Synthesis of Pyroglutamic Acid Derivatives via Double Michael Addition Reactions of Alkynones

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To my mum and dad

*“**F**atti non foste a viver come bruti,*
ma per seguir virtute e canoscenza”

(Dante Alighieri
Inferno, XXVI 85-142)

Declaration

I declare that the work contained within this thesis is my own, unless otherwise stated and that it is submitted in accordance with university guidelines.

Acknowledgments

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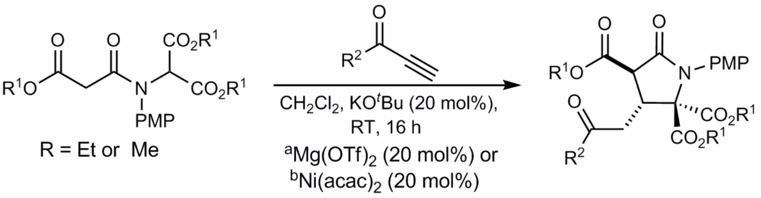
Last but not least I want to thank the person whose constant encouragement, help, love and patience accompanied me in every single step of this journey, Chris Watts.

Abstract

I. Synthesis of pyroglutamic acid derivatives *via* double Michael reactions of alkynones

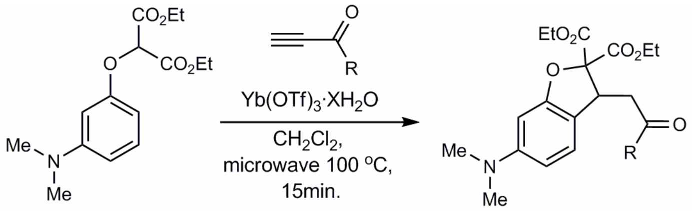
Pyroglutamic acids and their derivatives are common structural units of widespread chemical significance and they have been heavily utilised as building blocks for asymmetric synthesis.

A new method for the synthesis of highly functionalised pyroglutamic acid derivatives, which consists in a Double Michael addition route that utilises amide-tethered carbon diacids and aromatic alkynones as substrates, is here described. The reaction proceeds with good levels of *trans*-diastereoselectivity, provided that substoichiometric quantities of $Mg(OTf)_2$ or $Ni(acac)_2$ are employed.



II. Michael additions combined with Friedel-Crafts cyclisations

A domino Michael/Friedel-Crafts alkyation of aryl ethers with propargyl ketones was developed as a continuation of our double Michael additions. The reaction, here described, proceeds in good yield over two steps, when the aryl ethers and alkynones are treated with substoichiometric quantities of $Yb(OTf)_3$ and heated to 100 °C in a microwave oven.



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List of abbreviations

ac	acethyl
acac	acetylacetonate
aq.	aqueous
Ar	aromatic group
Bn	benzyl
BOMCl	bezyloxy methyl chlorideacetonate
$BF_3 \cdot OEt_2$	boron trifluoride diethyletherate
Bu	butyl
^{o}C	degree Celsius
CAN	ceric ammonium nitrite
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
Cbz	carbobenzyloxy
CSA	camphorsulfonic acid
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublet
DIBAL	diisobutylaluminium hydride solution
dm	doublet of multiplet
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNsOH	2,4-dinitrobenzenesulfonic acid
dppe	1,2-bis(diphenylphosphino)ethane

dppp	1,3-Bis(diphenylphosphino)propane
dr	diastereomeric ratio
2,6-DTDB	2,6-di-*tert*-butyl pyridine
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
ES	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
GABA	γ-aminobutyric acid transmembrane
h	hours
Hz	Hertz
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high pressure liquid chromatography
HIV	human immunodeficiency virus
HRMS	high resolution mass spectrometry
^{i}Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
min.	minutes
M	molar; metal

Me	methyl
MeCN	acetonitrile
mg	milligram
min.	minute
mL	millilitre
mmol	millimol
mol	mole(s)
m.p.	melting point
MS	molecular sieves
n/a	not applicable
Ph	Phenyl
PMP	4-methoxyphenol
PMB	4-methoxybenzyl
p-TsOH	*p*-toluenesolfonic acid
q	quartet
rt	room temperature
t	triplet
^{t}Bu	*tert*-butyl
Tf	trifluoromethansufonate
Tf_2O	triflic anhydride
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride

TMDS	tetramethyldisiloxane
TMEDA	*N,N,N,N*-tetramethylethylenediamine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	*p*-toluenesulfonic acid
TsOH	*p*-toluenesulfonic acid
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine

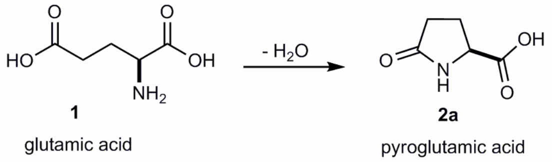
1. INTRODUCTION

1.1 Pyroglutamic acids

1.1.1 Background

Glutamic acid (**1**) is one of the 20 α-amino acids commonly found in animal and vegetal proteins as the L-form. It is very abundant in nature and can be found as the terminal group in biologically active peptides.[1] Almost half of the antibodies reported in the literature contain a glutamic acid residue at the *N*-terminus.[2] L-Glutamate also serves as a major excitatory neurotransmitter in the mammalian central nervous system. It contributes not only to fast synaptic neurotransmission but also to complex physiological processes like plasticity, learning, and memory.[3] Glutamic acid is the most widely used α-amino acid in asymmetric synthesis because of its versatility and low cost.

Pyroglutamic acid or 2-oxotetrahydropyrrole-5-carboxylic acid (**2**), a naturally occurring α-amino acid, can be regarded as a glutamic acid derivative with the carboxylate γ to the nitrogen internally protected. It can be easily obtained from glutamic acid by intramolecular dehydration,[4] or by enzymatic[5] or nonenzymatic[2] degradation in proteins (**Scheme 1**). It is, therefore, very abundant in nature.



Scheme 1

Pyroglutamic acid and its derivatives have a wide range of chemical significance since they can be employed in numerous chemical processes, including:

1.1.1.1 as building blocks for the synthesis of natural products,

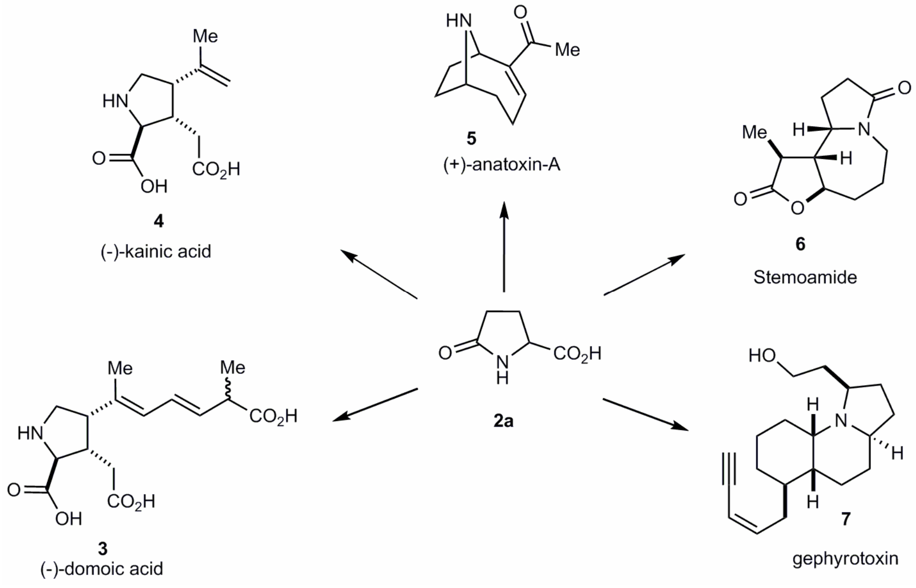
1.1.1.2 as precursors of azabicyclic compounds,

1.1.1.3 as scaffolds for the *de novo* design of peptides,

1.1.1.4 as chiral auxiliaries.

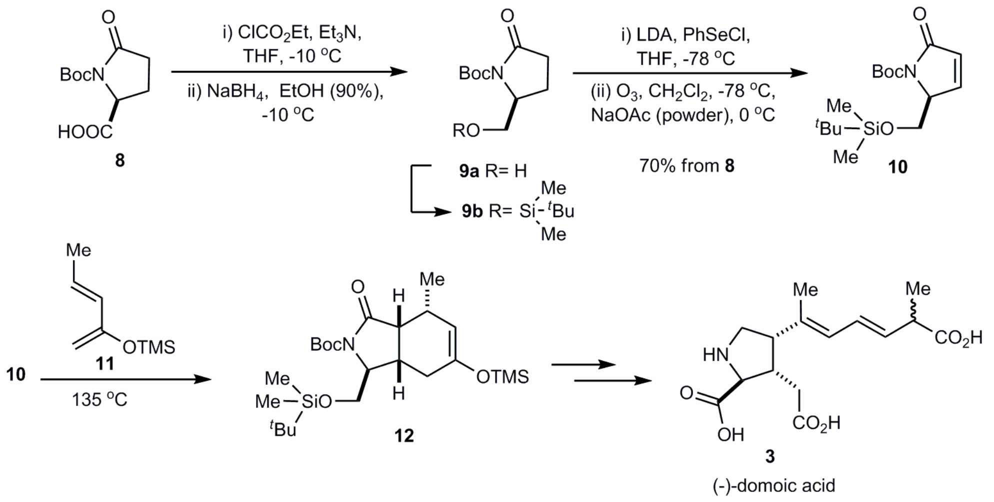
1.1.1.1 **Pyroglutamic acids as building blocks for the synthesis of natural products**

Enantiomerically pure derivatives of pyroglutamic acid can be used as scaffolds in the synthesis of numerous biologically active compounds and natural products including domoic acid (**3**),[6] kainic acid (**4**),[6] the neurotoxin anatoxin A (**5**),[7] (-)-stemoamide (**6**),[8] and the alkaloid (+)-gephyrotoxin (**7**)[9] (**Scheme 2**).



Scheme 2

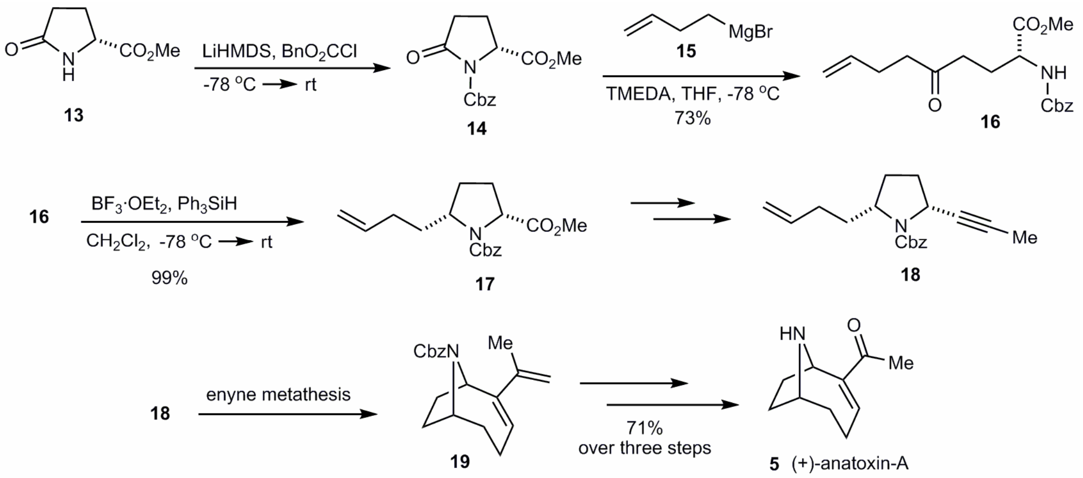
The synthetic routes for the synthesis of the aforementioned natural products are reported here, beginning with the synthesis of (-)-domoic acid (**3**), isolated from the red algae *Chondria armata* (Rhodomelaceae) by Okamura (**Scheme 3**).[6]



Scheme 3

The synthesis, performed by Ohfune and co-workers,[6] starts with *N*-tert-butoxycarbonyl-L-pyrroglutamic acid (**8**), which is converted into the alcohol **9a**. Adduct **9a**, upon treatment with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide, afforded silyl ether **9b**, which was converted into the unsaturated amide **10** by the selenenylation oxidative-deselenenylation[10] procedure. Cycloaddition of 2-(trimethylsi1yl)oxy-1,3-pentadiene (prepared from trans-3-pentene-2-one/LDA/trimethylsily chloride, -78 °C) with the pyrrolone **10** in toluene (135 °C, sealed tube, 3 days) proceeded stereoselectively to afford a single adduct **12**. After several further steps adduct **12** was transformed into the desired product **3**.

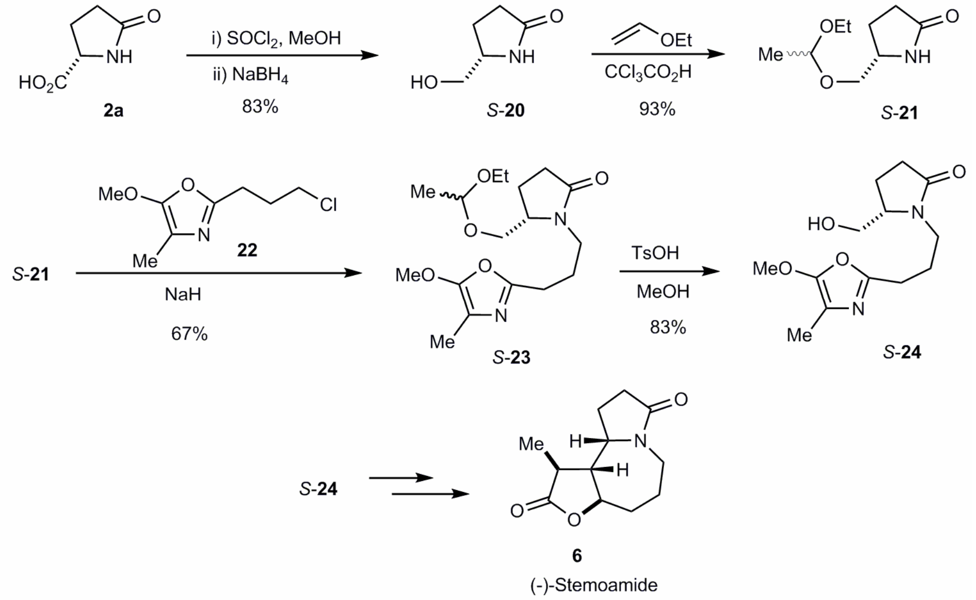
The total synthesis of anatoxin A (**5**), a potent nerve-depolarising agent, was performed by Martin and Brenneman,[11] and commenced with the *N*-protection of the commercially available D-methyl pyroglutamate (**13**) (**Scheme 4**).



Scheme 4

The resulting Cbz-lactam **14** was reacted with 3-butenylmagnesium bromide (**15**) in the presence of TMEDA to afford the ring-opened product **16**. Ketone **16** was subsequently transformed into the cis-2,5-disubstituted pyrrolidine **17** (dr) 11:1 by a highly diastereoselective cyclisation-reduction strategy. At this stage, **17** was converted into the acetylene **18.** Subsequently the intramolecular enyne metathesis converted (2*R*,5*R*)-**18**, into (1*R*,6*R*)-**19**. Conversion of (1*R*,6*R*)-**19** into (+)-anatoxin-A (**5**) was achieved through osmylation of the alkene, followed by cleavage of the resulting diol (71% yield over three steps).[7]

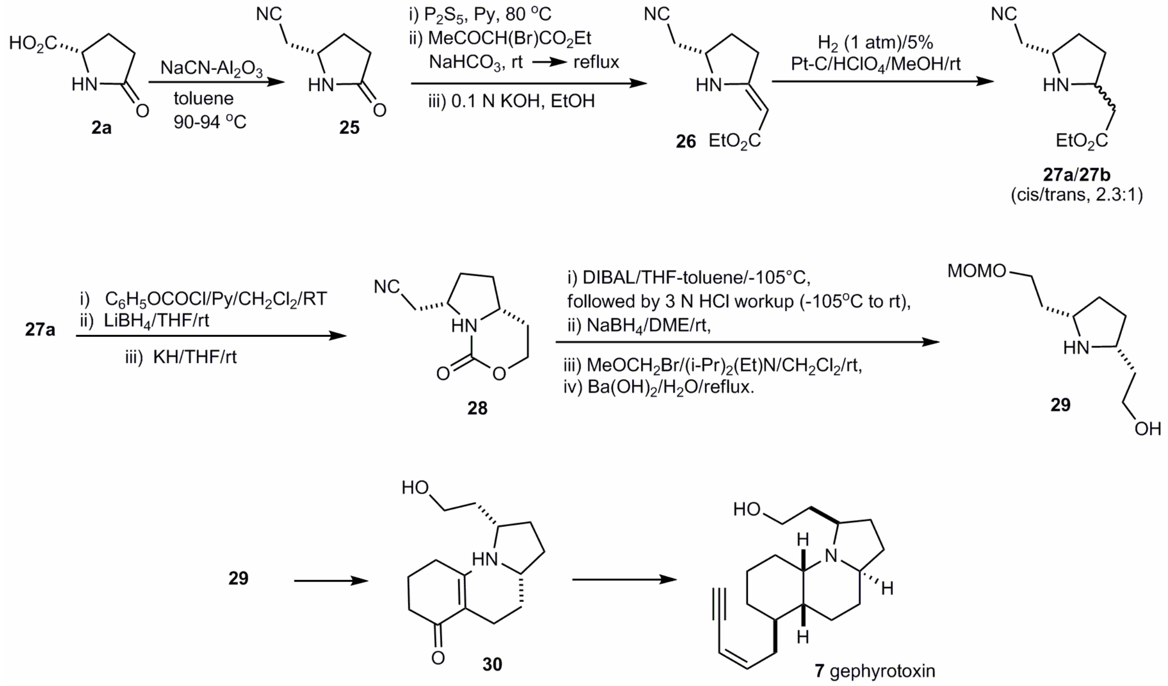
(-)-Stemoamide (**6**) is an alkaloid isolated from *Stemona tuberose*, extracts of which have been employed in Chinese traditional medicine for many years.[8] Similarly to the previous examples, its synthesis began with a pyroglutamate derivative, the known hydroxymethyl lactam **21** (**Scheme 5**).



Scheme 5

The hydroxymethyl lactam *S*-**21**, was obtained from L-pyroglutamic acid (**2a**) through a three-step route involving esterification by treatment with thionyl chloride in methanol (90%), followed by ester reduction by treatment with $NaBH_4$ (92%), and protection of the resulting primary alcohol *S*-**20** with ethyl vinyl ether and trichloroacetic acid (93%).[8] The oxazole *S*-**23** was then obtained by alkylation of *S*-**21** with 2-(3-chloropropyl) oxazole (**22**) and NaH in dimethylformamide (67%), followed by deprotection upon treatment with TsOH in MeOH that produced adduct *S*-**24** (83%). After further steps oxazole *S*-**24** was then transformed into (-)-stemoamide (**6**).

The Kishi-Fujimoto synthesis of (+)-gephyrotoxin (**7**),[9] isolated from dendrobatid frogs**,** also began with the commercially available L-pyroglutamic acid (**2a)**, which was converted into the nitrile **25** following the Silverman procedure[12] (**Scheme 6**).



Scheme 6

Treatment of the nitrile **25** with P_2S_5 gave a thiolactam which was subjected to the Eschenmoser sulfide contraction and deacylation reactions[13] to give the vinylogous urethane **26**. Hydrogenation of **26** afforded a 2.3:1 mixture of cis- and trans-pyrrolidines **27a/27b**. The cis-pyrrolidine **27a** was then converted into the urethane **28** in a three-step procedure involving treatment of **27a** with phenylchloroformate, followed by ester reduction with $LiBH_4$ and ring closure by treatment with potassium hydride. DIBAL reduction of **28**, followed by acid hydrolysis, gave an aldehyde which was reduced and protected as a methoxymethyl ether. Base hydrolysis of this product gave the pyrrolidine **29**, which had the indicated absolute configuration. The pyrrolidine **29** was converted to the vinylogous amide **30**. Finally, following a known procedure,[14] the vinylogous amide **30** was converted to gephyrotoxin (7).

The total syntheses reported above showed the importance of pyroglutamic acid and its derivatives as precursors in the construction of pharmacologically important compounds. Pyroglutamic acid could also be regarded as γ-lactam and since the γ-lactam subunit is widespread in nature, it serves as an important pharmacophore in the drug-discovery process. For example, compounds containing γ-lactams have direct applications in the treatment of epilepsy, HIV, neurodegenerative diseases, and depression.[15] The neurotrophic agent lactacystin (**31**)[16], and its derivative omuralide

(**32**),[17] the potent anticancer agent salinosporamide A (**33**),[18] the HIV protease inhibitor (**35**) and (-)-pramanicin (**34**),[19] are just a few examples of pharmacologically active natural products containing the γ-lactam moiety (**Figure 1**).

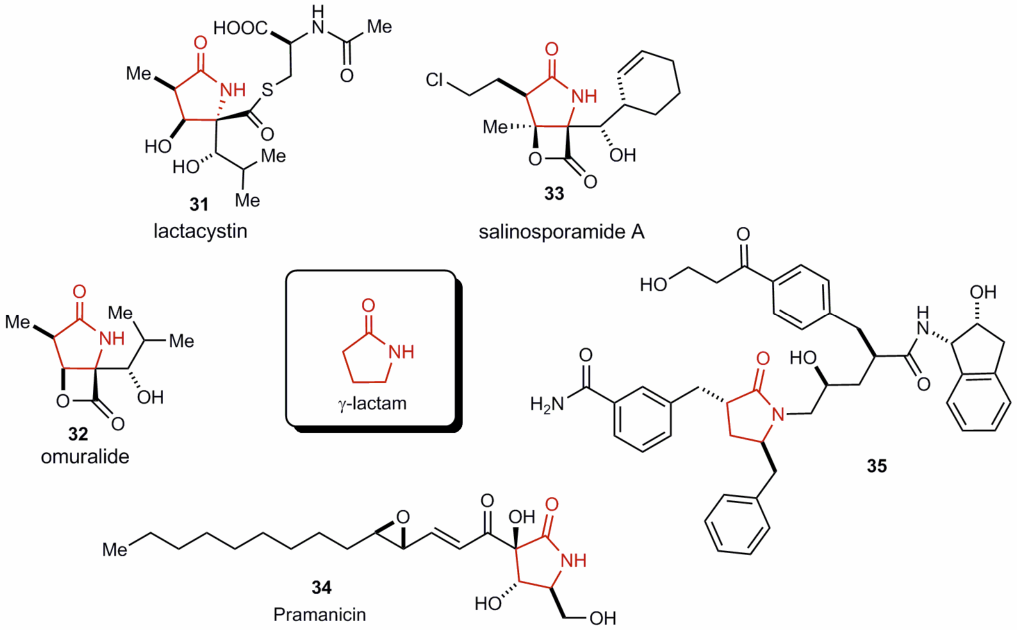
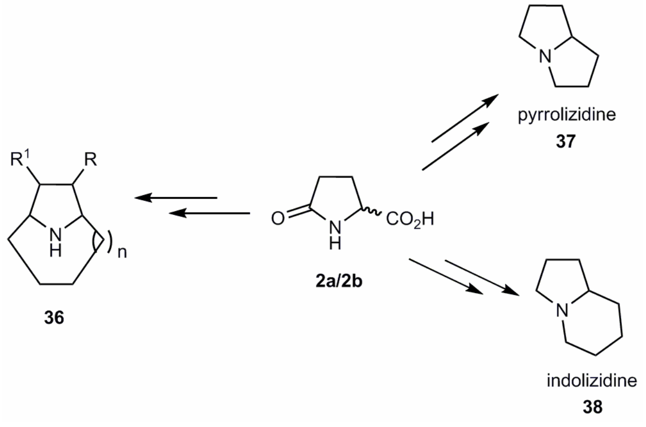


Figure 1

1.1.1.2 Pyroglutamic acids as precursors of azabicyclic compounds

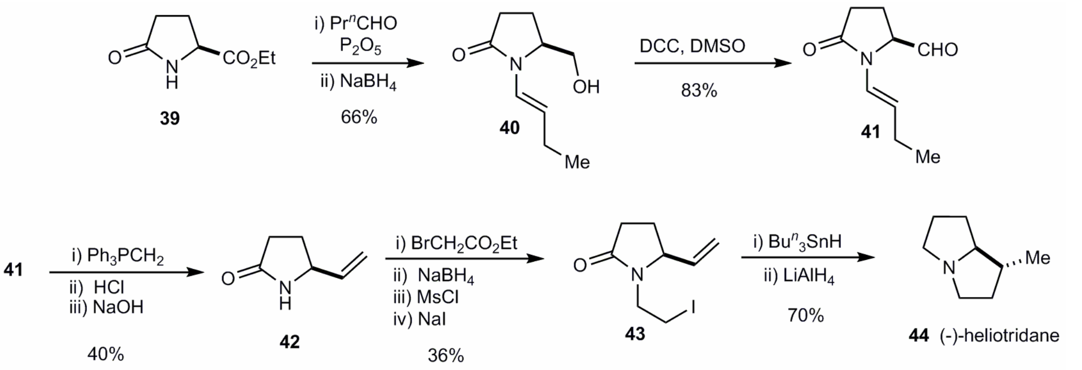
As well as being important precursors for the synthesis of natural products pyroglutamic acid derivatives can be efficiently transformed into numerous pharmacologically active azabicyclic[20,21] compounds as *N*-bridged species **36**,[20,22] pyrrolizidines **37** and indolizidines **38**[20,23] **(Scheme 7)**.



Scheme 7

In general, azabicyclic ring skeletons are important structural subunits present in numerous alkaloids and are common scaffolds in biologically active and pharmaceutically significant compounds. The *N*-bridged compound anatoxin A, of which the synthesis has been reported above (**Scheme 4**, pp. 4), is a nerve depolarising agent, and several pyrrolizidine derivatives, isolated mostly from plants,[24] are responsible for chronic liver poisoning in animals.[25] Moreover, indolizidine alkaloids have been isolated from a myriad of sources, including ants, frogs, fungi, and trees, and can exhibit phytotoxic, fungicidal, antibacterial, and neurological properties.[26]

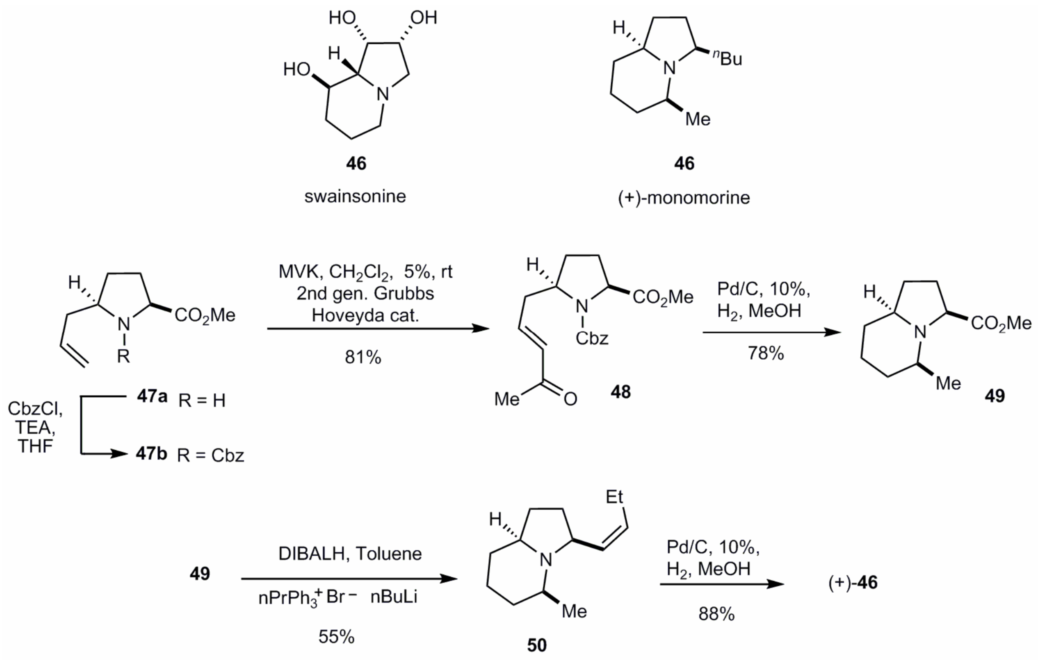
The pyrrolizidine (-)-heliotridane (**44**)[27], provided a framework for testing new synthetic methodologies applicable to alkaloid total synthesis (**Scheme 8**).



Scheme 8

The synthesis began with the pyroglutamate derivative **39** which, after condensation with n-butanal and ester reduction with NaBH$_4$, gave the enamide **40** in 66% yield. Enamide **40** underwent Moffat oxidation affording aldehyde **41** (83% yield), which subsequently underwent Wittig olefination and hydrolysis of the butenyl group affording lactam **42**. Adduct **42** was alkylated with ethylbromoacetate, reduced, and transformed into the iodide **43** (36%). Finally the iodide **43** was cyclised stereoselectively and reduced to the desired (-)-heliotridane **44**.

Two examples of indolizidines derived from pyroglutamic acids are swainsonine (**45**), known for its ability to inhibit glycosidases, and (+)-monomorine (**46**), a trial pheromone of the pharaoh ant *Monomorium pharaonis L.* The synthesis of the latter is shown below (**Scheme 9**).[28]

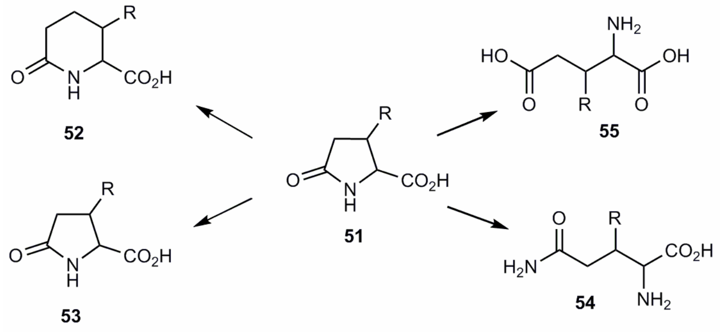


Scheme 9

After protection of **47a**, which is derived from commercially available L-pyroglutamic acid as the Cbz derivative **47b**, cross metathesis reactions were carried out with a stoichiometric quantity of methyl vinyl ketone in a 0.05 M dichloromethane solution, using the Grubbs-Hoveyda catalyst. The reaction proceeded in CH_2Cl_2 at room temperature affording **48** in 81% yield. Adduct **48** was then subjected to removal of the Cbz group by treatment with catalytic Pd/C (10%) under hydrogen atmosphere, resulting in concomitant intramolecular reductive amination and cyclisation to compound **49**. Reduction of **49** with DIBALH afforded the intermediate corresponding aldehyde, which was immediately added to the propyl Wittig ylide to give the *Z*-alkene **50** in satisfactory yield. Finally, Pd catalysed reduction of **50** afforded (+)-**46**.

1.1.1.3 **Pyroglutamic acids as scaffolds for the *de novo* design of peptides**

The examples reported above showed in general the importance of pyroglutamic acid derivatives in the synthesis of azabicyclic compounds. Among the pyroglutamic acids, the β-substituted derivatives **52** are also very important as they can give access to a family of sterically constrained β-substituted amino acids **53-56**. These serve as indispensable χ-(chi)-constrained scaffolds for the *de novo* design of peptides and peptidomimetics with a predetermined tridimensional structure (**Scheme 10**).[20]



Scheme 10

In a peptide, the χ-(chi)-angles, in conjunction with the backbone angles, define the position of side-chain functional groups in space (chi space) (**Figure 2**). The conformation of a peptide (including the chi space) is crucial for biological activity and is regarded as the critical issue in the design of more selective and/or more potent peptides as enzyme inhibitors, and agonists or antagonists at receptors. Thus the χ-(chi)-angles are of key importance in understanding the mode of action of peptides.[29]

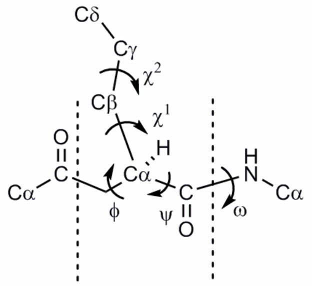
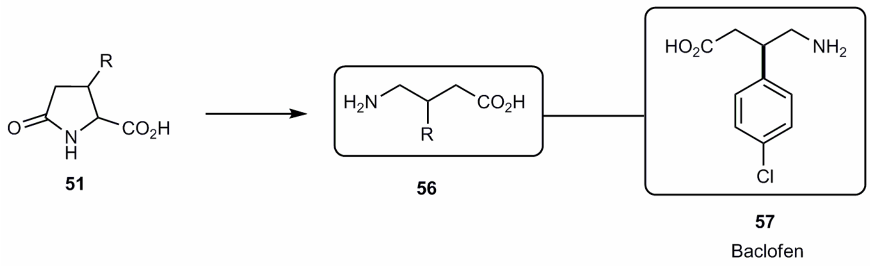


Figure 2 Definition of the dihedral angles φ, ψ, ω and χ of a peptide.

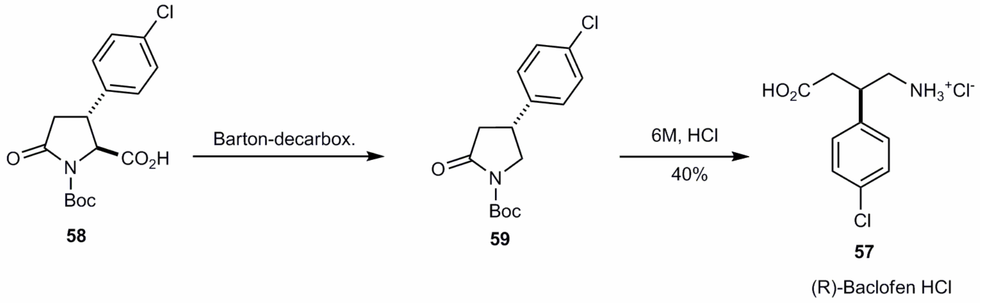
The β-substituted derivatives of pyroglutamic acid can be regarded as conformationally restricted α-amino acids with well-defined complementary χ-characteristics. Therefore they are of considerable importance among the many tools that are required to aid investigations of χ-space.[29]

β-Substituted derivatives of pyroglutamic acids can also be used as precursors in the synthesis of pharmacologically important compounds. Transformation of **51** (**Scheme 11**) into the β-substituted γ-amino acid derivatives **56** led to the synthesis of the very well known commercial drug Baclofen (**57**)[30,31].



Scheme 11

Baclofen **57** is a GABA_B (γ-aminobutyric acid transmembrane) receptor agonist that is used to treat spasms caused by spinal cord injuries and also shows some potential as a treatment for cocaine addiction. The synthesis, performed by Herdeis and Hubmann, is reported below (**Scheme 12**).

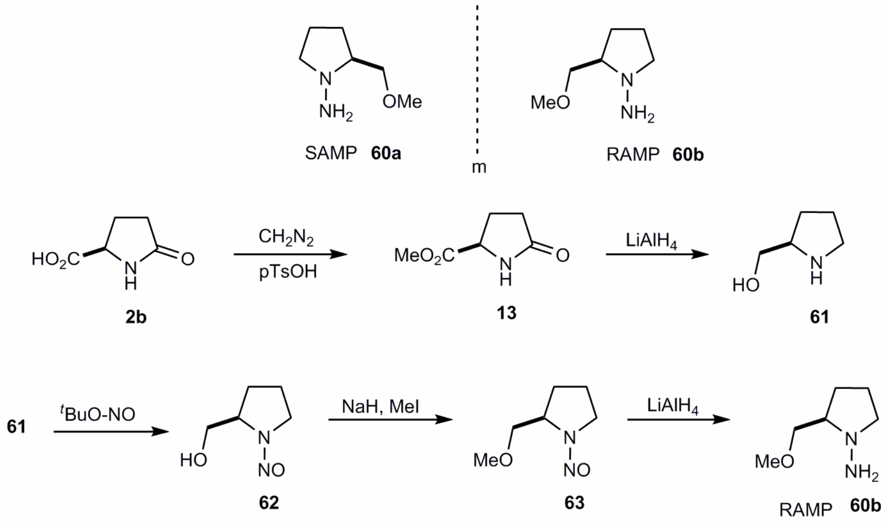


Scheme 12

Once the pyroglutamic acid derivative **58** was obtained the synthesis proceeded in a reasonably straightforward way.[31] Barton-decarboxylation[32] of **59** followed by ring opening with acid treatment (HCl, 6M) gave the desired product R-Baclofen·HCl **57**.

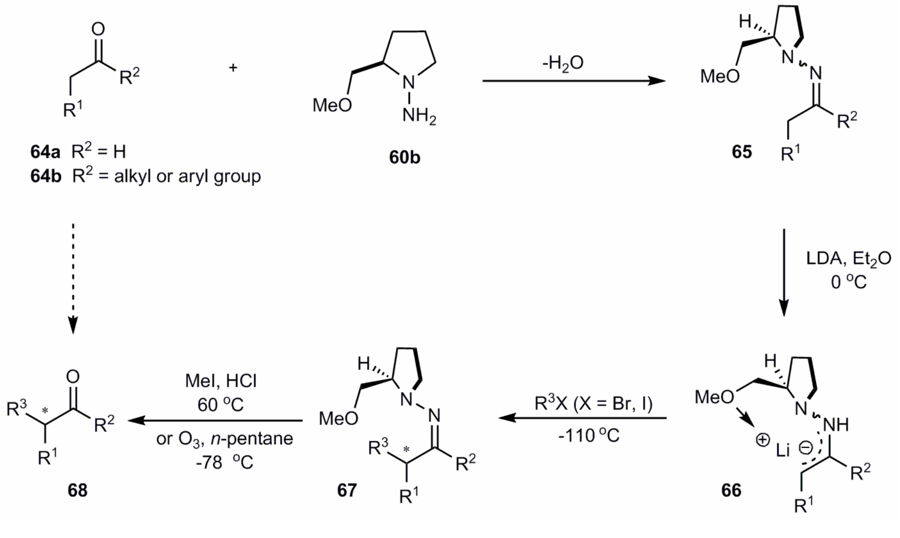
1.1.1.4 **Pyroglutamic acids as chiral auxiliaries**

As well as versatile building blocks for the asymmetric synthesis of natural products and numerous pharmacologically interesting compounds, pyroglutamic acid derivatives have also been widely employed as chiral auxiliaries.[1] The well known chiral auxiliary (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) **60b**, to give an example, is easily prepared in five steps from (*R*)-pyroglutamic acid **2b** [33,34] and it has been employed, together with its enantiomer (*S*)-1-amino-2-methoxymethylpyrrolidine SAMP **60a**, in a wide range of reactions involving C-C or C-heteroatom bond formation (**Scheme 13**).[35,36]



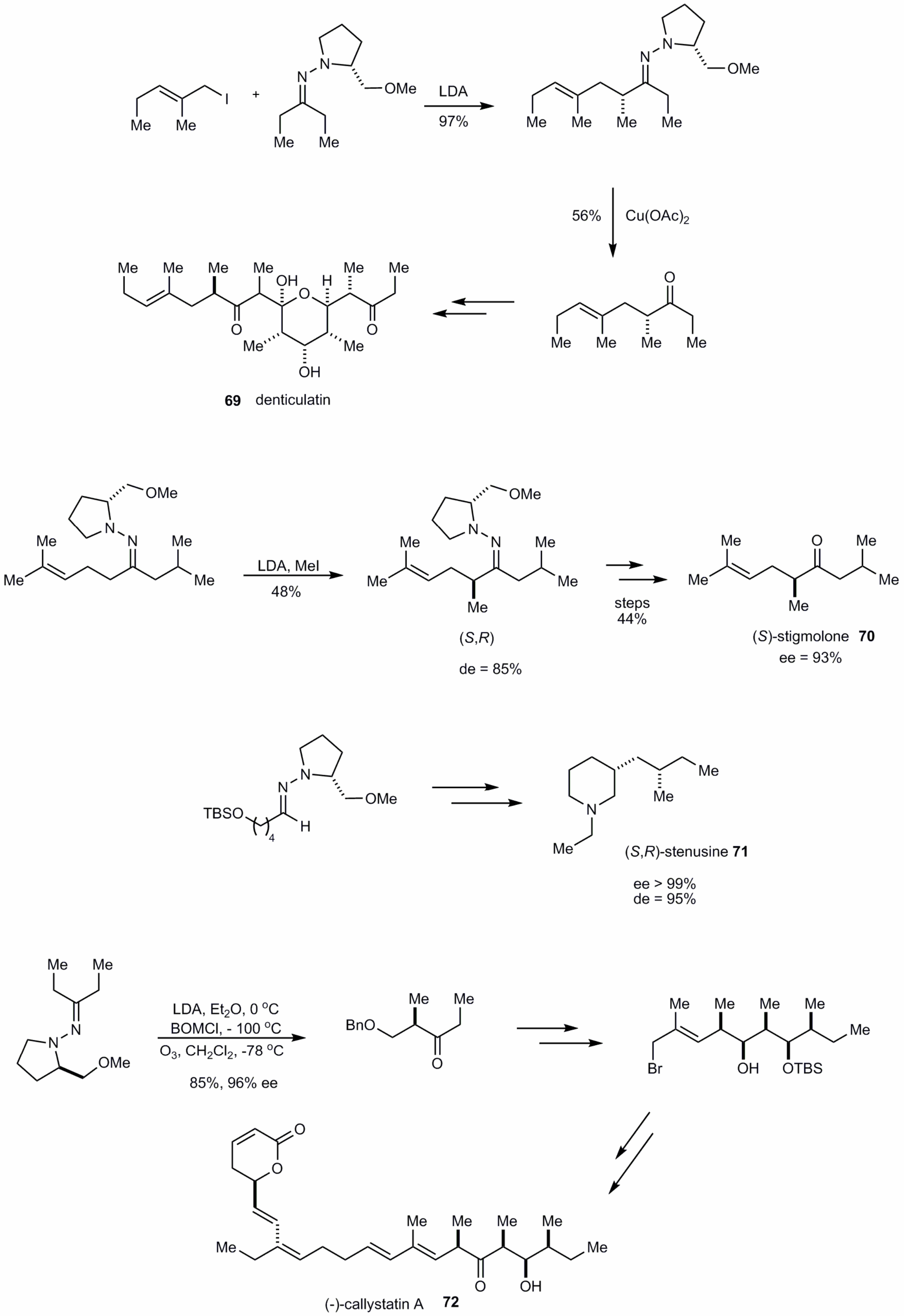
Scheme 13

The so-called “hydrazone method”, involving the RAMP/SAMP chiral auxiliaries, has mostly been used to carry out an asymmetric version of the classical alkylation α to the CO group of aldehydes and ketones.[34] According to the general mechanism, which is summarised in four steps below, the chiral hydrazone **65** was easily obtained by mixing RAMP **60b** or its analogue **60a** and the carbonyl compound under water separation conditions (**Scheme 14**).[35] With the aldehydes **64a**, the reaction runs at 0 °C without any solvent, while the ketones **64b** have to be heated to reflux with catalytic amount of acid in benzene or cyclohexane using a Dean and Stark separator. Metallation with lithium diisopropylamide in ether at 0 °C formed the chiral azaenolates **66** followed by alkylation with various iodides and bromides at -110 °C, furnished the product hydrazones **67**.



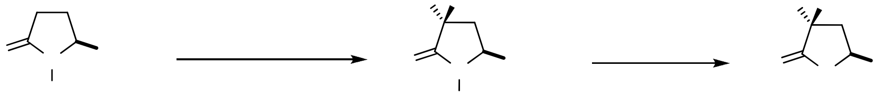
Scheme 14

Finally hydrazone cleavage, either by acidic hydrolysis of the methyl iodide in a two phase system of 3N HCl/n-pentane, or by ozonolysis in n-pentane at -78 ^{o}C, leads to the α-susbstituted acyclic carbonyl compound **68**. The "chiral information" contained in the hydrazine enables the enantioselective control of the C-C bond-forming reaction. The broad application and versatility of the RAMP/SAMP hydrazone methodology makes it a very useful tool for the synthesis of natural products. RAMP-Derivatives have been employed in the past for the synthesis of the polypropionate metabolites denticulatin (**69**)[33,37], isolated from *Simphonaria denticulate*; the fruiting body-inducing pheromone of the myxobacterium *S. aurantica* (*S*)-stigmolone (**70**);[33,38] stenusine (**71**),[33,39] a propulsion fluid produced by the beetle *Stenus comma* and the polyketide marine natural product callystatin (**72**)[33,39] isolated from the sponge *Callyspongia truncate*, to name just a few (**Scheme 15**).


LDA
97%
56%
Cu(OAc)2
69 denticulatin
LDA, MeI
48%
(S,R)
de = 85%
steps
44%
(S)-stigmolone 70
ee = 93%
(S,R)-stenusine 71
ee > 99%
de = 95%
LDA, Et2O, 0 °C
BOMCl, - 100 °C
O3, CH2Cl2, -78 °C
85%, 96% ee
(-)-callystatin A 72

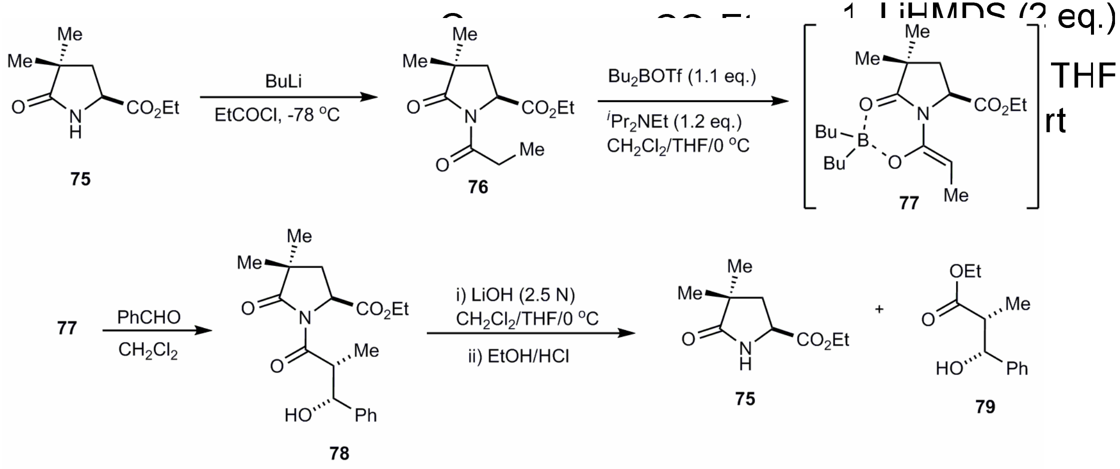
Scheme 15

Other examples of pyroglutamic acid derivatives used as chiral auxiliaries include ethyl (*S*)-4,4-dimethylpyroglutamate (**75**) reported by Ezquerra and co-workers, which has been used in aldol reactions[40] and Michael addition reactions[41] (**Scheme 16**). Ethyl (*S*)-4,4-dimethylpyroglutamate (**75**) was prepared from *N*-Boc protected pyroglutamate **73** by dimethylation of the corresponding lithium lactame enolate with CH_3I. After the urethane protecting group removal with TFA, **75** was obtained with a 70% overall yield from **74**.[42]



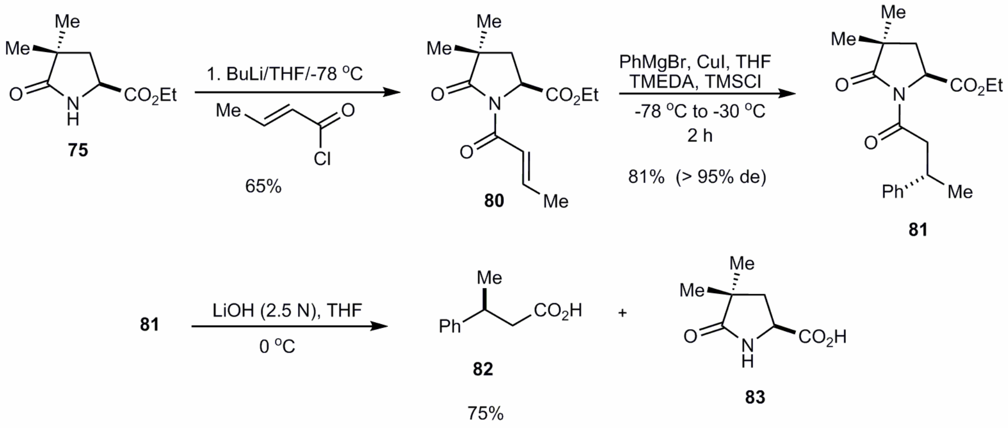
Scheme 16

The chiral auxiliary thus obtained was employed in the aldol reaction reported below (**Scheme 17**). It was treated with butyllithium and propionyl chloride affording the N-propionyl derivative **76** in 80% yield. The (*Z*)-boron enolate of **77** was then allowed to react with benzaldehyde giving the *syn* product **78** in 70% isolated yield and > 98% de[40] After hydrolysis of **78**, the ester **79** was obtained in good yield (94%) and the chiral auxiliary **75** was effectively recovered (70%). Remarkably, the potentially labile pyroglutamate C-2 stereogenic centre, which is responsible for the asymmetric induction, was preserved during the aldol reaction.



Scheme 17

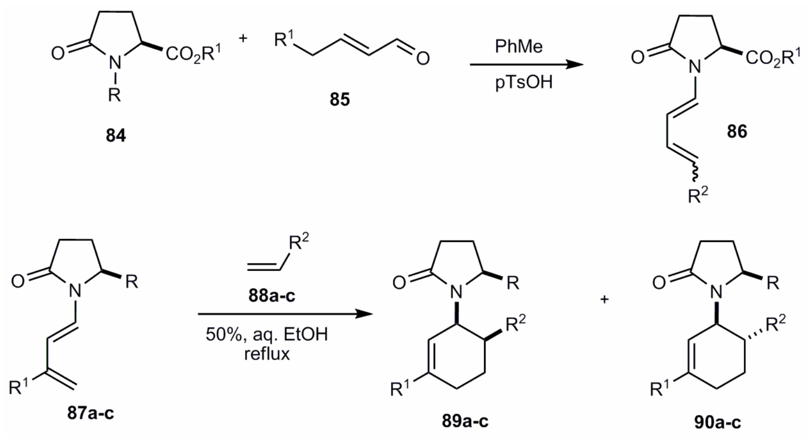
The chiral auxiliary **75** was employed again by Ezquerra and co-workers to perform conjugate addition reaction of Grignard-derived organocopper reagents to α,β-unsaturated *N*-acyl fragments, as an effective means of preparing enantiopure β-substituted carboxylic acids.[41] Ezquerra *et al.* reported in their work that deprotonation of **75** with n-BuLi followed by treatment with crotonyl chloride furnished the Michael acceptor ethyl (S)-*N*-trans-2-butenoyl-4,4-dimethylpyroglutamate (**80**) in 65% yield (**Scheme 18**). It was found that the best general reaction conditions for conjugate additions required the addition of TMSC1 to generate the PhCu-TMEDA-TMSCl as an organocopper-Lewis acid reagent. This methodology afforded product **81** in good yield (81%) and excellent stereoselectivity (> 95% de).



Scheme 18

Adduct **81** was then hydrolysed with LiOH in THF yielding a chromatographically separable mixture of (*S*)-4,4-dimethylpyroglutamic acid **83** (71% yield) and the corresponding β-branched carboxylic acid, (*S*)-3-phenylbutanoic acid (**82**) (75% yield).

