H, d, J = 8.5 Hz, CHCHCOCH$_3$), 6.75 (2H, d, J = 8.5 Hz, CH=COCH$_3$), 5.73 (1H, br s, COCH=C), 5.45 (1H, t, J = 4.8 Hz, CH=C), 4.62 (2H, s, CH$_2$N), 3.70 (3H, s, OCH$_3$), 2.54 (2H, t, J = 5.7 Hz, CH$_2$), 2.19 (2H, d, J = 5.7 Hz, CH$_2$), 1.71 (2H, quint, J = 6.4 Hz, CH$_2$), ^{13}C (75 MHz; CDCl$_3$) δ 170.7 (s), 159.1 (s), 147.9 (s), 140.1 (s), 130.2 (s), 128.8 (d x 2), 115.9 (d), 114.3 (d x 2), 112.3 (d), 55.6 (q), 44.6 (t), 24.7 (t), 24.6 (t), 23.8 (t); EI-MS m/z 255 (M$^+$ 45), 121 (100), 84 (25), 49 (55); HRMS Calcd for C$_{16}$H$_{17}$NO$_2$: 255.1259, found 255.1262.

3-Chloro-1-(4-methoxy-benzyl)-3a-methyl-1,3,3a,4,5,6-hexahydro-indol-2-one (126)



Precursor (107) was cyclised using the general procedure 5.1.3 (Method B) to furnish the following bicyclic systems in a 6:1 mixture of *trans* (126a) : *cis* (126b) isomers. Data for isomers: yield (96%); clear oil; IR (neat, cm^{-1}) 1645, 1609; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 (2H, d, J = 8.7 Hz, $\mathrm{C\underline{H}CHCOCH_3}$), 6.74 (2H, d, J = 8.7 Hz, $\mathrm{C\underline{H}{=}COCH_3}$), 4.85 (1H, t, J = 3.8 Hz, $\mathrm{C\underline{H}{=}C}$), 4.69 (1H, d, J = 15.0 Hz, $\mathrm{C\underline{H}HN^{trans}}$), 4.55 (1H, d, J = 15.2 Hz, $\mathrm{C\underline{H}HN^{cis}}$), 4.45 (1H, d, J = 15.2 Hz, $\mathrm{CH\underline{H}N^{cis}}$), 4.28 (1H, d, J = 15.0 Hz, $\mathrm{CH\underline{H}N^{trans}}$), 4.22 (1H, s, $\mathrm{C\underline{H}Cl^{trans}}$), 4.00 (1H, s, $\mathrm{C\underline{H}Cl^{cis}}$), 3.68 (3H, s, $\mathrm{OC\underline{H}_3}$), 1.97 (2H, m, $\mathrm{C\underline{H}_2}$) 1.82 (1H, m, $\mathrm{C\underline{H}H}$), 1.65 (2H, m, $\mathrm{C\underline{H}_2}$), 1.45 (1H, m, $\mathrm{CH\underline{H}}$), 1.12 (3H, s, $\mathrm{CH_3^{cis}}$), 1.04 (3H, s, $\mathrm{CH_3^{trans}}$); ^{13}C for trans isomer (75 MHz; CDCl$_3$) δ 169.3 (s), 159.3 (s), 141.4 (s), 130.4 (d x 2), 128.9 (s), 114.4 (d x 2), 101.3 (d), 67.6 (d), 55.6 (q), 43.9 (t), 42.7 (s), 33.0 (t), 23.1 (t), 21.2 (q), 18.2 (t); ^{13}C for cis isomer (75 MHz; CDCl$_3$) δ 170.6 (s), 159.2 (s), 141.8 (s), 129.9 (d x 2), 128.2 (s), 114.3 (d x 2), 102.6 (d), 60.8 (d), 55.6 (q), 43.9 (t), 43.5 (s), 33.0 (t), 25.6 (q), 23.1 (t), 17.8 (t); EI-MS m/z 305 (M$^+$ 47), 269 (49), 121 (100); HRMS Calcd for $C_{17}H_{20}ClNO_2$: 305.1183, found 305.1177.

3-Chloro-5-isopropylidene-1-(4-methoxy-benzyl)-1,5-dihydro-pyrrol-2-one (140)

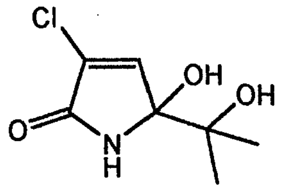


Precursor (139) was cyclised using the general procedure 5.1.3 to furnish the following lactam (140): yield (Method A 60%), (Method B 89%); brown solid; mp 45 °C; IR (neat, cm^{-1}) 1690, 1644, 938; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (1H, s, CH=C), 6.94 (2H, d, *J* = 8.9 Hz, C<u>H</u>CHCOCH$_3$), 6.76 (2H, d, *J* = 8.9 Hz, C<u>H</u>=COCH$_3$), 4.99 (2H, s, C<u>H$_2$</u>N), 3.70 (3H, s, OC<u>H$_3$</u>), 1.89 (3H, s, C<u>H$_3$</u>), 1.84 (3H, s, C<u>H$_3$</u>); ^{13}C (75 MHz; $CDCl_3$) δ 166.8 (s), 159.0 (s), 133.1 (s), 130.0 (s), 129.9 (d), 127.3 (d x 2), 125.3 (s), 124.9 (s), 114.5 (d x 2), 55.6 (q), 45.9 (t), 23.8 (q), 21.0 (q); EI-MS m/z 277 (M$^+$ 55), 247 (20), 121 (100); HRMS Calcd for $C_{15}H_{16}ClNO_2$: 277.0870, found 277.0868.

5.1.4 General method for the deprotection of *p*-methoxybenzylamides

Ceric ammonium nitrate (548 mg, 1 mmol) was added to a solution of the required cyclised compound (0.25 mmol) in 4 ml of 3:1 acetonitrile/H_2O and stirred for 1-2 hrs (followed by TLC). The resulting solution was dropped onto H_2O (25ml) and extracted with ethyl acetate (25ml x 3), dried with $MgSO_4$ and reduced to dryness *in vacuo.* Purification was carried out by flash chromatogtraphy (1:2 petroleum ether : ethyl acetate), to give the following deprotected product.

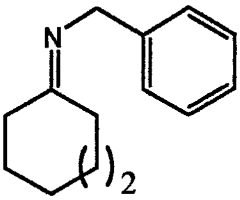
3-Chloro-5-hydroxy-5-(1-hydroxy-1-methyl-ethyl)-1,5-dihydro-pyrrol-2-one (141)



Compound (140) was deprotected according to the general procedure 5.1.4: yield (22%); brown solid; mp 50 °C IR (neat, cm^{-1}) 3342, 1683, 1493, 1312; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (1H, br s, N<u>H</u>), 6.84 (1H, s, C<u>H</u>=C), 4.48 (1H, br s, O<u>H</u>), 3.25 (1H, br s, O<u>H</u>), 1.33 (3H, s, C<u>H$_3$</u>), 1.19 (3H, s, C<u>H$_3$</u>); ^{13}C (100 MHz; $CDCl_3$) δ 167.1 (s), 141.6 (d), 130.6 (s), 91.2 (s), 74.4 (s), 25.1 (q), 23.7 (q); CI-MS m/z 192 (MH^+ 50), 174 (20), 158 (90), 124 (85), 98 (50), 32 (100); HRMS Calcd for $C_7H_{10}ClNO_3$: 192.0427, found 192.0425.

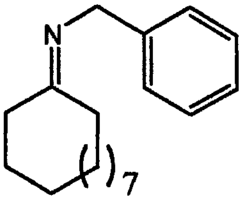
5.2 Experimental for Chapter 3

Benzyl-cycloheptylidene-amine (367)



Cycloheptanone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (367): yield (88%); yellow oil; IR (solution, cm^{-1}) 1656, 1620; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22-7.13 (5H, m, Ar-H), 4.41 (2H, s, NCH_2), 2.56 (2H, m, CH_2), 2.40 (2H, m, CH_2), 1.70-1.57 (8H, m, CH_2 x 4); ^{13}C (75 MHz, $CDCl_3$) δ 177.3 (s), 143.8 (s), 128.7 (d x 2), 128.2 (d x 2), 126.8 (d), 54.8 (t), 42.7 (t), 41.7 (t), 32.9 (t), 30.8 (t), 30.5 (t), 27.7 (t), 24.7 (t); EI-MS *m/z* 201 (M^+, 151), 173 (10), 91 (100); HRMS Calcd for $C_{14}H_{19}N$ 201.1518, found 201.1518.

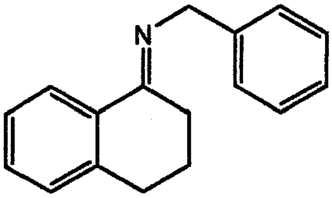
Benzyl-cyclododecylidene-amine (368)



Cyclododecalone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (368): yield (98%); yellow oil;

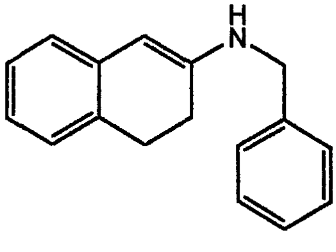
IR (neat, cm^{-1}) 1660, 1600; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26-7.17 (5H, m, Ar-H), 4.61 (2H, s, NCH$_2$), 2.48-2.37 (4H, m, CH$_2$ x 2), 1.82 (2H, m, CH$_2$), 1.70 (2H, m, CH$_2$), 1.68-1.38 (14H, m, CH$_2$ x 7); ^{13}C (75 MHz, $CDCl_3$) δ 173.9 (s), 143.6 (s), 129.2 (d x 2), 128.3 (d x 2), 126.7 (d), 56.2 (t), 34.7 (t), 30.6 (t), 26.0 (t), 25.2 (t), 25.1 (t), 24.8 (t), 24.6 (t), 24.0 (t), 23.6 (t), 23.4 (t), 22.9 (t); EI-MS *m/z* 271 (M$^+$, 10), 195 (80), 91 (100); HRMS Calcd for $C_{19}H_{29}N$ 271.2306, found 271.2307.

Benzyl-(3,4-dihydro-2H-naphthalen-1-ylidene)-amine (369)



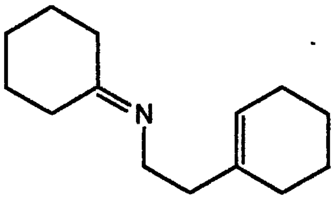
α-Tetralone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (369): yield (93%); brown oil; IR (neat, cm^{-1}) 1679, 730; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57-7.11 (9H, m, Ar-H), 4.81 (2H, s, NCH$_2$), 2.55 (2H, m, CH$_2$), 1.72 (2H, m, CH$_2$), 1.38 (2H, m, CH$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 164.9 (s), 140.6 (s), 137.5 (s), 137.0 (s), 130.9 (d), 129.5 (d), 129.2 (d x 2), 128.4 (d x 2), 127.9 (d), 125.9 (d), 125.6 (d), 52.2 (t), 31.7 (t), 31.0 (t), 28.0 (t); EI-MS *m/z* 235 (M$^+$, 19), 195 (62), 117 (31), 91 (100); HRMS Calcd for $C_{17}H_{17}N$ 235.1361, found 235.1365.

Benzyl-(3,4-dihydro-naphthalen-2-yl)-amine (370)



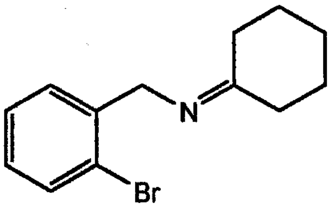
β-Tetralone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (370): yield (96%); yellow oil; IR (neat, cm^{-1}) 3410, 1629, 1600, 730; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.24 (5H, m, Ar-H), 7.16-7.08 (2H, s, Ar-H), 6.97-6.93 (2H, m, Ar-H), 5.40 (1H, s, C=CH), 4.31 (2H, s, NCH_2), 2.91 (2H, dd, J = 8.3, 7.5 Hz), 2.40 (2H, ddd, J = 8.3, 7.6, 6.4 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 146.5 (s), 139.3 (s), 137.8 (s), 131.5 (s), 129.0 (d), 128.3 (d), 127.8 (d), 127.3 (d), 127.0 (d), 125.8 (d), 123.0 (d), 93.7 (d), 48.3 (t), 29.5 (t), 25.1 (t); EI-MS *m/z* 235 (M^+, 100), 144 (57), 117 (95), 91 (95); Anal Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found C, 86.27; H, 7.42; N, 6.17.

(2-Cyclohex-1-enyl-ethyl)-cyclohexylidene-amine (371)



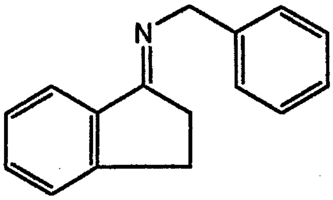
2-(1-cyclohexenyl)ethylamine and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (371): yield (82%); yellow oil; IR (neat, cm^{-1}) 1650, 1637; ^1H NMR (250 MHz, $CDCl_3$) δ 5.41 (1H, s, C=CH), 3.37 (4H, t, J = 7.5 Hz, CH_2 x 2), 2.72 (2H, t, J = 7.5 Hz, CH_2), 2.33-1.50 (16H, m, CH_2 x 8); ^{13}C (75 MHz, $CDCl_3$) δ 173.5 (s), 136.5 (s), 122.1 (d), 49.1 (t), 44.2 (t), 40.4 (t), 28.4 (t), 28.1 (t), 27.7 (t), 26.4 (t), 25.8 (t), 23.9 (t), 23.6 (t), 22.8; EI-MS *m/z* 205 (M^+, 19), 176 (26), 110 (92), 81(64), 67(68); Anal Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found C, 82.04; H, 10.99; N, 6.79.

(2-Bromo-benzyl)-cyclohexylidene-amine (372)



Cyclohexanone and *o*-bromobenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (372): yield (64%); yellow oil; IR (neat, cm^{-1}) 1711, 747; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50-6.87 (4H, m, Ar-H), 4.45 (2H, s, NCH$_2$), 2.40 (4H, m, CH$_2$ x 2), 1.67 (4H, m, CH$_2$ x 2), 1.00 (2H, m, CH$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 164.6 (s), 139.3 (s), 131.7 (d), 131.5 (d), 129.0 (d), 128.3 (d),123.0 (s), 48.3 (t), 29.5 (t), 29.0 (t), 26.4 (t) 25.1 (t x 2); EI-MS *m/z* 266 (M^+, 100), 178 (77), 106 (80), 85 (50); Anal Calcd for $C_{13}H_{16}BrN$: C, 58.66; H, 6.06; N, 5.26. Found C, 58.77; H, 5.91; N, 5.03.

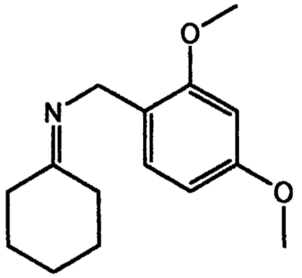
Benzyl-indan-1-ylidene-amine (373)



α-Indanone and benzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (373): yield (92%); yellow oil; IR (neat, cm^{-1}) 1653, 735; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46-7.10 (9H, m, Ar-H), 4.69 (2H, s, NCH$_2$), 3.07 (2H, dd, J = 6.7, 6.1 Hz, CH$_2$), 2.75 (2H, dd, J = 6.7, 6.1 Hz, CH$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 175.6 (s), 150.1 (s), 140.7 (s), 140.3 (s), 131.6 (d), 128.8 (d x 2), 128.0 (d x 2), 127.4 (d), 127.2 (d), 126.7 (d), 122.9 (d), 57.7 (t), 28.8 (t), 28.6 (t);

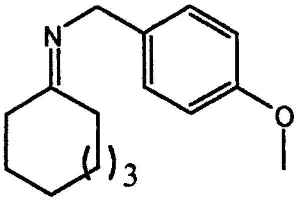
EI-MS *m/z* 221 (M^+, 100), 91 (96) 44 (44); Anal Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found C, 86.83; H, 6.88; N, 6.17.

2,4-Dimethoxy-*N*-benzyl-cyclohexylimine (374)



Cyclohexanone and 2,4-dimethoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (374): yield (79%); yellow oil; IR (neat, cm^{-1}) 1661, 735; ^1H NMR (250 MHz, $CDCl_3$) δ 7.20 (1H, d, J = 8.1 Hz, Ar-H), 6.47 (2H, d, J = 8.1 Hz, Ar-H), 6.45 (1H, s, C=CH), 4.48 (2H, s, NCH_2), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.40-2.35 (4H, m, CH_2 x 2), 2.10-1.95 (2H, m, CH_2), 1.67-1.65 (4H, m, CH_2 x 2); ^{13}C (75 MHz, $CDCl_3$) δ 174.1 (s), 159.9 (s), 158.3 (s), 129.7 (d), 121.6 (d), 104.3 (d), 98.7 (d), 55.6 (q), 55.1 (q), 48.5 (t), 40.5 (t), 29.0 (t), 27.9 (t), 27.7 (t), 26.5 (t); EI-MS *m/z* 247 (M^+, 10), 166 (25), 151 (100), 121 (30); HRMS Calcd for $C_{15}H_{21}NO_2$ 247.1577, found 247.1573.

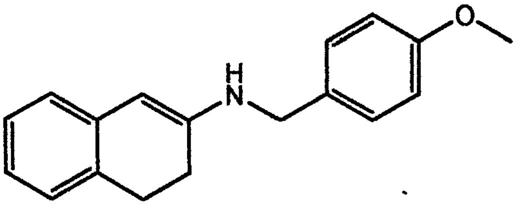
4-Methoxy-*N*-benzyl-cyclooctylimine (375)



Cyclooctanone and *p*-methoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (375): yield (87%);

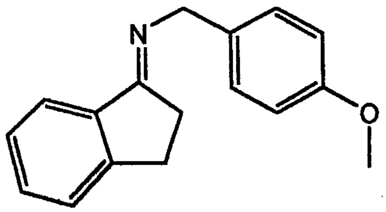
yellow oil; IR (neat, cm^{-1}) 1640, 1589, 1560; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.15 (2H, d, *J* = 8.6Hz, C<u>H</u>CHCOCH$_3$), 6.76 (2H, d, *J* = 8.6Hz, C<u>H</u>=COCH$_3$), 4.40 (2H, s, C<u>H$_2$</u>N), 3.70 (3H, s, OC<u>H$_3$</u>), 2.32 (4H, m, C<u>H$_2$</u>C=N), 1.70 (4H, m, CH$_2$ x 2), 1.42 (6H, m, CH$_2$ x 3); ^{13}C (75 MHz, CDCl$_3$) δ 177.4 (s), 158.2 (s), 133.4 (s), 129.4 (d x 2), 114.7 (d x 2), 55.4 (q), 54.0 (t), 40.9 (t), 40.8 (t), 30.4 (t), 27.6 (t), 27.2 (t), 26.0 (t), 25.7 (t); EI-MS *m/z* 245 (M$^+$, 30), 136 (25), 121 (100), 77 (25); HRMS Calcd for C$_{16}$H$_{23}$NO 246.1857, found 246.1857.

(3,4-Dihydro-naphthalen-2-yl)-(4-methoxy-benzyl)-amine (376)



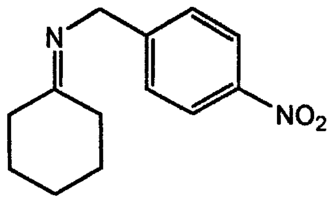
β-Tetralone and *p*-methoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (376): yield (92%); orange oil; IR (neat, cm^{-1}) 3391, 1658, 1611, 737; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.25 (2H, d, *J* = 8.5Hz, C<u>H</u>CHCOCH$_3$), 7.07 (4H, m, Ar-H), 6.95 (2H, d, *J* = 8.5Hz, C<u>H</u>=COCH$_3$), 5.36 (1H, s, C<u>H</u>=CH$_2$), 4.21 (2H, s, C<u>H$_2$</u>N), 3.83 (3H, s, OCH$_3$), 3.40 (1H, br, N<u>H</u>), 2.87 (2H, dd, *J* = 8.6, 7.3 Hz, C<u>H$_2$</u>), 2.33 (2H, ddd, *J* = 8.6, 7.3, 6.2 Hz); ^{13}C (75 MHz, CDCl$_3$) δ 160 (s), 147.3 (s), 137.9 (s), 134.7 (s), 134.3 (s), 128.1 (d x 2), 127.8 (d),127.6 (d), 126.1 (d), 125.6 (d), 114.1 (d x 2), 99.8 (d), 56.0 (q), 50.8 (t), 38.2 (t), 26.7 (t); EI-MS *m/z* 265 (M$^+$, 45), 136 (87), 121 (100), 106 (40), 77 (30); HRMS Calcd for C$_{18}$H$_{19}$NO 265.1466, found 265.1464.

Indan-1-ylidene-(4-methoxy-benzyl)-amine (377)



α-Indanone and *p*-methoxybenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (377): yield (91%); brown oil; IR (neat, cm^{-1}) 1698, 1610, 703; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (4H, m, Ar-H), 7.38 (2 H, d, *J* = 8.7Hz, C<u>H</u>CHCOCH$_3$) 6.95 (2H, d, *J* = 8.7Hz, C<u>H</u>=COCH$_3$), 4.66 (2H, s, C<u>H$_2$</u>N), 3.81 (3H, s, OC<u>H$_3$</u>), 3.07 (2H, m, C<u>H$_2$</u>C=N), 2.76 (2H, m, C<u>H$_2$</u>CH$_2$C=N); ^{13}C (75 MHz, $CDCl_3$) δ 175 (s), 158.5 (s), 152.1 (s), 141.9 (s), 134.0 (s), 131.6 (d), 129.3 (d x 2), 126.7 (d),125.8 (d), 122.9 (d), 114.3 (d x 2), 57.1 (t), 55.7 (q), 28.8 (t), 28.6 (t); EI-MS *m/z* 251 (M^+, 46), 121 (100), 115 (40), 77 (36); HRMS Calcd for $C_{17}H_{17}NO$ 252.1388, found 252.1387.

Cyclohexylidene-(4-nitro-benzyl)-amine (378)

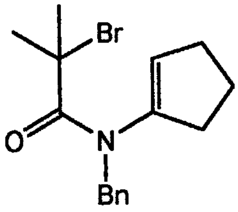


Cyclohexanone and *p*-nitrobenzylamine were reacted under the conditions described in the general procedure 5.1.1 to give the required compound (378): yield (90%); orange oil; IR ($CHCl_3$, cm^{-1}) 1655, 1600, 1521, 1345; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 8.5Hz, C<u>H</u>=CNO$_2$), 7.43 (2H, d, *J* = 8.5Hz, C<u>H</u>CHCNO$_2$), 4.53 (2H, s, C<u>H$_2$</u>N), 2.31 (4H, m, C<u>H$_2$</u> x 2), 1.62 (6H, m, C<u>H$_2$</u> x 3); ^{13}C (75 MHz, $CDCl_3$) δ 176.2 (s), 148.9 (s), 145.4 (s), 128.8 (d x 2), 124.0 (d x 2), 53.7 (t), 40.4 (t), 29.9 (t), 28.1 (t), 27.3 (t), 26.3 (t); EI-MS *m/z* 232 (M^+ 82), 149 (55), 136 (40), 106 (100), 77 (25); HRMS Calcd for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1217.

5.2.1 General procedure for the synthesis of tertiary bromoacetamide cyclisation precursors

The appropriate imine (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. 2-bromoisobutyryl-bromide (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was then stirred for 2 hours at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (9:1).

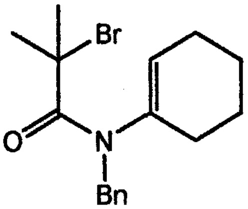
N-Benzyl-2-bromo-N-(cyclopent-1-enyl)-2-methyl-propanamide (146)



Imine (362) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (146): yield (60%); clear oil; IR (neat, cm^{-1}) 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (5H, m, Ar-H), 5.58 (1H, m, CH=C), 4.68 (2H, br s, CH_2N), 2.50-2.41 (2H, m, CH_2), 2.32-2.23 (2H, m, CH_2), 2.00 (6H, br s, CH_3 x 2), 1.94-1.85 (2H, m, CH_2); ^{13}C (75 MHz; $CDCl_3$) δ 170.9 (s), 142.6 (s), 137.9 (s), 130.3 (d), 128.7 (d x 2), 128.3 (d x 2), 127.5 (d), 58.3 (s), 52.4 (t), 33.6 (q x 2), 33.0 (t), 30.5

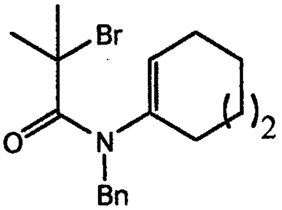
(t), 22.4 (t); EI-MS *m/z* 322 ($M^{+,}$ 22), 243 (92), 172 (81); 91 (100); Anal. Calcd for $C_{16}H_{20}BrNO$: C, 59.64; H, 6.26; N, 4.35. Found: C, 59.67; H, 6.28; N, 4.17.

N-Benzyl-2-bromo-N-(cyclohex-1-enyl)-2-methyl-propanamide (145)



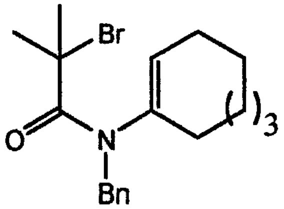
Imine (102) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (145): yield (69%); clear oil; IR (neat, cm^{-1}) 1627; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.18 (5H, m, Ar-$\underline{H}$), 5.58 (1H, br m, C$\underline{H}$=C), 4.98 (1H, br s, C$\underline{H}$HN), 4.27 (1H, br s, CH$\underline{H}$N), 2.18 (2H, m, C$\underline{H}_2$), 2.02 (8H, br m, C$\underline{H}_2$, C$\underline{H}_3$ x 2), 1.67 (2H, m, C$\underline{H}_2$), 1.55 (2H, m, C$\underline{H}_2$); ^{13}C (75 MHz; $CDCl_3$) δ 170.8 (s), 138.1 (s), 129.9 (s), 128.8 (d x 2), 128.6 (d x 3), 127.5 (d), 58.8 (s), 52.8 (t), 35.0 (q x 2), 28.4 (t), 24.9 (t), 22.9 (t), 21.7 (t); EI-MS *m/z* 336 (M^+, 39), 256 (85), 164 (60), 91 (100); Anal. Calcd for $C_{17}H_{22}BrNO$: C, 60.71; H, 6.54; N, 4.17. Found: 60.88; H, 6.61; N, 4.26.

N-Benzyl-2-bromo-N-(cyclohept-1-enyl)-2-methyl-propanamide (147)



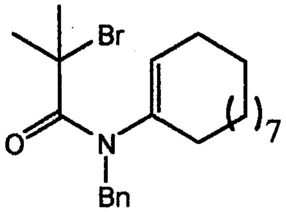
Imine (367) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (147): yield (71%); clear oil; IR (neat, cm^{-1}) 1632; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.11 (5H, m, Ar- $\underline{H}$), 5.54 (1H, br t, J = 5.5 Hz, C$\underline{H}$=C), 5.04 (1H, br s, C$\underline{H}$HN) 3.99 (1H, br s, CH$\underline{H}$N), 2.50-1.03 (10H, br m, C$\underline{H}_2$ x 5), 1.99 (6H, br s, C<u>H</u>$_3$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 170.4 (s), 137.7 (s), 129.7 (s), 129.3 (d x 2), 128.6 (d x 2), 127.7 (d), 105.9 (d), 58.8 (s), 52.1 (t), 34.7 (t), 33.6 (br q x 2), 32.0 (t), 27.2 (t), 26.9 (t), 26.3 (t); EI-MS *m/z* 350 (M$^+$, 2), 269 (97), 254 (26), 91 (100); HRMS Calcd for $C_{18}H_{25}BrNO$ 350.1119, found 350.1128. Anal. Calcd for $C_{18}H_{25}BrNO$: C, 61.72; H, 6.91; N, 4.00. Found: 61.49; H, 6.93; N, 4.22.

N-Benzyl-2-bromo-*N*-(cyclooct-1-enyl)-2-methyl-propanamide (148)



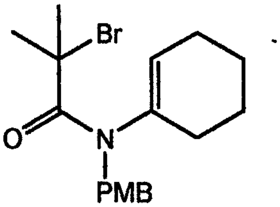
Imine (363) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (148): yield (95%); yellow oil; IR (neat, cm^{-1}) 1632; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29-7.20 (5H, m, Ar-<u>H</u>), 5.58 (1H, m, C<u>H</u>=C), 5.20-4.00 (2H, br s, C<u>H</u>$_2$N), 2.50-2.44 (2H, m, C<u>H</u>$_2$), 2.05 (6H, br s, C<u>H</u>$_3$ x 2), 2.00-1.45 (10H, m, C<u>H</u>$_2$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 171.0 (s), 138.0 (s), 130.5 (s), 128.7 (d x 2), 128.6 (d x 2), 128.3 (d), 127.4 (d), 59.0 (s), 53.5 (t), 32.8 (t), 32.6 (t), 30.6 (br q x 2), 28.8 (t), 26.5 (t), 26.3 (t), 26.0 (t); EI-MS *m/z* 364 (M$^+$, 8), 243 (83), 268 (58), 228 (76), 91 (100); HRMS Calcd for $C_{19}H_{26}BrNO$ 364.1276, found 364.1273.

N-Benzyl-2-bromo-*N*-(cyclododec-1-enyl)-2-methyl-propanamide (149)



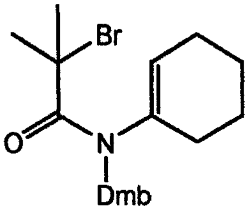
Imine (368) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (149): yield (78%); yellow oil; IR (neat, cm^{-1}) 1624; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.08 (5H, m, Ar-H), 5.10 (1H, t, J = 6.9 Hz, $C\underline{H}=C$), 2.41-2.36 (2H, m, $C\underline{H}_2$), 1.98-1.83 (8H, m, $C\underline{H}_2$, $C\underline{H}_3$ x 2), 1.60-1.53 (2H, m, $C\underline{H}_2$), 1.30-1.04 (14H, m, $C\underline{H}_2$), $C\underline{H}_2N$ proton signals too broad to be observed; ^{13}C (75 MHz, $CDCl_3$) δ 170.8 (s), 139.3 (s), 137.9 (s), 128.8 (d x 2), 128.6 (d x 3), 127.6 (d), 59.2 (s), 54.5 (t), 40.7 (t), 34.0 (q x 2), 26.6 (t), 25.7 (t), 25.2 (t), 25.0 (t), 24.8 (t), 24.6 (t), 23.1 (t), 23.0 (t), 22.7 (t) EI-MS *m/z* 420 (M$^+$, 9), 340 (100), 322 (70), 91 (84); HRMS Calcd for $C_{22}H_{34}BrNO$ 420.1902, found 420.1899.

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-2-methyl-propionamide (150)



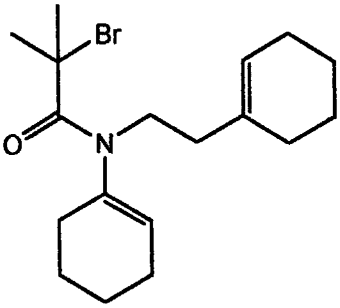
Imine (364) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (150): yield (78%); clear oil; IR (neat, cm^{-1}) 1632; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20 (2H, d, J = 8.5 Hz, $C\underline{H}CHCOCH_3$), 6.80 (2H, d, J = 8.5 Hz, $C\underline{H}=COCH_3$) 5.52 (1H, m, $C\underline{H}=C$), 4.94 (1H, br s, $C\underline{H}HN$), 4.11 (1H, br s, $CH\underline{H}N$), 3.79 (3H, s, $OC\underline{H}_3$), 2.15 (2H, br, $C\underline{H}_2$), 1.99 (6H, s, $C\underline{H}_3$ x 2), 1.98 (2H, m, $C\underline{H}_2$), 1.68-1.53 (4H, m, $C\underline{H}_2$ x 2); ^{13}C (75 MHz; $CDCl_3$) δ 170.7 (s), 159.1 (s), 137.9 (s), 130.3 (d x 2), 130.1 (s), 113.9 (d x 2), 58.9 (s), 55.5 (q), 52.0 (t), 33.5 (q), 33.2 (q), 28.3 (t), 25.7 (t), 24.9 (t), 23.5 (t); EI-MS *m/z* 366 (M$^+$, 20), 286 (92), 208 (77), 121 (100); HRMS Calcd for $C_{18}H_{24}BrNO_2$: 365.0990, found 365.0994.

2-Bromo-*N*-cyclohex-1-enyl-*N*-(2,4-dimethoxy-benzyl)-2-methyl-propionamide (151)



Imine (374) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (151): yield (84%); clear oil; IR (neat, cm^{-1}) 1630; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.23 (1H, d, *J* = 8.2 Hz, C<u>H</u>CHCOCH$_3$), 6.42 (1H, d, *J* = 8.2 Hz, C<u>H</u>=COCH$_3$), 6.40 (1H, m, Ar-<u>H</u>), 5.54 (1H, br t, C<u>H</u>=C), 4.78-4.72 (2H, br, C<u>H</u>$_2$N), 3.75 (3H, s, OC<u>H</u>$_3$), 3.74 (3H, s, OC<u>H</u>$_3$), 2.14 (2H, m, C<u>H</u>$_2$), 2.00 (6H, br s, C<u>H</u>$_3$ x 2), 1.93 (2H, m, C<u>H</u>$_2$), 1.63-1.49 (4H, m, C<u>H</u>$_2$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 170.6 (s), 160.3 (s), 158.8 (s), 130.6 (d), 118.6 (s), 104.3 (d), 98.3 (d), 59.1 (s), 55.4 (q), 55.1 (q), 34.4 (q), 33.7 (q), 28.2 (t), 25.7 (t), 23.3 (t), 21.6 (t); EI-MS *m/z* 396 (M$^+$, 20), 316 (30), 151 (100), 121 (50), 84 (80); HRMS Calcd for $C_{19}H_{26}BrNO_3$: 396.1174, found 396.1174.

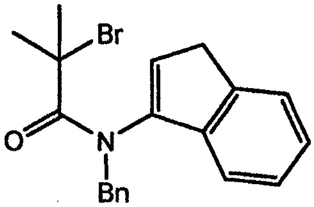
2-Bromo-*N*-cyclohex-1-enyl-*N*-(2-cyclohex-1-enyl-ethyl)-2-methyl-propionamide (162)



Imine (371) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (162): yield (40%); yellow oil; IR (neat, cm^{-1}) 1632; ^{1}H

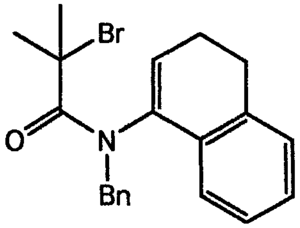
NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, br s, C<u>H</u>=C) 5.43 (1H, br s, C<u>H</u>=C), 3.71-2.90 (4H, br m, $C\underline{H}_2C\underline{H}_2$), 2.12-1.45 (16H, m, $C\underline{H}_2$ x 8), 1.89 (6H, br s, $C\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 170.2 (s), 136.2 (s), 135.3 (s), 124.6 (d), 123.0 (d), 50.3 (s), 48.1 (t), 34.9 (t), 33.3 (q), 32.8 (q), 29.5 (t), 29.0 (t), 28.2 (t), 25.7 (t), 25.0 (t), 23.4 (t), 23.3 (t), 22.9 (t); EI-MS *m/z* 353 (M^+, 83), 273 (61), 258 (100), 180 (85), 81 (75); HRMS Calcd for $C_{18}H_{28}BrNO$ 353.1354, found 353.1354.

N-Benzyl-2-bromo-N-(3H-inden-1-yl)-2-methyl-propionamide (167)



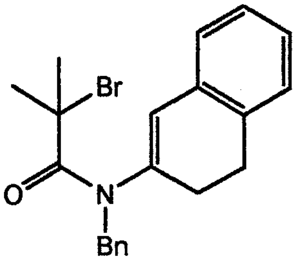
Imine (373) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (167): yield (77%); dark oil; IR (neat, cm^{-1}) 1641; ^1H NMR (250 MHz, $CDCl_3$) δ 7.87-7.29 (9H, m, Ar-H), 6.37 (1H, br s, C<u>H</u>=C), 5.02 (1H, br d, J = 6.1 Hz, C<u>H</u>HN), 4.33 (1H, br d, J = 6.1 Hz, CH<u>H</u>N), 3.35 (2H, br s, $CHC\underline{H}_2$), 2.06 (6H, s, $C\underline{H}_3$ x 2); ^{13}C (75 MHz, $CDCl_3$) δ 170.9 (s), 142.7 (s), 141.9 (s), 138.3 (s), 136.4 (s), 133.8 (d), 130.4 (d), 129.4 (d), 128.7 (d x 2), 127.7 (d), 127.2 (d x 2), 126.1 (d), 119.4 (d), 57.8 (s), 49.2 (t), 36.4 (t), 32.0 (q x 2); EI-MS *m/z* 370 (M^+, 35), 290 (100), 91 (15); HRMS Calcd for $C_{20}H_{20}BrNO$: 370.0807, found 370.0806.

N-Benzyl-2-bromo-N-(3,4-dihydro-naphthalen-1-yl)-2-methyl-propionamide (168)



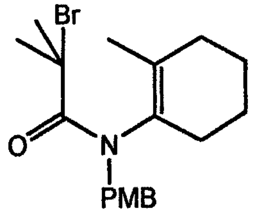
Imine (369) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (168): yield (58%); yellow oil; IR (neat, cm^{-1}) 1632;. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31-7.27 (9H, m, Ar-H), 5.90 (1H, t, J = 4.6 Hz, C<u>H</u>=C), 5.64 (1H, d, J = 13.8 Hz, C<u>H</u>HN), 3.76 (1H, br d, J = 13.8 Hz, CH<u>H</u>N), 2.79 (2H, t, J = 8.1 Hz, CHC<u>H</u>$_2$), 2.32 (2H, m, C<u>H</u>$_2$), 2.05 (3H, m, C<u>H</u>$_3$), 1.84 (3H, s, C<u>H</u>$_3$); ^{13}C (75 MHz, $CDCl_3$) δ 171.6 (s), 137.8 (s), 137.3 (s), 137.2 (s), 132.3 (s), 130.7 (d), 130.1 (d) 129.4 (d x 2), 128.7 (d x 2), 128.6 (d), 128.5 (d), 127.8 (d), 127.2 (d), 123.0 (d), 58.5 (s), 53.3 (t), 35.0 (q), 31.9 (q), 27.4 (t), 23.0 (t); EI-MS *m/z* 383 (M$^+$, 15), 359 (70), 303 (70), 288 (100) 91 (79); HRMS Calcd for $C_{21}H_{22}BrNO$ 383.0885, found 383.0814.

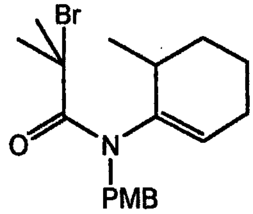
N-Benzyl-2-bromo-N-(3,4-dihydro-naphthalen-1-yl)-2-methyl-propionamide (169)



Imine (370) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (169): yield (84%); dark oil; IR (neat, cm^{-1}) 1649; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34-6.89 (9H, m, Ar-H), 6.28 (1H, br s, C<u>H</u>=C), 4.80 (2H, br s, C<u>H</u>$_2$N), 2.97 (2H, t, J = 8.1 Hz, CHC<u>H</u>$_2$), 2.56 (2H, t, J = 8.1 Hz, C<u>H</u>$_2$), 2.07 (6H, s, C<u>H</u>$_3$ x 2); ^{13}C (75 MHz, $CDCl_3$) δ 171.0 (s), 139.9 (s), 137.6 (s), 134.5 (s), 133.2 (s), 128.9 (d), 128.8 (d x 2), 128.3 (d x 2), 127.9 (d), 127.8 (d), 127.2 (d), 127.0 (d), 126.7 (d), 58.9 (s), 53.4 (t), 34.0 (q x 2), 28.7 (t), 27.9 (t); EI-MS *m/z* 383 (M$^+$, 35), 303 (100), 288 (80), 171 (65) 91 (95); HRMS Calcd for $C_{21}H_{22}BrNO$: 383.0885, found 383.0856.

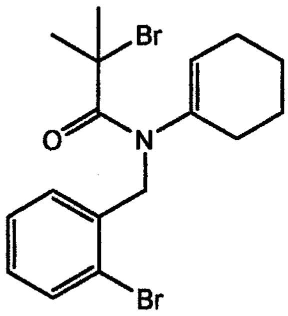
2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(2-methyl-cyclohex-1-enyl)-propionamide (179a) and 2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(6-methyl-cyclohex-1-enyl)-propionamide (179b)





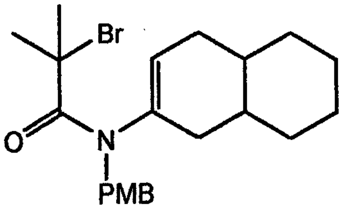
The imine derived from the condensation of 2-methylcyclohexanone and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.1 to give a 1:1 mixture of regioisomeric compounds (179a) and (179b): yield (85%); clear oil; IR (neat, cm^{-1}) 1666, 1645; ^{1}H NMR for mixture of regioisomers (250 MHz, $CDCl_3$) δ 7.18 (2H, m, $C\underline{H}CHCOCH_3$), 6.75 (2H, m, $C\underline{H}=COCH_3$) 5.39 (1H, br m, $C\underline{H}=C$), 4.62 (1H, d, J = 14.0 Hz, $C\underline{H}HN$), 4.40 (1H, d, J = 14.0 Hz, $CH\underline{H}N$), 3.70 (3H, s, $OC\underline{H}_3$), 2.29 (2H, br, $C\underline{H}_2$), 1.97 (6H, s, $C\underline{H}_3$ x 2), 1.89 (2H, m, $C\underline{H}_2$), 1.87 (3H, br m, $CHC\underline{H}_3$), 1.77-1.09 (4H, m, $C\underline{H}_2$, $C\underline{H}CH_3$, $C\underline{H}H$), 1.08 (3H, br s, $C\underline{H}_3$), 0.99 (1H, m, $CH\underline{H}$); ^{13}C for mixture of regioisomers (75 MHz; $CDCl_3$) δ 170.8 (s), 159.3 (s), 133.9 (s), 133.1 (s), 130.9 (d x 2), 130.2 (d), 113.8 (d x 2), 60.4 (s), 59.2 (s), 55.5 (q), 53.4 (t), 32.0 (q x 2), 31.2 (t), 29.8 (t), 25.4 (t), 22.5 (t), 18.4 (q); EI-MS *m/z* 379 (M$^+$, 60), 121 (100), 83 (40); HRMS Calcd for $C_{19}H_{26}BrNO_2$: 379.1147, found 379.1142.

2-Bromo-*N*-(2-bromo-benzyl)-*N*-cyclohex-1-enyl-2-methyl-propionamide (188)



Imine (372) was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (188): yield (33%); yellow oil; IR (neat, cm^{-1}) 1630; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 (1H, app dd, *J* = 1.1, 7.7 Hz, Ar-H), 7.32 (1H, app dd, *J* = 1.5, 7.7 Hz, Ar-H), 7.19 (1H, app dt, *J* = 1.1, 7.7 Hz, Ar-H), 7.00 (1H, app dt, *J* = 1.5, 7.7 Hz, Ar-H), 5.65 (1H, app t, *J* = 3.8 Hz, CH=C), 4.57-4.43 (2H, br m, CH$_2$N), 1.64-1.45 (8H, m, CH$_2$ x 4), 1.17 (6H, br s, CH$_3$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 169.5 (s), 136.8 (s), 135.7 (s), 131.4 (d), 128.2 (d), 127.5 (d), 126.5 (d), 125.5 (d), 57.7 (s), 51.2 (t), 31.5 (q x 2), 27.4 (t), 23.9 (t), 22.5 (t), 19.8 (t); EI-MS *m/z* 415 (M$^+$, 85), 334 (80), 169 (80), 91 (100); HRMS Calcd for $C_{17}H_{21}Br_2NO$: 412.9989, found 413.0013.

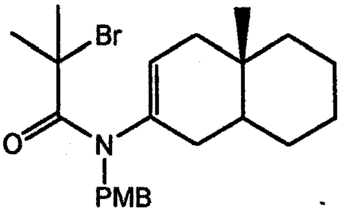
2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (257)



The imine derived from the condensation of decalone and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (257): yield (63%); yellow oil; IR (neat, cm^{-1}) 1635; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.19 (2H, d, *J* = 8.4 Hz, CHCHCOCH$_3$), 6.81 (2H, d, *J* = 8.4 Hz,

$\mathrm{C\underline{H}{=}COCH_3}$), 5.44 (1H, s, $\mathrm{C\underline{H}{=}C}$), 4.78-4.21 (2H, br m, $\mathrm{C\underline{H}_2N}$), 3.78 (3H, s, $\mathrm{OCH_3}$), 2.22-1.85 (4H, m, $\mathrm{C\underline{H}_2}$ x 2), 1.87 (6H, m, $\mathrm{CBr(C\underline{H}_3)_2}$), 1.60-1.19 (10H, m, $\mathrm{C\underline{H}_2}$ x 5); ^{13}C (75 MHz, $\mathrm{CDCl_3}$) δ 170.6 (s), 159.2 (s), 134.0 (br d), 130.4 (d x 2), 129.8 (s), 129.8 (s), 114.4 (d x 2), 58.9 (s), 55.6 (q), 49.7 (t), 33.7 (q x 2), 33.0 (d), 32.3 (d), 32.2 (t), 30.2 (t), 29.1 (t), 26.8 (t), 23.9 (t), 23.7 (t); EI-MS *m/z* 420 (M$^+$, 45), 339 (70), 324 (15), 121 (100); HRMS Calcd for $\mathrm{C_{22}H_{30}BrNO_2}$ 420.1538, found 420.1534.

2-Bromo-*N*-(4-methoxy-benzyl)-2-methyl-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (272)

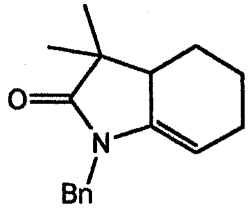


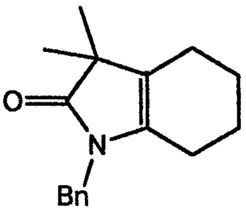
The imine derived from the condensation of 4a-methyl-octahydro-naphthalen-2-one (266)[147] and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.1 to give the required compound (272): yield (51%); yellow oil; IR (neat, cm^{-1}) 1633; ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$) δ 7.19 (2H, d, J = 8.6 Hz, $\mathrm{C\underline{H}CHCOCH_3}$), 6.83 (2H, d, J = 8.6 Hz, $\mathrm{C\underline{H}{=}COCH_3}$), 5.32 (1H, s, $\mathrm{C\underline{H}{=}C}$), 4.90-4.56 (3H, br m, $\mathrm{C\underline{H}_2N}$), 3.76 (3H, s, $\mathrm{OCH_3}$), 2.60-1.99 (3H, m, $\mathrm{C\underline{H}CCH_3}$, $\mathrm{CHC\underline{H}_2}$), 1.98 (6H, m, $\mathrm{CBr(C\underline{H}_3)_2}$), 1.69-1.16 (10H, m, $\mathrm{C\underline{H}_2}$ x 5), 1.17 (3H, m, $\mathrm{C\underline{H}_3}$); ^{13}C (75 MHz, $\mathrm{CDCl_3}$) δ 170.6 (s), 159.2 (s), 134.4 (d), 130.2 (d x 2), 130.1 (s), 130.0 (s), 113.9 (d x 2), 58.8 (s), 55.6 (q), 49.7 (t), 40.0 (d), 38.8 (t), 34.1 (s), 33.9 (q x 2), 31.0 (t), 28.9 (t), 26.6 (q), 25.7 (t), 22.5 (t), 22.0 (t); CI-MS *m/z* 434 (MH$^+$, 80), 354 (100), 184 (95), 121 (45); HRMS Calcd for $\mathrm{C_{23}H_{32}BrNO_2}$ 434.1694, found 434.1695.

5.2.2 General procedure for copper mediated cyclisations of tertiary bromoacetamides (catalytic method).

Cu(I)Br (12.9 mg, 0.09 mmol) was added to solution of the appropriate precursor (0.3 mmol) and Me$_6$-tren (39) (20.7 mg, 0.09 mmol) in dichloromethane (2.5 ml) and stirred at room temperature for 20 minutes under N$_2$. The resulting solution was filtered through a small silica plug with ethyl acetate to remove the copper residues. The filtrate was then reduced to dryness *in vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (9:1), to give the observed cyclised products.

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (152b) and1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (152a)

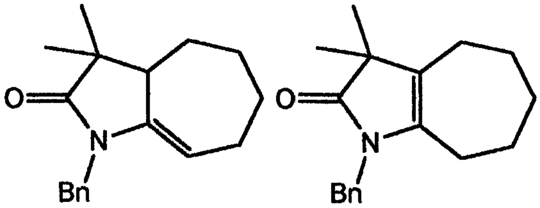




Precursor (145) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (152b): yield (43%); clear oil; IR (neat, cm^{-1}) 1672, 1621; ^{1}H NMR (300 MHz, C_6D_6) δ 7.30-7.19 (5H, m, Ar-$\underline{H}$), 4.67 (1H, br s, $C\underline{H}CH_2$), 4.65 (1H, d, J = 15.2 Hz, $C\underline{H}HN$), 4.55 (1H, d, J = 15.2 Hz, $CH\underline{H}N$), 2.17 (1H, m, $C\underline{H}$), 1.95 (2H, m, $C\underline{H}_2$), 1.62 (2H, m, $C\underline{H}_2$), 1.40-1.25 (2H, m, $C\underline{H}_2$), 1.25 (3H, s, $C\underline{H}_3$), 1.01 (3H, s, $C\underline{H}_3$); ^{13}C (75 MHz; C_6D_6) δ 183.1 (s), 139.4 (s), 134.2 (s), 128.8 (d x 2), 127.8 (d x 2), 127.5 (d), 97.5 (d), 46.0 (d), 43.8 (t), 42.9 (s), 23.7 (t), 23.4 (q), 22.6 (t), 22.1 (t), 20.9 (q); EI-MS *m/z* 255 (M$^+$, 59), 240 (45), 91 (100), 65 (24); HRMS Calcd for $C_{17}H_{21}NO$: 255.1623, found 255.1617.

Data for (152a): yield (39%); clear oil; IR (neat, cm^{-1}) 1702, 1612; ^{1}H NMR (300 MHz, C_6D_6) δ 7.21-7.12 (5H, m, Ar-$\underline{H}$), 4.59 (2H, s, $C\underline{H}_2N$), 1.80 (4H, m, $C\underline{H}_2$ x 2), 1.42 (4H, m, C<u>H</u>$_2$ x 2), 1.29 (6H, s, C<u>H</u>$_3$ x 2); ^{13}C (75 MHz; C_6D_6) δ 183.0 (s), 140.2 (s), 138.0 (s), 128.9 (s), 128.6 (d x 2), 127.4 (d x 2), 120.4 (d), 46.1 (s), 43.1 (t), 22.9 (t x 2), 22.8, (q x 2) 20.9 (t), 19.8 (t); EI-MS m/z 255 (M$^+$, 51), 240 (45), 91 (100); HRMS Calcd for $C_{17}H_{21}NO$: 255.1623, found 255.1618.

1-Benzyl-3,3-dimethyl-3,3a,4,5,6,7-hexahydro-1H-cyclohepta[b]pyrrol-2-one (156b) and 1-Benzyl-3,3-dimethyl-3,4,5,6,7,8-hexahydro-1H-cyclohepta[b]pyrrol-2-one (156a)

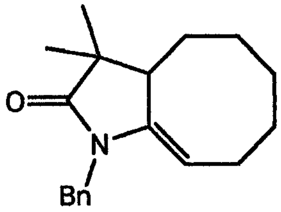


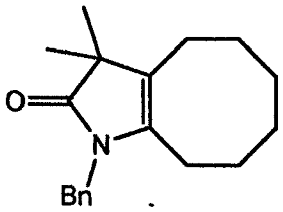
Precursor (147) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (156b): yield (52%); clear oil; IR (neat, cm^{-1}) 1713, 1666; ^{1}H NMR (300 MHz, C_6D_6) δ 7.20-7.01 (5H, m, Ar-<u>H</u>), 4.89 (1H, ddd, *J* = 7.0, 4.5, 2.1 Hz, C<u>H</u>=C), 4.71 (1H, d, *J* = 15.4 Hz, C<u>H</u>HN), 4.53 (1H, d, *J* = 15.4 Hz, CH<u>H</u>N), 2.30 (1H, m, C<u>H</u>), 2.02-1.46 (6H, m, C<u>H</u>$_2$ x 3), 1.18 (3H, s, C<u>H</u>$_3$), 1.14-1.10 (2H, m, C<u>H</u>$_2$), 1.07 (3H, s, C<u>H</u>$_3$); ^{13}C (75 MHz, C_6D_6) δ 180.0 (s), 145.1 (s), 138.0 (s), 129.7 (d x 2), 127.7 (d x 3), 102.5 (d), 49.1 (d), 44.1 (t), 43.3 (s), 30.7 (t), 28.6 (t), 27.8 (t), 27.1 (t), 26.0 (t), 22.8 (q), 21.7 (q); EI-MS *m/z* 269 (M$^+$, 87), 215 (76), 198 (65), 91 (100); HRMS Calcd for $C_{18}H_{23}NO$: 269.1779, found 269.1779; Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.15; H, 8.47; N, 5.21.

Data for (156a): yield (10%); clear oil; IR (neat, cm^{-1}) 1701, 1682, 1664; ^{1}H NMR (300 MHz, C_6D_6) δ 7.19-7.03 (5H, m, Ar-<u>H</u>), 4.61 (2H, s, C<u>H</u>$_2$N), 1.99 (2H, m, C<u>H</u>$_2$), 1.79 (2H, m, C<u>H</u>$_2$), 1.41 (4H, m, C<u>H</u>$_2$ x 2), 1.35 (2H, m, C<u>H</u>$_2$), 1.24 (6H, s, C<u>H</u>$_3$ x 2); ^{13}C (75

MHz, C_6D_6) δ 185.0 (s), 139.6 (s), 137.0 (s), 129.2 (d x 2), 127.6 (d), 127.3 (d x 2), 124.4 (s), 47.9 (s), 43.4 (t), 30.8 (t), 28.7 (t), 26.9 (t x 2), 24.5 (t), 22.7 (q x 2); HRMS Calcd for $C_{18}H_{23}NO$: 269.1779, found 269.1770; EI-MS *m/z* 269 (M^+, 80), 215 (65), 91 (100); Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.22; H, 8.49; N, 5.11.

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6,7,8-octahydro-cycloocta[b]pyrrol-2-one (157b) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7,8,9-octahydro-cycloocta[b]pyrrol-2-one (157a)



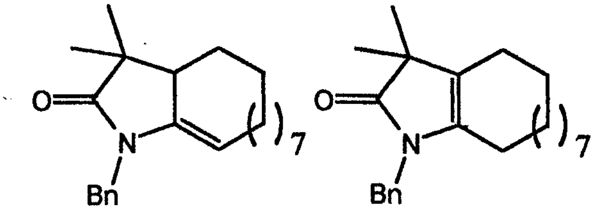


Precursor (148) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (157b): yield (60%); clear oil; IR (neat, cm^{-1}) 1706, 1604; ^1H NMR (300 MHz, C_6D_6) δ 7.39-7.13 (5H, m, Ar-$\underline{H}$), 4.76 (1H, d, J = 15.3 Hz, C$\underline{H}$HN), 4.70 (1H, m, C$\underline{H}$=C), 4.59 (1H, d, J = 15.3 Hz, C$\underline{H}$HN), 2.38 (1H, m, C$\underline{H}$), 2.19-1.99 (2H, m, C$\underline{H}_2$), 1.69-1.45 (2H, m, C$\underline{H}_2$), 1.31-1.00 (4H, m, C$\underline{H}_2$ x 2), 1.23 (3H, s, C$\underline{H}_3$), 1.18 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz, C_6D_6) δ 179.8 (s), 143.2 (s), 138.0 (s), 129.5 (d x 2), 127.9 (d x 2), 127.7 (d), 101.2 (d), 47.7 (d), 44.0 (t), 33.8 (t), 32.6 (t), 30.2 (t), 27.9 (q), 26.0 (t), 25.7 (t), 24.3 (t), 19.1 (q); EI-MS *m/z* 283 (M^+, 46), 268 (35), 255 (49), 83 (100); Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.19; H, 8.67; N, 4.72.

Data for (157a): yield (21%); clear oil; IR (neat, cm^{-1}) 1713, 1671, 1605; ^1H NMR (300 MHz, C_6D_6) δ 7.30-7.04 (5H, m, Ar-$\underline{H}$), 4.66 (2H, s, C$\underline{H}_2$N), 2.10 (4H, m, C$\underline{H}_2$ x

2), 1.50-1.29 (8H, m, CH_2 x 4), 1.33 (6H, s, $C\underline{H}_3$ x 2); ^{13}C (75 MHz, C_6D_6) δ 184.3 (s), 139.6 (s), 135.6 (s), 129.2 (d x 2), 127.7 (d), 127.4 (d x 2), 121.7 (s), 47.7 (s), 43.5 (t), 30.7 (t), 27.6 (t), 26.5 (t), 26.3 (t), 23.5 (t), 23.4 (t), 23.1 (q x 2); EI-MS *m/z* 283 (M^+, 31), 268 (28), 228 (19), 91 (100); HRMS Calcd for $C_{19}H_{25}NO$: 283.1936, found 283.1929; Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.01; H, 8.77; N, 4.89.

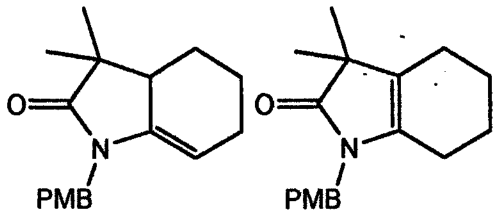
1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6,7,8,9,10,11,12-dodecahydro-cyclododeca[b]pyrrol-2-one (158b) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-cyclododeca[b]pyrrol-2-one (158a)



Precursor (149) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (158b): yield (15%); clear oil; IR (neat, cm^{-1}); 1700, 1609; ^1H NMR (300 MHz, C_6D_6) δ 7.16-7.05 (5H, m, Ar-$\underline{H}$), 4.72 (1H, dd, J = 11.4, 3.6 Hz, $C\underline{H}$=C), 4.63 (1H, d, J = 15.3 Hz, $C\underline{H}HN$), 4.57 (1H, d, J = 15.3 Hz, $CH\underline{H}N$), 2.48 (1H, m, $C\underline{H}$), 2.13-1.10 (18H, m, $C\underline{H}_2$ x 9), 1.26 (3H, s, $C\underline{H}_3$), 1.17 (3H, s, $C\underline{H}_3$); ^{13}C (75 MHz, C_6D_6) δ 179.6 (s), 141.6 (s), 138.2 (s), 129.2 (d), 127.7 (d x 2), 127.6 (d x 2), 123.5 (s), 106.0 (d), 46.0 (d), 44.1 (s), 43.9 (t), 30.9 (t), 27.9 (t), 27.5 (q), 26.7 (t x 2), 26.4 (t), 25.7 (t), 24.5 (t), 24.1 (t), 23.2 (t), 19.1 (q); EI-MS *m/z* 339 (M^+, 75), 269 (75), 91 (100); HRMS Calcd for $C_{23}H_{33}NO$: 339.2562, found 339.2564; Anal. Calcd for $C_{23}H_{33}NO$: C, 81.37; H, 9.80; N, 4.13. Found: C, 81.09; H, 9.67; N, 4.29.

Data for (158a): yield (55%); clear oil; IR (neat, cm^{-1}) 1719, 1675, 1601; ^{1}H NMR (300 MHz, C_6D_6) δ 7.11-7.02 (5H, m, Ar$\underline{H}$), 4.68 (2H, s, $C\underline{H}_2N$), 2.00 (4H, m, $C\underline{H}_2$ x 2), 1.45-1.17 (16H, m, $C\underline{H}_2$ x 8), 1.33 (6H, s, $C\underline{H}_3$ x 2); ^{13}C (75 MHz, C_6D_6) δ 183.7 (s), 139.8 (s), 136.6 (s), 129.2 (d x 2), 127.6 (d), 127.3 (d x 2), 123.6 (s), 47.6 (s), 43.9 (t), 28.1 (t), 27.3 (t), 26.3 (t), 26.0 (t), 25.4 (t), 25.0 (t), 24.3 (q x 2), 23.0 (t), 22.4 (t x 2), 21.8 (t); EI-MS *m/z* 339 (M$^+$, 75), 269 (75), 91 (100); HRMS Calcd for $C_{23}H_{33}NO$: 339.2562, found 339.2564; Anal. Calcd for $C_{23}H_{33}NO$: C, 81.37; H, 9.80; N, 4.13. Found: C, 81.29; H, 9.87; N, 4.17.

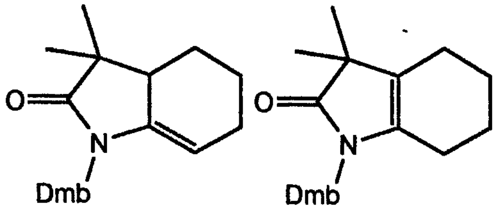
1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (159b) and 1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (159a)



Precursor (150) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (159b): yield (47%); clear oil; IR (neat, cm^{-1}) 1676, 1613; ^{1}H NMR (250 MHz, C_6D_6) δ 7.22 (2H, d, J = 8.5 Hz, $C\underline{H}CHCOCH_3$), 6.74 (2H, d, J = 8.5 Hz, $C\underline{H}{=}COCH_3$), 4.73 (1H, m, $C\underline{H}{=}C$), 4.65 (1H, d, J = 15.0 Hz, $C\underline{H}HN$), 4.55 (1H, d, J = 15.0 Hz, $CH\underline{H}N$), 3.27 (3H, s $OC\underline{H}_3$), 2.14 (1H, m, $C\underline{H}$), 1.93 (2H, m, $C\underline{H}_2$), 1.68 (2H, m, $C\underline{H}_2$), 1.38-1.08 (2H, m, $C\underline{H}_2$), 1.25 (3H, s, $C\underline{H}_3$), 0.97 (3H, s, $C\underline{H}_3$); ^{13}C (75 MHz; C_6D_6) δ 183.2 (s), 165.4 (s), 159.5 (s), 131.6 (s), 129.5 (d x 2), 114.7 (d x 2), 99.5 (d), 55.5 (q), 46.1 (d), 43.8 (t), 42.9 (s), 23.7 (t), 23.2 (q), 22.6 (t), 22.1 (t), 19.9 (q); EI-MS *m/z* 285 (M$^+$, 30), 121 (100); HRMS Calcd for $C_{18}H_{23}NO_2$: 285.1728, found 285.1729.

Data for (159a): yield (36%); clear oil; IR (neat, cm^{-1}) 1702, 1613; ^{1}H NMR (250 MHz, C_6D_6) δ 7.15 (2H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.75 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.51 (2H, s, C$\underline{H}_2$N), 3.28 (3H, s, OC$\underline{H}_3$), 1.82 (4H, m, C$\underline{H}_2$ x 2), 1.39 (4H, m, C$\underline{H}_2$ x 2), 1.26 (6H, s, C$\underline{H}_3$ x 2); ^{13}C (75 MHz; C_6D_6) δ 183.5 (s), 164.3 (s), 159.7 (s), 134.5 (s), 129.1 (d x 2), 120.1 (s), 114.3 (d x 2), 55.1 (q), 46.5 (s), 42.9 (t), 23.1 (t x 2), 22.7, (q x 2) 21.9 (t), 20.0 (t); EI-MS m/z 285 (M$^+$, 70), 121 (100); HRMS Calcd for $C_{18}H_{23}NO_2$: 285.1728, found 285.1733.

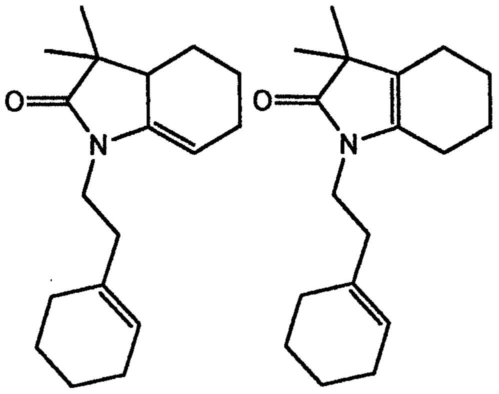
1-(2,4-Dimethoxy-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (160b) and 1-(2,4-Dimethoxy-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (160a)



Precursor (151) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (160b): yield (54%); clear oil; IR (neat, cm^{-1}) 1677, 1613; ^{1}H NMR (250 MHz, C_6D_6) δ 7.22 (1H, d, *J* = 8.2 Hz, C$\underline{H}$CHCOCH$_3$), 6.42-6.33 (2H, m, C$\underline{H}$=COCH$_3$), 5.00 (1H, d, *J* = 15.6 Hz, C$\underline{H}$HN), 4.89 (1H, m, C$\underline{H}$=C), 4.80 (1H, d, *J* = 15.6 Hz, CH$\underline{H}$N), 3.34 (3H, s OC$\underline{H}_3$), 3.28 (3H, s OC$\underline{H}_3$), 2.21 (1H, m, C$\underline{H}$), 1.94 (2H, m, C$\underline{H}_2$), 1.68 (2H, m, C$\underline{H}_2$), 1.43-1.14 (2H, m, C$\underline{H}_2$), 1.27 (3H, s, C$\underline{H}_3$), 1.02 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz; C_6D_6) δ 180.2 (s), 160.9 (s), 158.6 (s), 140.8 (s), 129.2 (d), 118.4 (s), 104.7 (d), 99.5 (d), 97.6 (s), 55.2 (q x 2), 46.1 (d), 43.3 (s), 38.2 (t), 23.8 (t), 23.2 (q), 22.9 (t), 22.5 (t), 20.2 (q); EI-MS *m/z* 315 (M$^+$, 10), 151 (100), 121 (55); HRMS Calcd for $C_{19}H_{25}NO_3$: 315.8344, found 315.1837.

Data for (160a): yield (36%); clear oil; IR (neat, cm^{-1}) 1710, 1612; ^{1}H NMR (250 MHz, C$_6$D$_6$) δ 7.15 (1H, m, J = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.42-6.30 (2H, m, C$\underline{H}$=COCH$_3$), 4.84 (2H, s, C$\underline{H}_2$N), 3.35 (3H, s, OC$\underline{H}_3$), 3.24 (3H, s, OC$\underline{H}_3$), 1.94 (2H, m, C$\underline{H}_2$), 1.83 (2H, m, C$\underline{H}_2$), 1.43 (4H, m, C$\underline{H}_2$ x 2), 1.30 (6H, s, C$\underline{H}_3$ x 2); ^{13}C (75 MHz; C$_6$D$_6$) δ 182.6 (s), 164.3 (s), 160.9 (s), 158.3 (s), 135.0 (s), 129.1 (d), 120.0 (s), 104.7 (d), 99.4 (d), 55.2 (q), 55.1 (q), 46.5 (s), 37.7 (t), 23.3 (t x 2), 22.9, (q x 2) 21.6, (t), 20.2 (t); EI-MS m/z 315 (M$^+$, 35), 151 (100), 121 (35); HRMS Calcd for C$_{19}$H$_{25}$NO$_3$: 315.1834, found 315.1833.

1-(2-Cyclohex-1-enyl-ethyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (163b) and 1-(2-Cyclohex-1-enyl-ethyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (163a)

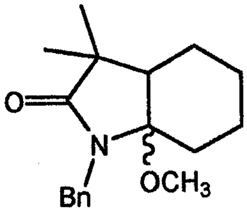


Precursor (162) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (163b): yield (55%); clear oil; IR (neat, cm^{-1}) 1720, 1676; ^{1}H NMR (250 MHz, C$_6$D$_6$) δ 5.48 (1H, br s, C$\underline{H}$=C), 4.66 (1H, m, CHC=C$\underline{H}$), 3.57 (1H, dt, J = 6.7, 13.7 Hz, CH$_2$C$\underline{H}_2$N), 3.48 (1H, dt, J = 6.7, 13.7 Hz, CH$_2$C$\underline{H}_2$N), 2.22 (2H, m, C$\underline{H}_2$CH$_2$N), 2.00 (5H, m, C$\underline{H}$, C$\underline{H}_2$ x 2), 1.96 (6H, m, C$\underline{H}_2$ x 3), 1.65-1.40 (4H, m, C$\underline{H}_2$ x 2), 1.21 (3H, s, C$\underline{H}_3$), 0.95 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz; C$_6$D$_6$) δ 179.6 (s), 140.8 (s), 135.4 (s), 123.0 (d), 96.5 (d), 46.5 (d), 42.0 (s), 38.1

(t), 35.9 (t), 28.6 (t), 26.0 (t), 24.2 (t), 23.8 (q), 23.6 (t), 23.1 (t), 23.0 (t), 22.5 (t), 21.2 (q); EI-MS *m/z* 273 (M^+, 85), 178 (100), 166 (90), 150 (60); HRMS Calcd for $C_{18}H_{27}NO$: 273.2092, found 273.2093; Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.81; H, 9.72; N, 5.16.