Ethyl *N*-dienylpyroglutamates **94** have been used as chiral dienes in Diels-Alder reactions (**Scheme 19**).[43] The dienes **96** are easily prepared in one step from ethyl pyroglutamate **94** and the α,β-unsaturated aldehydes **95** in toluene with *p*-TsOH.[44] Reported here is an example of a Diels–Alder reaction, presented by Smith and co-workers, where **87a-c** reacts with acrylates (**88a-c**) (50% aq. EtOH reflux) giving the cycloadducts **31a-c** and **32a-c** in very good yield (77%-91%).[43]

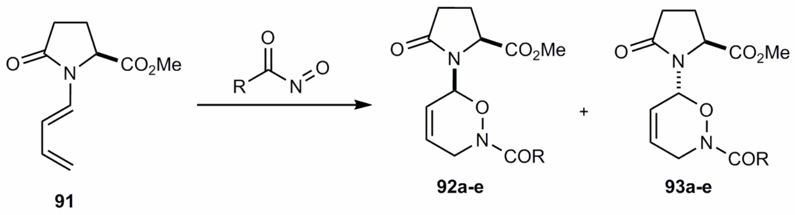


entry	R	R^1	R^2	Y (%)	dr (%)
1	CO_2Et	H	CO_2Et	91	93:7
2	CO_2Et	Me	CO_2Et	77	92:8
3	CO_2Et	H	COMe	79	82:18

Scheme 19

The diastereoselectivity was also excellent and the cis-adducts **89a-c** were isolated in 91-97% de

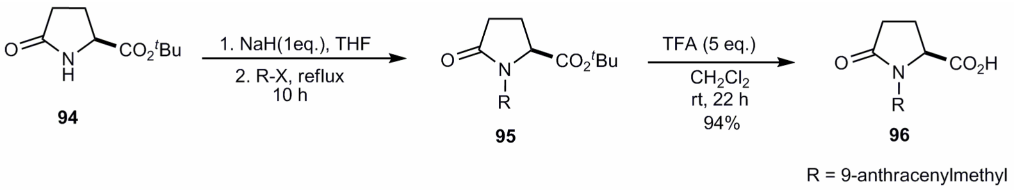
The hetero Diels-Alder reaction of dienes **91** with nitrosodienophiles generated *in situ*, reported by J. B. Behr *et al*,[44] took place in a regioselective manner leading to cycloadducts **92a-e** and **93a-e** in a range of 62% - 80% yield (**Scheme 20**). The best asymmetric induction was found when R = NMe_2 (de = 84 %), whereas induction was small when R = NH_2 (de = 28 %), as shown below.



entry	R	Yield (%)	de (%)
1	NMe_2	70	84
2	OMe	63	52
3	Ph	70	44
4	Me	62	34
5	NH_2	80	28

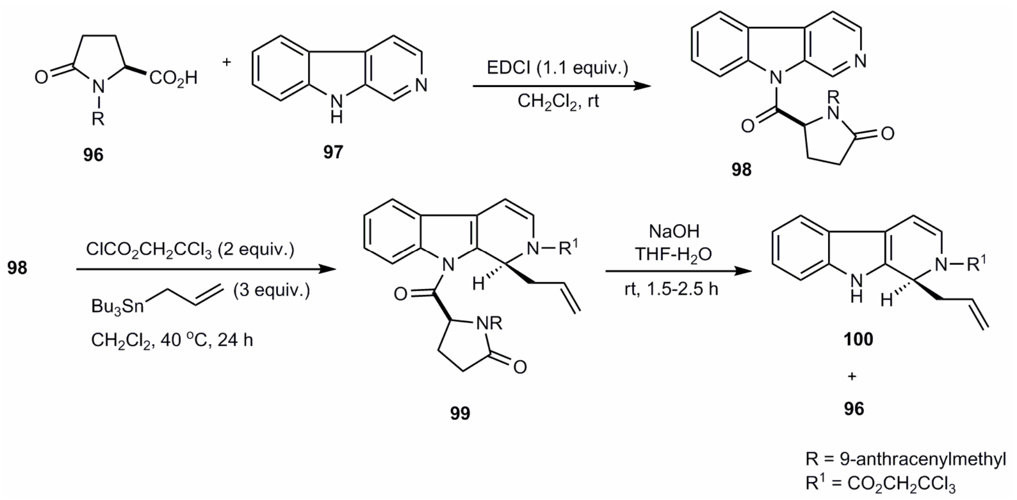
Scheme 20

Ohsawa and co-workers,[45] in their asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carbolines **110**, carried out a screening of chiral auxiliaries made from pyroglutamic acid derivatives. (*S*)-Pyroglutamic acid **2a** was chosen as the starting material for the design of new chiral auxiliaries owing to its similarity with other standard amino acids employed in the past as chiral auxiliaries, including alanine, valine, or phenylalanine (**Scheme 21**). However, in contrast to these, (*S*)-pyroglutamic acid **2a** possesses a more rigid structure. Thus, *tert*-butyl (*S*)-pyroglutamic **94** was treated with 9-anthracenylmethyl halide in the presence of sodium hydride, to give derivative **95**, which was then transformed into the corresponding carboxylic acid **96**.



Scheme 21

The chiral auxiliary **96** thus prepared readily reacted with β-carboline **97**, a common nucleus of various indole alkaloids, through the use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), to give 9-acyl-β-carbolines **98** (**Scheme 22**). Adduct **98** then underwent asymmetric addition with allyltributyltin and reacted with 2,2,2-trichloroethyl chloroformate to give a 1,2-dihydro adduct **99** in 98% yield, which was subsequently hydrolysed to **100** in a quantitative yield and 91% ee. Finally the chiral auxiliary **96** was completely recovered under mild hydrolytic conditions.



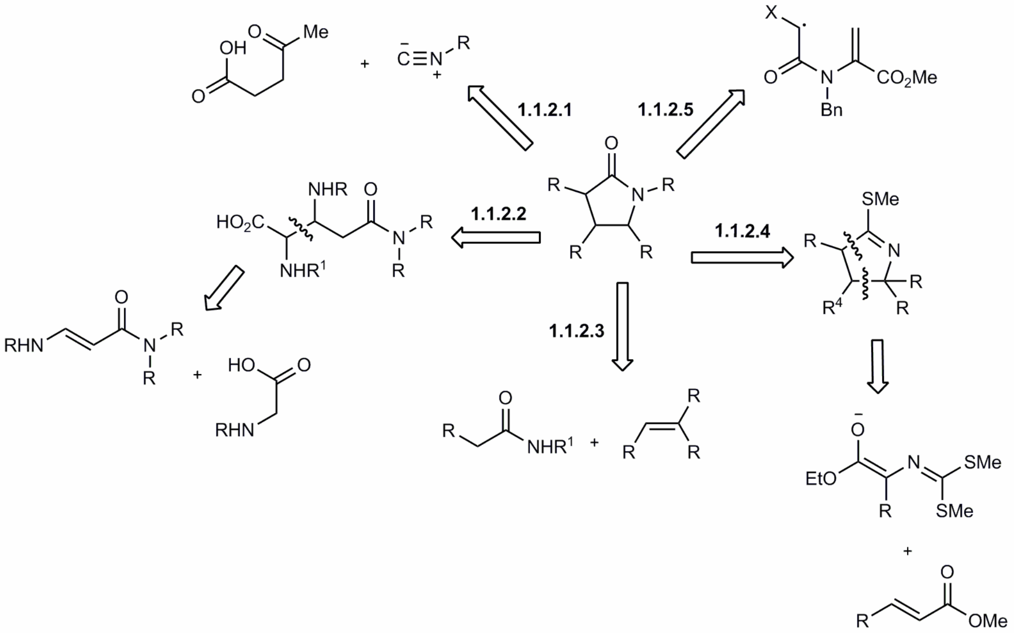
Scheme 22

Owing to the reasons outlined above, the development of asymmetric methods for the preparation of enantiomerically pure pyroglutamic acid derivatives would give access to a whole family of these extraordinarily valuable compounds.

1.1.2 Previous Methodologies for the Synthesis of Pyroglutamic Acid Derivatives

As previously mentioned, L-pyroglutamic acid is very abundant in nature and can be easily derived from L-glutamic acid by dehydration; both L and D-pyroglutamic acid are commercially available. Nevertheless, highly substituted and enantiomerically pure derivatives of pyroglutamic acid, which are key components for a wide range of synthetic applications, are not easily accessible. There is no straightforward general synthesis available for this simple framework and many research groups have been focusing on the development of new synthetic routes toward pyroglutamic acid derivatives. Some selected methods that have been employed in the past are summarised below (**Scheme 23**):

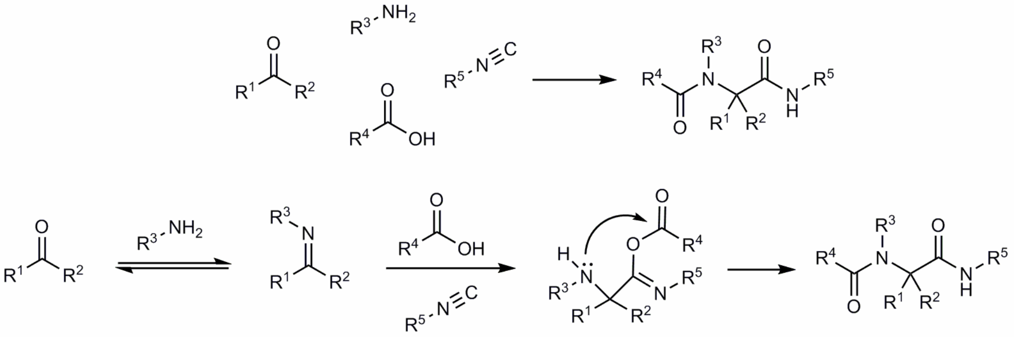
1.1.2.1 Ugi condensation
1.1.2.2 Michael addition
1.1.2.3 [3+2] Annulations
1.1.2.4 1,3-Dipolar cycloaddition
1.1.2.5 Radical cyclisation



Scheme 23

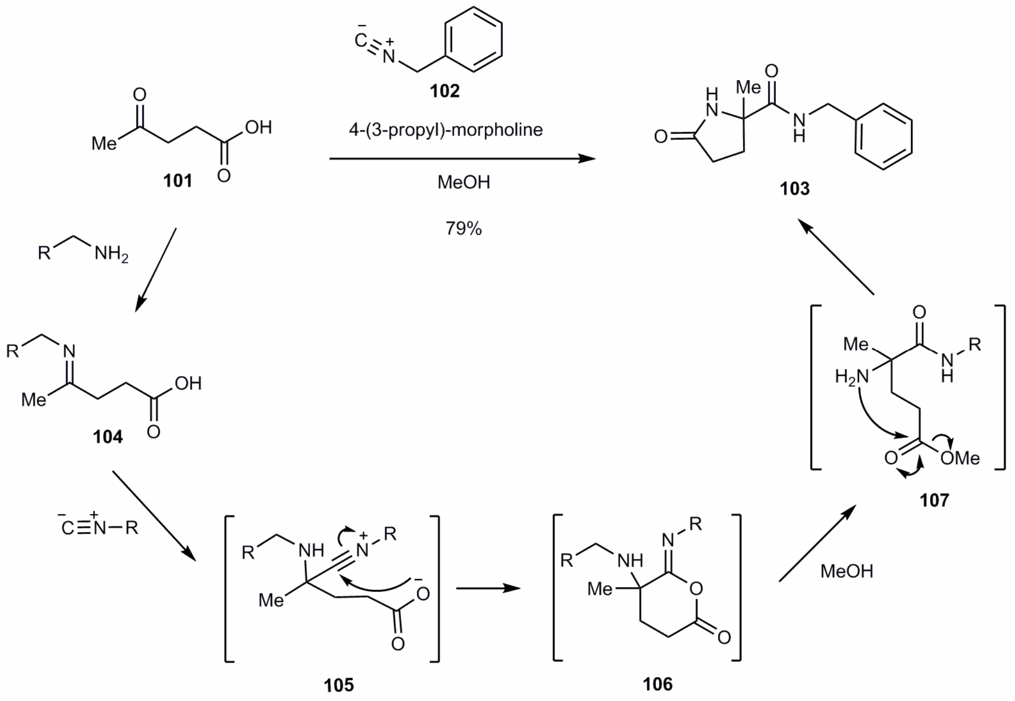
1.1.2.1 Ugi condensation

The Ugi reaction is a four component condensation which involves the reaction of an aldehyde or a ketone, an imine, an isocyanide and a carboxylic acid forming a bis-amide in one single step (**Scheme 24**). Therefore it is a very useful method for the syntheis of complex molecules.



Scheme 24

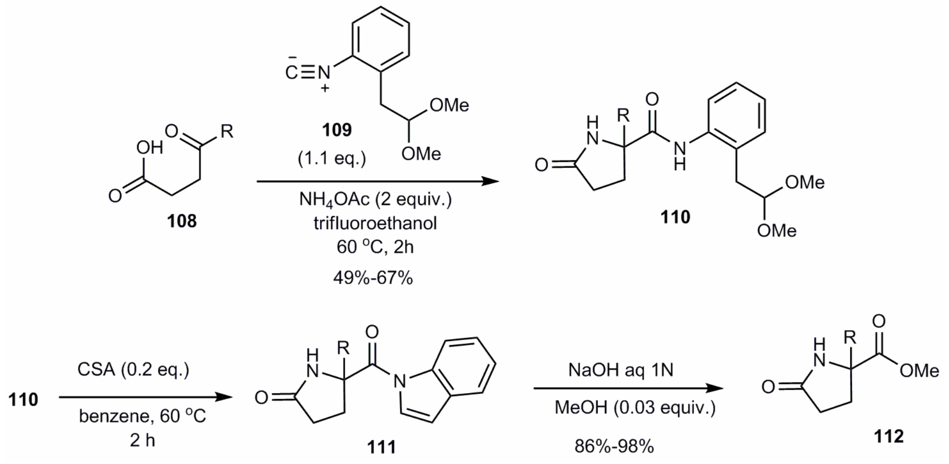
When two of the components, for example a ketone and a carboxylic acid, are incorporated into a single molecule, cyclic products are formed. The Ugi 4-centre-3-component reaction of γ-ketoacids, for example, provides ready access to the carbon framework of many pyroglutamic acid analogues. Harriman *et al.* reported an intramolecular Ugi reaction leading to the γ-lactam **103** in good yield (79%) (**Scheme 25**).[46]



Scheme 25

In the proposed mechanism the reaction proceeds first through the formation of imine **104**. Additon of the isocyanide **102** then provides the nitrilium intermediate **105**. Intramolecular attack of the carboxylate on the nitrilium carbon provides the cyclic intermediate **106** which, upon treatment with methanol, resultes in ring-opening and formation of intermediate **107**. Subsequently, intramolecular nucleophilic attack of the amine to the carbonyl group affordes the desired γ-lactam **102**.[46]

Kobayashi and co-workers also employed the Ugi condensation to prepare a range of unprotected 2-substituted pyroglutamic acids, starting from levulinic acid (**108**) (**Scheme 26**).[47] Ammonium acetate and levulinic acid (**108**) were premixed in trifluoroethanol at 60 °C to promote imine formation. Addition of the isonitrile **109** to the mixture then afforded product **110** from average to good yield (49%-67%). The Ugi product (**110)**, when treated with camphorsulphonic acid (0.2 equiv.), afforded the *N*-acyl-indole (**111)**, which was subsequently cleaved to form the free pyroglutamic acid (**112**).[47]

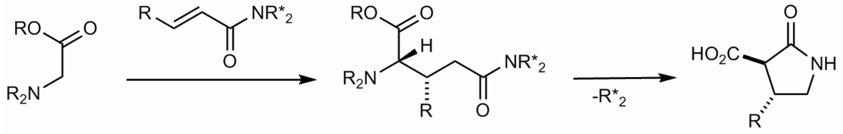


Scheme 26

In addition to being a key step in the formal synthesis of omuralide (Introduction, pp.6), this methodology was also applied by Kobayashi and co-workers for the total synthesis of (-)-dysibetaine,[48] a natural product isolated from the Micronesian sponge *Dysidea herbacea*.[49]

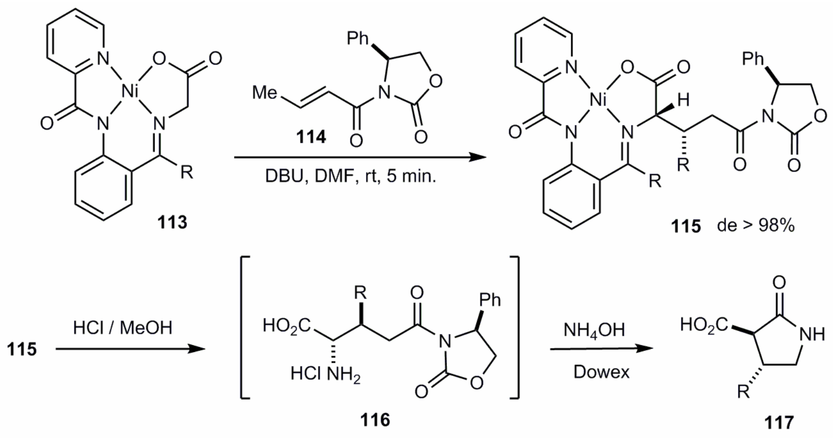
1.1.2.2 Michael addition

Michael addition between a nucleophilic glycine equivalent and a substituted acrylic acid derivatives represents a very straightforward and general route to β-substituted prolines, glutamic and pyroglutamic acids (**Scheme 27**).



Scheme 27

Soloshonok *et al.* developed a stereoselective Michael addition employing chiral derivatives of α,β-unsaturated carboxylic acids with achiral glycine equivalents.[21] Their idea was to provide geometric homogeneity of the glycine enolate (*E*- or *Z*-enolate only) and conformational homogeneity of the Michael acceptor (s-cis or s-trans only), in order to impart high diastereoselectivity to the reaction. Therefore, Soloshonok and co-workers designed and produced *o*-aminoacetophenone-derived Ni(II) complexes of glycine **113**, which were then employed in a Michael addition with the α,β-unsaturated ester **114**, generating the product **115** in quantitative yield and high diastereoselectivity (98%) (**Scheme 28**).

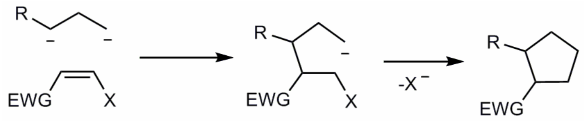


Scheme 28

Adduct **115** was subsequently decomposed with HCl to give the glutamic acid intermediate **116**, which was generally converted into the target pyroglutamic acid **117** by treatment with ammonia.

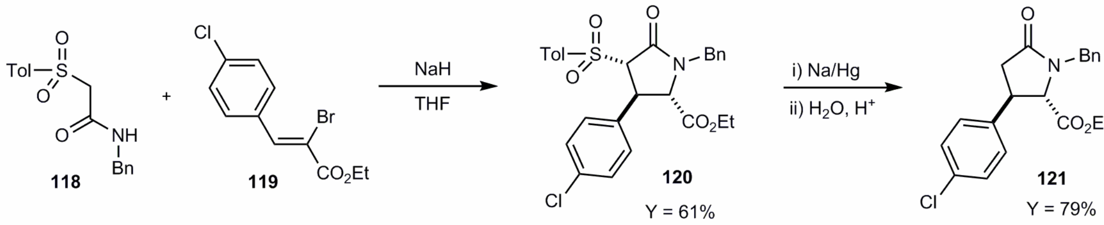
1.1.2.3 [3+2] Annulations

Another easy access to the pyroglutamic skeleton is through the [3+2] annulation reaction between a dianion and an activated alkene (**Scheme 29**).



Scheme 29

An example is the reaction between the α-sulfonylacetamide **118** and the α,β-unsaturated ester **119** employed by Chang and co-workers[13,20] for the synthesis of the commercial drug Baclofen mentioned above (**Scheme 12**, pp. 11). The one-pot synthesis begins with the 1,4 addition of dianion **118** to α-bromoester **119** and proceedes through ring closure after bromide substitution resulting in the formation of adduct **120** as a single isomer in 61% yield. Treatment of **120** with sodium amalgam and sodium phosphate, followed by addition of water to the resulting mixture and acidification, afforded product **121** (**Scheme 30**).

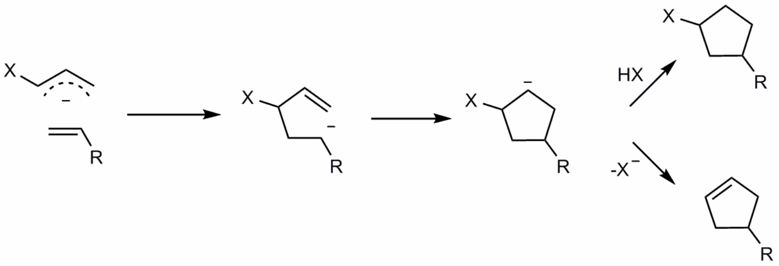


Scheme 30

Despite the excellent stereo- and regioselective outcome the reaction requires at least three steps, plus formation of the α-sulfonylacetamide.

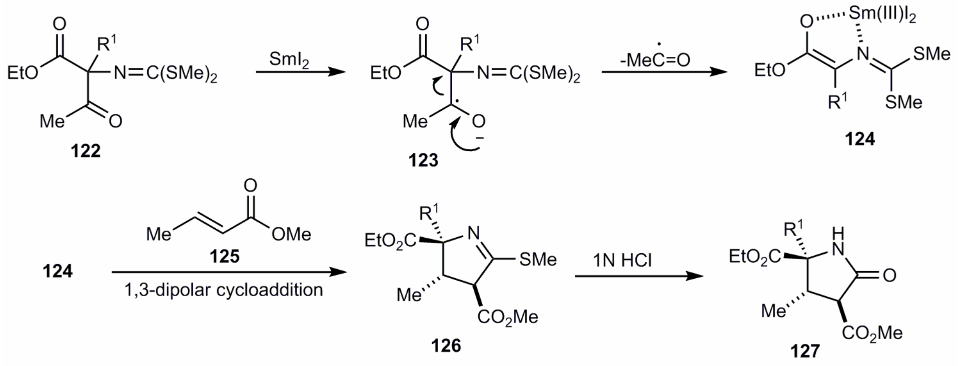
1.1.2.4 1,3-dipolar reactions.

Similar to [3+2]-annulations are the 1,3-dipolar reactions, which represent another easy route toward heterocyclic five-membered rings and pyroglutamic acids. The latter involves a reaction between a 1,3-dipol (a species with a nucleophilic and an electrophilic end) and a dipolarophile species such as an activated alkene (electron-deficient or electron rich) (**Scheme 31**).



Scheme 31

In order to prepare pyroglutamate derivatives Alverez-Ibarra *et al.* selected a Sm(III)-azomethine ylide **124** as the dipole (**Scheme 32**).[50] In the past metalloazomethine ylides have been used for the synthesis of highly substituted prolines.[51] In his reaction Alverez-Ibarra replaced the azomethine counterpart with an imidothiocarbonate. The Sm(III)-azomethine ylide **124** was prepared in three steps from **122**. The radical fragmentation of compound **122** was triggered by addition of SmI_2, producing the Sm(III)-azomethine ylid **124** through intermediate **123**. **124** Was then employed in the cycloaddition with α,β-unsaturated ester **125** affording adduct **126**, which upon acid treatment afforded the γ-carboxypyroglutamate **127** in good yield (70-85%) and high diastereoselectivity (80-85%).[50]

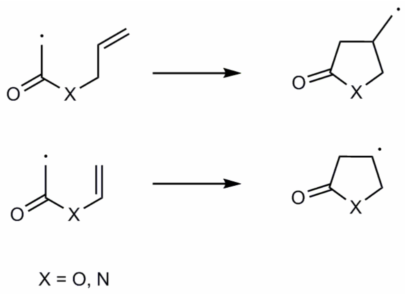


Scheme 32

Although elegant this process requires several steps, including the synthesis of the Sm(III) ylide **124** and acid hydrolysis to give the final product **127** and gives access only to the racemic adduct.

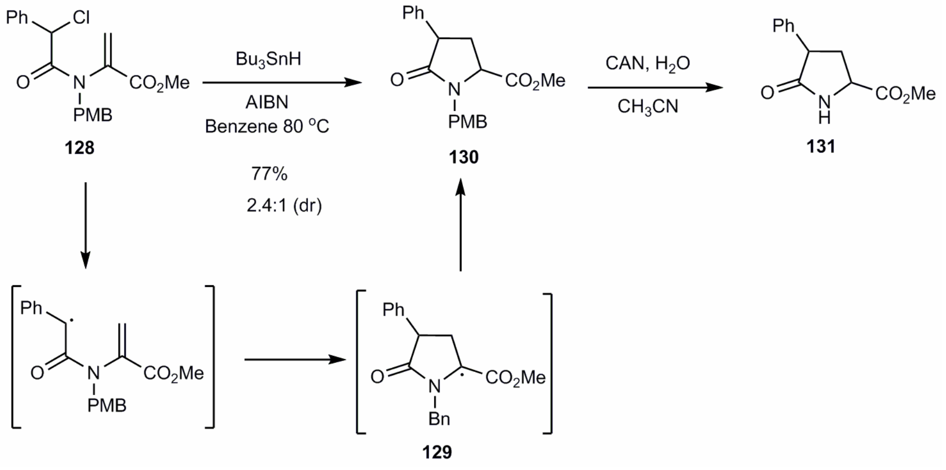
1.1.2.5 Radical cyclisations

Pyroglutamates can also be prepared via a radical mechanism. Radical cyclisations of carbamoylmethyl radicals onto N-allyl[52] or N-vinyl[53] groups producing pyrrolidinones have long been known (**Scheme 33**).



Scheme 33

Parsons and co-workers, inspired by previous work, developed a radical cyclisation to generate pyroglutamate derivatives using dehydroalanine **128** with Bu$_3$SnH (**Scheme 34**).[54] In the proposed mechanism the dehydroalanine **128** undergoes radical cyclisation through the formation of the intermediate **129**, which is relatively stable and easy to form.



Scheme 34

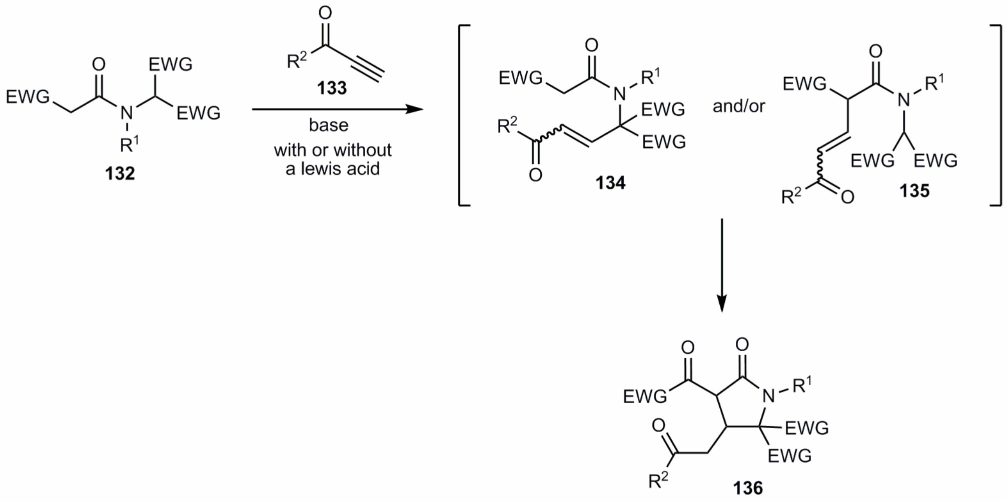
The reaction then proceedes in a 5-*endo*-trig mode that produce the 4-substituted pyroglutamate **130** in 77% yield, which upon treatment with ceric ammonium nitrite (CAN) in acetonitrile affordes the unprotected product **131**. Unfortunately, there is not an asymmetric version of this radical cyclisation.

1.2 Double Michael additions

1.2.1 Proposed methodology

The aforementioned methodologies are all well designed, giving the desired product in high yield, and in some cases with a stereoselective outcome. However, they often require many steps, stoichiometric amounts of promoters, or the use of strong bases, all of which diminish their attractiveness.

An ideal pathway in a synthetic sequence should have the following features: brevity, convergence and modularity. A route which satisfies these ideal requirements in the synthesis of pyroglutamic acid derivatives is a domino Michael-Michael reaction between a tethered diacid and a propargyl ketone (**Scheme 35**). A domino, tandem, or cascade reaction consists of two or more intramolecular reactions which often proceed via highly reactive intermediates. The reaction is often fast, and displays high atom economy, since it is intramolecular and does not involve workup or isolation of the intermediates.



Scheme 35

The suggested strategy would be concise and convergent since an amide-tethered diacid **132** would react with an alkynone **133** to give the mono-Michael product **134** and/or **135,** which would then cyclise to give the highly functionalised product **136** in a maximum of one or two steps. This strategy would provide significant modularity because small modification on the alkynone, or on the tethered diacid moiety, would provide a small library of Michael acceptors and nucleophiles, allowing the production of a wide array of pyroglutamate building blocks. Moreover, the possible use of substoichiometric amounts of a base or Lewis acid could offer good prospects for asymmetric catalysis. The proposed strategy belongs to a broader group of reactions known as double Michael additions, of which a brief overview is reported in the following section.

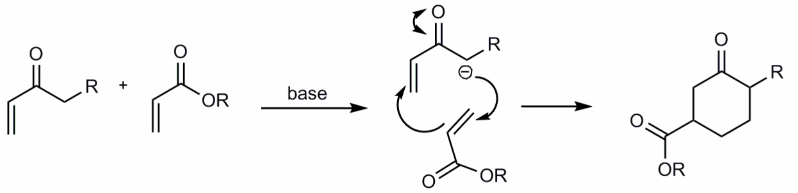
1.2.2 Double Michael additions

Domino Michael-Michael reactions, better known as double Michael additions, had been known for a very long time since they can quickly lead to the construction of polycyclic compounds and therefore they hold a great potential in the synthesis of complex natural products.[55] Although there are many different examples of 1,4 double conjugate additions they can be divided into four main classes:

1.2.2.1 addition of two ambiphilic species,
1.2.2.2 addition between a 1,1-dinucleophile and a 1,n-dielectrophile,
1.2.2.3 addition between a 1,n-dinucleophile and a 1,n-dielectrophile,
1.2.2.4 addition between a 1,n-dienucleophile and a 1,1-dielectrophile.

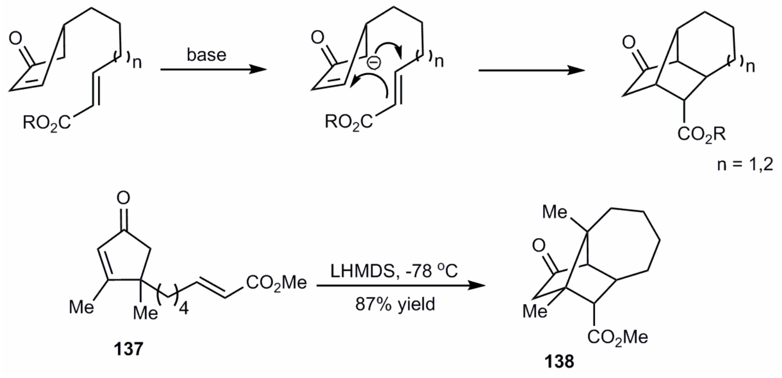
1.2.2.1 Additions of two ambiphilic species

Ambiphilic species possess one or more groups which can act as both a nucleophile and an electrophile, such as α,β-unsaturated ketones (**Scheme 36**). This feature allows them to undergo domino conjugate additions with other α,β-unsaturated carbonylic compounds.



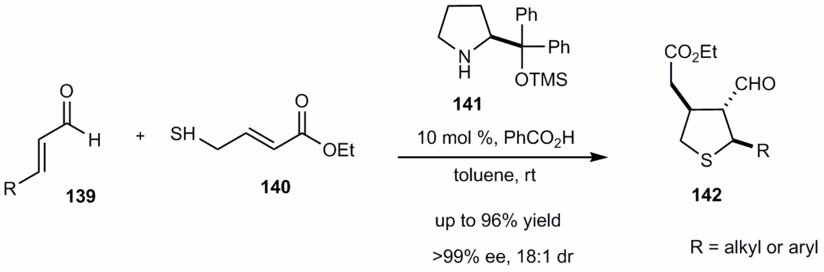
Scheme 36

An intramolecular version of these domino additions is the reaction employed as the key step in the synthesis of (±)-culmorin and (±)-longiborneol, performed by Ihara and co-workers,[56] where the two ester groups within the methylcyclopentenone derivative **137** react with each other, with the aid of a base (LiHMDS), giving the functionalised polycyclic product **138** (**Scheme 37**).



Scheme 37

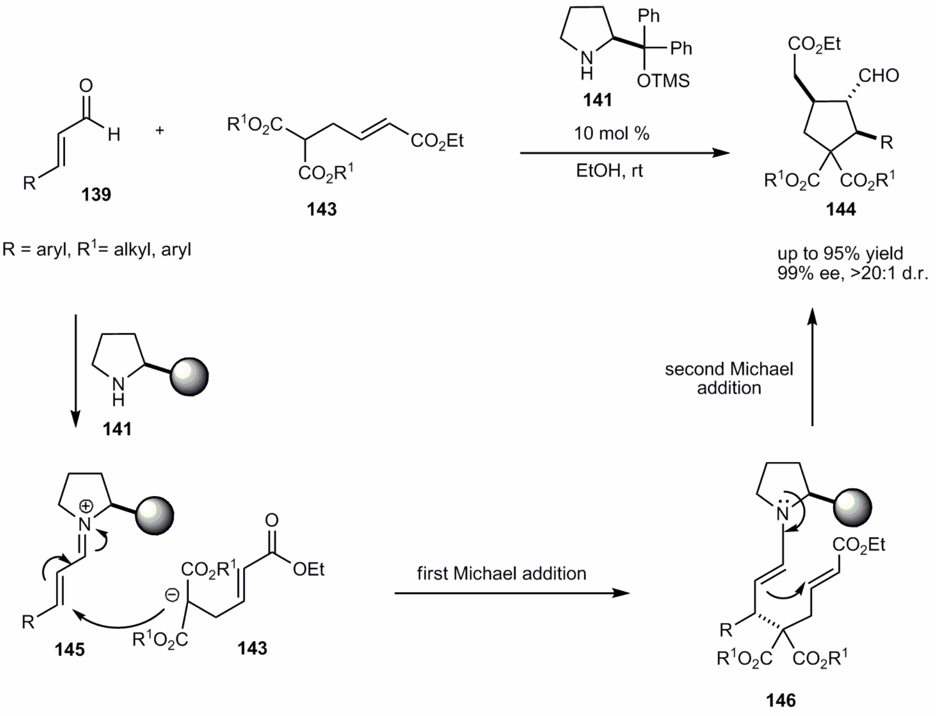
A more recent and slightly different example is the organocatalytic asymmetric thio-Michael-Michael intermolecular reaction performed by Wang and co-workers in which a heteroatom (sulphur) linked to an α,β-unsaturated ester acts as the nucleophile which initiates the domino process (**Scheme 38**).[57]



Scheme 38

According to Wang's report,[57] *trans*-ethyl 4-mercapto-2-butenoate **140** undergoes double Michael reaction with α,β-unsaturated aldehyde **139** when treated with chiral diphenylprolinol TMS ether (**141**) (10 mol %) in toluene at room temperature, affording tetrahydrothiophenes **142** in high yield (up to 96%) and excellent enantioselectivity (>99% ee, 18:1 dr).

With regards to organocatalytic asymmetric reactions it is also worth mentioning the domino organocatalytic Michael-Michael reaction performed by Wang *et al.* for the diastereoselective and enantioselective synthesis of cyclopentanes **144** (**Scheme 39**).[58] Similarly to the previous example, the α,β-unsaturated aldehyde **139** undergoes a cascade process when treated with the catalyst **141** (10 mol %) and the ester **143** in EtOH, at room temperature, affording the cyclopentene **144** in good yield (up to 95%) and high enantioselectivity (99% ee).[58]

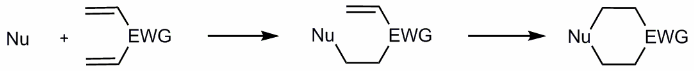


Scheme 39

In the proposed mechanism the α,β-unsaturated aldehyde **139** forms a reactive intermediate **145** with catalyst **141**. The intermediate **145** then undergoes a first Michael addition with the α,β-unsaturated ester **143** forming intermediate **146**, which subsequently reacts in a second Michael addition affording the desired cyclopentane **144**.

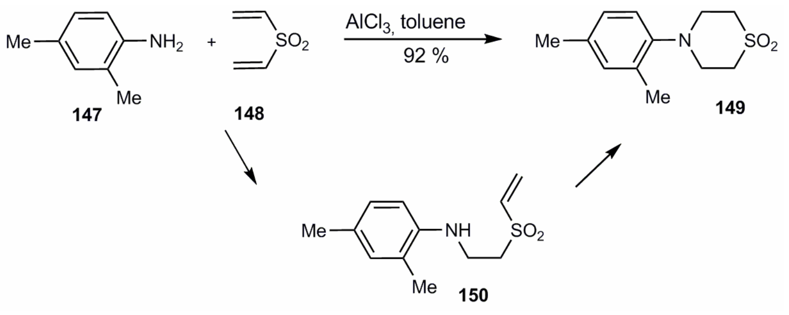
1.2.2.2 Additions between a 1,1-dinucleophile and a 1,n-dielectrophile

In this process a 1,1-dinucleophile, e.g. a primary amine, reacts with a 1,n-dielectrophile, e.g. a bis(enone) (**Scheme 40**).[59]



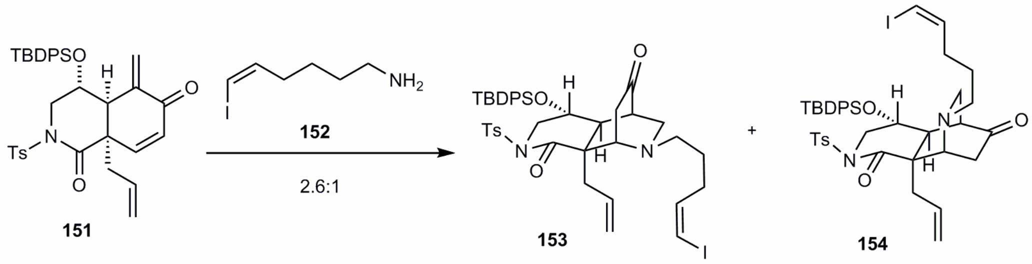
Scheme 40

In the process, shown below, aniline **147** (the nucleophile) is treated with vinyl sulfone **148** (the electrophile) and $AlCl_3$ in toluene giving phenylthiomorpholine dioxide **149** (**Scheme 41**).



Scheme 41

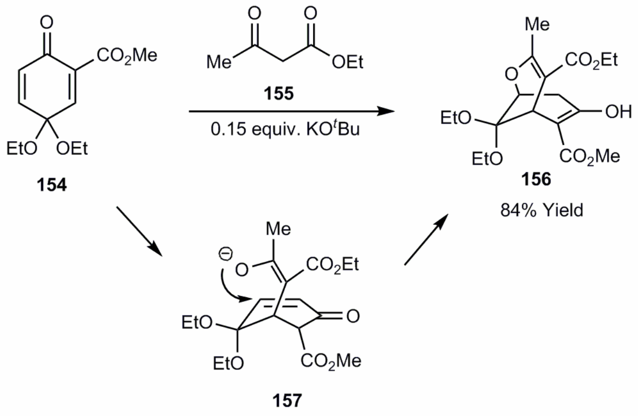
In their efforts towards the synthesis of xestocyclamine, Danishefsky and co-workers[60] also developed a type of cascade reaction where the primary amine **152** reacts with the (bis)enone **151** affording the two complex structured products **153** and **154** in good yield (90%) (**Scheme 42**).



Scheme 42

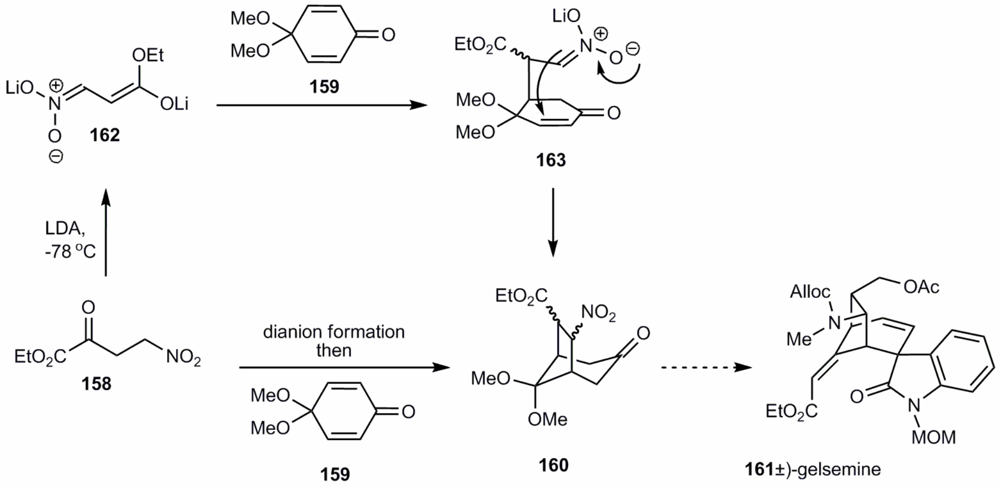
1.2.2.3 Addition between a 1,n-dinucleophile and a 1,n-dielectrophile

This type of conjugate addition is similar to the previous one, except that the nucleophile has two separate reactive centres, such as in a ketoester or nitroester. An example of an addition of a (bis)enone and a 1,n dienucleophile is the reaction reported by Aube and co-workers.[61] They carried out a regioselective double conjugate addition between ethyl acetoacetate (**155)**, and the cyclohexadienone **154** producing intermediate **157**, which then cyclises in the *oxo*-bridge bicyclic compound **156**, in good yield (84%) (**Scheme 43**).



Scheme 43

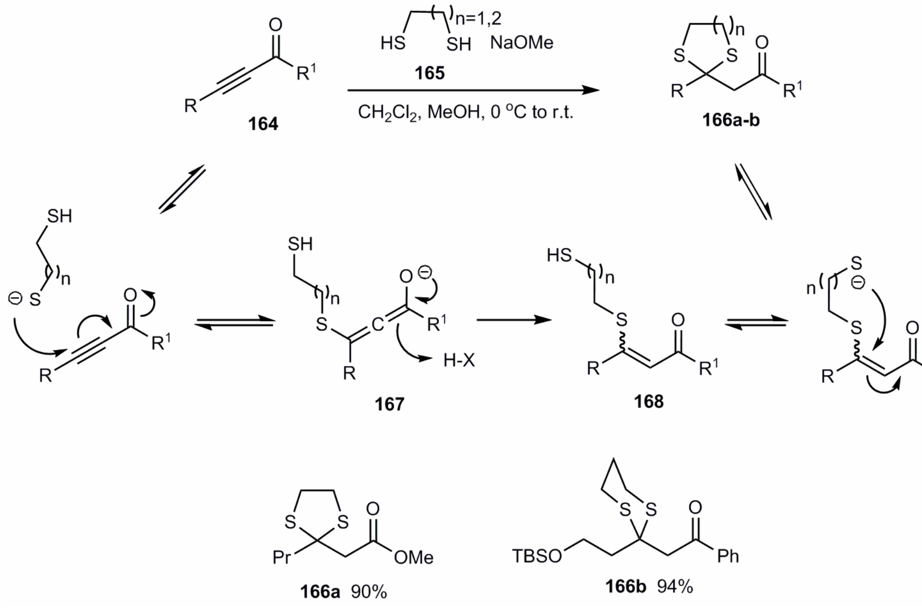
Two years later, Aube published another report on double conjugate additions using a very similar mechanism.[62] In this more recent work an addition between the lithium dianion **162** of ethyl 3-nitropropionate (**158**) and *p*-benzoquinone dimethyl ketal **159** was carried out and this afforded intermediate **163** which then cyclised to give a mixture of diastereomeric [3.2.1]bicyclooctanones **160**. These products were then converted into an advanced intermediate, which was previously used in the formation of (±)-gelsemine (**161**) by Fukuyama and Liu (**Scheme 44**).[63]



Scheme 44

1.2.2.4 Additions between a 1,n-dinucleophile and a 1,1-dielectrophile

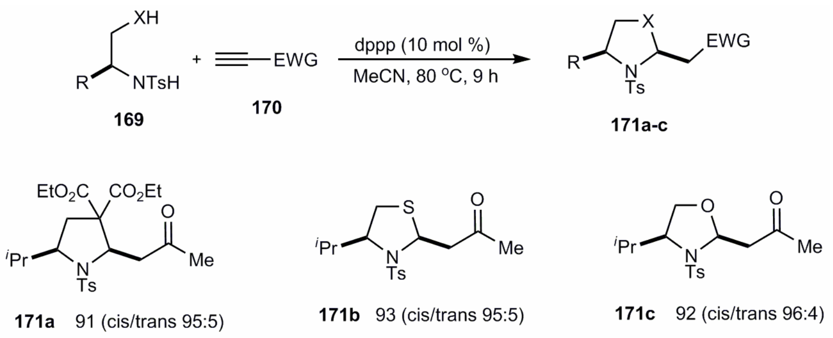
In this process, a 1,1-dielectrophile, which in most cases is a propargyl ketone, undergoes a double nucleophilic attack with a generic tethered dienucleophile, such as a diamine, a dithiocompound, an amino alcohol or a diacid. A recent example of this methodology, first developed by Grossman and co-workers, is the synthesis of β-keto dithiane derivatives performed by Ley *et al.*[64] In their efforts to produce a robust and efficient route to orthogonally protected 1,3-dicarbonyl precursors to use in polyketide assembly programs, they developed a double conjugate addition for the synthesis of β-keto dithiane derivatives.[64] In the reaction shown below, ethane or propane dithiol **165**, was added to the ynones **164** in the presence of methoxide in dichloromethane and methanol, to give β-keto dithiolanes **166a** and β-keto dithianes **166b** in high yields (90% and 94%) (**Scheme 45**).[64]



Scheme 45

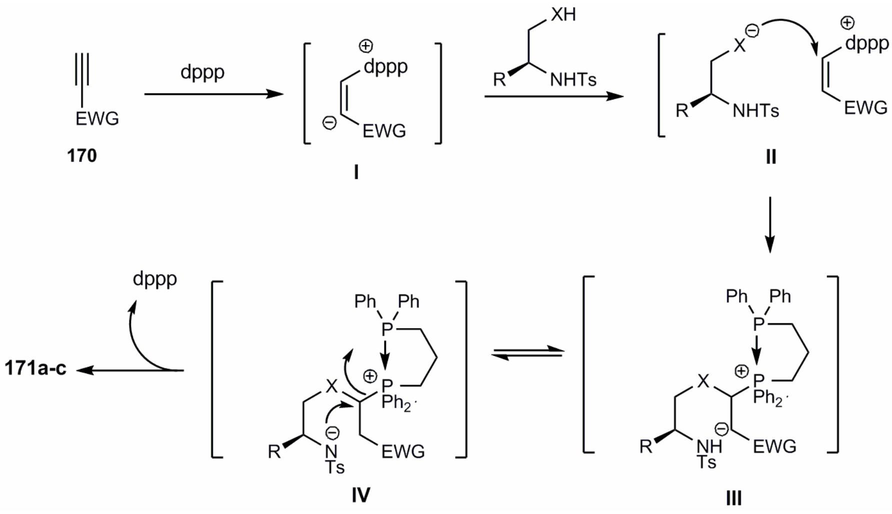
In the proposed mechanism the dithiol **165**, would initially undergo mono-deprotonation followed by addition to the ynones **164** to give intermediate **167**, which then rearranges to **168**. The α,β-unsaturated carbonyl compound **168** leads to the desired product **166a-b** after a second and intramolecular conjugate addition.[64]

Another recent example of a hetero domino Michael-Michael reaction between a 1,n-dinucleophile and a 1,1-dielectrophile is the asymmetric synthesis of azolidines reported by Kwon and co-workers.[65] Amino-acid-derived pronucleophiles **169** were employed as Michael donors, and electron deficient acetylenes **170** as Michael acceptors, providing efficient access to azolidines **171a-c**, containing both diversity and asymmetry, with the aid of a phosphine ligand (dppp) (**Scheme 46**).[65]



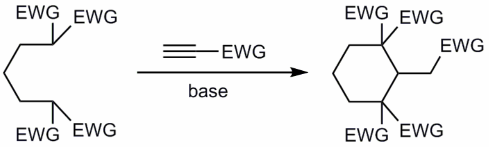
Scheme 46

The proposed mechanism, reported below, begins with the conjugate addition of the phosphine ligand to the acetylene **170** and proton transfer, followed by the mono-deprotonated amino alcohol attack on the intermediate **I**, that produces the intermediates III and IV. An intramolecular nucleophilic attack from the amine would then occur affording the desired product **171a-c** (**Scheme 47**).



Scheme 47

The last example presented here is of most interest to us not only within this particular category of Michael additions, but also within the whole range of double conjugate additions. In fact, the reaction occurs between a 1,1-dielectrophile (the usual alkynone that has been so commonly employed in this type of double Michael additions) and a 1,n-dinucleophile that possesses two carbon acidic centres connected by a tether to give the resulting cyclised product. In the previous examples the nucleophilic centres were heteroatoms, thio, aza or oxygen based (**Scheme 48**).



Scheme 48

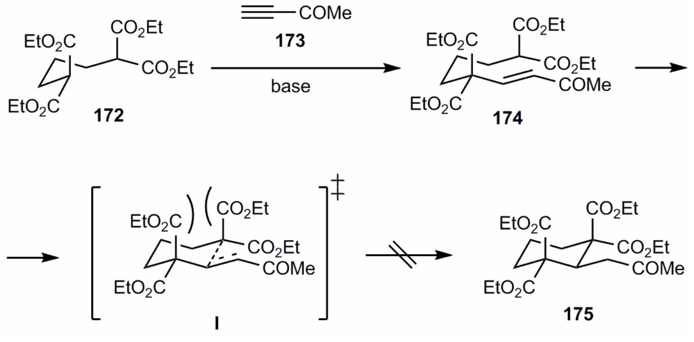
Grossman, in his effort to find a suitable pathway for the synthesis of the natural product Azadirachtin, was the pioneer in this field, being the first to employ electrophilic alkynes as the 1,1 dielectrophiles.[66]

An overview of Grossmann double Michael additions is provided in the next section.

1.2.3 Grossman's double Michael additions

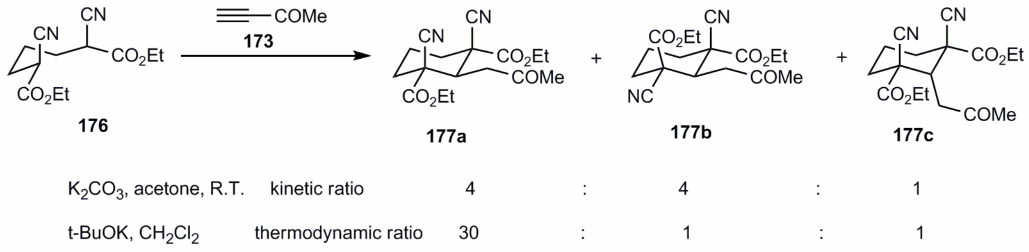
Over the past few years, Grossman and co-workers have described a range of reactions where compounds containing two acidic carbon atoms (tethered diacids) undergo double Michael reactions with electron deficient alkynes (mostly 3-butyn-2-one) to provide highly functionalised cyclic products, generating two new carbon-carbon bonds and up to three new stereogenic centres, often with high levels of diastereoselectivity.[66] This reaction has been effectively utilised in the preparation of a range of five- and six-membered carbocycles. In comparison, application of this methodology to heterocycle construction has been limited, with just one report of a [5 +1] annulation route to piperidines having been described.[67]

Grossmann's first attempt of intramolecular double Michael addition between the tetraester **172** and the ketone **173** actually failed. He did not obtain the desired product **175** but only the mono-Michael adduct **174** and in very poor yield. It was suggested that the reason for this failure was an incipient 1,3-diaxial interaction between the two ester groups of the hypothetical transition state **I** (**Scheme 44**).



Scheme 49

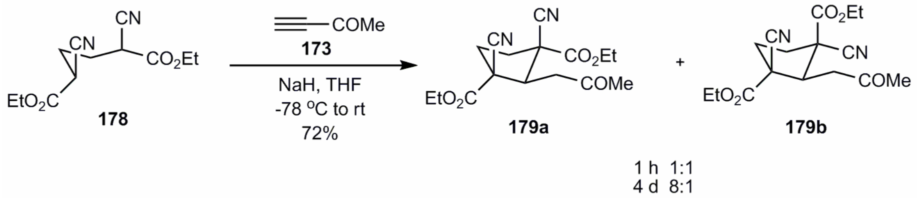
The problem was overcome by substituting one or more esters with a cyano group. The cyano group was in fact a powerful electron-withdrawing group (*K*a of ethyl cyanoacetate was about five orders of magnitude smaller than the *K*a of diethyl malonate) and had a smaller 1,3-diaxial interaction in cyclohexanes than almost any other group. As expected the reaction with the dicyano diester **176** was successful giving the three products **177a**, **177b**, and **177c** in 83% combined yield and 4:4:1 dr, after treatment of the cyanoester **176** and alkynone **173** with a substoichiometric quantity of potassium carbonate in acetone (**Scheme 50**).



Scheme 50

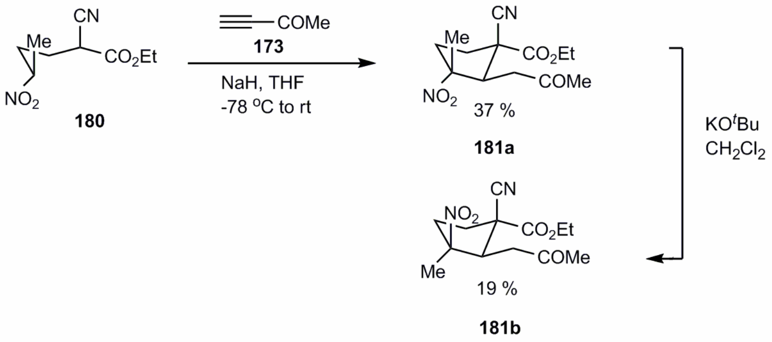
They also discovered that **177b** and **177c** could be converted into the lower energy **177a** by treatment with potassium *tert*-butoxide in dichloromethane. Indeed when **176** and **173** were combined under these conditions the dr of the crude mixture was 30:1:1 in favour of **177a**.

The double Michael reaction also proceeds well when the two carbon acidic atoms in the substrate were connected by a shorter tether as in diethyl 2,5-dicyanoadipate **178** giving the five-membered rings **179a** and **179b** in good yield (72%) (**Scheme 51**).[68]



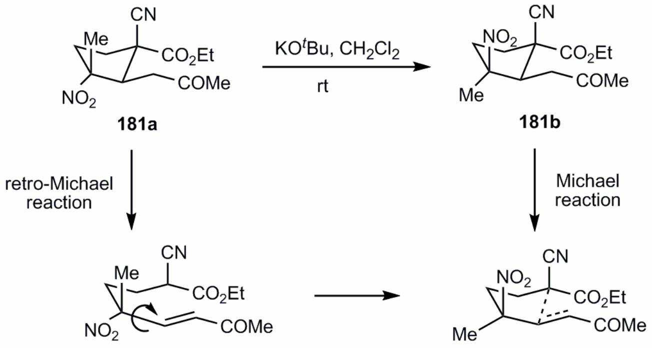
Scheme 51

It was observed when using sodium hydride as a base in tetrahydrofuran that the dr after 1 h was 1:1 but if the reaction mixture was stirred at room temperature for four days the ratio improved to 8:1. A further example is the cyclisation of the nitroester **180** into the cyclopentanes **181a** and **181b** (**Scheme 52**).[66]



Scheme 52

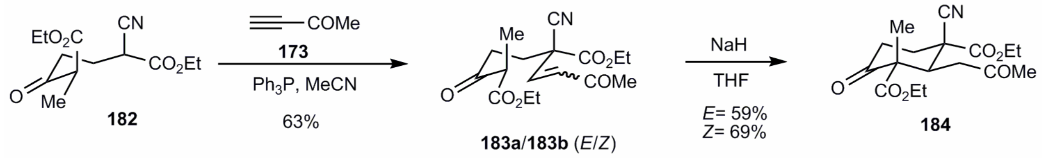
In this case the mixture of tethered diacids and the propargyl ketone was first treated with sodium hydride in tetrahydrofuran giving the products **181a** and **181b** in a 2:1 dr. After treatment with potassium *tert*-butoxide in dichloromethane at room temperature, **181a** was completely converted into **181b**. It was concluded that thermodynamic ratios of products are obtained with potassium *tert*-butoxide in dichloromethane, whereas kinetic ratios of products are obtained under other conditions such as sodium hydride in tetrahydrofuran, potassium carbonate in acetone at room temperature, and triphenyl phoshpine in acetonitrile. It was also found that the kinetic products can be converted into the thermodynamically more stable products by treatment with potassium *tert*-butoxide in dichloromethane. It was speculated that the mechanism behind the equilibration was probably a retro-Michael-Michael process, during which a first retro-Michael reaction occurs, followed by rotation about the σ bond and then ring reclosure via a second Michael addition (**Scheme 53**).