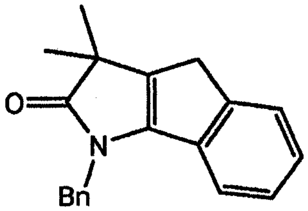
Data for (163a): yield (21%); clear oil; IR (neat, cm^{-1}) 1704, 1675; ^1H NMR (250 MHz, C_6D_6) δ 5.37 (1H, br s, $C\underline{H}$=C), 3.41 (2H, t, J = 7.0 Hz, $CH_2C\underline{H_2}N$), 2.11 (2H, t, J = 7.0 Hz, $C\underline{H_2}CH_2N$), 1.98-1.80 (8H, m, $C\underline{H_2}$ x 4), 1.64-1.46 (8H, m, $C\underline{H_2}$ x 4), 1.21 (6H, s, $C\underline{H_3}$ x 2); ^{13}C (75 MHz; C_6D_6) δ 179.9 (s), 135.5 (s), 134.3 (s), 123.9 (d), 120.4 (s), 46.4 (s), 38.9 (t), 38.5 (t), 28.7 (t), 26.0 (t), 23.7 (t), 23.4 (t), 23.0 (t x 2), 22.8 (q x 2), 21.8 (t), 20.2 (t); EI-MS *m/z* 273 (M^+, 30), 178 (100), 166 (40), 150 (65); HRMS Calcd for $C_{18}H_{27}NO$: 273.2092, found 273.2101; Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.77; H, 9.87; N, 5.06.

1-Benzyl-7a-methoxy-3,3-dimethyl-octahydro-indol-2-one (164)



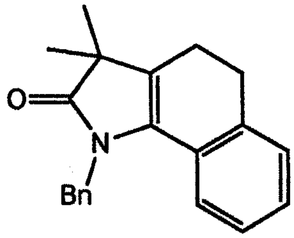
Cu(I)Br (12.9 mg, 0.09 mmol) was added to solution of compound (145) (0.3 mmol), tren-Me_6 (20.7 mg, 0.09 mmol) and 10 equivalents of methanol (0.12 ml) in dichloromethane (2.5 ml) and stirred at room temperature for 22 hrs under N_2. The resulting solution was filtered through a small silica plug with ethyl acetate to remove the copper residues. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (9:1), to give the cyclised products, 1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (152b) in 26% yield, 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (152a) in 19% yield and also the cyclised product (164): yield (36%); clear oil; IR (neat, cm^{-1}) 1704, 1677; ^{1}H NMR (300 MHz, C_6D_6) δ 7.55 (2H, app d, *J* = 7.2 Hz, Ar-H), 7.26-7.19 (3H, m, Ar-H), 4.84 (1H, d, *J* = 14.9 Hz, CHHN), 4.10 (1H, d, *J* = 14.9 Hz, CHHN), 2.73 (3H, s, OCH$_3$), 1.89 (3H, m, CH, CH$_2$), 1.46 (2H, m, CH$_2$), 1.40-1.15 (4H, m, CH$_2$), 1.33 (3H, s, CH$_3$), 1.16 (3H, s, CH$_3$); ^{13}C (75 MHz; C_6D_6) δ 178.8 (s), 139.9 (s), 128.6 (d x 2), 128.1 (d x 2), 127.4 (d), 92.6 (s), 50.0 (d), 47.8 (q), 45.7 (s), 42.2 (t), 34.0 (t), 25.8 (q), 22.0 (q), 21.7 (t), 21.4 (t), 20.4 (t); EI-MS *m/z* 287 (M$^+$, 15), 255 (90), 240 (70), 212 (60), 91 (100); HRMS Calcd for $C_{18}H_{25}NO_2$: 287.1885, found 287.1883.

3-Benzyl-1,1-dimethyl-3,8-dihydro-1H-3-aza-cyclopenta[a]inden-2-one (170)



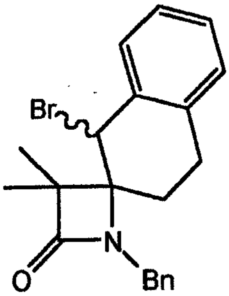
Precursor (167) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compound: yield (99%); clear oil; IR (neat, cm^{-1}) 1727; ^{1}H NMR (250 MHz, C_6D_6) 7-24-7.10 (9H, m, Ar-H), 5.06 (2H, s, CH$_2$N), 3.30 (2H, m, CH$_2$), 1.38 (6H, s, CH$_3$ x 2); ^{13}C (75 MHz; C_6D_6) δ 178.3 (s), 140.9 (s), 139.2 (s), 138.1 (s), 136.0 (s), 130.1 (s), 127.8 (d x 2), 127.2 (d), 127.2 (d x 2), 126.8 (d), 126.7 (d), 125.8 (d), 121.9 (d), 46.2 (s), 46.0 (t), 31.9 (t), 23.9 (q x 2); EI-MS m/z 289 (M$^+$, 60), 274 (93), 91 (100); HRMS Calcd for $C_{20}H_{19}NO$: 289.1466, found 289.1475.

1-Benzyl-3,3-dimethyl-1,3,4,5-tetrahydro-benzo[g]indol-2-one (171)



Precursor (168) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compound: yield (99%); clear oil; IR (neat, cm^{-1}) 1706; ^{1}H NMR (250 MHz, C_6D_6) 7-28-6.83 (9H, m, Ar-H), 4.99 (2H, s, CH_2N), 2.54 (2H, t, J = 8.0Hz, CH_2), 1.91 (2H, t, J = 8.0Hz, CH_2), 1.24 (6H, s, CH_3 x 2); ^{13}C (75 MHz; C_6D_6) δ 184.5 (s), 139.2 (s), 137.2 (s), 135.4 (s), 130.0 (s), 130.0 (d x 2), 129.3 (d x 2), 128.9 (d), 128.7 (d), 128.4 (d), 128.1 (d), 127.7 (s), 122.4 (d), 46.2 (s), 46.0 (t), 29.9 (t), 22.9 (q x 2), 14.6 (t); EI-MS m/z 303 (M$^+$, 35), 288 (55), 91 (100); HRMS Calcd for $C_{21}H_{21}NO$: 303.1623, found 303.1629; Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 82.87; H, 6.90; N, 4.51.

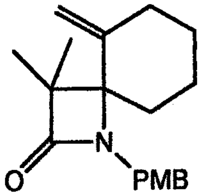
1-Benzyl-1'-bromo-3,3-dimethylspiro(azetidine-4,2'-1',2',3',4'-tetrahydronapthalen)-2-one (172)

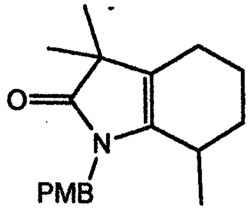


Precursor (169) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compound as a mixture of 1:1 diastereomers: yield (99%); clear oil; IR (neat, cm^{-1}) 1747; ^{1}H NMR for mixture of diastereomers (250 MHz, C_6D_6) 7-23-7.03 (6H, m, Ar-H), 6.90 (1H, m, Ar-H), 6.65 (2H, m, Ar-H), 5.05

(1H, app d, *J* = 2.2 Hz, CHBr), 3.90 (1H, d, *J* = 15.6 Hz, CHHN), 3.75 (1H, d, *J* = 15.6 Hz, CHHN), 3.09 (1H, m, CHH), 2.84 (1H, m, NCCHH), 2.63 (1H, m, CHH), 1.96 (1H, m, NCCHH), 1.60 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C for mixture of diastereomers (75 MHz; C_6D_6) δ 175.0 (s), 138.1 (s), 136.4 (s), 135.7 (s), 130.0 (d), 129.6 (d), 129.4 (d), 128.8 (d x 2), 127.7 (d x 2), 127.2 (d), 127.0 (d), 67.8 (s), 57.1 (d), 52.4 (d), 43.8 (t), 25.7 (t), 25.3 (t), 20.2 (q), 18.4 (q); EI-MS m/z 384 (M^+, 15), 304 (100), 288 (82), 172 (60), 128 (65), 91 (55); HRMS Calcd for $C_{21}H_{22}BrNO$: 384.0963, found 384.0960; Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found: C, 65.51; H, 5.67; N, 3.60.

1-(4-Methoxy-benzyl)-3,3-dimethyl-5-methylene-1-aza-spiro[3.5]nonan-2-one (180) and 1-(4-Methoxy-benzyl)-3,3,7-trimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (181)



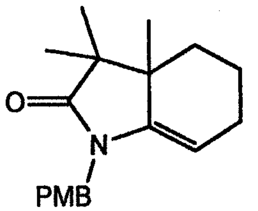


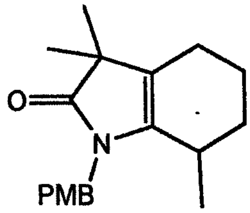
Cu(I)Br (12.9 mg, 0.09 mmol) was added to solution of precursor (179) (0.3 mmol), tren-Me$_6$ (20.7 mg, 0.09 mmol) in dichloromethane (2.5 ml) and stirred at room temperature for 18 hrs under N_2. The resulting solution was filtered through a small silica plug with ethyl acetate to remove the copper residues. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (4:1), to give the cyclised products (180) and (181): Data for (180): yield (47%); clear oil; IR (neat, cm^{-1}) 1705, 1620; ^1H NMR (250 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.6 Hz, CHCHCOCH$_3$), 6.81 (2H, d, *J* = 8.5 Hz, CH=COCH$_3$), 4.91 (1H, s, CHH=C), 4.66 (1H, s, CHH=C), 4.57 (1H, d, *J* = 15.0 Hz, CHHN), 3.90 (1H, d, *J* = 15.0 Hz, CHHN), 3.78 (3H, s OCH$_3$), 2.42 (2H, m, CHH), 1.88 (1H, m, CHH), 1.77-1.67

(6H, m, $C\underline{H}_2$ x 3), 1.32 (3H, s, $C\underline{H}_3$), 1.15 (3H, s, $C\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 174.4 (s), 159.1 (s), 147.9 (s), 130.8 (s), 129.7 (d x 2), 114.2 (d x 2), 109.7 (d), 71.1 (s), 57.0 (s), 55.6 (q), 43.3 (t), 35.9 (t), 33.8 (t), 26.8 (t), 24.8 (t), 19.2 (q), 18.5 (q); EI-MS *m/z* 299 (M^+, 60), 121 (100); HRMS Calcd for $C_{19}H_{25}NO_2$: 299.1885, found 299.1885.

Data for (181): yield (41%); clear oil; IR (neat, cm^{-1}) 1669; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (2H, d, J = 8.7 Hz, $C\underline{H}CHCOCH_3$), 6.75 (2H, d, J = 8.7 Hz, $C\underline{H}{=}COCH_3$), 4.85 (1H, d, J = 15.0 Hz, $C\underline{H}HN$), 4.23 (1H, d, J = 15.0 Hz, $CH\underline{H}N$), 3.70 (3H, s $OC\underline{H}_3$), 2.21 (1H, m, $C\underline{H}CH_3$), 1.88 (2H, m, $C\underline{H}_2$), 1.65-1.41 (4H, m, $C\underline{H}_2$ x 2), 1.09 (3H, s, $C\underline{H}_3$), 1.07 (3H, s, $C\underline{H}_3$), 0.97 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 185.0 (s), 159.0 (s), 138.3 (s), 130.7 (s), 128.1 (d x 2), 121.4 (s), 114.1 (d x 2), 55.6 (q), 45.6 (s), 42.8 (t), 31.1 (t), 25.5 (t), 22.5 (q), 22.3 (q), 20.7 (t), 20.6 (q), 19.4 (t); EI-MS *m/z* 299 (M^+, 55), 121 (100); HRMS Calcd for $C_{19}H_{25}NO_2$: 299.1885, found 299.1883.

1-(4-Methoxy-benzyl)-3,3,3a-trimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (184) and 1-(4-Methoxy-benzyl)-3,3,7-trimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (181)

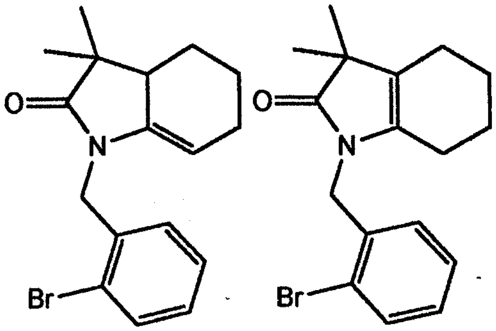




Cu(I)Br (12.9 mg, 0.09 mmol) was added to solution of precursor (179) (0.3 mmol), TPA (26.1 mg, 0.09 mmol) in toluene (2.5 ml) and refluxed with stirring for 1 hr. The resulting solution was filtered through a small silica plug with ethyl acetate to remove the copper residues. The filtrate was then reduced to dryness *in vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (4:1), to give the cyclised products (184) and (181). Data for (184): yield (64%); clear oil; IR (neat, cm^{-1}) 1680, 1611; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.81 (2H, d, *J* = 8.5 Hz, C<u>H</u>=COCH$_3$), 4.79 (1H, m, C<u>H</u>=C), 4.67 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.45 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.76 (3H, s OC<u>H</u>$_3$), 2.07 (2H, m, C<u>H</u>$_2$), 1.70 (2H, m, C<u>H</u>$_2$), 1.42 (2H, m, C<u>H</u>$_2$), 1.22 (3H, s, C<u>H</u>$_3$), 1.15 (3H, s, C<u>H</u>$_3$), 0.97 (3H, s, C<u>H</u>$_3$); ^{13}C (75 MHz; $CDCl_3$) δ 182.2 (s), 159.0 (s), 144.4 (s), 130.7 (s), 129.0 (d x 2), 114.1 (d x 2), 99.2 (d), 55.5 (q), 47.9 (s), 43.0 (t), 42.8 (s), 27.9 (t), 23.7 (q), 23.3 (t), 22.7 (q), 20.0 (t), 17.3 (q); EI-MS *m/z* 299 (M$^+$, 40), 121 (100), 83 (20); HRMS Calcd for $C_{19}H_{25}NO_2$: 299.1885, found 299.1890.

Data for (181): yield (21%); clear oil; Spectral details matched those previously cited above.

1-(2-Bromo-benzyl)-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (189) and 1-(2-Bromo-benzyl)-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (190)

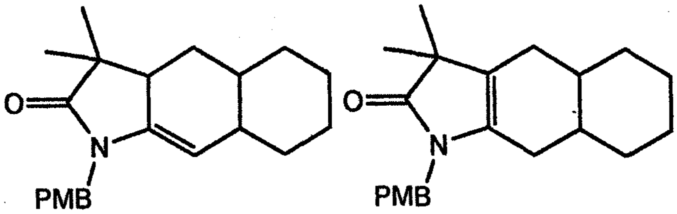


Precursor (188) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (189): yield (64%); clear oil; IR (neat, cm^{-1}) 1711, 1681; ^{1}H NMR (250 MHz, C_6D_6) δ 7.35 (1H, app dd, *J* = 1.1, 7.9 Hz, Ar-<u>H</u>), 7.19-7.11 (1H, m, Ar-<u>H</u>), 6.92 (1H, app t, *J* = 7.3, 7.6 Hz), 6.65 (1H, app t, *J* = 6.4, 7.6 Hz), 4.81 (2H, s, C<u>H</u>$_2$N), 4.61 (1H, m, C<u>H</u>=C), 2.22 (1H, m, C<u>H</u>), 1.82 (2H, m, C<u>H</u>$_2$), 1.60 (2H, m, C<u>H</u>$_2$), 1.49 (2H, m, C<u>H</u>$_2$), 1.25 (3H, s, C<u>H</u>$_3$), 0.98 (3H, s, C<u>H</u>$_3$); ^{13}C

(75 MHz; C_6D_6) δ 180.3 (s), 140.1 (s), 136.7 (s), 133.3 (d x 2), 129.6 (d x 2), 123.5 (s), 98.3 (d), 46.3 (d), 44.7 (t), 43.2 (s), 23.9 (q), 22.8 (t), 22.2 (t), 21.3 (t), 20.3 (q); EI-MS *m/z* 333 (M^+, 70), 254 (100), 169 (75), 91 (55); HRMS Calcd for $C_{17}H_{20}BrNO$: 333.0728, found 333.0728.

Data for (190): yield (19%); clear oil; IR (neat, cm^{-1}) 1709, 1680; ^1H NMR (250 MHz, C_6D_6) δ 7.33 (1H, app dd, *J* = 1.1, 7.9 Hz, Ar-$\underline{H}$), 7.19-7.10 (1H, m, Ar-$\underline{H}$), 6.91 (1H, app t, *J* = 7.3, 7.6 Hz), 6.65 (1H, app t, *J* = 6.5, 7.6 Hz), 4.72 (2H, s, C$\underline{H}_2$N), 1.82 (2H, m, C$\underline{H}_2$), 1.66 (2H, m, C$\underline{H}_2$), 1.49-1.32 (2H, m, C$\underline{H}_2$ x 2), 1.26 (6H, s, C$\underline{H}_3$ x 2); ^{13}C (75 MHz; C_6D_6) δ 180.1 (s), 143.1 (s), 136.0 (s), 133.0 (d x 2), 129.9 (d x 2), 123.8 (s), 121.3 (s), 43.1 (t), 42.9 (s), 22.9 (t), 22.8 (t), 21.8 (t), 21.1 (q x 2), 19.8 (t); EI-MS *m/z* 333 (M^+, 25), 254 (100), 169 (70), 91 (35); HRMS Calcd for $C_{17}H_{20}BrNO$: 333.0728, found 333.0734.

1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,3a,4,4a,5,6,7,8,8a-decahydro-benzo[f]indol-2-one (258b) and 1-(4-Methoxy-benzyl)-3,3-dimethyl-1,3,4,4a,5,6,7,8,8a,9-decahydro-benzo[f]indol-2-one (258a)



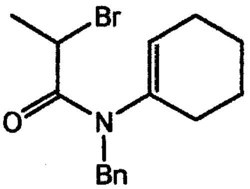
Precursor (257) was reacted under the conditions described in the general procedure 5.2.2 to give the following cyclic compounds. Data for (258b): yield (47%); clear oil; IR (neat, cm^{-1}) 1679, 1610; ^1H NMR (300 MHz, C_6D_6) δ 7.20 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 6.74 (2H, d, *J* = 8.5 Hz, C$\underline{H}$=COCH$_3$), 4.67 (1H, m, C$\underline{H}$=C), 4.57 (1H, d, *J* = 15.5 Hz, C$\underline{H}$HN), 4.41 (1H, d, *J* = 15.5 Hz, CH$\underline{H}$N), 3.70 (3H, s OC$\underline{H}_3$), 2.27 (1H, m, CH), 1.93-1.10 (12H, m, CH_2 x 5, CH x 2), 1.18 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C (75 MHz; C_6D_6) δ 183.0 (s), 166.0 (s), 159.5 (s), 131.0 (s), 129.9 (d x 2), 114.0 (d x 2), 99.2 (d), 55.5 (q), 47.0 (d), 44.0 (t), 43.0 (s), 34.3 (d), 30.8 (d), 29.7 (t), 29.3 (t), 23.9 (t), 23.5 (q), 22.6 (t), 22.1 (t), 19.0 (q); EI-MS *m/z* 339 (M^+, 70), 219 (15), 121 (100); HRMS Calcd for $C_{22}H_{29}NO_2$: 339.2198, found 339.2198.

Data for (258a): yield (36%); clear oil; IR (neat, cm^{-1}) 1714, 1611; ^1H NMR (300 MHz, C_6D_6) δ 7.18, (2H, d, *J* = 8.6 Hz, CHCHCOCH$_3$), 6.77 (2H, d, *J* = 8.6 Hz, CH=COCH$_3$), 4.60 (2H, s, CH_2N), 3.70 (3H, s, OCH_3), 1.82 (4H, m, CH_2 x 2), 1.39-1.05 (10H, m, CH_2 x 4, CH x 2), 1.28 (6H, s, CH_3 x 2); ^{13}C (75 MHz; C_6D_6) δ 184.0 (s), 164.1 (s), 160.5 (s), 134.4 (s), 129.0 (d x 2), 121.5 (s), 114.1 (d x 2), 55.5 (q), 47.1 (s), 42.4 (t), 34.5 (d), 31.8 (d), 29.7 (t), 28.6 (t), 23.0 (t x 2), 22.6, (q x 2) 21.1 (t), 20.7 (t); CI-MS m/z 340 (M^+, 100), 220 (15), 121 (15); HRMS Calcd for $C_{22}H_{29}NO_2$: 339.2198, found 339.2198.

5.2.3 General synthesis of secondary bromoacetamide cyclisation precursors

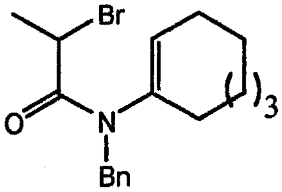
The appropriate imine (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. 2-bromopropionyl-bromide (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was then stirred for 2 hours at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (9:1).

N-Benzyl-2-bromo-*N*-(cyclohex-1-enyl)-propanamide (196)



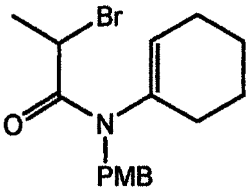
Imine (102) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (197): yield (66%); clear oil; IR (neat, cm^{-1}) 1656; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22-7.09 (5H, m, Ar-H), 5.46 (1H, m, CH=C), 4.87-4.55 (3H, br s, CH$_2$N, CHBrCH$_3$), 2.10 (2H, m, CH$_2$), 1.97 (2H, m, CH$_2$), 1.76 (3H, d, *J* = 8.5 Hz, CH$_3$), 1.63 (2H, m, CH$_2$), 1.50 (2H, m, CH$_2$); ^{13}C (75 MHz, CDCl$_3$) δ 169.6 (s), 137.9 (s), 137.8 (s), 129.4 (d), 128.9 (d x 2), 128.7 (d x 2), 127.9 (d), 50.3 9 (t), 39.9 (d), 28.3 (t), 27.4 (t), 25.0 (t), 21.7 (q), 21.4 (t); EI-MS *m/z* 322 (M$^+$, 80), 243 (92), 241 (74), 91 (75), 55 (100); HRMS Calcd for C$_{16}$H$_{20}$BrNO: 322.0807, found 322.0809.

N-Benzyl-2-bromo-*N*-(cyclooct-1-enyl)-propanamide (202)



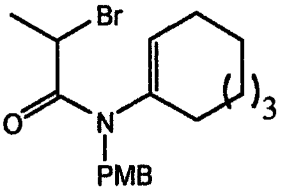
Imine (363) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (202): yield (68%); clear oil; IR (neat, cm^{-1}) 1651; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21-7.09 (5H, m, Ar-H), 5.37 (1H, m, CH=C), 4.75 (1H, br s, CHBrCH$_3$), 4.80-4.30 (2H, br m, CH$_2$N), 2.36-2.28 (2H, m, CH$_2$), 2.00 (2H, m, CH$_2$), 1.76 (3H, d, *J* = 6.7 Hz, CHBrCH$_3$), 1.45-1.15 (8H, m, CH$_2$ x 4); ^{13}C (75 MHz, CDCl$_3$) δ 170.0 (s), 140.1 (s), 137.9 (s), 131.5 (d), 128.7 (d x 2), 128.6 (d x 2), 127.3 (d), 51.1 (t), 40.3 (d), 29.2 (t), 28.5 (t), 26.6 (t), 26.2 (t x 2), 26.0 (t), 22.5 (q); CI-MS *m/z* 350 (MH^+, 39), 270 (100), 216 (11); HRMS Calcd for $C_{18}H_{24}BrNO$: 350.1119, found 350.1121.

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-propionamide (204)



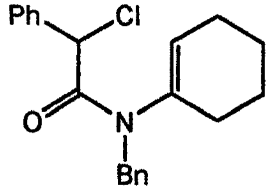
Imine (364) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (204): yield (78%); clear oil; IR (neat, cm^{-1}) 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.78 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.44 (1H, br s, C<u>H</u>=C), 4.70 (1H, br s, C<u>H</u>BrCH$_3$), 4.50 (2H, br m, C<u>H</u>$_2$N), 3.73 (3H, s, OC<u>H</u>$_3$), 2.11-1.94 (4H, m, C<u>H</u>$_2$ x 2), 1.76 (3H, d, *J* = 6.6 Hz, CHBrC<u>H</u>$_3$), 1.64 (2H, m, C<u>H</u>$_2$), 1.52 (2H, m, C<u>H</u>$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 169.4 (s), 159.2 (s), 137.8 (s), 130.9 (d x 2), 130.0 (s), 129.4 (d), 114.0 (d x 2), 55.5 (q), 49.7 (t), 40.0 (d), 27.1 (t), 25.7 (t), 22.6 (t), 22.2 (q), 21.3 (t); CI-MS *m/z* 352 (M^+, 30), 272 (90), 121 (60); HRMS Calcd for $C_{17}H_{22}BrNO$: 352.0912, found 352.0911.

2-Bromo-N-cyclooct-1-enyl-N-(4-methoxy-benzyl)-propionamide (205)



Imine (375) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (205): yield (84%); clear oil; IR (neat, cm^{-1}) 1784; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.80 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.38 (1H, br s, C<u>H</u>=C), 4.80 (1H, br s, C<u>H</u>BrCH$_3$), 4.48 (2H, br m, C<u>H</u>$_2$N), 3.74 (3H, s, OC<u>H</u>$_3$), 2.38-2.00 (4H, br m, C<u>H</u>$_2$ x 2), 1.79 (3H, d, $J = 6.6$ Hz, CHBrC<u>H</u>$_3$), 1.51 (8H, m, C<u>H</u>$_2$ x 4); ^{13}C (75 MHz, CDCl$_3$)* δ 169.9 (s), 159.2 (s), 131.5 (d), 130.0 (d x 2), 114.0 (d x 2), 55.5 (q), 50.5 (t), 40.4 (d), 31.3 (t), 29.5 (t), 29.2 (t), 26.6 (t), 26.3 (t x 2), 22.5 (q); CI-MS *m/z* 380 (M$^+$, 90), 300 (45), 121 (100); HRMS Calcd for $C_{19}H_{26}BrNO$: 380.1225, found 380.1225. * 2 quaternary carbon signals were not observed, even after the application of slower relaxation time experiments.

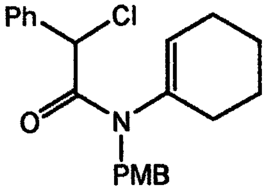
N-Benzyl-2-chloro-2-phenyl-*N*-cyclohex-1-enyl-acetamide (203)



Imine (102) (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. Chloro-phenyl-acetyl chloride (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was then stirred for 2 hours at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated in *vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (4:1): yield, (72%); clear orange oil; IR (neat, cm^{-1}) 1632; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61-7.50 (5H, m, Ar-<u>H</u>), 7.12-7.20 (5H, m, Ar-<u>H</u>), 5.78 (1H, s, CH=C), 5.41-5.15 (1H, br m, C<u>H</u>ClPh), 4.91-4.30 (2H, br m, C<u>H</u>$_2$N), 2.40 (2H, m, CHC<u>H</u>$_2$), 2.17-1.50 (6H, m, C<u>H</u>$_2$ x 3); ^{13}C (75 MHz; CDCl$_3$) δ 164.0 (s), 137.5 (s), 129.6 (s), 129.3 (d), 129.2 (d x 2), 129.1 (d x 2), 128.7 (d), 121.1 (s), 128.7 (d x 2), 128.6 (d x 2), 127.8 (d), 61.4 (d), 49.9 (t), 27.7 (t), 24.5 (t), 22.4 (t), 21.1 (t); EI-MS *m/z*

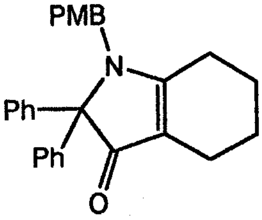
339 (M^+, 15), 304 (95), 185 (14), 149 (55), 91 (100); HRMS Calcd for $C_{21}H_{22}ClNO$: 339.1389, found 339.1377.

2-Chloro-*N*-cyclohex-1-enyl-*N*-(4-methoxy-benzyl)-2-phenyl-acetamide (206)



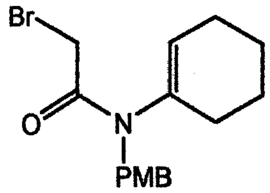
Imine (364) was reacted under the conditions described for (203) to give the required compound (206): yield, (84%); clear yellow oil; IR (neat, cm^{-1}) 1660, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53-7.15 (7H, m, Ar-H), 6.84-6.79 (2H, m, Ar-H), 5.74 (1H, s, CH=C), 5.40-4.39 (3H, br m, CH_2N, CHClPh), 3.79 (3H, s, OCH_3), 2.07 (2H, m, $CHCH_2$), 1.79-1.53 (6H, m, CH_2 x 3); ^{13}C (75 MHz; $CDCl_3$) δ 167.3 (s), 164.2 (s), 159.3 (s), 137.6 (s), 130.8 (d x 2), 129.8 (s), 129.2 (d x 2), 129.0 (d x 2), 128.8 (d), 128.7 (d), 114.0 (d x 2), 60.8 (d), 55.6 (q), 49.9 (t), 28.5 (t), 25.1 (t), 23.0 (t), 21.7 (t); EI-MS *m/z* 369 (M^+, 10), 333 (100), 279 (25), 121 (45); HRMS Calcd for $C_{22}H_{24}ClNO_2$: 369.1495, found 369.1499.

1-(4-Methoxy-benzyl)-2,2-diphenyl-1,2,4,5,6,7-hexahydro-indol-3-one (217)



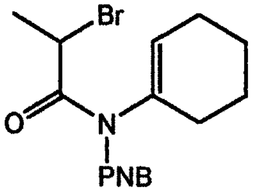
Imine (364) (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. Chloro-diphenyl-acetyl chloride (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was stirred for 2 hours at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (5:1): yield, (80%); clear yellow oil; IR (neat, cm^{-1}) 1704, 1677; ^{1}H NMR (350 MHz, $CDCl_3$) δ 7.31-7.09 (12H, m, Ar-H), 6.82 (2H, d, J = 8.6 Hz, CH=$COCH_3$), 4.64 (2H, s, CH_2N), 3.77 (3H, s, OCH_3), 2.19 (2H, m, CH_2), 2.00 (2H, m, CH_2), 1.69 (2H, m, CH_2); ^{13}C (75 MHz; $CDCl_3$) δ 179.8 (s), 159.2 (s), 141.3 (s x 2), 137.3 (s), 130.4 (s), 128.9 (d x 5), 128.7 (d x 4), 127.3 (d x 2), 119.3 (s), 114.4 (d x 2), 65.5 (s), 55.6 (q), 43.3 (t), 23.0 (t), 22.6 (t), 22.2 (t), 21.8 (t); EI-MS *m/z* 409 (M^+, 100), 288 (15), 121 (70), 83 (25); HRMS Calcd for $C_{28}H_{27}NO_2$: 409.2041, found 409.2036.

2-Bromo-N-cyclohex-1-enyl-N-(4-methoxy-benzyl)-acetamide (225)



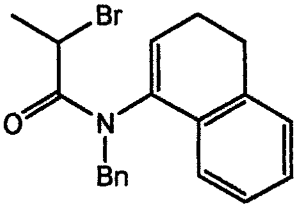
Imine (364) (9 mmol) was dissolved in dry toluene (50 ml) and cooled to 0°C with stirring. Bromo-acetyl bromide (9 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (9 mmol). The reaction was stirred for 3 hours at room temperature and dropped onto H_2O (50 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated in *vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (4:1): yield (62%); clear oil; IR (neat, cm^{-1}) 1652; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16 (2H, d, J = 8.6 Hz, CHCHCOCH_3), 6.78 (2H, d, J = 8.6 Hz, CH=$COCH_3$), 5.45 (1H, br s, CH=C), 4.53 (2H, br m, CH_2N), 3.90 (2H, s, CH_2Br), 3.76 (3H, s, OCH_3), 2.01 (4H, m, C$\underline{H}_2$ x 2), 1.68 (2H, m, C$\underline{H}_2$), 1.52 (2H, m, C$\underline{H}_2$); ^{13}C (75 MHz, CDCl$_3$) δ 166.3 (s), 159.3 (s), 138.1 (s), 130.5 (d x 2), 129.7 (s), 129.6 (d), 114.5 (d x 2), 55.6 (q), 49.6 (t), 28.3 (t), 27.7 (t), 25.1 (t), 23.0 (t), 21.7 (t); CI-MS *m/z* 338 (M$^+$, 10), 260 (40), 121 (100); HRMS Calcd for $C_{16}H_{20}BrNO_2$: 338.0755, found 338.0756.

2-Bromo-*N*-cyclohex-1-enyl-*N*-(4-nitro-benzyl)-propionamide (207)



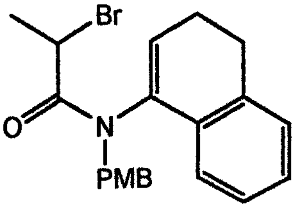
Imine (378) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (207): yield (83%); clear oil; IR (neat, cm^{-1}) 1669, 1552, 1346; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.12 (2H, d, J = 8.6 Hz, C$\underline{H}$=CNO$_2$), 7.40 (2H, d, J = 8.6 Hz, C$\underline{H}$CHCNO$_2$), 5.59 (1H, s, C$\underline{H}$=C), 4.82 (1H, m, C$\underline{H}_a$H$_b$N), 4.75 (1H, s, C$\underline{H}$BrCH$_3$), 4.50 (1H, m, C$\underline{H}_a$H$_b$N), 2.25-2.00 (4H, m, C$\underline{H}_2$ x 2), 1.77 (3H, d, J = 6.6 Hz, CHBrC$\underline{H}_3$), 1.69 (2H, m, C$\underline{H}_2$), 1.52 (2H, m, C$\underline{H}_2$); ^{13}C (75 MHz, CDCl$_3$) δ 173.5 (s), 170.4 (s), 147.9 (s),145.2 (s), 129.8 (d), 129.4 (d x 2), 124.0 (d x 2), 49.9 (t), 39.2 (d), 28.2 (t), 25.0 (t), 23.0 (t), 22.3 (q), 21.4 (t); CI-MS *m/z* 367 (M$^+$, 30), 287 (20), 257 (75), 152 (70), 106 (65) ; HRMS Calcd for $C_{16}H_{19}BrN_2O_3$: 367.0657, found 367.0671.