Scheme 53

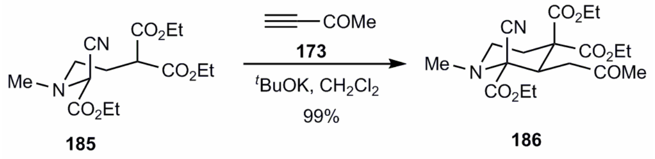
Grossman and co-workers also extended the double Michael reactions to carbon diacids that have a ketone group or a heteroatom in the tether, for the synthesis of cyclic ketones[69] and piperidines[67] respectively. Treatment of tethered diacid **182** and

3-butyn-2-one (**173**) with triphenylphosphine in acetonitrile led to the two diasteromeric mono-Michael products **183a** and **183b** which both cyclised and afforded ketone **184** as a single stereisomer, in 59% and 69% yield respectively after treatment with sodium hydride in tetrahydrofuran (**Scheme 54**).[69]



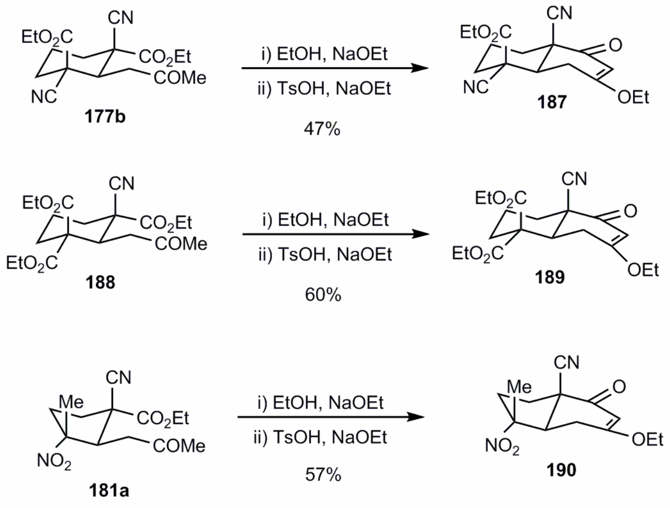
Scheme 54

Tethered diacid **185** and 3-butyn-2-one (**173**) were treated with potassium *tert*-butoxide in dichloromethane affording the desired piperidine **186** as a single stereisomer in very good yield (99%) (**Scheme 55**).[67]



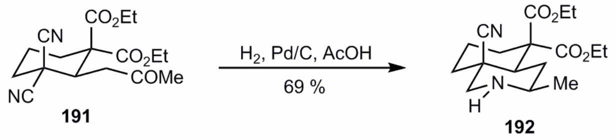
Scheme 55

The six- and five-membered cyclic compounds thus obtained were considered useful for the synthesis of densely functionalised and architecturally complex compounds such as *trans*-fused bicyclic products, usually *trans*-decalins, but also *trans*-hydrindane. For example the six- and five-memebered rings **177b**, **188**, and **181a**, underwent Dieckman reaction when treated with sodium ethoxide in ethanol and the resulting products were immediately treated with TsOH and ethanol in benzene affording the corresponding enol ethers **187**, **189** and **190** (**Scheme 56**). [68]



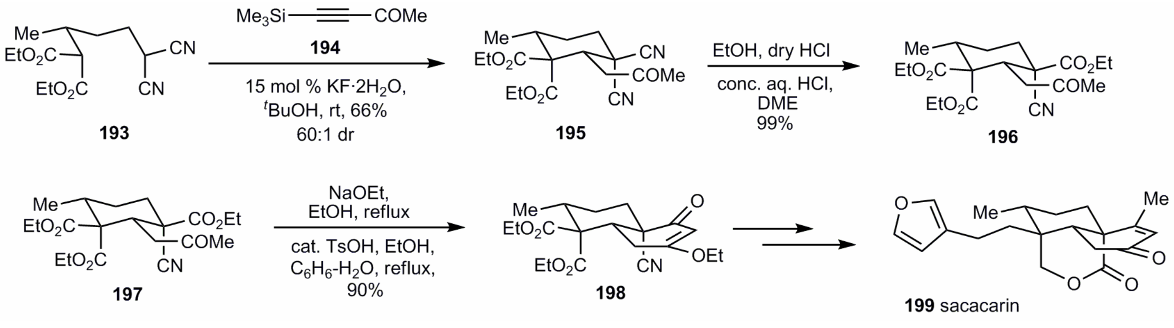
Scheme 56

Double Michael adducts with two cyano groups, of which one is equatorial, may undergo hydrogenation over Pd/C in AcOH, affording *trans*-perhydroisoquinoline as in the example shown below, where **191** was obtained as a single stereoisomer in 69% yield upon reduction of **192** (**Scheme 57**).



Scheme 57

Grossman finally applied the strategy he discovered for the synthesis of the naturally occurring product (±)-sacacarin (**199**)[70], a minor component in the bark of a Brazilian tree used as a natural drug for the treatment of digestive upset (**Scheme 58**).



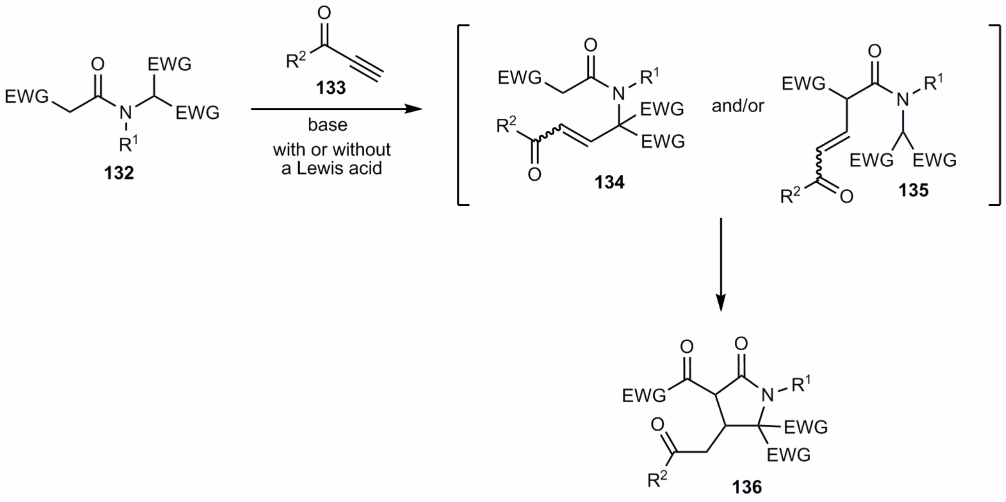
Scheme 58

The key part of the synthesis is a double annulation, which consists of a combined double Michael addition, Pinner and Dieckman reactions. The Michael addition of the tethered carbon diacid **193** to a 3-butyn-2-one (**194**) gave the six-membered ring product **195** in 66% yield and 60:1 dr after recrystallisation. Then the Pinner reaction, followed by the Dieckman reaction provided the *trans*-octalone **198** in 90% yield, which after further steps afforded the desired product **199**.

2. RESULTS AND DISCUSSION

2.1 Design and synthesis of starting materials

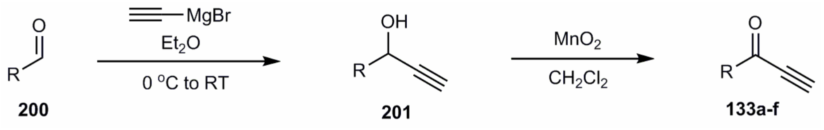
In view of the convergent and modular nature of double Michael reactions of alkynones, we were drawn to the prospect of utilising these transformations in a concise synthesis of highly functionalised pyroglutamic derivatives, according to the strategy outlined below (**Scheme 59**).



Scheme 59

It was hoped that under suitable conditions, an amide-tethered diacid **132** would react with an alkynone **133** with the aid of a base and with or without a Lewis acid to first give mono-Michael adduct **134** and/or **135**, which would then cyclise to the pyroglutamic acid derivative **136**.

As far as the choice of alkynones was concerned, we selected the aromatic alkynones **133a**-**f**, since they were easy to prepare with a two-step synthesis, which consisted of a nucleophilic addition of the Grignard reagent to the corresponding aromatic aldehyde **200** (**Table 1**). The resulting alcohols **201**, without further purification, were oxidised with Mn(IV) oxide to give the desired ketones **133a**-**f** in 48%-65% yield.



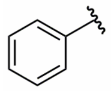
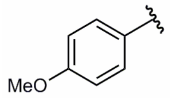
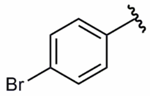
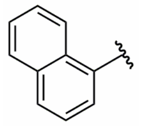
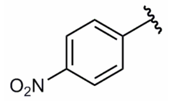
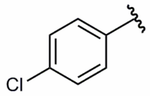
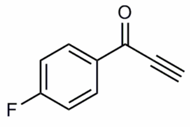
entry	**alkynone**	**R**	**yield** (%) Over two steps
1	**133a**		61
2	**133b**		65
3	**133c**		60
4	**133d**		58
5	**133e**		54
6	**133f**		48

Table 1

The *p*-fluoro alkynone **133g** was already available because it had been previously prepared by a former postdoc in the Lam group Dr Hu (**Figure 2**).



133g

Figure 2

In all previous examples of double Michael reactions reported by Grossman and co-workers,[4,5] a mandatory requirement for success was the presence of at least one cyano substituent in the tethered diacid, which ends up in a pseudoaxial position in the product (see, **Scheme 49**, pp 40). It was proposed that the small size of the nitrile group reduces the magnitude of unfavourable 1,3-diaxial interactions between acidifying groups in the transition state for cyclisation, which would otherwise inhibit ring closure. Therefore at the outset of this work, we chose to make a preliminary screening of the amides containing a nitrile group. Tethered diacids **202**,

203 were already available because they had been previously prepared by Dr Hu (**Figure 3**).

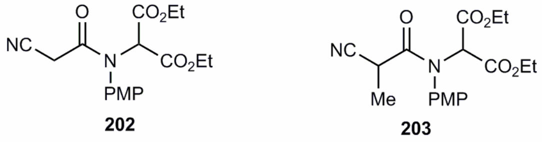
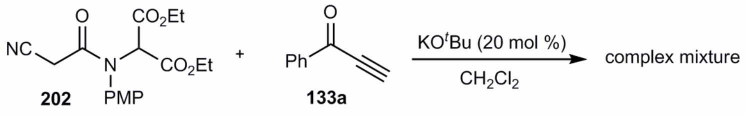


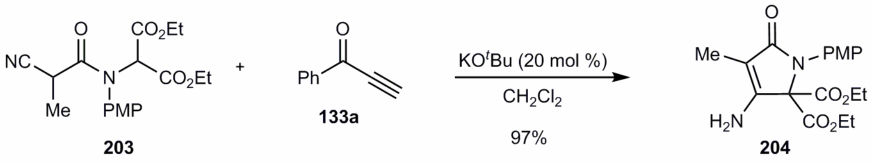
Figure 3

The amide-tethered diacid **202** was then treated with potassium *tert*-butoxide and with a solution of the aromatic alkynone **133a** in dry dichloromethane at room temperature (**Scheme 61**). The reaction provided a complex mixture of products.



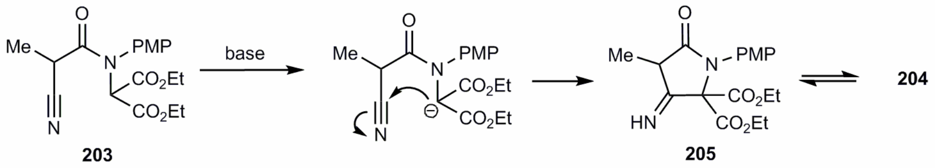
Scheme 60

The reaction was then repeated using the tethered diacid **203** with a methyl group in the β-position to the amide producing the unexpected five-membered heterocycle **204** (**Scheme 61**).



Scheme 61

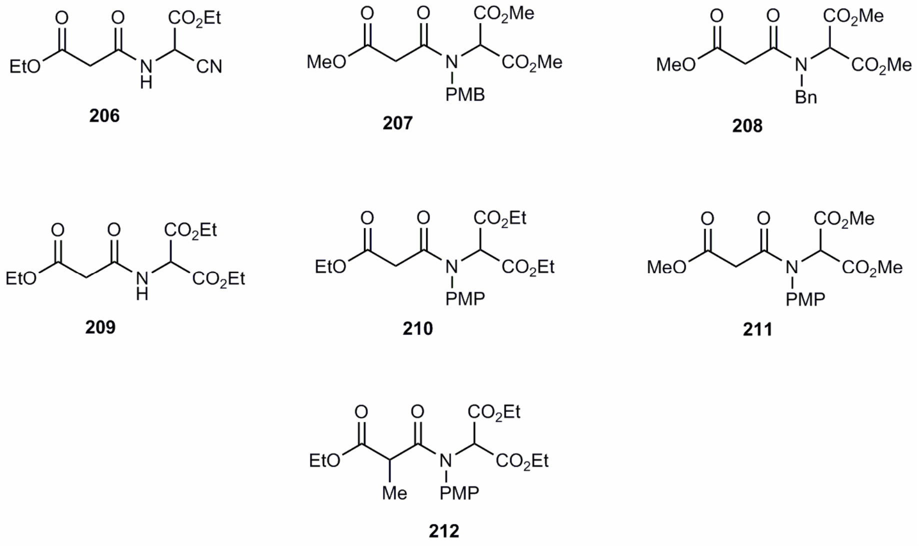
The likely explanation of this result is an intramolecular nucleophilic attack of the malonyl group onto the nitrile group, followed by formation of intermediate **205**. Intermediate **205**, thus obtained, would then tautomerise to give the five-membered ring **204** (**Scheme 62**).



Scheme 62

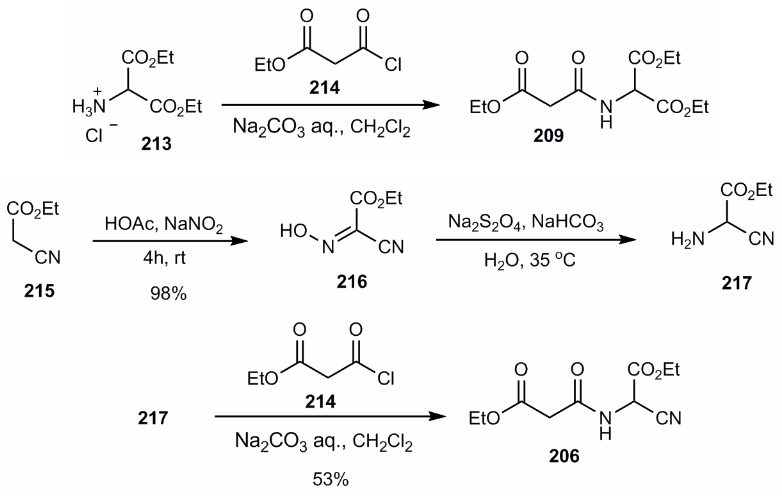
Other starting materials were selected including substrates both with or without protecting groups. Tethered diacids with only esters as electron withdrawing groups were also targeted, although it was uncertain whether diacids without a cyano substituent would undergo successful double Michael addition. Tethered diacids **207**,

212, were already available because they had been previously prepared by Dr Hu (**Scheme 63**).



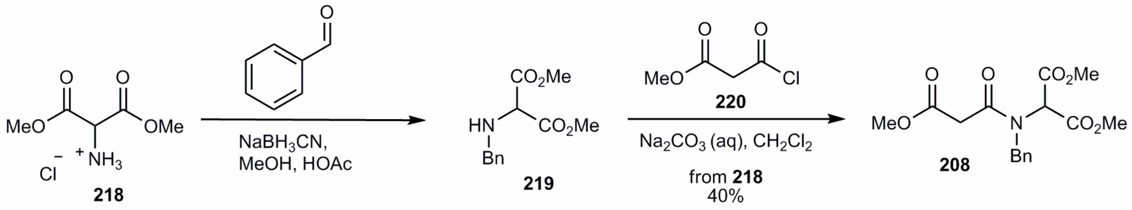
Scheme 63

The amide-tethered diacids not bearing a protecting group (**206** and **209**) were easily prepared by treatment of the corresponding aminomalonate **213** and aminocyanoacetate **217** with ethyl chloromalonate (**214**) in dichloromethane (**Scheme 64**). Aminocyanoacetate **217**, unlike the aminomalonate **213**, was not commercially available and was prepared from **215**. The cyanoester **215** underwent oxidation upon treatment with sodium nitrite and acetic acid at room temperature. The resulting oxime **216** was then treated with sodium dithionite and sodium bicarbonate in water affording adduct **217**, which was used for the next step without further purification. Upon treatment of adduct **217** with ethylchloromalonate (**214**), diacid **206** was produced in 53% yield.



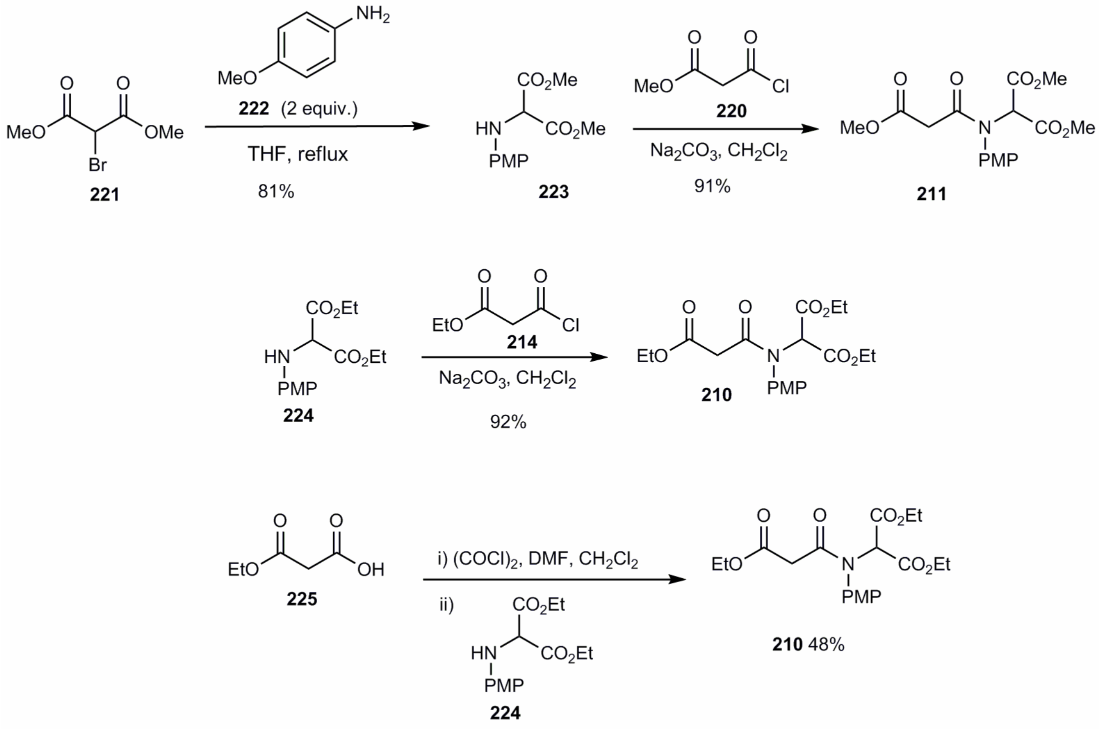
Scheme 64

In order to generate the starting material **208** with a benzyl group as the protecting group, we started from the aminomalonate **218** (**Scheme 65**). Upon treatment with benzaldehyde and sodium cyanoborohydride in methanol, the aminomalonate **218** underwent reductive amination. The resulting residue **219**, without further purification, was treated with chloromalonate **220** and a saturated aqueous solution of sodium carbonate in dichloromethane affording the desired product **208** in 40% yield.



Scheme 65

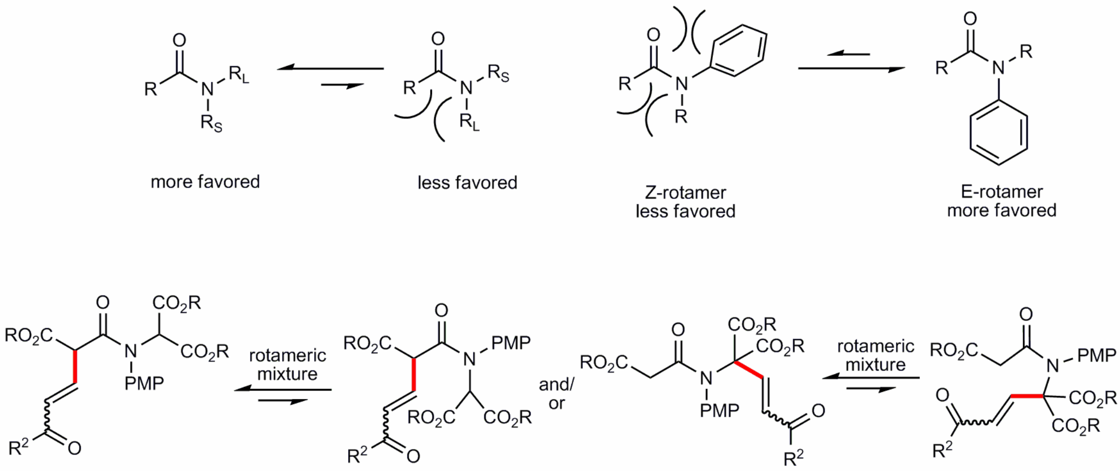
Diacids **211** and **210** were prepared in generally good yield upon treatment of amines **223** and **224** with methyl or ethyl malonyl chloride (**214**, **220**) in dichloromethane (**Scheme 66**). In some cases the malonyl chloride was generated *in situ* from the corresponding acid with oxalyl chloride and DMF. Amine **225** was already available because it was prepared by Isabel Villanueva Mrgalef (a former PhD student in the Lam group)**,** while **223** was prepared by treatment of methyl bromomalonate **222** with an excess of aniline **222**. The mixture was heated to reflux in tetrahydrofuran and after purification afforded the amine **211**.


MeO
NH$_2$
222 (2 equiv.)
THF, reflux
81%
MeO
OMe
O
O
Br
221
CO$_2$Me
HN
CO$_2$Me
PMP
223
MeO
Cl
220
Na$_2$CO$_3$, CH$_2$Cl$_2$
91%
MeO
N
CO$_2$Me
PMP
211
CO$_2$Et
HN
CO$_2$Et
PMP
224
EtO
Cl
214
Na$_2$CO$_3$, CH$_2$Cl$_2$
92%
EtO
N
CO$_2$Et
210
PMP
EtO
OH
225
i) (COCl)$_2$, DMF, CH$_2$Cl$_2$
ii)
224
210 48%

Scheme 66

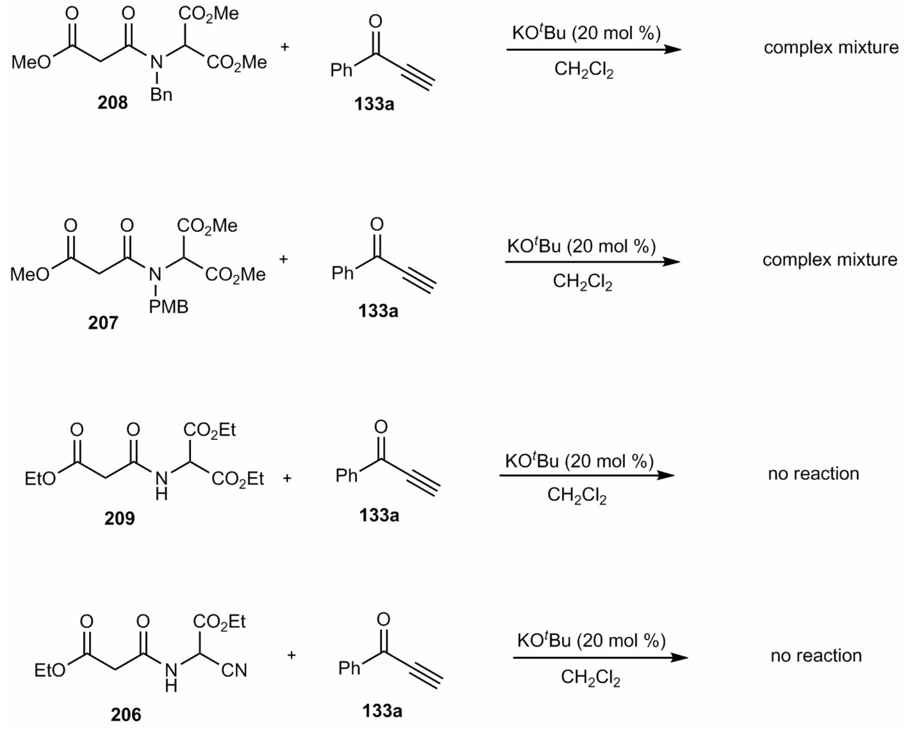
2.2 Double Michael additions

It is known that *N,N*-disubstituted amides generally prefer to exist as the *Z*-amide rotamer, presumably for steric reasons, and also that *N*-alkyl-*N*-arylamides exist predominantly as the *E*-amide rotamer, with the aryl group twisted such that the plane of the aromatic ring is approximately perpendicular to that of the amide group (**Scheme 67**).[71]



Scheme 67

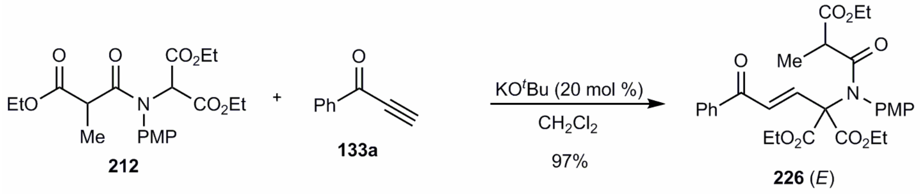
At the outset of these investigations it was not clear whether this rotamer distribution would have any impact on the ability of these substrates to undergo cyclisation. However, using the aforementioned conditions (potassium *tert*-butoxide in dichloromethane), several reactions were performed employing tethered diacids with a benzyl group as a protecting group or without protecting group (**Scheme 68**).



Scheme 68

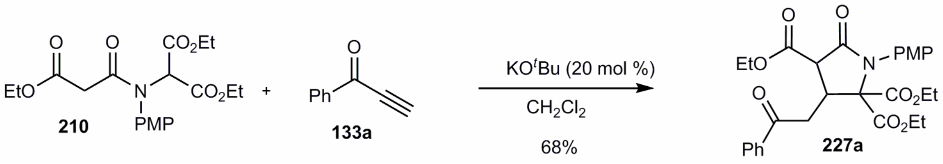
When amides **206** and **207** were treated with potassium *tert*-butoxide the reaction produced a complex mixture of products, while when amides **209** and **206** were treated under the same conditions, no product was observed. The results of these experiments clearly indicated the importance of the protecting group in the reactivity of the double Michael reaction. Most likely these results depend on a different acidity of the protons in the tethered diacids and/or on the steric hindrance of the protecting group. The total absence of reactivity in the unprotected diacids is perhaps due to the deprotonation of the N-H group.

Substrate **212** was treated with potassium *tert*-butoxide and a solution of the aromatic alkynone **133a** in dichloromethane at room temperature (**Scheme 69**). The reaction produced the mono-Michael product **226** as single diastereoisomer (*E*). Although **226** was not the desired product it could be treated with different bases in order to cyclise it.



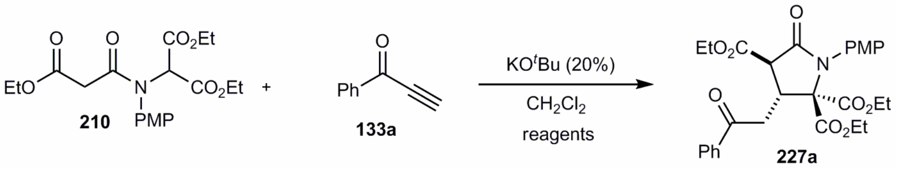
Scheme 69

Several methods to cyclise the mono-Michael product **226** were attempted but in most cases only starting material was recovered. These results suggested that the acidic centre β to the amide was possibly too hindered to undergo a second Michael addition. Therefore the tethered diacid **210** was selected. We were particularly pleased to observe the formation of the double Michael product **227a** upon treatment of **210** with potassium *tert*-butoxide and a solution of the aromatic alkynone **133a** in dichloromethane at room temperature. The reaction produced the Michael product **227a** in good yield, albeit as a 1:1 mixture of the two diastereomers (**Scheme 70**).



Scheme 70

We next investigated the effect on the reaction of different bases, along with Lewis acidic additives.[72] Among the conditions explored, treatment of **210** with triphenylphosphine, which was employed by Grossman in his double Michael reactions (**Scheme 54**, pp. 40) the cyclisation did not occur, while triethylamine gave the cyclised product in poor yield. Treatment of **210** with potassium *tert*-butoxide and substoichiometric quantities of Lewis acid additives were found either to inhibit or improve the yield and the diastereomeric ratio of the conjugate addition (**Table 2**). Many metal salts were used as additives and the most representative examples are shown below.



entry	**reagent** (20 mol %)	**dr**	**yield**(%)
1	KO^{t}Bu	1:1	68
2	KO^{t}Bu, Fe(acac)$_3$	1:1	31
3	KO^{t}Bu, Zn(OTf)$_2$	> 19:1	27
4	KO^{t}Bu, Mg(OTf)$_2$	11:1	68
5	KO^{t}Bu, Ni(acac)$_2$	18:1	76

Table 2

Addition of Fe(acac)$_3$[73] and Zn(OTf)$_2$[74] was found to inhibit the reaction (**entries 2** and **3**), even if Zn(OTf)$_2$ had a beneficial effect on diastereoselectivity (**entry 3**). Mg(OTf)$_2$[75,76] (**entry 4**) and Ni(acac)$_2$[77] (**entry 5**) gave better results allowing double Michael product **227a** to be isolated in 68-76% yield and with up to an 18:1 diastereomeric ratio. Interestingly the use of sodium *tert*-butoxide as a base gave a 1:1 mixture of diastereomers even in the presence of Lewis acid additives.

It was expected that the major diastereomer would possess *trans* configuration as it was thermodynamically more favourable. This hypothesis was endorsed by the coupling constant values of the protons in C(3) and C(4), analysed by ^{1}H NMR spectroscopy, which was about 11Hz. Following the rules of the Karplus equation, this value usually suggests a trans interaction between two vicinal protons in six-membered rings (**Figure 4**).

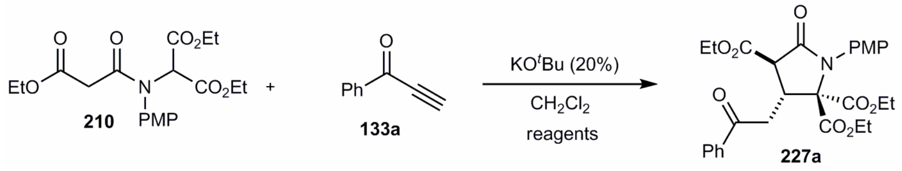


Figure 4

Nevertheless **227a** is a five-membered ring and because it has a different conformation from a six-membered ring, its coupling constant values do not necessarily obey the Karplus equation. Therefore the stereochemistry was analysed by crystallographic methods. The major diastereomer was consequently isolated by recrystallisation of **227a** from a mixture of diethyl ether and hexane affording colourless crystals. The crystals were suitable for X-ray crystallography, which allowed us to confirm that the major diastereomer obtained in these reactions possesses *trans* configuration (**Figure 5**).

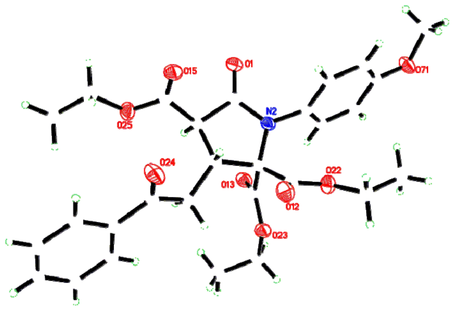
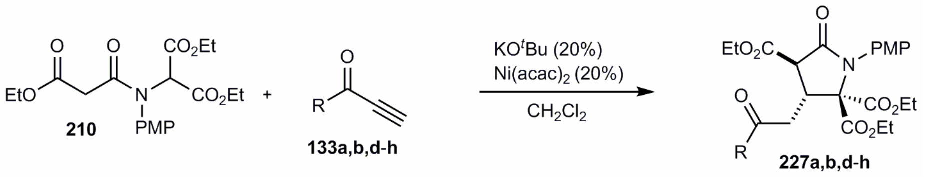
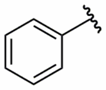
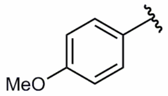
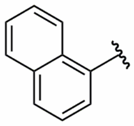
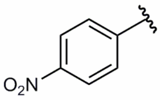
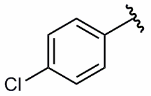
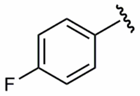


Figure 5

With optimised conditions in hand, the scope of the reaction was explored (**Table 3**). Using **210** as the tethered diacid, a range of different aromatic alkynones **133a-e** possessing substituents of varying electronic character underwent double Michael reactions, when treated with potassium *tert*-butoxide and Ni(acac)$_2$, to provide pyroglutamic acid derivatives **227a-e** in 49-77% yield and 10:1->19:1 dr.



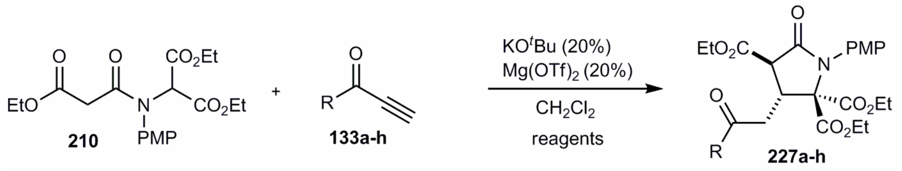
entry	alkynone	R	product	yield (%)	dr
1	**133a**		**227a**	76	**18:1**
2	**133b**		**227b**	49	**> 19:1**
3	**133d**		**227d**	60	10:1
4	**133e**		**227e**	77	**18:1**
5	**133f**		**227f**	60	12:1
6	**133g**		**227g**	76	**> 19:1**
7	**133h**	Me	**227h**	traces	**n/a***

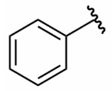
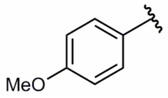
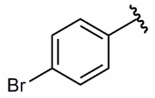
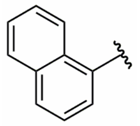
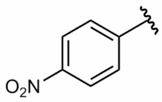
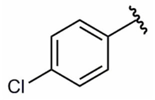
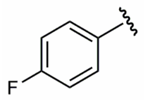
* The peaks of the cyclised product were just visible in the ^{1}H NMR spectrum.

Table 3

The double Michael addition of aryl alkynones generally produced the corresponding cyclised products in high yield with the exception, as expected, of the more electron rich alkynone **133b** (**entry 2**). The aliphatic alkynone **133h** (**entry 7**) surprisingly gave only traces of product.

The tethered diacid **210** and the range of alkynones **133a-e** underwent double Michael reactions, also when treated with potassium *tert*-butoxide and Mg(OTf)$_2$, to provide pyroglutamic acid derivatives **227a-g** in 50-75% yield and 8:1->19:1 dr (**Table 4**). Comparing Table **3** and Table **4** it is not possible to observe major differences other than that in the latter the most activated ketone **133e** gave the lowest yield and the dr values were generally lower then in the previous range of reactions.

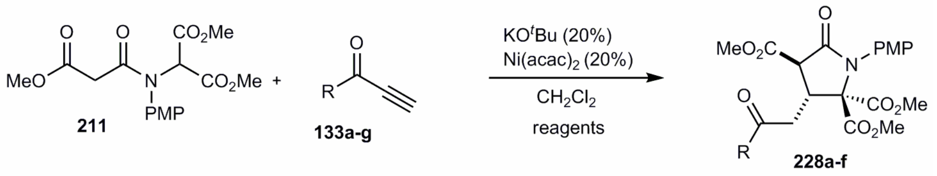


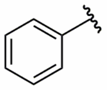
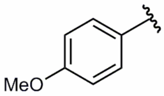
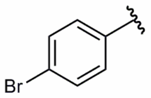
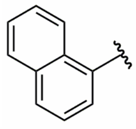
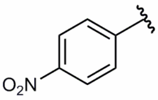
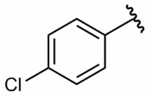
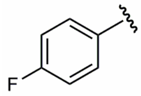
entry	alkynone	R	product	yield(%)	dr
1	**133a**		**227a**	68	11:1
2	**133b**		**227b**	69	10:1
3	**133c**		**227c**	45	**> 19:1**
4	**133d**		**227d**	69	8:1
5	**133e**		**227e**	50	**> 19:1**
6	**133f**		**227f**	61	14:1
7	**133g**		**227g**	75	15:1
8	**133h**	Me	**227h**	traces	**n/a***

* The peaks of the cyclised product were just visible in the ^{1}H NMR spectrum

Table 4

The tethered diacid **211**, containing methyl esters in place of the ethyl esters, likewise underwent double conjugate addition affording double Michael products **228a-f** with lower yields (39%-68%) but comparable dr (10:1->19:1) to the previous **(Table 3, Table 4)**.



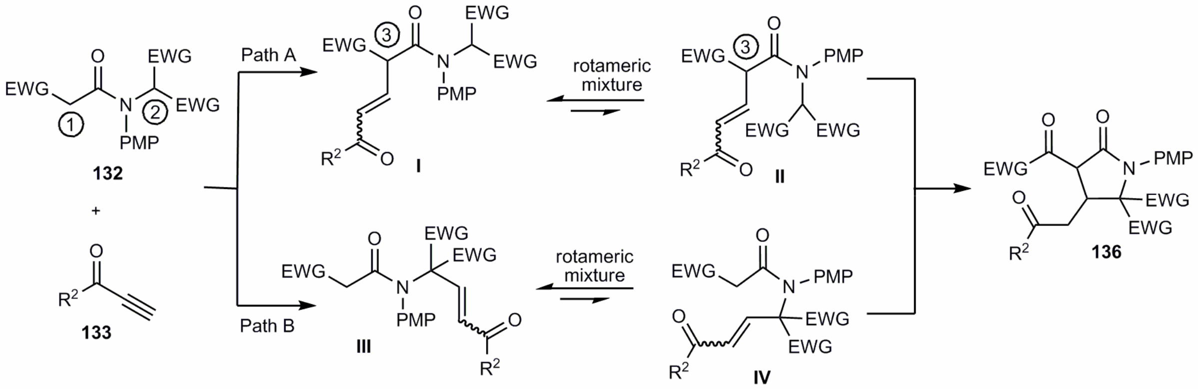
entry	alkynone	R	product	yield(%)	dr
1	**133a**		**228a**	60	10:1
2	**133b**		**228b**	36	**> 19:1**
3	**133c**		**228c**	60*	10:1*
4	**133d**		**228d**	68	15:1
5	**133e**		**228e**	39	**> 19:1**
6	**133f**		**228f**	45	**> 19:1**
7	**133g**		**228g**	59	10:1

* This result was obtained with Mg(OTf)$_2$ (20 mol %).

Table 5

2.3 Mechanistic investigations

There are two reasonable pathways for a double Michael addition, as was briefly outlined at the beginning of this chapter (**Scheme 59**). When the tethered diacid **132** reacts with the alkynone **133** an initial Michael reaction takes place either at Site 1 of **132** (due to this carbon being less sterically hindered (Path A)), or at Site 2 (due to this carbon possessing a lower pK_a value (Path B)) (**Scheme 71**). Hypothetically Path B seems to be the one more likely to happen on the basis of the aforementioned acidity argument and also on the assumption that intermediates **I/II** formed in Path A, being a very acidic vinylogous ketoester amide will undergo rapid deprotonation (at site 3), thus inhibiting ring closure to the product **136**.

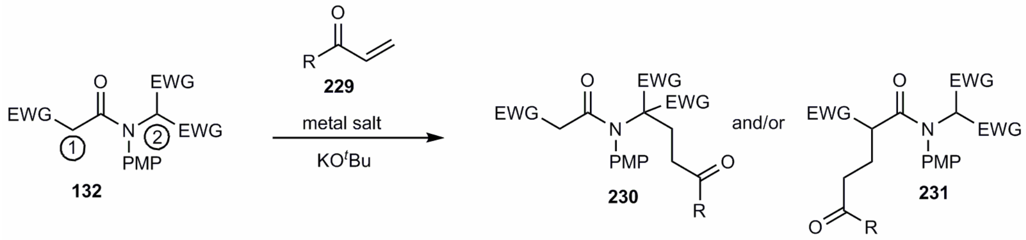


Scheme 71

However, to shed more light on whether one or both pathways are operative and to understand the role played by the metal salts, additional experiments were carried out. A number of methods might be employed: (i) monitoring the reaction by NMR spectroscopy, and/or (ii) quenching the reaction at low conversions and analysing the composition of the resulting mixture.

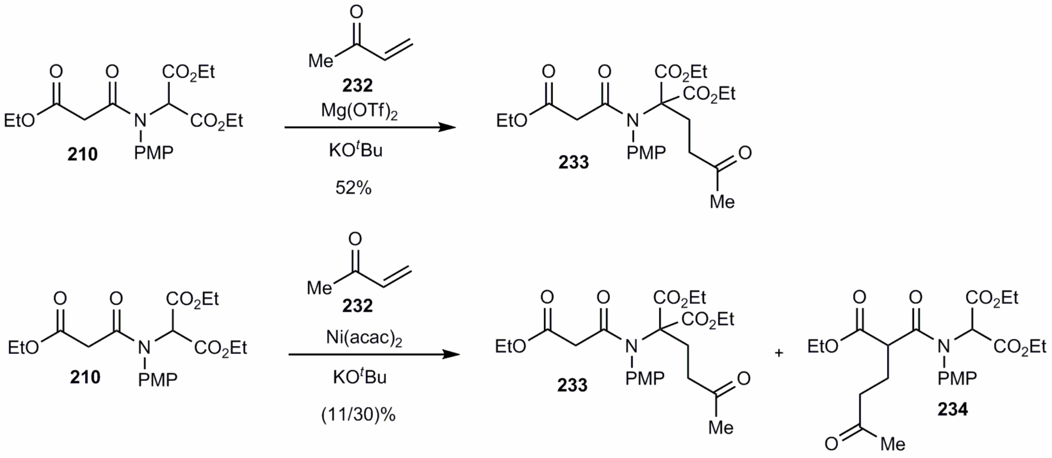
Normally crude ^{1}H NMR spectra of double Michael products are not very clear and the addition of peaks of intermediates could have caused further uncertainity in the spectra. For this reason it was decided not to use method (i). Method (ii) was also discounted as TLC analysis showed only spots resulting from the starting material and the product, suggesting that the transformation of the intermediate into the product was too fast.

Nevertheless a simple way to gauge the relative reactivity of Site 1 and 2 was to perform a Michael addition with a tethered diacid **132** and a simple enone **229** in the place of an alkynone. This would result in products **230** or/and **231** (**Scheme 72**).



Scheme 72

A reaction of methyl vinyl ketone (**232**) with diacid **210**, using $Mg(OTf)_2$ as an additive, was performed producing **233** as the only observable Michael product in 52% yield, with the remainder of the starting material being unreacted (**Scheme 73**).

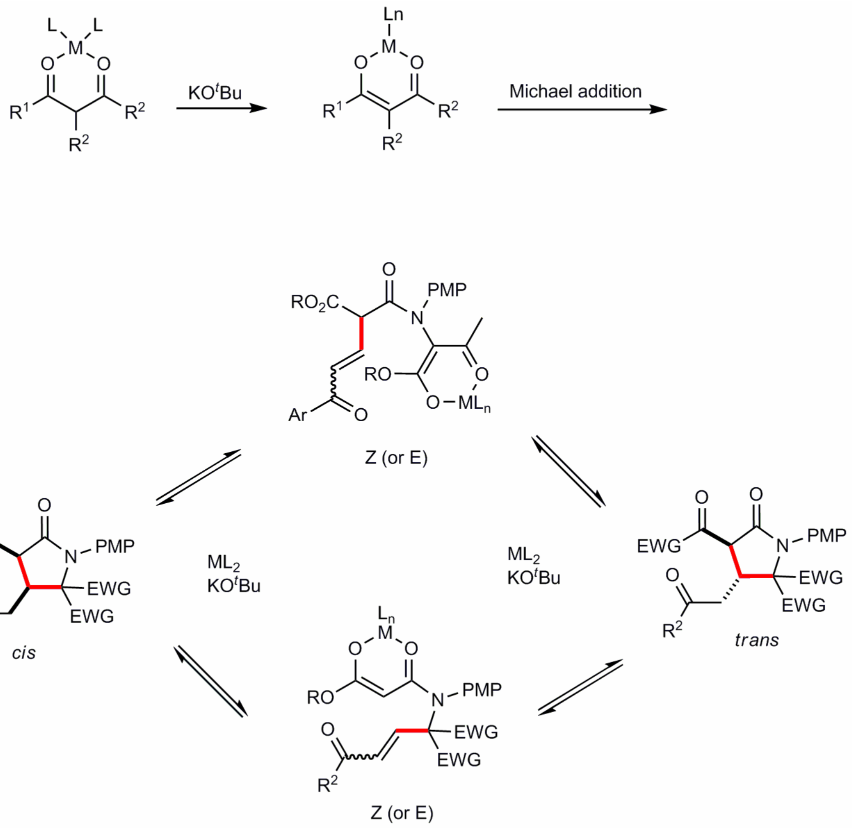


Scheme 73

The experiment showed that under these conditions, the carbon on Site 2 of **210** is more reactive than that on Site 1, as was expected. However, the analogous experiment carried out using $Ni(acac)_2$ provided a mixture of **233** and the alternative Michael product **234**, respectively 11% and 30% among other side-products. The experiment highlights the differences in the effect of $Mg(OTf)_2$ and $Ni(acac)_2$ on the reaction and how different metal salts have different affinity toward the two groups in the tethered diacid, thus enhancing C-H acidity either on Site 1 or Site 2.

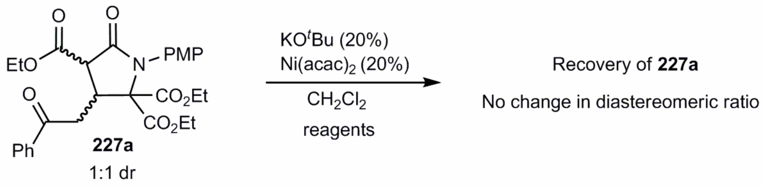
In his work Grossman explained how different conditions generate both thermodynamic or kinetic products and how this influences the diastereoselectivity of the double Michael reaction (see **Scheme 53**, pp. 42). In particular, treating tethered diacids and alkynones with potassium *tert*-butoxide in dichloromethane preferably generated the thermodynamically more stable products. Even treatment of a 1:1 mixture of the kinetic double Michael products with the above mentioned conditions would cause the conversion in to the more thermodynamically stable product.

We have also found that an additional Lewis acid (in addition to the potassium ions from potassium *tert*-butoxide) is important for the efficiency and steroselectivity of the double Michael reaction. The beneficial effect on the conversion is most likely due to deprotonation of the reactive sites being facilitated through metal chelation of the 1,3-dicarbonyl functions (**Scheme 74**). Lewis acid activation of the alkynone is another possibility. The beneficial effect on diastereoselectivity could be due to: (i) inherently greater *trans*-selectivity when additional metal ions are bound to the substrate in the ring-closing step, or (ii) metal promoted equilibration of the *cis*-isomer to the more thermodynamically stable *trans*-isomer.



Scheme 74

We could test whether this latter scenario is operative by subjecting a 1:1 mixture of the product **227a**, obtained using potassium *tert*-butoxide alone, to the reaction conditions in the presence of the metal salt and observing whether the diastereomeric composition is altered (**Scheme 75**). This treatment led to the recovery of **227a** in high yield with no discernible change in diastereomeric composition.



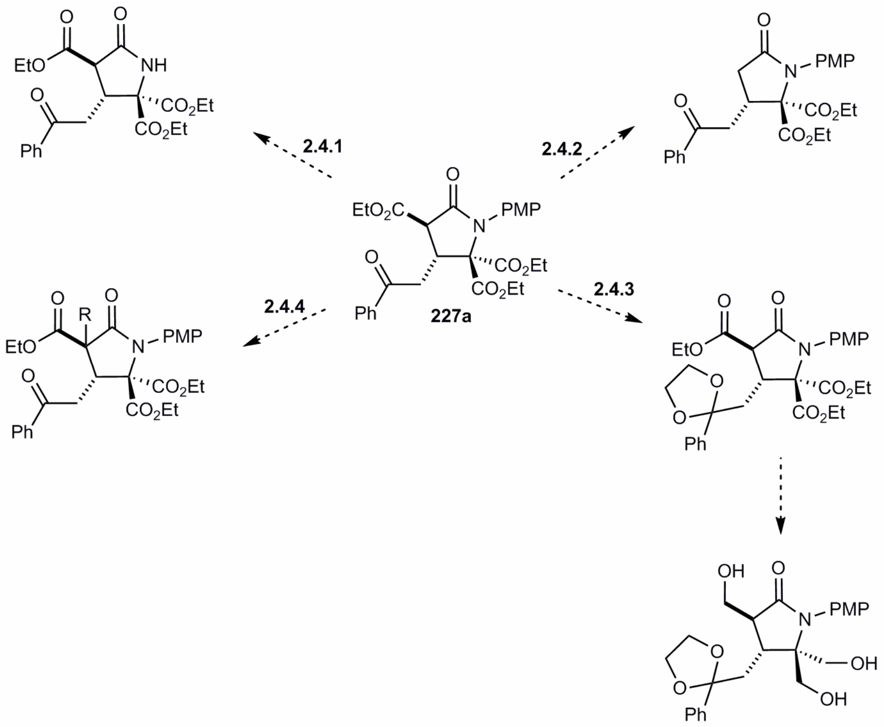
Scheme 75

This result suggests that under these conditions, post-cyclisation epimerisation (which could occur via a deprotonation-reprotonation sequence or a retro-Michael-Michael sequence, as in Grossmann case) does not occur, and therefore diastereoselection observed in the presence of additional metal salt is the result of a kinetically controlled process. However, the manner in which the metal salt imparts diastereoselectivity is not clear at this time.

2.4 Synthetic elaboration of the products

The double Michael reaction that we have presented allows for the formation of two new C-C bonds and up to three new stereogenic centres, resulting in highly functionalised heterocycles. Although the density of functionality that exists in the double Michael product could be considered a virtue, it could also present a challenge for subsequent selective synthetic manipulation, restricting the utility of the process. Therefore, as a completion of our work several experiments were carried out on one of the most representative products to establish what type of transformations were possible. Several of these are sumarised below (**Scheme 76**):

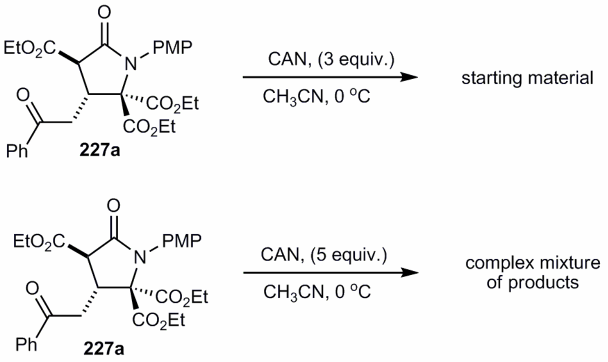
2.4.1 removal of the protecting group,
2.4.2 decarboxylation,
2.4.3 protection of the ketone and eventually ester reduction,
2.4.4 insertion of a functional group in the C(4) position.



Scheme 76

2.4.1 Removal of the protecting group

Our first step toward the derivatisation of compound **227a** was trying to remove the *p*-methoxyphenyl group on the nitrogen. That was attempted through an oxidising process involving the oxidizing agent ceric ammonium nitrate (CAN). Following a known procedure[78] compound **227a** was treated with CAN in acetonitrile at 0 °C (**Scheme 77**). The reaction produced either only starting material (with three equivalents of CAN) or a complex mixture of products (with five equivalents of CAN).

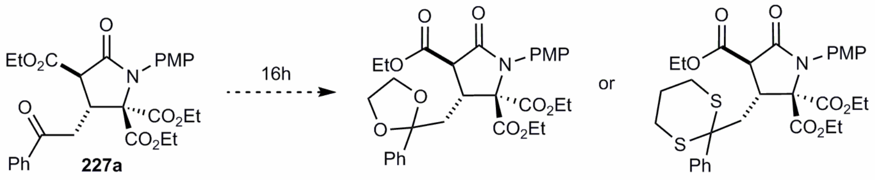


Scheme 77

After these results we proceeded towards other derivatisation methods.