N-Benzyl-2-bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-propionamide (227)



Imine (369) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (227): yield (60%); clear oil; IR (neat, cm^{-1}) 1677; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.21-7.15 (9H, m, Ar-H), 5.86 (1H, t, *J* = 4.6 Hz, CH=C), 5.54 (1H, d, *J* = 14.3 Hz, CH$_a$H$_b$N), 4.40 (1H, q, *J* = 6.7, 6.4 Hz, CHBrCH$_3$), 3.83 (1H, d, *J* = 14.3 Hz, CH$_a$H$_b$N), 2.82 (2H, m, CH$_2$), 2.33 (2H, m, CH$_2$), 1.75 (3H, d, *J* = 6.7 Hz, CHBrCH$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 170.9 (s), 137.8 (s), 137.4 (s), 136.5 (s), 133.3 (s), 130.3 (d), 129.7 (d), 129.4 (d), 128.8 (d x 2), 128.7 (d x 2), 128.0 (d), 127.3 (d), 51.0 (t), 40.2 (d), 27.6 (t), 23.1 (t), 22.4 (q); EI-MS *m/z* 370 (M$^+$, 10), 290 (81), 145 (30), 91(60), 83 (100); HRMS Calcd for C$_{20}$H$_{20}$BrNO: 370.0806, found 370.0805.

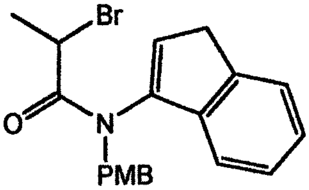
2-Bromo-*N*-(3,4-dihydro-naphthalen-1-yl)-*N*-(4-methoxy-benzyl)-propionamide (228)



Imine (370) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (228): yield (80%); clear oil; IR (neat, cm^{-1}) 1661; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20-7.17 (5H, m, Ar-H), 6.84-6.80 (3H, m, Ar-H), 5.84 (1H, t, *J* = 4.6 Hz, CH=C), 5.58 (1H, d, *J* = 10.4 Hz, CH$_a$H$_b$N), 4.40 (1H, q, *J* = 6.7, 6.6 Hz, CHBrCH$_3$), 3.85 (1H, d, *J* = 10.4 Hz, CH$_a$H$_b$N), 3.78 (3H, s, OCH$_3$), 2.84 (2H, m, CH$_2$), 2.34 (2H, m, CH$_2$), 1.76 (3H, d, *J* = 6.6 Hz, CHBrCH$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 170.7 (s), 159.4 (s), 137.3 (s), 136.4 (s), 131.8 (s), 130.7 (d), 130.3 (d x 2), 129.3 (d), 129.0 (s), 128.4 (d), 127.4 (d), 121.9 (d), 114.0 (d x 2), 55.6 (q), 50.3 (t), 40.2 (d), 27.5

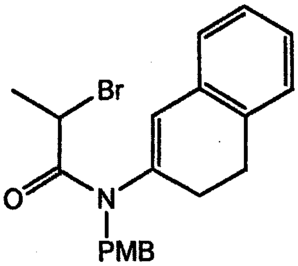
(t), 23.1 (t), 21.5 (q); CI-MS *m/z* 400 (MH^+, 65), 320 (100), 200 (80), 121 (50); HRMS Calcd for $C_{21}H_{22}BrNO_2$: 400.0912, found 400.0911.

2-Bromo-*N*-(3H-inden-1-yl)-*N*-(4-methoxy-benzyl)-propionamide (229)



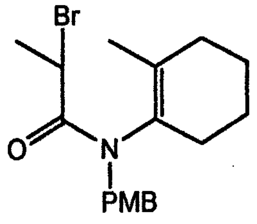
Imine (377) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (229): yield (56%); clear oil; IR (neat, cm^{-1}) 1669; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 7.31-7.16 (4H, m, Ar-<u>H</u>), 6.81 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 6.30 (1H, s, C<u>H</u>=C), 5.40 (1H, m, C<u>H</u>BrCH$_3$), 4.35-4.09 (2H, br m, C<u>H</u>$_2$N), 3.75 (3H, s, OCH$_3$), 3.41 (2H, br s, C<u>H</u>$_2$), 1.75 (3H, d, *J* = 6.4 Hz, CHBrC<u>H</u>$_3$); ^{13}C (75 MHz, $CDCl_3$) δ 170.8 (s), 160.1 (s), 143.9 (s), 141.2 (s), 136.2 (s), 131.4 (d x 2), 129.9 (s), 128.6 (d), 128.4 (d), 127.2 (d), 126.6 (d), 126.3 (d), 114.1 (d x 2), 55.6 (q), 50.7 (t), 39.4 (d), 36.7 (t), 22.2 (q); EI-MS *m/z* 385 (M^+, 80), 305 (50), 250 (30), 121 (100); HRMS Calcd for $C_{20}H_{20}BrNO_2$: 386.0755, found 386.0754.

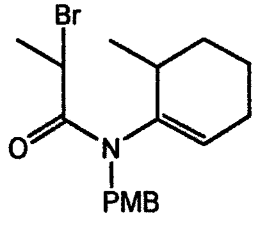
2-Bromo-*N*-(3,4-dihydro-naphthalen-2-yl)-*N*-(4-methoxy-benzyl)-propionamide (230)



Imine (376) was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (230): yield (69%); clear oil; IR (neat, cm^{-1}) 1645; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 (2H, d, J = 8.6 Hz, C$\underline{\text{H}}$CHCOCH$_3$), 7.22 (3H, m, Ar-$\underline{\text{H}}$), 7.05 (1H, m, Ar-$\underline{\text{H}}$), 6.90 (2H, d, J = 8.6 Hz, C$\underline{\text{H}}$=COCH$_3$), 6.31 (1H, s, C$\underline{\text{H}}$=C), 4.94 (1H, m, C$\underline{\text{H}}$BrCH$_3$), 4.77 (2H, br m, C$\underline{\text{H}_2}$N), 3.85 (3H, s, OCH$_3$), 2.99 (2H, m, C$\underline{\text{H}_2}$), 2.45 (2H, m, C$\underline{\text{H}_2}$), 1.91 (3H, d, J = 6.8 Hz, CHBrC$\underline{\text{H}_3}$); ^{13}C (75 MHz, CDCl$_3$) δ 169.5 (s), 159.5 (s), 139.1 (s), 134.4 (s), 133.0 (s), 130.6 (d x 2), 129.5 (s), 128.9 (d), 128.8 (d), 128.1 (d), 127.3 (d), 127.2 (d), 114.3 (d x 2), 55.6 (q), 50.3 (t), 40.0 (d), 28.9 (t), 27.4 (t), 22.5 (q); CI-MS m/z 400 (MH$^+$, 55), 320 (60), 200 (30), 121 (100); HRMS Calcd for $C_{21}H_{22}BrNO_2$: 400.0912, found 400.0909.

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(2-methyl-cyclohex-1-enyl)-propionamide (235a) and 2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(6-methyl-cyclohex-1-enyl)-propionamide (235b)

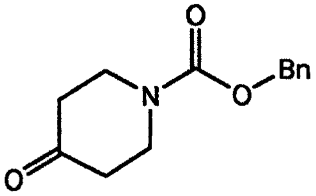




Imine derived from the condensation of *p*-methoxybenzylamine and 2-methylcyclohexanone was reacted under the conditions described in the general procedure 5.2.3 to give a 1:1 mixture of double bond regioisomers: yield (60%); clear oil; IR (neat, cm^{-1}) 1659, 1645; ^{1}H NMR for mixture of regioisomers (250 MHz, CDCl$_3$) δ 7.12 (2H, d, J = 8.7, C$\underline{\text{H}}$CHCOCH$_3$), 6.73 (2H, d, J = 8.7 Hz, C$\underline{\text{H}}$=COCH$_3$), 5.55 (1H, br s, C$\underline{\text{H}}$=C), 5.00 (1H, d, J = 14.2, C$\underline{\text{H}}$HN), 4.58 (1H, m, C$\underline{\text{H}}$BrCH$_3$), 3.82 (1H, d, J = 14.2, C$\underline{\text{H}}$HN), 3.78 (3H, s, OC$\underline{\text{H}_3}$), 2.29-1.94 (4H, m, C$\underline{\text{H}_2}$ x 2), 1.70 (3H, d,

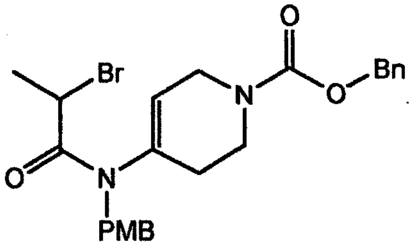
$J = 6.6$ Hz, $CHBrC\underline{H}_3$), 1.56 (2H, m, $C\underline{H}_2$), 1.38 (2H, m, $C\underline{H}_2$), 0.83 (3H, d, $J = 7.0$ Hz, $C\underline{H}_3$); ^{13}C for mixture of regioisomers (75 MHz, $CDCl_3$) δ 169.7 (s), 159.4 (s), 142.7 (s), 130.4 (d x 2), 129.9 (s), 129.3 (d), 114.7 (d x 2), 67.8 (s), 55.6 (q), 46.4 (t), 40.7 (d), 40.4 (q), 31.0 (t), 30.8 (d), 25.0 (t), 24.9 (t), 22.0 (t), 21.5 (t), 19.8 (q); CI-MS *m/z* 365 (M^+, 57), 121 (100); HRMS Calcd for $C_{18}H_{24}BrNO_2$: 365.0990, found 365.0988.

4-Oxo-piperidine-1-carboxylic acid benzyl ester (239)



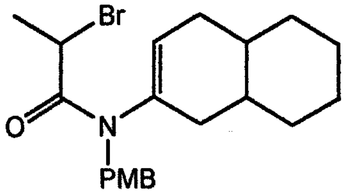
Benzyl chloroformate (2.4 g, 14.3 mmol) was added dropwise to a stirring solution of 4-piperidone hydrochloride (2 g, 13 mmol) and sodium carbonate (3 g, 28.6 mmol) in a 2:1 water/THF solution at 0°C. The reaction mixture was allowed warm to room temperature, stirred for a further 30 minutes, extracted with diethyl ether (2 x 50 mls), washed with brine and dried with $MgSO_4$ before being reduced to dryness in *vacuo*. The compound (239) was used directly for the next step: yield (83%); clear oil; IR (neat, cm^{-1}) 2962, 1703, 1429, 1273; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (5H, m, Ar-H), 5.15 (2 H, s, $OC\underline{H}_2$) 3.76 (4H, t, $J = 6.1$Hz, $C\underline{H}_2CO$), 2.42 (4H, t, $J = 6.1$Hz, $C\underline{H}_2NCO$); ^{13}C (75 MHz, $CDCl_3$) δ 207.0 (s), 155.5 (s), 136.7 (s), 128.9 (d x 2), 128.4 (d x 2), 128.4 (d), 67.9 (t), 43.5 (t x 2), 41.4 (t x 2); EI-MS *m/z* 233 (M^+, 45), 142 (20), 91 (100), 65 (20); HRMS Calcd for $C_{13}H_{15}NO_3$ 233.1051, found 233.1050.

4-[(2-Bromo-propionyl)-(4-methoxy-benzyl)-amino]-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (240)



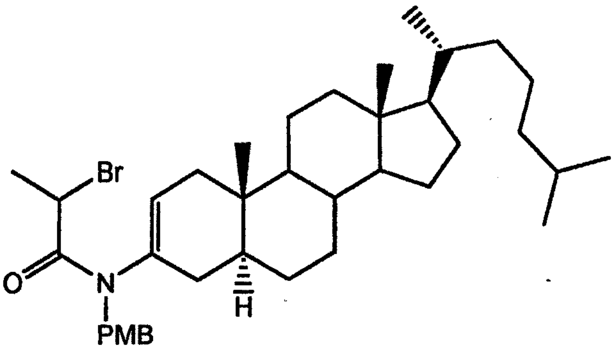
The imine derived from the condensation of (239) and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (240): yield (35%); clear oil; IR (neat, cm^{-1}) 1663, 1655; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38-7.34 (5H, m, Ar-H), 7.16 (2H, d, *J* = 8.5 Hz, C$\underline{H}$CHCOCH$_3$), 6.81 (2H, d, *J* = 8.5 Hz, C$\underline{H}$=COCH$_3$), 5.49 (1H, br s, C$\underline{H}$=C), 5.17 (2H, s, OC$\underline{H}_2$Ar), 4.62-4.53 (3H, br s, C$\underline{H}$BrCH$_3$, C$\underline{H}_2$N), 3.98 (2H, m, CHC$\underline{H}_2$N), 3.77 (3H, s, OC$\underline{H}_3$), 3.56 (2H, m, CH$_2$C$\underline{H}_2$N), 2.44 (2H, t, *J* = 5.9 Hz, C$\underline{H}_2$CH$_2$N), 1.80 (3H, d, *J* = 6.6 Hz, CHBrC$\underline{H}_3$); ^{13}C (75 MHz, CDCl$_3$) δ 169.3 (s), 159.4 (s), 155.5 (s), 136.7 (s), 130.8 (d), 130.4 (d), 129.8 (d x 2), 129.4 (d x 2), 129.2 (s), 128.8 (s), 128.4 (d x 2), 114.5 (d x 2), 68.0 (t), 55.6 (q), 49.7 (t), 43.1 (t), 43.0 (t), 41.3 (t), 39.7 (d), 22.2 (q); CI-MS *m/z* 487 (M$^+$, 15), 407 (70), 274 (45), 234 (100), 121 (75), 108 (80), 91 (92); HRMS Calcd for $C_{24}H_{27}BrN_2O_4$: 487.1232, found 487.1234.

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (255)



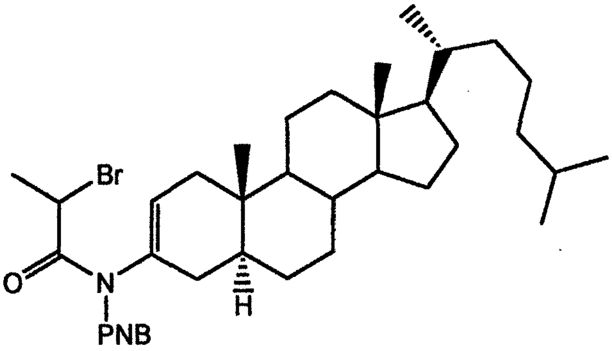
The imine derived from the condensation of decalone and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (255): yield (76%); clear yellow oil; IR (neat, cm^{-1}) 1650; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.77 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.36 (1H, s, C<u>H</u>=C), 4.69-4.20 (3H, br m, C<u>H$_2$</u>N, C<u>H</u>BrCH$_3$), 3.74 (3H, s, OCH$_3$), 2.22-1.85 (4H, m, C<u>H$_2$</u> x 2), 1.77 (3H, d, *J* = 6.4 Hz, CHBrC<u>H$_3$</u>), 1.60-1.19 (10H, m, C<u>H$_2$</u> x 5); ^{13}C (75 MHz, $CDCl_3$) δ 169.5 (s), 159.3 (s), 134.4 (d), 131.3 (d x 2), 130.0 (s), 129.8 (s), 114.0 (d x 2), 55.6 (q), 49.7 (t), 36.1 (d), 33.0 (d), 32.3 (d), 32.2 (t), 30.2 (t), 26.8 (t), 23.9 (t), 23.7 (t) 22.6 (q); EI-MS *m/z* 406 (M$^+$, 70), 326 (82), 121 (100); HRMS Calcd for $C_{21}H_{28}BrNO_2$: 406.1381, found 406.1379.

2-Bromo-*N*-[17-(1,5-dimethyl-hexyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl]-*N*-(4-methoxy-benzyl)-propionamide (261)



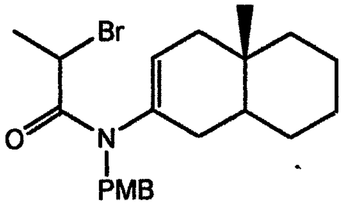
The imine derived from the condensation of α-cholesterone and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (261): yield (89%); yellow crystals; mp 32-35°C; IR (KBr Disc, cm^{-1}) 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 8.9 Hz, C<u>H</u>CHCOCH$_3$), 6.77 (2H, d, *J* = 8.9 Hz, C<u>H</u>=COCH$_3$), 5.30 (1H, br s, C<u>H</u>=C), 4.64-4.30 (3H, br m, C<u>H$_2$</u>N, C<u>H</u>BrCH$_3$), 3.72 (3H, s, OCH$_3$), 1.96-1.91 (2H, m, CHCH_2), 1.76 (3H, d, J = 6.7 Hz, CHBrCH_3), 1.65-0.96 (27H, m, CH_2 x 10, CH x 7), 0.87 (3H, d, J = 6.7 Hz, CHCH_3), 0.84 (3H, m CH_3), 0.83 (3H, m CH_3), 0.70-0.61 (6H, m CH(CH_3)$_2$), ; ^{13}C (75 MHz, CDCl$_3$) δ 169.4 (s), 159.4 (s), 130.4 (d x 2), 130.0 (s), 129.9 (s), 128.4 (d), 114.0 (d x 2), 56.7 (q), 55.5 (d), 53.2 (d), 48.1 (t), 42.3 (t), 41.6 (d), 40.1 (t), 40.0 (d), 38.9 (t), 38.6 (t), 36.9 (t), 36.1 (d), 35.8 (d), 34.6 (s), 32.8 (s), 32.2 (t), 28.5 (t), 28.4 (t), 28.3 (t), 24.7 (t), 24.3 (t), 23.2 (q), 23.0 (q), 22.6 (d), 22.5 (q), 21.0 (t), 19.1 (q), 12.4 (q x 2); CI-MS m/z 640 (MH$^+$, 10), 560 (25), 194 (35), 121 (100); HRMS Calcd for $C_{38}H_{58}BrNO_2$: 640.3729, found 640.3722.

2-Bromo-*N*-[17-(1,5-dimethyl-hexyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl]-*N*-(4-nitro-benzyl)-propionamide (262)



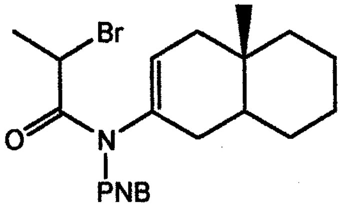
The imine derived from the condensation of α-cholesterone and *p*-nitrobenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (262). Crystals of X-ray quality were produced *via* slow recrystallisation from chloroform: yield (72%); white crystals; mp 43-46°C; IR (KBr disc, cm^{-1}) 1657, 1607, 1522, 1343; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.15 (2H, d, J = 8.7 Hz, CH=CNO$_2$), 7.42 (2H, d, J = 8.7 Hz, CHCHCNO$_2$), 5.43 (1H, br s, CH=C), 4.85-4.42 (3H, br m, CH_2N, CHBrCH$_3$), 2.03 (2H, m, CHCH_2), 1.80 (3H, d, J = 6.8 Hz, CHBrCH_3), 1.69-0.95 (27H, m, CH_2 x 10, CH x 7), 0.89 (3H, d, J = 6.7 Hz, CHCH_3), 0.85 (3H, m C<u>H</u>$_3$), 0.83 (3H, m C<u>H</u>$_3$), 0.73-0.64 (6H, m CH(C<u>H</u>$_3$)$_2$), ; ^{13}C (75 MHz, CDCl$_3$) δ 169.5 (s), 147.0 (s), 144.7 (s), 135.7 (s), 128.9 (d x 2), 128.1 (d), 123.4 (d x 2), 56.0 (d), 53.1 (d), 48.0 (t), 42.3 (t), 41.6 (d), 40.0 (t), 39.9 (d), 38.9 (t), 38.5 (t), 36.9 (t), 36.1 (d), 35.8 (d), 34.6 (s), 32.8 (s), 32.0 (t), 28.5 (t), 28.4 (t), 28.0 (t), 24.7 (t), 24.3 (t), 23.1 (q), 23.0 (q), 22.8 (d), 22.5 (q), 21.0 (t), 19.1 (q), 13.0 (q x 2); CI-MS *m/z* 640 (MH$^+$, 55), 575 (30), 545 (100), 440 (60), 106 (65); HRMS Calcd for $C_{37}H_{55}BrN_2O_2$: 655.3474, found 655.3462.

2-Bromo-*N*-(4-methoxy-benzyl)-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-propionamide (269)



The imine derived from the condensation of 4a-methyl-octahydro-naphthalen-2-one (266)^{147} and *p*-methoxybenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (269): yield (84%); clear yellow oil; IR (thin film, cm^{-1}) 1652; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.18 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.80 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.30 (1H, s, C<u>H</u>=C), 4.67-4.20 (3H, br m, C<u>H</u>$_2$N, C<u>H</u>BrCH$_3$), 3.74 (3H, s, OCH$_3$), 2.56-1.89 (3H, m, C<u>H</u>CCH$_3$, CHC<u>H</u>$_2$), 1.78 (3H, d, *J* = 6.7 Hz, CHBrC<u>H</u>$_3$), 1.67-1.08 (10H, m, C<u>H</u>$_2$ x 5), 1.18 (3H, m, CHCC<u>H</u>$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 169.6 (s), 159.2 (s), 134.4 (d), 130.5 (d x 2), 130.1 (s), 130.0 (s), 114.0 (d x 2), 55.6 (q), 49.7 (t), 41.8 (d), 40.0 (d), 38.8 (t), 34.1 (s), 31.0 (t), 28.9 (t), 26.6 (q), 25.7 (t) 22.6 (q), 22.5 (t), 22.0 (t); CI-MS *m/z* 420 (MH$^+$, 15), 340 (65), 243 (15), 121 (100); HRMS Calcd for $C_{22}H_{30}BrNO_2$: 420.1538, found 420.1539.

2-Bromo-*N*-(4a-methyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl)-*N*-(4-nitro-benzyl)-propionamide (273)

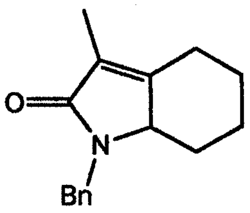


The imine derived from the condensation of 4a-methyl-octahydro-naphthalen-2-one (266)[147] and *p*-nitrobenzylamine was reacted under the conditions described in the general procedure 5.2.3 to give the required compound (273): yield (47%); clear yellow oil; IR (thin film, cm^{-1}) 1650, 1545, 1339; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (2H, d, *J* = 8.4 Hz, C$\underline{H}$=CNO$_2$), 7.39 (2H, d, *J* = 8.4 Hz, C$\underline{H}$CHCNO$_2$), 5.37 (1H, s, C$\underline{H}$=C), 4.94-4.29 (3H, m, C$\underline{H}_2$N, C$\underline{H}$BrCH$_3$), 2.60-1.85 (3H, m, C$\underline{H}$CCH$_3$, CHC$\underline{H}_2$), 1.81 (3H, d, *J* = 6.7 Hz, CHBrC$\underline{H}_3$), 1.76-1.18 (10H, m, C$\underline{H}_2$ x 5), 1.16 (3H, m, CHCC$\underline{H}_3$); ^{13}C (75 MHz, $CDCl_3$) δ 170.0 (s), 147.6 (s), 145.5 (s), 145.4 (s), 129.6 (d x 2), 128.5 (d), 124.0 (d x 2), 49.9 (t), 41.7 (d), 40.5 (d), 38.8 (t), 34.2 (s), 31.4 (t), 28.9 (t), 26.6 (q), 25.6 (t) 22.6 (q), 22.4 (t), 22.1 (t); CI-MS *m/z* 435 (MH$^+$, 90), 355 (30), 325 (100), 220 (85), 106 (70); HRMS Calcd for $C_{21}H_{27}BrN_2O_2$: 435.1284, found 435.1283.

5.2.4 General procedure for cyclisation of secondary bromoacetamides (stoichiometric method)

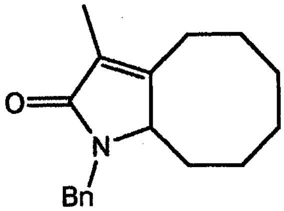
Cu(I)Br (43mg, 0.3 mmol) was added to solution of bromoacetamide (0.3mmol) and TPA-ligand (123) (290 mg, 0.3mmol) in 2.5ml of the appropriate solvent. The resulting solution was refluxed with stirring for 2hrs. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography (9:1 petroleum ether : ethyl acetate).

1-Benzyl-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (197)



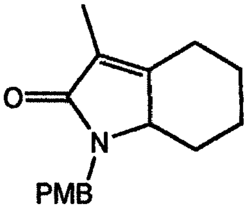
Precursor (196) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (72%); clear oil; IR (neat, cm^{-1}) 1687; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.17-7.09 (5H, m, Ar-H), 4.90 (1H, d, *J* = 15.0 Hz, CHHN), 4.12 (1H, d, *J* = 15.0 Hz, CHHN), 3.39 (1H, m, CH), 2.65 (1H, m, CHH), 2.19 (1H, m, CHH), 1.95 (1H, m, CHH), 1.83 (2H, m, CH$_2$), 1.74 (3H, m, CH$_3$), 1.20 (2H, m, CH$_2$), 0.85 (1H, m, CHH); ^{13}C (75 MHz, CDCl$_3$) δ 172.6 (s), 153.4 (s), 138.5 (s), 129.4 (d x 2), 128.2 (d x 2), 127.6 (d), 124.6 (s), 60.3 (d), 44.1 (t), 33.4 (t), 27.5 (t), 26.3 (t), 22.5 (t), 8.8 (q); EI-MS *m/z* 241 (M$^+$, 100), 226 (35), 91 (85); HRMS Calcd for $C_{16}H_{19}NO$: 241.1466, found 241.1459.

1-Benzyl-3-methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (208)



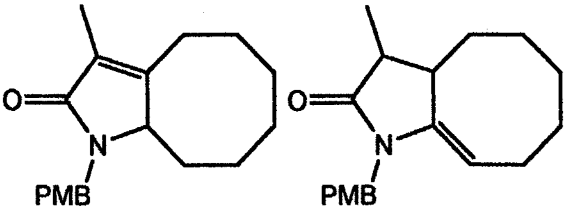
Precursor (202) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (78%); clear oil; IR (neat, cm^{-1}) 1706; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.17-7.09 (5H, m, Ar-H), 4.99 (1H, d, *J* = 15.2 Hz, CHHN), 3.87 (1H, d, *J* = 15.2 Hz, CHHN), 3.60 (1H, m, CH), 2.51 (1H, m, CHH), 2.12 (1H, m, CHH), 1.87 (1H, m, CHH), 1.82 (2H, m, CH_2), 1.75 (3H, m, CH_3), 1.690-1.14 (7H, m, CH_2 x 3, CHH); ^{13}C (75 MHz, $CDCl_3$) δ 172.8 (s), 153.0 (s), 139.1 (s), 129.4 (d x 2), 128.1 (d x 2), 127.3 (d), 123.6 (s), 60.1 (d), 44.5 (t), 29.2 (t), 28.4 (t), 27.5 (t), 26.3 (t), 22.5 (t), 21.3, (t), 9.3 (q); EI-MS *m/z* 269 (M^+, 43), 191 (70), 91 (100); HRMS Calcd for $C_{18}H_{23}NO$: 269.1779, found 269.1779.

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (210)



Precursor (204) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (86%); clear oil; IR (neat, cm^{-1}) 1690; ^1H NMR (300MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.6 Hz, $CHCHCOCH_3$), 6.80 (2H, d, *J* = 8.6 Hz, $CH=COCH_3$), 4.92 (1H, d, *J* = 15.0 Hz, CHHN), 4.12 (1H, d, *J* = 15.0 Hz, CHHN), 3.78 (3H, s, OCH_3), 3.42 (1H, m, CH), 2.65 (1H, m, CHH), 2.19 (1H, m, CHH), 1.95 (1H, m, CHH), 1.85 (2H, m, CH_2), 1.78 (3H, m, CH_3), 1.29 (2H, m, CH_2), 0.95 (1H, m, CHH); ^{13}C (75 MHz, $CDCl_3$) δ 172.6 (s), 159.1 (s), 153.3 (s), 130.5 (s), 129.6 (d x 2), 124.7 (s), 114.3 (d x 2), 60.2 (d), 55.6 (q), 43.6 (t), 33.4 (t), 27.5 (t), 26.3 (t), 23.8 (t), 8.8 (q); EI-MS *m/z* 271 (M^+, 85), 163 (40), 121 (100); HRMS Calcd for $C_{17}H_{21}NO_2$: 271.1572, found 271.1576.

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (211) and 1-(4-Methoxy-benzyl)-3-methyl-1,3,3a,4,5,6,7,8-octahydro-cycloocta[b]pyrrol-2-one (214)

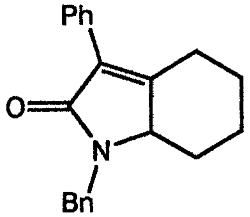


Precursor (205) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compounds. Data for (211): yield (82%); clear oil; IR (neat, cm^{-1}) 1700; ^{1}H NMR (300MHz, CDCl$_3$) δ 7.10 (2H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.72 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.99 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 3.87 (1H, d, *J* = 15.0 Hz, CH$\underline{H}$N), 3.70 (3H, s, OC$\underline{H_3}$), 3.64 (1H, m, C$\underline{H}$), 2.57 (1H, m, C$\underline{H}$H), 2.08 (1H, m, C$\underline{H}$H), 1.90 (1H, m, C$\underline{H}$H), 1.85 (2H, m, C$\underline{H_2}$), 1.78 (3H, app d, *J* = 1.7 Hz, C$\underline{H_3}$), 1.60-1.17 (7H, m, C$\underline{H_2}$ x 3, C$\underline{H}$H); ^{13}C (75 MHz, CDCl$_3$) δ 172.9 (s), 159.1 (s), 155.7 (s), 130.5 (s), 129.6 (d x 2), 128.7 (s), 114.3 (d x 2), 61.9 (d), 55.6 (q), 43.4 (t), 28.8 (t), 26.7 (t), 26.4 (t), 25.2 (t), 24.4 (t), 21.9 (t), 9.3 (q); CI-MS *m/z* 300 (MH$^+$, 70), 192 (45), 121 (100); HRMS Calcd for C$_{19}$H$_{25}$NO$_2$: 300.1963, found 300.1973.

Data for (214): yield (7%); clear oil; IR (neat, cm^{-1}) 1652; ^{1}H NMR (300MHz, CDCl$_3$) δ 7.13 (2H, d, *J* = 8.9 Hz, C$\underline{H}$CHCOCH$_3$), 6.83 (2H, d, *J* = 8.9 Hz, C$\underline{H}$=COCH$_3$), 4.65 (1H, m, CH=C), 4.60 (1H, d, *J* = 15.3 Hz, C$\underline{H}$HN), 4.42 (1H, d, *J* = 15.3 Hz, CH$\underline{H}$N), 3.71 (3H, s, OC$\underline{H_3}$), 2.45 (1H, m, C$\underline{H}$), 2.16 (1H, s, C$\underline{H}$CH$_3$), 2.57 (1H, m, C$\underline{H}$H), 2.03 (1H, m, C$\underline{H}$H), 1.96 (1H, m, C$\underline{H}$H), 1.84-1.40 (7H, m, C$\underline{H_2}$ x 3, C$\underline{H}$H), 1.15 (3H, d, *J* = 7.4 Hz, C$\underline{H_3}$); ^{13}C (75 MHz, CDCl$_3$) δ 178.9 (s), 159.0 (s), 143.2 (s), 130.1 (s), 129.8 (d x 2), 114.2 (d x 2), 101.7 (d), 55.6 (q), 45.0 (d), 44.0 (d), 43.1 (t), 38.2 (t), 29.3 (t), 25.8

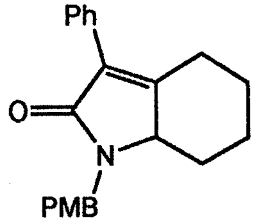
(t), 25.4 (t), 23.7 (t), 18.1 (q); EI-MS *m/z* 299 (M^+, 65), 244 (45), 180 (50), 121 (100); HRMS Calcd for $C_{19}H_{25}NO_2$: 299.1885, found 299.1884.

1-Benzyl-3-phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (209)



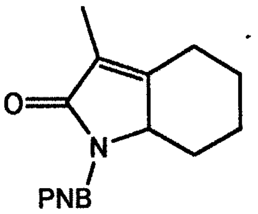
Cu(I)Cl (29.7 mg, 0.3 mmol) was added to solution of (203) (0.3mmol) and TPA-ligand (123) (290 mg, 0.3mmol) in toluene (2.5ml). The resulting solution was refluxed with stirring for 2hrs. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (9:1): yield (59%); clear oil; IR (neat, cm^{-1}) 1676; ^1H NMR (250MHz, $CDCl_3$) δ 7.45-7.12 (10H, m, Ar-$\underline{H}$), 5.10 (1H, d, *J* = 15.2 Hz, C$\underline{H}$HN), 4.15 (1H, d, *J* = 15.2 Hz, CH$\underline{H}$N), 3.26 (1H, m, C$\underline{H}$), 2.70 (1H, m, C$\underline{H}$H), 1.89 (1H, m, C$\underline{H}$H), 1.65 (1H, m, C$\underline{H}$H), 1.25 (2H, m, C$\underline{H}_2$), 0.95-0.62 (3H, m, C$\underline{H}_2$, C$\underline{H}$H); ^{13}C (75 MHz, $CDCl_3$) δ 170.7 (s), 155.5 (s), 138.3 (s), 131.9 (s), 129.7 (d x 2), 129.2 (d), 129.0 (d x 2), 128.9 (d x 2), 128.8 (s), 128.1 (d x 2), 127.7 (d), 60.3 (d), 44.4 (t), 33.5 (t), 27.7 (t), 27.0 (t), 23.6 (t); EI-MS *m/z* 303 (M^+, 100), 225 (20), 91 (70); HRMS Calcd for $C_{21}H_{21}NO$: 303.1623, found 303.1624.

1-(4-Methoxy-benzyl)-3-phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (212)



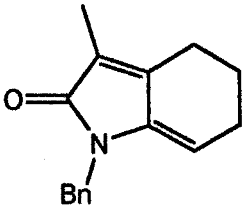
Precursor (206) was reacted under the conditions described above for (209) to give the following cyclic compound: yield (87%); clear oil; IR (neat, cm^{-1}) 1726; ^{1}H NMR (250MHz, $CDCl_3$) δ 7.50-7.19 (7H, m, Ar-$\underline{H}$), 6.83 (2H, d, J = 8.6 Hz, $C\underline{H}=COCH_3$), 5.04 (1H, d, J = 15.0 Hz, $C\underline{H}HN$), 4.15 (1H, d, J = 15.0 Hz, $CH\underline{H}N$), 3.78 (3H, s, $OC\underline{H}_3$), 3.65 (1H, dd, J = 5.5 Hz, $C\underline{H}$), 3.00 (1H, m, $C\underline{H}H$), 2.40 (1H, m, $C\underline{H}H$), 2.18 (1H, m, $C\underline{H}H$), 1.80 (2H, m, $C\underline{H}_2$), 1.37-1.06 (3H, m, $C\underline{H}_2$, $C\underline{H}H$); ^{13}C (75 MHz, $CDCl_3$) δ 170.6 (s), 159.3 (s), 155.4 (s), 132.0 (s), 130.5 (s), 129.8 (d x 2), 129.7 (d x 2), 129.1 (s), 128.6 (d x 2), 128.0 (d), 114.3 (d x 2), 60.1 (d), 55.7 (q), 43.7 (t), 33.6 (t), 27.8 (t), 27.0 (t), 23.7 (t); EI-MS *m/z* 333 (M$^+$, 50), 121 (100), 83 (55); HRMS Calcd for $C_{22}H_{23}NO_2$: 333.1728, found 333.1732.