2.4.2 Protection of the ketone and ester reduction

Our attention then focused on the protection of the ketone, which was believed to be easily achieved by treatment of **227a** with ethylene glycole or 1,3-propane dithiol (**Table 6**). Although several conditions were applied, including treatment of **227a** with either ethylene glycol or 1,3-propane and triethyl orthoformate and TsOH, or iodine in tetrahydrofuran, or BF$_3$·OEt$_2$ in dichloromethane, but without success. In most cases only the starting material was recovered.



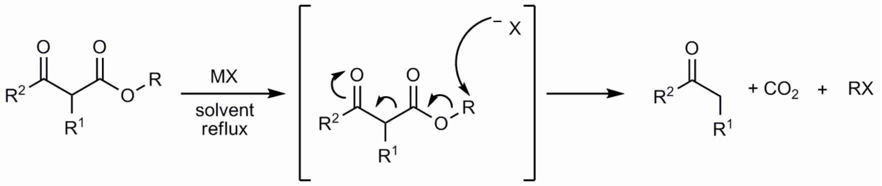
entry	reagents	solvent	T (°C)	results
1	ethyleneglycol, orthoformate, TsOH	-	rt	s. m.
2	ethyleneyglycol, triethylorthoformate, TsOH	CH_2Cl_2	rt	s. m.
2	ethyleneyglycol, TsOH	toluene	rt	s. m.
3	Ethyleneyglycol, I_2	-	rt	s. m.
4	ethyleneyglycol, triethylorthoformate TsOH	toluene	reflux	s. m.
4	1,3-propandithiol, I_2	THF	rt	s. m.
5	1,3-propandithiol, $BF_3{\cdot}OEt_2$	CH_2Cl_2	0-rt	s. m.

s. m. = only starting material recovered

Table 6.

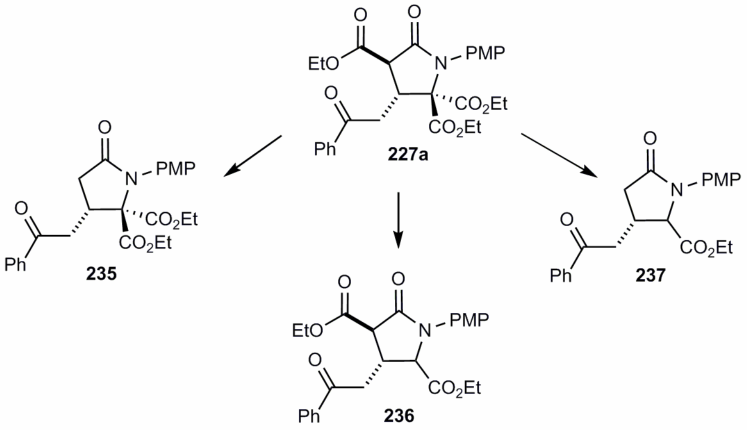
2.4.3 Decarboxylation

Another approach to the product elaboration was to try to selectively remove one of the ester groups present in the molecule **227a**. The ester group, in order to be removed, must contain an electron-withdrawing group in the β-position (in a Krapcho-type decarboxylation).[79] The reaction is then usually heated to reflux and catalysed by metal salts (**Scheme 78**).



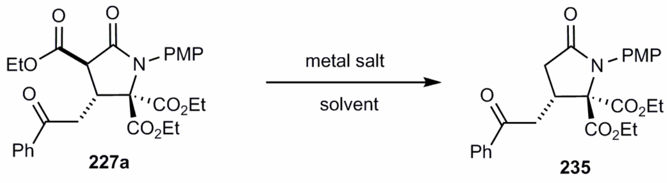
Scheme 78

Compound **227a** contains two ester groups which could be both decarboxylated having each a withdrawing group in the β-position (amide and an ester). Therefore treatment of compound **227a** with the Krapcho conditions could give the three different decarboxylated products: **235**, **236** and **237** or even a mixture of them (**Scheme 79**).



Scheme 79

A short screening of conditions was carried out, in which a solution of compound **227a** in dimethylformamide or dimethylsulfoxide was heated at different temperatures, with or without the aid of a metal salt (**Table 7**). In most cases, for example, the use of metal salts (LiBr or NaCl) with DMF or DMSO or the use of DMSO by itself generates a mixture of **235** and a complex mixture of products (entry 1, 3, 4, 5, 6, 7). In some cases when the temperature was raised the formation of a mixture of products could be observed without any trace of products **235** (**entry 2, entry 5**). Finally, by heating a DMF solution of **227a** to 110 °C for three days without metal additives the desired product **235** was obtained in 60% yield.

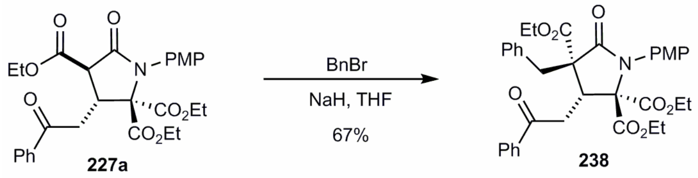


entry	solvent	T °C	metal salt	time	yield %
1	DMF	100	LiBr	16h	mixture
2	DMF	130	LiBr	16h	mixture
3	DMF	115	NaCl	16h	mixture
4	DMF	reflux	NaCl	16h	mixture
5	DMSO/H_2O (1:1)	reflux	NaCl	1h	mixture
6	DMSO/H_2O (5:1)	130	-	16h	27
7	DMSO/H_2O (5:1)	130	-	2d	29
8	DMF	110	-	3d	60

Table 7

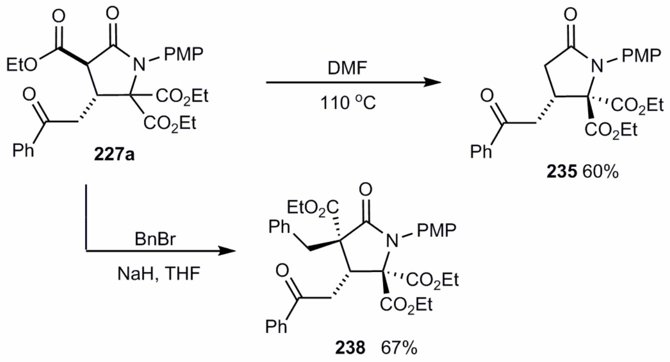
2.4.4 Insertion of a functional group in the C(4) position

Finally, insertion of a substituent, in particular a benzyl group, in the C(4) position of double Michael product **227a** was also achieved by treatment of **227a** with sodium hydride and benzylbromide, providing the alkylated product **236** in 67% yield (**Scheme 80**).



Scheme 80

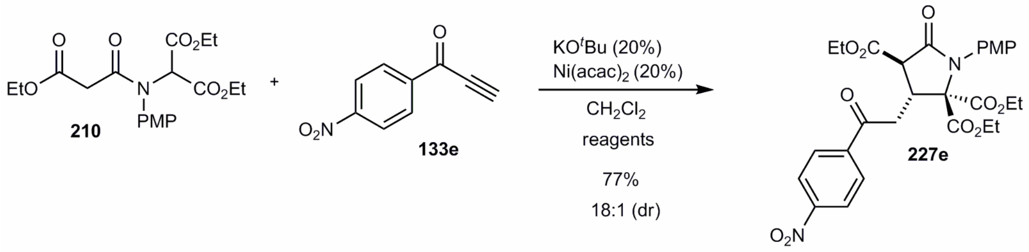
To summarise our results, the double Michael product **227a** was successfully derivatised in two different products of which one was the product of monodecarboxylaction **235** and the other was the benzylated product **238** (**Scheme 81**).


EtO
N
PMP
CO2Et
CO2Et
Ph
227a
DMF
110 °C
235 60%
BnBr
NaH, THF
EtO2C
238 67%

Scheme 81

2.5 Conclusions

In summary, we have developed a double Michael addition route to highly functionalised pyroglutamic acid derivatives that utilises amide-tethered carbon diacids and aromatic alkynones as substrates. The reaction proceeds with good levels of *trans*-diastereoselectivity, provided that substoichiometric quantities of $Mg(OTf)_2$ or $Ni(acac)_2$ are employed as Lewis acids (**Table 3**, **4**, pp.56, 57). In particular the best yield and best diastereoselectivity was achieved when tethered diacid **210** and the nitro substituted alkynone **133e** were treated with substoichiometric amount of $Ni(acac)_2$ and potassium *tert*-butoxide, producing the desired double Michael product **227e** in 77% yield and >19:1 dr (**Scheme 82**).



Scheme 82

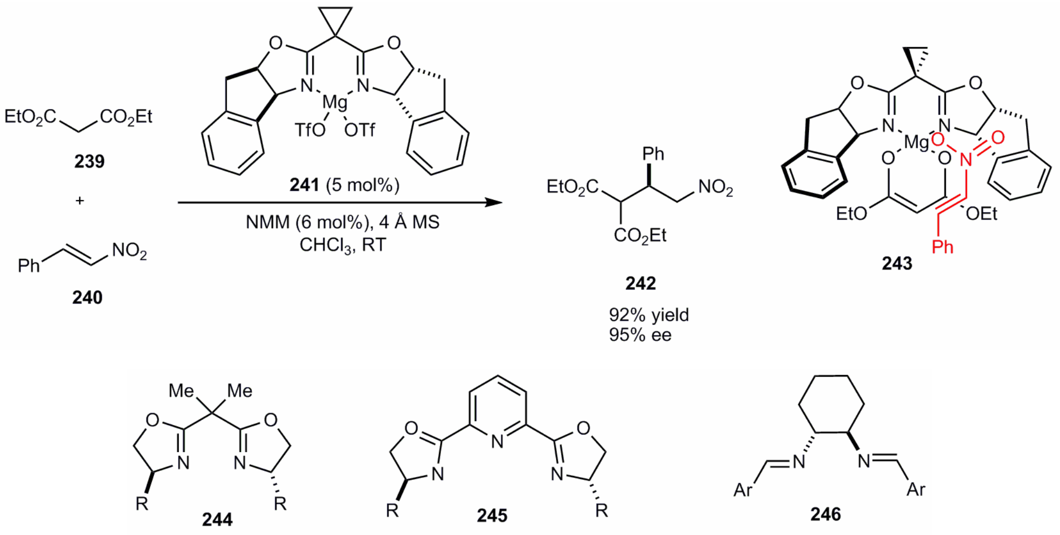
The double Michael product **227a** (**Scheme 81**) was also successfully derivatised to synthetically useful products **235** and **236**, by decarboxylation and benzyl insertion as previously described. Furthermore, we were able to analyse the crystals of product **227a** with x-ray crystallography and therefore to prove that the major diastereomer possesses *trans* configuration.

Although we achieved some of the targets that we set up at the outset of this work, there are limitations to this methodology. For example, only two of all the selected starting materials (**210** and **211**, **Scheme 63**, pp. 48) undergo double Michael reaction when treated with an alkynone in the presence of a base. When the protecting group was changed from PMP to PMB or a benzyl group the reaction did not occur **(Scheme 68**, pp. 52) and if a cyano group is placed in the substrate in the place of an ester group the result is either a complex mixture of products or a byproduct generated by an intramolecular reaction of the diacid (**Scheme 60** and **61**, pp. 47). Moreover the selected starting materials that undergo double Michael reaction seem to be mainly active toward aryl alkynones. The aliphatic methyl alkynone **133h** that was targeted only gave traces of product (**Table 3** and **4** pp. 56, 57).

Finally in the derivatisation of the product we failed to remove the protecting group (PMP) (**Scheme 77**, pp. 60). We were also not able to separate the enantiomeric peaks of the double Michael product with HPLC chiral columns, ruling out the possibility of conducting asymmetric reactions at this time.

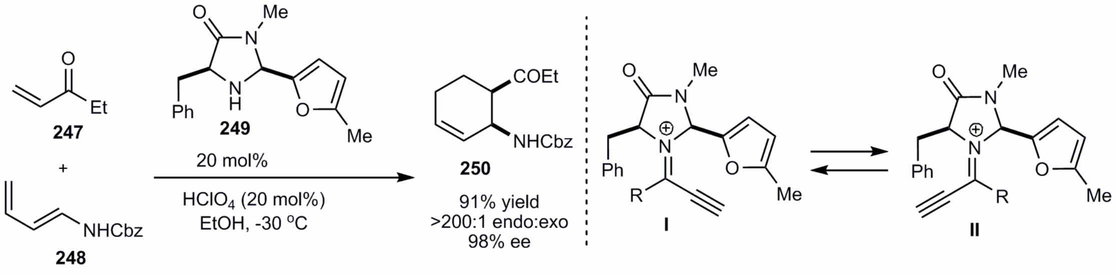
2.6 Further work

One of the future targets is the development of enantioselective variants of the double Michael reactions. Asymmetric induction could arise in an enantioselective intermolecular or intramolecular Michael addition of chiral metal-bound enolate. Previous literature for this mode of induction comes in the form of magnesium triflate-bis(oxazoline) **241** catalysed enantioselective Michael addition of 1,3-dicarbonyl compounds such as **239** to nitroalkenes such as **240** described by Barnes and co-workers (**Scheme 83**).[76] Enantioinduction is proposed to arise through the approach of a chiral metal bound enolate to nitroalkene **240** according to the stereochemical model **243.** Other chiral ligands for possible evaluation are **244**, **245**, and **246** shown below



Scheme 83

An alternative approach to achieve asymmetric induction might be through activation of the alkynone using iminium catalysis. In recent years, numerous examples of asymmetric reactions using imidazolidinone catalysts and α,β-unsaturated aldehydes as electrophiles have been reported.[80] One report that may have relevance to our work is in the selective activation of α,β-unsaturated ketones using iminium catalyst, developed by MacMillan and co-workers.[81] For example ethyl vinyl ketone **247** undergoes a highly enantioselective Diels-Alder reaction with the diene **248** under the influence of imidazolidinone **249** (**Scheme 84**).[81] Hopefully, in our case, the iminium catalysis would be applicable to the selective activation of aliphatic alkynones and this activation will be sufficient to promote reaction with a diacid with or without an additional base.

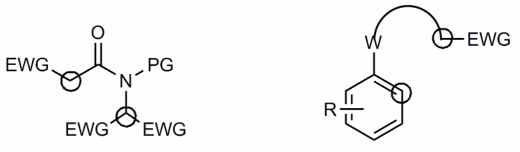


Scheme 84

3. DOMINO MICHAEL ADDITIONS/FRIEDEL-CRAFTS-TYPE ALKYLATIONS

3.1 Proposed mechanism

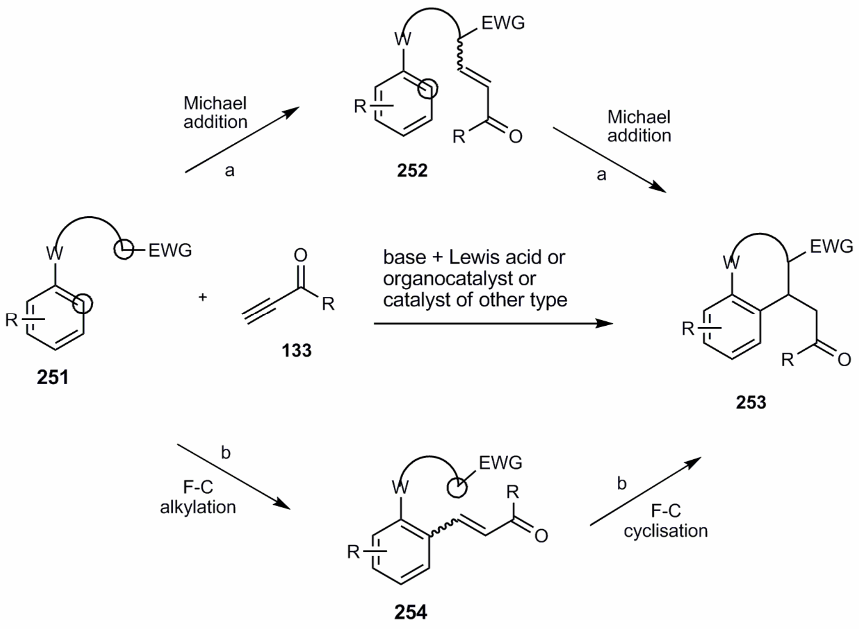
In the previous chapter we have extensively reported about double Michael reactions, their importance in organic synthesis and their versatility, and we have shown a series of double conjugate additions that we carried out using amide-tethered diacids and a range of aromatic alkynones (CHAPTER II, pp 41). Subsequently, we decided to carry out further experiments in a similar field and a new idea arose by comparing amide-tethered diacids **132** (**Figure 6**) that we targeted for our double Michael additions with arenes **251**.



132 **251**

Figure 6

Both compounds possess two nucleophilic centres connected by a tether and since diacids **132** undergo a domino Michael-Michael reaction when treated with alkynones with a suitable base and a Lewis acid, we thought that arenes **251** could undergo a domino Michael-Friedel-Crafts-type reaction when treated similarly. It was expected that upon treatment with alkynones **133** and a base the tethered dinucleophile **251** would first undergo a Michael addition giving the intermediate **252** as a mixture of *E*/*Z* isomers and that ideally intermediate **252** would be reactive enough to subsequently undergo a nucleophilic attack from the tethered arene moiety with a Friedel-Crafts (F-C) alkylation (path a), affording a range of cyclised products **253**. The order of events could of course be different, with the F-C alkylation happening first and the Michael addition afterwards (path b) (**Scheme 85**).

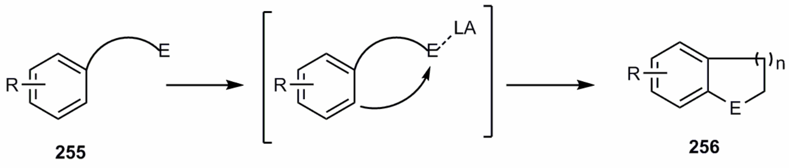


Scheme 85

Due to their importance in our strategy and in general as a class of powerful reactions for the synthesis of complex cyclic compounds, an overview on Friedel-Crafts cyclisatons is presented in the next section.

3.2 Ring closing Friedel-Crafts-type alkylation of arenes

The intramolecular alkylation of aromatics has become a matter of increasing importance since it gives access to synthetically challenging polycyclic fused aromatic compounds, which are important for agrochemical and pharmaceutical purposes.[82] Of particular interest are catalytic alkylation processes that involve the use of milder experimental conditions and unactivated C_{aryl}-H bonds rather than C-X (X = halide) analogues because they would increase the atom economy of the reactions. In general, intramolecular aromatic C-H alkylations are triggered by a catalyst (a Lewis acid or an organocatalyst) that activates the electrophilic species linked to the arene **255**, thus promoting cyclisation to form polycyclic compounds **256** (**Scheme 86**).



Scheme 86

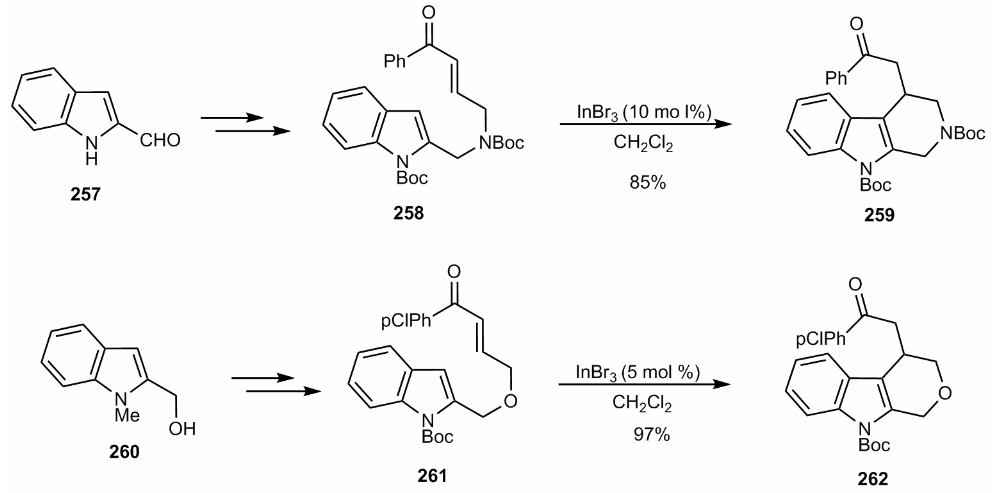
This group of reactions can be further divided into different categories depending on the electrophilic framework of the substrates. Here we report several reaction classes that more closely concern our project:

3.2.1 Michael-type Friedel-Crafts alkylations,
3.2.2 Pictet-Spengler condensation,
3.2.3 Cyclisation of aryl alkynes,
3.2.4 Allylic reactions.

3.2.1 Michael-type Friedel-Crafts alkylations

Among all the Friedel-Crafts type alkylations, the conjugate addition of electron-rich aromatic systems to α,β-unsaturated carbonyl compounds is particularly interesting for our work. These types of Michael additions have received much attention over the last decade as a straightforward synthetic shortcut to the chemo- and regioselective synthesis of functionalised aromatic systems, and what makes these reactions so attractive is the mildness of the reaction conditions and the large number of known strategies to achieve these cyclisations.[82]

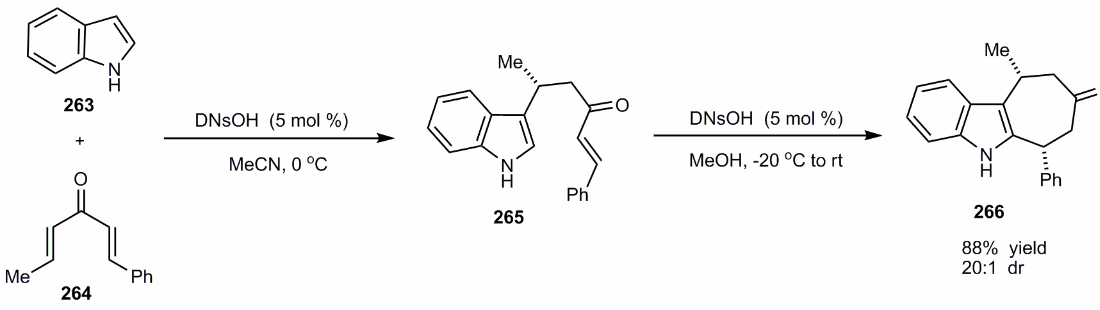
An example of the aforementioned strategy is the catalytic Friedel-Crafts alkylation of indoles with electrophilic carbon synthons in the presence of low loadings of anhydrous indium(III) bromide developed by Umani-Ronchi and co-workers for the synthesis of 4-substituted tetrahydro-β-carbolines **259** (**THBC**) and tetrahydropyrano[3,4-b]indoles **261** (**Scheme 87**).[83]



Scheme 87

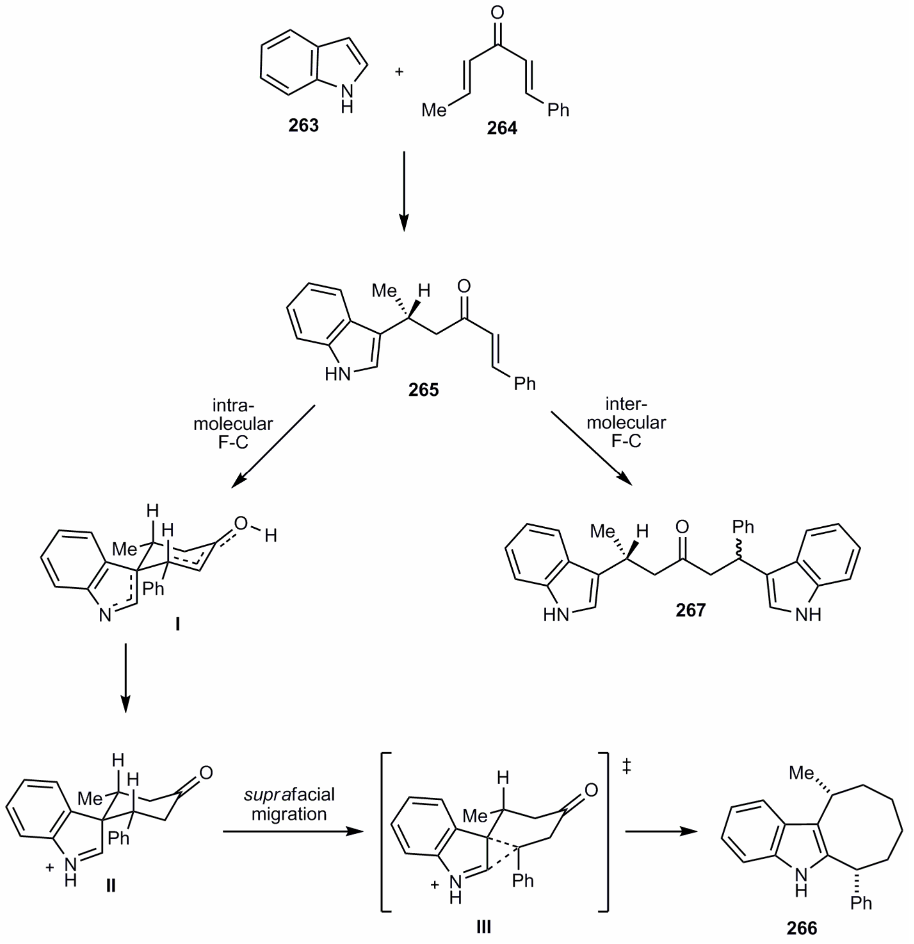
The synthesis of the requisite indolyl enone **258** was accomplished from readily available indole-2 carbaldehyde (**257**). With the starting material in hand several reactions conditions were screened, and it was found that in the presence of 10% indium(III) bromide, the enone **258** underwent cyclisation affording the protected carboline **259** in high yield (85%). Similarly, the indolyl enone **261** was obtained from the corresponding N-Me-indolyl alcohol **260** and initial attempts for the intramolecular cyclisation were performed with 10 mol % indium(III) bromide affording the product **262** in 75% yield. However it was found that with a lower catalytic loading (5 mol %) the reaction afforded the product **262** in 97% yield and in similar time.[83] The results were partially rationalised with the occurrence of a concomitant intermolecular Michael addition and undesired degradation processes of the α,β-unsaturated indolyl ketone **261** observed with higher catalyst loading. Generally, intramolecular F-C cycloalkylations often suffer from moderate yields and a lack of regioselectivity and thus significant quantities of Lewis acid are normally required. On the contrary, indium(III) bromide was able to promote the aforementioned reactions under mild experimental conditions (rt) and in catalytic amount (5-10 mol %).

Very unusual is the double F-C alkylation of divinyl ketones reported by Carbery and co-workers,[84] in which a divinyl ketone (a double electrophile usually exploited in double conjugate additions or Nazarov reactions), undergoes a tandem nucleophilic attack by indole species. Thus, when indole **263** was treated with the non-symmetrical divinyl ketone **264** and 2,4-dinitrobenzenesulfonic acid (DNsOH) in acetonitrile at 0 °C it underwent a first F-C alkylation producing monoadduct **265** (**Scheme 88**). This was followed by a solvent swap, which led to cyclisation of the monoadduct **265**, affording the fused tricyclic indole **266** in good yield (88%) and good diasteroselectivity (20:1).



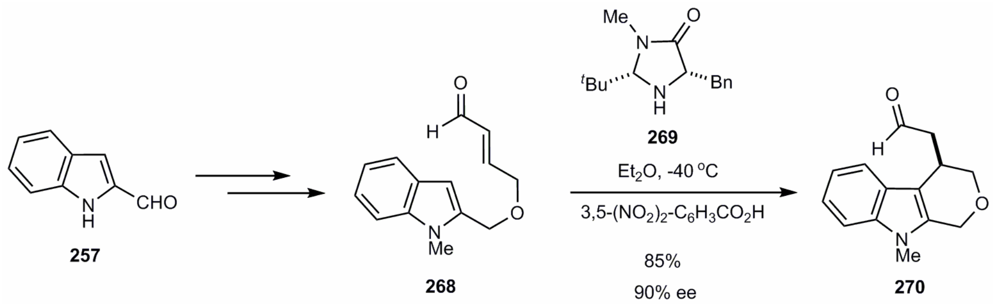
Scheme 88

It was speculated that monoadduct **265**, formed after the first F-C alkylation, would both react with a second divinyl ketone to form the bis-product **267** in small quantity and undergo a second intramolecular F-C alkylation giving the spiroindoleninium intermediate **II** (**Scheme 89**). The *syn* relationship between the methyl and phenyl groups is established in the cyclisation process that occurs *via* a chair transition state (**I**). The final tricyclic indole product **266** is then obtained after the suprafacial migration of benzylic group (transition state **III**) followed by rearomatisation. The *syn* arrangement of the methyl and phenyl group in the product was preserved due to the suprafacial migration occurring with retention of configuration. The consecutive addition of two molecules of indoles to the divinyl ketone was minimised by keeping the reaction temperature below 40 °C because higher temperatures would favour the formation of the bis-products.



Scheme 89

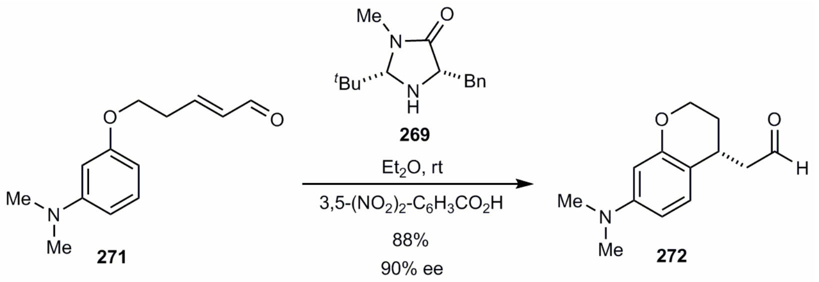
A recent example of Michael-type Friedel-Crafts cyclisation was reported by Xiao and co-workers in which the alkylation of indolyl α,β-unsaturated adehyde **268** is involved (**Scheme 90**).[85] This organocatalytic methodology gives access to the synthesis of tetrahydropyrano[3,4-b]indoles (THPIs) and THBCs with the aid of a MacMillan catalyst.[86] This example is important since organocatalytic intramolecular alkylations of indoles are not so common in the literature.



Scheme 90

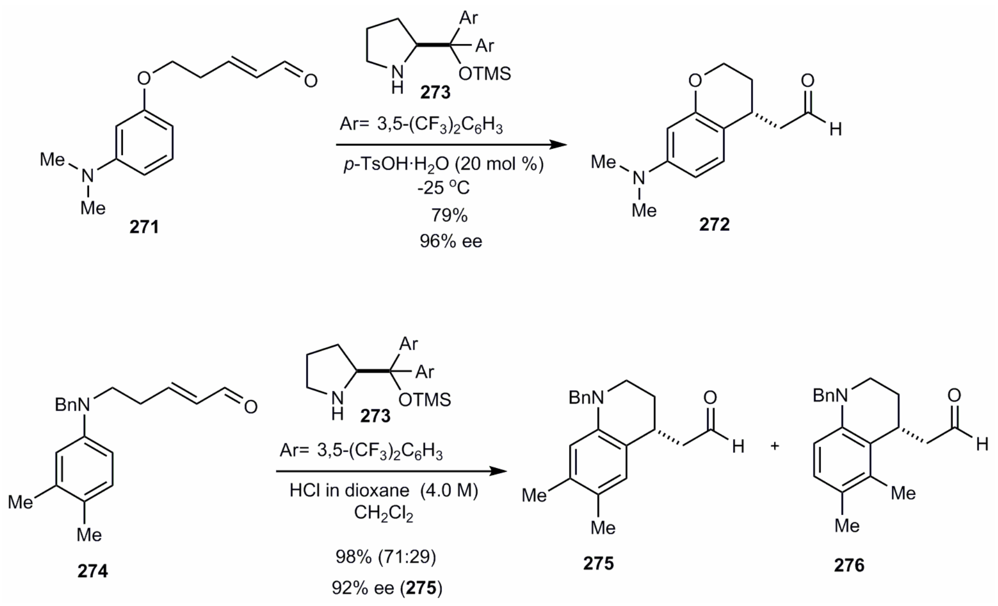
The starting material **268** was obtained in few steps from the corresponding and commercially available indole-2 carbaldehyde (**257**). After the screening of several reaction conditions it was found that MacMillan's second-generation catalyst **269** along with 3,5-dinitrobenzoic acid as additive, gave the desired product **270** in good yield (85%) and high enantioselectivity (90%).

In order to prove its generality, this methodology was also applied to a similar substrate, the phenoxyl-substituted α,β-unsaturated adehyde **271** (**Scheme 91**). After 25h the corresponding chroman-4-yl acetaldehyde (**272**) was obtained as expected in excellent enantiomeric excess (90%) and good yield (88%).[85]



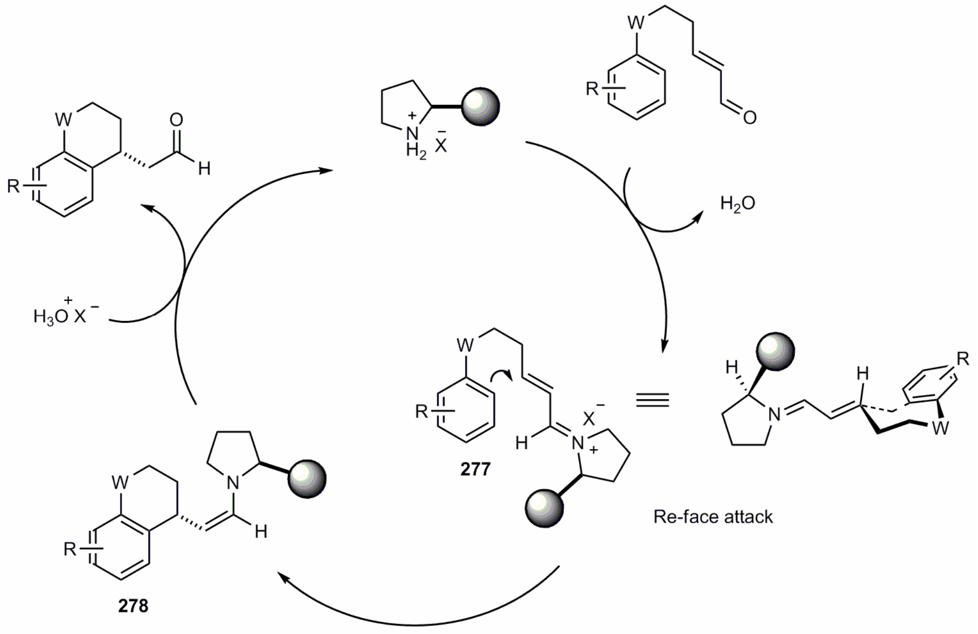
Scheme 91

It was later found that treatment of aryl aldehyde **271** with catalyst **273** instead of the MacMillan catalyst **269** could improve the enantioselectivity (96%) (**Scheme 92**).[87] Moreover it was possible to expand the hydroarylation not only to phenol-derived enals (for the synthesis of chromans) but also to aniline-derived enals (for the synthesis of tetrahydroquinolines). The aniline aldehyde **274**, upon treatment with catalyst **273** and hydrochloridric acid (in dioxane 4.0 M) in dichloromethane, afforded the isomeric mixture of tetrahydroquinolines **275** (71%yield, 92% ee) and **276** (29%).[87]



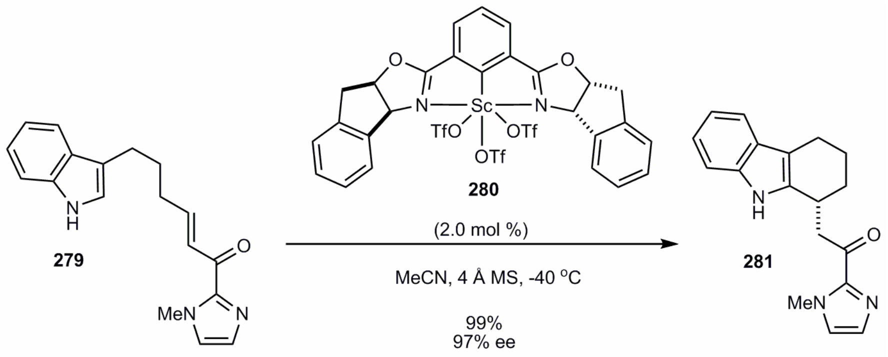
Scheme 92

In the proposed mechanism the α,β-unsaturated aldehyde reacts with the pyrrolidine-based catalyst to form the iminium ion **277**. Subsequently, the electron-rich benzene framework attacks from the *re* face of the activated alkene (since the *si* face is shielded by the bulky group of the catalyst) thus generating the bicyclic system **278** (**Scheme 93**). Hydrolysis of the enamine **278** affords the desired product and regenerates the catalyst.



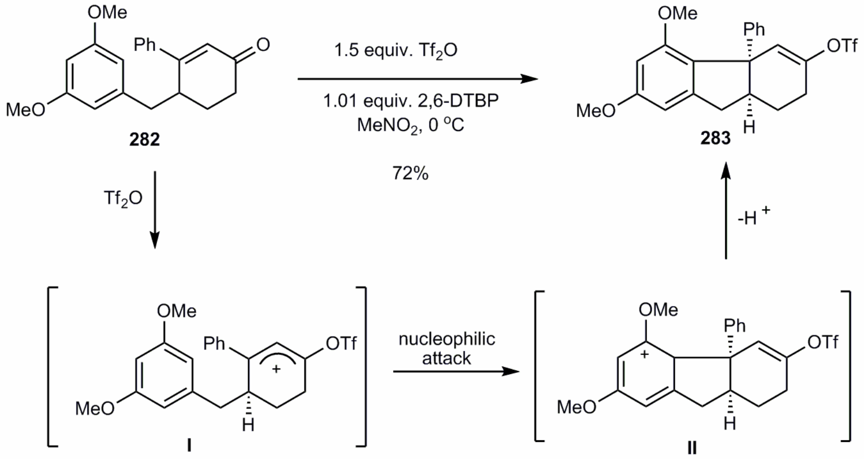
Scheme 93

Chiral Lewis acids have also been exploited in enantioselective intramolecular F-C alkylations. Sc(OTf)$_3$-Pybox complex **280**, for example, employed by Evans and co-workers[88] mostly for intermolecular F-C alkylation, was also effective in the cyclisation of the arene ketone **279** affording the tetrahydrocarbazole **281** in excellent yield (99%) and high enantioselectivity (97%) (**Scheme 94**).



Scheme 94

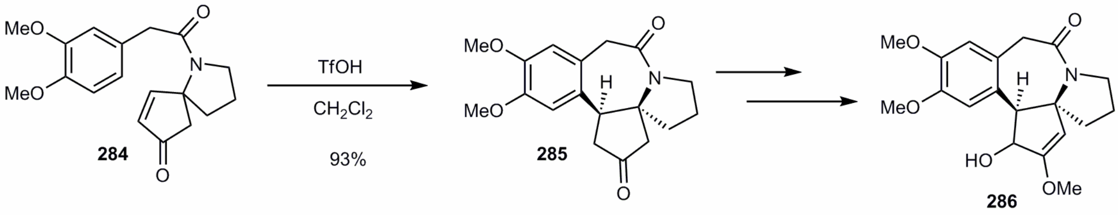
Similar to Michael-type F-C-cyclisations are the F-C-triflations,[89] where enones are activated by triflic anhydride toward reactions with an electron-rich arene with the concomitant formation of an enol triflate. In the reaction reported below (**Scheme 95**), the nucleophilic arene **282** underwent F-C alkylation upon treatment with triflic anhydride and 2,6-di-*tert*-butyl pyridine in MeNO$_2$, affording the cyclised product **283** in good yield (72%).



Scheme 95

Polar solvents, such as MeNO$_2$, were thought to stabilise the allylic cation **I**, allowing it to undergo ring closure, leading toward intermediate **II**, rather then loss of a proton. The reaction seemed to work best with a sterically demanding, non-nucleophilic base such as 2,6–di-*tert*-butyl pyridine.

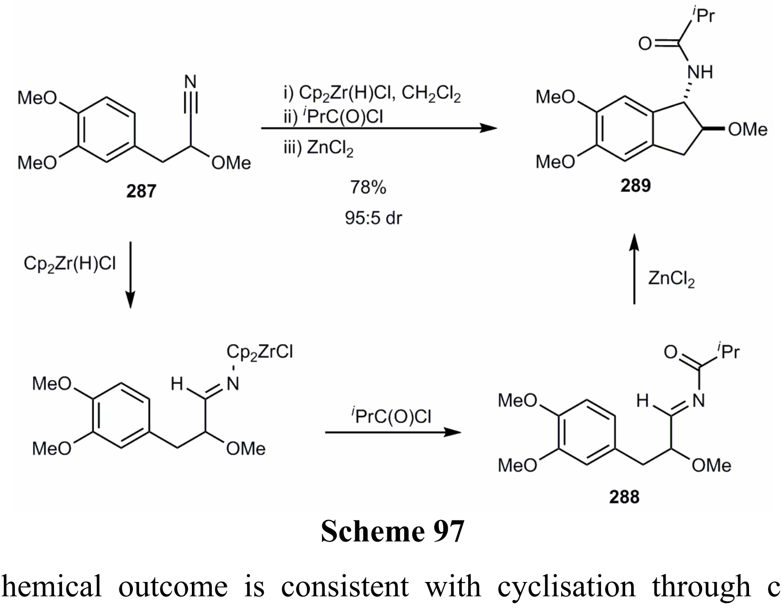
A further example of F-C-cyclisation employing triflic acid (TfOH) was reported by Li and Wang in their effort toward the synthesis of cephalotaxine and its derivatives.[90] In the reaction reported below (**Scheme 96**) spiro-cyclopentenone precursor **284** underwent Friedel-Crafts-type enone cyclisation upon treatment with triflic acid (2.5 equiv.), as a slurry mixture in dichloromethane at room temperature, giving the desired product **284** in good yield (93%).



Scheme 96

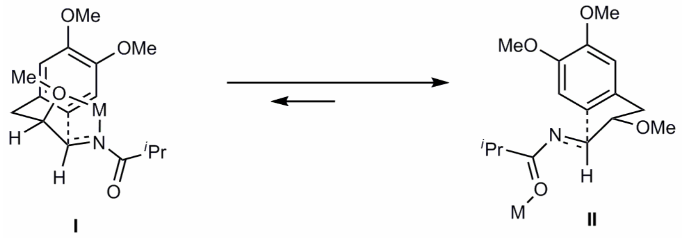
Product **285** could then be transformed into the cephalotaxine analogue **286** by a known procedure.[91]

Another noteworthy reaction similar to Michael- F-C alkylations is the annulation of aryl-substituted α-alkoxy acylimines performed with mild Lewis acid.[92] The one-pot reaction reported below (**Scheme 97**) included hydrozirconation and acylation[93] of cyanohydrine ether **287** that led to the *in situ* formation of acylamine **288**, which then underwent F-C cyclisation upon treatment with $ZnCl_2$. The desired product β-alcoxy-amide **289** was obtained in 78% yield and excellent diastereoselectivity.



Scheme 97

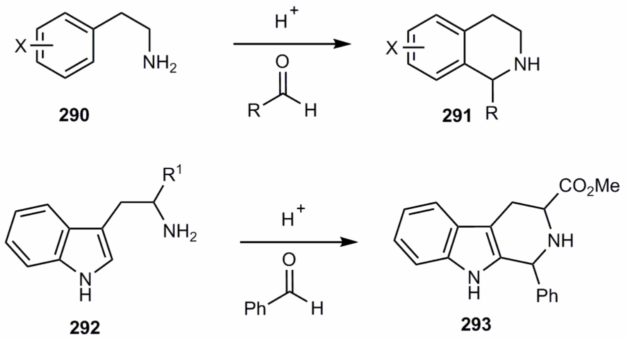
The stereochemical outcome is consistent with cyclisation through conformer **II** rather than chelated conformer **I** (**Scheme 98**).



Scheme 98

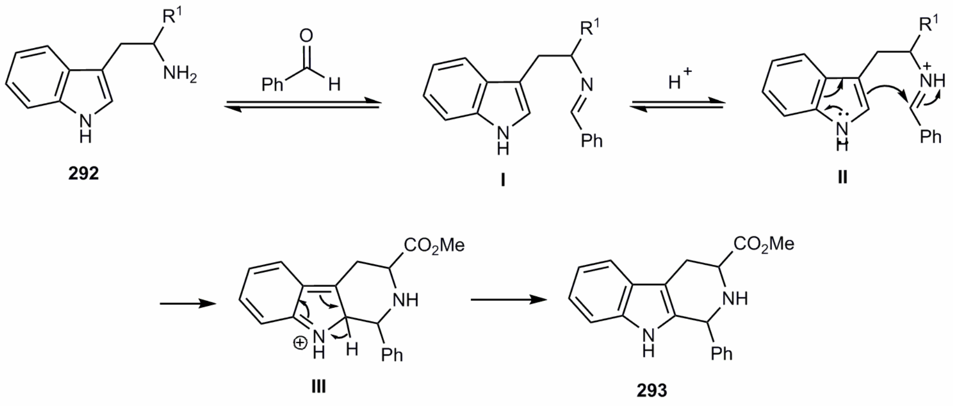
3.2.2 Pictet-Spengler condensation

Another interesting class of F-C-type alkylation are the acid-promoted annulation of amino arenes in the presence of carbonyl compounds, better known as the Pictet-Spengler condensation.[94] This process, known for a very long time, was first discovered by Amè Pictet and Theodor Spengler in 1911[95] and involves the condensation of *β*-arylethylamine **290** with an aldehyde or its synthetic equivalent (**Scheme 99**). Therefore, this condensation is a convenient method for the synthesis of tetrahydroisoquinoline **291** derivatives or related heterocyclic systems as substitutedtetrahydro-β-carbolines **293** through the replacement of benzene rings with indole derivatives.



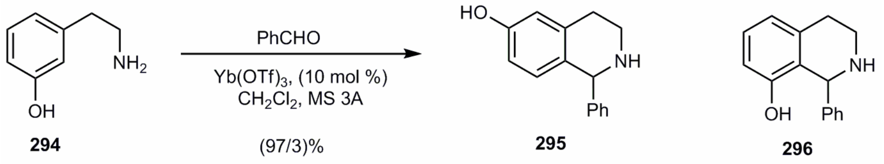
Scheme 99

The mechanism starts with the reaction of amine **292** with benzaldehyde and formation of the imine **I**, which by protonation forms the iminium ion **II** (**Scheme 100**). Subsequently, electrophilic substitution at the 2-position gives the cyclised intermediate **III**. After deprotonation, the desired product **293** is formed. The electrophilicity of the imine is thought to be the driving force of the cyclisation.



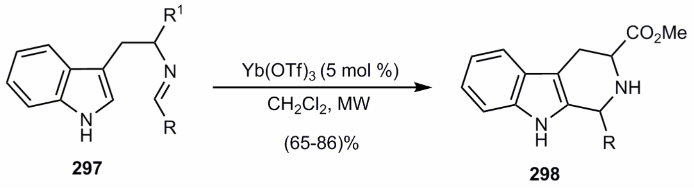
Scheme 100

The reaction commonly involves the use of Brønsted acid for the activation step. However, there are examples in the literature where Lewis acids and even organocatalysts are used in their place. Kobayashi and co-workers,[96] for example, carried out a screening of Lewis acids for the Pictet-Spengler condensation of *m*-tyramine (**294**) and benzaldehyde and they found that Yb(OTf)$_3$ (with a 10 mol % loading) was a good catalyst giving the cyclised product **295** in 98% yield with good regioselectivity (the regioisomer **296** was obtained in only 3% yield) (**Scheme 101**).



Scheme 101

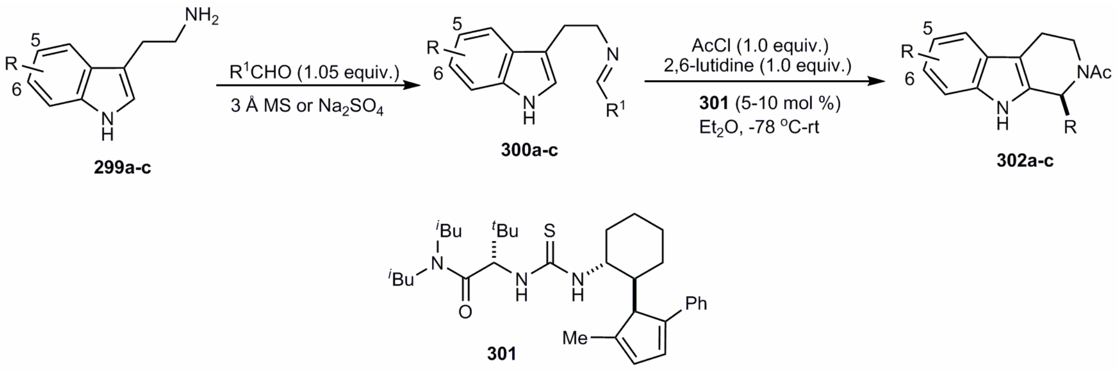
Previous to this work, a parallel screening approach for the discovery of effective Lewis acid catalysts for the Pictet-Spengler condensation was reported.[97] This method was focused on the synthesis of substituted tetrahydro-β-carbolines **298** and the alkylation occurred on the preformed starting compounds **297** by activation of the imine moiety (**Scheme 102**).



Scheme 102

Many Lewis acids were found to be effective catalysts, however, Yb(OTf)$_3$ gave the best results. In fact with 5 mol % of Yb(OTf)$_3$ and 30 min of microwave irradiation, high conversions were obtained with both aliphatic and aromatic imines. The above conditions were equally applicable to a one-pot version in which the imine was formed *in situ* and these consistently gave even higher yields and cleaner products mixtures.[98]

Asymmetric versions of the Pictet-Spengler reaction are well known in the literature. Particularly well known is the reaction developed by Jacobsen and co-workers,[99] catalysed by thiourea derivatives such as **301**. The reaction provides a range of substituted tetrahydro-*β*-carbolines **302a-c** starting from tryptamine **299a-c** (**Scheme 103**).

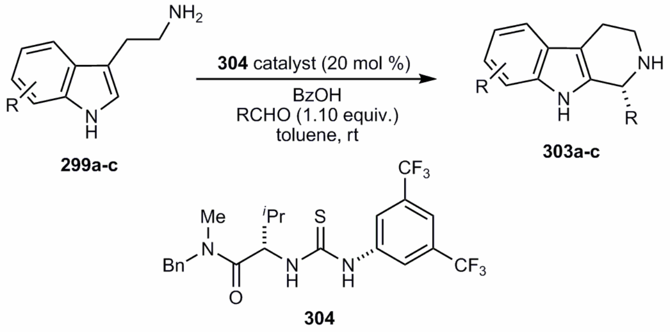


entry	R	R^1	T(°C)	yield(%) 301	ee(%)
1	H	$CH_2CH(CH_3)_2$	-60	75	93
2	5-MeO	$CH(CH_2CH_3)_2$	-40	81	93
3	6-MeO	$CH(CH_2CH_3)_2$	-50	76	86

Scheme 103

The two-step procedure consisted of condensation of tryptamine **299a-c** with an aldehyde, generating the imine adducts **300a-c** which are employed in the next step without further purification. The imines **300a-c** were then cyclised to give the *β*-carbolines products **302a-c** in good yield (75-81)% over two steps and high enantiomeric excess (86-93)%. Although variation of the indole moiety was tolerated (**entries 2** and **3**), substrates derived from aromatic aldehydes or trimethylacetaldehyde displayed lower reactivity, which is a limitation to this elegant methodology.

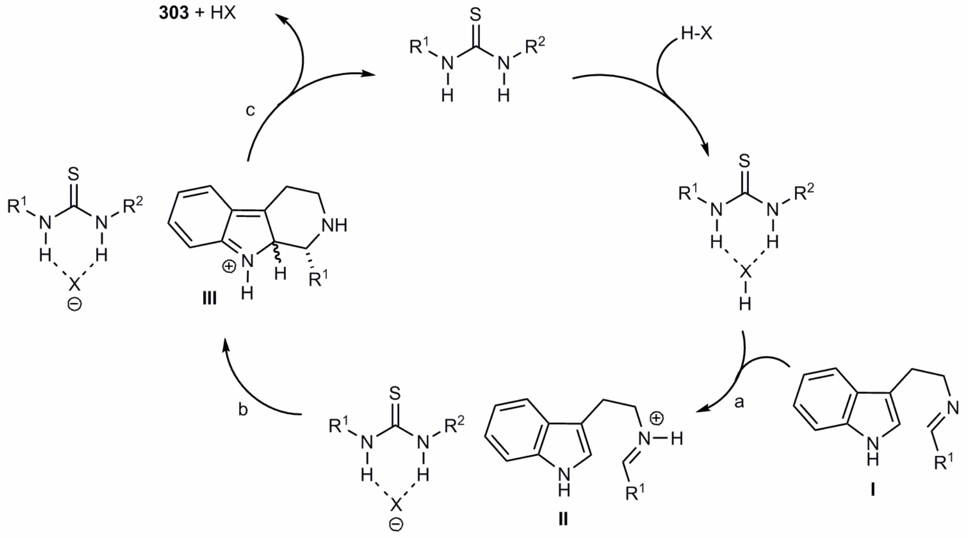
An improvement of this methodology was reported in a recent work,[100] where a one-pot Pictet-Spengler reaction co-catalysed by the thiourea catalyst **304** and benzoic acid is described (**Scheme 104**). The reaction proceeds smoothly giving the unprotected tetrahydro-β-carbolines **303a-c** in high yield (78-90)% and high enantiomeric excess (94-99)% either with aliphatic or aromatic aldehydes (**entries 1-3**).



entry	**R**	**BzOH**(mol %)	**t**(h)	**yield**(%) **302**	**ee**(%)
1	*p*-ClC_6H_4	20	66	78	94
2	^{i}Pr	0	88	90	94
3	*o*-BrC_6H_4	40	50	82	99

Scheme 104

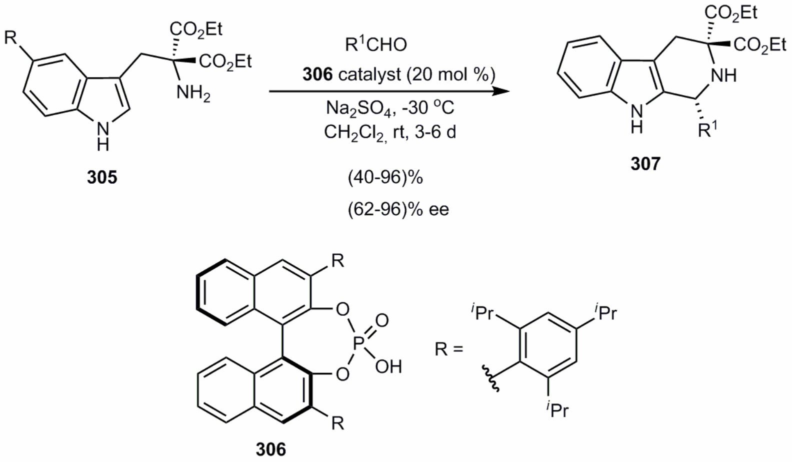
The suggested mechanism for the catalytic cycle reported below includes: a) protonation of the imine, b) cyclisation of the highly reactive iminium and c) re-aromatisation of the cyclised product (**Scheme 105**).[100]



Scheme 105

The protonation of the imine **I** is induced by the thiourea catalyst associated *via* H-bonding to the conjugate base of a weak Brønsted acid additive (such as BzOH), thus generating the reactive iminium ion **II**, which then undergoes cyclisation. Finally, the cyclised product **III** undergoes rearomatisation, which affords the product **303** and regenerates the acid co-catalyst HX.