3-Methyl-1-(4-nitro-benzyl)-1,4,5,6,7,7a-hexahydro-indol-2-one (213)



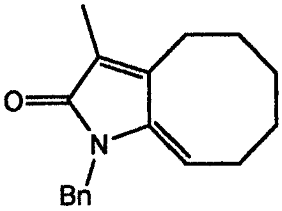
Precursor (207) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (65%); clear oil; IR (neat, cm^{-1}) 1698, 1530; ^{1}H NMR (250MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.8 Hz, $C\underline{H}=CNO_2$), 7.30 (2H, d, J = 8.8 Hz, $C\underline{H}CHCNO_2$), 4.89 (1H, d, J = 16.0 Hz, $C\underline{H}HN$), 4.35 (1H, d, J = 16.0 Hz, $CH\underline{H}N$), 3.47 (1H, m, $C\underline{H}$), 2.69 (1H, m, $C\underline{H}H$), 2.18 (1H, m, $C\underline{H}H$), 1.97 (1H, m, $C\underline{H}H$), 1.85 (2H, m, $C\underline{H}_2$), 1.83 (3H, m, $C\underline{H}_3$), 1.32-0.92 (3H, m, $C\underline{H}_2$, $C\underline{H}H$); ^{13}C (75 MHz, $CDCl_3$) δ 172.9 (s), 153.9 (s), 147.6 (s), 146.2 (s), 128.8 (d x 2), 124.8 (s), 124.3 (d x 2), 60.9 (d), 43.9 (t), 33.5 (t), 27.4 (t), 26.4 (t), 23.7 (t), 8.8 (q); EI-MS *m/z* 286 (M$^+$, 100), 271 (45), 256 (35), 106 (55); HRMS Calcd for $C_{16}H_{18}N_2O_3$: 286.1317, found 286.1313.

1-Benzyl-3-methyl-1,4,5,6-tetrahydro-indol-2-one (218)



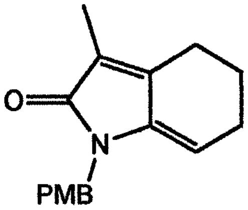
Precursor (196) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (42%); clear oil; IR (neat, cm^{-1}) 1706; ^{1}H NMR (250MHz, $CDCl_3$) δ 7.23-7.02 (5H, m, Ar-H), 5.00 (1H, t, $J = 4.5$ Hz, CH=C), 4.69 (2H, s, CH_2N), 1.99 (2H, t, $J = 5.5$ Hz, CH_2), 1.87 (3H, s, CH_3), 1.74 (2H, q, $J = 5.5$ Hz, CH_2), 1.34 (2H, quint, $J = 5.5$ Hz, CH_2); ^{13}C (75 MHz, $CDCl_3$) δ 164.3 (s), 150.1 (s), 140.0 (s), 138.9(s), 128.9 (d x 2), 127.6 (d x 2), 127.5 (d), 121.9 (s), 108.5 (d), 43.2 (t), 24.6 (t), 23.7 (t), 22.9 (t), 8.8 (q); EI-MS *m/z* 239 (M^+, 91), 216 (60), 91 (100); HRMS Calcd for $C_{16}H_{17}NO$: 239.1310, found 239.1316.

1-Benzyl-3-methyl-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (219)



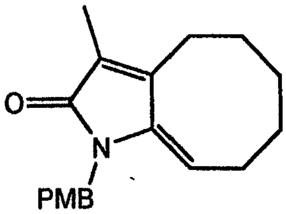
Precursor (202) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (57%); clear oil; IR (neat, cm^{-1}) 1685; ^{1}H NMR (250MHz, $CDCl_3$) δ 7.38-7.13 (5H, m, Ar-H), 5.27 (1H, t, $J = 8.8$ Hz, CH=C), 4.83 (2H, s, CH_2N), 2.77 (2H, t, $J = 7.0$ Hz, CH_2), 2.43 (2H, app q, $J = 7.0, 7.9$ Hz, CH_2), 1.91 (3H, s, CH_3), 1.69-1.18 (6H, m, CH_2 x 3); ^{13}C (75 MHz, $CDCl_3$) δ 170.9 (s), 143.1 (s), 142.8 (s), 138.2(s), 128.9 (d x 2), 127.9 (d x 2), 127.5 (d), 122.0 (s), 109.8 (d), 42.8 (t), 26.3 (t), 25.8 (t), 24.7 (t), 23.6 (t), 21.8 (t), 8.6 (q); EI-MS *m/z* 267 (M^+, 25), 160 (30), 91 (100); HRMS Calcd for $C_{18}H_{21}NO$: 267.1623, found 267.1620.

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6-tetrahydro-indol-2-one (221)



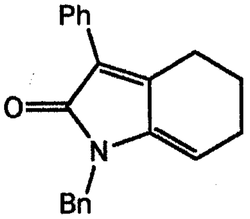
Precursor (204) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (71%); clear oil; IR (neat, cm^{-1}) 1704; ^1H NMR (250MHz, $CDCl_3$) δ 7.14 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.82 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.05 (1H, t, *J* = 6.0 Hz, C<u>H</u>=C), 4.68 (2H, s, C<u>H</u>$_2$N), 3.72 (3H, s, OCH$_3$), 1.97 (2H, t, *J* = 5.5 Hz, C<u>H</u>$_2$), 1.80 (3H, s, C<u>H</u>$_3$), 1.72 (2H, q, *J* = 5.5 Hz, C<u>H</u>$_2$), 1.35 (2H, quint, *J* = 5.5 Hz, C<u>H</u>$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 169.1 (s), 159.2 (s), 150.1 (s), 140.0 (s), 138.9(s), 129.9 (d x 2), 121.8 (s), 114.5 (d x 2), 110.2 (d), 55.6 (q), 43.1 (t), 25.8 (t), 24.7 (t), 22.5 (t), 8.9 (q); EI-MS *m/z* 269 (M^+, 55), 246 (26), 121 (100); HRMS Calcd for $C_{17}H_{19}NO_2$: 269.1415, found 269.1416.

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,6,7,8-hexahydro-cycloocta[b]pyrrol-2-one (222)



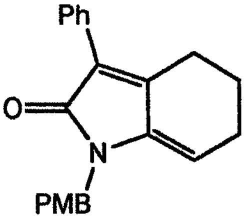
Precursor (205) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (86%); clear oil; IR (neat, cm^{-1}) 1701; ^{1}H NMR (250MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.7 Hz, C<u>H</u>CHCOCH_3), 6.85 (2H, d, *J* = 8.7 Hz, C<u>H</u>=COCH_3), 5.26 (1H, t, *J* = 8.6 Hz, C<u>H</u>=C), 4.89 (2H, s, C<u>H$_2$</u>N), 3.76 (3H, s, OC<u>H$_3$</u>), 2.80 (2H, t, *J* = 7.0 Hz, C<u>H$_2$</u>), 2.45 (2H, m, C<u>H$_2$</u>), 1.93 (3H, s, C<u>H$_3$</u>), 1.72-1.15 (6H, m, C<u>H$_2$</u> x 3); ^{13}C (75 MHz, $CDCl_3$) δ 170.9 (s), 158.3 (s), 143.2 (s), 143.0 (s), 138.5(s), 129.3 (d x 2), 122.0 (s), 114.0 (d x 2), 109.5 (d), 55.4 (q), 42.5 (t), 27.0 (t), 25.8 (t), 24.3 (t), 23.4 (t), 21.9 (t), 9.0 (q); EI-MS *m/z* 297 (M$^+$, 65), 121 (100); HRMS Calcd for $C_{19}H_{23}NO_2$: 297.1729, found 297.1725.

1-Benzyl-3-phenyl-1,4,5,6-tetrahydro-indol-2-one (220)



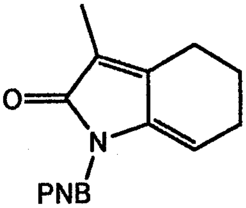
Cu(I)Cl (29.7 mg, 0.3 mmol) was added to solution of (203) (0.3mmol) and TPA-ligand (123) (290 mg, 0.3mmol) in 1,2-dichloroethane (2.5ml). The resulting solution was refluxed with stirring for 2 hours. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography, petroleum ether : ethyl acetate (9:1): yield (64%); clear oil; IR (neat, cm^{-1}) 1707; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.45-7.12 (10H, m, Ar-<u>H</u>), 5.32 (1H, t, *J* = 6.4 Hz, C<u>H</u>=C), 4.69 (2H, s, C<u>H$_2$</u>N), 3.73 (3H, s, OC<u>H$_3$</u>), 2.78 (2H, t, *J* = 6.4 Hz, C<u>H$_2$</u>), 2.33 (2H, q, *J* = 5.8 Hz, C<u>H$_2$</u>), 1.75 (2H, quint, *J* = 6.4 Hz, C<u>H$_2$</u>); ^{13}C (75 MHz, $CDCl_3$) δ 170.0 (s), 150.0 (s), 139.5 (s), 132.8 (s), 131.1 (s), 129.9 (d x 2), 129.6 (d x 2), 129.3 (d), 128.4 (d x 2), 128.2 (d x 2), 128.0 (d), 127.7 (s), 109.6 (d), 42.8 (t), 25.0 (t), 24.7 (t), 24.3 (t); EI-MS *m/z* 301 (M$^+$, 65), 91 (100); HRMS Calcd for $C_{21}H_{19}NO$: 301.1467, found 301.1466.

1-(4-Methoxy-benzyl)-3-phenyl-1,4,5,6-tetrahydro-indol-2-one (223)



Precursor (206) was reacted under the conditions described above for (220) to give the following cyclic compound: yield (74%); clear oil; IR (neat, cm^{-1}) 1700; ^1H NMR (250MHz, $CDCl_3$) δ 7.68-7.22 (7H, m, Ar-H), 6.83 (2H, d, J = 8.5 Hz, CH=$COCH_3$), 5.64 (1H, t, J = 6.4 Hz, CH=C), 4.77 (2H, s, CH_2N), 3.76 (3H, s, OCH_3), 2.80 (2H, t, J = 6.5 Hz, CH_2), 2.30 (2H, q, J = 5.8 Hz, CH_2), 1.77 (2H, quint, J = 6.4 Hz, CH_2); ^{13}C (75 MHz, $CDCl_3$) δ 169.5 (s), 159.5 (s), 139.1 (s), 136.9 (s), 132.1 (s), 130.7 (s), 129.8 (d x 2), 129.6 (d x 2), 129.3 (d x 2), 128.0 (d), 125.7 (s), 114.3 (d x 2), 111.2 (d), 55.6 (q), 42.7 (t), 24.7 (t), 24.5 (t), 23.9 (t); EI-MS *m/z* 331 (M^+, 70), 121 (100); HRMS Calcd for $C_{22}H_{21}NO_2$: 331.1572, found 331.1573.

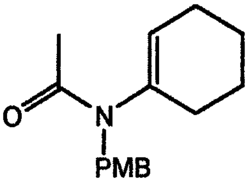
3-Methyl-1-(4-nitro-benzyl)-1,4,5,6-tetrahydro-indol-2-one (224)



Precursor (207) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (60%); clear oil; IR (neat, cm^{-1}) 1706, 1544; ^1H NMR (300MHz, $CDCl_3$) δ 8.14 (2H, d, J = 8.8 Hz, CH=CNO_2), 7.34 (2H, d, J = 8.8 Hz, $CHCHCNO_2$), 5.31 (1H, t, J = 4.7 Hz, CH=C), 4.77 (2H, s, CH_2N), 2.48 (2H, t, J = 6.2 Hz, CH_2), 2.18 (2H, q, J = 5.0 Hz, CH_2), 1.77 (3H, s, CH_3), 1.35 (2H, m, CH_2); ^{13}C (75 MHz, $CDCl_3$) δ

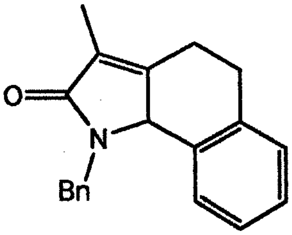
171.4 (s), 147.6 (s), 145.7 (s), 141.0 (s), 138.9(s), 128.9 (d x 2), 124.3 (d x 2), 123.9 (s), 109.0 (d), 42.6 (t), 24.6 (t), 23.6 (t), 22.9 (t), 8.8 (q); EI-MS *m/z* 284 (M^+, 75), 248 (20), 106 (35), 83 (100); HRMS Calcd for $C_{16}H_{16}N_2O_3$: 284.1160, found 284.1160.

N-Cyclohex-1-enyl-N-(4-methoxy-benzyl)-acetamide (226)



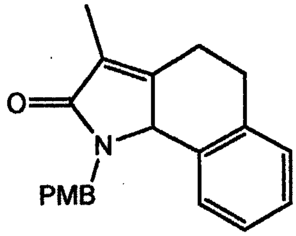
Cu(I)Br (43mg, 0.3 mmol) was added to solution of (225) (0.3mmol) and TPA-ligand (123) (290 mg, 0.3mmol) in toluene (2.5ml). The resulting solution was degassed and heated in a sealed tube at 120°C for 48 hours. On cooling, the copper residue was removed from solution by flushing it through a silica plug with ethyl acetate. The filtrate was then reduced to dryness in *vacuo* and purified by flash chromatography (9:1 petroleum ether : ethyl acetate) to give starting precursor (225) in 58% yield and compound (226): yield (17%); clear oil; IR (neat, cm^{-1}) 1700; ^1H NMR (250 MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.5 Hz, C$\underline{H}$CHCOCH$_3$), 6.79 (2H, d, J = 8.5 Hz, C$\underline{H}$=COCH$_3$), 5.33 (1H, br s, C$\underline{H}$=C), 4.47 (2H, br m, C$\underline{H_2}$N), 3.76 (3H, s, OC$\underline{H_3}$), 1.97 (3H, s, CH_3), 1.86 (4H, m, C$\underline{H_2}$ x 2), 1.56 (2H, m, C$\underline{H_2}$), 1.45 (2H, m, C$\underline{H_2}$); ^{13}C (75 MHz, $CDCl_3$) δ 170.1 (s), 159.1 (s), 139.2 (s), 130.7 (s), 130.4 (d x 2), 129.5 (d), 114.3 (d x 2), 55.6 (q), 49.1 (t), 28.5 (t), 25.1 (t), 23.1 (t), 22.0 (t), 21.9 (t); CI-MS *m/z* 259 (M^+, 57), 216 (15), 121 (100); HRMS Calcd for $C_{16}H_{21}NO_2$: 259.1572, found 259.1571.

1-Benzyl-3-methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (231)



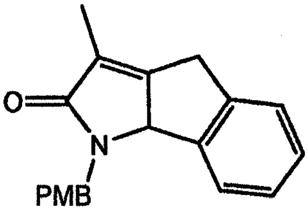
Precursor (227) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (85%); clear oil; IR (neat, cm^{-1}) 1711; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.30-7.11 (9H, m, Ar-H), 5.53 (1H, d, *J* = 15.0 Hz, CHHN), 4.58 (1H, s, CH), 4.43 (1H, d, *J* = 15.0 Hz, CHHN), 2.83 (2H, t, *J* = 7.3 Hz, CH$_2$), 2.66 (1H, t, *J* = 7.3 Hz, CH$_2$), 1.63 (3H, br s, CH$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 172.5 (s), 154.3 (s), 140.5 (s), 138.2 (s), 137.0 (s), 130.8 (d), 129.0 (d x 2), 128.8 (d x 2), 128.3 (d), 128.1 (d), 126.8 (s), 121.1 (d), 115.8 (d), 60.7 (d), 41.8 (t), 29.2 (t), 24.6 (t), 8.7 (q); EI-MS *m/z* 289 (M$^+$, 80), 91 (100); HRMS Calcd for $C_{20}H_{19}NO$: 289.1467, found 289.1465.

1-(4-Methoxy-benzyl)-3-methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (232)



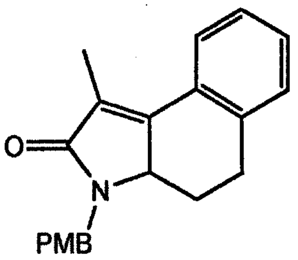
Precursor (228) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (91%); clear oil; IR (neat, cm^{-1}) 1706; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.21-7.14 (6H, m, Ar-H), 6.81 (2H, d, *J* = 8.9 Hz, CH=COCH$_3$), 5.55 (1H, d, *J* = 15.0 Hz, CHHN), 4.51 (1H, s, CH), 4.60 (1H, d, *J* = 15.0 Hz, CHHN), 3.76 (3H, s, OCH$_3$), 2.87 (3H, m, CH$_2$, CHH), 2.30 (1H, m, CHH), 1.78 (3H, br s, CH$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 175.3 (s), 159.4 (s), 153.4 (s), 137.8 (s), 136.1 (s), 130.1 (s), 130.0 (d x 2), 128.3 (d), 128.0 (d), 127.6 (d), 126.5 (s), 123.6 (d), 114.5 (d x 2), 60.7 (d), 55.6 (q), 46.9 (t), 28.6 (t), 23.7 (t), 9.5 (q); EI-MS *m/z* 320 (M^+, 75), 184 (20), 121 (100), 83 (45); HRMS Calcd for $C_{21}H_{21}NO_2$: 320.1650, found 320.1653.

3-(4-Methoxy-benzyl)-1-methyl-3a,8-dihydro-3H-3-aza-cyclopenta[a]inden-2-one (233)



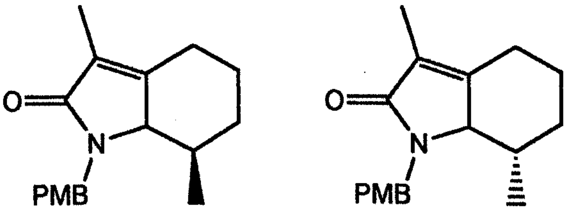
Precursor (229) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (84%); clear yellow oil; IR (neat, cm^{-1}) 1682; ^1H NMR (250MHz, $CDCl_3$) δ 7.28-7.15 (6H, m, Ar-<u>H</u>), 6.84 (2H, d, *J* = 8.9 Hz, C<u>H</u>=COCH₃), 5.14 (1H, br s, C<u>H</u>), 5.09 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.60 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.77 (3H, s, OC<u>H</u>₃), 3.61 (3H, m, C<u>H</u>₂), 1.81 (3H, br s, C<u>H</u>₃); ^{13}C (75 MHz, $CDCl_3$) δ 175.1 (s), 159.4 (s), 157.4 (s), 144.6 (s), 139.7 (s), 130.3(s), 129.8 (d x 2), 128.5 (d), 128.3 (d), 127.6 (s), 126.9 (d), 125.8 (d), 114.5 (d x 2), 67.2 (d), 55.7 (q), 46.7 (t), 31.0 (t), 10.0 (q); EI-MS *m/z* 305 (M^+, 55), 170 (40), 121 (100); HRMS Calcd for $C_{20}H_{19}NO_2$: 305.1415, found 305.1414.

3-(4-Methoxy-benzyl)-1-methyl-3,3a,4,5-tetrahydro-benzo[e]indol-2-one (234)



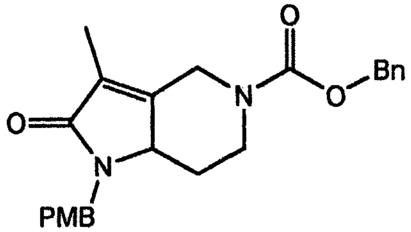
Precursor (229) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (96%); clear oil; IR (neat, cm^{-1}) 1675; ^{1}H NMR (250MHz, $CDCl_3$) δ 7.22-7.15 (6H, m, Ar-H), 6.81 (2H, d, *J* = 8.5 Hz, C<u>H</u>=$COCH_3$), 5.00 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.60 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.99 (1H, s, C<u>H</u>), 3.73 (3H, s, $OC\underline{H}_3$), 2.85 (3H, m, $C\underline{H}_2$, C<u>H</u>H), 2.32 (1H, m, CH<u>H</u>), 2.01 (3H, br s, $C\underline{H}_3$); ^{13}C (75 MHz, $CDCl_3$) δ 172.9 (s), 159.3 (s), 143.6 (s), 134.7 (s), 130.4 (s), 130.0 (s), 129.8 (d x 2), 129.4 (d), 129.1 (d), 128.3 (d), 127.4 (s), 123.8 (d), 114.4 (d x 2), 59.3 (d), 55.6 (q), 44.5 (t), 29.4 (t), 28.7 (t), 10.9 (q); EI-MS *m/z* 320 (M^+, 75), 121 (20), 83 (100); HRMS Calcd for $C_{21}H_{21}NO_2$: 320.1650, found 320.1648.

1-(4-Methoxy-benzyl)-3,7-dimethyl-1,4,5,6,7,7a-hexahydro-indol-2-one (236)



Precursor (235) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following mixture of diastereomers in a ratio of 2:1 respectively. Yield for mixture (88%); yellow oil; IR for mixture (neat, cm^{-1}) 1650, 1647; ^{1}H NMR for major diastereomer (250MHz, $CDCl_3$) δ 6.94 (2H, d, *J* = 8.6 Hz, C<u>H</u>CH$COCH_3$), 6.62 (2H, d, *J* = 8.6 Hz, C<u>H</u>=$COCH_3$), 4.89 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 3.60 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.55 (3H, s, $OC\underline{H}_3$), 3.39 (1H, d, *J* = 4.0 Hz, C<u>H</u>), 2.57 (2H, m, $C\underline{H}_2$), 2.24 (3H, m, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.78 (1H, m, C<u>H</u>H), 1.62 (3H, m, $C\underline{H}_3$), 0.99 (1H, m, C<u>H</u>H), 0.34 (3H, d, *J* = 7.0 Hz, $CHC\underline{H}_3$); ^{13}C for major diastereomer (75 MHz, $CDCl_3$) δ 173.0 (s), 159.2 (s), 150.3 (s), 130.3 (s), 129.7 (d x 2), 126.1 (s), 114.3 (d x 2), 62.4 (d), 55.6 (q), 43.4 (t), 32.2 (d), 30.0 (t), 25.9 (t), 21.1 (t), 10.9 (q), 8.8 (q); ^{1}H NMR for minor diastereomer (250MHz, $CDCl_3$) δ 6.85 (2H, d, *J* = 8.8 Hz, C<u>H</u>CHCOCH$_3$), 6.59 (2H, d, *J* = 8.8 Hz, C<u>H</u>=COCH$_3$), 4.92 (1H, d, *J* = 15.6 Hz, C<u>H</u>HN), 4.10 (1H, d, *J* = 15.6 Hz, CH<u>H</u>N), 3.55 (3H, s, OC<u>H</u>$_3$), 2.95 (1H, d, *J* = 8.5 Hz, C<u>H</u>), 2.50 (1H, m, C<u>H</u>H), 1.61 (3H, m, C<u>H</u>$_3$), 1.50-1.31 (5 H, m, CH$_2$ x 2, C<u>H</u>CH$_3$), 1.00 (1H, m, C<u>H</u>H), 0.94 (3H, d, *J* = 6.1 Hz, CHC<u>H</u>$_3$); ^{13}C for minor diastereomer (75 MHz, $CDCl_3$) δ 174.4 (s), 158.9 (s), 153.8 (s), 130.6 (s), 129.0 (d x 2), 124.6 (s), 114.3 (d x 2), 66.8 (d), 55.6 (q), 46.3 (t), 42.0 (d), 34.1 (t), 26.4 (t x 2), 21.6 (q), 8.9 (q); EI-MS *m/z* mixture 265 (M^+, 61), 177 (53), 121 (100), 83 (40); HRMS Calcd for $C_{18}H_{23}NO_2$: 285.1729, found 285.1734.

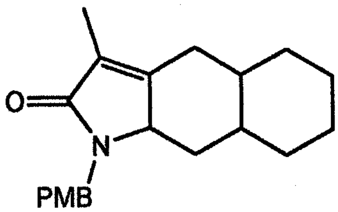
1-(4-Methoxy-benzyl)-3-methyl-2-oxo-1,2,4,6,7,7a-hexahydro-pyrrolo[3,2c]pyridine-5-carboxylic acid benzyl ester (241)



Precursor (240) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (42%); clear oil; IR (neat, cm^{-1}) 1690; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.27-7.22 (5H, m, Ar-<u>H</u>), 7.04 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.75 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.03 (2H, br s, C<u>H</u>$_2$Ar), 4.80 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.10 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 4.09 (2H, br m, C<u>H</u>$_2$NCO), 3.67 (3H, s, OC<u>H</u>$_3$), 3.58 (1H, m, C<u>H</u>), 3.42 (1H, m, C<u>H</u>H), 2.73 (1H, m, C<u>H</u>H), 2.06 (1H, m, C<u>H</u>H), 1.78 (3H, br s, C<u>H</u>$_3$), 1.00 (1H, m, C<u>H</u>H); ^{13}C (75 MHz, $CDCl_3$) δ 173.9 (s), 171.9 (s), 159.4 (s), 155.4 (s), 145.6 (s), 136.7 (s), 129.9 (s), 129.5 (d x 2), 128.9 (d x 2), 128.6 (d), 128.3 (d x 2), 114.4 (d x 2), 67.9

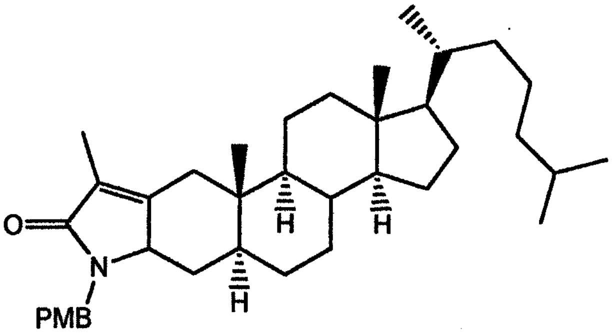
(t), 58.8 (d), 55.6 (q), 43.9 (t), 42.8 (t), 42.0 (t), 32.6 (t), 9.2 (q); EI-MS *m/z* 406 (M^+, 20), 121 (100); HRMS Calcd for $C_{24}H_{26}N_2O_4$: 406.1892, found 406.1891.

1-(4-Methoxy-benzyl)-3-methyl-1,4,4a,5,6,7,8,8a,9,9a-decahydro-benzo[f]indol-2-one (256)



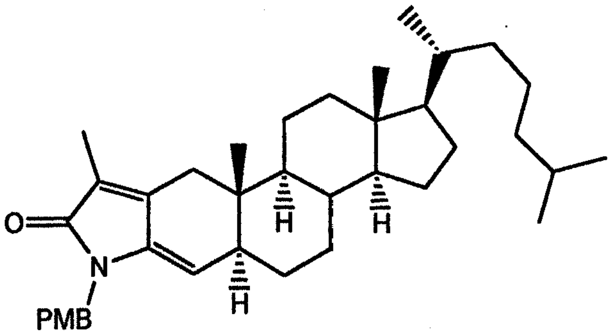
Precursor (255) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (75%); clear oil; IR (neat, cm^{-1}) 1697; ^1H NMR (300MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.84 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.90 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.13 (1H, d, *J* = 15.0 Hz, CH$\underline{H}$N), 3.80 (3H, s, OC$\underline{H}_3$), 3.42 (1H, dd, *J* = 5.0, 6.4 Hz, C$\underline{H}$), 2.80 (1H, m, C$\underline{H}$H), 2.43 (1H, m, C$\underline{H}$H), 2.28 (1H, m, C$\underline{H}$H), 1.85 (4H, m, C$\underline{H}_2$ x 2), 1.82 (3H, br s, C$\underline{H}_3$), 1.80-1.39 (6H, m, C$\underline{H}_2$ x 2, C$\underline{H}$ x 2), 0.95 (1H, m, C$\underline{H}$H); ^{13}C (75 MHz, $CDCl_3$) δ 172.7 (s), 159.1 (s), 151.6 (s), 130.7 (s), 129.6 (d x 2), 124.3 (s), 114.2 (d x 2), 60.7 (d), 55.6 (q), 44.5 (t), 38.0 (d), 37.9 (d), 34.2 (t), 31.1 (t), 27.6 (t), 27.1 (t), 24.1 (t), 20.9 (t), 8.8 (q); EI-MS *m/z* 325 (M^+, 85), 217 (20), 121 (100); HRMS Calcd for $C_{21}H_{27}NO_2$: 325.2041, found 325.2039.

1-(1,5-Dimethyl-hexyl)-7-(4-methoxy-benzyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,6,6a,7,10,10a,10b,11,12,12a-hexadecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (263)



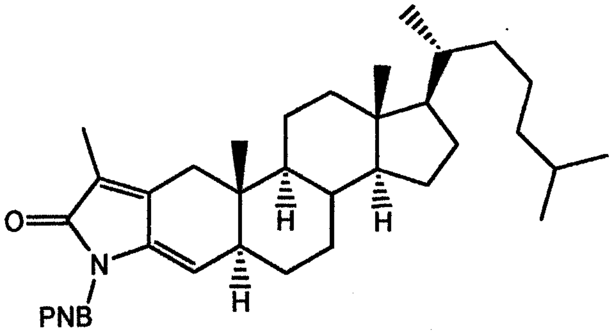
Precursor (261) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (69%); clear oil; IR (neat, cm^{-1}) 1751, 1719, 1701; ^{1}H NMR (300MHz, CDCl$_3$) δ 7.12 (2H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.79 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.98 (1H, d, *J* = 14.8 Hz, C$\underline{H}$HN), 3.87 (1H, d, *J* = 14.8 Hz, CH$\underline{H}$N), 3.74 (3H, s, OC$\underline{H}_3$), 3.48 (1H, dd, *J* = 5.8, 9.0 Hz, C$\underline{H}$), 2.64 (1H, d, *J* = 13.0 Hz, C$\underline{H}$H), 1.98 (1H, dt, *J* = 2.8, 12.5 Hz, C$\underline{H}$), 1.80 (2H, m, CHC$\underline{H}_2$), 1.77 (3H, s, C$\underline{H}_3$), 1.64 (3H, m, CH$\underline{H}$, C$\underline{H}_2$), 1.59-0.87 (22H, m, C$\underline{H}$ x 6, C$\underline{H}_2$ x 8), 0.86 (3H, d, *J* = 6.4 Hz, CHC$\underline{H}_3$), 0.83 (3H, d, *J* = 6.6 Hz, CH(C$\underline{H}_3$)$_2$), 0.82 (3H, d, *J* = 6.6 Hz, CH(C$\underline{H}_3$)$_2$), 0.61 (3H, s, C$\underline{H}_3$), 0.56 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz, CDCl$_3$) δ 172.6 (s), 159.1 (s), 152.1 (s), 130.5 (s), 129.7 (d x 2), 126.8 (s), 114.4 (d x 2), 60.1 (d), 56.7 (d), 56.6 (d), 56.5 (d), 55.6 (q), 54.4 (d), 43.8 (d), 43.6 (d), 42.8 (t), 40.1 (t), 39.9 (t), 38.9 (t), 36.5 (t), 36.1 (d), 35.9 (t), 35.8 (d), 32.2 (t), 28.8 (s), 28.6 (s), 28.4 (t), 24.6 (t), 24.2 (t), 23.2 (q), 22.9 (q), 21.6 (t), 19.0 (q) 12.3 (q x 2), 8.8 (q); CI-MS *m/z* 560 (MH$^+$, 70), 306 (100), 136 (70), 121 (75); HRMS Calcd for $C_{38}H_{57}NO_2$: 560.4467, found 560.4464.

1-(1,5-Dimethyl-hexyl)-7-(4-methoxy-benzyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,7,10,10a,10b,11,12,12a-tetradecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (264)



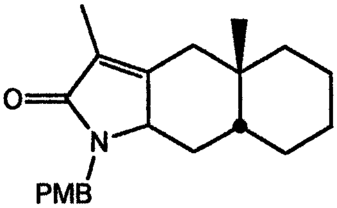
Precursor (261) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (79%); clear oil; IR (neat, cm^{-1}) 1710, 1700; ^{1}H NMR (300MHz, CDCl$_3$) δ 7.15 (2H, d, *J* = 8.6 Hz, CHCHCOCH$_3$), 6.82 (2H, d, *J* = 8.6 Hz, CH=COCH$_3$), 5.00 (1H, d, *J* = 15.0 Hz, CHHN), 4.66 (1H, br s, CH=C), 4.14 (1H, d, *J* = 15.0 Hz, CHHN), 3.76 (3H, s, OCH$_3$), 2.67 (1H, d, *J* = 14.8 Hz, CHH), 2.12 (1H, dt, *J* = 3.0, 12.8 Hz, CH), 1.95 (2H, m, CHCH$_2$), 1.79 (3H, s, CH$_3$), 1.68 (1H, m, CHH), 1.65-0.88 (22H, m, CH x 6, CH$_2$ x 8), 0.87 (3H, d, *J* = 6.5 Hz, CHCH$_3$), 0.84 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)$_2$), 0.83 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)$_2$), 0.64 (3H, s, CH$_3$), 0.59 (3H, s, CH$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 173.0 (s), 159.1 (s), 152.2 (s), 145.6 (s), 130.1 (s), 129.8 (d x 2), 125.8 (s), 114.3 (d x 2), 110.9 (d), 56.8 (d), 56.6 (d), 56.5 (d), 55.8 (q), 54.4 (d), 43.7 (d), 42.9 (t), 40.6 (t), 39.9 (t), 38.7 (t), 37.0 (t), 36.3 (d), 36.1 (t), 35.8 (d), 32.1 (t), 28.9 (s), 28.6 (s), 28.1 (t), 24.6 (t), 24.4 (t), 23.2 (q), 23.0 (q), 21.6 (t), 19.1 (q), 12.9 (q), 12.4 (q), 8.8 (q); CI-MS *m/z* 557 (MH$^+$, 52), 303 (66), 121 (100); HRMS Calcd for C$_{38}$H$_{55}$NO$_2$: 557.4233, found 557.4232.

1-(1,5-Dimethyl-hexyl)-9,10a,12a-trimethyl-7-(4-nitro-benzyl)-2,3,3a,3b,4,5,5a,7,10,10a,10b,11,12,12a-tetradecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (265)



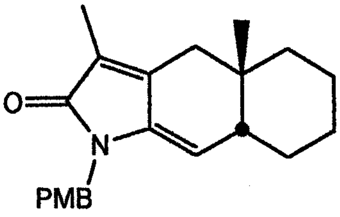
Precursor (262) was dissolved in toluene or 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (76%) and (59%) respectively; clear oil; IR (neat, cm^{-1}) 1683, 1522; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.14 (2H, d, J = 8.7 Hz, $\underline{H}$C=CNO_2), 7.27 (2H, d, J = 8.7 Hz, C$\underline{H}$CHCNO_2), 4.88 (1H, d, J = 16.6 Hz, C$\underline{H}$HN), 4.83 (1H, d, J = 2.3 Hz, CH=C), 4.74 (1H, d, J = 16.6 Hz, CH$\underline{H}$N), 2.70 (1H, d, J = 15.8 Hz, C$\underline{H}$H), 2.15 (1H, dt, J = 2.8, 12.8 Hz, C$\underline{H}$), 2.00 (2H, m, CHC$\underline{H_2}$), 1.87 (3H, s, CH_3), 1.76 (1H, m, CH$\underline{H}$), 1.60-0.87 (22H, m, C$\underline{H}$ x 6, C$\underline{H_2}$ x 8), 0.88 (3H, d, J = 6.4 Hz, CHC$\underline{H_3}$), 0.85 (3H, d, J = 6.6 Hz, CH(C$\underline{H_3}$)$_2$), 0.82 (3H, d, J = 6.6 Hz, CH(C$\underline{H_3}$)$_2$), 0.71 (3H, s, C$\underline{H_3}$), 0.63 (3H, s, C$\underline{H_3}$); ^{13}C (75 MHz, $CDCl_3$) δ 171.6 (s), 147.5 (s), 145.7 (s), 141.0 (s), 138.2 (s), 128.0 (d x 2), 125.4 (s), 124.2 (d x 2), 112.2 (d), 56.6 (d), 56.5 (d), 53.4 (d), 45.9 (d), 43.4 (t), 42.9 (t), 42.6 (t), 41.2 (t), 40.2 (t), 36.7 (s), 36.5 (s), 36.1 (d), 35.7 (d), 32.2 (t), 28.5 (t), 28.3 (t), 28.2 (d), 27.1 (t), 24.5 (t), 23.2 (q), 22.9 (q), 21.6 (t), 19.0 (q) 13.3 (q), 12.4 (q), 8.8 (q); EI-MS m/z 572 (MH^+, 15), 542 (20), 439 (100), 315 (25), 106 (70); HRMS Calcd for $C_{37}H_{52}N_2O_3$: 572.3978, found 572.3977.

1-(4-Methoxy-benzyl)-3,4a-dimethyl-1,4,4a,5,6,7,8,8a,9,9a-decahydro-benzo[f]indol-2-one (270)



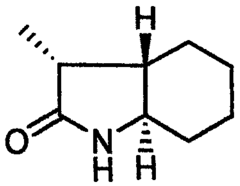
Precursor (269) was dissolved in toluene (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (86%); clear oil; IR (neat, cm^{-1}) 1697; ^{1}H NMR for mix of diastereomers (300MHz, CDCl$_3$) δ 7.14 (2H, d, *J* = 8.8 Hz, C$\underline{H}$CHCOCH$_3$), 6.80 (2H, d, *J* = 8.8 Hz, C$\underline{H}$=COCH$_3$), 5.00 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.90 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.10 (1H, d, *J* = 15.0 Hz, CH$\underline{H}$N), 3.97 (1H, d, *J* = 15.0 Hz, CH$\underline{H}$N), 3.77 (3H, s, OC$\underline{H}_3$), 3.63 (1H, m, C$\underline{H}$), 3.47 (1H, m, C$\underline{H}$), 2.80 (1H, m, C$\underline{H}$H), 2.43 (1H, m, C$\underline{H}$H), 2.28 (1H, m, C$\underline{H}$H), 1.85 (4H, m, C$\underline{H}_2$ x 2), 1.77 (3H, m, C$\underline{H}_3$), 1.48-1.08 (5H, m, C$\underline{H}_2$ x 2, C$\underline{H}$), 1.08 (3H, s, C$\underline{H}_3$), 0.95 (1H, m, C$\underline{H}$H), 0.74 (3H, s, C$\underline{H}_3$); ^{13}C for mixture of diastereomers (75 MHz, CDCl$_3$) δ 172.6 (s), 159.2 (s), 151.9 (s), 130.0 (s), 129.6 (d x 2), 126.1 (s), 114.3 (d x 2), 60.3 (d), 60.0 (d), 55.6 (q), 43.7 (t), 43.5 (d), 41.2 (t), 40.1 (t), 38.0 (t), 36.1 (d), 34.8 (t), 31.7 (s), 30.5 (s), 26.9 (q), 26.4 (q), 22.5 (t), 22.2 (t), 22.1 (t), 21.9 (t), 20.2 (t), 16.4 (t), 8.7 (q); EI-MS *m/z* mixture 340 (M$^+$, 40), 300 (60), 256 (20), 212 (40), 121 (100); HRMS Calcd for C$_{22}$H$_{29}$NO$_2$: 340.2277, found 340.2287.

1-(4-Methoxy-benzyl)-3,4a-dimethyl-1,4,4a,5,6,7,8,8a-octahydro-benzo[f]indol-2-one (271)



Precursor (269) was dissolved in 1,2-dichloroethane (2.5 ml) and reacted under the conditions described in the general procedure 5.2.4 to give the following cyclic compound: yield (70%); clear yellow oil; IR (neat, cm^{-1}) 1704; ^1H NMR (250MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.7 Hz, $C\underline{H}CHCOCH_3$), 6.79 (2H, d, J = 8.7 Hz, $C\underline{H}{=}COCH_3$), 5.09 (1H, d, J = 16.0 Hz, $C\underline{H}HN$), 4.92 (1H, d, J = 3.0 Hz, CH=C), 4.84 (1H, d, J = 16.0 Hz, $CH\underline{H}N$), 3.77 (3H, s, OCH_3), 1.97 (2H, m, $C\underline{H}$), 1.92 (2H, m, $C\underline{H}_2$), 1.77 (3H, s, $C\underline{H}_3$), 1.72-1.35 (8H, m, $C\underline{H}_2$ x 4), 1.16 (3H, br s, CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 171.6 (s), 159.1 (s), 150.1 (s), 140.1 (s), 139.0(s), 129.8 (d x 2), 124.8 (s), 114.3 (d x 2), 111.1 (d), 55.7 (q), 43.2 (t), 39.2 (d), 31.6 (s), 26.9 (t), 25.8 (t), 25.0 (t), 24.0 (t), 22.7 (q), 22.5 (t), 8.7 (q); EI-MS *m/z* 337 (M^+, 81), 121 (100); HRMS Calcd for $C_{22}H_{27}NO_2$: 337.2042, found 337.2039.

3-Methyl-octahydro-indol-2-one (244)

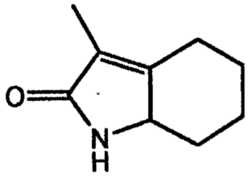


A solution of 1-Benzyl-3-methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (197) (50 mg, 0.21 mmol in 10 ml of dry tetrahydrofuran) was added to a stirred solution of lithium metal (40 mg, 5.8 mmol) in liquid ammonia (20 ml) at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 20 minutes. Quenching was carried out by the cautious addition of H_2O (10 ml). Removal of excess NH_3 was achieved by exposing the reaction mixture to air for 30 minutes. The resulting solution was diluted with dichloromethane (30 ml), washed with H_2O (10 ml), brine (10 ml), dried with $MgSO_4$ and reduced to dryness in *vacuo*. yield (95%); white crystalline solid; IR (KBr Disc, cm^{-1}) 3421, 3104, 1696, 1694; ^1H NMR (250 MHz, $CDCl_3$) δ 6.03 (1H, br s, N$\underline{H}$), 2.92 (1H, m, NHC$\underline{H}$), 1.95 (2H, m, C$\underline{H}$$CH_3$, C$\underline{H}$H), 1.77 (3H, m, CH$\underline{H}$, C$\underline{H}_2$), 1.29-1.18 (5H, m, C$\underline{H}CHCH_3$, CH$\underline{H}$ x 2, C$\underline{H}_2$), 1.06 (3H, d, J = 7.0 Hz, C$\underline{H}$$CH_3$); ^{13}C (75 MHz, $CDCl_3$) δ 181.3 (s), 58.9 (d), 52.9 (d), 47.6 (d), 31.2 (d), 27.7 (t), 26.2 (t), 24.8 (t), 12.9 (q); EI-MS *m/z* 153 (M^+, 100), 110 (95), 81 (55), 67 (70); HRMS Calcd for $C_9H_{15}NO$: 153.1154, found 153.1155; Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found C, 70.51; H, 9.87; N, 9.10.

5.2.5 General method for the deprotection of *p*-methoxybenzylamides

Ceric ammonium nitrate (438 mg, 0.8 mmol) was added to a solution of the required cyclised compound (0.32 mmol) in 3.2 ml of 3:1 acetonitrile/H_2O and stirred for 1hour. The resulting solution was dropped onto H_2O (25 ml) and extracted with ethyl acetate (25 ml x 3), dried with $MgSO_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:2 petroleum ether : ethyl acetate), to give the following oxidised/deprotected products.

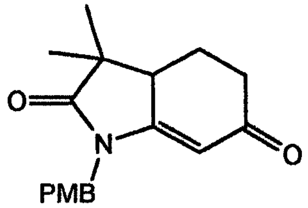
3-Methyl-1,4,5,6,7,7a-hexahydro-indol-2-one (245)



Compound (210) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (96%); white crystalline solid; IR (neat, cm^{-1}) 3437, 3263, 1644; ^1H NMR (250 MHz, $CDCl_3$) δ 6.98 (1H, br s, N$\underline{H}$), 3.67 (1H, dd, J = 5.8 Hz, NHC$\underline{H}$), 2.73 (1H, m, C$\underline{H}$H), 2.28 (1H, m, CHC$\underline{H}$H), 2.01 (2H, m, C$\underline{H}_2$), 1.81 (1H, m, C$\underline{H}$H), 1.75 (3H, app t, J = 1.5 Hz, C$\underline{H}_3$), 1.42 (1H, m, CH$\underline{H}$), 1.18 (1H, m, CH$\underline{H}$), 1.03, m, CHC$\underline{H}$H); ^{13}C (75 MHz, CDCl$_3$) δ 175.8 (s), 156.0 (s), 124.6 (s), 57.8 (d), 35.1 (t), 27.0 (t), 26.5 (t), 23.7 (t), 8.4 (q); EI-MS *m/z* 151 (M$^+$, 100), 136 (80), 122 (80), 94 (50), 80 (45); HRMS Calcd for C$_9$H$_{13}$NO: 151.0997, found 151.0997; Anal. Calcd for C$_9$H$_{13}$NO: C, 71.29; H, 8.67; N, 9.26. Found C, 71.29; H, 8.61; N, 9.27.

Compound (210) (0.7 mmol) was refluxed with stirring in trifluoroacetic acid (8.5 ml) for 2 hours (followed by TLC). The reaction mix was cooled to room temperature, quenched on ice and extracted with dichloromethane (25 ml x 3). The organic layer was then washed with saturated sodium hydrogen carbonate (25 ml x 3), dried with MgSO$_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:2 petroleum ether : ethyl acetate), to give the deprotected lactam (245): yield (83%). The spectral details matched those shown above.

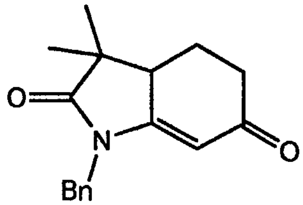
1-(4-Methoxy-benzyl)-3,3-dimethyl-3,3a,4,5-tetrahydro-1H-indole-2,6-dione (246)



Compound (159b) was reacted under the conditions described in the general procedure 5.2.5 to give the following compound (246): yield (74%); clear oil; IR (neat, cm^{-1}) 1732, 1706; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.14 (2H, d, *J* = 8.5 Hz, C$\underline{H}$CHCOCH$_3$), 6.80 (2H, d, *J* = 8.5 Hz, C$\underline{H}$=COCH$_3$), 5.51 (1H, d, *J* = 1.8 Hz, C$\underline{H}$=C), 4.60 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.55 (1H, d, *J* = 15.0 Hz, CH$\underline{H}$N), 3.76 (3H, s OC$\underline{H}_3$), 2.75 (1H, ddd, *J* = 1.8, 2.8 Hz, C$\underline{H}$), 2.50 (1H, m, C$\underline{H}$HCO), 2.32 (1H, m, CH$\underline{H}$CO), 2.00 (1H, m, C$\underline{H}$HCH), 1.83 (1H, m, CH$\underline{H}$CH), 1.33 (3H, s, C$\underline{H}_3$), 1.07 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz; CDCl$_3$) δ 197.0 (s), 181.8 (s), 163.8 (s), 159.6 (s), 129.3 (d x 2), 127.4 (s), 114.6 (d x

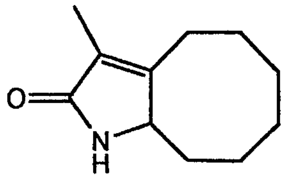
2), 103.6 (d), 55.6 (q), 46.2 (d), 44.1 (t), 42.8 (s), 37.6 (t), 23.5 (q), 22.4 (t), 21.7 (q); EI-MS *m/z* 299 (M^+, 55), 271 (100), 121 (75); HRMS Calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1521.

1-Benzyl-3,3-dimethyl-3,3a,4,5-tetrahydro-1H-indole-2,6-dione (247)



Compound (152b) was reacted under the conditions described in the general procedure 5.2.5 to give the following compound (246): yield (68%); clear oil; IR (neat, cm^{-1}) 1713, 1700; ^1H NMR (250 MHz, $CDCl_3$) δ 7.29-7.19 (5H, m, Ar-H), 5.47 (1H, d, *J* = 1.8 Hz, CH=C), 4.69 (1H, d, *J* = 15.0 Hz, CHHN), 4.60 (1H, d, *J* = 15.0 Hz, CHHN), 2.75 (1H, ddd, *J* = 1.8, 2.5 Hz, CH), 2.58 (1H, m, CHHCO), 2.32 (1H, m, CHHCO), 2.01 (1H, m, CHHCH), 1.83 (1H, m, CHHCH), 1.33 (3H, s, CH_3), 1.08 (3H, s, CH_3); ^{13}C (75 MHz; $CDCl_3$) δ 198.3 (s), 181.8 (s), 163.9 (s), 135.2 (s), 129.3 (d x 2), 128.2 (d), 127.4 (d x 2), 103.6 (d), 46.2 (d), 44.5 (t), 42.8 (s), 37.6 (t), 23.5 (q), 22.4 (t), 21.7 (q); EI-MS *m/z* 269 (M^+, 85), 226 (90), 91 (100); HRMS Calcd for $C_{17}H_{19}NO_2$: 269.1415, found 269.1416.

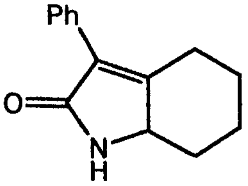
3-Methyl-1,4,5,6,7,8,9,9a-octahydro-cycloocta[b]pyrrol-2-one (248)



Compound (211) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (88%); white crystalline solid;

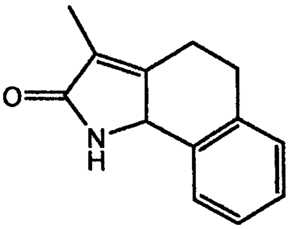
IR (neat, cm^{-1}) 3379, 3263, 1676, 1476; ^{1}H NMR (250 MHz, CDCl$_3$) δ 6.65 (1H, br s, N$\underline{H}$), 4.00 (1H, br s, NHC$\underline{H}$), 2.62 (1H, app dt, J = 5.5, 5.6 Hz, C$\underline{H}$H), 2.17 (1H, m, CH$\underline{H}$), 2.00 (1H, m, CHC$\underline{H}$H), 1.73 (3H, br s, C$\underline{H}_3$), 1.67 (1H, m, CHCH$\underline{H}$), 1.40 (4H, m, C$\underline{H}_2$ x 2); ^{13}C (75 MHz, CDCl$_3$) δ 175.6 (s), 158.3 (s), 129.2 (s), 60.0 (d), 28.3 (t), 28.1 (t), 27.2 (t), 26.7 (t), 25.3 (t), 22.0 (t), 8.9 (q); EI-MS *m/z* 179 (M$^+$, 85), 151 (70), 136 (100), 122 (65), 110 (55); HRMS Calcd for $C_{11}H_{17}NO$: 179.1310, found 179.1304; Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found C, 73.38; H, 9.47; N, 7.87.

3-Phenyl-1,4,5,6,7,7a-hexahydro-indol-2-one (249)



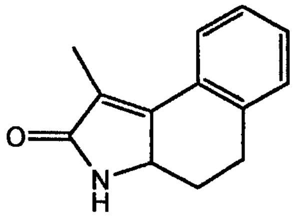
Compound (212) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (84%); white crystalline solid; IR (KBr disc, cm^{-1}) 3374, 3083, 1684, 1600; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.42 (5H, m, Ar-$\underline{H}$), 6.79 (1H, br s, N$\underline{H}$), 3.84 (1H, m, NHC$\underline{H}$), 3.06 (1H, m, C$\underline{H}$H), 2.40 (2H, m, C$\underline{H}_2$), 2.25-1.82 (4H, m, C$\underline{H}_2$ x 2), 1.25 (1H, m, CH$\underline{H}$); ^{13}C (75 MHz, CDCl$_3$) δ 173.7 (s), 158.1 (s), 131.6 (s), 129.6 (d x 2), 129.0 (s), 128.7 (d x 2), 128.0 (d), 57.7 (d), 35.3 (t), 27.3 (t), 27.1 (t), 23.6 (t); EI-MS *m/z* 213 (M$^+$, 90), 184 (80) 151 (60), 135 (100), 77 (45); HRMS Calcd for $C_{14}H_{15}NO$: 213.1154, found 213.1150; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found C, 78.56; H, 7.06; N, 6.58.

3-Methyl-1,4,5,9b-tetrahydro-benzo[g]indol-2-one (250)



Compound (232) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (86%); white crystalline solid; IR (KBr disc, cm^{-1}) 3401, 3267, 1680, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, br s, NH), 6.92 (1H, m, Ar-H), 6.65-6.57 (3H, m, Ar-H), 3.53 (1H, m, NHCH), 2.67 (1H, m, CHH), 2.34-2.21 (3H, m, CH_2, CHH), 1.19 (3H, br s, CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 173.9 (s), 154.8 (s), 136.4 (s), 136.2 (s), 128.8 (d), 128.1 (d), 126.6 (d), 125.4 (d), 125.3 (s), 84.9 (d), 29.4 (t), 20.7 (t), 8.9 (q); EI-MS *m/z* 200 (M$^+$, 55), 167 (55) 149 (100); HRMS Calcd for $C_{13}H_{13}NO$: 200.1075, found 200.1076; Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found C, 77.96; H, 6.32; N, 7.07.

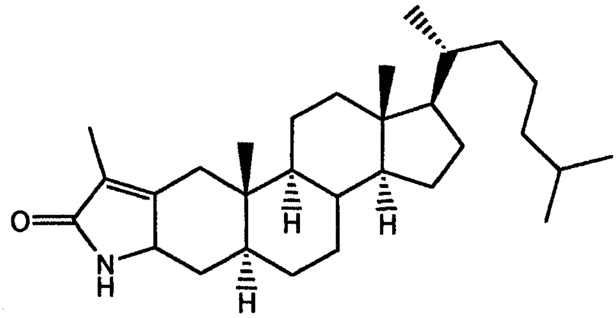
1-Methyl-3,3a,4,5-tetrahydro-benzo[e]indol-2-one (251)



Compound (234) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (79%); white crystalline solid; IR (KBr disc, cm^{-1}) 3407, 3209, 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, br s, Ar-H), 7.24 (1H, m, NH), 7.22-7.19 (3H, m, Ar-H), 4.09 (1H, m, NHCH), 2.97 (2H, m, CH_2), 2.39 (1H, m, CHCHH), 2.07 (3H, m, CH_3), 1.55 (1H, m, CHCHH; ^{13}C (75 MHz, $CDCl_3$) δ 176.0 (s), 150.6 (s), 137.6 (s), 130.7 (s), 129.5 (d), 129.3 (d), 127.9 (d), 126.8

(d), 125.6 (s), 56.6 (d), 31.2 (t), 28.7 (t), 10.4 (q); EI-MS *m/z* 199 (M^+, 100), 184 (75) 170 (30), 128 (20); HRMS Calcd for $C_{13}H_{13}NO$: 199.0997, found 199.0999; Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found C, 77.90; H, 6.33; N, 7.04.

1-(1,5-Dimethyl-hexyl)-9,10a,12a-trimethyl-2,3,3a,3b,4,5,5a,6,6a,7,10,10a,10b,11,12,12a-hexadecahydro-1H-7-aza-dicyclopenta[a,h]phenanthren-8-one (379)



Compound (379) was deprotected under the conditions described in the general procedure 5.2.5 to give the following compound: yield (81%); white crystalline solid; IR (KBr disc, cm^{-1}) 3222, 1708, 1680; ^{1}H NMR (300MHz, CDCl$_3$) δ 7.06 (1H, br s, N<u>H</u>), 3.72 (1H, dd, *J* = 10.7, 6.6 Hz, NHC<u>H</u>), 2.63 (1H, d, *J* = 13.4 Hz, C<u>H</u>H), 1.93 (2H, m, CHC<u>H</u>$_2$), 1.69 (3H, s, C<u>H</u>$_3$), 1.65 (3H, m, CH<u>H</u>, C<u>H</u>$_2$), 1.59-0.87 (23H, m, C<u>H</u> x 7, C<u>H</u>$_2$ x 8), 0.84 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$), 0.80 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$), 0.79 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$), 0.58 (3H, s, C<u>H</u>$_3$), 0.55 (3H, s, C<u>H</u>$_3$); ^{13}C (75 MHz, CDCl$_3$) δ 176.0 (s), 164.0 (s), 126.7 (s), 58.0 (d), 56.7 (d), 56.6 (d), 54.6 (d), 43.9 (d), 42.9 (s), 40.2 (s), 40.1 (t), 39.9 (t), 39.1 (t), 37.7 (t), 36.5 (t), 36.1 (d), 35.8 (d), 32.2 (t), 28.7 (t), 28.6 (t), 28.4 (d), 24.6 (t), 24.2 (t), 23.2 (q), 22.9 (q), 21.6 (t), 19.1 (t), 12.4 (q x 2), 8.3 (q); CI-MS *m/z* 439 (MH^+, 15), 279 (30), 167 (45), 149 (100), 83 (25); HRMS Calcd for $C_{30}H_{49}NO$: 440.3892, found 440.3896; Anal. Calcd for $C_{30}H_{49}NO$: C, 81.94; H, 11.23; N, 3.19. Found C, 81.97; H, 11.21; N, 3.17.

5.2.6 General procedure for copper mediated cyclisations of bromoacetamides in the ionic liquid [bmim][PF$_6$]

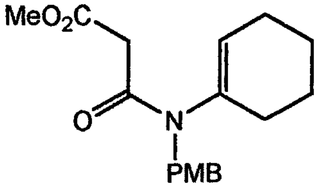
Cu(I)Br (12.9 mg, 0.09 mmol) was added to solution of the appropriate precursor (0.3 mmol) and Me$_6$-tren (39) (20.7 mg, 0.09 mmol) in 1-butyl-3-methylimidazolium hexaflurophosphate[157] [bmim][PF$_6$] (2.5 ml) and stirred at room temperature for 20 minutes under N_2. The resulting solution was washed with toluene (5 ml x 2) and reduced to dryness *in vacuo* to give the observed cyclised products. To recycle the catalyst the remaining [bmim][PF$_6$]/CuBr:(39) solution was added to another 0.3 mmol of the appropriate precursor and the procedure was carried out again.

5.3 Experimental for Chapter 4

5.3.1 General procedure for the preparation of *N*-Acyl Enamines

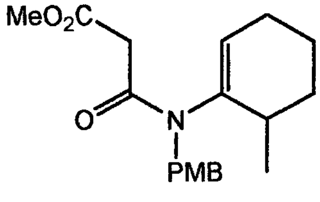
A solution of ketone (10 mmol) and the appropriate benzylamine (10 mmol) in toluene (15 ml) was stirred under reflux in a Dean Stark apparatus for until no starting material could be detected by tlc analysis (typically 4-8 hours). The solution was then cooled to 0°C with stirring. Methyl malonyl chloride (10 mmol) was added dropwise to this solution, followed by the slow, dropwise addition of *N,N*-diethylaniline (10 mmol). The reaction was then stirred for 2 hours at room temperature and dropped onto H_2O (30 ml). The organic layer was washed with 10% aq.HCl (10 ml), dried over $MgSO_4$ and concentrated in *vacuo* to give a residue which was purified by column chromatography, petroleum ether : ethyl acetate (1:1).

N-Cyclohex-1-enyl-N-(4-methoxy-benzyl)-malonamic acid methyl ester (290)



The imine derived from the condensation of cyclohexanone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford the required compound (290): yield (57%); clear yellow oil; IR (neat, cm^{-1}) 1768, 1634; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.5 Hz, C<u>H</u>CHCOCH$_3$), 6.72 (2H, d, *J* = 8.5 Hz, C<u>H</u>=COCH$_3$), 5.31 (1H, s, C<u>H</u>=C), 4.47 (2H, br s, C<u>H$_2$</u>N), 3.67 (3H, s, OC<u>H$_3$</u>), 3.62 (3H, s, OC<u>H$_3$</u>), 3.44 (2H, s, COC<u>H$_2$</u>CO), 1.90 (4H, m, CH$_2$ x 2), 1.54 (2H, m, C<u>H$_2$</u>), 1.43 (2H, m, C<u>H$_2$</u>); ^{13}C (75 MHz; $CDCl_3$) δ 168.8 (s), 165.6 (s), 159.1 (s), 138.2 (s), 130.3 (d x 2), 129.9 (s), 129.6 (d), 114.4 (t), 55.4 (q), 52.5 (q), 48.7 (t), 39.4 (t), 27.5 (t), 24.3 (t), 22.5 (t), 21.3 (t); EI-MS m/z 317 (M$^+$ 67), 217 (45), 121 (100), 83 (35); HRMS Calcd for $C_{18}H_{23}NO_4$: 317.1627, found 317.1630.

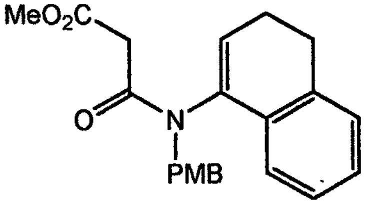
N-(4-Methoxy-benzyl)-N-(6-methyl-cyclohex-1-enyl)-malonamic acid methyl ester (301a)



The imine derived from the condensation of 2-methylcyclohexanone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford the required compound (301a): yield (69%); clear oil; IR (neat, cm^{-1}) 1766, 1633, 1610; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (2H, m, C<u>H</u>CHCOCH$_3$), 6.76 (2H, m, C<u>H</u>=COCH$_3$), 5.24 (1H, s, C<u>H</u>=C), 4.60 (1H, *J* = 14.0 Hz, C<u>H</u>HN), 4.40 (1H, *J*

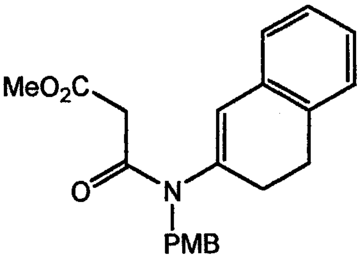
= 14.0 Hz, CH<u>H</u>N), 3.71 (3H, s, OC<u>H</u>$_3$), 3.66 (3H, s, OC<u>H</u>$_3$), 3.30 (1H, d, J = 15.3 Hz, COC<u>H</u>HCO), 3.20 (1H, d, J = 15.3 Hz, COCH<u>H</u>CO), 2.33 (1H, m, C<u>H</u>CH$_3$), 1.91 (2H, m, C<u>H</u>$_2$), 1.61-1.37 (4H, m, C<u>H</u>$_2$ x 2); ^{13}C (75 MHz; CDCl$_3$) δ 169.0 (s), 168.7 (s), 159.3 (s), 134.7 (s), 131.0 (s), 131.7 (d), 130.4 (d x 2), 113.8 (d x 2), 55.4 (q), 52.6 (q), 48.9 (t), 41.5 (t), 29.1 (d), 25.5 (t), 23.6 (t), 19.7 (t), 18.4 (q); EI-MS m/z 331 (M$^+$ 57), 231 (43), 121 (100); HRMS Calcd for $C_{19}H_{25}NO_4$: 331.1784, found 331.1781.

N-(3,4-Dihydro-naphthalen-1-yl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (303)



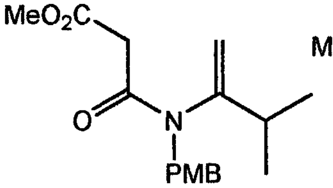
The imine derived from the condensation of α-tetralone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford the required compound (303): yield (66%); orange oil; IR (neat, cm^{-1}) 1772, 1640, 1613, 735; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.24-7.04 (6H, m, Ar-<u>H</u>), 6.81 (2H, d, J = 8.6 Hz, C<u>H</u>=COCH$_3$), 5.79 (1H, t, J = 4.6 Hz, C<u>H</u>=C), 5.47 (1H, d, J = 14.0 Hz, C<u>H</u>HN), 3.80 (1H, d, J = 14.0 Hz, CH<u>H</u>N), 3.74 (3H, s, OC<u>H</u>$_3$), 3.64 (3H, s, OC<u>H</u>$_3$), 3.42 (1H, d, J = 15.6 Hz, COC<u>H</u>HCO), 3.29 (1H, d, J = 15.6 Hz, COCH<u>H</u>CO), 2.75 (2H, t, J = 8.0 Hz, C<u>H</u>$_2$), 2.28 (2H, m, C<u>H</u>$_2$); ^{13}C (75 MHz; CDCl$_3$) δ 168.7 (s), 166.8 (s), 159.3 (s), 137.4 (s), 137.3 (s), 131.3 (s), 130.8 (d x 2), 130.1 (d), 129.9 (s), 128.8 (d), 128.5 (d), 127.4 (d), 122.3 (d), 114.0 (d x 2), 55.5 (q), 52.6 (q), 49.9 (t), 41.1 (t), 27.9 (t), 23.1 (t); EI-MS m/z 365 (M$^+$ 40), 265 (25), 145 (100), 121 (45); HRMS Calcd for $C_{22}H_{23}NO_4$: 365.1627, found 365.1627.

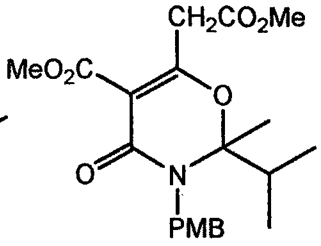
N-(3,4-Dihydro-naphthalen-2-yl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (304)



The imine derived from the condensation of β-tetralone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford the required compound (304): yield (69%); orange oil; IR (neat, cm^{-1}) 1763, 1638, 1610, 735; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.25-7.12 (6H, m, Ar-$\underline{\mathrm{H}}$), 6.82 (2H, d, *J* = 8.7 Hz, C$\underline{\mathrm{H}}$=COCH$_3$), 6.18 (1H, br s, C$\underline{\mathrm{H}}$=C), 4.73 (2H, br s, C$\underline{\mathrm{H}}_2$N), 3.79 (3H, s, OC$\underline{\mathrm{H}}_3$), 3.72 (3H, s, OC$\underline{\mathrm{H}}_3$), 3.55 (2H, s, COC$\underline{\mathrm{H}}_2$CO), 2.88 (2H, t, *J* = 6.7 Hz, C$\underline{\mathrm{H}}_2$), 2.34 (2H, t, *J* = 6.7 Hz, C$\underline{\mathrm{H}}_2$); ^{13}C (75 MHz; CDCl$_3$) δ 168.7 (s), 165.6 (s), 159.4 (s), 139.5 (s), 134.2 (s), 133.0 (s), 130.5 (d x 2), 129.4 (s), 128.7 (d), 128.4 (d), 128.2 (d), 127.8 (d), 127.2 (d), 114.1 (d x 2), 55.7 (q), 52.7 (q), 49.7 (t), 41.7 (t), 28.8 (t), 27.5 (t); EI-MS m/z 365 (M$^+$ 77), 265 (15), 145 (26), 121 (100); HRMS Calcd for C$_{22}$H$_{23}$NO$_4$: 365.1627, found 365.1631.

N-(1-Isopropyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (316) and 2-Isopropyl-3-(4-methoxy-benzyl)-6-methoxycarbonylmethyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid methyl ester (318)

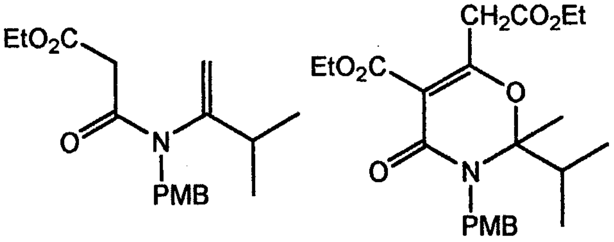




The imine derived from the condensation of 3-methyl-2-butanone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford compounds (316) and (318). Data for (316): yield (33%); clear oil; IR (neat, cm^{-1}) 1742, 1652; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.8 Hz, $C\underline{H}CHCOCH_3$), 6.76 (2H, d, *J* = 8.8 Hz, $C\underline{H}{=}COCH_3$), 4.98 (1H, s, $C\underline{H}H{=}C$), 4.64 (1H, s, $CH\underline{H}{=}C$), 4.60 (2H, br s, $C\underline{H_2}N$), 3.72 (3H, s, $OC\underline{H_3}$), 3.67 (3H, s, $OC\underline{H_3}$), 3.44 (2H, s, $COC\underline{H_2}CO$), 2.39 (1H, sep, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$), 1.04 (6H, d, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$); ^{13}C (75 MHz; $CDCl_3$) δ 168.9 (s), 166.1 (s), 159.2 (s), 153.0 (s), 130.3 (d x 2), 129.6 (s), 114.1 (t), 114.0 (d x 2), 55.6 (q), 55.5 (q), 48.8 (t), 41.4 (t), 31.9 (d), 21.4 (q x 2); EI-MS m/z 305 (M^+ 15), 204 (25), 184 (30), 121 (100); HRMS Calcd for $C_{17}H_{23}NO_4$: 305.1627, found 305.1627.