Asymmetric Pictet-Spengler reactions can also occur with the aid of chiral Brønsted acid catalysts such as that reported by List and co-workers,[101] where geminally disubstituted tryptamine **305** and aldehydes are treated with chiral binaphtol-derived phosphoric acid **306** (**Scheme 106**).

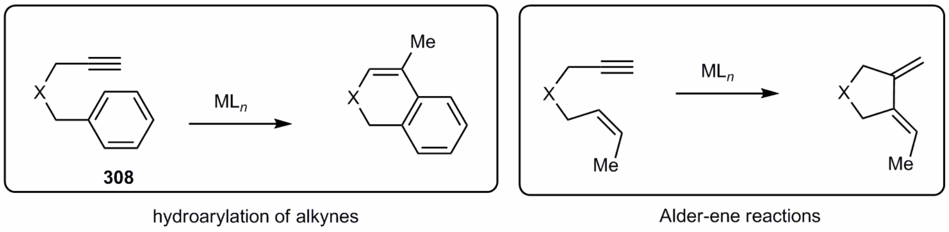


Scheme 106

This one-pot procedure, which led to the synthesis of enantioenriched tetrahydro-*β*-carbolines, tolerates a variety of different aldehydes both aliphatic and aromatic and proceedes from average to good yield (40-96)% and from average to high enatiomeric excess (62-96)%.

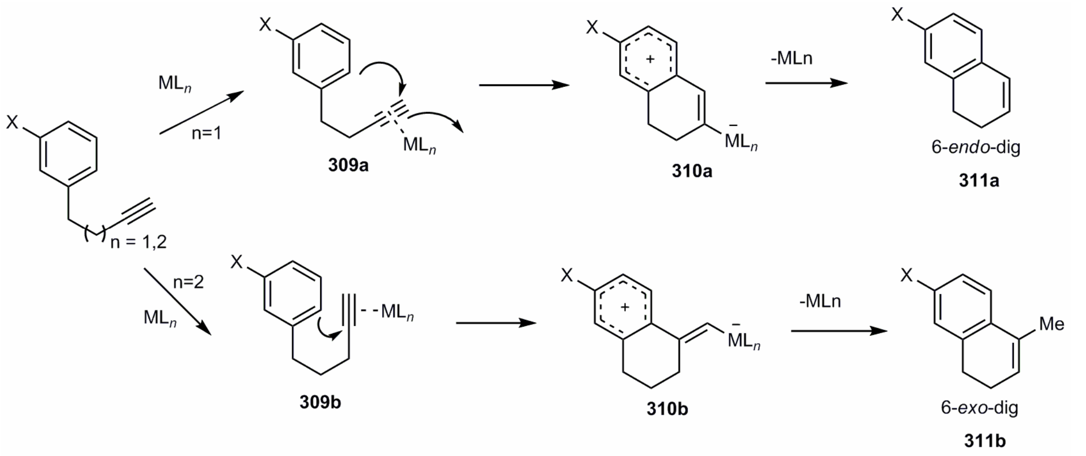
3.2.3 Cyclisation of aryl alkynes

This process, also called F-C alkenylation of arenes, or hydroarylation of alkynes involves the reaction between the alkyne and the aromatic group of a ω-aryl-1-alkyne **308** (**Scheme 107**). It was first described by Murai *et al*[82,102] and is considered an extension to the intramolecular rearrangement of 1,n-enynes, also called Alder-ene reaction.



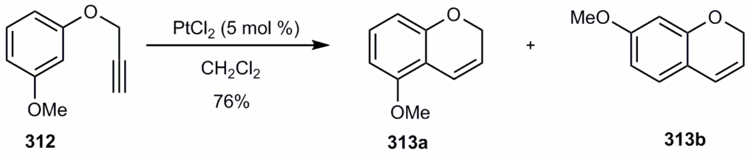
Scheme 107

The F-C alkenylation of arenes is believed to be triggered by the interaction between a Lewis acid catalyst and the C-C triple bond of the substrate **309a/310b**. This interaction leads to the Wheland-type intermediates **310a/311b**, which can produce either the 6-*endo*-dig product **311a** or the 6-*exo*-dig product **311**b. In accordance with the mechanism shown below, electron-donating substituents should facilitate the hydroarylation process (**Scheme 108**). The metal salts involved in the process are usually late transition metals such as Pt^{II} and Ru^{II}, Ga^{II}, In^{II} and Au^{I} which have high electron affinity toward π-systems.[82]



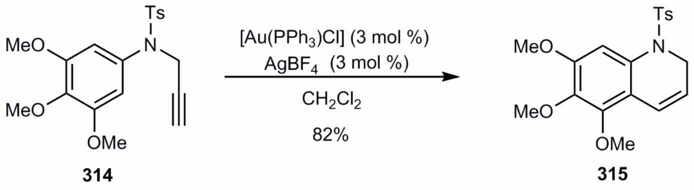
Scheme 108

Echavarren and co-workers[103] found that the cyclisation of aryl alkynes can be catalysed by gold and platinum complexes and they reported that resorcinol **312**, upon treatment with a catalytic amount of $PtCl_2$ (5 mol %), underwent a 6-*endo-dig* cyclisation giving a (1:2) mixture of the two regioisomers **313a** and **313b** in 76% combined yield (**Scheme 109**).



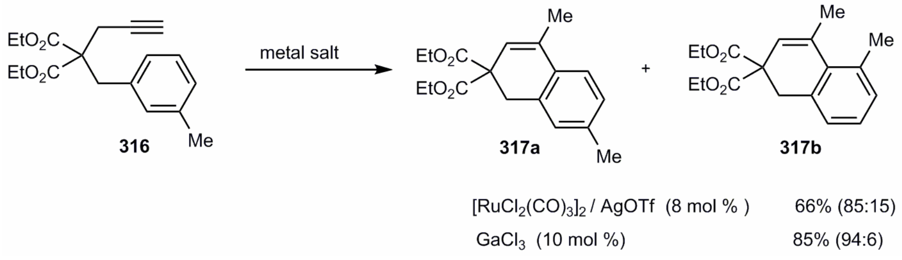
Scheme 109

Arene **314** upon treatment with a gold complex in dichloromethane afforded product **315** in good yield (82%) (**Scheme 110**).[103]



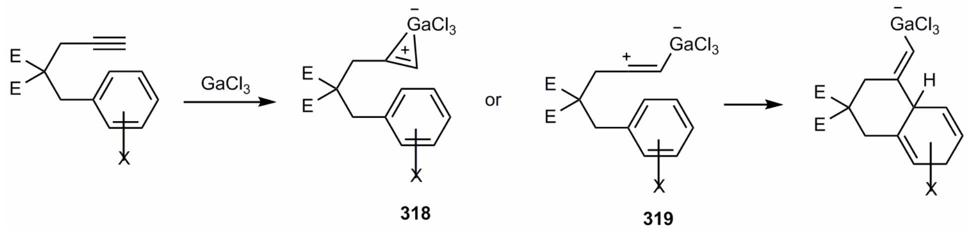
Scheme 110

Murai and co-workers[104,105] carried out a screening of metal salts for the cycloisomerisation of ω-aryl-1-alkynes and they found that reactions catalysed by Ru^{II} salts and $GaCl_3$ produced the desired dihydronaphthalenes through a 6-*exo*-dig process. They observed that generally Ru^{II} salts work better with highly activated arenes (with electrondonating groups in the aromatic ring) while $GaCl_3$ is compatible with only mildly activated arenes. For instance, the reaction of the mildly activated ω-aryl-1-alkyne **316,** with Ru^{II} salts produced the two isomeric dihydronaphthalenes **317a** and **317b** in 66% yield and (85:15) diastereoselectivity, while with $GaCl_3$ the yield and diastereoselectivity are higher (85% and 94:6) (**Scheme 111**).



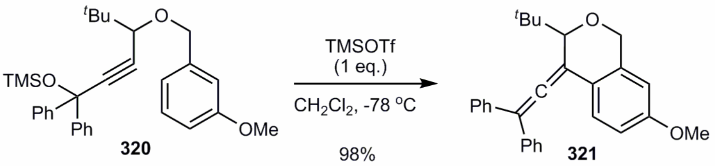
Scheme 111

In the proposed mechanism for the $GaCl_3$ cycloisomerisation, the key step is represented by the formation of the bridged-type cation complex **318** or the open-type vinyl cation complex **319** that would occur when the metal salt coordinates to the alkyne. The complexes **318** and **319** would both be expected to serve as a good electrophile for nucleophilic attack of the benzene moiety (**Scheme 112**).[105]



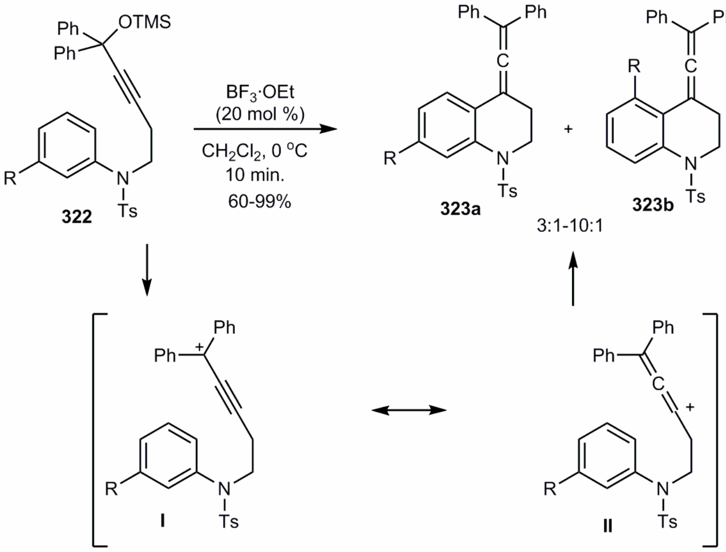
Scheme 112

TMSOTf and $BF_3{\cdot}OEt_2$ are catalysts not commonly used for the cyclisation of arene alkynes. A rare example is the intramolecular TMSOTf-promoted Friedel-Crafts reaction of propargylic silyl ethers **320**[106] that led to the formation of the allenyl isochromane derivative **321** through an 6-*exo-dig* process in high yield (98%) (**Scheme 113**).[106]



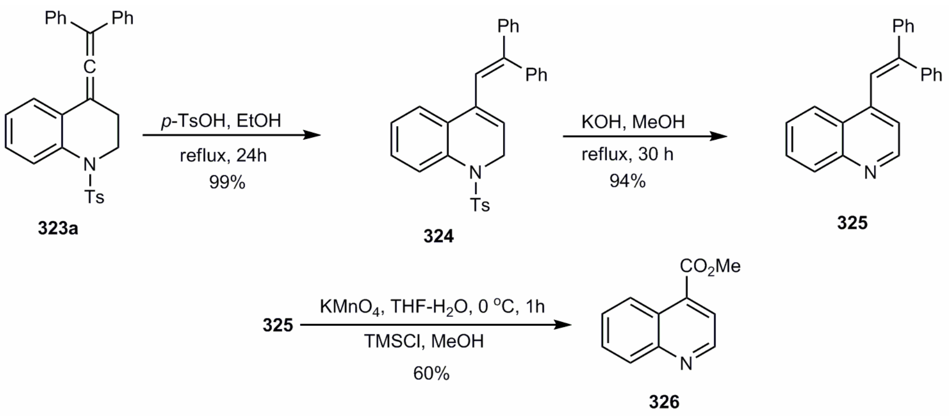
Scheme 113

In a more recent work, it was reported that tethered propargyl arenes **322**, when treated with $BF_3{\cdot}OEt_2$, underwent intramolecular Friedel-Crafts reactions producing allenyl species **323a** and **323b** in high yield (60-99)% and good regioselectivity (3:1-10:1)[107]. It was speculated that in the mechanism reported below (**Scheme 114**) the intermediate species **I/II** were formed and that the regioisomeric products **323a** and **323b** were dependent upon the canonical form **II**.[107]



Scheme 114

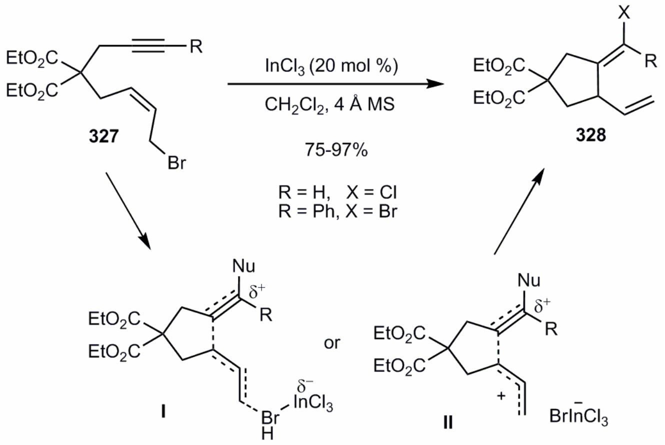
The allenyl products **323a** and **323b** thus obtained were subsequently employed for the synthesis of quinolines.[107] For this purpose substrate **323a** was treated with TsOH in ethanol, producing species **324** that after desulfonylation by exposure to KOH in MeOH gave adduct **325**. Subsequently oxidative cleavage of the diphenylvnyl moiety of **325** followed by esterification afforded quinoline (**326**) (**Scheme 115**).



Scheme 115

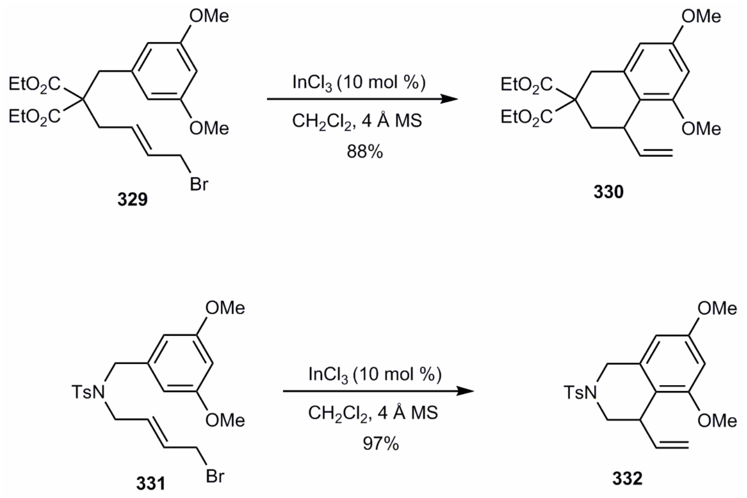
3.2.4 Allylic reactions

A very straightforward and mild Friedel-Crafts-type cyclisation is the intramolecular arene addition to allylic halides catalysed by Lewis acids reported by Cook and Hayashi.[108] According to this a catalytic amount of $InCl_3$ can trigger a mild and efficient atom transfer cyclisation in aliphatic compounds. The suggested mechanism includes an electrophilic allylation of the alkyne **327** *via* the polarised species **I** or the ionic species **II**, which then affords the cyclised product **328** (**Scheme 116**).



Scheme 116

The same methodology was employed to carry out F-C cyclisations of compounds with an allylic bromide moiety attached to an electron-rich arene, such as **329** or **330** (**Scheme 117**).[108] The arene compound **329** or **331**, upon treatment with sub-stoichiometric amount of indium(III) chloride (10 mol %) in dichloromethane at room temperature and in the presence of molecular sieves, afforded carbocycles **330** and **332** in excellent yields (88% and 97% respectively).



Scheme 117

All the previous examples showed the importance of Friedel-Crafts-type cyclisations in the synthesis of complex fused cyclic compounds. Among different reaction classes Michael-type-Friedel-Crafts cyclisations are the most interesting for us since our target is to carry out a domino-Michael-addition/ Friedel-Crafts-type alkylations as outlined previously (Introduction pp. 69). Other examples of Friedel-Crafts reactions, such as the Pictet-Spengler, the cyclisation of aryl alkynes and the allylic cyclisations are also important as they suggest possible methodologies that could be applied to our reactions.

Although many asymmetric Michael-type-Friedel-Crafts cyclisations have been carried out in the past, several of them asymmetrically, a domino-Michael-addition/ Friedel-Crafts-type alkylation has never been performed before to the best of our knowledge.

4. RESULTS AND DISCUSSION: FRIEDEL-CRAFTS-TYPE ALKYLATIONS

4.1 First steps toward domino Michael addition/Friedel-Crafts alkylation

At the outset of our work, substrate **333** was initially targeted as a suitable starting material for our Michael addition/Friedel-Crafts-type cyclisations (**Figure 7**). It possesses an acidic centre in the malonyl moiety and an electron-donating group (the dimethylamine) in the arene moiety, which could promote the F-C alkylation; moreover it is easy to prepare.

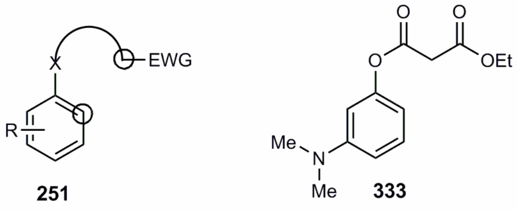
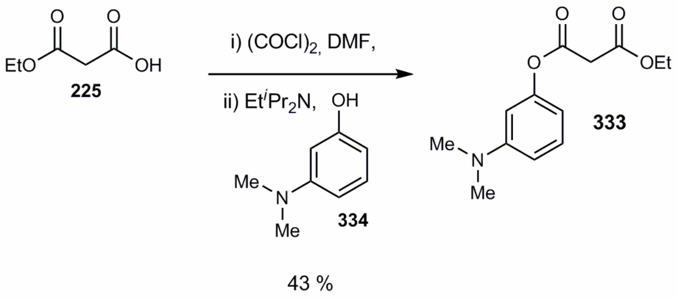


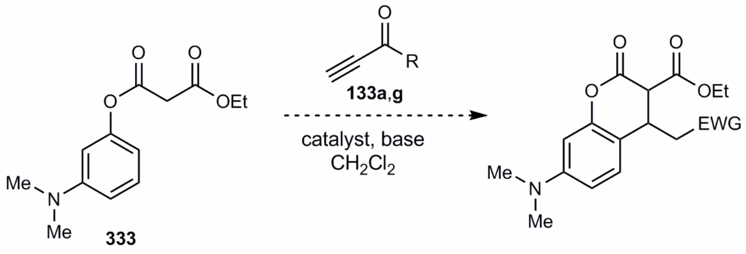
Figure 7

Treatment of the commercially available phenol **334** with the acid chloride of the ethyl malonic ester **225**, produced the desired product **333** in 43% yield (**Scheme 118**).



Scheme 118

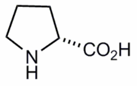
Substrate **333**, thus obtained, was subsequently treated with alkynones **133a** and **133h** and a metal salt (($Mg(OTf)_2$, $Mg(ClO_4)_2$ or $Ni(acac)_2$)) plus base (KO^tBu, or NEt_3) in dichloromethane. However, in all cases, only the starting material was recovered (**Table 8**).

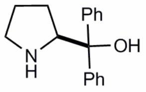


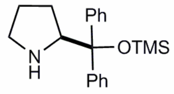
entry	**alynones**	**R**	**metal salt** (20 mol %)	**base** (1 equiv.	**Yield** (%)
1	**133a**	Ph	Mg(OTf)$_2$	NEt$_3$	_
2	**133a**	Ph	Mg(OCl$_4$)$_2$	NEt$_3$	_
3	**133a**	Ph	Ni(acac)$_2$	NEt$_3$	_
4	**133h**	Me	Mg(OTf)$_2$	KO^{t}Bu	_
5	**133a**	Ph	Mg(OTf)$_2$	KO^{t}Bu	_

Table 8

A few pyrrolidine-based and MacMillan-type organocatalysts (**335**, **336**, **141**, **337**) were also selected to catalyse the reaction (**Figure 8**).


335


336


141

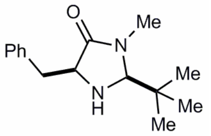
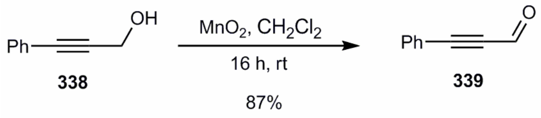

337

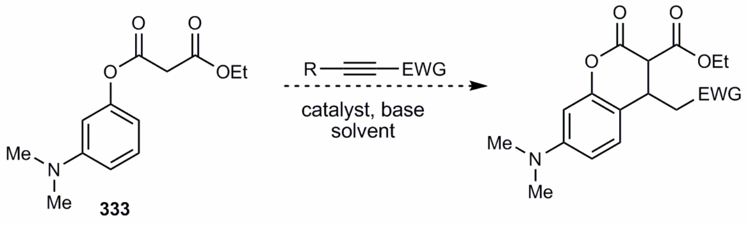
Figure 8

Together with propargyl ketone **133h**, propargyl aldehyde **339** was targeted for our reaction (**Scheme 119**). It is known that aldehydes in general are more reactive toward pyrrolidine based organocatalysts then ketones.[109] Aldehyde **339** was also chosen because it is easily obtained by oxidation of the corresponding and commercially available alcohol and it is more stable then an unsubstituted propargyl aldehyde. The latter would not be easy to prepare, since it is very reactive and unstable.



Scheme 119

Nevertheless, after treatment of substrate **333** and propargyl aldehyde **339** with a few of the organocatalysts only the starting material **333** was recovered in most cases (**Table 9**). The same results were obtained with propargyl ketone **133h**.



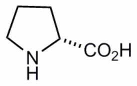
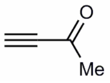
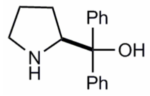
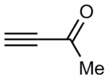
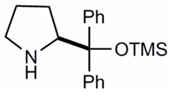
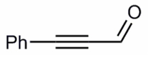
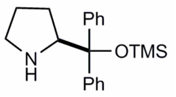
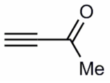
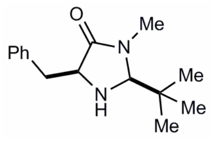
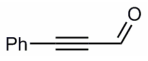
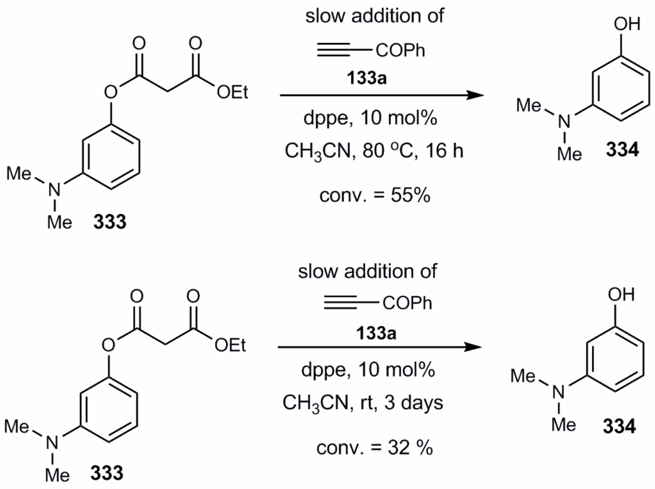
entry	organocatalyst	Michael acceptors	solvent	Yield(%)
1	 **335**	 **133h**	MeCN	–
2	 **336**	 **133h**	MeCN	–
3	 **141**	 **338**	MeCN	–
4	 **141**	 **133h**	MeCN	–
5	 **337**	 **338**	CH_2Cl_2, THF, Et_2O, toluene, MeCN	–

Table 9

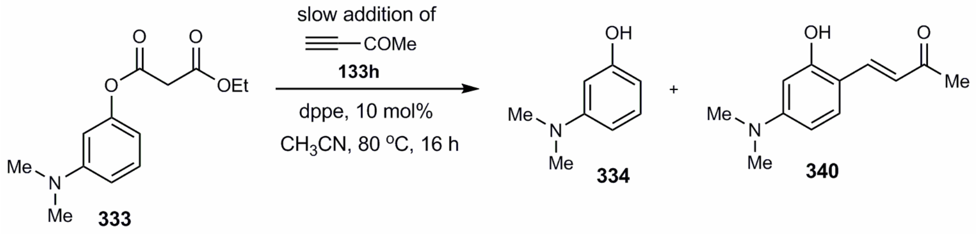
After the first results, we started to consider new methodologies and our attention focused on the elegant work reported by Kwon and co-workers (see **Scheme 46**, pp.33),[65] concerning double conjugate additions of amino alcohols to alkynones, (mostly 3-butyn-2-one) employing phosphine ligands as catalysts. This suggested the idea of exploiting phosphine-based catalysts in our cyclisation.

Therefore several reactions were screened employing dppe as the phosphine catalyst, in acetonitrile (as described in the Kwon procedure), at either 80 °C or room temperature, with slow addition of alkynone **133a** to substrate **333 (Scheme 120)**.



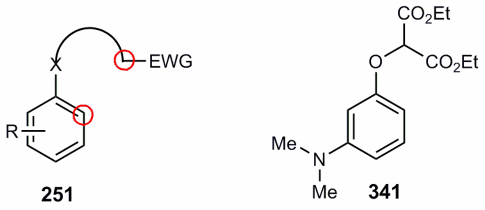
Scheme 120

In both cases the desired product was not observed, but instead the starting material **333** decomposed to generate phenol **334**. The reaction was then repeated at room temperature and over a longer period of time (3 days), but again phenol **334** was obtained. Interestingly, the use of the methyl alkynone **133h** gave byproduct **340** along with phenol **334** (**Scheme 121**).



Scheme 121

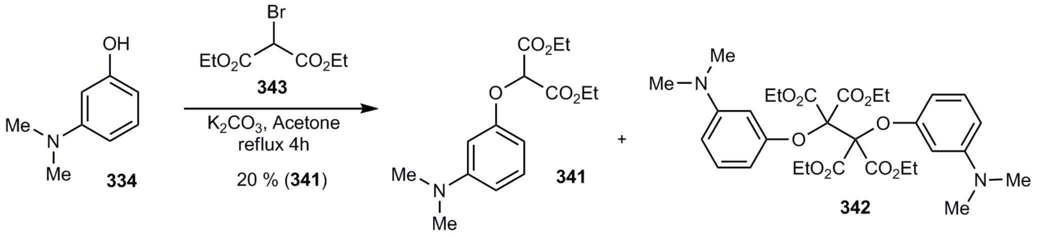
After these results we thought about the design of a different tethered dinucleophile that would be unable to undergo similar fragmentation, such as the phenol ether **341** **(Scheme 122)**.



Scheme 122

At the first attempt of carrying out the synthesis of the phenol ether **341**, phenol **334** was treated with bromomalonate **343** and potassium carbonate in refluxing acetone. Following this procedure, the desired product **341** was generated in poor yield (20%)

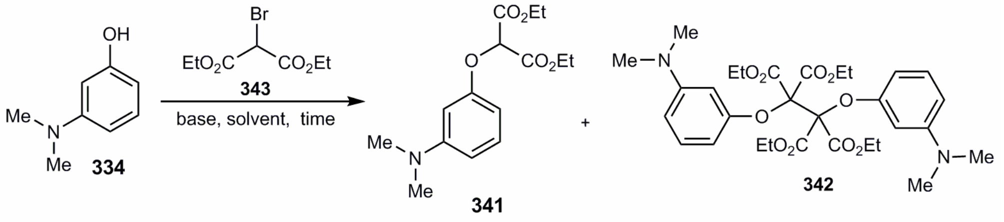
along with some starting material and a large quantity of a byproduct **342**, which by ^{1}H NMR analysis seemed to be a dimer of arene ether **341** (**Scheme 123**).



Scheme 123

It was speculated that the formation of byproduct **342** occured through a radical mechanism, maybe due to the presence of oxygen in the solvent. Therefore the solvent (acetone) was degassed and the reaction repeated in the same conditions, but no significant improvement in the reaction was observed.

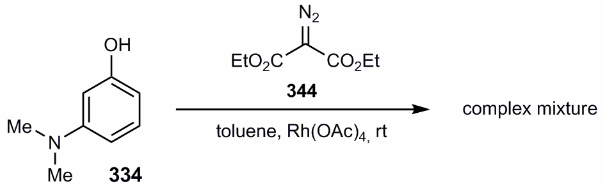
In an effort to improve the yield of the reaction, other methodologies were employed, including: the slow addition of bromomalonate **343** to a stirred mixture of the phenol **334** and Et_3N in acetonitrile at 0 °C; treatment of a stirred mixture of phenol **334** and NaOEt in ethanol with bromomalonate **343** at room temperature; and a slow addition of bromomalonate **343** to a stirred mixture of phenol **334** and potassium *tert*-butoxide in tetrahydrofuran (**Table 10**). In most cases the reaction produced a very small amount of product **341** along with a large quantity of byproduct **342**, or a complex mixture of products.



entry	base	solvent	t(h)	T	yield(%)
1	Et_3N	CH_3CN	16	0 °C-rt	complex mixture
2	NaOEt	EtOH	16	rt-reflux	traces of **x**
3	K^tBuO	THF	16	rt-reflux	complex mixture
4	K_3CO_3	acetone	16	rt	12
5	K_3CO_3	acetone	4	reflux	20

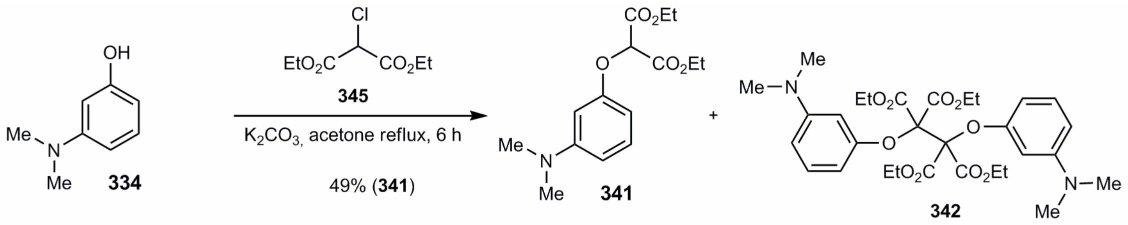
Table 10

Further attempts were made to improve the yield, such as the treatment of phenol **334** with diazomalonate **344** and $Rh_2(OAc)_4$, but the result was a complex mixture of products (**Scheme 124**).



Scheme 124

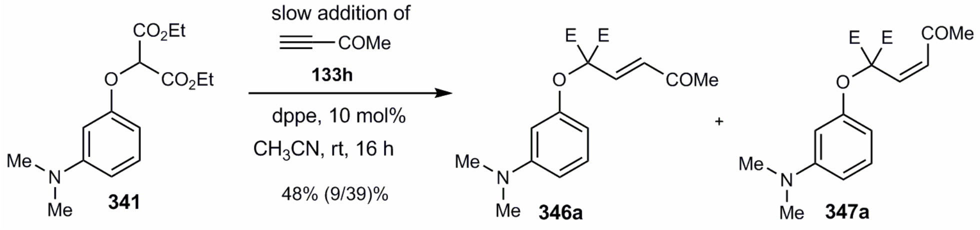
Finally, an improvement in the reaction (49% yield) was obtained by employing chloromalonate **345** instead of bromomalonate **343** (**Scheme 125**).



Scheme 125

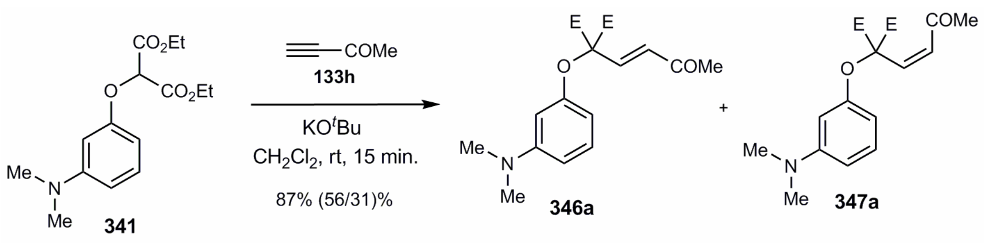
The reaction was stopped before completion, in order to minimise the formation of byproduct **342**, which complicates the purification of the phenol ether **341**.

Once substrate **341** was obtained, it was subjected to treatment with propargyl ketone **133h** (slow addition) and dppe in acetonitrile at room temperature. The reaction mixture thus obtained was stirred for 16h (**Scheme 126**).



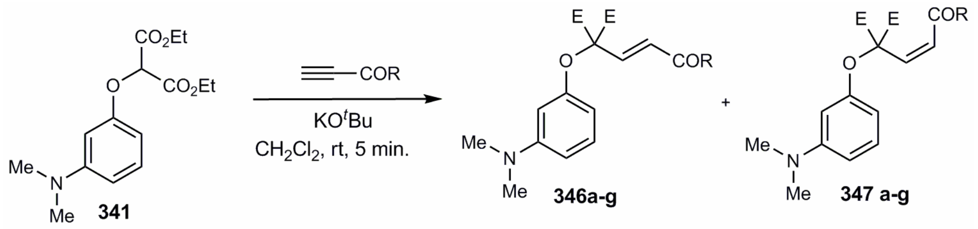
Scheme 126

As expected phenol ether **341** did not undergo fragmentation and although the F-C cyclisation did not occur, the Michael addition was successful, giving products **346a** and **347a** as a mixture of *E*/*Z* isomers (1:3) in 48% yield. An improvement in the yield was achieved by treatment of phenol ether **341** with potassium *tert*-butoxide in dichloromethane. After 15 minutes this procedure afforded a 2:1 mixture of *E*/*Z* isomers **346a** and **347a** in 87% yield (**Scheme 127**). The addition of a metal salt ($Mg(OTf)_2$ or $Ni(acac)_2$) in the reaction mixture did not have any significant effect.



Scheme 127

After these encouraging results, the arene ether **341** was treated with a range of propargyl ketones **133a,b**,**d-f,h,i**, propargyl ester **133h** and with potassium *tert*-butoxide in dichloromethane at room temperature thus generating a small library of Michael products **346a-g** and **347a-g** from average to good yield (59%-92%) (**Table 11**).



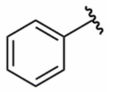
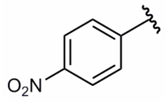
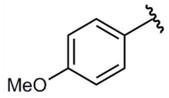
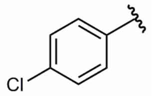
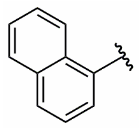
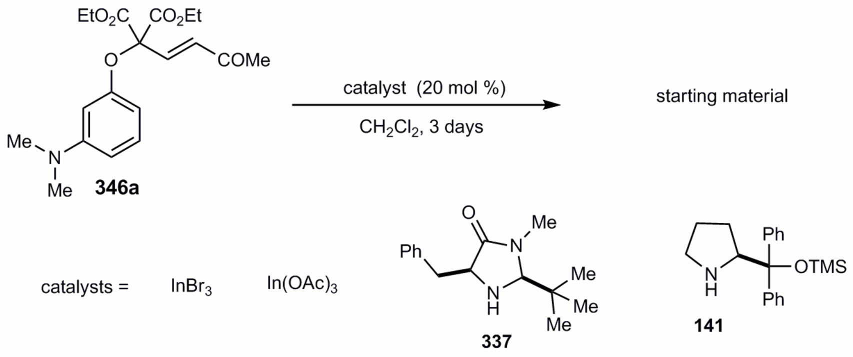
entry	alkynone	R	product	yield %	(*E*/*Z*)
1	**133h**	Me	**346a/347a**	87	2:1
2	**133i**	OEt	**346b/347b**	75	4:1
3	**133a**		**346c/347c**	92	2:1
4	**133e**		**346d/347d**	59	1:4
5	**133b**		**346e/347e**	69	2:1
6	**133f**		**346f/347f**	75	1.3:1
7	**133d**		**346g/347g**	73	8:1

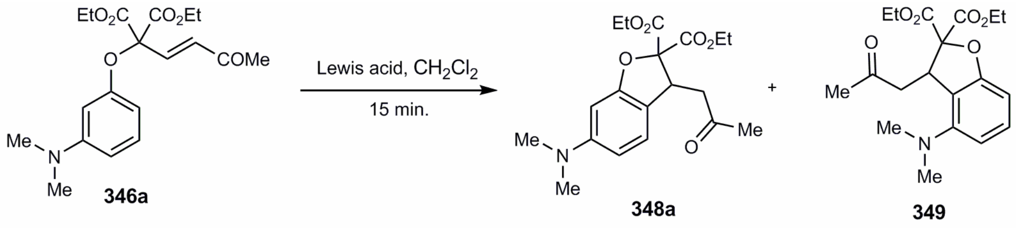
Table 11

Several organocatalysts and metal salts were screened with the Michael product **346a** in dichloromethane, in order to carry out the Friedel-Crafts cyclisation, including the pyrrolidine-based organocatalyst **141**, the imidazolidine-based catalyst **337** and the Lewis acids indium(III) bromide and indium(III) acetate. However no product was observed (**Scheme 128**).



Scheme 128

Finally, upon treatment with an excess of TMSOTf in dichloromethane the Michael adduct **346a** underwent intramolecular F-C alkylation affording the cyclised product **348a** in good yield (72%) along with a small quantity of the regioisomer **349** in very small quantity (16% yield) (**Scheme 129**). Also when treated with $BF_3{\cdot}OEt_2$ in dichloromethane **346a** underwent intramolecular F-C alkylation affording **348a** (64%). However in the latter reaction the regioisomer **349** was not observed.



entry	Lewis acid	equiv.	yield(%) 348a	yield(%) 349
1	TMSOTf	4	72	16
2	$BF_3{\cdot}OEt_2$	3	64	n/a

Scheme 129

The regioselectivity was proven by comparison of the ^{1}H NMR spectra of two regioisomers, in particular by observing the coupling constant values of the aromatic hydrogens. Reported below are the sections of the ^{1}H NMR spectra of compound **348a** and **349** that concern the aromatic region (**Figure 9** and **Figure 10**). The spectrum in **Figure 9** shows two doublets (Hc and H_A) and a doublet of doublets (H_B). The coupling constant values indicated an *ortho* coupling (H_c, d, $J_{CB} = 8.4$ Hz), a *meta* coupling (H_A, d, $J_{AB} = 1.8$ Hz) and an *ortho*/*meta* coupling (H_B, dd, $J_{BA,}$ J_{BC} = 8.4, 1.8 Hz), which is consistent with compound **348a**.

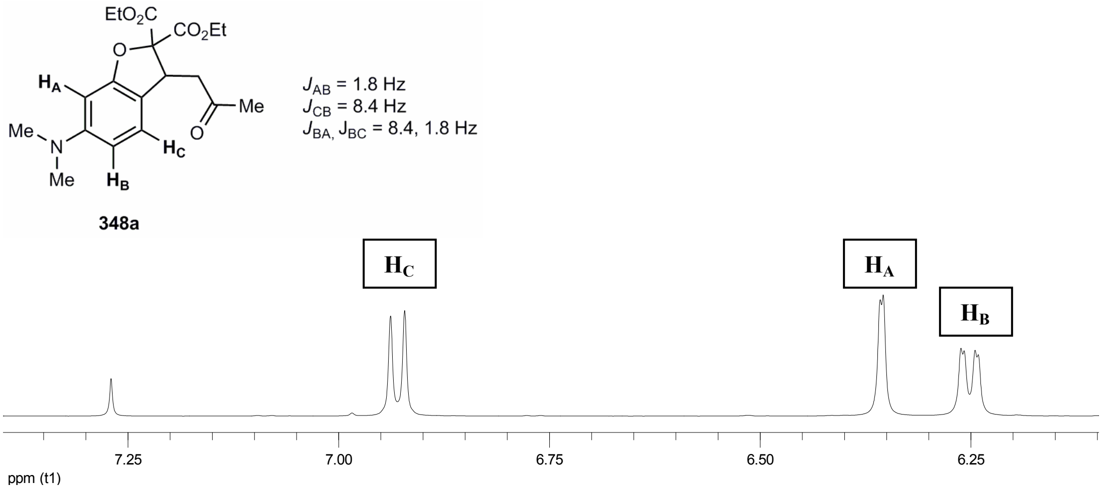


Figure 9

The spectrum in **Figure 10** shows a pseudotriplet (H_B) and two doublets (H_A and H_C). The coupling constant values of the two doublets indicated two *ortho* couplings (H_A, d, $J_{AB} = 8.1$ Hz), (H_C, d, $J_{CB} = 8.1$ Hz) which are consitent with compound **349**.

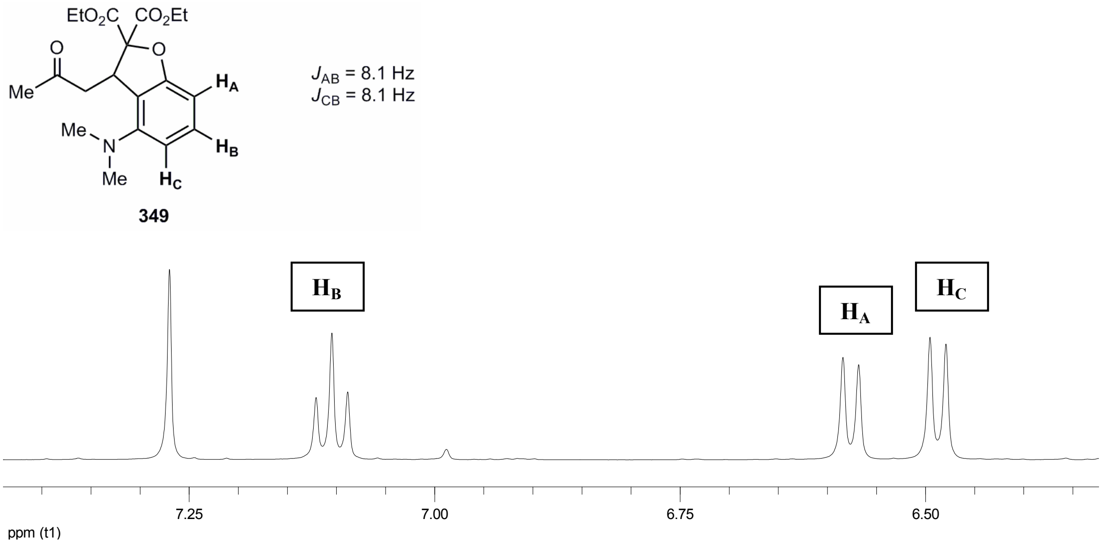
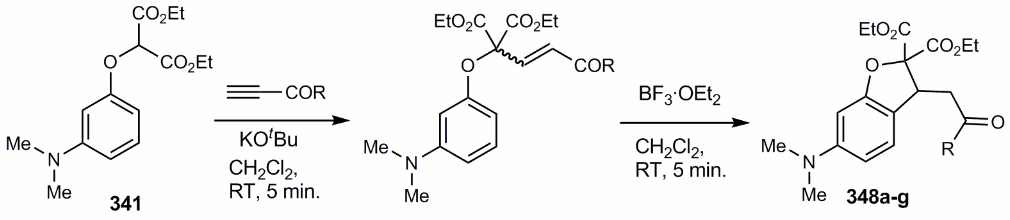


Figure 10

Consequently we applied the two-step method developed (Michael addition followed by F-C cyclisation) to the arene compound **341** and a range of propargyl ketone **133a,b,d-g** and propargyl ester **133h**. In order to improve the efficiency of the reaction, the crude mixture obtained from the first step was not separated but only subjected to aqueous work-up (washed with a saturated solution of $NaHCO_3$ and extracted with dichloromethane). The crude product thus obtained was then dissolved with dichloromethane and then treated with $BF_3{\cdot}OEt_2$. The two-step procedure afforded a small library of cyclised products **348a-g** from average to good yield (37%-65% over two steps) (**Table 12**).



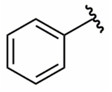
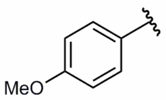
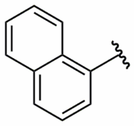
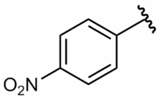
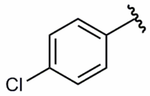
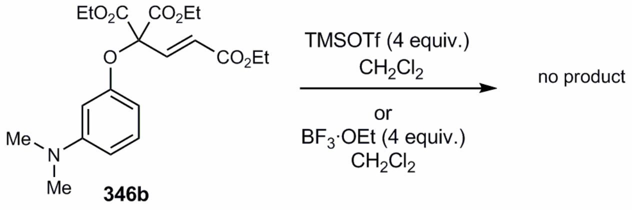
entry	**alkynone**	**R**	**product**	**yield %** (over two steps)
1	**133a**		**348a**	37%
2	**133b**		**348b**	35
3	**133d**		**348d**	65
4	**133e**		**348e**	traces
5	**133f**		**348f**	44
6	**133h**	Me	**348h**	59
7	**133i**	OEt	**348i**	-

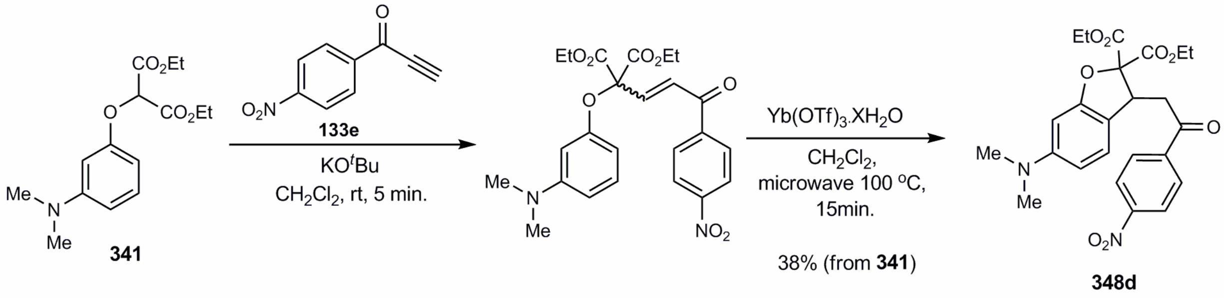
Table 12

The isomeric mixture of Michael products generated by treatment of substrate **341** with propargyl ester **133i** failed to undergo F-C cyclisation when treated with $BF_3{\cdot}OEt_2$ (**entry 7**). The same result was obtained even when the cyclisation was attempted on the isolated Michael adduct **346b** (*E* isomer), either with TMSOTf or $BF_3{\cdot}OEt_2$ (**Scheme 130**)



Scheme 130

The isomeric mixture of Michael products generated by treatment of substrate **341** with propargyl ketone **133e**, afforded only traces of product when treated with $BF_3 \cdot OEt_2$ (**entry 4**). The mixture obtained (which mostly contained arene ether **341** and the isomeric Michael products **346d**/**347d**) was then dissolved in dichloromethane and heated to reflux with $Yb(OTf)_3 \cdot XH_2O$ (20 mol %). However after 16h the reaction was not complete. The Michael addition was then repeated and a solution of substrate **341** in dichoromethane was treated with propargyl ketone **133**e and potassium *tert*-butoxide. The crude product obtained was dissolved in dichloromethane treated with $Yb(OTf)_3 \cdot XH_2O$ (20 mol %) and microwaved to 100°C for 15 min. The reaction reached completion and the desired product was obtained in 38% yield over two steps (**Scheme 131**).

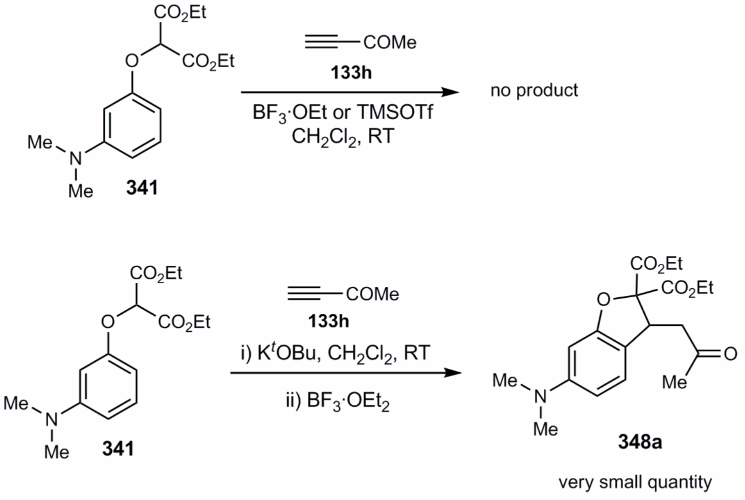


Scheme 131

Microwave techniques have been employed before in F-C cyclisation, for example the Pictet-Spengler reaction reported by Ganesan and co-workers (**Scheme 102**, pp. 80).[97]

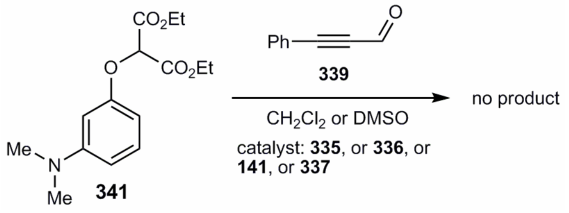
4.2 Domino Michael addition/Friedel-Crafts alkylation

Several attempts to carry out a tandem reaction (Michael addition plus Friedel-Crafts-type alkylation) were tried: for example by treating the phenol ether **340** and the alkynone **133h** directly with $BF_3 \cdot OEt_2$ or TMSOTf in dichloromethane. However those procedures did not produce any product and only starting material was recovered (**Scheme 132**). A one-pot cyclisation was also attempted, in which, after the consumption of the starting material in the Michael addition step, an excess of $BF_3 \cdot OEt_2$ (7 equiv.) was directly added to the reaction flask by syringe. Some product was obtained this time, although with very low conversion.



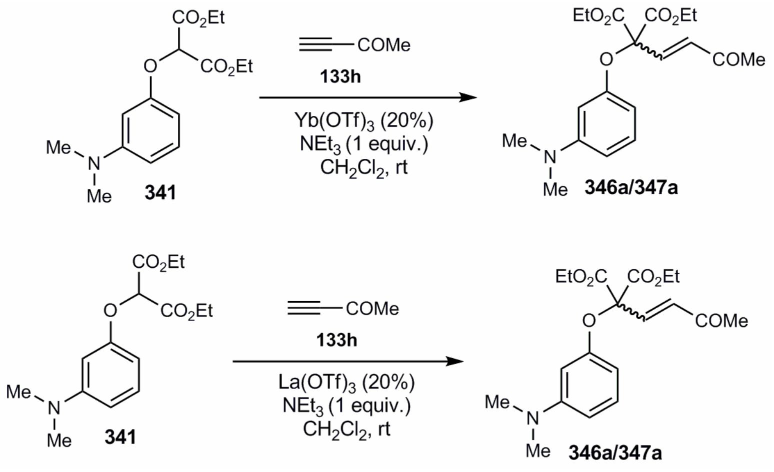
Scheme 132

An organocatalytic approach was also attempted by treating the phenol ether **341** and aldehyde **339** with pyrrolidine- imidazolidine-based catalysts **335**, **336**, **141** or **337** (**Figure 8**, pp. 90) in dichloromethane or dimethylsulphoxide (**Scheme 133**).



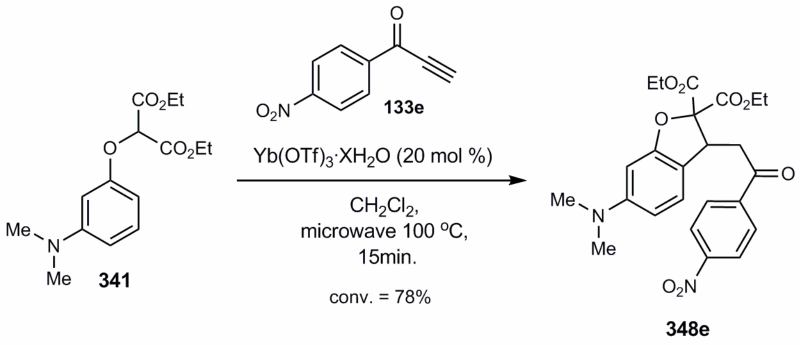
Scheme 133

Lewis acids were also employed in the attempted tandem F-C alkylation. Phenol ether **341** and alkynone **133h** were treated with $Yb(OTf)_3$ or $La(OTf)_3$ and triethylamine in dichloromethane at room temperature. Only Michael products could be observed without any trace of the cyclised product (**Scheme 134**).



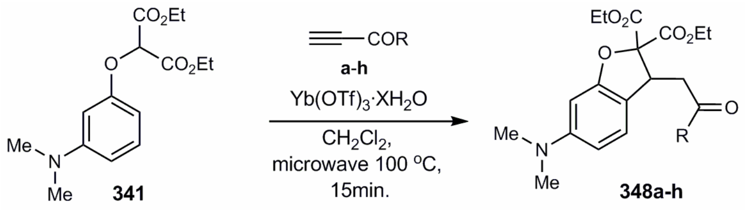
Scheme 134

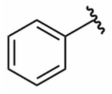
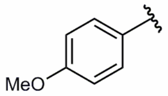
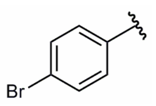
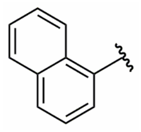
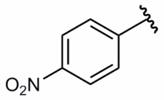
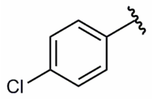
A domino Michael/F-C-cyclisation was attempted employing a microwave technique. Thus a solution of phenol ether **341** and propargyl ketone **133e** in dichloromethane was treated with a sub-stoichiometric quantity of $Yb(OTf)_3{\cdot}XH_2O$ and heated to100 °C (**Scheme 137**).



Scheme 135

Although the reaction did not reach completion and it was not possible to isolate the product at this stage, the conversion was very good (78%). This encouraged us to try different alkynones, many of which proved to be compatible with this methodology. A small library of cyclised products was therefore obtained by heating to 100 °C a mixture of phenol ether **341** and Michael acceptors **133a-h** with $Yb(OTf)_3{\cdot}XH_2O$ in dichloromethane (**Table 13**).



Entry	**alkynone**	**R**	**product**	**Yield** (%)
1	**133a**		**348a**	47%
2	**133b**		**348b**	53
3	**133c**		**348c**	80
4	**133d**		**348d**	44
5	**133e**		**348e**	n/a*
6	**133f**		**348f**	n/a*
7	**133h**	Me	**348h**	54
8	**133i**	OEt	**348i**	n/a*

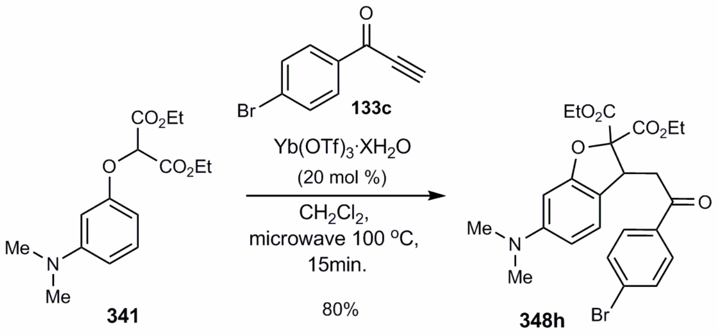
* **entry 2**,4,**6**: it was not possible to separate the desired product from the starting materials and/or by-products.

Table 13

The result in **Entry 8** is particularly interesting, although the product has not yet been separated, because the cyclisation failed when either the isomeric mixture of Michael products **346a**/**347a** (*E*/*Z*), or the isolated Michael adduct **346a** (*E*) were treated with TMSOTf or $BF_3{\cdot}OEt_2$ (**Table 12** and **Scheme 132**, pp. 100)

4.3 Conclusions

In summary, we have developed a domino-Michael-addition/F-C-type-cyclisation for the synthesis of fused bicyclic compounds by heating a mixture of an arene ether and an alkynone with Yb(OTf)$_3$ in dichloromethane to 100 ^{o}C in a microwave oven. The reaction afforded the desired product from average to good yield (44-80)% when the arene ether **341** is treated with a range of different alkynones (mostly aromatic) or propargyl ester (**Scheme 136**).

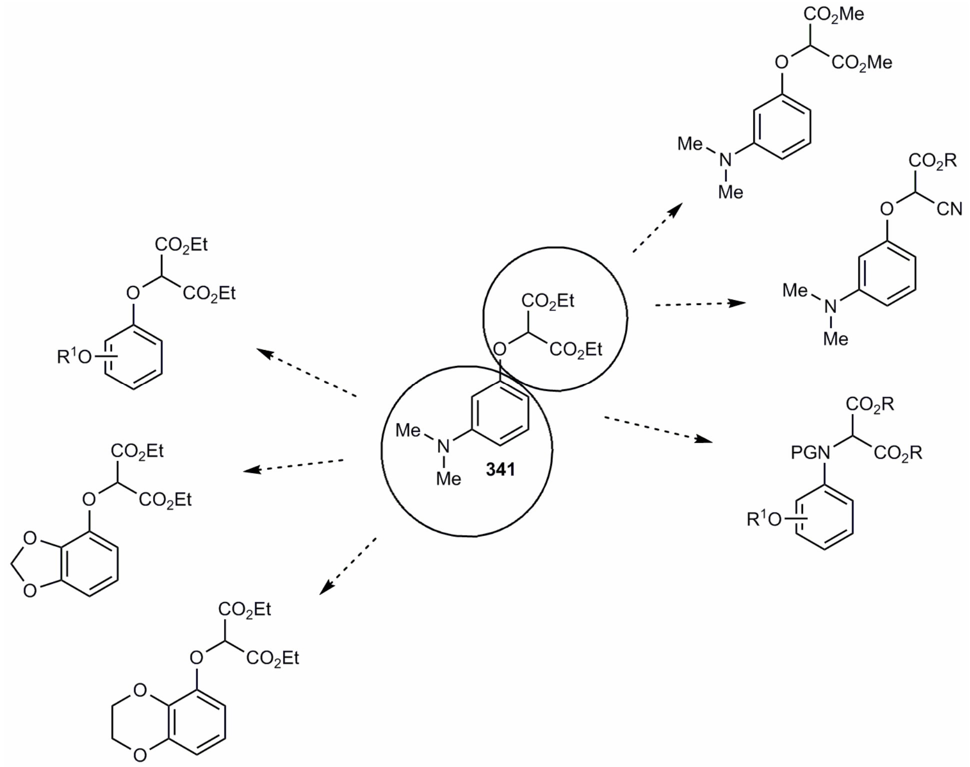


Scheme 136

Only one of the two starting materials selected at the outset of this work, the arene ether **341**, seems to be able to undergo F-C cyclisation. After a screening of several reaction conditions, arene **333** failed to undergo both Michael addition and F-C alkylation. Nevertheless there are still other alternatives that need to be considered to differentiate the starting material and other Michael acceptors that could be selected in a future work (different aliphatic alkynones or propargyl aldehydes).

4.4 Further work

Although only arene ether **341** seems to be able to undergo F-C cyclisation, a wide range of different starting materials could be prepared by modifying both the arene moiety and the molonyl-ether moiety (**Scheme 137**).



Scheme 137

The possibility of carrying out an asymmetric domino-Michael-addition/F-C-cyclisation could be considered if the reaction is promoted by Brønsted acid catalysis. In this circumstance a chiral acid such as binaphtyl phosphoric acid derivative, or a thiourea based organocatalyst could be employed. In fact, asymmetric F-C cyclisations which employ these conditions have already been reported in the past (**Scheme 103**, **104**, **106**, pp. 81, 82, 83 respectively).

5. EXPERIMENTAL

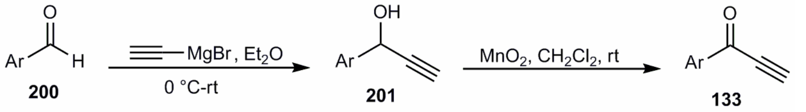
5.1 General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60°C. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[110] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) or a Bruker ARX500 (500 MHz)spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{19}F NMR spectra were recorded on a Bruker ARX250 (235 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales

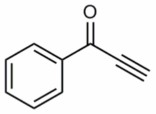
Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

5.2 Double Michael additions

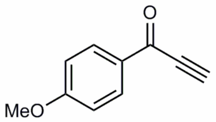
5.2.1 General procedure for the preparation of alkynones



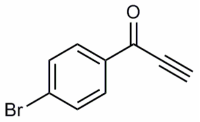
Ethynyl magnesium bromide (1.2 equiv., 0.5 M in THF) was added to a solution of the aldehyde **200a-g** (1 equiv.) in dry Et_2O (1.0 M) at 0 °C. The reaction mixture was then allowed to warm up to room temperature and left under stirring. After 2h saturated aqueous NH_4Cl (10 mL) solution was added to the mixture. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The collected organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow residue, without any further purification, was dissolved in dry CH_2Cl_2 (0.05 M) and treated with activated manganese dioxide (10 equiv.) at room temperature. After 3h, the reaction mixture was filtered through ceelite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography (petrol/diethyl ether, 4:1) affording the alkynones **133a-133g** as yellow solids.



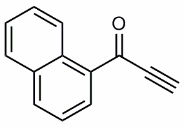
1-Phenylpropynone (133a).[111] The title compound was prepared according to the General procedure from aldehyde **200a** (5.7 mL, 57 mmol), and ethynyl magnesium bromide (136 mL, 67 mmol) and purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (4.50 g, 61 %); m.p. 46-48°C (50-51°C, lit.[111]); ^{1}H NMR (500 MHz, CDCl3) δ 8.18 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.65 (1H, t, *J* = 7.3 Hz, Ar**H**), 7.52 (2H, t, *J* = 7.8 Hz, Ar**H**), 3.44 (s, 3H, C≡C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.3(C), 135.9 (C), 134.4 (CH), 129.5 (2 x CH), 128.5 (2 x CH), 80.9 (CH), 80.1 (C).



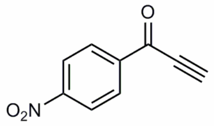
1-(4-Methoxyphenyl)propynone (133b).[112] The title compound was prepared according to the General procedure from aldehyde **200b** (0.8 mL, 6.6 mmol), and ethynyl magnesium bromide (15.8 mL, 7.9 mmol). The yellow residue (533 mg) resulting from the first step, without any further purification, was dissolved in dry CH_2Cl_2 (30 mL) and treated with activated manganese dioxide (4.0 g, 40 mmol) at room temperature. After 3h, the reaction mixture was filtered through ceelite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (339 mg, 54 %); m.p. 78-80 °C (82-83 °C, lit.[112]); IR ($CHCl_3$) 3253, 2914, 2094, 1639 (C=O), 1599, 1574, 1259, 1171, 11024, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.96 (2H, d, *J* = 8.8 Hz, Ar**H**), 3.89 (3H, s, OC**H**$_3$), 3.39 (1H, s, C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.9 (C), 164.7 (C), 132.1 (2 x CH), 129.5 (C), 113.9 (2 x CH), 80.3 (C), 80.0 (CH).



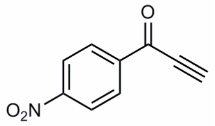
1-(4-Bromophenyl)propynone (133c).[113] The title compound was prepared according to the General procedure from aldehyde **200c** (1.0 g, 5.4 mmol), and ethynyl magnesium bromide (12.9 mL, 6.5 mmol) and purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (651 mg, 60 %); m.p. 98-100 °C; IR ($CHCl_3$) 3219, 3093, 2098, 1635 (C=O), 1583, 1261, 1174, 1068, 1007, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.65 (2H, d, *J* = 8.3 Hz, Ar**H**), 3.48 (1H, s, C≡C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.2 (C), 134.9 (2 x CH), 132.0 (C), 131.5 (2 x CH), 130.1 (C), 81.3 (CH), 79.9 (C).



1-Naphthalenylpropynone (133d).[112] The title compound was prepared according to the General procedure from aldehyde **200d** (1.5 mL, 11 mmol), and ethynyl magnesium bromide (26.4 mL, 13.2 mmol) and purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (1.12 g, 58 %); m.p. 64-66 °C (70-71 °C, lit.[112]); IR ($CHCl_3$) 3226, 3041, 3006, 2090, 1635 (C=O), 1589, 1574, 1238, 1190, 771 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (1H, d, *J* = 8.7 Hz, Ar**H**), 8.63 (1H, dd, *J* = 7.3, 1.1 Hz, Ar**H**), 8.11 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.92 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.71-7.68 (1H, m, Ar**H**), 7.61-7.58 (2H, m, Ar**H**), 3.46 (1H, s, C≡C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.8 (C), 135.6 (CH), 135.5 (CH), 133.7 (C), 131.8 (C), 130.6 (C), 129.2 (CH), 128.6 (CH), 126.8 (CH), 125.8 (CH), 124.4 (CH), 81.6 (C), 79.4 (CH).

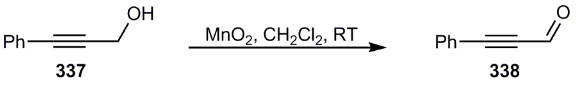


1-(4-Nitrophenyl)propynone (133e).[114] The title compound was prepared according to the General procedure from aldehyde **200e** (1.0 g, 6.6 mmol), and ethynyl magnesium bromide (15.8 mL, 7.9 mmol). The yellow residue (545 mg) resulting from the first step, without any further purification, was dissolved in dry CH_2Cl_2 (30 mL) and treated with activated manganese dioxide (4.0 g, 40 mmol) at room temperature. After 3h, the reaction mixture was filtered through ceelite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (386 mg, 54 %); m.p. 78-80 °C (74-75 °C, lit.[114]); IR ($CHCl_3$) 3280, 3114, 2098, 1657 (C=O), 1603, 1522, 1321, 1236, 1007, 854 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.38-8.32 (4H, m, Ar**H**), 3.61 (1H, s, C≡C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.4 (C), 151.1 (C), 140.1 (C), 130.6 (2 x CH), 123.9 (2 x CH), 82.8 (CH), 79.6 (C).



1-(4-Chloro)phenylpropynone (133f).[115] The title compound was prepared according to the General procedure from aldehyde **200f** (1.0 g, 6.6 mmol), and ethynyl magnesium bromide (15.8 mL, 7.9 mmol). The yellow residue (513 mg) resulting from the first step, without any further purification, was dissolved in dry CH_2Cl_2 (30 mL) and treated with activated manganese dioxide (4.0 g, 40 mmol) at room temperature. After 3h, the reaction mixture was filtered through ceelite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography (petrol ether/ Et_2O, 4:1) to give a yellow solid (287 mg, 48 %); m.p. 94-96 °C (96-97 °C, lit.[115]); IR (thin film) 3217, 2092, 1633 (C=O), 1587, 1568, 1485, 1400, 1259, 1092, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (2H, d, J = 8.0 Hz, Ar**H**), 7.47(2H, d, J = 8.0 Hz, Ar**H**), 3.48 (1H, s, C≡C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.0 (C), 141.2 (C), 134.5 (C), 130.9 (2 x CH), 129.0 (2 x CH), 81.3 (CH), 79.9 (C).

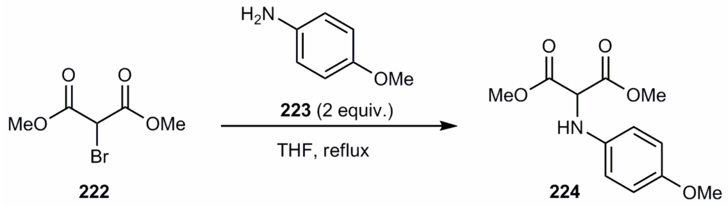
Phenylpropynal (338)[116]



A solution of alcohol **337** (1.8 mL, 15.1 mmol) was dissolved in dry CH_2Cl_2 (250 mL) and treated with activated manganese dioxide (13g, 150 mmol) at room temperature. After 3h, the reaction mixture was filtered through ceelite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane/AcOEt, 10:1) affording aldehyde the **338** as a yellow oil; (1.53 g, 76%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.43 (1H, d, *J* = 0.7 Hz C**HO**), 7.62-7.59 (2H, m, Ar**H**), 7.52-7.47 (1H, m, Ar**H)**, 7.43-7.38 (2H, m, Ar**H**); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 176.8 (C), 133.2 (2 x CH), 131.2 (CH), 128.7 (2 x CH), 119.3 (C), 95.1 (C), 88.4 (C).

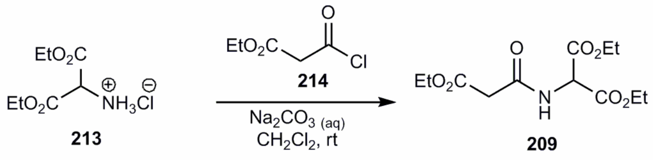
5.2.2 Preparation of Tethered Diacids

Dimethyl 2-(4-methoxyphenyl)aminomalonate (224).[117]



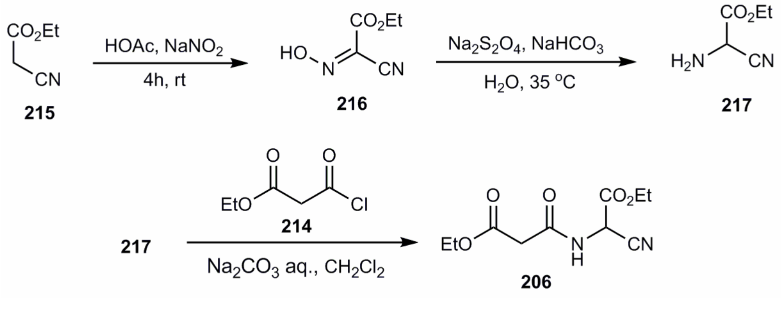
A mixture of methyl bromomalonate (2.91 mL, 20.0 mmol) and *p*-anisidine (4.93 g. 40.0 mmol) in THF (90 mL) was heated to reflux, then allowed to cool to room temperature and left under stirring. The reaction mixture was concentrated *in vacuo* and the residue was triturated with Et_2O (100 mL). The filtrate was concentrated *in vacuo* and purification of the residue by column chromatography (petrol ether/EtOAc, 5:1-3:1) afforded the product **224** as a pale brown solid (4.81 g, Y = 96%); m.p. 70-72 °C (78-79 °C lit.[117]); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.78 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.63 (2H, dm, *J* = 9.1 Hz, Ar**H**), 4.74 (1H, s, C**H**NH), 3.80 (6H, s, 2 x OC**H**$_3$), 3.74 (3H, s, OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.2 (2 x C), 153.2 (C), 139.2 (C), 115.1 (2 x CH_2), 114.9 (2 x CH_2), 61.4 (CH), 55.5 (OCH_3), 53.1 (2 x OCH_3).

Diethyl *N*-(2-carbethoxyacetyl)aminomalonate (209)



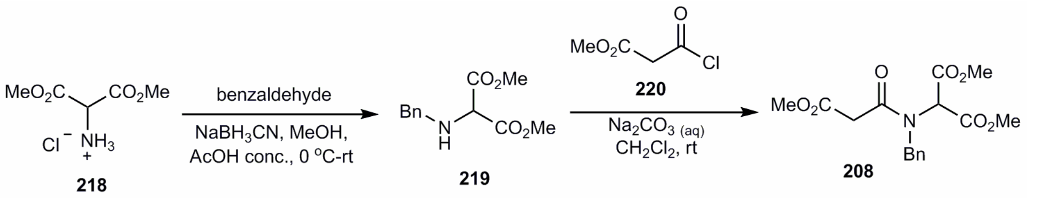
To a vigorously stirred mixture of the diethyl aminomalonate hydrochloride **213** (1.00 g, 4.72 mmol) in CH_2Cl_2 (4 mL) and saturated aqueous Na_2CO_3 solution (4 mL) at room temperature was added ethyl malonyl chloride **214** (0.73 mL, 5.67 mmol) in one portion. The mixture was stirred for 1 h and then partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the *amide* **209** (1.32 g, 97%) as white solid (1.32 g, Y= 97%); m.p. 69-71 °C; IR (film) 3342 (NH), 2985, 1743 (C=O), 1684 (C=O), 1525, 1373, 1344, 1182, 1030, 860 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.07 (1H, d, *J* = 7.2 Hz, CHN**H**), 5.1 (1H, d, *J* = 7.2 Hz, C**H**NH), 4.28-4.10 (4H, m, 2 x C**H**$_2$CH$_3$), 4.12 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.44 (2H, s, C**H**$_2$C=O), 1.26-1.21 (9H, m, 3 x CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.4 (C), 165.8 (2 x C), 164.9 (C), 62.4 (2 x CH_2), 61.6 (CH_2), 56.4 (CH), 40.8 (CH_2), 13.9 (CH_3), 13.8 (2 x CH_3); LRMS (ES) Exact mass calcd for $C_{12}H_{20}NO_7$ $[M+H]^+$: 289.1, found: 290.1.

Ethyl-*N*-(2-carbethoxyacetyl)aminocyanoacetate (206)



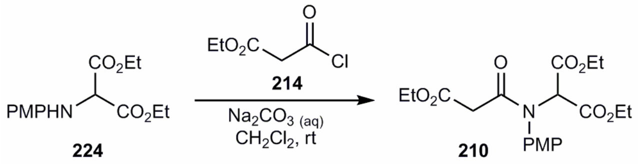
To a stirred mixture of ethylcyanoacetate **215**[118] (18.8 mL, 177 mmol) and glacial acetic acid (80 mL) at room temperature, $NaNO_2$ (36.5 g, 530 mmol) was added portionwise over 1.5h. The mixture was stirred for 3 h and then partitioned between H_2O (100 mL) and Et_2O (150 mL). The aqueous layer was separated and extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the adduct **216** as a white solid (24.0 g). Without any further purification adduct **216**[118] (10.0 g) was added to a saturated aqueous solution of $NaHCO_3$ (6.4 mL), then $Na_2S_2O_4$ (86%, 34.0 g, 196 mmol) was added portionwise to the mixture until completion of the reaction. The aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated. The resulting crude oil **217 (**1.00 g**)**, without any further purification, was dissolved in CH_2Cl_2 (10 mL) and mixed with a saturated aqueous solution of Na_2CO_3 (10 mL). Ethyl malonyl chloride (12.0 mL, 9.36 mmol) was added in one portion to the vigorously stirred mixture. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (3:1 hexane/EtOAc) afforded the amide **206 (**1.00 g, 19%, over three steps) as a white solid; m.p. 66-70 °C; IR ($CHCl_3$) 3329 (NH), 2987, 2939, 1745 (C=O), 1680 (C=O), 1522, 1271, 1211, 1028, 852 cm^{-1}, ^1H NMR (360 MHz, $CDCl_3$) δ 8.37-8.35 (1H, m, CHN**H**), 5.52 (1H, d, *J* = 7.5 Hz, C**H**C≡N), 4.35 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 4.23 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.43 (2H, s, C**H**$_2$), 1.35 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.29 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.7 (C), 165.2 (2 x C), 163.0 (C), 113.7 (C), 64.1 (CH_2), 62.0 (CH_2), 42.8 (CH), 40.2 (CH_2), 13.9 (CH_3), 13.8 (CH_3), 13.8 (CH_3); LRMS (ES) Mass calcd for $C_{10}H_{14}NaN_2O_5$ $[M+Na]^+$: 265.1, found: 265.0.

Dimethyl *N*-benzyl-*N*-(carbomethoxyacetyl)aminomalonate (208)



To a solution of diethyl aminomalonate hydrochloride **218 (**363 mg, 1.93 mmol) in dry MeOH at 0 °C, $NaBH_3CN$ (121 mg, 1.93 mmol) and benzaldehyde (213 µL, 2.11 mmol) were added.[119] Glacial acetic acid was added dropwise (until pH = 6) to the reaction mixture, which was then allowed to warm up to room temperature and stirred for 24h. The mixture was diluted with H_2O (10 mL) and Na_2CO_3 was added portionwise (until pH = 9-10). The aqueous layer was then saturated with NaCl, extracted with $CHCl_3$ (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow residue (428 mg). The residue (200 mg), without any further purification, was dissolved in CH_2Cl_2 (1 mL) and mixed with a saturated aqueous solution of Na_2CO_3. To the vigorously stirred mixture, methyl-3-chloro-3-oxopropionate **220** (110 µL, 1.01 mmol) was added in one portion. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (1:1, hexane/EtOAc) afforded the amide **208** as a white solid (190 mg, 29 %, over two steps); m.p. 69-72 °C; IR ($CHCl_3$) 2364, 1745 (C=O), 1664 (C=O), 1434, 1253, 1197, 1163, 1018, 992, 746 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.29-7.35 (5H, m, Ar**H**), 5.57 (1H, s, C**H**N), 4.75 (2H, s, C**H**$_2$C=O), 3.74 (3H, s, OC**H**$_3$), 3.66 (6H, s, OC**H**$_3$), 3.48 (2H, s, ArC**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.7 (C), 167.1 (C), 166.1 (C), 135.4 (C), 128.8 (2 x CH), 127.8 (2 x CH), 60.5 (CH), 52.8 (2 x CH_3), 52.4 (CH_3). 51.2 (CH_2), 40.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_7$ $[M+H]^+$: 338.1234, found: 338.1237.

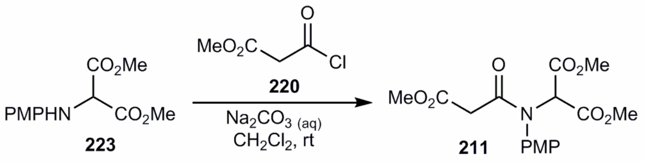
Diethyl *N*-(2-carbethoxyacetyl)-*N*-(4-methoxyphenyl)aminomalonate (210)



To a vigorously stirred mixture of the amine **224**[120] (1.00 g, 3.56 mmol) in CH_2Cl_2 (4 mL) and saturated aqueous Na_2CO_3 solution (4 mL) at room temperature was added ethyl malonyl chloride (0.61 mL, 4.47 mmol) in one portion. The mixture was stirred for 1 h and then partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 solution (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the *amide* **210** (1.39 g, 98%) as a brown oil. IR (film) 2983, 2938, 2840, 1742 (C=O), 1672 (C=O), 1510, 1250, 1034, 843 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41 (2H, dm, J = 8.9 Hz, Ar**H**), 6.88 (2H, d, J = 8.9 Hz, Ar**H**), 5.55 (1H, s, C**HN**), 4.23-4.09 (6H, m, 3 x CO_2C**H**$_2CH_3$), 3.82 (3H, s, OC**H**$_3$), 3.24 (2H, s, C**H**$_2$C=O), 1.29-1.14 (9H, m, 3 x CO_2CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.9 (2 x C), 165.6 (2 x C), 159.9 (C), 131.9 (C), 130.7 (2 x CH), 114.5

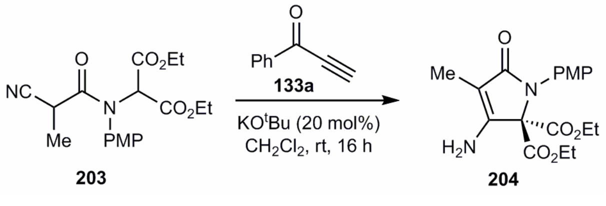
(2 x CH), 64.3 (CH), 62.0 (2 x CH_2), 61.2 (CH_2), 55.4 (CH_3), 41.4 (CH_2), 14.0 (CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{26}NO_8$ $[M+H]^+$: 395.1653, found: 395.1654.

Dimethyl *N*-(2-carbomethoxyacetyl)-*N*-(4-methoxyphenyl)aminomalonate (211)



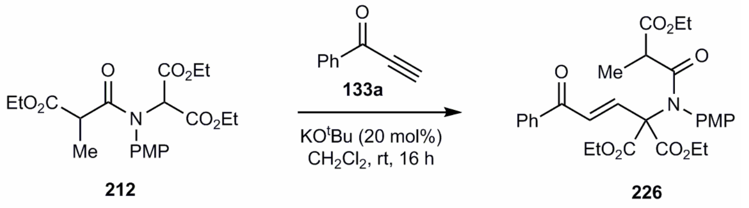
To a vigorously stirred mixture of the amine **223** (3.00 g, 11.8 mmol)[117] in CH_2Cl_2 (11 mL) and saturated aqueous Na_2CO_3 solution (11 mL) at room temperature was added methyl malonyl chloride (1.57 mL, 14.2 mmol) over 1 min. The mixture was stirred for 4 h, and a further portion of methyl malonyl chloride **220** (0.65 mmol, 5.92 mmol) was added. After stirring for another 1 h, the reaction was partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 solution (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the *amide* **211** (4.00 g, 96%) as a brown oil. IR (film) 3004, 2954, 2843, 1747 (C=O), 1671 (C=O), 1509, 1436, 1249, 1218, 1167; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38 (2H, dm, *J* = 8.3 Hz, Ar**H**), 6.89 (2H, dm, *J* = 8.3 Hz, Ar**H**), 5.54 (1H, s, C**H**N), 3.82 (3H, s, OC**H**$_3$), 3.72 (6H, s, 2 x OC**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 3.26 (2H, s, C**H**$_2$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.3 (C), 166.8 (C), 165.9 (2 x C), 159.9 (C), 131.8 (C), 130.4 (2 x CH), 114.6 (2 x CH), 64.1 (CH), 55.4 (CH_3), 52.8 (2 x CH_3), 52.3 (CH_3), 41.1 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_8$ $[M+H]^+$: 353.1183, found: 353.1183.

3-Amino-2,2-dicarbethoxy-1-(4-methoxyphenyl)-4-methyl-1,5-dihydropyrrol-2-one (204)



To a stirred solution of tethered diacid **203** (36 mg, 0.10 mmol), KO^tBu (2 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature was added a solution of alkynone **133a** (16 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) *via cannula* dropwise over 1 min. The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (3:1, hexane/EtOAc) afforded the cyclised product **204** as a white solid (27.8 mg, 99%); m.p. 102-106 °C; IR ($CHCl_3$) 3342, 3209, 2981, 1739 (C=O), 1652 (C=O), 1512, 1367, 1248, 1035, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.82 (2H, dm, *J* = 9.0 Hz, Ar**H**), 4.64 (2H, bs, N$\mathbf{H}_2$), 4.23-4.12 (4H, m, 2 x $OCH_2C\mathbf{H}_3$), 3.76 (3H, s, $OC\mathbf{H}_3$), 1.72 (3H, s, $C\mathbf{H}_3$), 1.15 (6 H, t, *J* = 7.1 Hz, 2 x $OC\mathbf{H}_2CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.6 (C), 166.0 (2 x C), 158.2 (C), 150.7 (C), 129.8 (C), 129.0 (2 x CH), 113.8 (2 x CH), 101.2 (C), 75.2 (C), 62.8 (2 x CH_2), 55.3 (CH_3), 13.8 (2 x CH_3), 6.9 (CH_3); HRMS (ES) Exact mass calcd. for $C_{18}H_{23}N_2O_6$ $[M+H]^+$: 363.1551, found: 363.1552.

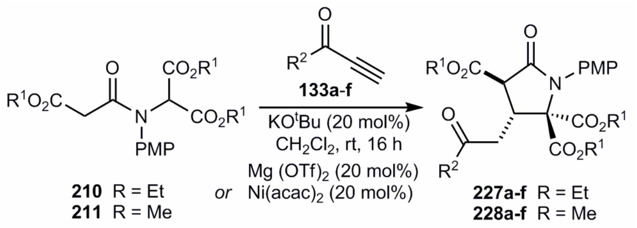
(*E*)-Diethyl 2-(3-ethoxy-*N*-(4-methoxyphenyl)-2-methyl-3-oxopropanamido)-2-(3-oxo-3-phenylprop-1-enyl)malonate (226)



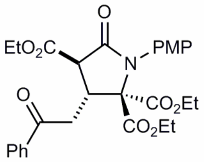
To a stirred solution of tethered diacid **212** (41 mg, 0.10 mmol), KO^tBu (2 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature was added a solution of alkynone **133a** (16 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) *via* cannula dropwise over 1 min. The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (3:1, hexane/EtOAc) afforded the mono-Michael adduct **226** (*E*) as colourless oil (42 mg, 97%). IR (film) 3066, 2985, 2941, 1745 (C=O), 1670 (C=O), 1510, 1446, 1373, 1244, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.88-7.86 (2H, m, Ar**H**), 7.58-7.54 (1H, m, Ar**H**), 7.47-7.43 (4H, m, Ar**H**), 7.22 (1H, d, *J* = 15.8 Hz; C**H**=CHC=O), 7.07 (1H, d, *J* = 15.8 Hz; CH=C**H**C=O), 6.91 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.36-3.99 (6H, m, 3 x $OC\mathbf{H}_2CH_3$), 3.83 (3H, s, $OC\mathbf{H}_3$), 3.88 (1H, q, *J* = 7.0 Hz; C**H**CH_3), 1.33-1.30 (6H, m, $CHC\mathbf{H}_3$, 2 x

OCH_2CH_3), 1.20 (3H, t, *J* = 7.1 Hz; OCH_2CH_3), 1.13 (3H, t, *J* = 7.1 Hz; OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.9 (C), 170.6 (C), 170.2 (C), 165.8 (C), 165.3 (C), 160.0 (C), 140.4 (CH), 278.7 (C), 132.9 (CH), 132.3 (CH), 131.5 (C), 131.1 (CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.1 (CH), 114.5 (2 x CH), 75.1 (C), 62.9 (CH_2), 62.7 (CH_2), 61.2 (CH_2), 55.4 (CH_3), 44.1 (CH), 14.0 (CH_3),13.9 (CH_3), 13.8 (CH_3), 13.7 (CH_3); LRMS (ES) Exact mass calcd. for $C_{23}H_{29}NO_8$ $[M+H]^+$: 540.2, found: 540.2.

5.2.3 Double Michael Reactions: General Procedure

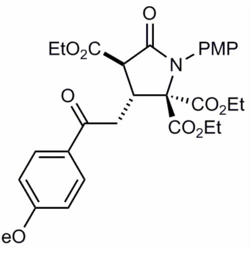


To a stirred solution of the appropriate tethered diacid (0.20 mmol), KO^tBu (4.7 mg, 0.04 mmol) and the appropriate metal salt (0.04 mmol) in CH_2Cl_2 (0.5 mL) at room temperature was added a solution of the appropriate alkynone (0.22 mmol) in CH_2Cl_2 (0.5 mL) *via* cannula dropwise over 1 min. The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the double Michael product.

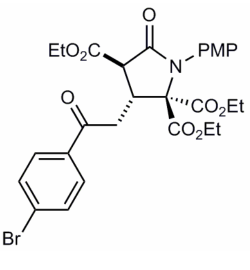


(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (227a). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133a** (29 mg, 0.22 mmol) and $Ni(acac)_2$ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (80 mg, 76%) as an 18:1 inseparable mixture of diastereomers **227a**. Trituration with Et_2O, followed by recrystallization from Et_2O/hexane gave colorless crystals suitable for X-ray diffraction. m.p 101–102 °C; IR (film) 3047, 2980, 1733 (C=O), 1713 (C=O), 1674 (C=O), 1509, 1249, 1053, 803, 778 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97-7.95 (2H, m, Ar**H**), 7.63-7.57 (1H, m, Ar**H**), 7.51-7.47 (2H, m, Ar**H**), 7.16 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.87 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.37-4.24 (4H, m, 2 x OCH_2CH_3), 4.18-4.06 (3H, m, OCH_2CH_3 and CH_2CH), 3.80

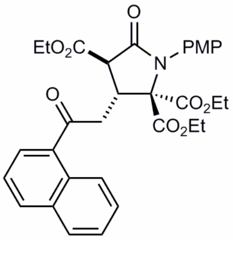
(3H, s, OC**H**$_3$), 3.64 (1H, d, *J* = 11.3 Hz, C**H**C=O), 3.61 (1H, dd, *J* = 16.7, 4.7 Hz, C**H**$_2$CH), 3.02 (1H, dd, *J* = 16.7, 9.1 Hz, C**H**$_2$CH), 1.31-1.26 (6H, m, 2 x OCH$_2$C**H**$_3$), 1.06 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 196.4 (C), 170.1 (C), 168.4 (C), 167.9 (C), 166.1 (C), 159.2 (C), 136.1 (C), 133.5 (CH), 129.3 (2 x CH), 129.1 (C), 128.7 (2 x CH), 128.1 (2 x CH), 114.0 (2 x CH), 75.4 (C), 62.8 (CH$_2$), 62.4 (CH$_2$), 61.9 (CH$_2$), 55.4 (CH$_3$), 52.7 (CH), 40.3 (CH), 39.1 (CH$_2$), 14.0 (CH$_3$), 14.0 (CH$_3$), 13.6 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{28}H_{32}NO_9$ [M+H]$^+$: 526.2072, found: 526.2069.



(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrolidin-2-one (227b). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133b** (35 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (25% EtOAc/petrol) to give a yellow oil (77 mg, 69%) as a 10:1 inseparable mixture of diastereomers. IR (film) 2981, 2937, 2840, 1734 (C=O), 1717 (C=O), 1679 (C=O), 1600, 1511, 1249, 1171, 1026 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.94 (2H, dm, *J* = 9.0 Hz, Ar**H**), 7.15 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.95 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.87 (2H, dm, *J* = 9.1 Hz, Ar**H**), 4.39-4.22 (4H, m, 2 x OC**H**$_2$CH$_3$), 4.18-4.03 (3H, m, OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.88 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.64 (1H, d, *J* = 11.3 Hz, C**H**C=O), 3.57 (1H, dd, *J* = 16.3, 4.6 Hz, C**H**$_2$CH), 2.91 (1H, dd, *J* =16.3, 9.3 Hz, C**H**$_2$CH), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.05 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 194.9 (C), 170.2 (C), 168.4 (C), 167.9 (C), 166.1 (C), 163.7 (C), 159.2 (C), 130.4 (2 x CH), 129.3 (2 x CH), 129.2 (2 x C), 114.0 (2 x CH), 113.8 (2 x CH), 75.4 (C), 62.8 (CH$_2$), 62.4 (CH$_2$), 61.8 (CH$_2$), 55.5 (CH$_3$), 55.4 (CH$_3$), 52.7 (CH), 40.5 (CH), 38.7(CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$), 13.5 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{29}H_{34}NO_{10}$ [M+H]$^+$: 556.2177, found: 556.2175.

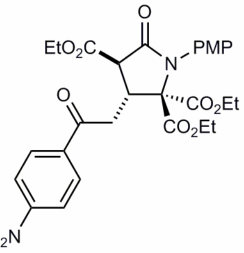


(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-4-[2-(4-bromophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (227c). The title compound was prepared according to the General Procedure from tethered diacid **210** (39.5 mg, 0.1 mmol), alkynone **133c** (25 mg, 0.12 mmol) and Mg(OTf)$_2$ (5 mg, 0.02 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (25 mg, 45%) as a > 19:1 inseparable mixture of diastereomers. IR (film) 2981, 2928, 1734(C=O), 1692(C=O), 1585, 1511, 1249, 1179, 1010, 829; ^{1}H NMR (360 MHz, $CDCl_3$) 7.84 (2H, dm, *J* = 8.7 Hz, Ar**H**), 7.63 (2H, dm, *J* = 8.7 Hz, Ar**H**), 7.15 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.87 (2H, dm, *J* = 9.1 Hz,, Ar**H**), 4.39-4.22 (4H, m, 2 x OC**H**$_2$CH$_3$), 4.17-4.03 (3H, m, OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.80 (3H, s, OC**H**$_3$), 3.63 (1H, d, *J* = 11.4, C**H**C=O), 3.57 (1H, dd, *J* = 16.4, 4.7 Hz, C**H**$_2$CH), 2.92 (1H, dd, *J* =16.4, 9.2, C**H**$_2$CH), 1.29 (3H, t, *J* = 7.1, OCH$_2$C**H**$_3$), 1.28 (3H, t, *J* = 7.2, OCH$_2$C**H**$_3$), 1.05 (3H, t, *J* = 7.1, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 195.6 (C), 169.9 (C), 168.4 (C), 167.9 (C), 166.1 (C), 159.3 (C), 134.8 (C), 132.1 (2 x CH), 129.6 (2 x CH), 129.3 (2 x CH), 129.1 (C), 128.8 (C), 114.1 (2 x CH), 75.3 (C), 63.3 (CH$_2$), 62.9 (CH$_2$), 62.4 (CH$_2$), 55.8 (CH$_3$), 52.9 (CH), 40.7 (CH), 39.5 (CH$_2$), 14.4 (CH$_3$), 14.4 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{28}H_{31}{}^{79}BrNO_9$ $[M+H]^+$: 604.1177, found: 604.1177.

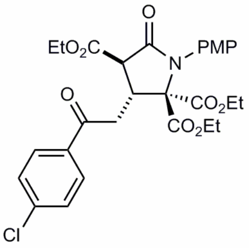


(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(2-naphthyl)-2-oxoethyl]pyrrolidin-2-one (227d). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133d** (40 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (79 mg, 69%) as an 8:1 inseparable mixture of diastereomers. IR (film) 2981, 2935, 2848, 1735 (C=O), 1716 (C=O), 1687 (C=O), 1511, 1249, 1214, 1025 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.66-8.63 (1H, m, Ar**H**), 8.04-8.02 (1H, m, Ar**H**), 7.96-7.94 (1H, m, Ar**H**), 7.90-7.88 (1H, m, Ar**H**), 7.64-7.51 (3H, m, Ar**H**), 7.18 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.88 (2H, dm, *J* = 9.0 Hz, Ar**H**), 4.40-4.09 (7H, m, 3 x OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.80 (3H, s, OC**H**$_3$), 3.68 (1H, dd, *J* = 17.0, 4.9 Hz, C**H**$_2$CH), 3.67 (1H, d, *J* = 11.3 Hz, C**H**C=O), 3.16 (1H, dd, *J* = 17.0, 8.9 Hz, C**H**$_2$CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.25 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$), 1.09 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.0 (C), 170.1 (C), 168.5 (C), 168.0

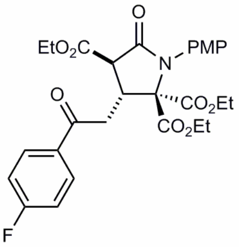
(C), 166.1 (C), 159.2 (C), 134.5 (C), 134.0 (C), 133.3 (CH), 130.1 (C), 129.2 (2 x CH and CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 125.8 (CH), 124.2 (CH), 114.0 (2 x CH), 73.4 (C), 62.8 (CH_2), 62.4 (CH_2), 61.9 (CH_2), 55.3 (CH_3), 52.9 (CH), 42.3 (CH_2), 40.7 (CH), 14.0 (2 x CH_3), 13.6 (CH_3); HRMS (ES) Exact mass calcd. for $C_{32}H_{34}NO_9$ $[M+H]^+$: 576.2228, found: 576.2231.



(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(4-nitrophenyl)-2-oxoethyl]pyrrolidin-2-one (227e). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133e** (39 mg, 0.22 mmol) and Ni(acac)$_2$ (10.8 mg, 0.04 mmol) and purified by column chromatography (25% EtOAc/petrol) to give a yellow oil (88 mg, 77%). IR (film) 2936, 2849, 1734 (C=O), 1717 (C=O), 1604, 1526, 1511, 1348, 1249, 1223, 1026 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.35 (2H, dm, *J* = 8.9 Hz, Ar**H**), 8.15 (2H, dm, *J* = 8.9 Hz, Ar**H**), 7.14 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.88 (2H, dm, *J* = 9.0 Hz, Ar**H),** 4.39-4.23 (4H, m, 2 x OC**H**$_2$CH$_3$), 4.18-4.05 (3H, m, OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.80 (3H, s, OC**H**$_3$), 3.66 (1H, dd, *J* = 16.3, 4.6 Hz, C**H**$_2$CH), 3.64 (1H, d, *J* = 11.4 Hz, C**H**C=O), 2.97 (1H, dd, *J* =16.3, 9.2 Hz, C**H**$_2$CH), 1.31 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$), 1.04 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.4 (C), 169.6 (C), 168.2 (C), 167.8 (C), 166.0 (C), 159.3 (C), 150.5 (C), 140.3 (C), 129.3 (2 x CH), 129.2 (2 x CH), 128.9 (C), 123.9 (2 x CH), 114.1 (2 x CH), 75.2 (C), 63.0 (CH_2), 62.6 (CH_2), 62.0 (CH_2), 55.4 (CH_3), 52.2 (CH), 40.2 (CH), 39.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 13.5 (CH_3); HRMS (ES) Exact mass calcd. for $C_{28}H_{31}N_2O_{11}$ $[M+H]^+$: 571.1922, found: 571.1923.

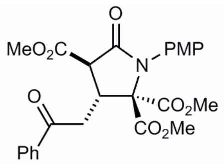


(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-4-[2-(4-chlorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (227f). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133f** (36 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (68 mg, 61%) as a 14:1 inseparable mixture of diastereomers. IR (film) 2983, 2940, 2841, 1743 (C=O), 1673 (C=O), 1510, 1250, 1035, 844 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.91 (2H, dm, *J* = 8.5 Hz, Ar**H**), 7.46 (2H, dm, *J* = 8.5 Hz, Ar**H**), 7.15 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.87 (2H, dm, *J* = 9.0 Hz, Ar**H**), 4.42-4.25 (4H, m, 2 x OC**H**$_2$CH$_3$), 4.21-4.07 (3H, m, OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.79 (3H, s, OC**H**$_3$), 3.63 (1H, d, *J* = 11.4 Hz, C**H**C=O), 3.58 (1H, dd, *J* = 16.3, 4.7 Hz, C**H**$_2$CH), 2.93 (1H, dd, *J* =16.4, 9.2, C**H**$_2$CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.05 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.4 (C), 170.0 (C), 168.4 (C), 167.9 (C), 166.1 (C), 159.2 (C), 140.0 (C), 134.4 (C), 129.5 (2 x CH), 129.3 (2 x CH), 129.0 (2 x CH and C), 114.1 (2 x CH), 75.3 (C), 62.9 (CH_2), 62.5 (CH_2), 61.9 (CH_2), 55.4 (CH_3), 52.5 (CH), 40.3 (CH), 39.1 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 13.5 (CH_3); HRMS (ES) Exact mass calcd. for $C_{28}H_{31}ClNO_9$ [M+H]$^+$: 560.01682, found: 560.1683.

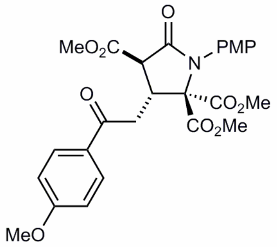


(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-4-[2-(4-fluorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (227g). The title compound was prepared according to the General Procedure from tethered diacid **210** (79 mg, 0.20 mmol), alkynone **133g** (30 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (81 mg, 75%) as a 15:1 inseparable mixture of diastereomers. IR (film) 2982, 2937, 2840, 1735 (C=O), 1718 (C=O), 1691 (C=O), 1597, 1511, 1249, 1230, 1158 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.02-7.98 (2H, m, Ar**H**), 7.17 (2H, dm, *J* = 8.7 Hz, Ar**H**), 7.15 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.87 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.39-4.21 (4H, m, 2 x OC**H**$_2$CH$_3$), 4.17-4.03 (3H, m, OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.80 (3H, s, OC**H**$_3$), 3.63 (2H, d, *J* = 11.4 Hz, C**H**C=O), 3.58 (1H, dd, *J* = 16.4, 4.6 Hz, C**H**$_2$CH), 2.93 (1H, dd, *J* = 16.4, 9.3 Hz, C**H**$_2$CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$), 1.05 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.0 (C), 170.0 (C), 168.3 (C), 167.9 (C), 166.0 (C), 165.9 (C, d, J_F = 255.0 Hz), 159.2(C), 132.5 (C, d, J_F = 2.9 Hz), 130.8 (2 x CH, d, J_F = 9.4 Hz), 129.3 (2 x CH), 129.0 (C), 115.8 (2 x CH, d, J_F = 21.9 Hz), 114.0 (2 x CH), 75.3 (C), 62.4 (CH_2), 62.8 (CH_2), 61.9 (CH_2), 55.3 (CH_3), 52.5 (CH), 40.3 (CH), 39.0 (CH_2),

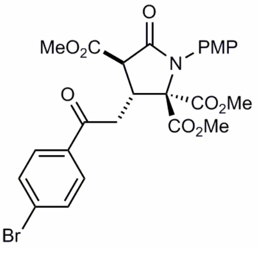
14.0 (CH$_3$), 13.9 (CH$_3$), 13.5 (CH$_3$); ^{19}F NMR (235 MHz, CDCl$_3$) δ –104.6; HRMS (ES) Exact mass calcd. for $C_{28}H_{31}FNO_9$ [M+H]$^+$: 544.1977, found: 544.1976.



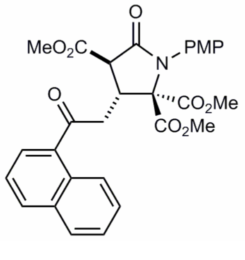
(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (228a). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.20 mmol), alkynone **133a** (29 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH$_2$Cl$_2$/Et$_2$O) to give a yellow oil (58 mg, 60%) as a 10:1 inseparable mixture of diastereomers. IR (film) 2954, 1740 (C=O), 1716 (C=O), 1687 (C=O), 1511, 1435, 1248, 830 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.63-7.57 (1H, m, Ar**H)**, 7.51-7.47 (2H, m, Ar**H**), 7.15 (2H, dm, *J* = 8.9 Hz, Ar**H**), 6.89 (2H, dm, *J* = 8.9 Hz, Ar**H**), 4.10 (1H, ddd, *J* = 11.3, 8.4, 5.1 Hz, CH$_2$C**H**), 3.67 (1H, d, *J* = 11.3 Hz, C**H**=O), 3.83 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 3.55 (1H, dd, *J* = 17.2, 5.1 Hz, C**H**$_2$CH), 3.07 (1H, dd, *J* = 17.2, 8.4 Hz, C**H**$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 196.4 (C), 169.9 (C), 168.8 (C), 168. x CH), 128.0 (2 x CH), 125.0 (C), 114.1 (2 x CH), 75.6 (C), 55.3 (CH$_3$), 53.2 (CH$_3$), 53.1 (CH$_3$), 52.8 3 (C), 166.5 (C), 159.3 (C), 136.0 (C), 133.5 (CH), 129.2 (2 x CH), 128.8 (C), 128.7 (2 (CH$_3$), 52.5 (CH), 40.4 (CH), 38.9 (CH$_2$); HRMS (ES) Exact mass calcd. for $C_{25}H_{26}NO_9$ [M+H]$^+$: 501.1868, found: 533.1875.



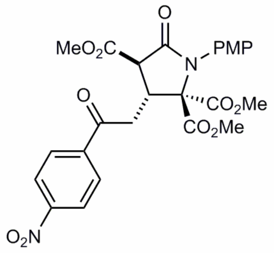
(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-4-[2-(4-methoxyphenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (228b). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.2 mmol), alkynone **133b** (50 mg, 0.24 mmol) and Mg(OTf)$_2$ (13 mg, 0.04 mmol) and purified by column chromatography (20:1 CH$_2$Cl$_2$/Et$_2$O) to give a yellow oil (68 mg, 60%) as a 8:1 inseparable mixture of diastereomers. IR (film) 2955, 2847, 1741 (C=O), 1715 (C=O), 1605, 1526, 1511, 1348, 1250, 855; ^{1}H NMR (360 MHz, CDCl$_3$) 7.93 (2H, dm, *J* = 9.0 Hz, Ar**H**), 7.14 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.95 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.88 (2H, dm, *J* = 9.1 Hz, Ar**H**), 4.08 (1H, ddd, *J* = 11.2, 8.7, 5.1 Hz, CH$_2$C**H**), 3.89 (3H, s, OC**H**$_3$), 3.82 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 3.67 (1H, d, *J* = 11.2 Hz, C**H**C=O**)**, 3.51 (1H, dd, *J* = 16.8, 5.1 Hz, C**H**$_2$CH), 2.98 (1H, dd, *J* = 16.8, 8.7 Hz, C**H**$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) 194.9 (C), 170.0 (C), 168.9 (C), 168.3 (C), 163.8 (C), 159.3 (C), 130.4 (2 x CH), 129.2 (2 x CH), 128.8 (C), 125.0 (C), 114.2 (2 x CH), 113.8 (2 x CH), 75.6 (C), 55.5 (CH$_3$), 55.3 (CH$_3$), 53.2 (CH$_3$), 53.1 (CH$_3$), 52.8 (CH$_3$), 52.5 (CH), 40.5 (CH), 38.6 (CH$_2$); HRMS (ES) Exact mass calcd. for $C_{26}H_{28}NO_{10}$ [M+H]$^+$: 514.16, found: 514.53.



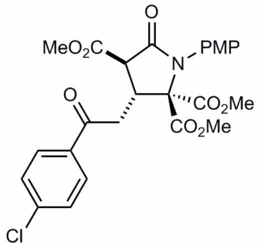
(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-4-[2-(4-bromophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (228c). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.20 mmol), alkynone **133c** (46 mg, 0.22 mmol) and Mg(OTf)$_2$ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH$_2$Cl$_2$/Et$_2$O) to give a yellow oil (68 mg, 60%) as a 10:1 inseparable mixture of diastereomers. IR (film) 2953, 2924, 2844, 1740 (C=O), 1716 (C=O), 1690, 1585, 1511, 1249 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.82 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.64 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.14 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.88 (2H, dm, *J* = 9.0 Hz, Ar**H**), 4.08 (1H, ddd, *J* = 11.4, 8.6, 5.1 Hz, CH$_2$C**H**), 3.83 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.68 (3H, s, OC**H**$_3$), 3.67 (1H, d, *J* = 11.4 Hz, C**H**=O), 3.51(1H, dd, *J* = 17.0, 5.1 Hz, C**H**$_2$CH**)**, 3.00 (1H, dd, *J* = 17.0, 8.6 Hz, C**H**$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 195.6 (C), 169.8 (C), 168.8 (C), 168.3 (C), 166.6 (C), 159.4 (C), 134.7 (C), 132.1 (2 x CH), 129.6 (2 x CH), 129.3 (2 x CH), 128.9 (C), 128.8 (C), 114.2 (2 x CH), 75.5 (C), 55.4 (CH$_3$), 53.3 (CH$_3$), 53.2 (CH$_3$), 53.0 (CH$_3$), 52.4 (CH), 40.4 (CH), 38.9 (CH$_2$); HRMS (ES) Exact mass calcd. for $C_{25}H_{25}{}^{79}BrNO_9$ [M+H]$^+$: 561.0707, found: 561.0706.



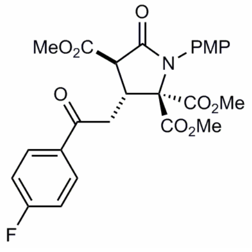
(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-1-(4-methoxyphenyl)-4-[2-(1-naphthyl)-2-oxoethyl]pyrrolidin-2-one (228d). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.20 mmol), alkynone **133d** (40 mg, 0.22 mmol) and Ni(acac)$_2$ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (72 mg, 67%) as a 15:1 inseparable mixture of diastereomers. IR (film) 2935, 2849, 2360, 1739 (C=O), 1715 (C=O), 1607, 1510, 1435, 1364, 1250 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 7.8 Hz, Ar**H**), 8.04 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.93-7.88 (2H, m, Ar**H**), 7.65-7.51 (3H, m, Ar**H**)**,** 7.17 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.89 (2H, d, *J* = 9.1 Hz, Ar**H**), 4.21 (1H, ddd, *J* = 11.3, 8.3, 5.6 Hz, CH_2C**H**), 3.84 (3H, s, OC$\mathbf{H}_3$), 3.81 (3H, s, OC$\mathbf{H}_3$), 3.77 (3H, s, OC$\mathbf{H}_3$), 3.72 (3H, s, OC$\mathbf{H}_3$), 3.69 (1H, d, *J* = 11.3 Hz, C**H**C=O)**,** 3.59 (1H, dd, *J* = 17.4, 5.6 Hz, C$\mathbf{H}_2$CH), 3.23 (1H, dd, *J* = 17.4, 8.3 Hz, C$\mathbf{H}_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.0 (C), 169.8 (C), 168.9 (C), 168.3 (C), 166.6 (C), 159.2 (C), 134.4 (C), 133.9 (C), 133.4 (CH), 130.0 (C), 129.1 (2 x CH), 128.8 (C), 128.4 (CH), 128.2 (CH), 127.9 (CH), 126.6 (CH), 125.7 (CH), 124.2 (CH), 114.2 (2 x CH), 75.6 (C), 55.3 (CH_3), 53.2 (2 x CH_3), 52.9 (CH_3), 52.6 (CH), 42.2 (CH_2), 40.7 (CH); HRMS (ES) Exact mass calcd. for $C_{29}H_{28}NO_9$ $[M+H]^+$: 533.1759, found: 533.1759.



(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-1-(4-methoxyphenyl)-4-[2-(4-nitrophenyl)-2-oxoethyl]pyrrolidin-2-one (228e). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.2 mmol), alkynone **133e** (42 mg, 0.24 mmol) and $Ni(acac)_2$ (10 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (41 mg, 39%) as a single diastereomer. IR (film) 2955, 2841, 1740 (C=O), 1715 (C=O), 1600, 1511, 1250, 1171, 1028, 834; ^1H NMR (360 MHz, $CDCl_3$) 8.35 (2H, dm, *J* = 9.0 Hz, Ar**H**), 8.13 (2H, dm, *J* = 9.0 Hz, Ar**H**), 7.13 (2H, dm, *J* = 9.1 Hz,, Ar**H**), 6.89 (2H, dm, *J* = 9.1 Hz, Ar**H**)**,** 4.10 (1H, ddd, *J* = 11.4, 8.6, 5.2 Hz, C**H**CH_2), 3.84 (3H, s, OC$\mathbf{H}_3$), 3.83 (3H, s, OC$\mathbf{H}_3$), 3.81 (3H, s, OC$\mathbf{H}_3$), 3.68 (1H, d, *J* = 11.4 Hz, C**H**C=O)**,** 3.69 (3H, s, OC$\mathbf{H}_3$), 3.59 (1H, dd, *J* = 17.0, 5.2 Hz, CHC$\mathbf{H}_2$), 3.07 (1H, dd, *J* = 17.0, 8.6 Hz, CHC$\mathbf{H}_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 195.3 (C), 169.5 (C), 168.7 (C), 168.2 (C), 166.6 (C), 159.4 (C), 150.6 (C), 140.3 (C), 129.3 (2 x CH), 129.2 (2 x CH), 128.6 (C), 124.0 (2 x CH), 114.3 (2 x CH), 75.4 (C), 55.4 (CH_3), 53.3 (CH_3), 53.2 (CH_3), 53.0 (CH_3), 52.2 (CH), 40.3 (CH), 39.5 (CH_2); HRMS (ES) Exact mass calcd. for $C_{25}H_{25}N_2O_{11}$ $[M+H]^+$: 530.14, found: 530.00.

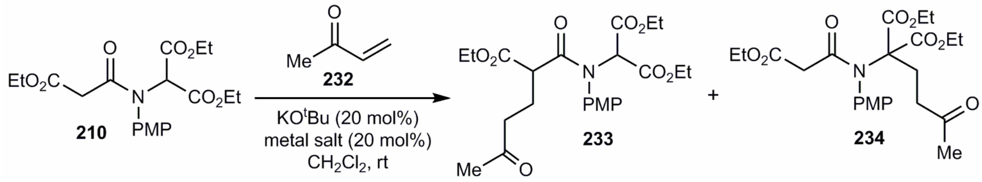


(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-4-[2-(4-chlorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (228f). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.20 mmol), alkynone **133f** (39 mg, 0.24 mmol) and Ni(acac)$_2$ (10 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow oil (47 mg, 45%) as a >20:1 inseparable mixture of diastereomers. IR (film) 2954, 2922, 1740 (C=O), 1716 (C=O), 1690, 1589, 1511, 1436, 1249, 829; ^{1}H NMR (360 MHz, $CDCl_3$) 7.89 (1H, dm, *J* = 8.6 Hz, Ar**H**), 7.47 (1H, dm *J* = 8.6 Hz, Ar**H**), 7.14 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.88 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.08 (1H, ddd, *J* = 13.6, 8.5, 5.1 Hz, C**H**CH$_2$), 3.83 (3H, s, OC**H**$_3$), 3.82 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.68-3.65 (4H, m, OC**H**$_3$ and C**H**C=O), 3.52(1H, dd, *J* = 17.0, 5.1 Hz, CHC**H**$_2$**)**, 3.23 (1H, dd, *J* = 17.0, 8.5 Hz, CHC**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 195.4 (C), 169.8 (C), 168.8 (C), 168.3 (C), 166.6 (C), 159.4 (C), 140.1 (C), 134.3 (C), 129.5 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 128.8 (C), 114.2 (2 x CH), 75.5 (C), 55.4 (OCH_3), 53.3 (CH_3), 53.2 (CH_3), 52.9 (CH_3), 52.4 (CH), 40.4 (CH), 38.9 (CH_2); HRMS (ES) Exact mass calcd. for $C_{25}H_{25}ClNO_9$ [M$^+$]: 518.1207, found: 518.1212.



(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-4-[2-(4-fluorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (228g). The title compound was prepared according to the General Procedure from tethered diacid **211** (71 mg, 0.20 mmol), alkynone **133g** (30 mg, 0.22 mmol) and Ni(acac)$_2$ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH_2Cl_2/Et_2O) to give a yellow solid (59 mg, 59%) as a 10:1 inseparable mixture of diastereomers. m.p. 146–147 °C; IR ($CHCl_3$) 2955, 2924, 2847, 1741 (C=O), 1716 (C=O), 1689 (C=O), 1597, 1510, 1249, 1231, 1158 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.00-7.96 (2H, m, Ar**H**), 7.18-7.13 (4H, m, Ar**H**), 6.88 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.08 (1H, ddd, *J* = 11.3, 8.6, 5.1 Hz, CH$_2$C**H**), 3.82 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.67 (1H, d, *J* = 11.3 Hz, C**H**C=O), 3.52 (1H, dd, *J* = 16.9, 5.1 Hz, C**H**$_2$CH), 3.01 (1H, dd, *J* = 16.9, 8.6 Hz, C**H**$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.9 (C), 169.8 (C), 168.7 (C), 168.2 (C), 166.6 (C), 165.9 (C, d, J_F = 255.5 Hz), 159.3 (C), 132.5 (C, d, J_F = 2.8 Hz), 130.8 (2 x CH, d, J_F = 9.4 Hz), 129.2 (2 x CH), 128.8 (C), 115.8 (2 x CH, d, J_F = 22.0 Hz), 114.2 (2 x CH), 75.5 (C), 55.3 (CH_3), 53.2 (CH_3), 53.1 (CH_3), 52.9 (CH_3), 52.4 (CH), 40.4 (CH), 38.8 (CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ –104.4; HRMS (ES) Exact mass calcd. for $C_{25}H_{25}FNO_9$ $[M+H]^+$: 519.1773, found: 533.1777.

Diethyl *N*-(2-carbethoxy-5-oxohexanoyl)-*N*-(4-methoxyphenyl)aminomalonate (233) and diethyl 2-[*N*-(2-carbethoxyacetyl)-*N*-(4-methoxyphenyl)amino]-2-(3-oxobutyl)malonate (234)



metal (20 mol%)	yield (%) 233	234
$Mg(OTf)_2$	52	0
$Ni(acac)_2$	11	30

Using $Mg(OTf)_2$: To a stirred solution of the tethered diacid **210** (79 mg, 0.20 mmol), KO^{t}Bu (4.7 mg, 0.04 mmol) and $Mg(OTf)_2$ (12.9 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) at room temperature was added methyl vinyl ketone (**232**) (20 μL, 0.22 mmol). The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) gave the *Michael adduct* **233** (48 mg, 52%) as a pale yellow oil.

Using $Ni(acac)_2$: To a stirred solution of the tethered diacid **210** (79 mg, 0.20 mmol), KO^{t}Bu (4.7 mg, 0.04 mmol) and $Ni(acac)_2$ (10.8 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) at room temperature was added methyl vinyl ketone (20 μL, 0.22 mmol). The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) gave the *Michael adduct* **233** (10 mg, 11%) as a pale yellow oil followed by the *Michael adduct* **234** (28 mg, 30%) as a pale yellow oil.

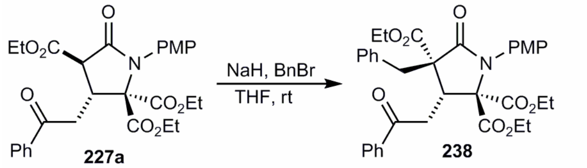
Data for **233**:

IR (film) 2983, 2938, 2908, 1741 (C=O), 1716 (C=O), 1668 (C=O), 1509, 1250, 1180, 1031 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36 (2H, br s, Ar**H**), 6.87 (2H, d, *J*

= 8.3 Hz, Ar**H**), 5.44 (1H, s, NC**H**), 4.28-4.00 (4H, m, 3 x OC**H**$_2$CH$_3$), 3.81 (3H, s, OC**H**$_3$), 3.46 (1H, dd, *J* = 8.1, 6.3 Hz, C**H**CH$_2$), 2.60-2.43 (2H, m, CHCH$_2$C**H**$_2$), 2.12 (3H, s, C**H**$_3$C=O), 2.10-2.05 (2H, m, CHC**H**$_2$), 1.26 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.16 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 207.7 (C), 169.6 (C), 169.1 (C), 165.9 (C), 165.4 (C), 159.9 (C), 131.9 (C), 131.2 (CH), 130.3 (CH), 114.5 (2 x CH), 64.9 (CH), 62.0 (2 x CH$_2$), 61.3 (CH$_2$), 55.4 (CH$_3$), 47.6 (CH), 40.1 (CH$_2$), 29.8 (CH$_3$), 23.1 (CH$_2$), 14.0 (CH$_3$), 13.9 (CH$_3$), 13.8 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{23}H_{32}NO_9$ [M+H]$^+$: 466.2072, found: 466.2070.

Data for **234**: IR (film) 2982, 2939, 2841, 1741 (C=O), 1671 (C=O), 1509, 1366, 1248, 1031, 843 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.36 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.91 (2H, dm, *J* = 9.0 Hz, Ar**H**), 4.19 (2H, q, *J* = 7.2 Hz, OC**H**$_2$CH$_3$), 4.19 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 4.12 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.83 (3H, s, OC**H**$_3$), 3.11 (2H, s, EtO$_2$CC**H**$_2$), 2.63-2.59 (2H, m, CH$_2$C**H**$_2$C=O), 2.17-2.13 (2H, m, C**H**$_2$CH$_2$C=O), 2.06 (3H, s, C**H**$_3$C=O), 1.28 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$), 1.21 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 206.6 (C), 167.6 (2 x C), 167.4 (C), 167.0 (C), 160.0 (C), 131.5 (2 x CH), 131.4 (C), 114.6 (2 x CH), 71.2 (C), 62.0 (2 x CH$_2$), 61.1 (CH$_2$), 55.5 (CH$_3$), 42.4 (CH$_2$), 38.5 (CH$_2$), 29.9 (CH$_3$), 28.9 (CH$_2$), 14.0 (2 x CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{23}H_{32}NO_9$ [M+H]$^+$: 466.2072, found: 466.2072.

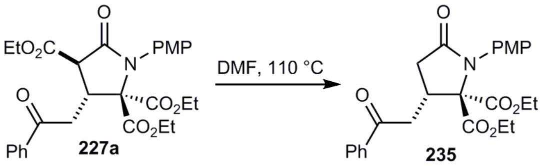
(±)-(3*R*,4*S*)-4-Benzyl 3,5,5-tricarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (238)



Tentative relative stereochemical assignment

To a solution of the double Michael product **227a** (53 mg, 0.10 mmol) in THF (1 mL) at room temperature was added NaH (60% dispersion in mineral oil, 40 mg, 0.10 mmol) in one portion, followed by BnBr (18 μL, 0.15 mmol). The mixture was stirred at room temperature for 5 h, quenched with H$_2$O (10 mL), and extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→33% EtOAc/hexane) gave the *benzylated pyrrolidinone* **238** (41 mg, 67%) as a yellow oil. IR (film) 2982, 2936, 2904, 1741 (C=O), 1706 (C=O), 1510, 1249, 1070, 1030, 913 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94-7.91 (2H, m, Ar**H**), 7.59 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.48 (2H, app t, *J* = 7.6 Hz, Ar**H**), 7.32 (5H, br s, Ar**H**), 7.19 (2H, dm, *J* = 8.9 Hz, Ar**H**), 6.83 (2H, dm, *J* = 8.8 Hz, Ar**H**), 4.31-4.25 (2H, m, OC**H**$_2$CH$_3$), 4.15-3.91 (5H, m, 2 x OC**H**$_2$CH$_3$ and CH$_2$C**H**), 3.79 (3H, s, OC**H**$_3$), 3.64 (1H, dd, *J* = 18.2, 10.8 Hz, C**H**$_2$CH), 3.64 (1H, d, *J* = 14.1 Hz, C**H**$_2$Ph), 3.24 (1H, d, *J* = 14.1 Hz, C**H**$_2$Ph), 3.10 (1H, dd, *J* = 18.2, 4.0 Hz, C**H**$_2$CH), 1.35 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$), 1.00-0.95 (6H, m, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.4 (C), 172.0 (C), 169.9 (C), 167.4 (C), 167.1 (C), 159.1 (C), 136.4 (C), 135.4 (C), 133.2 (CH), 131.0 (2 x CH), 130.4 (2 x CH), 129.3 (C), 128.6 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 113.7 (2 x CH), 75.7 (C), 62.3 (CH$_2$), 61.9 (CH$_2$), 61.7 (CH$_2$), 58.6 (C), 55.3 (CH$_3$), 40.4 (CH), 37.4 (CH$_2$), 36.7 (CH$_2$), 14.1 (CH$_3$), 13.6 (2 x CH$_3$); HRMS (ES) Exact mass calcd. for $C_{35}H_{38}NO_9$ $[M+H]^+$: 616.2541, found: 616.2538.

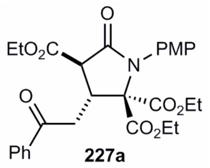
(±)-(4*R*)-5,5-Dicarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (235)



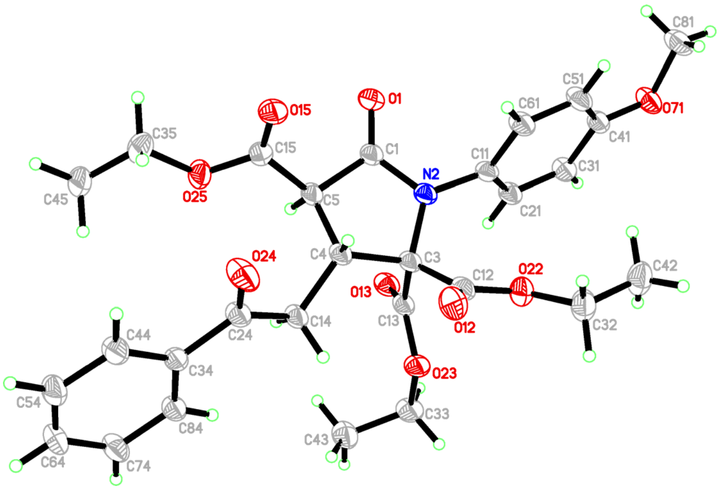
A solution of double Michael product **227a** (53 mg, 0.10 mmol) in DMF (1 mL) was heated to 110 °C for 72 h. After cooling to room temperature, the mixture was partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was separated and extracted with EtOAc (2 x 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→33% EtOAc/hexane) gave the *decarboxylated pyrrolidinone* **238** (27 mg, 60%) as a yellow oil. IR (film) 2981, 2936, 2838, 1730 (C=O), 1687 (C=O), 1511, 1294, 1248, 1031, 690 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 7.3 Hz, Ar**H**), 7.63-7.59 (1H, m, Ar**H**), 7.52-7.47 (2H, m, Ar**H**), 7.17 (2H, dm, *J* = 8.9 Hz, Ar**H**), 6.88 (2H, dm, *J* = 8.9 Hz, Ar**H**), 4.40-4.26 (2H, m, OC**H**$_2$CH$_3$), 4.19-4.03 (2H, m, OC**H**$_2$CH$_3$), 3.80 (3H, s, OC**H**$_3$), 3.80-3.70 (1H, m, CH$_2$C**H**), 3.54 (1H, dd, *J* = 17.2, 3.9 Hz, PhCOC**H**$_2$), 3.02-2.94 (2H, m, C**H**$_2$CON and PhCOC**H**$_2$), 2.40 (1H, dd, *J* = 16.7, 11.1 Hz, C**H**$_2$CON), 1.30 (3H, t, *J* = 7174.8 (C), 168.1 (C), 166.8 (C), 159.1 (C), 136.3 (C), 133.5 (CH), 129.5 (C and 2 x CH), 128.8 (2 x CH), 128.1 Hz, OCH$_2$C**H**$_3$), 1.06 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 196.7 (C), 174.8 (C), 168.1 (C), 166.8 (C), 159.2 (C), 136.3 (C),133.5 (CH), 129.5 (2 x CH), 128.8 (2 x CH), 128.0 (2 x CH), 114.1 (2 x CH), 62.5 (CH$_2$), 62.3 (CH$_2$), 60.4 (C), 55.4 (CH$_3$), 39.8 (CH$_2$), 36.7 (CH), 35.6 (CH$_2$), 14.2 (CH$_3$), 13.6 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{25}H_{28}NO_7$ [M+H]$^+$: 454.1860, found: 454.1863.

Stereochemical Determinations

The relative configuration of **227a** was determined by X-ray crystallography. Crystal structure deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 638217 Note – there is a small degree of disorder associated with one of the geminal diester groups (see CIF file for details)



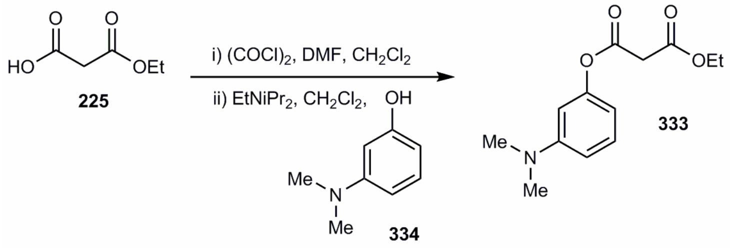
227a



The relative stereochemistries of the remaining double Michael products **9**–**17** were assigned by analogy.

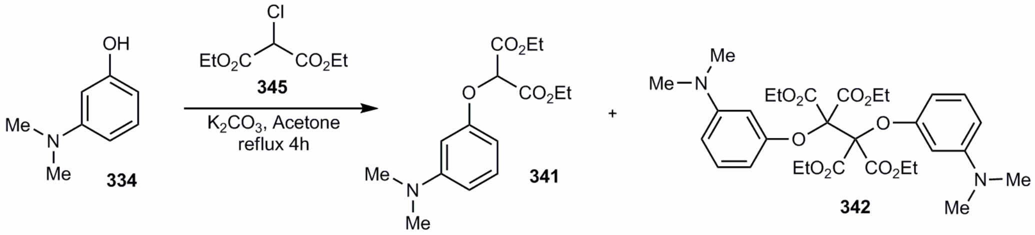
5.3 Michael addition combined with Friedel-Crafts alkylation

3-Dimethylaminophenyl ethyl malonate (333).



DMF (1 mL) was added dropwise over 15 min to a solution of the acid **225** (2.00 g, 15.1 mmol) and $(COCl)_2$ (1.28 mL, 15.1 mmol) in CH_2Cl_2 (5 mL) at room temperature. The solution thus obtained was transferred by cannula to a stirred solution of the alcohol **334** (1.48 g, 10.8 mmol) and EtN^iPr_2 (2.9 mL, 17.3 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 16h, after that was partitioned between saturated aqueous $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/hexane) afforded the desired ester **333** (1.17 g, 43%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19-7.12 (1H, m, Ar**H**), 6.54-6.50 (1H, m, Ar**H**), 6.42-6.35 (2H, m, Ar**H**), 4.2 (2H, q, *J* = 7.1 Hz OC**H**$_2$CH$_3$), 3.53 (2H, s, C**H**$_2$), 2.87 (6H, s, N(C**H**$_3$)$_2$), 1.26 (3H, t, *J* = 7.1 Hz OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1 (C), 165.0 (C), 151.5 (C), 151.4 (C), 129.5 (CH), 110.0 (CH), 108.7 (CH), 104.9 (CH), 61.5 (CH_2), 41.5 (CH_2), 40.2 (2 x CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd. for $C_{13}H_{18}NO_4$ $[M+H]^+$: 252.1230, found: 252.1227.

Diethyl 2-(3-dimethylaminophenoxy) malonate (341) and 2,3-bis-(3-dimethylaminophenoxy)-2,3-bis-diethylethoxycarbonylsuccinic acid diethyl ester (342).



A mixture of alcohol **334** (1.00 g, 7.3 mmol) and K_2CO_3 (2.00 g, 14.6 mmol) in acetone (20 mL) was heated to reflux. Diethylchloromalonate **345** (2.35 mL, 14.6 mmol) was then added dropwise to the mixture and the resulting suspension was stirred for 6 h. After that time the mixture was allowed to cool down to room temperature and quenched with a saturated aqueous $NaHCO_3$ solution (20 mL).). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) afforded the the byproduct **342** (96 mg, 2%) as a colourless oil, followed by the desired ester **341** (1.05 g, 49%) as a yellow oil.

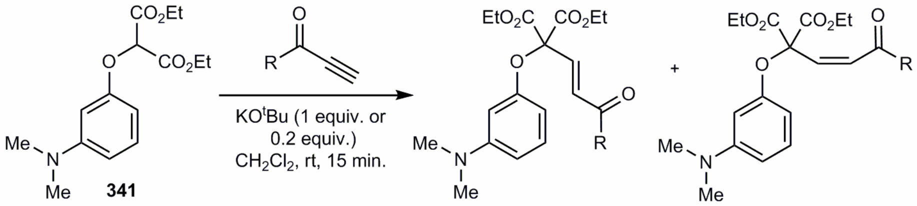
Data for **342**:

IR (film) 2983, 2812, 1763 (C=O), 1610 (C=O), 1504, 1267, 1228, 1153, 1051, 928 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.16-7.09 (2H, m, Ar**H**), 6.56-6.47 (6H, m, Ar**H**), 4.33 (8H, q, *J* = 7.1, OC**H**$_2$CH$_3$), 2.93 (12H, s, 2 x N(C**H**$_3$)$_2$), 1.26 (12H, t, *J* = 7.1, 4 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.5 (4 x C), 154.5 (2 x C), 151.6 (2 x C), 129.5 (2 x CH), 108.6 (2 x CH), 104.8 (2 x CH), 102.5 (2 x CH), 88.7 (2 x C), 63.8 (4 x CH_2), 40.3 (4 x CH_3), 13.6 (4 x CH_3); LRMS (EI) Mass calcd. for $C_{15}H_{22}NO_5$ $[M+H]^+$: 588.3, found: 588.2.

Data for **341**:

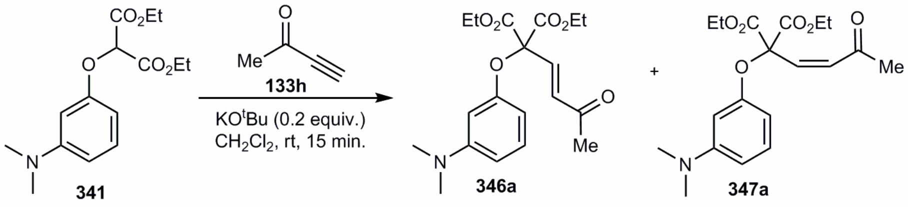
IR (film) 2979, 2924, 1749 (C=O), 1608 (C=O), 1502, 1225, 1159, 1022, 827, 754 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.16-7.11 (1H, m, Ar**H**), 6.55-6.49 (3H, m, Ar**H**), 5.31 (1H, s, C**H(**CO$_2$Et)$_2$), 4.31 (4H, q, *J* = 7.1 Hz OC**H**$_2$CH$_3$), 2.94 (6H, s, N(C**H**$_3$)$_2$), 1.27 (3H, t, *J* = 7.1 Hz OCH$_2$C**H**$_3$), 1.26 (3H, t, *J* = 7.1 Hz OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.8 (2 x C), 157.9 (C), 151.9 (C), 129.7 (CH), 107.2 (CH), 101.8 (CH), 100.6 (CH), 76.3 (CH), 62.3 (2 x CH_2), 40.8 (2 x CH_3), 14.4 (2 x CH_3); HRMS (EI) Exact mass calcd. for $C_{15}H_{22}NO_5$ $[M+H]^+$: 295.1387, found: 295.1415.

5.3.1 Michael Additions: General Procedure



To a stirred solution of the ester (1 equiv.) and KO^{t}Bu (1 equiv. or 0.2 equiv.) in CH_2Cl_2 (1 mL) at room temperature was added a solution of the appropriate alkynone (1.2 equiv.) in CH_2Cl_2 (1 mL) *via cannul*a dropwise over 1 min. The reaction was stirred at room temperature for 15 min., quenched with NH_4Cl saturated solution (2 mL), extracted with CH_2Cl_2 (5 x 3 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the two geometrical stereoisomers.

(*E*)-Diethyl-2-(3-dimethylaminophenoxy)-2-(3-oxobutenyl)malonate (346a) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-(3-oxobutenyl)malonate (347a).



The title compounds were prepared according to the General Procedure from the ester **341** (59 mg, 0.20 mmol), alkynone **133h** (15 μL, 0.24 mmol) and KO^{t}Bu (4 mg, 0.04 mmol) and purified by column chromatography (15% Et_2O/CH_2Cl_2) to give first diastereomer **346a** (*E*) as a yellow solid (40 mg, 56%), followed by diastereomer **347a** (*Z*) as a yellow oil (22 mg, 31%).

Data for **346a**:

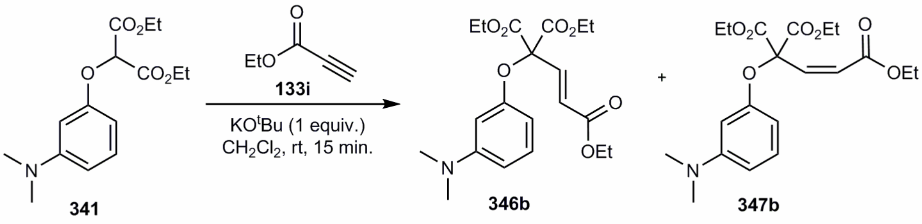
M.p 76–78 °C; IR (film) 2981, 2925, 1747 (C=O), 1687 (C=O), 1610, 1234, 1167, 1055, 845, 758 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 7.41 (1H, d, *J* = 16.2 Hz, C**H**=CHC=O), 7.07-7.20 (1H, m, Ar**H**), 6.55 (1H, d, *J* = 16.2 Hz, CH=C**H**C=O), 6.42-6.39 (2H, m, Ar**H)**, 6.11-6.08 (1H, m, Ar**H**), 4.37-4.23 (4H, m, 2 x $OC\mathbf{H}_2CH_3$), 2.95 (6H, s, $N(C\mathbf{H}_3)_2$), 2.32 (3H, s, $C\mathbf{H}_3C$=O), 1.25 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.1 (C), 169.9 (2xC), 155.4 (C), 151.8 (C), 138.4 (CH), 132.8 (CH), 129.3 (CH), 107.0 (CH), 104.0 (CH), 101.8

(CH), 83.5 (C), 63.0 (2 x CH$_2$), 40.4 (2 x CH$_3$), 28.1 (CH$_3$), 13.8 (2 x CH$_3$); HRMS (ES) Exact mass calcd. for $C_{19}H_{26}NO_6$ [M+H]$^+$: 364.1755, found: 364.1756.

Data for **347a**:

IR (film) 2981, 2808, 1739(C=O), 1676 (C=O), 1610 (C=O), 1502, 1238, 1171, 1041, 850 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.00 (1H, t, *J* = 8.2 Hz, Ar**H**), 6.70 (1H, d, *J* = 12.4 Hz, C**H**=CHC=O), 6.35 (1H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 6.29 (1H, t, *J* = 2.4 Hz, Ar**H**), 6.25 (1H, d, *J* = 12.4 Hz, CH=C**H**C=O), 6.10-6.07 (1H, m, Ar**H**), 4.26 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 2.89 (6H, s, N(C**H**$_3$)$_2$), 2.14 (3H, s, C**H**$_3$C=O), 1.21 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 199.7 (C), 166.4 (2 x C), 155.5 (C), 151.7 (C), 132.4 (CH), 132.1 (CH), 129.1 (CH), 106.9 (CH), 104.5 (CH), 102.3 (CH), 82.3 (C), 62.7 (2 x CH$_2$), 40.4 (2 x CH$_3$), 30.4 (CH$_3$), 13.7 (2 x CH$_3$); HRMS (ES) Exact mass calcd. for $C_{19}H_{26}NO_6$ [M+H]$^+$: 364.1755, found: 364.1755.

(*E*)-Triethyl-1-(3-dimethylaminophenoxy)propenyl-1,1,3-tricarboxylate (346b) and (*Z*)-triethyl-1-(3-dimethylaminophenoxy)propenyl-1,1,3-tricarboxylate (347b).



The title compounds were prepared according to the General Procedure from ester **341** (100 mg, 0.33 mmol), ester **133i** (0.04 mL, 0.39 mmol) and KO^{t}Bu (37 mg, 0.33 mmol) and purified by column chromatography (15% Et$_2$O/CH$_2$Cl$_2$) to give first diastereomer **346b** (*E*) yellow oil (78 mg, 60%), followed by diastereomer **347b** (*Z*) yellow oil (20 mg, 15%).

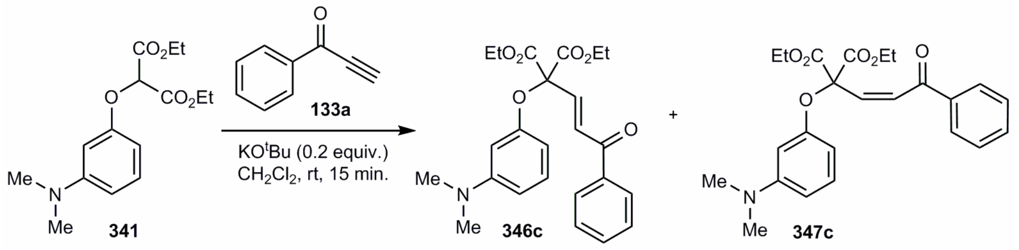
Data for **346b**:

IR (film) 2979, 2808, 1772 (C=O), 1745 (C=O), 1726 (C=O), 1614 (C=O), 1504, 1234, 1163, 858 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.54 (1 H, d, *J* = 15.9 Hz, C**H**=CHC=O), 7.04-6.99 (1H, m, Ar**H**), 6.38-6.35 (2H, m, Ar**H**), 6.29 (1H, d, *J* = 15.9 Hz, CH=C**H**C=O), 6.09-6.06 (1H, m, Ar**H**), 4.32-4.16 (6H, m, 3 x OC**H**$_2$CH$_3$), 2.91 (6H, s, N(C**H**$_3$)$_2$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.20 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.8 (2 x C), 165.3 (C), 155.4 (C), 151.8 (C), 139.8 (CH), 129.2 (CH), 125.2 (CH), 106.9 (CH), 104.2 (CH), 101.8 (CH), 83.6 (C), 62.9 (2 x CH_2), 60.8 (CH_2), 40.4 (2 x CH_3), 14.1 (CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{20}H_{28}NO_7$ $[M+H]^+$: 394.1860, found: 394.1860.

Data for **347b**:

IR (film) 2979, 2789, 1739 (C=O), 1745 (C=O), 1610 (C=O), 1560, 1238, 1171, 1041, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (1H, t, d, *J* = 8.2 Hz, Ar**H**), 6.98 (1H, d, *J* = 12.2 Hz, C**H**=CHC=O), 6.35 (1 H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 6.29 (1 H, t, *J* = 2.4 Hz, Ar**H**), 6.08-6.06 (1H, m, Ar**H**), 6.06 (1H, d, *J* = 12.2 Hz, CH=C**H**C=O), 4.26 (4H, q, *J* = 7.1 Hz, $OC\mathbf{H}_2CH_3$), 4.16 (2 H, q, *J* = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 2.89 (6H, s, $N(C\mathbf{H}_3)_2$), 1.25 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.21 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.5 (2 x C), 165.0 (C), 155.6 (C), 151.7 (C), 136.6 (CH), 129.1 (CH), 124.8 (CH), 107.0 (CH), 104.7 (CH), 102.5 (CH), 81.9 (C), 62.7 (2 x CH_2), 60.7 (CH_2), 40.4 (2 x CH_3), 14.0 (CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{20}H_{28}NO_7$ $[M+H]^+$: 394.1860, found: 394.1861.

(*E*)-Diethyl-2-(3-dimethylaminophenoxy)-2-(3-oxo-3-phenylpropenyl)malonate (346c) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-(3-oxo-3-phenylpropenyl)malonate (347c).



The title compounds were prepared according to the General Procedure from the ester **341** (59 mg, 0.20 mmol), alkynone **133a** (31 mg, 0.24 mmol) and KO^{t}Bu (4 mg, 0.04 mmol) and purified by column chromatography (15% Et_2O/CH_2Cl_2) to give first diastereomer **346c** (*E*) as a yellow oil (53 mg, 62%), followed by diastereomer **347c** (*Z*) yellow oil (25 mg, 30%).

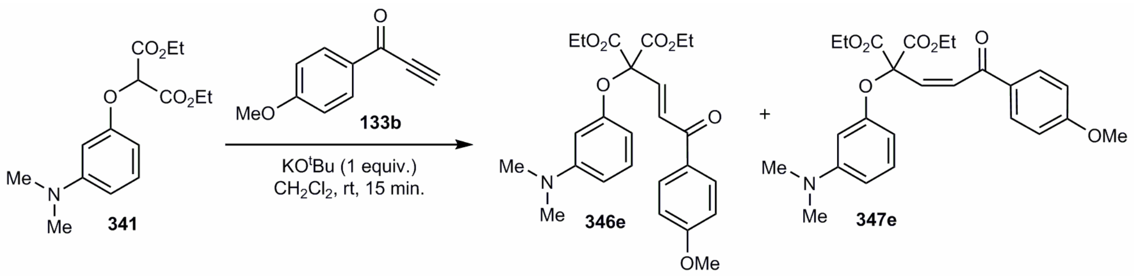
Data for **346c**:

IR (film) 2981, 2794, 1738 (C=O), 1685 (C=O), 1614 (C=O), 1508, 1448, 1234, 1095, 858 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.86-7.84 (2H, m, Ar**H**), 7.60 (1H, d, *J* = 15.7 Hz, C**H**=CHC=O), 7.55-7.53 (1H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 7.34 (1H, d, *J* = 15.7 Hz, CH=C**H**C=O), 7.03 (1H, t, *J* = 8.2 Hz, Ar**H)**, 6.42-6.41 (1H, m, Ar**H**), 6.38 (1H, dd, *J* = 8.2, 2.1 Hz, Ar**H**), 6.17-6.14 (1H, m, Ar**H**), 4.35-4.20 (4H, m, 2 x OC**H**$_2$CH$_3$), 2.92 (6H, s, N(C**H**$_3$)$_2$), 1.22 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 189.4 (C), 165.9 (2 x C), 155.5 (C), 151.8 (C), 139.3 (CH), 137.1 (C), 133.2 (CH), 129.4 (CH), 128.7 (3 x CH), 128.5 (2 x CH), 106.9 (CH), 104.4 (CH), 101.9 (CH), 84.0 (C), 62.9 (2 x CH_2), 40.4 (2 x CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.1911, found: 426.1917.

Data for **347c**:

IR (film) 2981, 2802, 1741(C=O), 1682 (C=O), 1622 (C=O), 1508, 1450, 1234, 1030, 858 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69-7.65 (2H, m, Ar**H**), 7.48-7.41 (1H, m, Ar**H**), 7.31-7.25 (2H, m, Ar**H**), 6.96 (1H, d, *J* = 12.4 Hz, C**H**=CHC=O), 6.91 (1H, t, *J* = 8.2 Hz, Ar**H**), 6.75 (1H, d, *J* = 12.4 Hz, CH=C**H**C=O), 6.25-6.21 (1H, m, Ar**H**), 5.99-5.95 (2H, m, Ar**H**), 4.28 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 2.70 (6H, s, N(C**H**$_3$)$_2$), 1.21 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 192.3 (C), 166.7 (2 x C), 155.4 (C), 151.5 (C), 136.4 (C), 133.8 (CH), 132.8 (CH), 130.7 (CH), 128.7 (3 x CH), 128.1 (2 x CH), 106.8 (CH), 104.4 (CH), 102.9 (CH), 82.3 (C), 62.7 (2 x CH_2), 40.3 (2 x CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.1911, found: 426.1911.

(*E*)-Diethyl-2-(3-Dimethylaminophenoxy)-2-[3-(4-methoxyphenyl)3-oxopropenyl)]malonate (346e) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-[3-(4-methoxyphenyl)-3-oxopropenyl]malonate (347e).



The title compounds were prepared according to the General Procedure from ester **341** (100 mg, 0.33 mmol), alkynone **133b** (62 mg, 0.39 mmol) and KO^{t}Bu (37 mg, 0.33 mmol) and purified by column chromatography (15% Et_2O/CH_2Cl_2) to give first diastereomer **346e** (*E*) as a yellow oil (70 mg, 46%), followed by diastereomer **347e** (*Z*) yellow oil (35 mg, 23%).

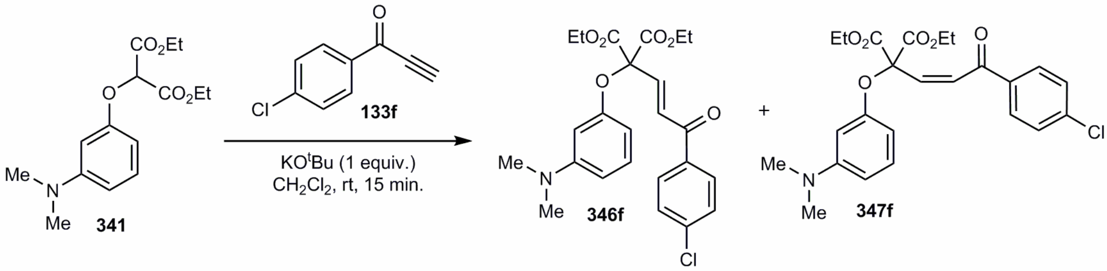
Data for **346e**:

IR (film) 2979, 1743 (C=O), 1668 (C=O), 1606 (C=O), 1508, 1452, 1254, 1174, 1039, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.57 (1H, d, *J* = 15.7 Hz, CH=C**H**C=O), 7.34 (1H, d, *J* = 15.7 Hz, C**H**=CHC=O), 7.02 (1H, t, *J* = 8.2 Hz, Ar**H**), 6.89 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.42-6.41 (1H, m, Ar**H**), 6.37 (1H, dd, *J* = 8.3, 2.2 Hz, Ar**H**), 6.16 (1H, dd, *J* = 8.1, 2.3 Hz, Ar**H**), 4.34-4.20 (4H, m, 2 x OC**H**$_2$CH$_3$), 3.85 (3H, s OC**H**$_3$), 2.91 (6H, s, N(C**H**$_3$)$_2$), 1.22 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 187.6 (C), 165.9 (2 x C), 163.7 (C), 155.6 (C), 151.8 (C), 138.4 (CH), 131.1 (2 x CH), 130.1 (C), 129.3 (CH), 128.6 (CH), 113.8 (2 x CH), 106.9 (CH), 104.4 (CH), 101.9 (CH), 84.1 (C), 62.9 (2 x CH$_2$), 55.4 (CH$_3$), 40.4 (2 x CH$_3$), 13.8 (2 x CH$_3$); $C_{25}H_{30}NO_7$ [M+H]$^+$: 456.2017, found: 456.2022.

Data for **347e**:

IR (film) 2927, 1745 (C=O), 1662 (C=O), 1604 (C=O), 1504, 1454, 1244, 1169, 1028, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.91 (1H, d, *J* = 12.4 Hz, CH=C**H**C=O), 6.94-6.91 (1H, m, Ar**H**), 6.75 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.73 (1H, d, *J* = 12.4 Hz, C**H**=CHC=O), 6.25-6.22 (1H, m, Ar**H**), 5.99-5.96 (2H, m, Ar**H**), 4.27 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 3.81 (3H, s, C**H**$_3$), 2.72 (6H, s, N(C**H**$_3$)$_2$), 1.22 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.1 (C), 166.7 (2 x C), 163.3 (C), 155.5 (C), 151.5 (C), 132.9 (CH), 131.0 (CH), 130.9 (2 x CH), 1129.7 (C), 128.6 (CH), 113.3 (2 x CH), 106.7 (CH), 104.4 (CH), 102.9 (CH), 82.2 (C), 62.7 (2 x CH$_2$), 55.3 (CH$_3$), 40.2 (2 x CH$_3$), 13.8 (2 x CH$_3$); $C_{25}H_{30}NO_7$ [M+H]$^+$: 456.2017, found: 456.2014.

(*E*)-Diethyl-2-(3-Dimethylaminophenoxy)-2-[3-(4-chlorophenyl)-3-oxopropenyl]malonate (346f) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-[3-(4-chlorophenyl)-3-oxopropenyl]malonate (347f)



The title compounds were prepared according to the General Procedure from the ester **341** (100 mg, 0.33 mmol), alkynone **133f** (63 mg, 0.39 mmol) and KO^{t}Bu (37 mg, 0.33 mmol) and purified by column chromatography (15% Et_2O/CH_2Cl_2) to give first diastereomer **346f** (*E)* yellow oil (64 mg, 42%), followed by diastereomer **347f** (*Z*) yellow oil (50 mg, 33%).

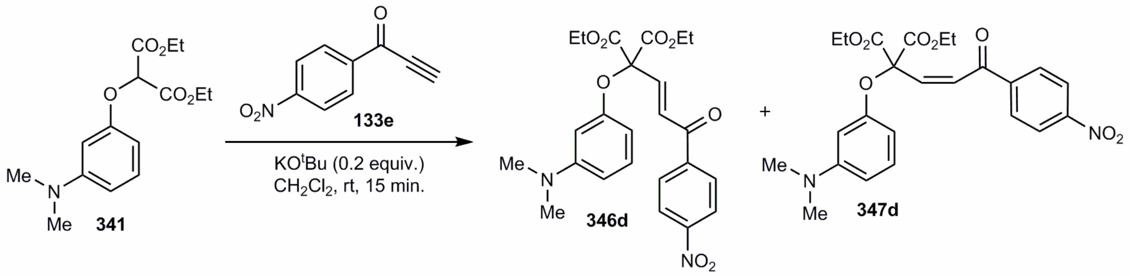
Data for **346f**:

IR (film) 2981, 1745 (C=O), 1672 (C=O), 1612 (C=O), 1502, 1450, 1248, 1167, 1057, 827 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.63 (1H, d, *J* = 15.7 Hz, CH=C**H**C=O), 7.42 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.32 (1H, d, *J* = 15.7 Hz, C**H**=CHC=O), 7.06 (1H, t, *J* = 8.2 Hz, Ar**H**), 6.45-6.44 (1H, m, Ar**H**), 6.40 (1H, dd, *J* = 8.3, 2.2 Hz, Ar**H**), 6.16 (1H, dd, *J* = 8.1, 2.3 Hz, Ar**H**), 4.38-4.24 (4H, m, Ar**H**), 2.95 (6H, s, N(C**H**$_3$)$_2$), 1.25 (6H, t, *J* = 7.1 Hz, 2 x OCH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 118.1 (C), 166.8 (2 x C), 155.5 (C), 151.8 (C), 139.8 (CH), 135.4 (C), 130.1 (2 x CH), 129.3 (CH), 128.9 (2 x CH), 128.3 (CH), 107.0 (CH), 104.3 (CH), 101.8 (CH), 84.0 (C), 63.0 (2 x CH_2), 40.3 (2 x CH_3), 13.8 (2 x CH_3); $C_{24}H_{27}ClNO_6$ [M+H]$^+$: 460.1521, found: 460.1520.

Data for **347f**:

IR (film) 2981, 1745 (C=O), 1670 (C=O), 1608 (C=O), 1506, 1452, 1232, 1149, 1061, 825 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.19 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.97 (1H, d, *J* = 12.4 Hz, C**H**=CHC=O), 6.89 (1H, t, *J* = 8.2 Hz, Ar**H**), 6.66 (1H, d, *J* = 12.4 Hz, CH=C**H**C=O), 6.21 (1H, dd, *J* = 8.3, 2.3 Hz, Ar**H**), 5.91 (1H, dd, *J* = 8.1, 2.2 Hz, Ar**H**), 5.85 (1H, t, *J* = 2.3 Hz, Ar**H**), 4.28 (4H, q, *J* = 7.1, 2 x OC**H**$_2$CH$_3$), 2.71 (6H, s, N(C**H**$_3$)$_2$), 1.22 (6H, t, *J* = 7.1, 2 x OCH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.7 (C), 166.5 (2 x C), 155.2 (C), 151.5 (C), 139.1 (C), 134.6 (C), 133.4 (CH), 130.6 (CH), 129.9 (2 x CH), 128.7 (CH), 128.3 (2 x CH), 106.6 (CH), 103.8 (CH), 102.4 (CH), 82.0 (C), 62.8 (2 x CH_2), 40.1 (2 x CH_3), 13.8 (2 x CH_3); $C_{24}H_{27}ClNO_6$ $[M+H]^+$: 460.1521, found: 460.1525.

(*E*)-Diethyl-2-(3-dimethylaminophenoxy)-2-[3-(4-nitrophenyl)-3-oxopropenyl]malonate (346d) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-[3-(4-nitrophenyl)-3-oxopropenyl]malonate (347d)



The title compounds were prepared according to the General Procedure from ester **341** (100 mg, 0.33 mmol), alkynone **133e** (63 mg, 0.39 mmol) and KO^{t}Bu (7.4 mg, 0.06 mmol) and purified by column chromatography (15% Et_2O/CH_2Cl_2) to give first diastereomer **345d** (*E*) as a yellow oil (64 mg, 42%), followed by diastereomer **346d** (*Z*) as a yellow oil (50 mg, 33%).

Data for **346d**:

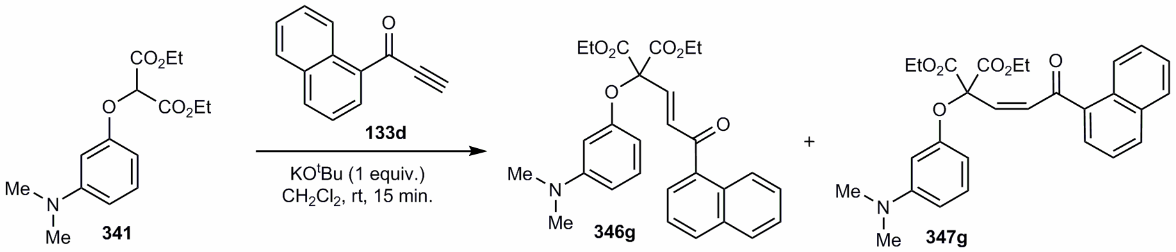
IR (film) 2892, 1771(C=O), 1746 (C=O), 1677 (C=O), 1614, 1526, 1348, 1256, 1170, 855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (2H, d, J = 9.0 Hz, Ar**H**), 7.95 (2H, J = 9.0 Hz, Ar**H**), 7.65 (1H, d, J = 15.7 Hz, C**H**=CHC=O), 7.28 (1H, d, J = 15.7 Hz, CH=C**H**C=O), 7.07-7.00 (1H, m, Ar**H**), 6.42-6.37 (2H, m, Ar**H**), 6.13-6.08 (1H, m, Ar**H**), 4.38-4.19 (4H, m, 2 x $OC\mathbf{H}_2CH_3$), 2.93 (6H, s, $N(C\mathbf{H}_3)_2$), 1.23 (6H, t, J = 7.1, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 187.9 (C), 165.6 (2 x C), 155.4 (C), 151.8 (C), 150.2 (C), 141.6 (C), 141.3 (CH), 129.7 (2 x CH), 129.4 (CH), 128.0 (CH), 123.8 (2 x CH), 107.0 (CH), 104.0 (CH), 101.8 (CH), 83.9 (C), 63.1 (2 x CH_2), 40.4 (2 x CH_3), 13.8 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{27}N_2O_8$ $[M+H]^+$: 471.1762, found: 471.1756.

Data for **347d**:

IR (film) 2978, 2924, 1741(C=O), 1684 (C=O), 1608 (C=O), 1527, 1344, 1228, 1059, 849 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 8.8 Hz, Ar**H**), 7.71 (2H, d, J = 8.8 Hz, Ar**H**), 7.06 (1H , d, J = 12.5 Hz, C**H**=CHC=O), 6.88 (1H, t, J =

8.3, Hz, Ar**H**), 6.67 (1H , d, J = 12.5 Hz, CH=C**H**C=O), 6.18 (1H, dd, J = 8.3, 2.4 Hz, Ar**H**), 5.86 (1H, dd, J = 8.1, 2.4 Hz, Ar**H**), 5.71 (1H, t, J = 2.40, Hz, Ar**H**), 4.28 (4H, q, J = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 2.65 (6H, s, N(C**H**$_3$)$_2$), 1.22 (6H, t, J = 7.1, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 191.7 (C), 166.1 (2 x C), 154.9 (C), 151.3 (C), 149.7 (C), 140.4 (C), 133.6 (CH), 130.3 (CH), 129.4 (2 x CH), 128.7 (CH), 122.9 (2 x CH), 106.4 (CH), 103.3 (CH), 101.6 (CH), 81.8 (C), 62.9 (2 x CH$_2$), 39.7 (2 x CH$_3$), 13.7 (2 x CH$_3$); HRMS (ES) Exact mass calcd. for $C_{24}H_{27}N_2O_8$ [M+H]$^+$: 471.1762, found: 471.1756.

(*E*)-Diethyl-2-(3-dimethylaminophenoxy)-2-(3-naphthalenyl-3-oxopropenyl)malonate (346g) and (*Z*)-diethyl-2-(3-dimethylaminophenoxy)-2-(3-naphthalenyl-3-oxopropenyl)malonate (347g).



The title compounds were prepared according to the General Procedure from the ester **341** (100 mg, 0.33 mmol), alkynone **133d** (70 mg, 0.33 mmol) and KO^{t}Bu (37 mg, 0.33 mmol) and purified by column chromatography (15% Et$_2$O/CH$_2$Cl$_2$) to give first diastereomer **346g** (*E*) yellow oil (102 mg, 65%), followed by diastereomer **347g** (*Z*) as a yellow oil (13 mg, 8%);

Data for **346g**:

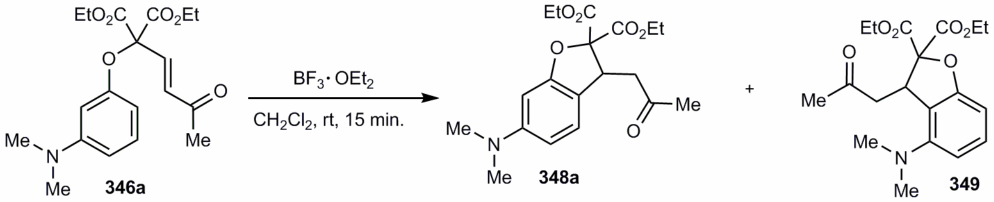
IR (film) 2981, 1749 (C=O), 1666 (C=O), 1614, 1506, 1450, 1238, 1167, 1055, 781 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.36-8.34 (1H, m, Ar**H**), 7.97 (1H, d, J = 7.0 Hz, Ar**H**), 7.88-7.86 (1H, m, Ar**H**), 7.65 (1H, d, J = 8.1 Hz, Ar**H**), 7.54-7.51 (3H, m, Ar**H**, C**H**=CHC=O), 7.44 (1H, t, J = 7.6 Hz, Ar**H**), 7.17 (1H, d, J = 15.9 Hz, CH=C**H**C=O), 7.08 (1H, t, J = 8.1, Hz, Ar**H**), 6.42-6.40 (2H, m, Ar**H**), 6.18-6.16 (1H, m, Ar**H**), 4.34-4.24 (4H, m, 2 x OC**H**$_2$CH$_3$), 2.92 (6H, s, N(C**H**$_3$)$_2$), 1.23 (6H, t, J = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 193.3 (C), 165.9 (2 x C), 155.4 (C), 151.8 (C), 139.7 (CH), 135.5 (C), 133.7 (C), 132.8 (CH), 132.6 (CH), 130.3 (C), 129.3 (CH), 128.5 (CH), 127.6 (CH), 126.4 (CH), 125.5 (CH), 124.3

(CH), 106.9 (CH), 104.2 (CH), 101.9 (CH), 83.7 (C), 62.9 (2 x CH_2), 40.4 (2 x CH_3), 13.8; HRMS (ES) Exact mass calcd. for $C_{28}H_{30}NO_6$ $[M+H]^+$: 476.2068, found: 476.2062.

Data for **347g**:

IR (film) 2922, 1741 (C=O), 1628, 1581, 1450, 1361, 1228, 1055, 810 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.36 (1H, d, *J* = 1.8 Hz, Ar**H**), 6.25 (1H, dd, *J* = 8.4, 1.8 Hz, Ar**H**), 4.65 (1H, dd, *J* = 9.2, 5.0 Hz, CH_2C**H**), 4.37-4.22 (4H, m, 2 x OC**H**$_2$$CH_3$), 2.91 (6H, s, N(C**H**$_3$)$_2$), 2.82 (1H, dd, *J* = 17.2, 5.0 Hz, C**H**$_2$CH), 2.68 (1H, dd, *J* = 17.2, 9.2 Hz, C**H**$_2$CH), 2.16 (3H, s, C**H**$_3$C=O), 1.31 (3H, m, OCH_2C**H**$_3$), 1.29 (3H, m, OCH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.6 (C), 167.5 (C), 166.8 (C), 158.6 (C), 151.9 (C), 124.7 (CH), 115.4 (C), 106.3 (CH), 94.6 (CH), 91.6 (C), 62.5 (CH_2), 62.3 (CH_2), 45.7 (CH_2), 42.5 (CH), 40.7 (2 x CH_3), 30.4 (CH_3), 14.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd. for $C_{19}H_{26}NO_6[M+H]^+$: 364.1755, found: 364.1759.

2,2-Dicarbethoxy-6-dimethylamino-3-(2-oxopropyl)-3*H*-benzofuran (348a) and 2,2-dicarbethoxy-4-dimethylamino-3-(2-oxopropyl)-3*H*-benzofuran (349).



To a stirred solution of the mono-Michael product **347a** (50 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at room temperature, $BF_3{\cdot}OEt_2$ (64 µL, 0.52 mmol) was added dropwise over 1 min. The reaction was stirred for 15 min. and then was quenched with aqueous $NaHCO_3$ solution (5 mL), extracted with CH_2Cl_2 (3 x 5mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/hexane) afforded the regioisomeric product **349** as a brown oil (8 mg, 16%), followed by product **348a** as a yellow oil (36 mg, 72%).

Data for **349**:

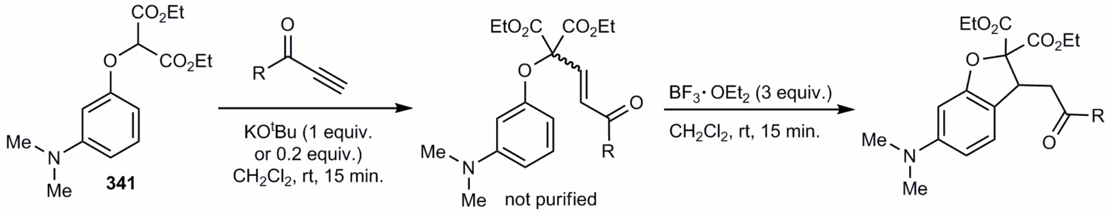
IR (film) 2925, 1739 (C=O), 1610, 1506, 1450, 1363, 1227, 1153, 1039, 854 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.10 (1H, t, *J* = 8.1 Hz, Ar**H**), 6.57 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.49 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.99 (1H, dd, *J* = 9.2, 3.5 Hz, CH_2C**H**), 4.37-

4.12 (4H, m, 2 x OC**H**$_2$CH$_3$), 2.88 (1H, dd, *J* = 17.5, 3.5 Hz, C**H**$_2$CH), 2.79 (6H, s, N(C**H**$_3$)$_2$), 2.68 (1H, dd, *J* = 17.5, 9.2 Hz, C**H**$_2$CH), 2.13 (3H, s, C**H**$_3$C=O), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 205.6 (C), 167.7 (C), 166.6 (C), 157.9 (C), 150.0 (C), 129.7 (CH), 117.1 (C), 110.3 (CH), 103.4 (CH), 90.8 (C), 62.6 (CH$_2$), 62.4 (CH$_2$), 43.6 (CH$_2$), 42.7 (2 x CH$_3$), 42.3 (CH), 30.0 (CH$_3$), 13.9 (CH$_3$), 13.8 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{19}H_{26}NO_6$ $[M+H]^+$: 364.1755, found: 364.1750.

Data for **348a**:

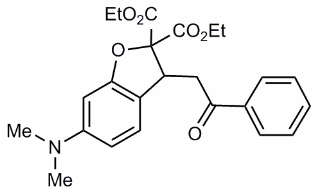
IR (film) 2922, 1741 (C=O), 1628, 1581, 1450, 1361, 1228, 1055, 810 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.36 (1H, d, *J* = 1.8 Hz, Ar**H**), 6.25 (1H, dd, *J* = 8.4, 1.8 Hz, Ar**H**), 4.65 (1H, dd, *J* = 9.2, 5.0 Hz, CH$_2$C**H**), 4.37-4.22 (4H, m, 2 x OC**H**$_2$CH$_3$), 2.91 (6H, s, N(C**H**$_3$)$_2$), 2.82 (1H, dd, *J* = 17.2, 5.0 Hz, C**H**$_2$CH), 2.68 (1H, dd, *J* = 17.2, 9.2 Hz, C**H**$_2$CH), 2.16 (3H, s, C**H**$_3$C=O), 1.31 (3H, m, OCH$_2$C**H**$_3$), 1.29 (3H, m, OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 205.6 (C), 167.5 (C), 166.8 (C), 158.6 (C), 151.9 (C), 124.7 (CH), 115.4 (C), 106.3 (CH), 94.6 (CH), 91.6 (C), 62.5 (CH$_2$), 62.3 (CH$_2$), 45.7 (CH$_2$), 42.5 (CH), 40.7 (2 x CH$_3$), 30.4 (CH$_3$), 14.0 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{19}H_{26}NO_6[M+H]^+$: 364.1755, found: 364.1759.

5.3.2 General two-step Procedure without purification.

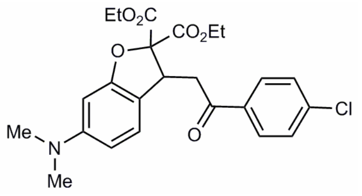


To a stirred solution of the ester (100 mg, 0.33 mmol) and KO^{t}Bu (37 mg, 0.33 mmol)) in CH$_2$Cl$_2$ (1 mL) at room temperature was added a solution of the appropriate alkynone (1.2 equiv.) in CH$_2$Cl$_2$ (1 mL) *via* cannula and dropwise over 1 min. The reaction was stirred at room temperature for 15 min., quenched with saturated aqueous NaHCO$_3$ solution (5 mL), extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The crude product was dissolved in CH$_2$Cl$_2$ (2 mL) and to the resulting mixture BF$_3$·OEt$_2$ (48 μL, 0.39 mmol) was added dropwise over 1 min. The reaction was stirred for 15 min and then was quenched with aqueous

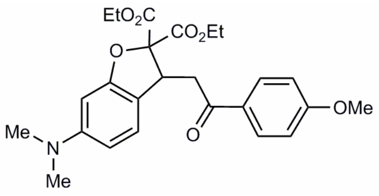
$NaHCO_3$ solution (5 mL), extracted with CH_2Cl_2 (3 x 5mL) and the combined organic layers were concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.



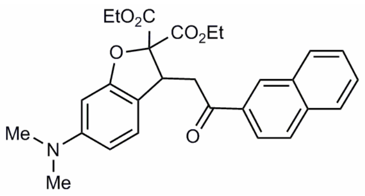
2,2-Dicarbethoxy-6-dimethylamino-3-(2-oxophenylethyl)-3*H*-benzofuran (348c). The title compound was prepared according to the General two-step Procedure from alkynone **133a** (50 mg, 0.39 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (40 mg, 37% over two steps). IR (film) 2924, 1741 (C=O), 1685 (C=O), 1628 (C=O), 1512, 1450, 1363, 1234, 1045, 808 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.95-7.92 (2H, m, Ar**H**), 7.59-7.54 (1H, m, Ar**H**), 7.48-7.43 (2H, m, Ar**H**), 6.97 (1H, dd, d, *J* = 8.4, 0.7 Hz, Ar**H**), 6.38 (1H, d, *J* = 2.3 Hz, Ar**H**), 6.23 (1H, dd, *J* = 8.4, 2.3 Hz, Ar**H**), 4.90 (1H, dd, *J* = 8.9, 5.0 Hz, $CH_2C\mathbf{H}$), 4.40-4.14 (4H, m, 2 x $OC\mathbf{H}_2CH_3$), 3.40 (1H, dd, *J* = 17.1, 5.0 Hz, $C\mathbf{H}_2CH$), 3.23 (1H, dd, *J* = 17.1, 8.9 Hz, $C\mathbf{H}_2CH$), 2.91 (6H, s, $N(C\mathbf{H}_3)_2$), 1.31 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.27 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.1 (C), 167.6 (C), 166.9 (C), 158.7 (C), 151.9 (C), 136.7 (C), 133.2 (CH), 128.6 (2 x CH), 128.1 (2 x CH), 125.0 (CH), 115.6 (C), 106.4 (CH), 94.7 (CH), 91.9 (C), 62.6 (CH_2), 62.3 (CH_2), 42.8 (CH), 41.1 (CH_2), 40.7 (2 x CH_3), 14.0 (2 x CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.1911, found: 426.1907.



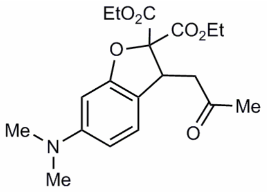
2,2-Dicarbethoxy-6-dimethylamino-3-[2-(4-chlorophenyl)-2-oxethyl]-3*H*-benzofuran (348f). The title compound was prepared according to the General two-step Procedure from alkynone **133f** (63.0 mg, 0.39 mmol) and K^tBuO (37 mg, 0.33 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a red solid (66 mg, 44% over two steps); m.p. 115-119 °C; IR (film) 2924, 1741 (C=O), 1687 (C=O), 1628 (C=O), 1512, 1450, 1275, 1232, 1049, 822 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ ^1H NMR (360 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.42 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.9 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.37 (1H, s, Ar**H**), 6.22 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.87-4.84 (1H, m, $CH_2C\mathbf{H}$), 4.37-4.15 (4H, m, 2 x OC**H**$_2$CH$_3$), 3.36 (1H, dd, *J* = 17.1, 5.0 Hz, C**H**$_2$CH), 3.19 (1H, dd, *J* = 17.1, 8.8 Hz, C**H**$_2$CH), 2.89 (6H, s, N(C**H**$_3$)$_2$), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.28-1.25 (3H, m, OCH$_2$C**H**$_3$);^{13}C NMR (125.8 MHz, CDCl$_3$) δ 195.9 (C), 167.5 (C), 166.8 (C), 58.7 (C), 151.9 (C), 139.7 (C), 134.9 (C), 129.4 (2 x CH), 128.9 (2 x CH), 124.9 (CH), 115.3 (C), 106.3 (CH), 94.6 (CH), 91.8 (C), 62.5 (CH$_2$), 62.3(CH$_2$), 42.8 (CH$_2$), 40.9 (CH), 40.6 (CH$_3$), 29.6 (CH$_3$), 14.0 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{24}H_{27}{}^{35}ClNO_6[M+H]^+$: 460.521, found: 460.520.



2,2-Dicarbethoxy-6-dimethylamino-3-[2-(4-methoxyphenyl)-2-oxethyl]-3*H*-benzofuran (348e). The title compound was prepared according to the General two-step Procedure from alkynone **133b** (53.0 mg, 0.33 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow solid (52 mg, 35% over two steps); m.p. 100-102 °C; IR (film) 2924, 1745 (C=O), 1676 (C=O), 1601, 1510, 1452, 1361, 1236, 1036, 827 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.91 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.95 (1H d, *J* = 8.4 Hz, Ar**H**), 6.92 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.37 (1H, d, *J* = 1.90 Hz, Ar**H**), 6.22 (dd, *J* = 8.4, 2.0 Hz, Ar**H**), 4.88 (1H, dd, *J* = 9.0, 5.0 Hz, CH$_2$C**H**), 4.37-4.14 (4H, m, 2 x OC**H**$_2$CH$_3$), 3.86 (3H, s, OC**H**$_3$), 3.32 (1H, dd, *J* = 16.8, 5.0 Hz, C**H**$_2$CH), 3.17 (1H, dd, *J* = 16.8, 9.0 Hz, C**H**$_2$CH), 2.89 (6H, s, N(C**H**$_3$)$_2$), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 195.6 (C), 167.6 (C), 166.9 (C), 163.5 (C), 158.7 (C), 151.9 (C), 130.3 (2 x CH$_2$), 129.8 (C), 125.0 CH), 115.7 (C), 113.7 (2 x CH$_2$), 106.3 (CH), 94.6 (CH), 91.9 (C), 62.5 (CH$_2$), 62.3 (CH$_2$), 55.4 (CH$_3$), 42.9 (CH), 40.7 (CH$_3$), 40.6 (CH$_2$), 29.6 (CH$_3$), 14.0 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{25}H_{30}NO_7[M+H]^+$: 456.2017, found: 456.2022.

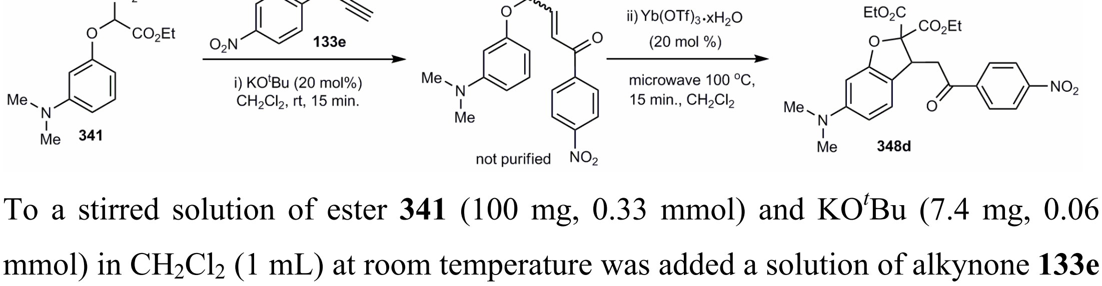


2,2-Dicarbethoxy-6-dimethylamino-3-(2-naphthalenyl-2-oxoethyl)-3*H*-benzofuran (348g). The title compound was prepared according to the General two-step Procedure from alkynone **133d** (72.0 mg, 0.39 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (102 mg, 65% over two steps); IR (film) 2922, 1743 (C=O), 1684 (C=O), 1628, 1510, 1452, 1360, 1230, 1053, 793 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.71 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.99 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.88 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.79 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.65-7.60 (1H, m, Ar**H**), 7.57-7.53 (1H, m, Ar**H**), 7.48-7.44 (1H, m, Ar**H**), 7.05 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.41 (1H, d, *J* = 2.2 Hz, Ar**H**), 6.25 (1H, dd, *J* = 8.4, 2.2 Hz, Ar**H**), 4.98 (1H, dd, *J* = 9.0, 5.0 Hz, CH$_2$C**H**), 4.42-4.14 (4H, m, 2 x OC**H**$_2$CH$_3$), 3.47 (1H, dd, *J* = 17.1, 5.0 Hz, C**H**$_2$CH), 3.36 (1H, dd, *J* = 17.1, 9.0 Hz, C**H**$_2$CH), 2.91 (6H, s, N(C**H**$_3$)$_2$), 1.33 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.26 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 200.9 (C), 167.6 (C), 166.9 (C), 158.7 (C), 151.9 (C), 135.3 (C), 133.9 (C), 132.9 (CH), 130.1 (C), 128.4 (CH), 128.0 (2 x CH), 125.8.5 (CH), 125.7 (CH), 124.9 (CH), 124.3 (CH), 115.5 9 (C), 106.4 (CH), 94.7 (CH), 91.9 (C), 62.6 (CH$_2$), 62.3 (CH$_2$), 44.2 (CH$_2$), 43.2 (CH), 40.7 (2 x CH$_3$), 14.0 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd. for $C_{28}H_{30}NO_6$ [M+H]$^+$: 476.2068, found: 476.2068.



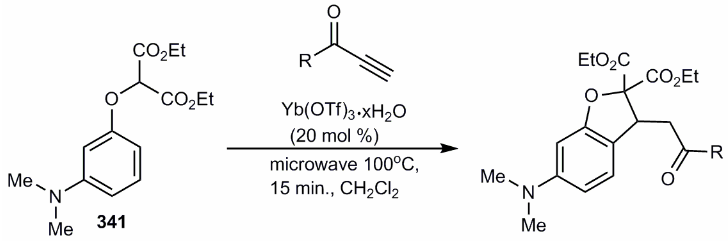
2,2-Dicarbethoxy-6-dimethylamino-3-(2-oxopropyl)-3*H*-benzofuran (348a). The title compound was prepared according to the General two-step Procedure from ester **341** (59 mg, 0.20 mmol), KO^{t}Bu (4 mg, 0.04 mmol), and alkynone **133h** (14 μL, 0.20 mmol) purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (40 mg, 55% over two steps). (See pp.139 for further information).

2,2-Dicarbethoxy-6-dimethylamino-3-[2-(4-nitrophenyl)-2-oxethyl]-3*H*-benzofuran (347d).

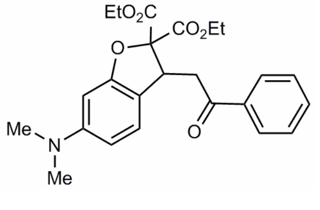


To a stirred solution of ester **341** (100 mg, 0.33 mmol) and KO^{t}Bu (7.4 mg, 0.06 mmol) in CH$_2$Cl$_2$ (1 mL) at room temperature was added a solution of alkynone **133e** (70 mg, 0.40 mmol) in CH$_2$Cl$_2$ (1 mL) *via* cannula and dropwise over 1 min. The reaction was stirred at room temperature for 15 min., quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with CH_2Cl_2 (3 x 5mL) and concentrated *in vacuo*. The crude product was diluted with CH_2Cl_2 (2 mL) and $Yb(OTf)_3 \cdot xH_2O$ (12 mg, 0.02 mmol) was added to the resulting mixture which was then microwaved at 100°C for 15 min. Purification of the resulting mixture by column chromatography afforded the cyclised product as an orange solid (59 mg, 38%); m.p. 150-153 °C; IR ($CHCl_3$) 2924, 2852, 1741 (C=O), 1695 (C=O), 1630, 1523, 1448, 1346, 1228, 854; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (2H , d, *J* = 8.8 Hz, Ar**H**), 8.07 (2H , d, *J* = 8.8 Hz, Ar**H**), 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.37 (1H, d, *J* = 2.2 Hz, Ar**H**), 6.22 (1H, dd, *J* = 8.4, 2.2Hz, Ar**H**), 4.85 (1H, dd, *J* = 8.5, 5.4 Hz, CH_2C**H**), 4.38-4.17 (4H, m, 2 x OC**H**$_2CH_3$), 3.45 (1H, dd, *J* = 17.3, 5.3 Hz, C**H**$_2$CH), 3.26 (1H, dd, *J* = 17.3, 8.5 Hz, C**H**$_2$CH), 2.90 (6H, s, N(C**H**$_3)_2$), 1.33-1.27 (6H, m, 2 x OCH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 195.9 (C), 167.5 (C), 166.8 (C), 158.7 (C), 152.1 (C), 150.3 (C), 141.0 (C), 129.1 (2 x CH), 124.7 (CH), 123.9 (2 x CH), 114.8 (C), 106.3 (CH), 94.6 (CH), 91.6 (C), 62.7 (CH_2), 62.4 (CH_2), 42.8 (CH_2), 41.5 (CH), 40.6 (CH_3), 14.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{27}N_2O_8$ $[M+H]^+$: 471.1762, found: 471.1764.

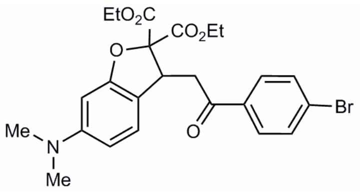
5.3.3 Combined Michael addition/Friedel-Crafts-cyclisation: General one-pot Procedure.



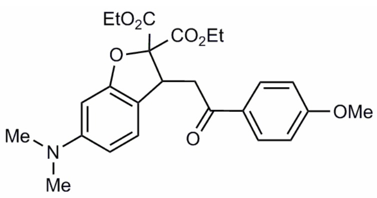
A solution of the ester **341** (30 mg, 0.10 mmol), the alkynone (0.12 mmol) and $Yb(OTf)_3 \cdot xH_2O$ (12 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature was microwaved at 100 °C for 15 min. Purification of the resulting mixture by column chromatography afforded the cyclised product.



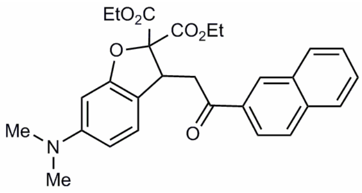
2,2-Dicarberthoxy-6-dimethylamino-3-(2-oxophenylethyl)-3*H*-benzofuran (348c). The title compound was prepared according to the General one-pot Procedure from alkynone **133a** (16 mg, 0.12 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (20 mg, 47%). (See pp. 141 for further information).



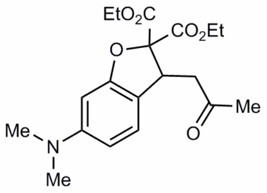
2,2-Dicarbethoxy-6-dimethylamino-3-[2-(4-Bromophenyl)-2-oxethyl]-3*H*-benzofuran (348h). The title compound was prepared according to the General one-pot Procedure from alkynone **133c** (31.0 mg, 0.15 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (40 mg, 80%); IR (film) 2924, 1743 (C=O), 1694 (C=O), 1627, 1512, 1450, 1275, 1360, 1043, 811 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.59 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.37 (1H, d, *J* = 2.2 Hz, Ar**H**), 6.22 (1H, dd, *J* = 8.4, 2.2 Hz, Ar**H**), 4.86 (1H, dd, *J* = 8.7, 5.2 Hz, $CH_2C\mathbf{H}$), 4.39-4.14 (4H, m, 2 x $OC\mathbf{H}_2CH_3$), 3.35 (1H, dd, *J* = 17.1, 5.2 Hz, $C\mathbf{H}_2CH$), 3.18 (1H, dd, *J* = 17.1, 8.7 Hz, $C\mathbf{H}_2CH$), 2.90 (6H, s, $N(C\mathbf{H}_3)_2$), 1.33-1.25 (6H, m, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.1 (C), 167.5 (C), 166.9 (C), 158.7 (C), 151.9 (C), 135.4 (C), 131.9 (2 x CH), 129.6 (2 x CH), 128.4 (C), 124.8 (CH), 115.3 (C), 106.3 (CH), 94.6 (CH), 91.8 (C), 62.6 (CH_2), 62.3 (CH_2), 42.8 (CH), 41.00 (CH_2), 40.6 (2 x CH_3), 14.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd. for $C_{24}H_{27}{}^{79}BrNO_6$ $[M+H]^+$: 504.1016, found: 504.1005.



2,2-Dicarbethoxy-6-dimethylamino-3-[2-(4-methoxyphenyl)-2-oxethyl]-3*H*-benzofuran (348e). The title compound was prepared according to the General one-pot Procedure from alkynone **133b** (24.0 mg, 0.15 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow solid (24 mg, 53% over two steps). (See pp. 142 for further information).



2,2-Dicarbethoxy-6-dimethylamino-3-(2-naphthalenyl-2-oxethyl)-3*H*-benzofuran (348g). The title compound was prepared according to the General one-pot Procedure from alkynone **133d** (27.0 mg, 0.15 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (22 mg, 44%). (See pp. 143 for further information)



2,2-Dicarbethoxy-6-dimethylamino-3-(2-oxopropyl)-3*H*-benzofuran (348a). The title compound was prepared according to the General one-pot Procedure from alkynone **133a** (9 µL, 0.12 mmol) and purified by column chromatography (15% EtOAc/hexane) to give yellow oil (19 mg, 54%). (See pp. 139 for further information).

6. REFERENCES

1. Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999,** *10*, 2245-2303.

2. Chelius, D.; Jing, K.; Lueras, A.; Rehder, D. S.; Dillon, T. M.; Vizel, A.; Rajan, R. S.; Li, T.; Treuheit, M. J.; Bondarenko, P. V. *Anal. Chem.* **2006,** *78*, 2370-2376.

3. Ma, D. *Bioorg. Chem.* **1999,** *27*, 20-34.

4. Bladè-Font, A. *Tetrahedron Lett.* **1980,** *21*, 2443-2446.

5. Jones, G. H. *Biochemistry* **1974,** *13*, 855-860.

6. Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982,** *104*, 3511-3513.

7. a) Tomita, T.; Kita, Y.; Kitamura, T.; Mori, M.; Sato, Y. *Tetrahedron* **2006**, 10518-10527. b) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984,** *106*, 4539-4541.

8. Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000,** *122*, 4295-4303.

9. Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981,** *22*, 4197-4198.

10. Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973,** *95*, 5813-5815.

11. Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004,** *6*, 1329-1331.

12. Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980,** *45*, 815-818.

13. Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971,** *54*, 710-734.

14. Fujimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980,** *102* 7154-7156.

15. Lettan, R. B. I.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2008,** *47*, 2294-297.

16. a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsusaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991,** *44*, 113-116. b) Omura, S.; Matsusaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991,** *44*, 117-118.

17. Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008,** *73*, 2041-2051.

18. Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem. Int. Ed.* **2003,** *42*, 355-357.

19. Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S. *Chem. Commun.* **1999**, 133–134.

20. Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005,** *127*, 15296–15303.

21. a) Wang, W. Y., J.; Ying, J.; Xiong, C.; Zhang, J.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002,** *67*, 6353-6360. b) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001,** *66*, 9056-9062.

22. a) Somfai, P.; Åhman, J. *Tetrahedron Lett.* **1992,** *33*, 3791-3794. Ahman, J.; Somfai, P. *Tetrahedron* **1992,** *48*, 9537-9544. b) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986,** *27*, 4799-4802.

23. a) Provot, O.; Celerier, J. P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992,** *57*, 2163-2166. b) Karstens, W. F.; Stol, M.; Rutjes, F. P.; Hiemstra, H. *Synlett* **1998**, 1126-1128.

24. Smith, L. W.; Culvenor, C. C. J. *J. Nat. Prod.* **1981,** *44* 129-152.

25. Mattocks, A. R. *Nature* **1968,** *217*, 723-728.

26. Michael, J. P. *Nat. Prod. Rep.* **2008,** *25*, 139-165.

27. Keusenkothen, P. F.; Smith, M. B. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2485-2492.

28. Lesma, G.; Colombo, A.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2008,** *74*, 590-596.

29. Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999,** *55*, 585-615.

30. Carpes, M. J. S.; Correia, C. R. D. *Tetrahedron Lett.* **2002,** *43*, 741-744.

31. Herdeis, C.; Hubmann, H. P. *Tetrahedron:Asymmetry* **1992,** *3*, 1213-1221.

32. Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988,** *44*, 5479-5486.

33. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002,** *58*, 2253-2329.

34. Enders, D.; Eichenauer, H. *Chem. Ber.* **1979,** *112*, 2933-2960.

35. Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984,** *40*, 1345-1359.

36. Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem.* **2005,** *44*, 1304-1325.

37. a) Ziegler, F. E.; Becker, M. R. *J. Org. Chem.* **1990,** *55* 2800–2805. b) Carling, R. W.; Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1989,** *30*, 6081-6084.

38. Enders, D.; Ridder, A. *Synlett.* **2000**, 1848-1851.

39. Enders, D.; Tiebes, J.; De Kimpe, N.; Keppens, M.; Stevens, C.; Smagghe, G.; Betz, O. *J. Org. Chem.* **1993,** *58*, 4881-4884.

40. Ezquerra, J.; Rubio, A.; Martín, J.; Navío, J. L. G. *Tetrahedron: Asymmetry* **1997,** *8*, 669-671.

41. Ezquerra, J.; Prieto, L.; Avendaño, C.; Martos, J. L.; Cuesta, E. *Tetrahedron Lett.* **1999,** *40*, 1575-1578.

42. Ezquerra, J.; Pedregál, C.; Rubio, A. *J. Org. Chem.* **1994,** *59*, 4327-4331.

43. Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989,** *30*, 3295-3298.

44. Behr, J.; Defoin, A.; Pires, J.; Streith, J.; Macko, L.; Zehnder, M. *Tetrahedron* **1996,** *52*, 3283-3302.

45. Itoh, T. M., M.; Ikeda, S.; Nagata, K.; Yokoya, M.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. 2003, 59, 3527. *Tetrahedron Lett.* **2003,** *59*, 3527.

46. Harriman, G. C. B. *Tetrahedron Lett.* **1997,** *38*, 5591-5594.

47. Isaacson, J.; Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2007,** *72*, 3913-3916.

48. Isaacson, J.; Loo, M.; Kobayashi, Y. *Org. Lett.* **2008,** *10*, 1461-1463.

49. Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007,** *9*, 3631-3634.

50. Alvarez-Ibarra, C.; Csákÿ, A. G.; López de Silanes, I.; Quiroga, M. L. *J. Org. Chem.* **1997,** *62*, 479-484.

51. Vedejs, E.; West, F. G. *Chem. Rev.* **1986,** *86*, 941-955.

52. a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988,** *110*, 7536-7538. Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991,** *56*, 2746-2750. b) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991,** *56*, 95-102.

53. Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron:Asymmetry* **1996,** *7*, 2531-2538.

54. Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998,** *39*, 2815-2818.

55. Ihara, M.; Fukumoto, K. *Angew. Chem. Int. Ed.* **1993,** *32*, 1010-1022.

56. Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. *J. Org. Chem.* **2000,** *65*, 4112-4119.

57. Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007,** *9*, 1833-1835.

58. Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem. Int. Ed.* **2007,** *46*, 3732 –3734.

59. Chen, J. J.; Lu, C. V.; Brockman, R. N. *Tetrahedron Lett.* **2003,** *44*, 3459-3462.

60. Gagnon, A.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2002,** *41*, 1581-1584.

61. Grecian, S.; Wrobleski, A. D.; Aube, J. *Org. Lett.* **2005,** *7*, 3167-3170.

62. Grecian, S.; Aube, J. *Org. Lett.* **2007,** *9*, 3153-3156.

63. Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996,** *118*, 7426-7427.

64. Sneddon, H. F.; van den Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. J.; Ley, S. V. *J. Org. Chem.* **2006,** *71*, 2715-2725.

65. Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007,** *129*, 12928-12929.

66. Grossman, R. B. *Synlett.* **2001,** *1*, 13-21.

67. Hughes Jr., F.; Grossman, R. B. *Org. Lett.* **2001,** *3*, 2911-2914.

68. Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999,** *64*, 340-341.

69. Grossman, R. B.; Pendharker, D. S.; Patrick, B. O. *J. Org. Chem.* **1999,** *64*, 7177-7183.

70. Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001,** *3*, 4027-4030.

71. (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965,** *6*, 2995-3001. (b) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989,** *30*, 6177-6180. (c) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997,** *8*, 3955-3975.

72. For a review of transition-metal-catalyzed Michael reactions of 1,3-dicarbonyl compounds see: Christoffers, J. *Eur. J. Org. Chem.* **1998,** *7*, 1259-1266.

73. For examples of iron-catalyzed Michael reactions of 1,3-dicarbonyl compounds see: (a) Fei, C. P.; Chan, T. H. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, 467-468. (b) Kočovský, P.; Dvořák, D. *Tetrahedron. Lett.* **1986,** *27*, 5015-5108. (c) Christoffers, J. *Chem. Commun.* **1997**, 943-944. (d) Christoffers, J. *J. Chem. Soc., Perkin Trans.* **1997,** *1* 3141-3149. (e) Christoffers, J. *Synlett* **2001**, 723-732.

74. For examples of zinc-catalyzed Michael reactions of 1,3-dicarbonyl compounds see: Brunner, H.; Krumey, C. *J. Mol. Catal. A* **1999,** *142*, 7-15.

75. For examples of magnesium-catalyzed Michael reactions of 1,3-dicarbonyl compounds see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999,** *121*, 10215-10216. (c) MacCulloch, A. C.; Yolka, S.; Jackson, R. F. W. *Synlett* **2002**, 1700-1702.

76. Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger; J., S.; Zhang, J. *J. Am. Chem. Soc.* **2002,** *124*, 13097-13105.

77. For examples of nickel-catalyzed Michael reactions of 1,3-dicarbonyl compounds see: (a) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980,** *45*, 1246-1249. (b) Clariana, J.; Gálvez, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999,** *55*, 7331-7344. (c) Christoffers, J.; Röβler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701-705. (d) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005,** *127*, 9958-9959. (e) Evans, D. A.; Thomson, R. J.; Franco, F. *J. Am. Chem. Soc.* **2005,** *127*, 10816-10817. (f) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005,** *7*, 979-981. (g) Yanagita, H.; Kodama, K.; Kanemasa, S. *Tetrahedron Lett.* **2006,** *47*, 9353-9357.

78. Pedrosa, R.; Sayalero, S.; Vicente, M.; Casado, B. *J. Org. Chem.* **2005,** *70*, 7273-7278.

79. Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967,** *3*, 215-217.

80. Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006,** *39*, 79-87.

81. Northrup, A. B.; MacMillan, D. W. C. *J. of Am. Chem. Soc.* **2002,** *124*, 2458-2460.

82. Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527-3544.

83. Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003,** *68*, 7126-7129.

84. Silvanus, A. C.; Heffernan, S. J.; Liptrot, D. J.; Kociok-Köhn, G.; Andrews, B. I.; Carbery, D. R. *Org. Lett.* **2009,** *11*, 1175-1178.

85. Li, C.; Liu, H.; Liao, J.; Cao, Y.; Liu, X.; Xiao, W. *Org. Lett.* **2007,** *9*, 1847-1850.

86. For selected references see: a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002,** *124*, 1172-1173. b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001,** *123*, 4370-4371. c) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122*, 4243-4244.

87. Lu, H.; Liu, H.; Wu, W.; Wang, X.; Lu, L.; Xiao, W. *Chem. Eur. J.* **2009**.

88. Evans, D. A.; Fandrick, K. R.; Song, H. J. *J. Am. Chem. Soc.* **2005,** *127*, 8942-8943.

89. Grundl, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. **2006,** *8*, 5429-5432.

90. Li, W. Z.; Wang, X. *Org. Lett.* **2007,** *9*, 1211-1214.

91. Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Letters,* **1986,** *27*, 2023-2026.

92. Xiao, Q.; Floreancig, P. E. *Org. Lett.* **2008,** *10*, 1139-1142.

93. a) Maraval, A.; Igau, A.; Donnadieu, B.; Majoral, J. P. *Eur. J. Org. Chem.* **2003**, 385-394. b) Wan, S.; Green, M. E.; Park, J. H.; Floreancig, P. E. *Org. Lett.* **2007,** *9*, 5385-5388.

94. a) Cox, D.; Cook, J. M. *Chem. Rev.* **1995,** *95*, 1797-1842. b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004,** *104*, 3341-3370.

95. Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911,** *44*, 2030-2036.

96. Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005,** *13*, 5154-5158.

97. Srinivasan, N.; Ganesan, A. *Chem. Comm.* **2003**, 916-917.

98. Srinivasan, N.; Ganesan, A. *Chem. Comm.* **2003**, 916-917.

99. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004,** *126*, 10558-10559.

100. Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009,** *11*, 887-890.

101. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006,** *128* 1086-1087.

102. Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994,** *116*, 6049-6050.

103. Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005,** *11*, 3155-3164.

104. Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000,** *65*, 4913-4918.

105. Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002,** *67*, 1414-1417.

106. Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001,** *66*, 4635-4642.

107. Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004,** *6*, 2361-2364.

108. Hayashi, R.; Cook, G. R. *Org. Lett.* **2007,** *9*, 1311-1314.

109. Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011.

110. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,,** *43*, 2923–2925.

111. Bowden, K.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 52-54.

112. Irving, F.; Jhonson, A. W. *J. Chem. Soc.* **1948**, 2037-2038.

113. Alvarez-Ibarra, C.; Csákÿ, A. G.; Ortega, E. M.; de la Morena, M. J.; Quiroga, M. L. *Tetrahedron Lett.* **1997,** *38*, 4501-4502.

114. Pigge, F. C.; Ghasedi, F.; Zheng, Z.; Rath, N. P.; Nichols, G.; Chickos, J. S. *J. Chem. Soc.* **2000,** *2*, 2458-2464.

115. Maeda, Y.; Washitake, Y.; Nishimura, T.; Iwai, K.; Yamauchi, T.; Uemuraa, S. *Tetrahedron* **2004,** *60*, 9031-9036.

116. Noro, M.; Masuda, T.; Ichimura, A. S.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1994,** *116*, 6179-6190.

117. Tombor, Z.; Greff, Z.; Nyitrai, J.; Kajtár-Peredy, M. *Liebigs Ann. Org. Bioorg. Chem.* **1995,** *5*, 825–836.

118. Gang, Y.; Shaozhong, W.; Kai, W.; Yuefei, H.; Hongwen, H. *Synthesis* **2004,** *7*, 1021-1028.

119. Scarpi, D.; Occhiato, E. G.; Guarna, A. *J. Org. Chem.* **1999** *64* 1727–1732.

120. Simig, G.; Doleschall, G.; Hornyak, G.; Fetter, J.; Lempert, K.; Nyitrai, J.; Huszthy, P.; Gizur, T.; Kajtár-Peredy, M. *Tetrahedron Lett.* **1985,** *41*, 479–484.

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Synthesis of Pyroglutamic Acid Derivatives via Double Michael Reactions of Alkynones

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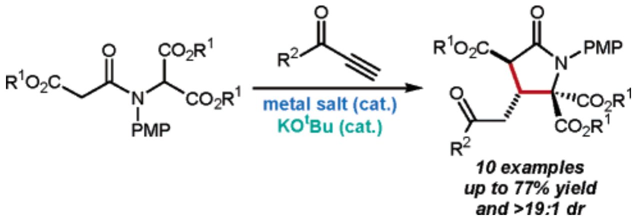
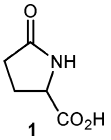
ABSTRACT



In the presence of substoichiometric quantities of potassium *tert*-butoxide and an additional metal salt, amide-tethered diacids undergo double Michael reactions with alkynones to provide highly functionalized pyroglutamic acid derivatives. The metal salt was found to play an important role in improving the diastereoselectivities of the reactions.

Pyroglutamic acid (**1**) and its derivatives are structural units of widespread chemical significance, having been heavily utilized as building blocks for the synthesis of numerous biologically active compounds.[1]



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Considering the multitude of synthetic applications for pyroglutamic acids, much research effort has been devoted to the development of new methods for the synthesis of functionalized derivatives.[1,2] In this Letter, we present a novel route to highly functionalized pyroglutamic acids using double Michael reactions[3] of amide-tethered diacids with alkynones.

Over the past few years, Grossman and co-workers have described a range of reactions where compounds containing two acidic carbon atoms undergo double Michael reactions with electron-deficient alkynes (mostly 3-butyn-2-one) to provide highly functionalized cyclic products.[4,5] Generating two new carbon−carbon bonds and up to three new stereogenic centers with often high levels of diastereoselectivity, this reaction has been effectively utilized in the preparation of a range of five- and six-membered carbocycles.[4] In

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(1) For a recent review, see: Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245−2303.

(2) For recent, representative examples, see: (a) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296−15303. (b) Chang, M.-Y.; Sun, P.-P.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 5271−5273. (c) Alvarez-Ibarra, C.; Csáky, A. G.; Gómez de la Olivia, C. *Eur. J. Org. Chem.* **2002**, 4190−4194. (d) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167−172.

(3) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315−512.

(4) (a) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340−341. (b) Grossman, R. B.; Rasne, R. M.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173−7177. (c) Grossman, R. B.; Pendharker, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178−7183. (d) Grossman, R. B.; Skaggs, A. J.; Kray, A. E.; Patrick, B. O. *Org. Lett.* **1999**, *1*, 1583−1586. (e) Grossman, R. B.; Pendharker, D. S.; Rasne, R. M.; Varner, M. A. *J. Org. Chem.* **2000**, *65*, 3255−3258. (f) Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001**, *3*, 4027−4030. (g) Holeman, D. S.; Rasne, R. M.; Grossman, R. B. *J. Org. Chem.* **2002**, *67*, 3149−3151. (h) Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409−1417. For a review, see: (i) Grossman, R. B. *Synlett* **2001**, 13−21.

(5) Hughes, F., Jr.; Grossman, R. B. *Org. Lett.* **2001**, *3*, 2911−2914.

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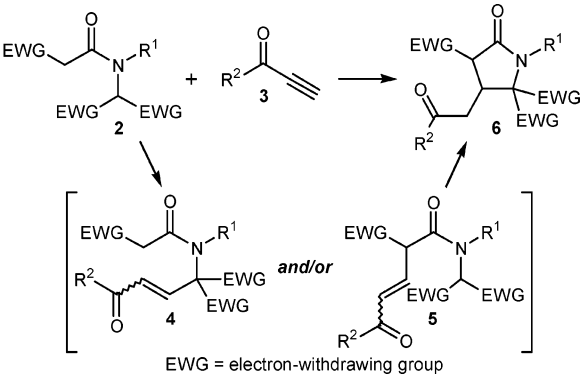
comparison, application of this methodology to heterocycle construction has been limited, with just one report of a [5 + 1] annulation route to piperidines having been described.[5]

In view of the convergent and modular nature of these transformations, we were drawn to the prospect of utilizing double Michael reactions of alkynones in a concise synthesis of highly functionalized pyroglutamic derivatives, according to the strategy outlined in Scheme 1. It was hoped that under suitable conditions, an amide-tethered diacid **2** would react with an alkynone **3** to first give mono-Michael adduct **4** and/or **5**, which would then cyclize to the pyroglutamic acid derivative **6**.

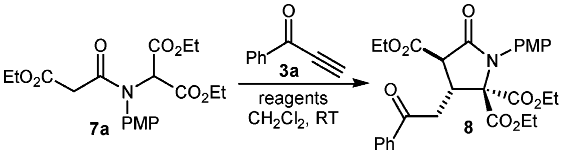
Scheme 1. Proposed Double Michael Addition Route to Pyroglutamic Acid Derivatives



EWG = electron-withdrawing group

Our preliminary investigations began with the double Michael reaction of amide-tethered diacid **7a** with aromatic alkynone **3a** (Table 1). In all previous examples of double Michael reactions reported by Grossman and co-workers,[4,5] a mandatory requirement for success is the presence of at least one nitrile substituent in the tethered diacid, which ends up in a pseudoaxial position in the product.[4i] It is proposed that the small size of the nitrile group reduces the magnitude of unfavorable 1,3-diaxial interactions between acidifying groups in the transition state for cyclization, which would otherwise inhibit ring closure.[4i] At the outset of this work, it was therefore uncertain whether diacid **7a**, which does not possess a nitrile substituent, would undergo successful double Michael reaction. Although treatment of a mixture of **7a** and **3a** with PPh_3 in acetonitrile[4c] gave no reaction (entry 1), we found that KO^{t}Bu in CH_2Cl_2[4a] led to the formation of the desired pyroglutamic acid derivative **8**, albeit as a 1:1 mixture of diastereomers (entry 2).

Table 1. Reaction Condition Optimization



entry	reagents	dr[a]	yield (%)[b]
1[c]	PPh_3 (20 mol %)	n/a	0
2	KO^{t}Bu (20 mol %)	1:1	68
3	KO^{t}Bu (20 mol %), Fe(acac)$_3$ (20 mol %)	1:1	31
4	KO^{t}Bu (20 mol %), Zn(OTf)$_2$ (20 mol %)	>19:1	27
5	KO^{t}Bu (20 mol %), Mg(OTf)$_2$ (20 mol %)	11:1	68
6	KO^{t}Bu (20 mol %), Ni(acac)$_2$ (20 mol %)	18:1	76

[a] As determined by ^{1}H NMR analysis of the isolated product. Due to overlapping signals from other compounds, diastereomeric ratios could not be determined from ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Isolated yields of mixtures of diastereoisomers that were inseparable by column chromatography. [c] MeCN used as solvent in place of CH_2Cl_2.

We next investigated the effect of Lewis acidic additives on the reaction.[6] Substoichiometric quantities of Fe(acac)$_3$[7] and Zn(OTf)$_2$[8] were found to inhibit the reaction (entries 3 and 4), though Zn(OTf)$_2$ had a beneficial effect on diastereoselectivity (entry 4). Finally, we identified Mg(OTf)$_2$[9] (entry 5) and Ni(acac)$_2$[10] (entry 6) as promising additives, allowing double Michael product **8** to be isolated in 68−76% yield and with up to 18:1 diastereomeric ratio.

Recrystallization of **8** from a mixture of diethyl ether and hexane afforded crystals that were suitable for X-ray crystallography, which allowed us to confirm that the major diastereomer obtained in these reactions possesses *trans* stereochemistry (Figure 1).

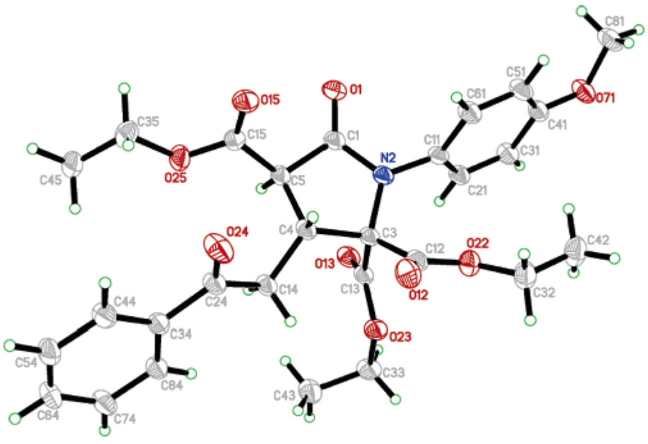


Figure 1. X-ray crystal structure of double Michael product **8**.

With optimized conditions in hand, the scope of the reaction was explored (Figure 2). Using **7a** as the tethered

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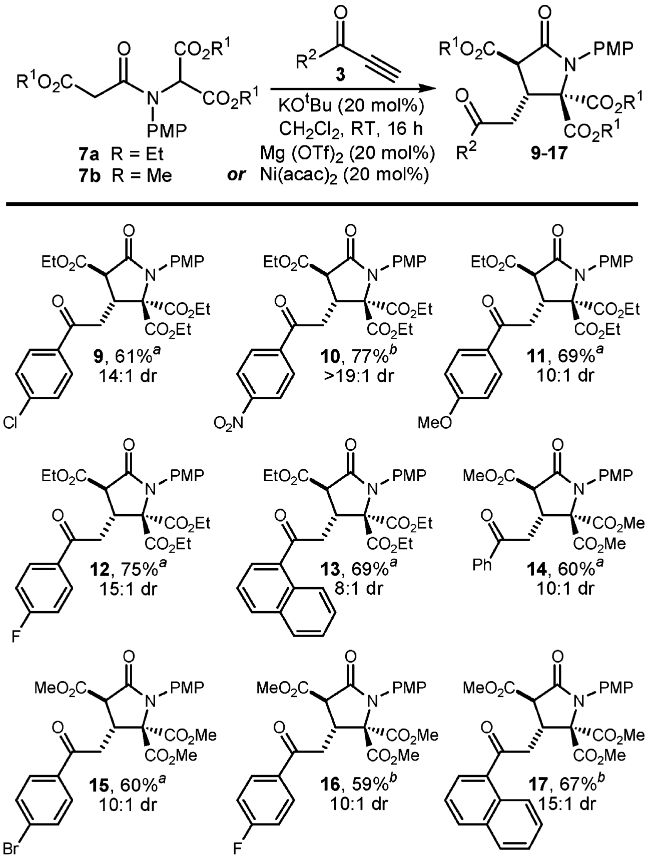
(6) For a review of transition-metal-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259−1266.

(7) For examples of iron-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Fei, C. P.; Chan, T. H. *Synthesis* **1982**, 467−468. (b) Kočovský, P.; Dvořák, D. *Tetrahedron. Lett.* **1986**, *27*, 5015−5108. (c) Christoffers, J. *Chem. Commun.* **1997**, 943−944. (d) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141−3149. (e) Christoffers, J. *Synlett* **2001**, 723−732.

(8) For examples of zinc-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: Brunner, H.; Krumey, C. *J. Mol. Catal. A* **1999**, *142*, 7−15.

(9) For examples of magnesium-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097−13105. (c) MacCulloch, A. C.; Yolka, S.; Jackson, R. F. W. *Synlett* **2002**, 1700−1702.



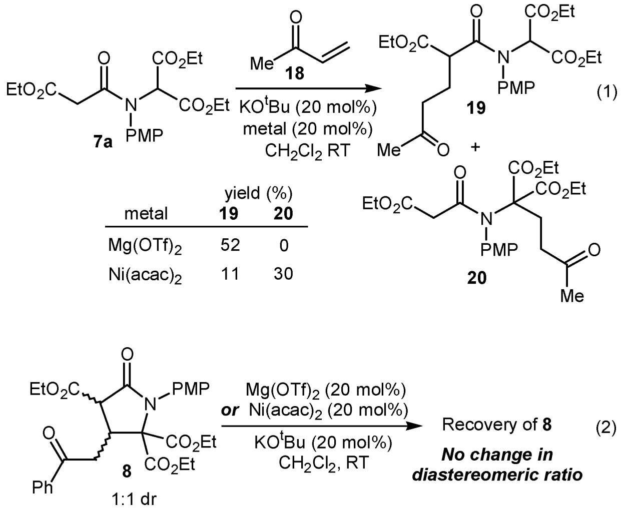
[a] Using Mg(OTf)$_2$. [b] Using Ni(acac)$_2$.

Figure 2. Double Michael reactions of amide-tethered diacids **7a** and **7b** with assorted aromatic alkynones. Cited yields are of isolated inseparable mixtures of diastereoisomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products. Due to overlapping signals from other compounds, diastereomeric ratios could not be determined by ^{1}H NMR analysis of unpurified reaction mixtures.

diacid, a range of different aromatic alkynones **3** possessing substituents of varying electronic character underwent double Michael reactions to provide pyroglutamic acid derivatives **9**−**13** in 61−77% yield. Tethered diacid **7b**, containing methyl esters in place of the ethyl esters in **7a**, also underwent reaction uneventfully, affording double Michael products **14**−**17**.

Additional experiments provided some insight into the reaction pathway and the role played by the metal salts (Scheme 2). Equation 1 highlights differences in the effect of Mg(OTf)$_2$ and Ni(acac)$_2$. Reaction of methyl vinyl ketone (**18**) with diacid **7a** using Mg(OTf)$_2$ as additive led to **19** as the only observable Michael product in 52% yield, with the remainder of material being unreacted **7a**. This experiment indicates that under these conditions, the methylene carbon adjacent to the amide carbonyl of **7a** is the more reactive of the two acidic positions. However, the analogous experiment using Ni(acac)$_2$ provided a mixture of **19** and the alternative Michael product **20**, among other side-products.

Scheme 2. Experiments Probing the Role of Mg(OTf)$_2$ and Ni(acac)$_2$

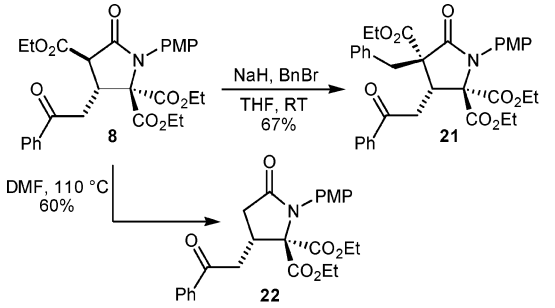


metal	yield (%) 19	yield (%) 20
Mg(OTf)$_2$	52	0
Ni(acac)$_2$	11	30

Exposure of a 1:1 diastereomeric mixture of double Michael product **8** obtained using KO^{t}Bu alone (Table 1, entry 2) to standard reaction conditions *including* additional Mg(OTf)$_2$ or Ni(acac)$_2$ led to recovery of **8** in high yield with no discernible change in diastereomeric composition (eq 2). These experiments suggest that under these conditions, post-cyclization epimerization (which could occur via a deprotonation−reprotonation sequence or a retro-Michael−Michael sequence) does not occur, and therefore diastereoselection observed in the presence of additional metal salt is the result of a kinetically controlled process. However, the manner in which the metal salt imparts diastereoselectivity is not clear at this time.

Conversion of double Michael product **8** into other potentially useful compounds is shown in Scheme 3. Treatment of **8** with NaH and BnBr provided alkylated product

Scheme 3. Elaboration of Double Michael Product **9**



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(10) For examples of nickel-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246−1249. (b) Clariana, J.; Gálvez, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331−7344. (c) Christoffers, J.; Rößler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701−705. (d) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958−9959. (e) Evans, D. A.; Thomson, R. J.; Franco, F. *J. Am. Chem. Soc.* **2005**, *127*, 10816−10817. (f) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979−981. (g) Yanagita, H.; Kodama, K.; Kanemasa, S. *Tetrahedron Lett.* **2006**, *47*, 9353−9357.

21,[11] and monodecarboxylation to **22** was accomplished by heating a DMF solution of **8** to 110 °C.

In summary, we have developed a double Michael addition route to highly functionalized pyroglutamic acid derivatives that utilizes amide-tethered carbon diacids and aromatic alkynones as substrates. The reactions proceed with good levels of *trans*-diastereoselectivity, provided that substoichiometric quantities of $Mg(OTf)_2$ or $Ni(acac)_2$ are employed as additives. Further work will address the development of enantioselective variants of these reactions.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Tentative relative stereochemical assignment. NOESY spectra proved inconclusive in establishing the relative stereochemistry of **21**.