Data for (318): yield (36%); yellow oil; IR (neat, cm^{-1}) 1742, 1732, 1652, 1616; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.6 Hz, $C\underline{H}CHCOCH_3$), 6.77 (2H, d, *J* = 8.6 Hz, $C\underline{H}{=}COCH_3$), 5.25 (1H, d, *J* = 15.9 Hz, $C\underline{H}HN$), 3.95 (1H, d, *J* = 15.9 Hz, $CH\underline{H}N$), 3.86 (1H, d, *J* = 15.9 Hz, $C\underline{H}HCO$), 3.79 (3H, s, $OC\underline{H_3}$), 3.73 (3H, s, $OC\underline{H_3}$), 3.69 (3H, s, $OC\underline{H_3}$), 3.50 (1H, d, *J* = 15.9 Hz, $CH\underline{H}CO$), 2.70 (2H, sep, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$), 1.44 (3H, s, $C\underline{H_3}$), 0.95 (3H, d, *J* = 6.7 Hz, $CHC\underline{H_3}$), 0.89 (3H, d, *J* = 6.7 Hz, $CHC\underline{H_3}$); ^{13}C (75 MHz; $CDCl_3$) δ 168.5 (s), 165.8 (s), 160.1 (s), 159.0 (s), 131.0 (s), 128.6 (d x 2), 114.3 (d x 2), 107.1 (s), 98.9 (s), 60.8 (s), 55.6 (q), 52.7 (q), 52.3 (q), 46.2 (t), 39.2 (t), 33.9 (d), 19.7 (q), 17.7 (q), 17.5 (q); EI-MS m/z 405 (M^+ 63), 291 (22), 121 (100); HRMS Calcd for $C_{21}H_{27}NO_7$: 405.1788, found 405.1784.

N-(1-Isopropyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid ethyl ester (330) and 2-Isopropyl-3-(4-methoxy-benzyl)-6-methoxycarbonylmethyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid ethyl ester (332)

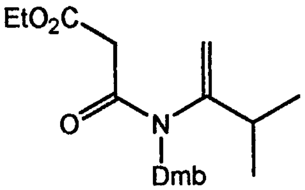


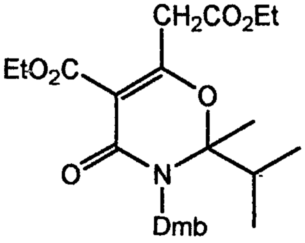
The imine derived from the condensation of 3-methyl-2-butanone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1, using ethyl malonyl chloride (9 mmol) as the acylating agent, to afford compound (330) and (332). Data for (330): yield (27%); clear oil; IR (neat, cm^{-1}) 1740, 1655; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.8 Hz, $C\underline{H}CHCOCH_3$), 6.79 (2H, d, *J* = 8.8 Hz, $C\underline{H}{=}COCH_3$), 4.98 (1H, aap d, *J* = 1.2 Hz, $C\underline{H}H{=}C$), 4.67 (1H, s, $CH\underline{H}{=}C$), 4.58 (2H, br s, $C\underline{H}_2N$), 4.15 (2H, q, *J* = 7.0 Hz, $OC\underline{H}_2CH_3$), 3.74 (1H, s, $OC\underline{H}_3$), 3.44 (2H, s, $COC\underline{H}_2CO$), 2.41 (1H, sep, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$), 1.23 (2H, q, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.06 (6H, d, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$); ^{13}C (75 MHz; $CDCl_3$) δ 168.5 (s), 166.2 (s), 159.2 (s), 153.1 (s), 130.3 (d x 2), 129.7 (s), 114.5 (br t), 114.0 (d x 2), 61.6 (t), 55.5 (q), 48.7 (t), 41.6 (t), 31.9 (d), 21.1 (q x 2), 14.5 (q); EI-MS m/z 319 (M^+ 20), 204 (30), 198 (35), 121 (100); HRMS Calcd for $C_{18}H_{25}NO_4$: 319.1783, found 319.1786.

Data for (332): yield (30%); yellow oil; IR (neat, cm^{-1}) 1742, 1740, 1643; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.5 Hz, $C\underline{H}CHCOCH_3$), 6.81 (2H, d, *J* = 8.5 Hz, $C\underline{H}{=}COCH_3$), 5.30 (1H, d, *J* = 15.8 Hz, $C\underline{H}HN$), 4.29 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.18 (2H, m, $CH_2OC\underline{H}_2CH_3$), 3.96 (1H, d, *J* = 15.8 Hz, $CH\underline{H}N$), 3.86 (1H, d, *J* = 16.0 Hz, $C\underline{H}HCO$), 3.77 (3H, s, $OC\underline{H}_3$), 3.50 (1H, d, *J* = 16.0 Hz, $CH\underline{H}CO$), 2.72 (2H, sep, *J*

= 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.46 (3H, s, $C\underline{H}_3$), 1.33 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.26 (3H, t, J = 7.1 Hz, $CH_2OCH_2C\underline{H}_3$), 0.99 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, J = 6.6 Hz, $CHC\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 167.9 (s), 165.0 (s), 160.2 (s), 159.0 (s), 131.1 (s), 128.6 (d x 2), 114.3 (d x 2), 107.6 (s), 98.7 (s), 61.8 (t), 61.5 (t), 60.7 (s), 55.6 (q), 46.1 (t), 39.4 (t), 33.9 (d), 19.7 (q), 17.7 (q), 17.6 (q), 14.6 (q), 14.5 (q); EI-MS m/z 433 (M^+ 15), 319 (15), 228 (25), 205 (100), 121 (67); HRMS Calcd for $C_{23}H_{31}NO_7$: 433.2100, found 433.2103.

N-(2,4-Dimethoxy-benzyl)-N-(1-isopropyl-vinyl)-malonamic acid ethyl ester (331) and 3-(2,4-Dimethoxy-benzyl)-6-ethoxycarbonylmethyl-2-isopropyl-2-methyl-4-oxo-3,4-dihydro-2H-[1,3]oxazine-5-carboxylic acid ethyl ester (333)

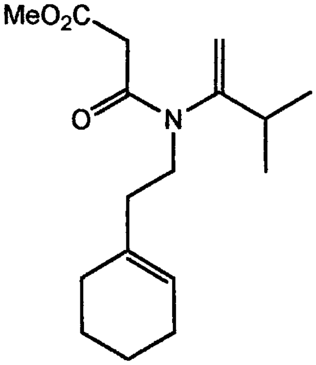




The imine derived from the condensation of 3-methyl-2-butanone and 2,4-dimethoxybenzylamine was reacted under the conditions described in general procedure 5.3.1, using ethyl malonyl chloride (9 mmol) as the acylating agent, to afford compounds (331) and (333). Data for (331): yield (34%); clear oil; IR (neat, cm^{-1}) 1747, 1661; ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 8.2 Hz, $C\underline{H}CHCOCH_3$), 6.33 (2H, m, $C\underline{H}{=}COCH_3$), 4.87 (1H, app d, J = 1.2 Hz, $C\underline{H}H{=}C$), 4.64 (1H, s, $CH\underline{H}{=}C$), 4.63 (2H, br s, $C\underline{H}_2N$), 4.10 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 3.69 (1H, s, $OC\underline{H}_3$), 3.66 (3H, s, $OC\underline{H}_3$), 3.41 (2H, s, $COC\underline{H}_2CO$), 2.43 (1H, sep, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 1.19 (2H, q, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.00 (6H, d, J = 7.0 Hz, $C\underline{H}(CH_3)_2$); ^{13}C (75 MHz; $CDCl_3$) δ 168.5 (s), 166.2 (s), 160.4 (s), 158.7 (s), 153.4 (s), 131.0 (d), 117.9 (s), 112.7 (t), 110.4 (d), 98.3 (d), 61.4 (t), 55.5 (q x 2), 42.2 (t), 41.6 (t), 31.5 (d), 20.9 (q x 2), 14.4 (q); EI-MS m/z 349 (M^+ 51), 306 (20), 234 (100), 198 (86) 151 (47); HRMS Calcd for $C_{19}H_{27}NO_5$: 349.1889, found 349.1889.

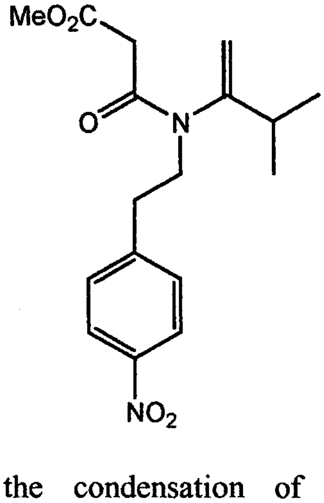
Data for (333): yield (37%); yellow oil; IR (neat, cm^{-1}) 1759, 1731, 1626; ^1H NMR (250 MHz, $CDCl_3$) δ 6.98 (1H, d, J = 7.9 Hz, $C\underline{H}CHCOCH_3$), 6.36 (2H, m, $C\underline{H}{=}COCH_3$), 5.10 (1H, d, J = 16.7 Hz, $C\underline{H}HN$), 4.23 (2H, m, $OC\underline{H}_2CH_3$), 4.08 (2H, m, $CH_2OC\underline{H}_2CH_3$), 4.02 (1H, d, J = 16.7 Hz, $CH\underline{H}N$), 3.85 (1H, d, J = 16.1 Hz, $C\underline{H}HCO$), 3.71 (3H, s, $OC\underline{H}_3$), 3.68 (3H, s, $OC\underline{H}_3$), 3.45 (1H, d, J = 16.1 Hz, $CH\underline{H}CO$), 2.74 (2H, sep, J = 6.7 Hz, $C\underline{H}(CH_3)_2$), 1.39 (3H, s, $C\underline{H}_3$), 1.28 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.17 (3H, t, J = 7.0 Hz, $CH_2OCH_2C\underline{H}_3$), 0.93 (3H, d, J = 6.7 Hz, $CHC\underline{H}_3$), 0.86 (3H, d, J = 6.7 Hz, $CHC\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 167.9 (s), 165.1 (s), 160.7 (s), 157.3 (s), 131.1 (s), 128.3 (d), 119.2 (s), 107.7 (s), 104.7 (d), 98.8 (s), 98.4 (d), 61.7 (t), 61.3 (t), 60.7 (s), 55.6 (q), 55.5 (q), 41.3 (t), 39.4 (t), 33.8 (d), 18.6 (q), 17.7 (q), 17.6 (q), 14.5 (q), 14.4 (q); EI-MS m/z 463 (M^+ 22), 235 (100), 200 (400), 151 (58); HRMS Calcd for $C_{24}H_{33}NO_8$: 463.2206, found 463.2206.

N-(2-Cyclohex-1-enyl-ethyl)-N-(1-isopropyl-vinyl)-malonamic acid methyl ester (336)



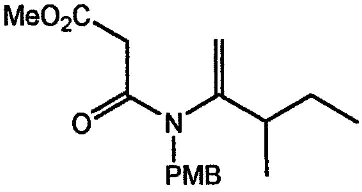
The imine derived from the condensation of 3-methyl-2-butanone and 2-(1-cyclohexenyl)ethylamine was reacted under the conditions described in general procedure 5.3.1, to afford the required compound (336): yield (39%); clear oil; IR (neat, cm^{-1}) 1744, 1630, 1612; ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.35 (1H, br s, CH=C), 5.06 (1H, s, C$\underline{H}$H=C), 4.89 (1H, s, CH$\underline{H}$=C), 3.64 (3H, s, OCH$_3$), 3.36 (2H, s, COC$\underline{H_2}$CO), 3.25 (2H, m, CH$_2$C$\underline{H_2}$N), 2.37 (1H, sep, J = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.09 (2H, m, C$\underline{H_2}$CH$_2$N), 1.87 (4H, m, C$\underline{H_2}$ x 2), 1.50 (4H, m, C$\underline{H_2}$ x 2), 1.05 (6H, d, J = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$); ^{13}C (75 MHz; CDCl$_3$) δ 168.9 (s), 164.5 (s), 153.6 (s), 134.9 (s), 123.2 (d), 113.0 (t), 51.5 (q), 44.5 (t), 41.4 (t), 35.8 (t), 31.8 (d), 28.5 (t), 25.5 (t), 23.2 (t), 22.6 (t), 21.0 (q x 2); EI-MS m/z 293 (M$^+$ 75), 193 (46), 125 (100), 109 (33); HRMS Calcd for $C_{17}H_{27}NO_3$: 293.1991, found 293.1986.

N-(1-Isopropyl-vinyl)-N-[2-(4-nitro-phenyl)-ethyl]-malonamic acid methyl ester (345)



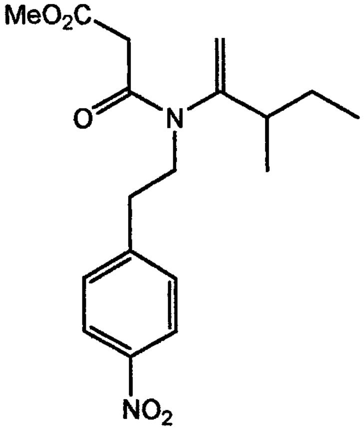
The imine derived from the condensation of 3-methyl-2-butanone and p-nitrophenylethylamine was reacted under the conditions described in general procedure 5.3.1, to afford the required compound (345): yield (42%); orange oil; IR (neat, cm^{-1}) 1735, 1628, 1531; ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.15 (1H, m, C$\underline{H}$CNO$_2$), 7.38 (2H, m, C<u>H</u>CHCOCH$_3$), 5.13 (1H, app d, J = 1.3 Hz, C<u>H</u>H=C), 4.88 (1H, s, CH<u>H</u>=C), 3.71 (2H, m, CH$_2$C<u>H$_2$</u>N), 3.70 (3H, s, OCH$_3$), 3.44 (2H, s, COC<u>H$_2$</u>CO), 3.00 (2H, m, C<u>H$_2$</u>CH$_2$N), 2.40 (1H, sep, J = 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 1.11 (6H, d, J = 6.8 Hz, C<u>H</u>(CH$_3$)$_2$); ^{13}C (75 MHz; CDCl$_3$) δ 168.9 (s), 166.2 (s), 164.5 (s), 153.7 (s), 146.9 (s), 130.0 (d x 2), 124.0 (d x 2), 113.5 (t), 52.7 (q), 47.1 (t), 40.9 (t), 35.7 (t), 32.0 (d), 21.4 (q x 2); EI-MS m/z 334 (M$^+$ 62), 107 (35), 91 (100); HRMS Calcd for $C_{17}H_{22}N_2O_5$: 334.1529, found 334.1533.

N-(1-sec-Butyl-vinyl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (339)



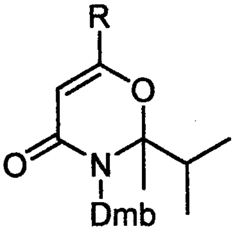
The imine derived from the condensation of 3-methyl-2-pentanone and *p*-methoxybenzylamine was reacted under the conditions described in general procedure 5.3.1 to afford the required compound (339): yield (41%); clear oil; IR (neat, cm^{-1}) 1757, 1650; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.14 (2H, d, J = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.76 (2H, d, J = 8.6 Hz, C<u>H</u>=COCH$_3$), 4.93 (1H, s, C<u>H</u>H=C), 4.66 (1H, s, CH<u>H</u>=C), 4.60 (2H, br s, C<u>H$_2$</u>N), 3.71 (3H, s, OC<u>H$_3$</u>), 3.68 (3H, s, OC<u>H$_3$</u>), 3.43 (2H, s, COC<u>H$_2$</u>CO), 2.10 (1H, app sex, J = 6.7 Hz, C<u>H</u>(CH$_3$)CH$_2$CH$_3$), 1.57 (1H, m, C<u>H</u>(CH$_3$)C<u>H</u>HCH$_3$), 1.22 (1H, m, C<u>H</u>(CH$_3$)CH<u>H</u>CH$_3$), 1.00 (3H, d, J = 6.7 Hz, CH(C<u>H$_3$</u>)CH$_2$CH$_3$), 0.84 (3H, app t, J = 7.6, 7.3 Hz, CH(CH$_3$)CH$_2$C<u>H$_3$</u>); ^{13}C (75 MHz; CDCl$_3$) δ 169.3 (s), 166.0 (s), 159.4 (s), 154.0 (s), 130.2 (d x 2), 129.4 (s), 114.4 (t), 114.1 (d x 2), 55.5 (q), 52.5 (q), 48.6 (t), 44.6 (t), 35.9 (d), 27.6 (t), 19.5 (q), 12.0 (q); EI-MS m/z 319 (M$^+$ 61), 121 (100), 83 (55); HRMS Calcd for $C_{18}H_{25}NO_4$: 319.1784, found 319.1778.

N-(1-sec-Butyl-vinyl)-N-[2-(4-nitro-phenyl)-ethyl]-malonamic acid methyl ester (346)



The imine derived from the condensation of 3-methyl-2-pentanone and *p*-nitrophenylethylamine was reacted under the conditions described in general procedure 5.3.1, to afford the required compound (346): yield (44%); orange oil; IR (neat, cm^{-1}) 1735, 1628, 1531; ^{1}H NMR (250 MHz, $CDCl_3$) 8.10 (2H, d, *J* = 8.8 Hz, $C\underline{H}CNO_3$), 7.32 (2H, d, *J* = 8.8 Hz, $C\underline{H}CH{=}NO_2$), 5.04 (1H, app d, *J* = 1.0 Hz, $C\underline{H}H{=}C$), 4.84 (1H, s, $CH\underline{H}{=}C$), 3.70 (3H, s, $OC\underline{H}_3$), 3.69 (2H, m, $CH_2C\underline{H}_2N$), 3.39 (2H, s, $COC\underline{H}_2CO$), 2.94 (2H, d, *J* = 7.7 Hz, $C\underline{H}_2CH_2N$), 2.10 (1H, app sex, *J* = 7.0 Hz, $C\underline{H}(CH_3)CH_2CH_3$), 1.60 (1H, m, $C\underline{H}(CH_3)C\underline{H}HCH_3$), 1.24 (1H, m, $C\underline{H}(CH_3)CH\underline{H}CH_3$), 1.02 (3H, d, *J* = 7.0 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 0.87 (3H, app t, *J* = 7.3 Hz, $CH(CH_3)CH_2C\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 168.8 (s), 166.2 (s), 152.7 (s), 146.7 (s), 130.0 (d x 2), 124.0 (d x 2), 113.7 (t), 52.6 (q), 45.7 (t), 41.0 (t), 40.6 (d), 33.9 (t), 27.6 (t), 18.3 (q), 12.1 (q); EI-MS m/z 348 (M$^+$ 36), 248 (47), 166 (100), 136 (56); HRMS Calcd for $C_{18}H_{24}N_2O_5$: 348.1685, found 348.1681.

3-(2,4-Dimethoxy-benzyl)-6-heptyl-2-isopropyl-2-methyl-2,3-dihydro-[1,3]oxazin-4-one (358)



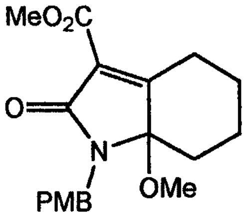
R = $(CH_2)_6CH_3$

The imine derived from the condensation of 3-methyl-2-pentanone and 2,4-dimethoxybenzylamine was acylated with 3-oxo-decanoyl chloride (352) under the conditions described in general procedure 5.3.1, to afford the required compound (358): yield (59%); yellow oil; IR (neat, cm^{-1}) 1767, 1728, 1613; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.98 (1H, d, J = 8.1 Hz, C<u>H</u>CHCOCH$_3$), 6.35 (2H, m, C<u>H</u>=COCH$_3$), 5.17 (1H, s, C<u>H</u>=C), 5.00 (1H, d, J = 17.0 Hz, C<u>H</u>HN), 4.00 (1H, d, J = 17.0 Hz, CH<u>H</u>N), 3.70 (3H, m, OC<u>H</u>$_3$), 3.67 (3H, m, OC<u>H</u>$_3$), 2.65 (2H, sep, J = 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 2.10 (2H, t, J = 7.4 Hz, C<u>H</u>$_2$), 1.46 (2H, m, C<u>H</u>$_2$), 1.32 (3H, s, C<u>H</u>$_3$), 1.22 (8H, m, C<u>H</u>$_2$ x 4), 0.90 (3H, d, J = 7.0 Hz, CHC<u>H</u>$_3$), 0.85 (3H, d, J = 7.0 Hz, CHC<u>H</u>$_3$), 0.80 (3H, s, C<u>H</u>$_3$); ^{13}C (75 MHz; $CDCl_3$) δ 166.4 (s), 164.1 (s), 160.0 (s), 157.4 (s), 128.4 (d), 119.5 (s), 104.6 (d), 98.4 (d), 98.1 (d), 97.3 (s), 55.6 (q), 55.5 (q), 40.4 (t), 38.6 (t), 38.5 (d), 29.8 (t), 29.3 (t x 2), 25.9 (t), 22.9 (t), 19.0 (q), 17.8 (q), 17.6 (q), 14.5 (q); HRMS Calcd for $C_{24}H_{37}NO_4$: 403.2722, found 403.2718.

5.3.2 General procedure for cyclisations utilising ceric ammonium nitrate

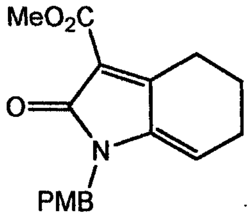
Ceric ammonium nitrate (723 mg, 1.32 mmol) was added to a stirring solution of the appropriate precursor (0.33 mmol) in methanol or acetonitrile (4 ml) and stirred at room temperature for 20 minutes. The resulting solution was dropped onto H_2O (25 ml) and extracted with ethyl acetate (25 ml x 3), dried with $MgSO_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:1 petroleum ether : ethyl acetate), to give the following cyclic products.

7a-Methoxy-1-(4-methoxy-benzyl)-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester (291)



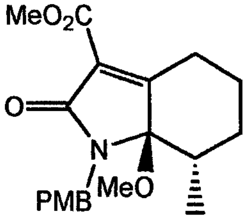
Precursor (290) was cyclised in methanol according to the general procedure 5.3.2: yield (65%); orange oil; IR (neat, cm^{-1}) 1752, 1687; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.25 (2H, d, *J* = 8.9 Hz, C<u>H</u>CHCOCH$_3$), 6.77 (2H, d, *J* = 8.9 Hz, C<u>H</u>=COCH$_3$), 4.62 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.13 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.86 (3H, s, OC<u>H</u>$_3$), 3.77 (3H, s, OC<u>H</u>$_3$), 3.46 (1H, m, C<u>H</u>H), 2.73 (3H, s, OC<u>H</u>$_3$), 2.19 (1H, m, C<u>H</u>H), 1.62 (2H, m, C<u>H</u>$_2$), 1.26 (1H, m, C<u>H</u>H), 1.20 (2H, m, C<u>H</u>$_2$), 1.00 (1H, m; C<u>H</u>H); ^{13}C (75 MHz, CDCl$_3$) δ 169.7 (s), 166.1 (s), 163.1 (s), 159.1 (s), 130.7 (s), 130.3 (d x 2), 123.0 (s), 114.0 (d x 2), 91.6 (s), 55.6 (q), 52.4 (q), 50.1 (q), 41.7 (t), 39.2 (t), 28.0 (t), 26.5 (t), 14.6 (t); EI-MS *m/z* 345 (M$^+$, 35), 315 (100), 121 (85); HRMS Calcd for $C_{19}H_{23}NO_5$: 345.1576, found 345.1573.

1-(4-Methoxy-benzyl)-2-oxo-2,4,5,6-tetrahydro-1H-indole-3-carboxylic acid methyl ester (300)



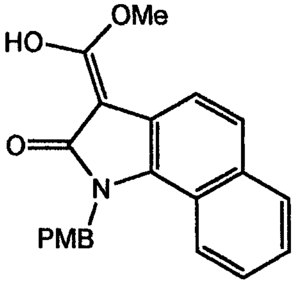
A crystal of tosic acid was added to a solution of compound (291) (0.25 mmol) in dichloromethane or toluene (2.5 mls) and refluxed for 1 hour The resulting solution was cooled, washed with water, dried with $MgSO_4$ and reduced to dryness in *vacuo*: yield (99%); clear yellow oil; IR (neat, cm^{-1}) 1709, 1650; ^1H NMR (250MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.5 Hz, C$\underline{H}$CHCOCH$_3$), 6.71 (2H, d, J = 8.5 Hz, C$\underline{H}$=COCH$_3$), 5.72 (1H, t, J = 5.3 Hz, C$\underline{H}$=C), 4.70 (2H, s, C$\underline{H}_2$N), 3.85 (3H, s, OC$\underline{H}_3$), 2.75 (3H, s, OC$\underline{H}_3$), 2.52 (1H, m, C$\underline{H}_2$), 2.22 (1H, m, C$\underline{H}_2$), 1.67 (2H, m, C$\underline{H}_2$); ^{13}C (75 MHz, $CDCl_3$) δ 167.5 (s), 163.4 (s), 156.1 (s), 155.7 (s), 143.5 (s), 130.7 (s), 130.4 (d x 2), 123.3 (s), 116.5 (d), 114.6 (d x 2), 55.5 (q), 52.4 (q), 41.7 (t), 39.2 (t), 28.0 (t), 26.5 (t); HRMS Calcd for $C_{18}H_{19}NO_4$: 313.1314, found 313.1312.

7a-Methoxy-1-(4-methoxy-benzyl)-7-methyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester (302)



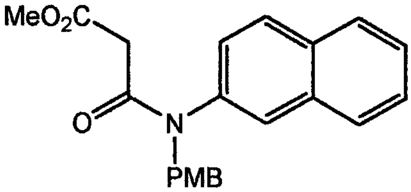
Precursor (301a) was cyclised in methanol according to the general procedure 5.3.2: yield (78%); orange oil; IR (neat, cm^{-1}) 1767, 1674; ^1H NMR (250MHz, $CDCl_3$) δ 7.41 (2H, d, J = 8.7 Hz, C$\underline{H}$CHCOCH$_3$), 6.78 (2H, d, J = 8.7 Hz, C$\underline{H}$=COCH$_3$), 4.41 (1H, d, J = 14.3 Hz, C$\underline{H}$HN), 4.15 (1H, d, J = 14.3 Hz, CH$\underline{H}$N), 3.86 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$), 3.42 (1H, m, C$\underline{H}$H), 2.56 (3H, s, OC$\underline{H}_3$), 2.46 (1H, m, C$\underline{H}$CH$_3$), 2.03 (2H, m, C$\underline{H}_2$), 1.78 (2H, m, C$\underline{H}_2$), 1.55 (1H, m, C$\underline{H}$H), 0.43 (3H, m, CHC$\underline{H}_3$); ^{13}C (75 MHz, $CDCl_3$) δ 168.3 (s), 166.7 (s), 162.9 (s), 159.3 (s), 131.3 (d x 2), 129.9 (s), 124.4 (s), 113.9 (d x 2), 95.3 (s), 55.6 (q), 52.6 (q),50.3 (q), 42.7 (t), 39.0 (d), 39.0 (d), 27.8 (t), 26.2 (t), 22.3 (t), 12.8 (q); EI-MS *m/z* 359 (M^+, 60), 329 (75), 121 (100); HRMS Calcd for $C_{20}H_{25}NO_5$: 359.1733, found 359.1731.

3-(Hydroxy-methoxy-methylene)-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[g]indol-2-one (305)



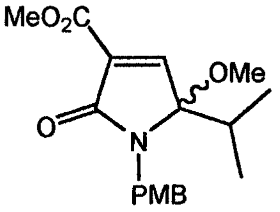
Precursor (303) was cyclised in methanol or acetonitrile according to the general procedure 5.3.2: yield (47% or 72% respectively); dark orange oil; IR (neat, cm^{-1}) 3326, 1687, 1528; ^1H NMR (250MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 7.6 Hz, Ar-H), 7.79 (1H, d, *J* = 7.6 Hz, Ar-H), 7.60 (1H, d, *J* = 7.6 Hz, Ar-H), 7.40 (2H, d, *J* = 8.5 Hz, CHCHCOCH$_3$), 7.24 (3H, m, Ar-H), 6.84 (2H, d, *J* = 8.7 Hz, CH=COCH$_3$), 5.50 (1H, d, *J* = 16.8 Hz, CHHN), 5.30 (1H, d, *J* = 16.8 Hz, CHHN), 3.77 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$); ^{13}C (75 MHz, $CDCl_3$) δ 175.6 (s), 170.7 (s), 165.0 (s), 159.3 (s), 140.6 (s), 136.3 (s), 129.8 (d), 128.6 (d x 2), 126.8 (d), 126.7 (d), 124.9 (d), 122.9 (d), 122.7 (s), 121.1 (s), 120.6 (s), 114.8 (d x 2), 55.6 (q), 54.4 (q), 46.2 (q); EI-MS *m/z* 361 (M^+, 73), 121 (100); HRMS Calcd for $C_{22}H_{19}NO_4$: 361.1~~1~~314, found 361.1318.

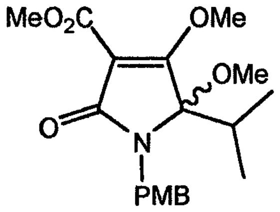
N-(4-Methoxy-benzyl)-N-naphthalen-2-yl-malonamic acid methyl ester (308)



Precursor (304) was cyclised in methanol or acetonitrile according to the general procedure 5.3.2: yield (45% or 77% respectively); dark orange oil; IR (neat, cm^{-1}) 1755, 1681, 1513, 935; ^1H NMR (250MHz, $CDCl_3$) δ 7.78 (2H, m, Ar-H), 7.68 (1H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.39 (1H, m, Ar-H), (2H, d, *J* = 8.7 Hz, $CHCHCOCH_3$), 6.99 (1H, m, Ar-H), 6.71 (2H, d, *J* = 8.7 Hz, $CH{=}COCH_3$), 4.85 (2H, s, CH_2N), 3.70 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.16 (2H, s, $COCH_2CO$); ^{13}C (75 MHz, $CDCl_3$) δ 168.6 (s), 166.4 (s), 159.4 (s), 139.3 (s), 133.8 (s), 133.0 (s), 130.7 (d x 2), 130.2 (d), 129.4 (s), 128.4 (d), 128.1 (d), 127.7 (d), 127.4 (d), 127.3 (d), 127.2 (d), 126.3 (d), 114.2 (d x 2), 55.6 (q), 53.0 (q), 52.6 (q), 42.1 (t); EI-MS *m/z* 363 (M^+, 25), 262 (20), 121 (100); HRMS Calcd for $C_{22}H_{21}NO_4$: 363.1471, found 363.1470.

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (317) and 5-Isopropyl-4,5-dimethoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (329)

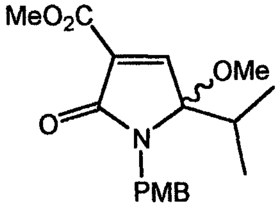




Ceric ammonium nitrate (723 mg, 1.32 mmol) was added to a stirring solution of precursor (316) (100 mg, 0.33 mmol) in MeOH (4 ml) and refluxed for 2 hrs. The resulting solution was dropped onto H_2O (25 ml) and extracted with ethyl acetate (25 ml x 3), dried with $MgSO_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:1 petroleum ether : ethyl acetate), to give the following cyclic products. Data for (317): yield (29%); orange oil; IR (neat, cm^{-1}) 1751, 1719, 1701, 1611, 1512; ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (1H, s, CH=C), 7.37 (2H, d, *J* = 8.6 Hz, $CHCHCOCH_3$), 6.77 (2H, d, *J* = 8.6 Hz, $CH{=}COCH_3$), 4.32 (2H, s, CH_2N), 3.86 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$), 2.74 (3H, s, OC$\underline{H}_3$), 2.20 (1H, sep, *J* = 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.07 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$), 0.43 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$); ^{13}C (75 MHz; CDCl$_3$) δ 165.6 (s), 161.8 (s), 159.2 (s), 153.3 (d), 133.8 (s), 131.0 (d x 2), 129.9 (s), 114.0 (d x 2), 98.3 (s), 55.6 (q), 52.8 (q), 51.7 (q), 42.2 (t), 33.9 (d), 18.4 (q), 16.5 (q); EI-MS m/z 333 (M$^+$ 25), 198 (45), 121 (100); HRMS Calcd for $C_{18}H_{23}NO_5$: 333.1576, found 333.1585.

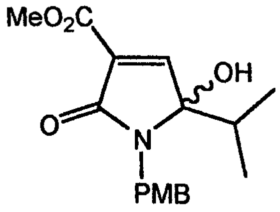
Data for (329): yield (23%); dark orange oil; IR (neat, cm^{-1}) 1752, 1719, 1701, 1615, 1513; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.38 (2H, d, *J* = 8.6 Hz, C$\underline{H}$CHCOCH$_3$), 6.82 (2H, d, *J* = 8.6 Hz, C$\underline{H}$=COCH$_3$), 4.33 (2H, s, C$\underline{H}_2$N), 3.87 (3H, s, OC$\underline{H}_3$), 3.79 (3H, s, OC$\underline{H}_3$), 3.61 (3H, s, OC$\underline{H}_3$), 2.85 (3H, s, OC$\underline{H}_3$), 2.22 (1H, sep, *J* = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 0.95 (3H, d, *J* = 7.0 Hz, CHC$\underline{H}_3$), 0.58 (3H, d, *J* = 7.0 Hz, CHC$\underline{H}_3$); ^{13}C (75 MHz; CDCl$_3$) δ 175.3 (s), 165.7 (s), 161.8 (s), 159.3 (s), 133.3 (s), 131.1 (d x 2), 129.6 (s), 113.9 (d x 2), 97.8 (s), 55.6 (q), 55.4 (q), 52.7 (q), 50.1 (q), 43.0 (t), 34.6 (d), 17.1 (q), 16.9 (q); EI-MS m/z 363 (M$^+$ 60), 333 (100), 198 (26), 121 (42); HRMS Calcd for $C_{19}H_{25}NO_6$: 363.1682, found 363.1685.

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (317)



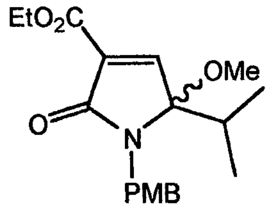
Precursor (316) was cyclised in methanol according to the general procedure 5.3.2 to afford (317) in 67% yield. The spectral details matched those previously cited above.

5-Hydroxy-5-isopropyl-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (323)



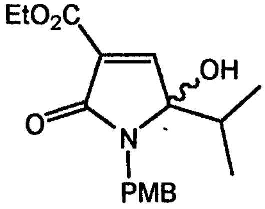
Precursor (316) was cyclised in acetonitrile according to the general procedure 5.3.2 and no purification was required: yield (95%); orange oil; IR (neat, cm^{-1}) 3366, 1749, 1718, 1613, 1513; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.54 (1H, s, CH=C), 7.31 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.75 (2H, d, *J* = 8.6 Hz, C<u>H</u>=COCH$_3$), 4.43 (1H, d, *J* = 15.0 Hz, C<u>H</u>HN), 4.30 (1H, d, *J* = 15.0 Hz, CH<u>H</u>N), 3.79 (3H, s, OC<u>H</u>$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 2.14 (1H, sep, *J* = 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 1.05 (3H, d, *J* = 6.8 Hz, CHC<u>H</u>$_3$), 0.35 (3H, d, *J* = 6.8 Hz, CHC<u>H</u>$_3$); ^{13}C (75 MHz; CDCl$_3$) δ 165.7 (s), 162.3 (s), 159.1 (s), 155.0 (d), 130.7 (d x 2), 130.5 (s), 130.3 (s), 114.1 (d x 2), 93.6 (s), 55.6 (q), 52.7 (q), 42.2 (t), 33.7 (d), 18.3 (q), 16.5 (q); EI-MS m/z 319 (M$^+$ 59), 216 (15), 136 (80), 121 (100); HRMS Calcd for $C_{17}H_{21}NO_5$: 319.1420, found 319.1420.

5-Isopropyl-5-methoxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (334)



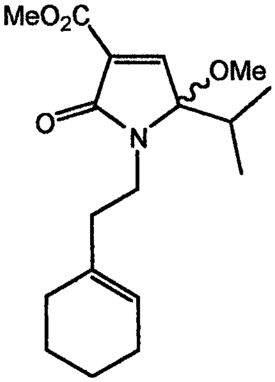
Precursor (330) was cyclised in methanol according to the general procedure 5.3.2: yield (58%); orange oil; IR (neat, cm^{-1}) 1755, 1722, 1704, 1616, 1514; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.42 (1H, s, CH=C), 7.37 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOCH$_3$), 6.77 (2H, d, J = 8.6 Hz, $C\underline{H}=COCH_3$), 4.32 (4H, m, $OC\underline{H}_2CH_3$, $C\underline{H}_2N$), 3.74 (3H, s, $OC\underline{H}_3$), 2.74 (3H, s, $OC\underline{H}_3$), 2.19 (1H, sep, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 1.34 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.07 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$), 0.43 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 165.7 (s), 161.3 (s), 159.2 (s), 152.6 (d), 134.0 (s), 130.6 (d x 2), 129.8 (s), 113.9 (d x 2), 97.9 (s), 61.9 (t), 55.7 (q), 51.6 (q), 42.1 (t), 33.9 (d), 18.3 (q), 17.2 (q), 14.5 (q); EI-MS m/z 347 (M^+ 25), 212 (60), 212 (60), 121 (100); HRMS Calcd for $C_{19}H_{25}NO_5$: 347.1733, found 347.1732.

5-Hydroxy-5-isopropyl-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (335)



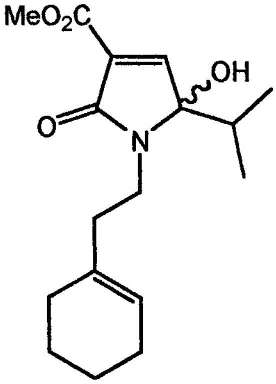
Precursor (330) was cyclised in acetonitrile according to the general procedure 5.3.2 and no purification was required: yield (97%); orange oil; IR (neat, cm^{-1}) 3373, 1752, 1728, 1620, 1511; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, s, CH=C), 7.27 (2H, d, J = 8.5 Hz, $C\underline{H}CHCOCH_3$), 6.69 (2H, d, J = 8.5 Hz, $C\underline{H}=COCH_3$), 4.43 (1H, d, J = 15.0 Hz, $C\underline{H}HN$), 4.20 (3H, m, $CH\underline{H}N$, $OC\underline{H}_2CH_3$), 3.67 (3H, s, $OC\underline{H}_3$), 2.09 (1H, sep, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 1.26 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.03 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$), 0.29 (3H, d, J = 7.0 Hz, $CHC\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 165.9 (s), 161.8 (s), 159.0 (s), 154.7 (d), 131.0 (d x 2), 130.6 (s), 130.3 (s), 114.0 (d x 2), 93.6 (s), 61.8 (t), 55.6 (q), 42.0 (t), 33.7 (d), 18.2 (q), 16.5 (q), 14.4 (q); EI-MS m/z 333 (M^+ 10), 212 (15), 136 (33), 121 (100); HRMS Calcd for $C_{18}H_{23}NO_5$: 333.1576, found 333.1570.

1-(2-Cyclohex-1-enyl-ethyl)-5-isopropyl-5-methoxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (337)



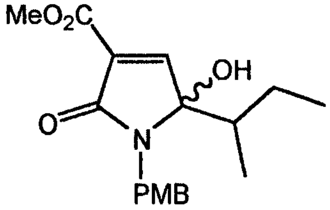
Precursor (336) was cyclised in methanol according to the general procedure 5.3.2: yield (52%); orange oil; IR (neat, cm^{-1}) 1755, 1717, 1617, 1511; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.47 (1H, s, CH=C), 5.43 (1H, br s, C$\underline{H}$=C), 3.81 (3H, s, OC$\underline{H}_3$), 3.75 (1H, m, CH$_2$C$\underline{H}_2$N), 2.72 (3H, s, OC$\underline{H}_3$), 2.44 (2H, m, C$\underline{H}_2$CH$_2$N), 2.21 (1H, sep, *J* = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.09 (4H, m, C$\underline{H}_2$ x 2), 1.66 (4H, m, C$\underline{H}_2$ x 2), 1.16 (3H, d, *J* = 7.0 Hz, CHC$\underline{H}_3$), 0.68 (3H, d, *J* = 7.0 Hz, CHC$\underline{H}_3$); ^{13}C (75 MHz; CDCl$_3$) δ 165.5 (s), 162.3 (s), 154.7 (d), 136.9 (s), 131.1 (s), 123.9 (d), 97.8 (s), 52.9 (q), 51.8 (q), 38.5 (t), 37.0 (t), 33.6 (d), 28.5 (t), 25.7 (t), 23.1 (t), 22.3 (t), 18.6 (q), 16.9 (q); EI-MS m/z 321 (M$^+$ 65), 303 (35), 125 (100); HRMS Calcd for $C_{18}H_{27}NO_4$: 321.1940, found 321.1938.

1-(2-Cyclohex-1-enyl-ethyl)-5-hydroxy-5-isopropyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (338)



Precursor (336) was cyclised in acetonitrile according to the general procedure 5.3.2 and no purification was required: yield (96%); orange oil; IR (neat, cm^{-1}) 3323, 1749, 1717, 1620, 1513; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 (1H, s, CH=C), 5.43 (1H, br s, C<u>H</u>=C), 3.84 (3H, s, OC<u>H</u>$_3$), 3.54 (1H, m, C<u>H</u>HN), 3.11 (1H, m, CH<u>H</u>N), 2.39 (1H, m, C<u>H</u>HCH$_2$N), 2.39-2.15 (2H, m, CH<u>H</u>CH$_2$N, C<u>H</u>(CH$_3$)$_2$), 2.02 (4H, m, C<u>H</u>$_2$ x 2), 1.57 (4H, m, C<u>H</u>$_2$ x 2), 1.14 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$), 0.66 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C (75 MHz; CDCl$_3$) δ 165.0 (s), 162.3 (s), 154.6 (d), 136.4 (s), 130.9 (s), 123.9 (d), 92.9 (s), 52.7 (q), 38.3 (t), 36.8 (t), 33.6 (d), 28.4 (t), 25.6 (t), 23.1 (t), 22.6 (t), 18.2 (q), 16.8 (q); EI-MS m/z 307 (M$^+$ 45), 292 (28), 125 (100); HRMS Calcd for $C_{17}H_{25}NO_4$: 307.1784, found 307.1781.

5-*sec*-Butyl-5-hydroxy-1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (340)



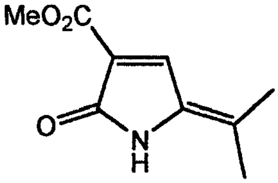
Precursor (339) was cyclised in acetonitrile according to the general procedure 5.3.2 to afford a 1:1 mixture of diastereomers. Data for mixture: yield (84%); orange oil; IR (neat, cm^{-1}) 3256, 1747, 1721, 1619, 1525; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (1H, s, CH=C), 7.51 (1H, s, CH=C), 7.33 (2H, m, $C\underline{H}CHCOCH_3$), 6.77 (2H, m, $C\underline{H}{=}COCH_3$), 4.62 (1H, d, J = 15.0 Hz, $C\underline{H}HN$), 4.44 (1H, d, J = 14.9 Hz, $C\underline{H}HN$), 4.36 (1H, d, J = 14.9 Hz, $CH\underline{H}N$), 4.20 (1H, d, J = 15.0 Hz, $CH\underline{H}N$), 3.79 (3H, s, $OC\underline{H}_3$), 3.75 (3H, s, $OC\underline{H}_3$), 2.08 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 1.77 (1H, m, $C\underline{H}(CH_3)CH_2CH_3$), 1.06 (3H, d, J = 7.0 Hz, $CH(C\underline{H}_3)CH_2CH_3$), 0.93 (3H, d, J = 7.0 Hz, $CH(CH_3)CH_2C\underline{H}_3$), 0.82 (2H, m, $CH(CH_3)C\underline{H}_2CH_3$), 0.44 (2H, m, $CH(CH_3)C\underline{H}_2CH_3$), 0.36 (3H, m, $CH(CH_3)CH_2C\underline{H}_3$), 0.33 (3H, m, $CH(C\underline{H}_3)CH_2CH_3$); ^{13}C (75 MHz; $CDCl_3$) δ 165.9 (s), 165.7 (s), 162.2 (s), 159.2 (s), 159.0 (s), 155.6 (d), 130.7 (d x 2), 130.6 (d x 2), 130.3 (s), 129.7 (s), 114.1 (d x 2), 114.0 (d x 2), 93.6 (s), 93.4 (s), 55.7 (q), 55.6 (q), 52.6 (q), 42.1 (t), 41.9 (t), 40.7 (d), 40.2 (d), 25.1 (t), 23.6 (t), 14.4 (q), 13.0 (q), 12.9 (q), 11.6 (q); EI-MS m/z 333 (M^+ 45), 230 (25), 121 (100); HRMS Calcd for $C_{18}H_{23}NO_5$: 333.1576, found 333.1576.

5.3.3 General method for the attempted deprotection of *p*-methoxybenzylamides

Method A: Ceric ammonium nitrate (548 mg, 1 mmol) was added to a solution of the required cyclised compound (0.25 mmol) in 4 ml of 3:1 acetonitrile/H_2O and stirred for 1-2 hrs (followed by TLC). The resulting solution was dropped onto H_2O (25 ml) and extracted with ethyl acetate (25 ml x 3), dried with $MgSO_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:2 petroleum ether : ethyl acetate), to give the following deprotected products.

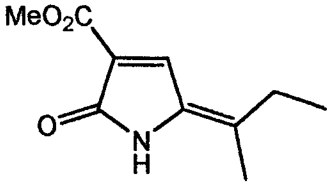
Method B: The required cyclised compound (0.7 mmol) was refluxed with stirring in trifluoroacetic acid (8.5 ml) for 1-2 hours (followed by TLC). The reaction mix was cooled to room temperature, quenched on ice and extracted with dichloromethane (25 ml x 3). The organic layer was then washed with saturated sodium hydrogen carbonate (25 ml x 3), dried with $MgSO_4$ and reduced to dryness *invacuo*. Purification was carried out by flash chromatogtraphy (1:2 petroleum ether : ethyl acetate), to give the following deprotected products.

5-Isopropylidene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (323)



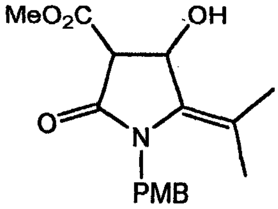
Compound (323) was deprotected according to the general procedure 5.3.3 (Method A, yield 95%), (Method B, yield 86%); brown solid; IR (neat, cm^{-1}) 3461, 1735, 1683, 1522; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.71 (1H, br s, N$\underline{H}$), 7.97 (1H, s, C$\underline{H}$=C), 3.86 (3H, s, OC$\underline{H}_3$), 2.11 (3H, s, C$\underline{H}_3$), 2.09 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz; $CDCl_3$) δ 168.8 (s), 163.2 (s), 140.1 (d), 133.3 (s), 133.0 (s), 127.6 (s), 52.4 (q), 21.4 (q), 20.9 (q); EI-MS m/z 181 (M^+ 100), 166 (35), 150 (50), 123 (72), 83 (70); HRMS Calcd for $C_9H_{11}NO_3$: 181.0739, found 181.0739.

5-sec-Butylidene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (343)



Compound (340) was deprotected according to the general procedure 5.3.3 to give a 1:1 mixture of *cis:trans* isomers. Data for isomers: (Method A, yield 97%), (Method B, yield 93%), light brown solid; IR (neat, cm^{-1}) 3443, 1742, 1686, 1520; ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.0 (1H, br s, N<u>H</u>), 9.84 (1H, br s, N<u>H</u>), 7.93 (1H, s, C<u>H</u>=C), 3.83 (3H, s, OC<u>H</u>$_3$), 2.43 (2H, m, C<u>H</u>$_2$CH$_3$), 2.10 (3H, s, C<u>H</u>$_3$), 2.04 (3H, s, C<u>H</u>$_3$), 1.13 (2H, m, CH$_2$C<u>H</u>$_3$); ^{13}C (75 MHz; CDCl$_3$) δ 168.8 (s), 168.6 (s), 163.2 (s), 140.5 (d), 139.7 (d), 138.6 (s), 138.3 (s), 132.7 (s), 132.3 (q), 124.9 (s), 124.7 (s), 52.4 (q), 28.0 (t), 27.8 (t), 18.8 (q), 18.3 (q), 14.3 (q), 12.6 (q); EI-MS m/z 195 (M$^+$ 75), 180 (35), 164 (78), 123 (76), 83 (100); HRMS Calcd for $C_{10}H_{13}NO_3$: 195.0895, found 195.0894.

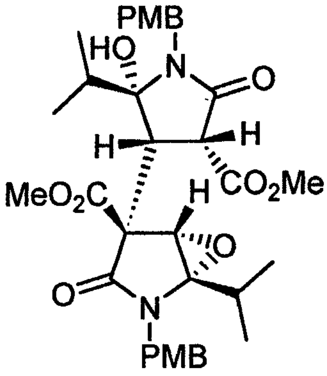
4-Hydroxy-5-isopropylidene-1-(4-methoxy-benzyl)-2-oxo-pyrrolidine-3-carboxylic acid methyl ester (344)



A solution of (323) (223 mg, 0.7 mmol, in 1 ml of ethyl acetate) was added to a stirring solution of 10% palladium/carbon (25 mg) in ethyl acetate (3 ml) under H$_2$. The resulting suspension was stirred for 3 days, filtered and reduced to dryness *invacuo*. Purification was carried out by flash chromatogtraphy (4:1 petroleum ether:ethyl acetate): yield (97%); clear oil; IR (neat, cm^{-1}) 3329, 1762, 1647; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.25 (2H, d, *J* = 8.5 Hz, C<u>H</u>CHCOCH$_3$), 6.82 (2H, d, *J* = 8.5 Hz, C<u>H</u>=COCH$_3$), 4.65 (1H, d, *J* = 14.3 Hz, C<u>H</u>HN), 4.55 (1H, d, *J* = 14.3 Hz, CH<u>H</u>N), 3.83 (3H, s, OC<u>H</u>$_3$), 3.76 (3H, s, OC<u>H</u>$_3$), 3.68 (2H, s, C<u>H</u> x 2), 1.82 (3H, s, C<u>H</u>$_3$), 1.64 (3H, s, C<u>H</u>$_3$); ^{1}H (300 MHz, DMSO-D$_6$) δ 7.18 (2H, d, *J* = 8.8 Hz, C<u>H</u>CHCOCH$_3$), 6.87

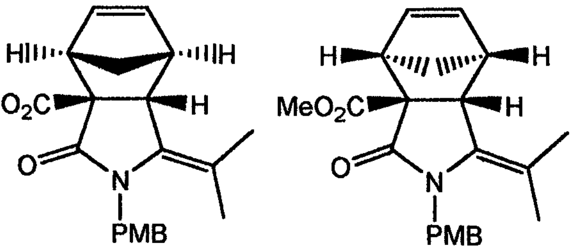
(2H, d, J = 8.8 Hz, C$\underline{H}$=COCH$_3$), 4.56 (1H, d, J = 14.7 Hz, C$\underline{H}$HN), 4.50 (1H, d, J = 14.3 Hz, CH$\underline{H}$N), 4.35 (1H, d, J = 5.8 Hz, C$\underline{H}$CH), 4.00 (1H, d, J = 5.8 Hz, CHC$\underline{H}$), 3.72 (3H, s, OC$\underline{H}_3$), 3.69 (3H, s, OC$\underline{H}_3$), 1.73 (3H, s, C$\underline{H}_3$), 1.58 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz, CDCl$_3$) δ 173.6 (s), 169.9 (s), 168.0 (s), 159.8 (s), 130.4 (d x 2), 127.3 (s), 114.1 (d x 2), 88.1 (s), 55.6 (q), 54.1 (q), 51.1 (d), 50.5 (d), 43.1 (t), 26.5 (q), 25.3 (q); EI-MS m/z 319 (M$^+$ 100), 313 (55), 216 (30), 136 (45), 121 (70); HRMS Calcd for $C_{17}H_{21}NO_5$: 319.1420, found 319.1421.

4-[4-Ethoxycarbonyl-2-hydroxy-2-isopropyl-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-1-isopropyl-2-(4-methoxy-benzyl)-3-oxo-6-oxa-2-aza-bicyclo[3.1.0]hexane-4-carboxylic acid ethyl ester (359)



Compound (323) (320 mg, 0.96 mmol) was added to a stirring solution of methyl lithium (2.4 ml, 3.8 mmol) in dry tetrahydrofuran (5 ml) at -78°C. The reaction was stirred for 1 hr and slowly allowed warm to room temperature (~20 minutes). The reaction was then quenched with slow addition of H$_2$O (5 ml) and the resulting suspension was extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with brine (10 ml), dried over MgSO$_4$ and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (1:1 petroleum ether : ethyl acetate). Discernible data for (359): yield (37%); clear oil; IR (neat, cm^{-1}) 3425, 1756, 1752, 1682, 1680, 1532, 730; ^{1}H NMR (250MHz, CDCl$_3$) δ 7.29 (2H, d, *J* = 8.7 Hz, C$\underline{H}$CHCOCH$_3$), 7.23 (2H, d, *J* = 8.7 Hz, C$\underline{H}$CHCOCH$_3$), 6.73 (2H, d, *J* = 8.7 Hz, C$\underline{H}$=COCH$_3$), 6.69 (2H, d, *J* = 8.7 Hz, C$\underline{H}$=COCH$_3$), 4.65 (1H, d, *J* = 14.5 Hz, C$\underline{H}$HN), 4.32 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.27 (1H, d, *J* = 15.0 Hz, C$\underline{H}$HN), 4.15 (5H, m, OC$\underline{H_2}$CH$_3$ x 2, CH), 3.93 (1H, d, *J* = 14.5 Hz, C$\underline{H}$HN), 3.82 (1H, d, *J* = 3.0 Hz, C$\underline{H}$CH), 3.70 (3H, s, OC$\underline{H_3}$), 3.68 (3H, s, OC$\underline{H_3}$), 3.39 (1H, s, O$\underline{H}$), 3.24 (1H, d, *J* = 3.0 Hz, C$\underline{H}$CH), 2.17 (1H, sep, *J* = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.88 (1H, sep, *J* = 7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.19 (6H, m, OCH$_2$C$\underline{H_3}$ x 2), 0.75 (3H, d, *J* = 7.0 Hz, CHC$\underline{H_3}$), 0.62 (3H, d, *J* = 7.0 Hz, CHC$\underline{H_3}$), 0.51 (3H, d, *J* = 7.0 Hz, CHC$\underline{H_3}$), 0.40 (3H, d, *J* = 7.0 Hz, CHC$\underline{H_3}$); ^{13}C (75 MHz, CDCl$_3$) δ 167.9 (s), 167.8 (s), 167.4 (s), 167.3 (s), 159.3 (s), 159.2 (s), 131.2 (d x 2), 130.4 (d x 2), 129.9 (s), 114.1 (d x 2), 113.8 (d x 2), 107.6 (d), 92.8 (s), 79.8 (d), 67.2 (s x 2), 63.1 (t), 62.6 (t), 55.6 (q), 55.5 (q), 51.7 (d), 47.5 (d), 43.7 (t), 43.5 (t), 35.9 (d), 34.1 (d), 17.3 (q), 17.2 (q), 16.8 (q), 16.7 (q), 14.5 (q), 14.2 (q); TOF MS ES+ *m/z* 689 (100, MNa$^+$), 617 (30), 510 (85), 428 (90), 328 (55); HRMS Calcd for C$_{36}$H$_{46}$N$_2$O$_{10}$Na: 689.3050, found 689.3040. A D$_2$O shake confirmed the position of the hydroxyl group.

5-Isopropylidene-4-(4-methoxy-benzyl)-3-oxo-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-2-carboxylic acid methyl ester (361)



A solution of (323) (300 mg, 0.94 mmol, in 1ml of toluene) was added to solution of cyclopentadiene (12.5 mg, 1.88 mmol) in toluene (5 ml) and refluxed for 1 hour. The reaction was cooled to room temperature and reduced to dryness *in vacuo*. Purification was carried out by flash chromatogtraphy (4:1 petroleum ether:ethyl acetate) to yield a 1:1 mixture of *exo* (361a) : *endo* (361b) products respectively. Data for *exo*-product (361a): yield (37%); clear oil; IR (neat, cm^{-1}) 1737, 1678, 1519; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.07 (2H, d, *J* = 8.9 Hz, C$\underline{H}$CHCOCH$_3$), 6.83 (2H, d, *J* = 8.9 Hz, C$\underline{H}$=COCH$_3$), 6.34 (1H, m, C$\underline{H}$=CH), 6.26 (1H, m, CH=C$\underline{H}$), 4.98 (1H, d, *J* = 16.2 Hz, C$\underline{H}$HN), 4.72 (1H, d, *J* = 16.2 Hz, CH$\underline{H}$N), 3.76 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.47 (1H, br s, C=CHC$\underline{H}$), 3.05 (1H, br s, C=CHCHC$\underline{H}$), 3.01 (1H, br s, C=CHC$\underline{H}$CH), 1.76 (3H, s, C$\underline{H}_3$), 1.68 (3H, s, C$\underline{H}_3$), 1.43 (2H, br s, C$\underline{H}_2$); ^{13}C (75 MHz; CDCl$_3$) δ 173.5 (s), 171.3 (s), 158.9 (s), 138.2 (d), 137.7 (d), 133.3 (s), 129.9 (s), 127.6 (d x 2), 114.4 (d x 2), 106.3 (s), 64.5 (s), 55.6 (q), 53.0 (q), 49.9 (d), 49.1 (d), 48.9 (d), 46.3 (t), 44.3 (t), 23.1 (q), 19.5 (q); EI-MS m/z 367 (M$^+$ 60), 302 (100), 269 (25), 121 (67); HRMS Calcd for C$_{22}$H$_{25}$NO$_4$: 367.1784, found 367.1782.

Data for *endo*-product (361b): yield (43%); clear oil; IR (neat, cm^{-1}) 1741, 1678, 1521; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.00 (2H, d, *J* = 8.5 Hz, C$\underline{H}$CHCOCH$_3$), 6.74 (2H, d, *J* = 8.5 Hz, C$\underline{H}$=COCH$_3$), 6.10 (1H, m, C$\underline{H}$=CH), 5.98 (1H, m, CH=C$\underline{H}$), 4.76 (1H, d, *J* = 16.5 Hz, C$\underline{H}$HN), 4.54 (1H, d, *J* = 16.5 Hz, CH$\underline{H}$N), 3.71 (3H, s, OC$\underline{H}_3$), 3.69 (3H, s, OC$\underline{H}_3$), 3.51 (1H, br s, C=CHC$\underline{H}$), 3.46 (1H, d, *J* = 3.5 Hz, C=CHCHC$\underline{H}$), 3.22 (1H, br s, C=CHC$\underline{H}$CH), 1.70 (3H, s, C$\underline{H}_3$), 1.58 (2H, m, C$\underline{H}_2$), 1.53 (3H, s, C$\underline{H}_3$); ^{13}C (75 MHz; CDCl$_3$) δ 173.5 (s), 173.6 (s), 158.8 (s), 136.4 (d), 136.1 (d), 132.7 (s), 130.4 (s), 127.6 (d x 2), 114.3 (d x 2), 105.9 (s), 62.6 (s), 55.6 (q), 52.9 (q), 52.0 (t), 49.9 (d), 49.3 (d), 46.9 (d), 46.1 (t), 23.0 (q), 19.4 (q); CI-MS m/z 368 (MH$^+$ 80), 359 (34), 302 (100), 121 (68); HRMS Calcd for C$_{22}$H$_{25}$NO$_4$: 367.1784, found 367.1783.

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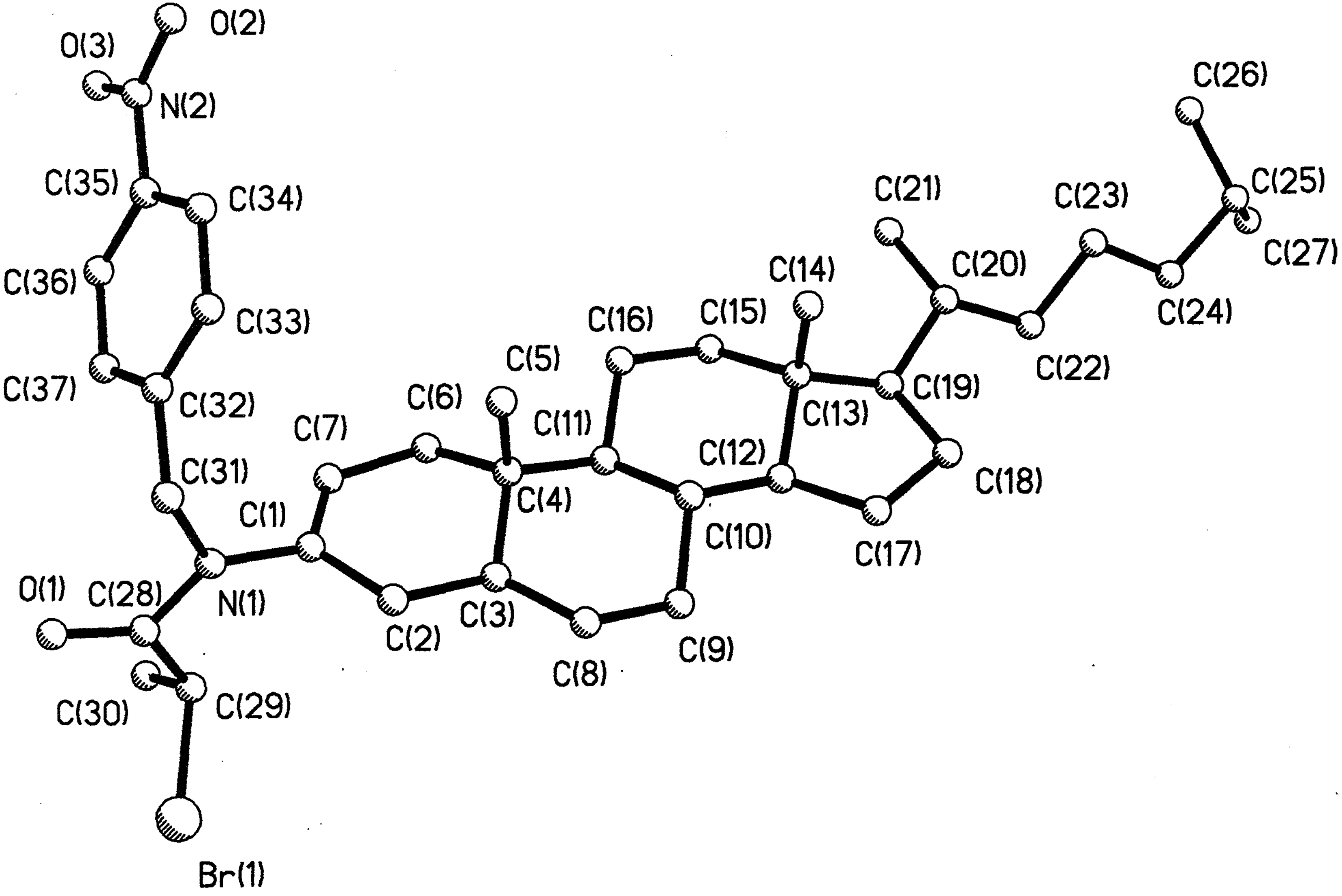
Appendix

Table 2. Crystal data and structure refinement for jmd.

Identification code	jmd	
Empirical formula	$C_{37}H_{54}BrN_2O_3$	
Formula weight	654.73	
Temperature	210(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.207(3) Å	alpha = 90°
	b = 10.818(5) Å	beta = 90°
	c = 53.38(3) Å	gamma = 90°
Volume, Z	$3584(3)\ Å^3$, 4	
Density (calculated)	$1.213\ Mg/m^3$	
Absorption coefficient	$1.182\ mm^{-1}$	
F(000)	1396	
Crystal size	0.20 x 0.13 x 0.04 mm	
θ range for data collection	1.92 to 22.49°	
Limiting indices	$-6 \le h \le 6$, $-7 \le k \le 11$, $-57 \le l \le 34$	
Reflections collected	13626	
Independent reflections	4690 (R_{int} = 0.1675)	
Completeness to θ = 22.49°	99.7 %	
Max. and min. transmission	0.9542 and 0.7979	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4690 / 216 / 434	
Goodness-of-fit on F^2	0.976	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0893, wR2 = 0.1958	
R indices (all data)	R1 = 0.1801, wR2 = 0.2273	
Absolute structure parameter	0.14(3)	
Extinction coefficient	0.023(2)	
Largest diff. peak and hole	0.264 and -0.247 $eÅ^{-3}$	


O(2)
O(3)
N(2)
C(35)
C(34)
C(36)
C(33)
C(37)
C(32)
C(31)
C(1)
C(7)
C(6)
C(5)
C(4)
C(11)
C(16)
C(15)
C(14)
C(12)
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C(10)
C(21)
C(20)
C(19)
C(22)
C(23)
C(24)
C(25)
C(26)
C(27)
C(18)
C(17)
O(1)
C(28)
N(1)
C(2)
C(3)
C(8)
C(9)
C(30)
C(29)
Br(1)

Table 3. Bond lengths [Å] and angles [°] for jmd.

C29-C30A	1.36(6)	C29-C28	1.495(14)
C29-C30	1.71(3)	C29-Br1	1.814(13)
C29-Br1A	1.851(13)	N1-C28	1.385(13)
N1-C1	1.419(12)	N1-C31	1.510(12)
O1-C28	1.226(11)	C1-C7	1.321(14)
C1-C2	1.495(14)	C2-C3	1.571(12)
C3-C4	1.490(13)	C3-C8	1.565(13)
C4-C6	1.521(12)	C4-C5	1.524(12)
C4-C11	1.573(12)	C6-C7	1.521(13)
C8-C9	1.509(12)	C9-C10	1.511(13)
C10-C11	1.483(12)	C10-C12	1.551(11)
C11-C16	1.564(13)	C12-C17	1.519(12)
C12-C13	1.523(13)	C13-C14	1.506(14)
C13-C15	1.577(12)	C13-C19	1.566(12)
C15-C16	1.494(11)	C17-C18	1.545(13)
C18-C19	1.530(12)	C19-C20	1.513(12)
C20-C21	1.512(16)	C20-C22	1.537(13)
C22-C23	1.587(14)	C23-C24	1.514(14)
C24-C25	1.54(2)	C24-C25A	1.578(16)
C31-C32	1.491(12)	C32-C33	1.3900
C32-C37	1.3900	C33-C34	1.3900
C34-C35	1.3900	C35-C36	1.3900
C35-N2	1.457(12)	C36-C37	1.3900
N2-O3	1.230(11)	N2-O2	1.317(11)
C25-C26	1.54(2)	C25-C27	1.56(2)
C25A-C27A	1.470(17)	C25A-C26A	1.519(17)

C30A-C29-C28	109(3)	C30A-C29-C30	90(3)
C28-C29-C30	105.8(14)	C30A-C29-Br1	17(2)
C28-C29-Br1	108.0(8)	C30-C29-Br1	106.2(12)
C30A-C29-Br1A	106(3)	C28-C29-Br1A	108.3(8)
C30-C29-Br1A	18.1(9)	Br1-C29-Br1A	120.6(6)
C28-N1-C1	123.3(10)	C28-N1-C31	119.9(8)
C1-N1-C31	116.5(8)	C7-C1-N1	120.4(11)
C7-C1-C2	121.3(9)	N1-C1-C2	117.9(10)
C1-C2-C3	111.5(9)	C4-C3-C8	113.6(8)
C4-C3-C2	112.5(9)	C8-C3-C2	109.0(8)
C3-C4-C6	106.8(8)	C3-C4-C5	111.9(9)
C6-C4-C5	109.5(8)	C3-C4-C11	107.4(7)
C6-C4-C11	109.2(8)	C5-C4-C11	111.9(7)
C7-C6-C4	111.7(8)	C1-C7-C6	124.8(10)
C9-C8-C3	110.5(9)	C8-C9-C10	111.4(9)
C11-C10-C9	111.2(8)	C11-C10-C12	109.9(7)
C9-C10-C12	112.2(8)	C10-C11-C4	112.7(8)
C10-C11-C16	113.3(7)	C4-C11-C16	113.1(8)
C17-C12-C13	103.3(8)	C17-C12-C10	118.5(8)
C13-C12-C10	115.3(8)	C14-C13-C12	113.5(9)
C14-C13-C15	108.5(8)	C12-C13-C15	104.7(7)
C14-C13-C19	111.7(7)	C12-C13-C19	101.5(7)
C15-C13-C19	116.7(8)	C16-C15-C13	112.4(8)
C15-C16-C11	114.7(8)	C12-C17-C18	103.8(8)
C19-C18-C17	108.1(8)	C20-C19-C18	112.0(8)
C20-C19-C13	119.7(8)	C18-C19-C13	101.5(7)
C21-C20-C19	113.4(8)	C21-C20-C22	110.7(10)
C19-C20-C22	111.3(9)	C20-C22-C23	113.2(10)

C24-C23-C22	108.9(9)	C23-C24-C25	111.9(16)
C23-C24-C25A	107.8(11)	C25-C24-C25A	5.2(17)
O1-C28-N1	121.9(11)	O1-C28-C29	123.0(11)
N1-C28-C29	114.9(10)	C32-C31-N1	112.0(8)
C33-C32-C37	120.0	C33-C32-C31	117.6(7)
C37-C32-C31	122.4(7)	C34-C33-C32	120.0
C33-C34-C35	120.0	C34-C35-C36	120.0
C34-C35-N2	124.1(8)	C36-C35-N2	115.8(8)
C37-C36-C35	120.0	C36-C37-C32	120.0
O3-N2-O2	122.5(13)	O3-N2-C35	124.2(12)
O2-N2-C35	113.2(12)	C24-C25-C26	119(3)
C24-C25-C27	97(3)	C26-C25-C27	89.0(14)
C27A-C25A-C26A	93.1(15)	C27A-C25A-C24	113.3(15)
C26A-C25A-C24	101.1(15)		

Symmetry transformations used to generate equivalent atoms: