New Approaches for the Synthesis of Advanced Precursors of Rhazinilam Analogues

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Titre:

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Le Doyen, Prof. B. Colbois

B. Colbois.

Les travaux décrits dans ce manuscrit ont été effectués de septembre 2007 à juillet 2012 à l'institut de Chimie de l'Université de Neuchâtel sous la direction du Prof. Reinhard Neier. Je tiens à lui exprimer ma profonde gratitude pour m'avoir donné l'opportunité de travailler sur un sujet extrêmement intéressant et plein de défi, pour m'avoir encadré et permis de m'épanouir tant au niveau professionnel que privé, pour sa disponibilité et son implication. Je tiens à le remercier tout particulièrement pour la confiance qu'il m'a accordée tout le long de ce parcours, pour ses conseils avisés, sa présence et son soutien dans les moments les plus difficiles.

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A ma mère, A ma grand-mère,

A mon mari, A mes enfants, avec tout mon amour

A mon grand-père à jamas dans mon cœur

"Le mystère est la plus belle chose de la vie; c'est la source de tout art et de toute science."

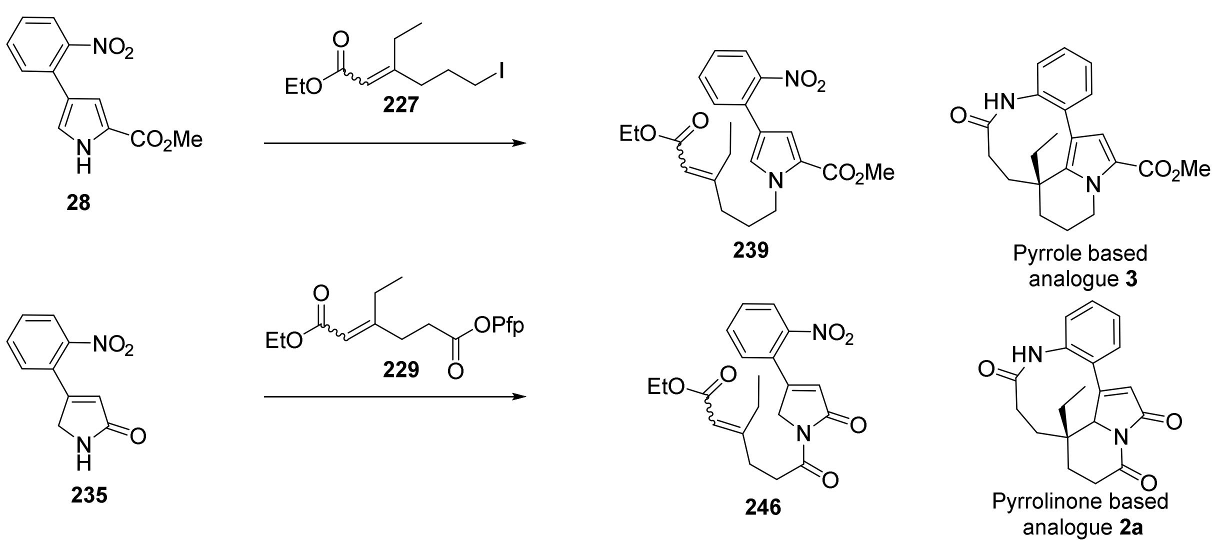
Albert Einstein

"Ce sont rarement les réponses qui apportent la vérité, mais l'enchaînement des questions"

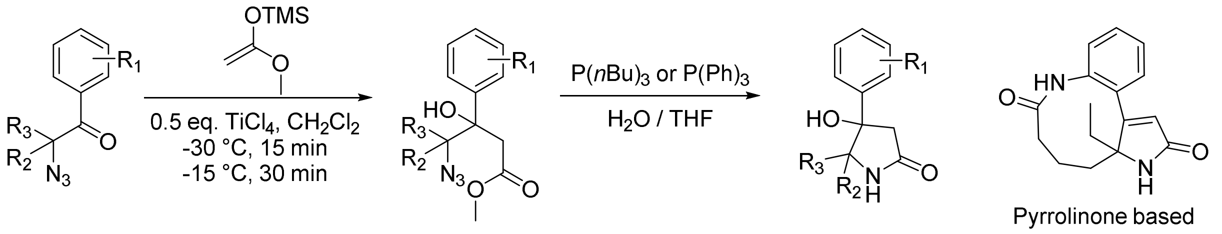
Daniel Pennac

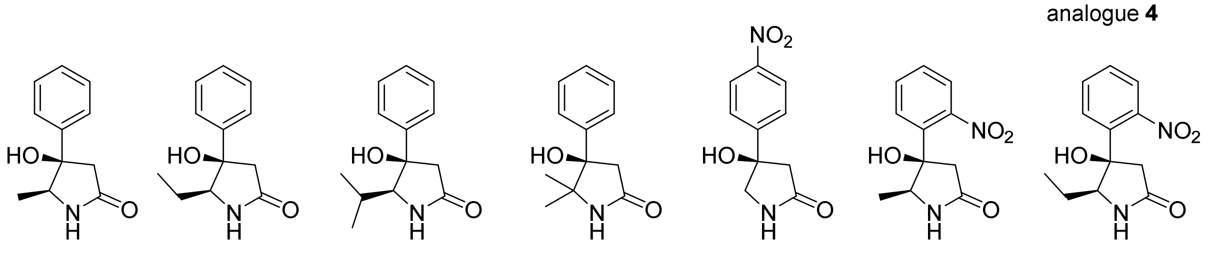
Abstract

The purpose of this thesis was to explore different approaches for the synthesis of advanced precursors of rhazinilam analogues. The intramolecular Michael Addition was envisaged in order to obtain the pyrrole or pyrrolinone based analogues. The aim of the first project was to develop a flexible, efficient synthesis towards model systems. N-acylation and N-alkylation of the corresponding substrates were intensively studied.



Oxydizing the pyrrole ring to pyrrolinone and blocking the C-5 position on the pyrrolinone ring seem to be a promising way to increase the chemical stability of rhazinilam analogues and avoid its enzymatic deactivation in target cells. The second project focused on the preparation of highly substituted 2-pyrrolidinones by a key Mukaiyama aldol reaction – Staudinger type reductive cyclisation sequence.





Author's declaration

This thesis represents the result of original work carried out by me during the period 2007-2012 unless explicit reference is made to the contribution of others in the text. The research was carried out in the Laboratory of synthetic organic chemistry at the Institute of chemistry, University of Neuchâtel under the supervision of Professor Reinhard Neier.

Certain aspects of this work have been published elsewhere as detailed below:

"Methods for the synthesis of rhazinilam and its analogues".
Inga Kholod, Reinhard Neier: *Targets in Heterocyclic Syst*ems **2009**, *13*, 252-272.

"Synthesis of Rhazinilam: A Comparative Review of Forty Years of Synthetic Endeavours".
Inga Kholod, Olivier Vallat, Ana-Maria Buciumas, and Reinhard Neier: *Heterocycles* **2011**, *82*, 917-948.

"Preparation of Precursors for the Synthesis of Analogues of Rhazinilam".
Inga Kholod, Olivier Vallat, Ana-Maria Buciumas, and Reinhard Neier: *ARKIVOC* **2014**, *iii*, 256-273, *commemorative issue in Honor of Prof. P. Vogel*.

"Synthetic strategies for the synthesis and transformation of substituted pyrrolinones as advanced intermediates for Rhazinilam analogues".
Inga Kholod, Olivier Vallat, Ana-Maria Buciumas, and Reinhard Neier: *European Journal of Organic Chemistry* **2014**, *35*, 7865-7877.

Key words:

Rhazinilam, Rhazinilam analogues, Crossed Aldol Mukaiyama reaction, Staudinger type reductive cyclisation, Diastereoselectivity, 3-pyrrolin-2-ones, N-acylation, N-alkylation.

Abbreviations:

AcOH	acetic acid
aq.	aqueous
Ar	aromatic
atm.	atmosphrere
Bn	benzyl
Boc	tert-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BuLi	butyl lithium
°C	degrees centigrade
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DCC	*N,N'*-dicyclohexylcarbodiimide
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
dtbpy	4,4-di-*tert*-butyl bipyridine
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
EI	electronic impact
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	Electron Spray Ionization

Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
IBX	2-iodoxybenzoic acid
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBT	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HR-MS	High Resolution Mass Spectroscopy
HWE	Horner-Wadsworth-Emmons
i-Pr	isopropyl
IR	infra-red
$[IrCl(cod)]_2$	bis(1,5-cyclooctadiene)diiridium(I) dichloride
IS	internal standard
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature
M	molar
m/z	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MHz	megahertz
min.	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mol(s)
Mp.	melting point
NaHMDS	Sodium hexamethyldisilazane
NMO	*N*-Methylmorpholine *N*-oxide

NMR	Nuclear Magnetic Resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
Ph	phenyl
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
r.t.	room temperature
*R*f	retention factor
SM	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMSQN	9-trimethylsilylquinine

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Chapter one

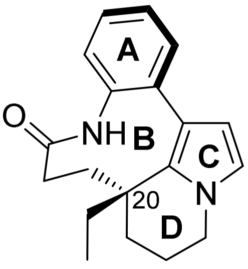
R-(–)-RHAZINILAM AND ITS ANALOGUES: BIOLOGICAL ACTIVITY AND SYNTHESES

1.1 R-(–)-Rhazinilam: occurrence, biosynthetic origins, semi-synthesis and structural elucidation

1.1.1 Isolation and structure determination of rhazinilam and its structural analogues

(*R*)-(−)-Rhazinilam (**1**) was first isolated by Linde from *Melodinus australis* in 1965.[1] The isolation from *Rhazya stricta* (1970)[2,3] some years later lead to the trivial name used today. The natural product has been found in other South-east Asian members of the family Apocynaceae.[4-12] The alkaloid **1** has also been obtained from somatic hybrid intragenic cell cultures.[13] More recently, (*R*)-(−)-rhazinilam (**1**) was isolated from the plant species *Kopsia arborea* (2007).[14,15]

The structure of (*R*)-(−)-rhazinilam (**1**) was established in 1972 through spectroscopic analysis, chemical degradation studies[3] and finally confirmed by X-ray crystallographic techniques[5] (Figure 1). The complete infra-red, mass spectra and ^{1}H and ^{13}C NMR analysis of compound **1** was reported later.[16] The four rings are identified as rings A to D. The quaternary carbon center at C20 and a phenyl-pyrrole chirality axis are the two stereogenic elements of (*R*)-(−)-rhazinilam (**1**). The dihedral angle between rings A and C is almost 90°. The lactam bond is in the *s-cisoid* conformation. The nine-membered ring adopts a boat-chair conformation imposed by the two aromatic bonds and the lactam bond contained in the medium sized ring rigidifying the ring. It was not possible to determine the absolute configuration (*R*, a*R*) by X-ray. The absolute configuration was deduced *via* semi-synthesis from an aspidosperma alkaloid, namely (+)-1,2-didehydroaspidospermidine (**15**).[17]



R-(–)-Rhazinilam **(1)**

Figure 1.1. (*R*)-(−)-Rhazinilam (**1**).

Other alkaloids with the same tetracyclic array as (*R*)-(−)-rhazinilam (**1**) have been isolated from different members of the family Apocynaceae: 5,21-dihydrorhazinilam *N*-oxide (**2**),[18] rhazinicine (**3**),[19-22] 3-oxo-14,15-dehydrorhazinilam (**4**),[23] nor-rhazinicine (**5**),[18] (−)-leuconolam (**6**),[8,10,22,24,25] *N*-methylleuconolam (**7**),[26] (+)-*epi*-leuconolam (**8**),[8,10] 3,14-dehydroleuconolam (**9**),[18] (*R*)-(−)-rhazinal (**10**),[22,27] Kopsiyunnanines C1 (**11**), C2 (**12**), C3 (**13**)[15] (Figure 2). The formation of all these alkaloids is postulated to occur *via* oxidative pathways from 5,21-dihydrorhazinilam (**5**), which is co-isolated with **1**.[8-10,14,28]

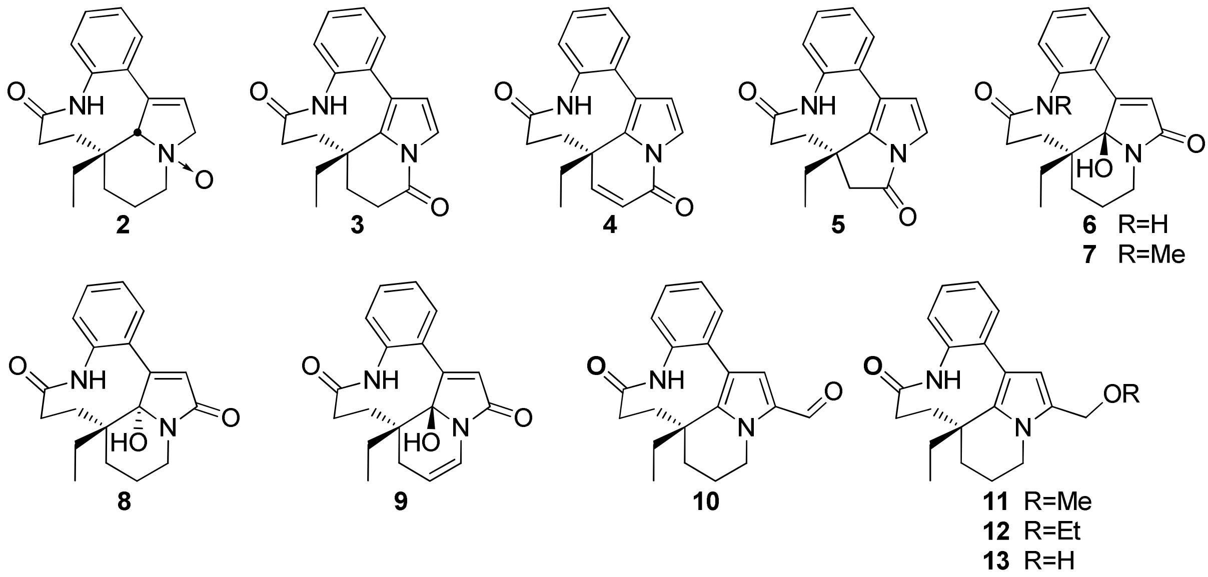
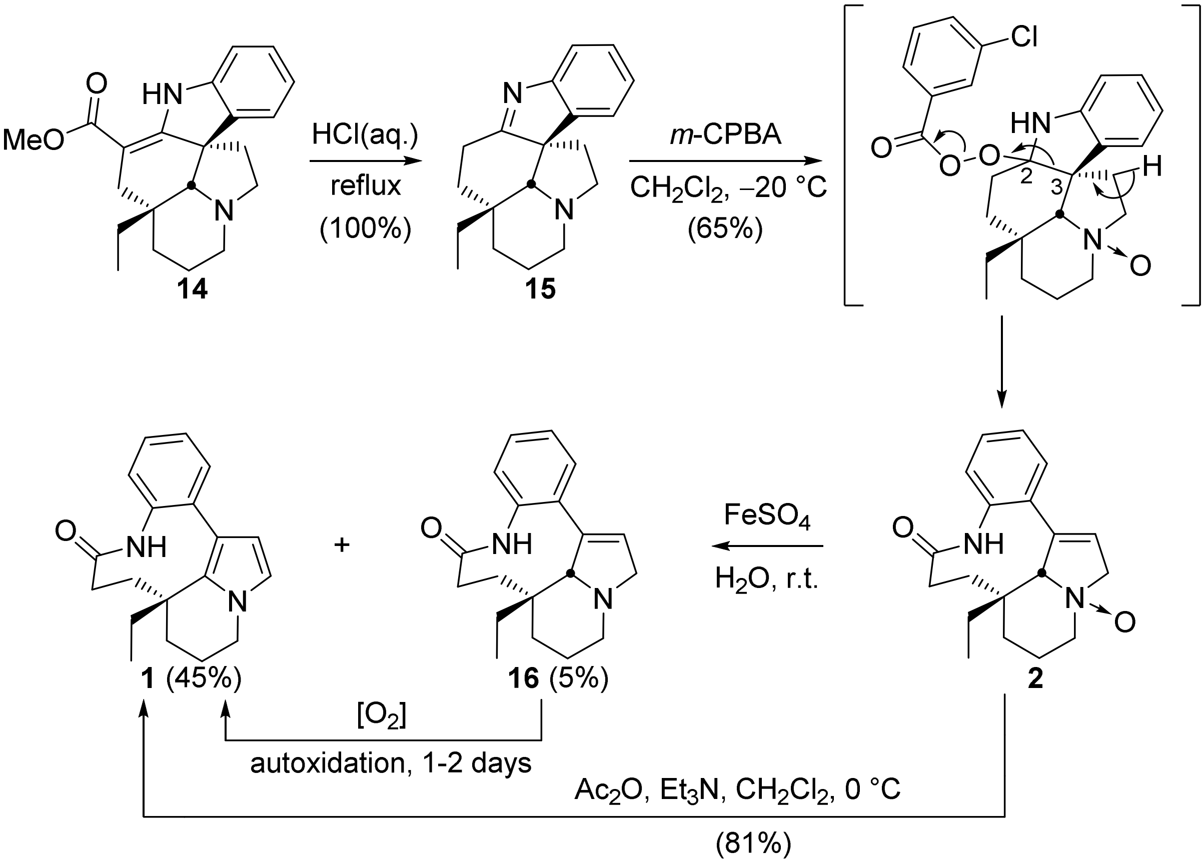


Figure 1.2. Naturally occurring analogues of (*R*)-rhazinilam (**1**):

1.1.2 Postulated formation of (*R*)-(−)-rhazinilam from indole alkaloids

(*R*)-(−)-Rhazinilam (**1**) is now considered to be an artefact of the extraction procedure. The unstable 1,2 dihydrorhazinilam (**16**)[3] aromatises spontaneously on exposure to air.[8,9] The dihydro-derivative **16** is believed to be the immediate natural precursor of (*R*)-(−)-rhazinilam (**1**). More significantly the natural product **1** can also be synthesized starting from (+)-vincadifformine (**14**) (Scheme 1.1). The mechanism of the stepwise conversion was proposed by Smith[17] and later experimentally confirmed by Guenard.[29,30] The sequence starts from (+)-vincadifformine (**14**) and comprises an acid-catalysed ester hydrolysis and decarboxylation followed by an oxidation-reduction-oxidation sequence. The key step in this sequence is the MCPBA-promoted oxidative cleavage of the C2-C3 indoline bond in (+)-1,2-didehydroaspidospermidine (**15**) producing the 5,21-dihydrorhazinilam *N*-oxide (**2**). This step produces the characteristic structural array of (*R*)-(−)-rhazinilam (**1**). The N-oxide **2** could be reduced with Fe(II) to give a 9:1 mixture of (*R*)-(−)-rhazinilam (**1**) and 5,21-dihydrorhazinilam (**16**). This conversion (*R*)-5,21-dihydrorhazinilam (**16**) → (*R*)-(−)-rhazinilam (**1**) was slow. This observation suggests that the formation of rhazinilam from the 5,21-dihydrorhazinilam *N*-oxide (**2**) occurred *via* a Polonovsky-type reaction.[30,31] (+)-1,2-Didehydroaspidospermidine (**15**) has never been detected *in vivo* together with 5,21-dihydrorhazinilam (**16**) or (*R*)-(−)-rhazinilam (**1**). If (+)-1,2-didehydroaspidospermidine (**15**) is the precursor of (*R*)-(−)-rhazinilam (**1**) remains an open question.



Scheme 1.1. Semi-synthesis of (*R*)-rhazinilam (**1**) from (+)-vincadifformine (**14**).

1.2 Biological activity of rhazinilam and its analogues

(*R*)-(−)-Rhazinilam **1** and some of its congeners have a unique activity on the tubulin-microtubules equilibrium involved in the formation of mitotic spindle.[9,32-34] They induce both the abnormal spiralisation of tubulin and formation of extensively bundled, short microtubules in interphase (vinblastine effect) and block mitotic cells in aster-like structure inhibiting the cold-induced disassembly of microtubules (paclitaxel (Taxol^{TM}) effect) (Figure 1.3 and Figure 1.4).

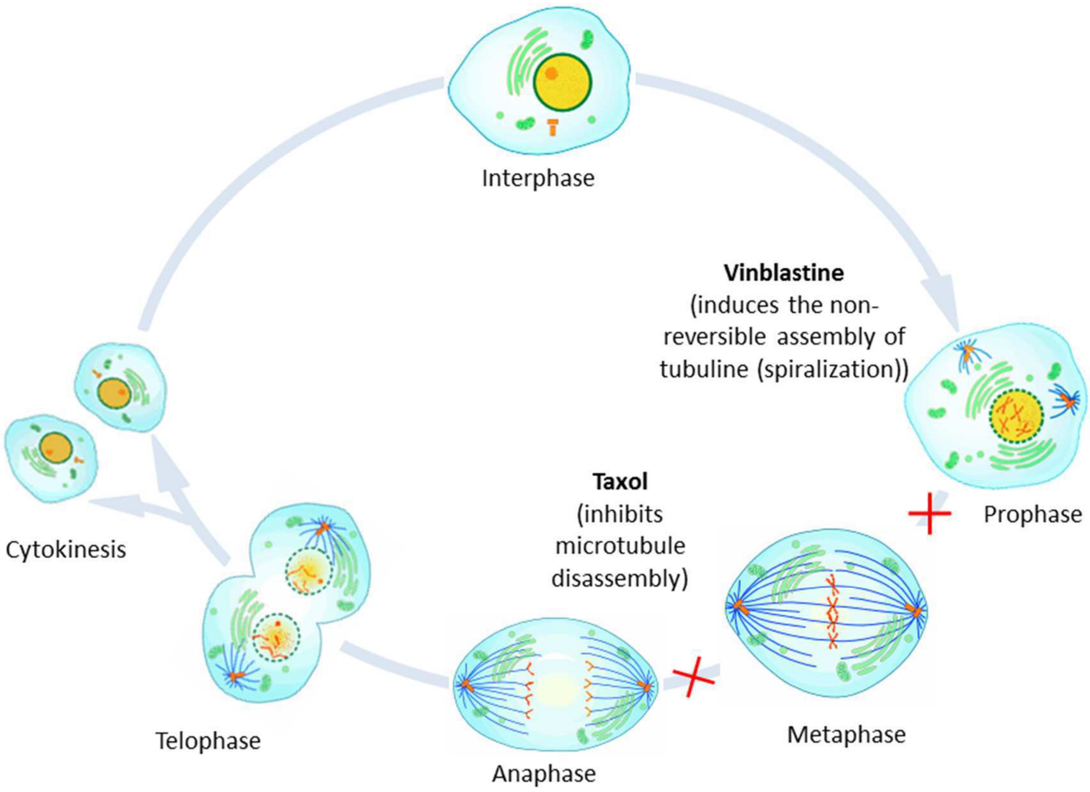
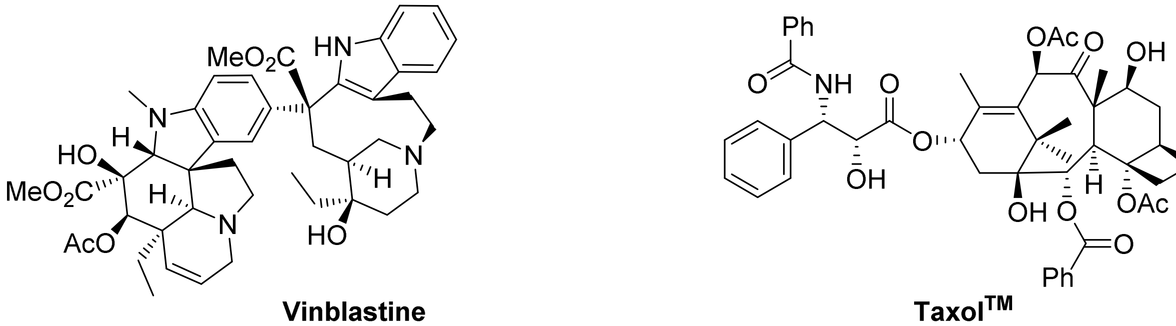


Figure 1.3. Schematic illustration of the cell cycle and its regulatory mechanisms that are relevant for the inhibitory effect imposed by Vionblastine and Paclitaxel (Taxol^{TM}).

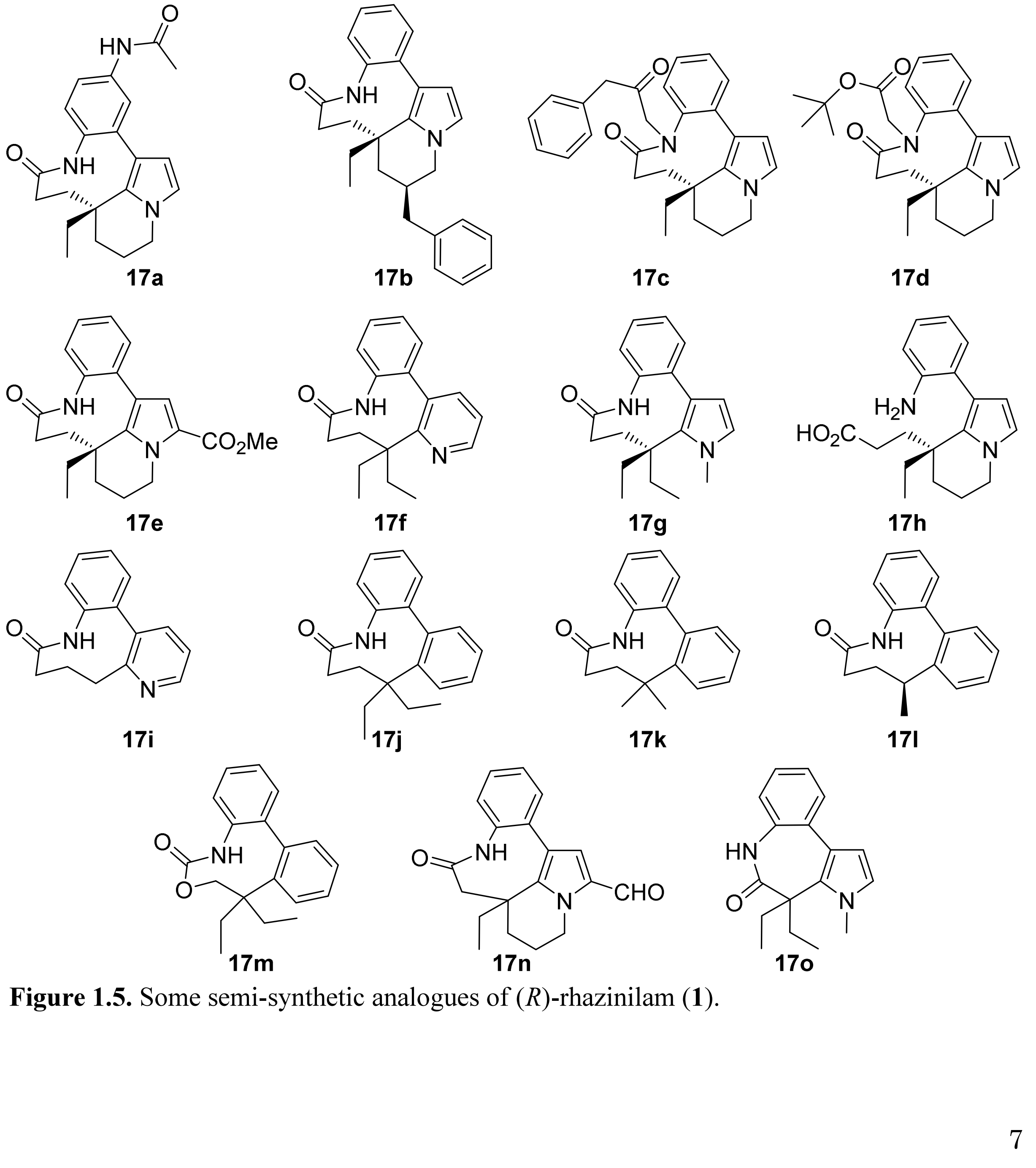
As a consequence, (*R*)-(−)-rhazinilam, shows appreciable cytotoxicity toward both drug-sensitive and vincristine-resistant KB cell lines, with IC_{50} values in the range of 0.5-1.16 μM.[22,32] In the absence of a crystallographic structure of the rhazinilam binding site in tubulin, a number of structure-activity relationship (SAR) studies have been conducted to gain greater understanding of the mode of interaction of these compounds with the protein and to solve the problem of *in vivo* inactivity. Despite huge synthetic efforts, none has succeeded thus far in producing a more cytotoxic analogue than (*R*)-(−)-rhazinilam.[33,35,36]



Vinblastine
Hodgkin's disease
advanced testicular carcinoma
breast carcinoma

Taxol^{TM}
metastatic ovarian carcinoma
metastatic breast carcinoma

Figure 1.4. Vinblastine and Taxol^{TM} structures and the cancers they are used to treat.



17a **17b** **17c** **17d**

17e **17f** **17g** **17h**

17i **17j** **17k** **17l**

17m **17n** **17o**

Figure 1.5. Some semi-synthetic analogues of (*R*)-rhazinilam (**1**).

However, the great structural diversity of the rhazinilam analogues[30,32,35-45] and the considerable number of assays carried out on them allow defining the minimum structural requirements necessary for their biological activity (Figure 1.5 and Table 1.1). Notably, the introduction of substituents on rings A, B, and D decreases the tubulin activity, suggesting a narrow tubulin binding pocket surrounding the phenyl-pyrrolic subunit annulated to an adjacent piperidine ring (compounds **17a-17c**). Increasing steric bulk on the A ring or replacement of the C-ring with heterocyclics such as pyridine (**17f**and **17i**) lead to reduction or loss of biological activity.[44,46] However, it was established that the D-ring conferring an additional structural rigidity to the natural product is not necessary for its binding activity (**17g**).[39,47,48] In contrast, the analogues devoid of the lactam B-ring were found to be inactive (**17h**).[37] It was shown that the conservation of the boat–chair conformation of B-ring, imposed by the cis-amide group and the quaternary C-20 carbon are essential for preserving the affinity for tubulin. The best substituents at C-20 seem to be ethyl group[36] or diethyl substituent in the absence of D-ring[42,45] (**17i-17l**) suggesting a direct interaction of the alkyl groups with tubulin. The replacement of lactam group with urethane resulted in the increase of the anti-tubulin activity (**17m**).[43] Another important point is he A-C dihedral angle which is closely related to the size of B-ring. According to X-ray data, the aromatic rings of (–)-rhazinilam are orthogonal with the A-C dihedral angle close to 95° and the amide bond possesses a *s-cisoid* conformation.[5] However, the recent SAR studies suggest that there are certain degrees of freedom available for rhazinilam-type analogues while preserving the tubulin-binding affinity.[41,45] Thus, the *rac*-B-norrhazinal (**17n**) with a more constrained 8-membered lactam was found to display comparable tubulin-binding properties and similar cytotoxicity to that of (–)-rhazinilam.[41] The X-ray analysis revealed, that the amide unit adopts an *s-cisoid* conformation and that the biaryl dihedral angle is ca. 56°.[40] A curious observation was made with the D-ring *seco*-analogue, containing more constrained 7-membered lactam (**17o**).[45] It was found to be inactive on the disassembly of microtubules, while it acts as an inhibitor of tubulin assembly and displays a significant toxicity towards tumour KB cell lines, indicating a different mode of action towards tubulin in comparison to (–)-rhazinilam. This confirms that the size of the lactam ring, and consequently the dihedral angle of the biaryl moiety, play an essential role in the inhibition of cold microtubules disassembly. Despite the interesting biological properties and the significant progress in the understanding of the drug-tubulin interactions of the rhazinilam-type compounds, transferring the knowledge from *in vitro* studies to *in vivo* experiments has proved to be quasi impossible.

Table 1.1. Cytotoxic and anti-mitotic properties of some natural and semi-synthetic analogues of (*R*)-rhazinilam (**1**).

Compound	IC_{50}/[IC_{50} (*R*)-**1**] in a cold-induced inhibition of microtubule disassembly assay	IC_{50} (μM) cytotoxicity towards KB cells
(–)-1	1	0.5
3	10	3
6	inactive	inactive
5	–	40
10	6	–
11	–	– [a]
12	–	– [a]
13	–	– [a]
17a	inactive	inactive
17b	inactive	44
17c	80	inactive
17d	80	inactive
17e	5	4
17f	9.5	–
17g	2	–
17h	inactive	inactive
17i	inactive	–
17j	8	5.5
17k	20	–
17l	inactive	–
17m	0.5	0.5
17n	similar	– [b]
17o	inactive[c]	7

[a] Active against lung and colon adenocarcinoma cell lines: **11** (IC_{50} 5 μM), **12** (IC_{50} 6-7 μM), **13** (IC_{50} 8-9 μM).[15]

[b] Active against CA46 Burkilt lymphoma cells (IC_{50} 3 μM).[41]

[c] Inhibits tubulin assembly (IC_{50} 27 μM).[45]

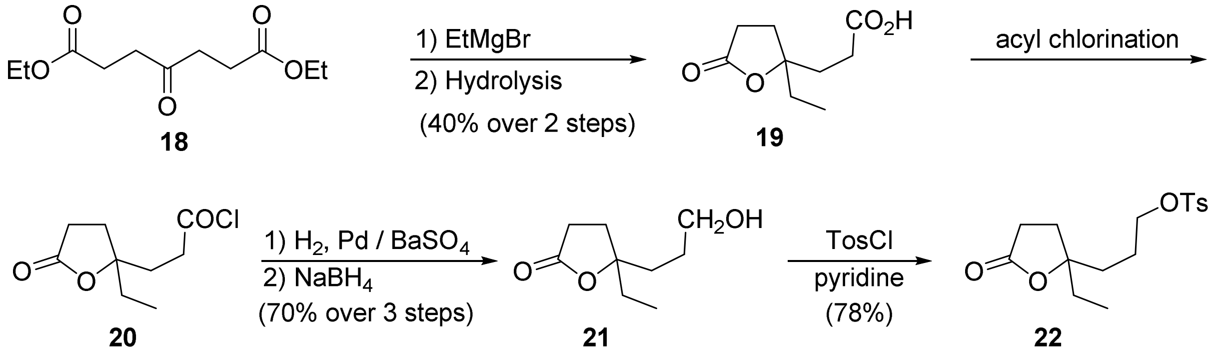
1.3 Previous total syntheses of rhazinilam

1.3.1 Total syntheses of *rac*-rhazinilam

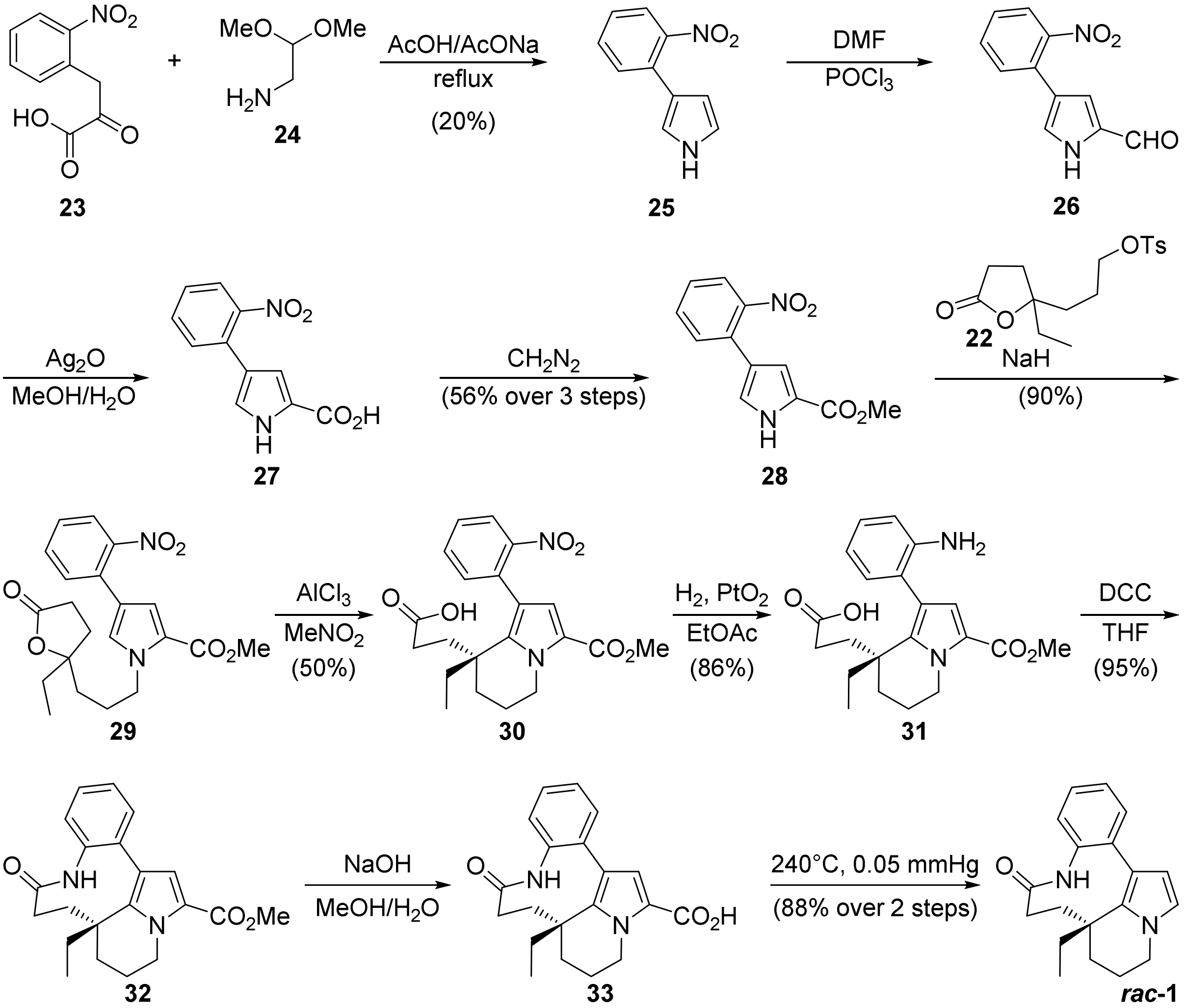
Six total syntheses of racemic (±)-rhazinilam have been reported. The main motivation for these studies was the unusual structure of (±)-rhazinilam. Over the almost forty years different strategies were applied to create the challenging elements contained in (±)-rhazinilam: the direct A-C biaryl link, the nine-membered lactam B ring, and the quaternary-carbon at C-20.

First total synthesis of *rac*-rhazinilam by Smith

The first total synthesis of the racemic (±)-rhazinilam (**1**) was reported by Smith and co-workers in 1973.[17] A convergent retrosynthetic plan was adopted by Smith. The natural product was cut into two pieces: the biaryl substructure containing the aromatic A ring directly linked to the pyrrolic C ring: intermediate **28**. The other intermediate contained all the missing aliphatic carbon atoms: intermediate **22**. Reacting ethyl magnesium bromide with diethyl 4-ketopimelate (**18**) gave after hydrolysis the lactone **19** in good yield (Scheme 1.2). Acyl chloride **20** was then reduced in a two-step sequence: Rosenmund reduction[49] first followed by $NaBH_4$ reduction. Tosylation of **21** with tosyl chloride in pyridine provided the desired tosyl derivative of γ-lactone **22** in 22% over six steps from commercially available **18**.



Scheme 1.2. Synthesis of intermediate **22**.



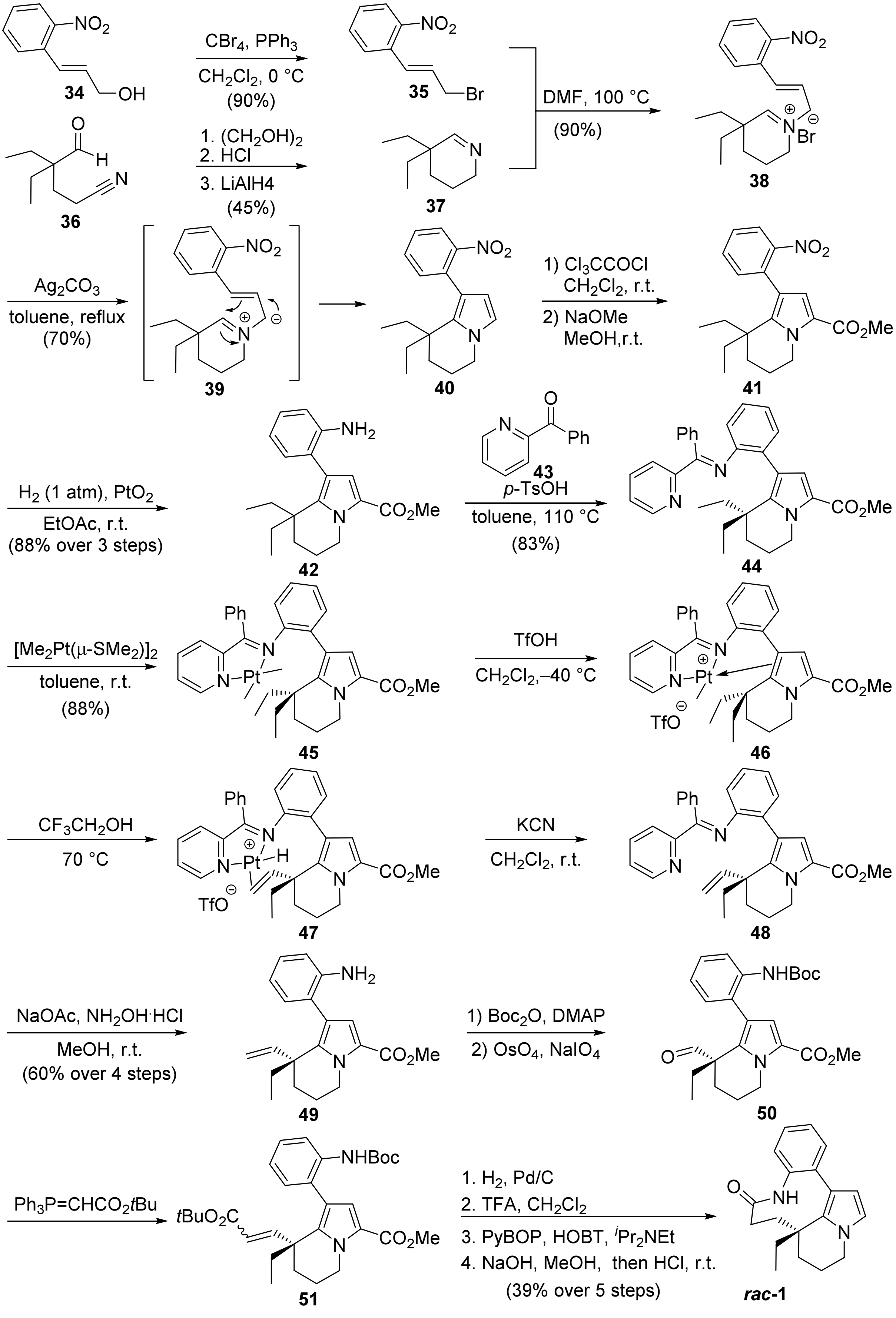
Scheme 1.3. Smith's total synthesis of *rac*-rhazinilam (**1**).

The pyrrole **25** was prepared *via* Knorr-type condensation (Scheme 1.3). Vilsmeier formylation of compound **25** followed by silver oxidation and subsequent esterification with diazomethane generated the pyrrole **28** in 11% yield over four steps from **23**.

The crucial combination of the two intermediates was achieved by the *N*-alkylation of the sodium salt of the pyrrole **28** with the tosyl derivative of the lactone **22**. The intramolecular Friedel-Crafts cyclisation of the pyrrole **29** gave the tetrahydroindolizine derivative **30** in 50% yield. The intermediate **30** contained all the carbons present in the target molecule. Catalytic reduction of the nitro group followed by lactamisation afforded compound **32**. A two-step sequence had to be applied to produce *rac*-rhazinilam (**1**) under harsh conditions but in good overall yield. The synthesis proceeds through ten steps starting from the commercially available acid **23** in a remarkable 3.6% overall yield.

Total synthesis of *rac*-rhazinilam by Sames

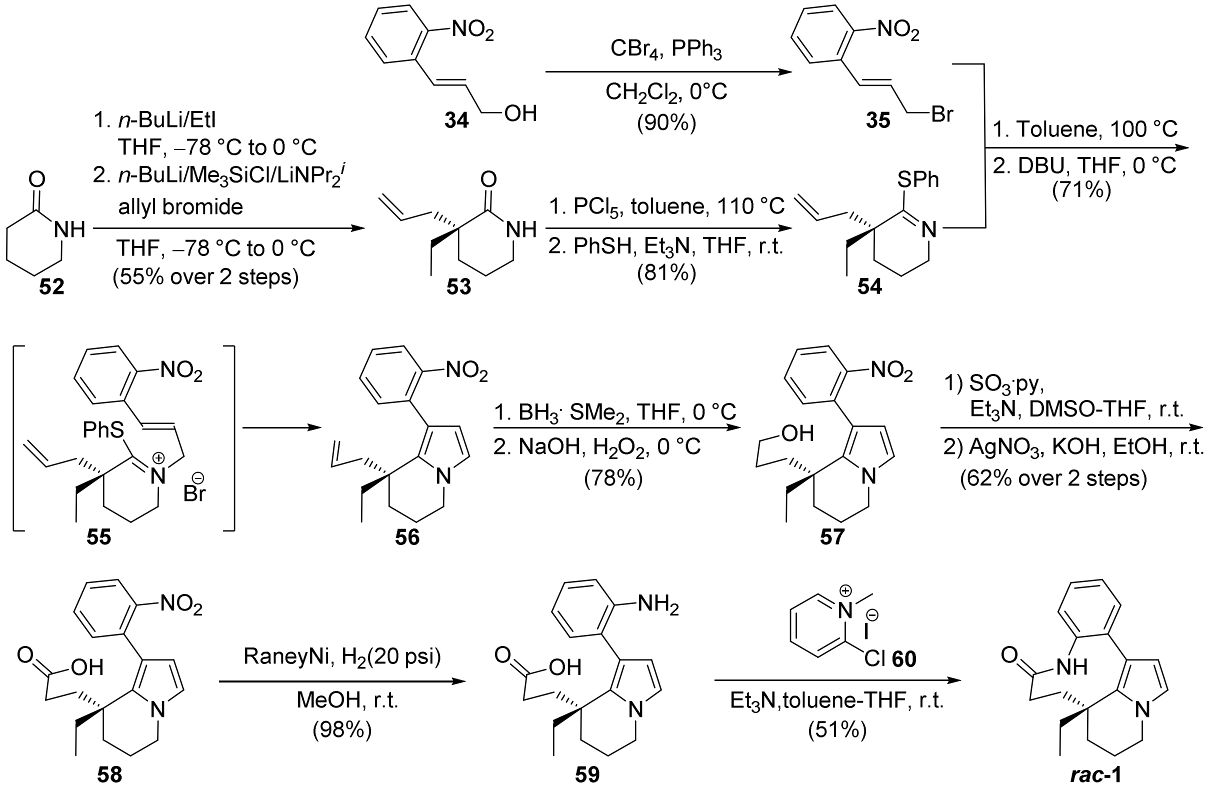
In 2000 a very elegant total synthesis of *rac*-(±)-rhazinilam (*rac*-**1**) was reported by Sames and co-workers.[50] The key intermediate **43** was synthesized in the efficient sequence depicted in Schema 1.4. The Grigg-type 1,5-electrocyclisation reaction[51] of **38** catalysed by silver carbonate produced the achiral intermediate **40** in 70% yield. The sensitive pyrrole ring was then protected in two steps as methyl ester **41**. Selective reduction of **41** provided the aniline **42** in 25% over seven steps from nitrile aldehyde **36**. The second key step was the transformation of one of the ethyl groups into ethenyl group. Six synthetic steps were necessary to achieve the transformation from **43** to **49**. The pivotal platinum complex **45** had to be synthesized, introducing a Schiff base first and treating the Schiff base **44** with the dimethyl platinum reagent $[Me_2Pt(\mu\text{-}SMe_2)]_2$[52] providing **45** in 88% yield. Treating the intermediate **45** successively with triflic acid followed by thermolysis in trifluoroethanol at 70 °C and then by decomplexation with potassium cyanide and hydrolysis of the Schiff base **48** provided the racemic alkene **49** in 60% yield over four steps. The total synthesis was then completed *via* a formal one-carbon extension of the vinyl group and the subsequent closure of the medium sized lactam ring in six synthetic steps. Lemieux-Johnson oxidation provided the aldehyde **50** followed by WHE olefination. Selective reduction of the alkene **51**, lactamisation and decarboxylation using Smith's methodology[17] afforded *rac*-**1**. The synthesis proceeds through twenty steps in 3.5% overall yield starting from nitrile aldehyde **36**. The sequence is considerably longer than the Smith synthesis, but the overall yield is almost identical with the yield of the first synthesis.



Scheme 1.4. Sames' total synthesis of *rac*-rhazinilam (**1**).

Total synthesis of *rac*-rhazinilam by Magnus

In 2001 Magnus and co-workers published a straightforward and elegant synthesis of *rac*-rhazinilam (*rac*-**1**)[53] (Scheme 1.5).

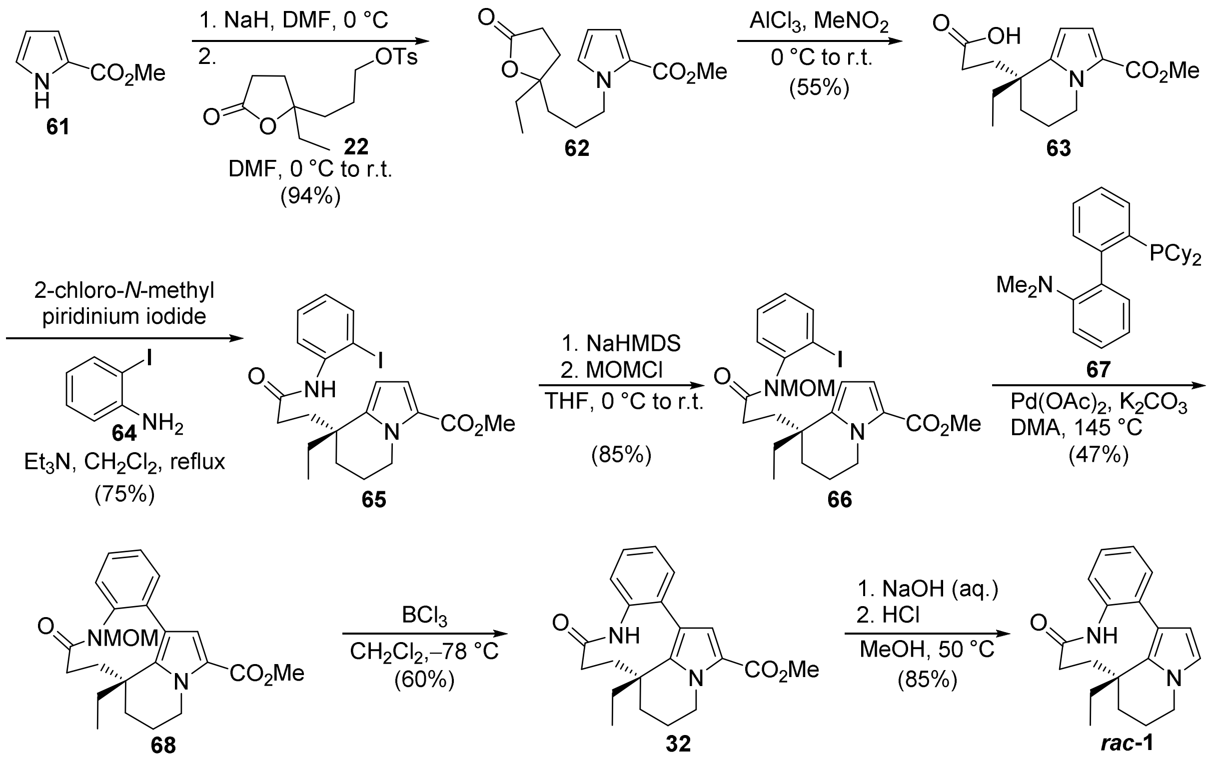


Scheme 1.5. Magnus' convergent total synthesis of *rac*-rhazinilam (*rac*-**1**).

The retrosynthetic analysis is very similar to the one used by Sames, with the difference that the two chains on the α-position of the pyrrole ring are already differentiated right from the start of the synthesis. The elegant but lengthy modification of one of the two ethyl groups can thereby be avoided, which reduces the number of steps. Starting from commercially available 2-piperidone **52** the ethyl and allyl group are sequentially introduced in a total of six synthetic operations. *N*-alkylation of this thiophenyl imino ether **54** with 2-nitrocinnamyl bromide **35** gave the corresponding iminium intermediate **55**. This intermediate underwent a Grigg-type 1,5-electrocyclisation/thiophenol elimination reaction[51] to provide compound **56** in 71% yield. The compound **56** was transformed into the natural product *rac*-**1** in a sequence of six steps: hydroboration, Swern-type oxidation with pyridine/sulphur trioxide/dimethylsulfoxide,[54] exhaustive oxidation using silver nitrate under alkaline condition, Raney nickel reduction and finally lactamisation. The reaction types used in the end game of the Sames and Magnus syntheses are very similar. It is therefore all the more surprising that the Magnus group did not need to introduce any protection on the pyrrole ring. The Magnus group could reduce considerably the number of steps. The synthesis proceeds through nine steps in an impressive 7.6% overall yield.

Total synthesis of *rac*-rhazinilam by Trauner

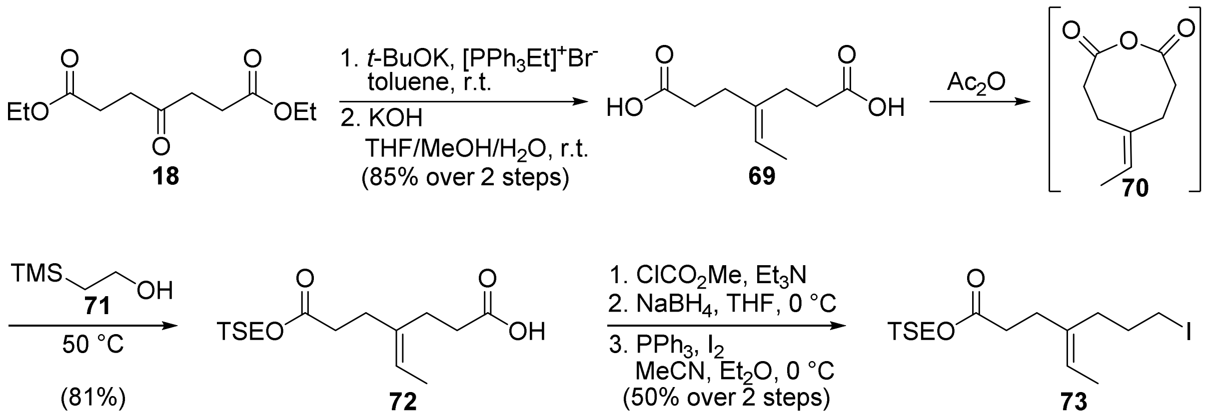
The Trauner's synthesis published in 2005 forms in the last step *rac*-(±)-rhazinilam (*rac*-**1**) using an intramolecular Heck-type reaction[55] starting from an intermediate containing the A-D-C rings and forming the aryl heteroaryl bond last (Scheme 1.6). The difference to the Sames and Magnus syntheses is the presence of the amide bond directly connecting the A and the D rings. The Trauner group starts with the 2-carbomethoxy pyrrole **61** which is N-alkylated with the tosyl derivative of γ-lactone **22.** The alkylation and the intramolecular Friedel-Crafts cyclisation are almost identical to the Smith procedure.[17] At this point the Trauner synthesis diverges from the Smith synthesis. Amide coupling introduces all the atoms of the rhazinilam skeleton. For the Heck type coupling the amide had to be protected with the with methoxymethyl (MOM) protecting group transforming compound **66** with 10 mol % of Buchwald's "DavePhos" ligand **67**[56] and $Pd(OAc)_2$ in the presence of potassium carbonate as base to give the strained nine-membered ring **68** in 47% yield. Removing first the MOM protecting group[17,50,57] followed by saponification and acid-catalysed decarboxylation produced *rac*-**1**. Only seven steps are needed starting from commercially available pyrrole **61** and an impressive 7.9% overall yield could be obtained. Starting from the commercially available diester **18** (*rac*)-rhazinilam (*rac*-**1**) can be obtained in thirteen steps and in 1.7% overall yield.



Scheme 1.6. Trauner's total synthesis of *rac*-rhazinilam (*rac*-**1**).

Total synthesis of *rac*-rhazinilam by Gaunt

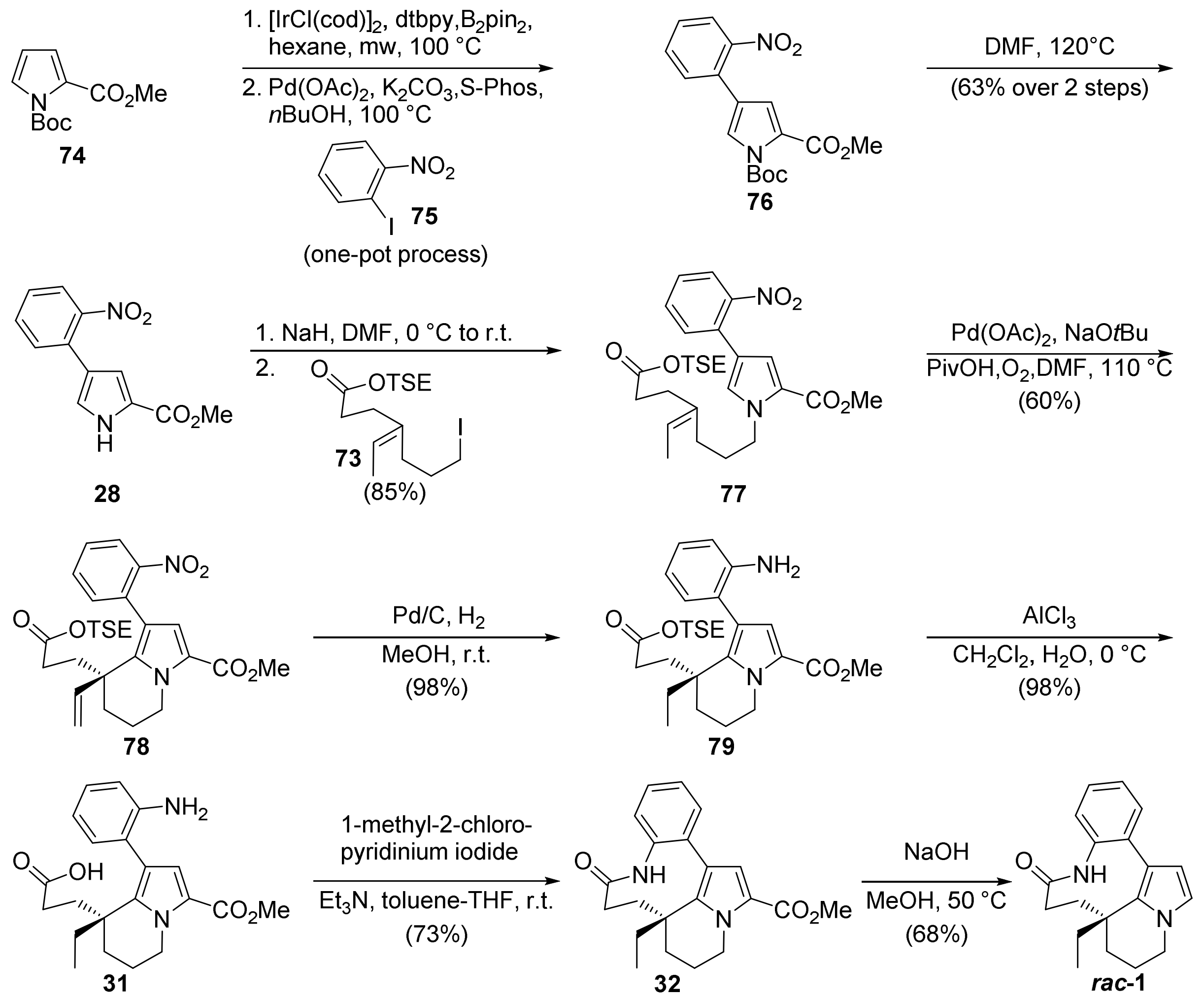
The synthesis of *rac*-rhazinilam reported by Gaunt and co-workers in 2012[58] adopts the synthetic strategy developed earlier for the synthesis of *rac*-rhazinicine.[59] The key steps of this convergent synthesis use modern organometallic reactions to connect the rings A and C first and then to form the D-ring. The B-ring is formed via a lactamisation. The connection between the phenyl ring and the pyrrole is achieved by the one-pot Ir^{I}-catalyzed C-H bond borylation[60,61] directly followed by subsequent Suzuki coupling reaction.[62] The oxidative Pd^{II}-catalysed pyrrole C-H bond cyclisation leads to the formation of the D-ring. The synthesis started with the preparation of the alkene monoester intermediate **73** (Scheme 1.7). The commercially available diethyl-4-oxo-pimelate (**18**) underwent the Wittig ethenylation followed by functional group manipulation (hydrolysis, esterification, acyl chlorination, reduction, and iodination) to obtain the intermediate **73** containing all the carbons for the rings B and D.



Scheme 1.7. Synthesis of iodide intermediate **73**.

The 3-arylated pyrrole **76** was obtained from pyrrole **74** and *o*-iodonitrobenzene (**75**) by the one-pot Ir^{I}-catalysed borylation/Suzuki coupling. Subsequent removal of Boc-protecting group under heating afforded in 63% overall yield the pyrrole **28** containing the A-C rings of rhazinilam (Scheme 1.8).

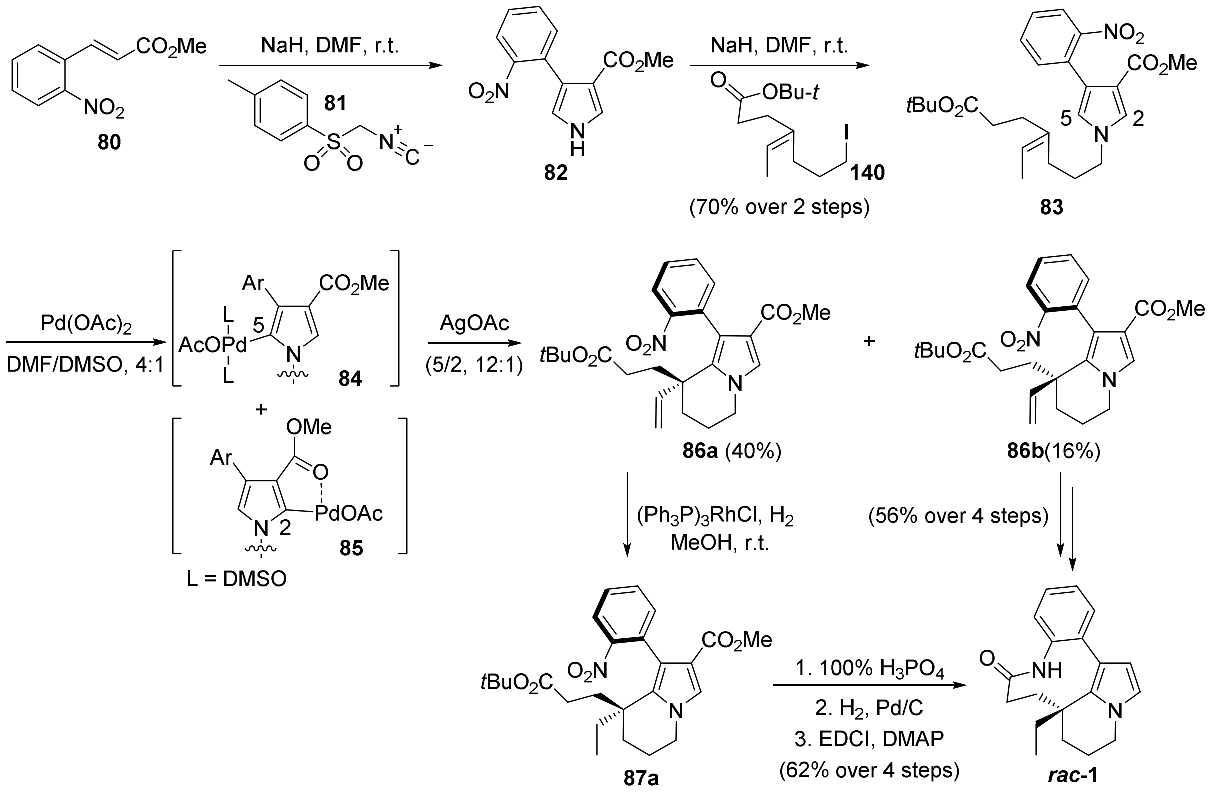
Reacting the sodium anion of **28** with iodide intermediate **73** the *N*-alkylated pyrrole **77** was obtained in 85% yield. The intermediate **77** contains all the carbons present in the target molecule. Treating **77** with $Pd(OAc)_2$ catalyst and NaO*t*Bu in the presence of pivalic acid and oxygen resulted in the formation of the tetrahydroindolizine **78** in 60% yield. Simultaneous reduction of the nitro and alkene group of compound **78** followed by $AlCl_3$-mediated removal of the 2-trimethylsilylethyl protecting group gave the carboxylic acid **31**. Lactamisation of this compound under Mukaiyama conditions produced the methyl ester **32** in 73% yield. Removal of the methyl ester group of the pyrrole by saponification and subsequent decarboxylation afforded **rac-1** in 68% yield. The synthesis proceeds through eight steps starting from pyrrole **74** in considerable 15.9% overall yield (through twelve steps starting from diester **18** in 8.4% overall yield).



Scheme 1.8. Gaunt's total synthesis of *rac*-rhazinilam (*rac*-**1**).

Total synthesis of *rac*-rhazinilam by Yao

A new synthesis of *rac*-rhazinilam was reported by Yao and co-workers in 2014.[63] The synthetic strategy is similar to that used by Zakarian group[64] and involves an alkenylation using $Pd(OAc)_2$ catalysed Heck reaction as a key step. The difference to Zakarian syntheses is a solvent-controlled regioselectivity based on the solvent effect. The pyrrole ring was synthesized first from phenyl acrylate **80** and toluenesulfonylmethyl isocyanide (TosMIC) (**81**) *via* a van Leusen procedure[65] (Scheme 1.9). Alkylation of the sodium salt of **82** with iodoolefin **140**[64] (Scheme 1.15) provided the key intermediate **83** in 70% yield. The palladation of **83** occurs at the more electron-rich C5 position due to the fact that the strong coordinating solvent as DMSO overweighs the chelation effect of the carboxylate group. The alkenyllated product **86** was obtained in 56% yield (C5/C2 = 12:1) as a mixture of separable stereoisomers **86a** and **86b**.



Scheme 1.9. Yao's total synthesis of *rac*-rhazinilam (*rac*-**1**).

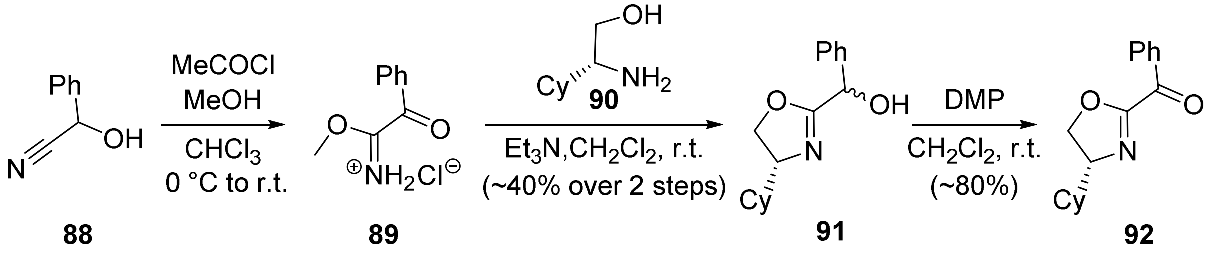
The total synthesis of *rac*-**1** was completed via hydrogenation of **86a** with Wilkinson's catalyst[66], decarboxylation, hydrogenation, and macrolactamization. The stereoisomer **86b** was also transformed to *rac*-**1** through the same sequence as **86a**, since the biaryl axis can rotate after decarboxylation. The synthesis proceeds through seven steps starting from the commercially available phenyl acrylate **80** in a remarkable 23% overall yield.

1.3.2 Total syntheses of R-(−)-rhazinilam

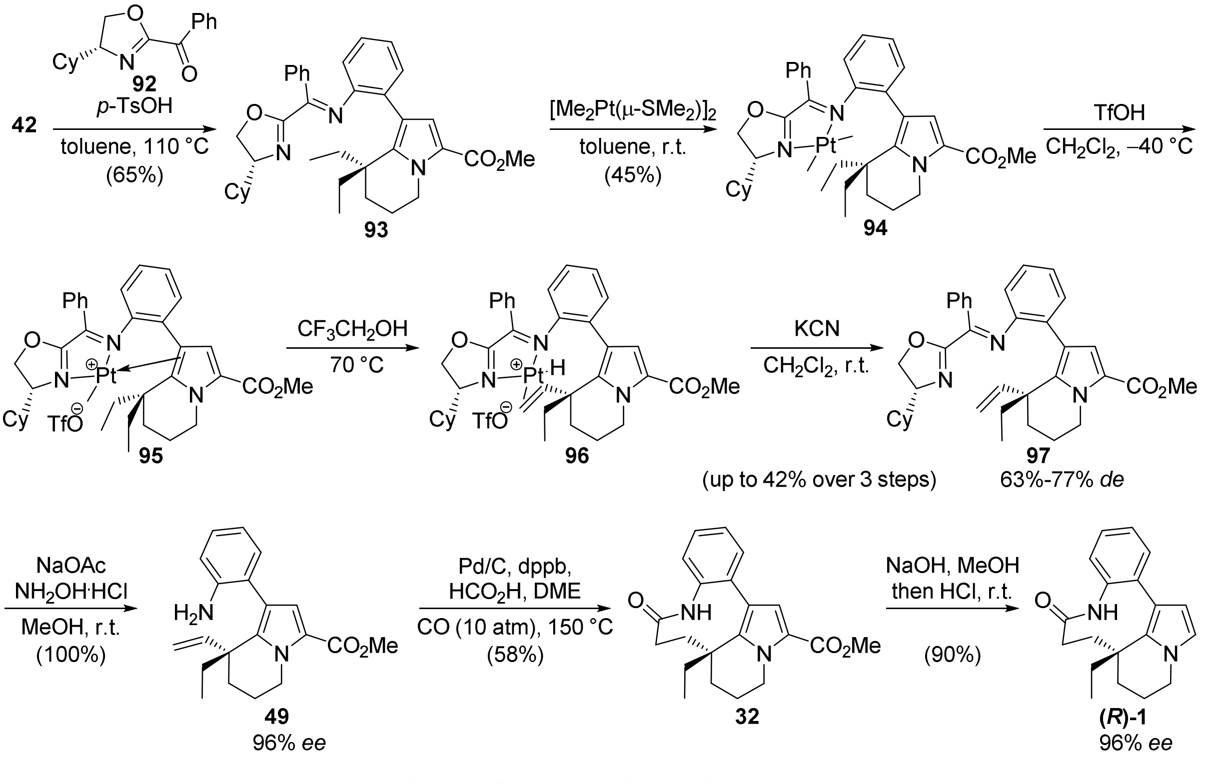
Besides the six syntheses of racemic (±)-rhazinilam, six of the naturally occurring (−)-enantiomer have been reported. The chirality of the A-C biaryl axis is determined by the absolute configuration of the quaternary-carbon at C-20. The challenge is therefore to obtain this quaternary center in enantiomerically pure form.

Sames' second enantioselective total synthesis of (*R*)-(–)-rhazinilam

The Sames group adapted their synthesis of (*rac*)-rhazinilam so that they could obtain the (*R*)-(–)-rhazinilam.[57] Sames choose to introduce a chiral auxiliary **92**, so as to functionalize diastereoselectively the intermediate **93** to the product **97** (see scheme 1.11). Before removing the chiral auxiliary a preparative HPLC separation of the diastereomers was used to obtain the product **49** in high enantiomeric excess. The chiral auxiliary phenyl-(5*R*)-cyclohexyl-2-oxazolinone **92** was prepared in three steps from commercially available mandelonitrile **88** in 32 % overall yield (Scheme 1.10).



Scheme 1.10. Synthesis of chiral oxazolyl ligand **92**.

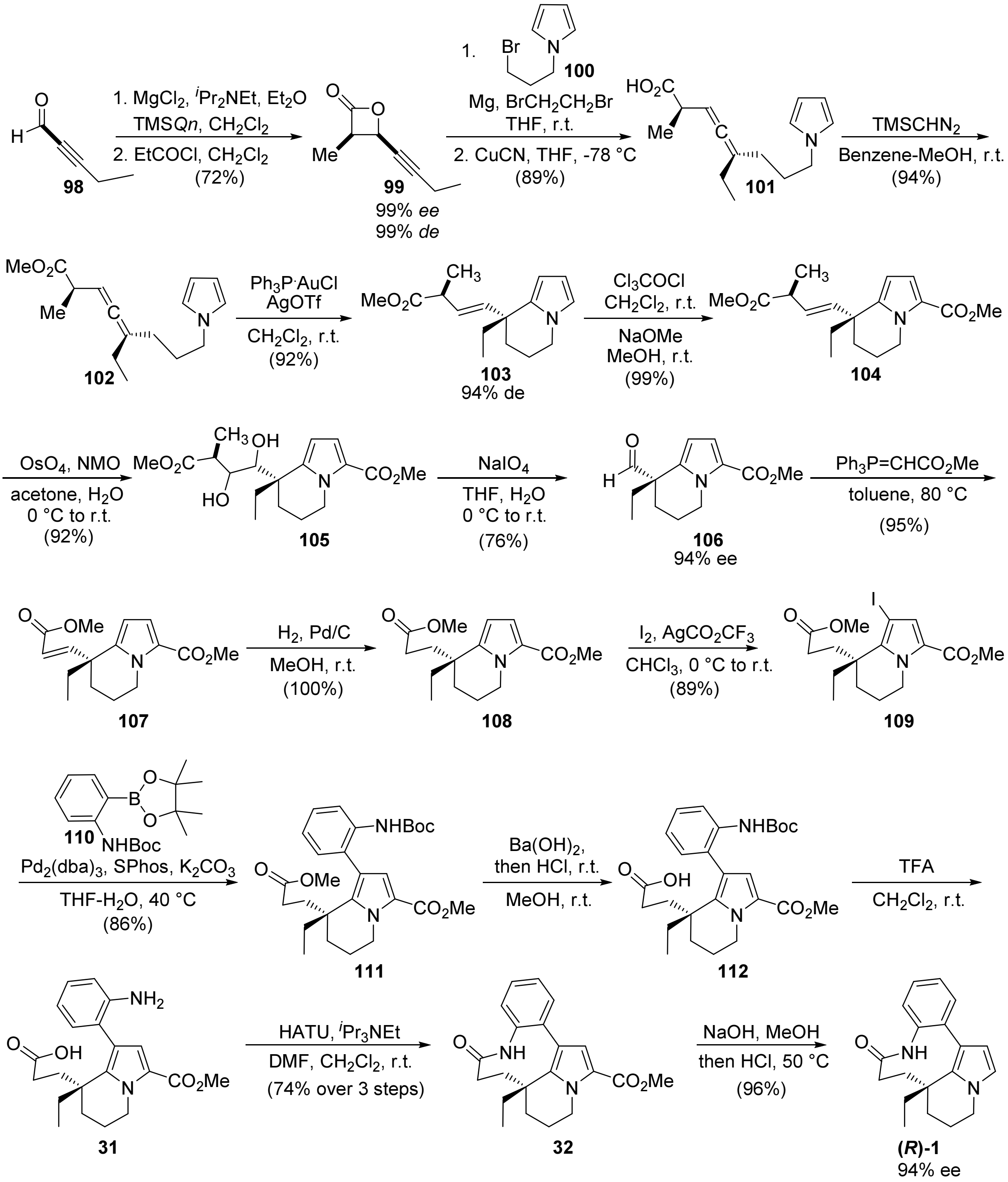


Scheme 1.11. Sames' total synthesis of (*R*)-(–)-rhazinilam (*R*)-**1**.

The desymmetrisation of the two enantiotopic ethyl groups in compound **42** was achieved by metal-induced C(sp^3)-H activation *via* the six steps sequence leading to the alkene **49** (96% *ee*) (Scheme 1.11). After decomplexation of the platinum with potassium cyanide a mixture of the diastereomers of **97** were obtained with a *de* of 63-77%. In this sequence the diastereomers were separated by preparative HPLC to give after removal of the ligand the alkene **49**. The palladium-catalysed carbonylation of the alkene **49** gave directly in 58% yield the required nine-membered ring lactam **32** which had been reported[17,50] previously in its racemic form. This metal catalysed transformation replaced favourably the five step sequence used in the synthesis of the racemate. The enantiomerically pure (*R*)-(−)-rhazinilam (**1**) was finally obtained in 90% yield and 96% *ee* following the procedure described by Smith[17]. The synthesis proceeds through fifteen steps starting from nitrile aldehyde **36** in 1.6% overall yield. The synthesis of the racemate was twenty steps long, but the overall yield was much better 3.6%. The diastereoselectivity (*de* = 63-77%) of the metal-induced C(sp^3)-H activation is the reason for this drop in the overall yield.

Total synthesis of (*R*)-(−)-rhazinilam by Nelson

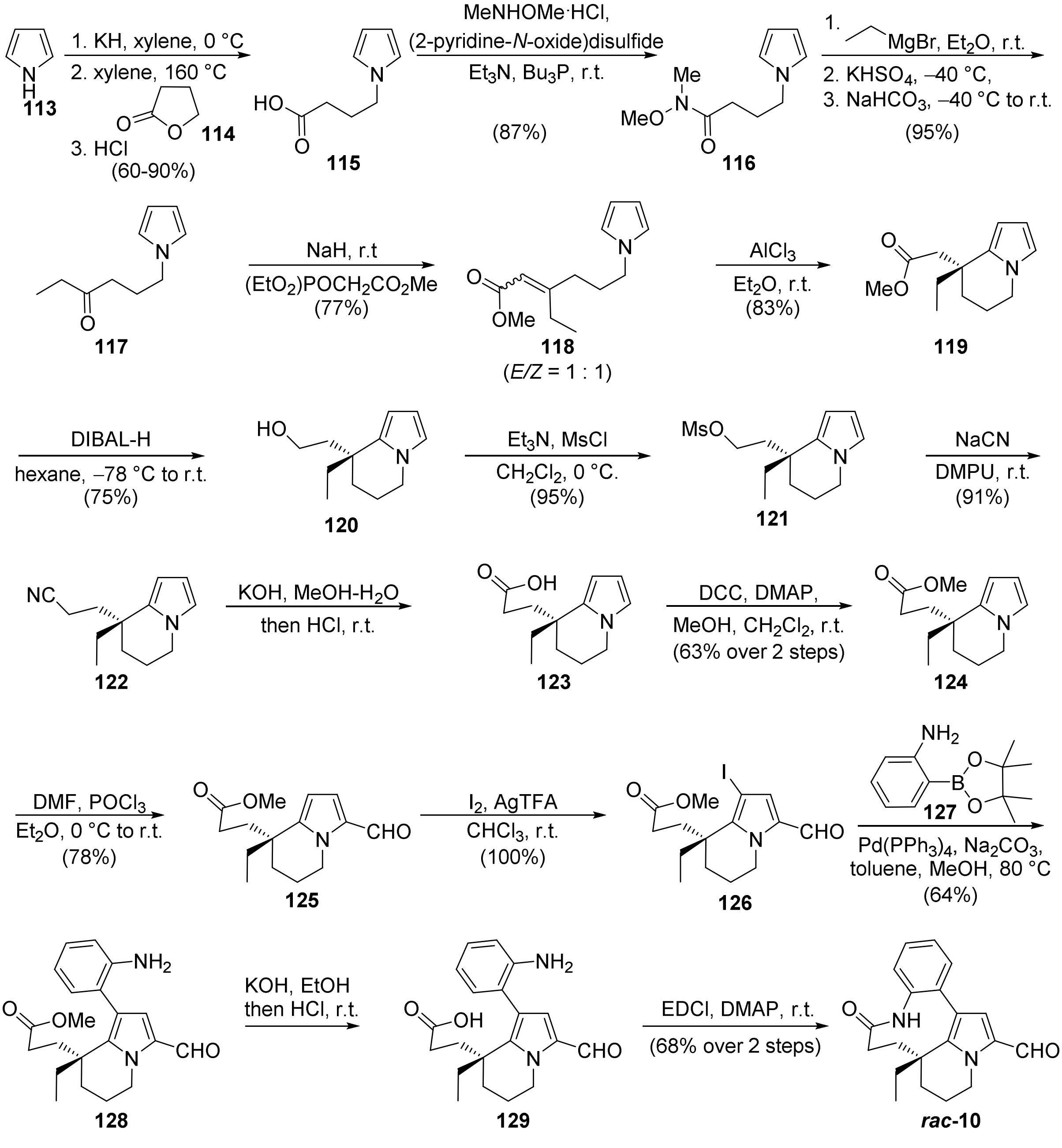
In 2006 Nelson and co-workers report an elegant, enantioselective total synthesis of (*R*)-(-)-rhazinilam (**1**) (Scheme 1.12).[67] The enantioselective synthesis of the almost enantiopure β-lactone **99** via a cyclocondensation[68-70] using a quinine derived asymmetric catalyst installed the two chiral centers[71] with high selectivity. From the β-lactone **99** the enantioenriched allene **102** was obtained by ring opening using the Grignard reagent **100** *via* an S_N2'-type reaction followed by a methylation with trimethylsilyldiazomethane. The intramolecular asymmetric Au(I)-catalysed pyrrole addition to the allene installed the quaternary carbon stereocenter with good control and formed the ring D of rhazinilam. To make the pyrrole ring C resistant to the following reaction steps a methyl ester group was introduced first giving **104**. In a four step sequence the functionalized side chain was first degraded and then reconstructed to obtain **108**. Electrophilic iodination[41] followed by Suzuki-Miyaura cross-coupling[72] of compound **109** with the commercially available 2-(*N*-Boc-amino)phenylboronic acid pinacol ester (**110**) using Buchwald's SPhos ligand[73] afforded the 3-aryl pyrrole **111** containing rings A, C and D of rhazinilam. Chemoselective ester saponification and TFA-mediated aniline *N*-deprotection resulted in the formation of the previously reported[17] amino acid **31**, the precursor for the formation of the B ring. Lactamisation of this compound was carried out with the HATU coupling reagent to produce the previously described[17,50,57,55] ester **32** in 74% yield. Removal of the methyl ester group in pyrrole **32**, as previously reported by Smith,[17] furnished (*R*)-(–)-rhazinilam (**1**) in 96% yield and 94% *ee*. Thus, the synthesis proceeds through fifteen steps starting from commercially available acyl aldehyde **98** in an impressive 19.8% overall yield.



Scheme 1.12. Nelson's total synthesis of (*R*)-(–)-rhazinilam (*R*)-**1**.

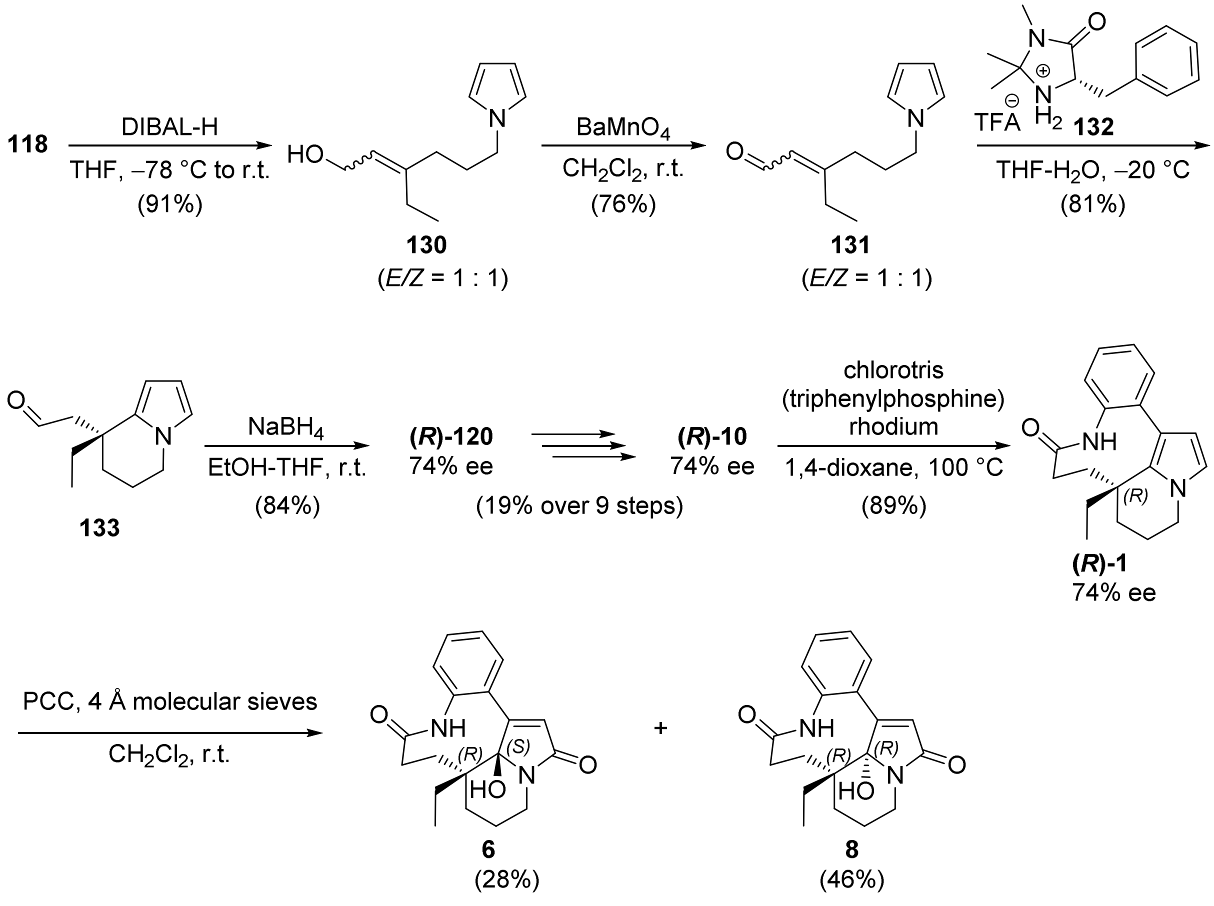
Total synthesis of (*R*)-(–)-rhazinilam by Banwell

Banwell and co-workers reported a synthesis of *rac*-(±)-rhazinal (*rac*-**10**)[41] (Scheme 1.13) and based on this chemistry an enantioselective total synthesis of (*R*)-(–)-rhazinilam ((*R*)-**1**)[74] (Scheme 1.14). The key step of the enantioselective synthesis is a MacMillan's chiral organocatalyst[75] promoted intramolecular Michael addition reaction closing the D ring and creating the quaternary center in 74% enantiomeric excess.



Scheme 1.13. Banwell's total synthesis of (*rac*)-rhazinal *rac*-**10**.

The synthetic route to the pivotal intermediate **131** started with the *N*-alkylation of pyrrole with γ-butyrolactone **114** under conditions defined by Li and Snyder.[76] Conversion into the corresponding Weinreb amide **116** using modified Mukaiyama conditions[77] and subsequent treatment with ethyl magnesium bromide furnished the ketone **117**. Wadsworth-Horner-Emmons (WHE) olefination provided the β,β-disubstituted methyl acrylate **108** followed by reduction with excess DIBAL-H to give the corresponding alcohol **130**. The alcohol **130** was oxidized with barium manganate[78] to the aldehyde **131** obtained in 76% as a roughly 1:1 mixture of *E*- and *Z*- isomers.



Scheme 1.14. Banwell's total synthesis of (*R*)-rhazinal, (*R*)-rhazinilam, (*R,S*) (–)-leuconolam and (*R,R*) (+)-*epi*-leuconolam.

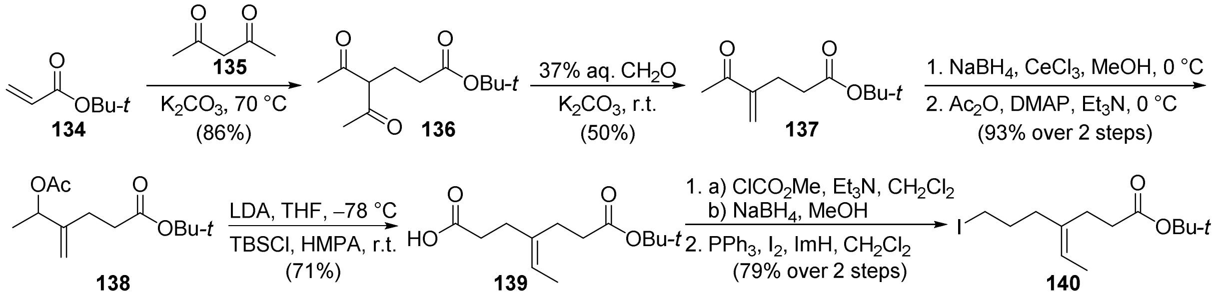
The pivotal intramolecular Michael addition reaction involved exposure of this mixture of aldehydes to (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate (**132**) (MacMillan's first generation organocatalyst) resulting in formation of the unstable indolizine aldehyde **133** in 81% yield. Subsequent reduction of compound **133** using sodium borohydride afforded the stable alcohol **120** in 84% yield in 74% ee. The completion of the synthesis of (*R*)-(–)-rhazinilam (**1**) involved the one-carbon homologation via S_N2 reaction using nitrile as one carbon nucleophile and the installation of the aniline moiety via by Suzuki-Miyaura cross-coupling.[72]

During this sequence a Vilsmeier-Haack formylation had to be inserted the pyrrole aldehyde **125**. The aldehyde is at the same time a protecting group for the sensitive pyrrole ring and it dictates the regioselectivity of the following electrophilic iodination to give the iodo-pyrrole **126** in quantitative yield. The final steps were the saponification of the ester followed by lactamisation delivering synthetic (*R*)-(-)-rhazinal (**10**). Conversion of (*R*)-**10** into (*R*)-(-)-rhazinilam (**1**) was achieved by heating of ((*R*)-**10**) with stoichiometric quantities of Wilkinsons "catalyst" in refluxing 1,4-dioxane. The synthesis proceeds through eighteen steps starting from pyrrole **113** and in 4.4% overall yield. Treatment of (*R*)-(-)-rhazinilam (**1**) with an excess of pyridinium chlorochromate (PCC) resulted in the conversion of this substrate into a chromatographically separable mixture of (-)-leuconolam (**6**) (28%) and (+)-*epi*-leuconolam (**8**) (46%).

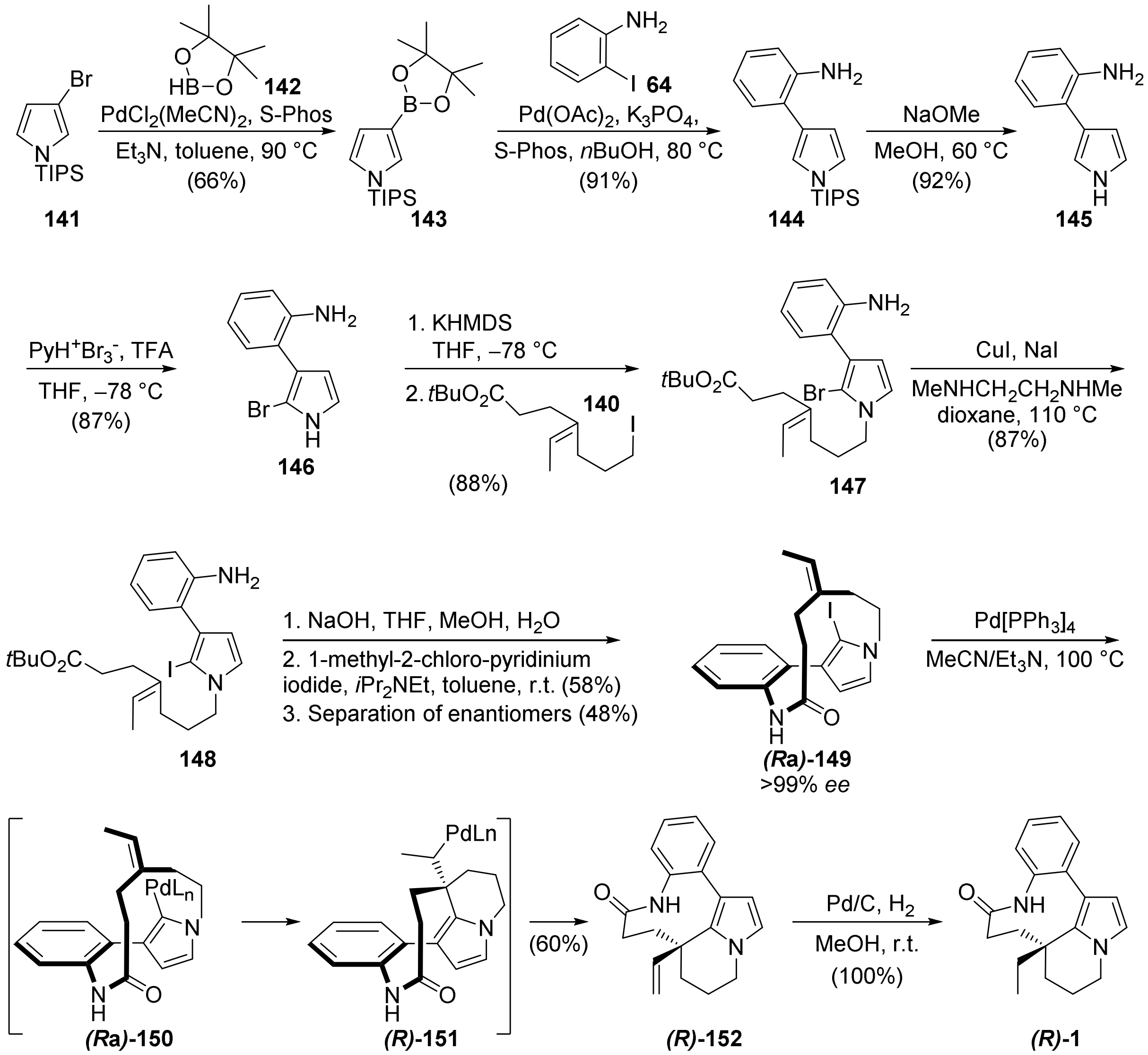
Total synthesis of (*R*)-(-)-rhazinilam by Zakarian

In 2010, Zakarian and co-workers reported a higly enantiospecific total synthesis of rhazinilam based on a Pd-catalyzed transannular cyclisation.[64] In difference to Trauner synthesis using the intramolecular Heck-type reaction to connect the A and C rings, Zakarian choose to exploit an axial chirality of a halogenated 13-membered lactam **149**, as so to create the quaternary chiral stereogenic center in target molecule and to form the B and D rings in a single bond-forming event. The synthesis of the aliphatic part proceeded through the iodoolefin **140** which was prepared from the commercially available *tert*-butyl acrylate (**134**) (Scheme 1.15). The Michael addition reaction of 2,4-pentanedione (**135**) to **134**, followed by a cascade condensation-fragmentation process[79] using aqueous formaldehyde afforded the enone **137**. Luche redaction[80] and acetylation of this intermediate, followed by Ireland-Claisen rearrangement[81] produced the acid **139**. Selective reduction and iododehydroxylation of **139**, gave the desired iodide **140** in 35% yield over seven steps. The precursor **144** containing A-C rings was synthesized via known Pd-catalysed cross-coupling reaction[82] of borylated TIPS-protected pyrrole **143** and 2-iodoaniline (**64**) (Scheme 1.16). After removal of TIPS-protecting group under basic conditions, the biaryl intermediate **145** was obtained in 92% yield. A regioselective halogenation of **145** was required preceding the macrolactam formation. *N*-alkylation of potassium anion of **146** with iodide **140** gave the intermediate **147**.

The synthesis of pivotal macrolactam **149** was achieved in three steps sequence by iodination, saponification of the ester **148** and subsequent macrocyclisation under Mukaiyama conditions.[83]



Scheme 1.15. Synthesis of intermediate **140**.

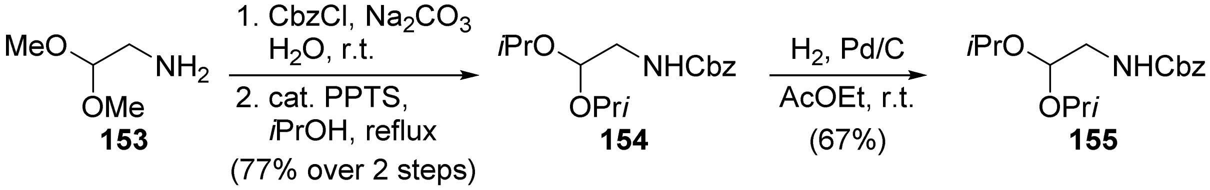


Scheme 1.16. Zakarian's total synthesis of (*R*)-(–)-rhazinilam (*R*)-**1**.

The resulting macrolactam presents axial chirality and the enantiomers were separated by preparative chiral HPLC to give enantioenriched (*R*a)-**149** and (*S*a)-**149** in high enantiomeric purity. The Pd-catalysed transannular cyclisation of key intermediate (*R*a)-**149** using $Pd[PPh_3]$ in the presence of Et_3N gave after hydrogenation (*R*)-(−)-rhazinilam (**1**) in 60% yield and 99% *ee*. The synthesis proceeds through eleven steps starting from commercially available TIPS-protected pyrrole **141** in 6.2% overall yield (through fourteen steps starting from *tert*-butyl acrylate **134** in 4.5% overall yield).

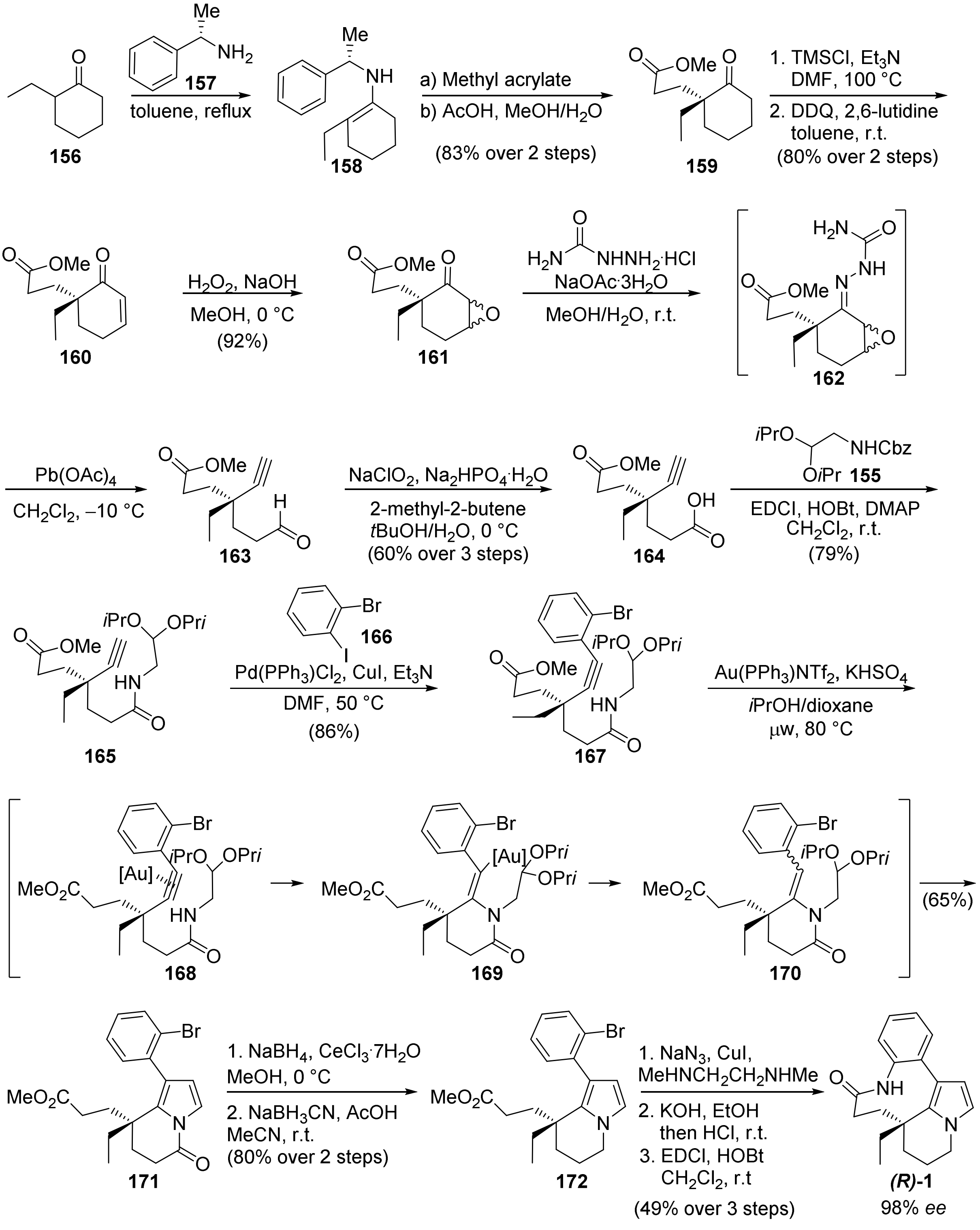
Total synthesis of (*R*)-(−)-rhazinilam by Tokuyama

In 2013, a protecting-group-free total synthesis of (*R*)-rhazinilam **1** was reported by Tokuyama and co-workers.[84] The key step of this elegant synthesis is a gold-catalysed cascade cyclisation of linear intermediate **167** resulting in the one-pot formation of C and D rings (Scheme 1.18). The use of the sterically demanding acetal substrate is crucial in this step to avoid the undesired side reactions. For this purpose, the dimethylacetal **153** was transformed into the diisopropyl acetal **155** in three steps in 52% overall yield (Scheme 1.17).



Scheme 1.17. Synthesis of intermediate **155**.

The synthesis of the fully functionalized ynamide **167** started with the construction of the quaternary stereocenter using the diastereoselective Michael addition reaction.[85] For this reason, the commercially available 2-ethylcyclohexanone (**156**) was functionalized with (*S*)-1-phenylethylamine (**157**) to provide a chiral enamine **158** which was engaged into the Michael addition reaction. Subsequent 2-step oxidation of ketoester **159** and epoxidation of the resulting cyclohexenone **160** afforded the epoxyketone **161**. The synthesis of key intermediate **167** was achieved in five steps sequence by Eschenmoser-Tanabe-type fragmentation of semicarbazone **162** under Warkentin conditions,[86] Pinnick oxidation[87] of the aldehyde **163**, condensation of the acid **164** with the diisopropyl acetal **155** and Sonogashira coupling of **165** with 2-bromoiodobenzene (**166**). The ynamide **167** contains all the carbons present in the natural product. The intramolecular nucleophilic addition of a nitrogen atom to the alkyne bond activated by [Au(PPh3)]NTf2 resulted in formation of enamide **170** which underwent the subsequent aromatisation to produce the indolizinone **171** in 65% yield. Reduction of *N*-acyl pyrrole functionality was achieved in two steps using Luche conditions followed by hydroboration in acidic media.



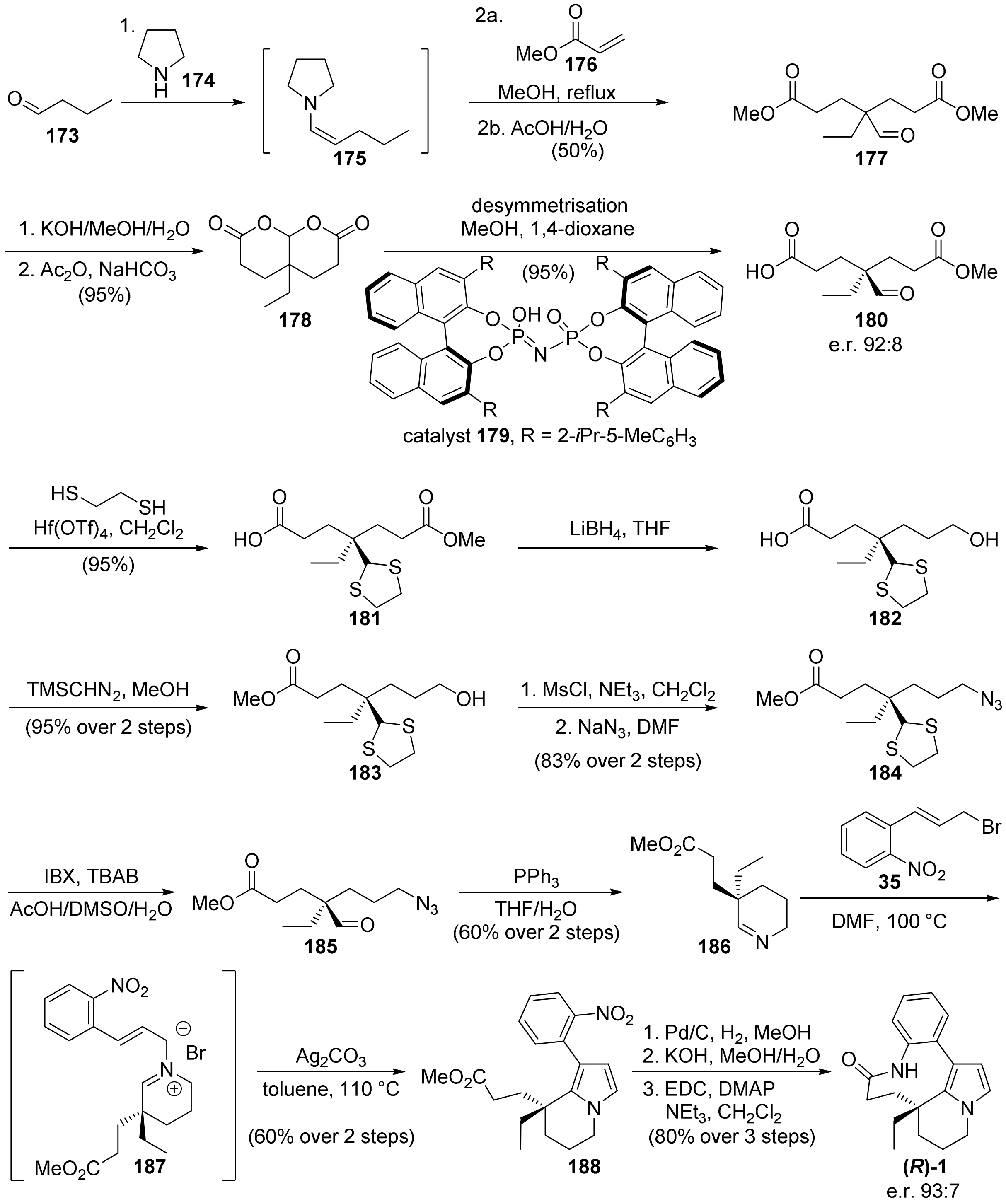
Scheme 1.18. Tokuyama's total synthesis of (*R*)-(−)-rhazinilam (*R*)-**1**.

The compound **172** was transformed into the (*R*)-(−)-rhazinilam (**1**) in a sequence of tree steps: one-pot copper-mediated amination, saponification and finally lactamisation. The two last reactions of Tokuyama and Banwell syntheses are very similar despite of the Tokuyama group could slightly increase the yield. The synthesis proceeds through sixteen steps starting from 2-ethylcyclohexanone (**156**) in a good 6.3% overall yield and 98% *ee*.

Total synthesis of (*R*)-(−)-rhazinilam by Zhu

In 2014, Zhu and co-workers reported a concise enantioselective synthesis of (*R*)-rhazinilam **1**.[88] In contrast to other reported methods for the synthesis of rhazinilam, the synthetic route started with a preparation of D ring bearing a chiral quaternary carbon (Scheme 1.19). The key step is an imidodiphosphoric acid catalysed desymmetrization of bicyclic bislactone **178**. This intermediate was prepared from the butanal (**173**) by three-step procedure. Reacting the in situ generated enamine **175** with methyl acrylate (**176**) afforded the Kuehne's aldehyde **177**.[89] Hydrolysis and subsequent reaction of diacid with acetic anhydride produced the key intermediate **178** in 48% overall yield. A dessymetrization of **178** using MeOH as nucleophile in presence of the chiral phosphoric acid **179**[90] gave the enantiomerically enriched monoacid **180** in 95% yield and 92:8 enanatiomeric ratio. Protection of aldehyde, chemoselective reduction of the ester and subsequent esterification of carboxylic acid afforded the alcohol **183**. Transformation of primary alcohol into the azide **184** followed by deprotection of dithiolan using *o*-iodoxybenzoic acid (IBX)[91] gave the azido aldehyde **185**. The azide **185** was converted into the cyclic imine **186** by Staudinger reduction and subsequent aza-Witig reaction.

The total synthesis was then completed via a formal [3+2] cycloaddition between the allyl bromide **35** and intermediate **186**, followed by reduction of **188** and macrolactamisation sequence. The synthesis proceeds through fifteen steps starting from butanal (**173**) in 9.8% overall yield.



Scheme 1.19. Zhu's total synthesis of (*R*)-(–)-rhazinilam (*R*)-**1**.

1.4 Previous total syntheses of analogues of rhazinilam

Several publications describe efforts dedicated to the total syntheses of analogues of rhazinilam. Some publications report the total syntheses of analogues obtained as “side products” of the efforts dedicated to the total synthesis of rhazinilam. Four different analogues isolated from nature have been synthesized so far: rhazinal in its racemic (two synthesis) and in its enantioenriched form (one synthesis, see Scheme 1.14), rhazinicine as racemate (one synthesis) and finally leuconolam and *epi*-leuconolam in enantioenriched form (one synthesis leading to the mixture of the two natural products, see Scheme 1.14).

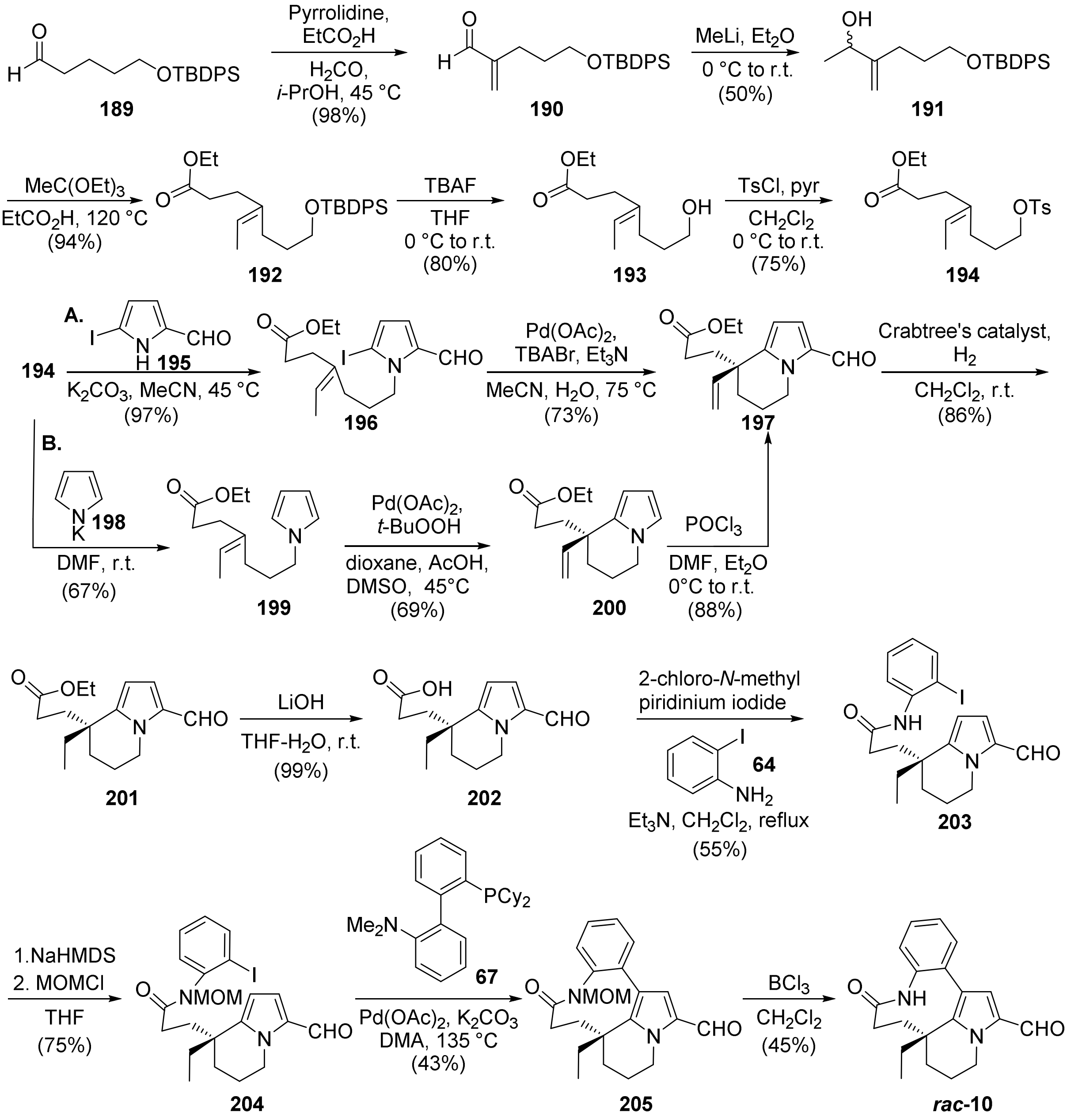
1.4.1 Total syntheses of rhazinal

Total synthesis of *rac*-rhazinal and of (*R*)-(–)-rhazinal by Banwell

Both syntheses use an intramolecular Michael addition as key step to form the C-D ring unit (Scheme 1.13 and 1.14). In 2003 Banwell and co-workers reported the first total synthesis of racemic *rac*-(±)-rhazinal (*rac*-**10**)[41] achieved in fifteen steps with 6.6% overall yield. In 2006 the Banwell group achieved the synthesis of the natural (*R*)-(–)-rhazinal ((*R*)-**10**)[74] in seventeen steps with 5.0% overall yield.

Total synthesis of *rac*-rhazinal of Trauner

Trauner and co-workers reported[92] a concise synthesis of *rac*-(±)-rhazinal (**10**) using Pd-catalysed coupling reactions to form the ring D (cyclisation of **196** or alternatively of **199**) and the ring B (cyclisation of **203**) (Scheme 1.20). The synthesis of the aliphatic part proceeded through the *E*-trisubstituted ester **194** which was constructed from the known[93] aldehyde **189.** The α-methylation followed by treatment with methyllithium afforded the allylic alcohol **191.** The Claisen rearrangement of the allylic alcohol produced the ester **192** in 94% yield. Deprotection of with tetra-*n*-butylammonium fluoride and subsequent tosylation of **193** afforded the desired intermediate **194**. Reaction of **194** with the potassium salt of pyrrole **198** gave the *N*-alkylated pyrrole **199** in 67% yield.



Scheme 1.20. Trauner's total synthesis of *rac*-rhazinal (**10**).

The oxidative cyclisation of compound **199** using $Pd(OAc)_2$ in the presence of *t*-BuOOH resulted in the formation of tetrahydroindolizine **200** in 69% yield. The C-D precursor was then protected as aldehyde **197** by subsequent Vilsmeier-Haack formylation (41% over three steps from compound **194**). The intermediate **197** was prepared in parallel by a very similar sequence, where the formyl group was introduced on the pyrrole ring right from the beginning and where a direct Heck coupling involving the iodopyrrole **195** formed the D-ring.

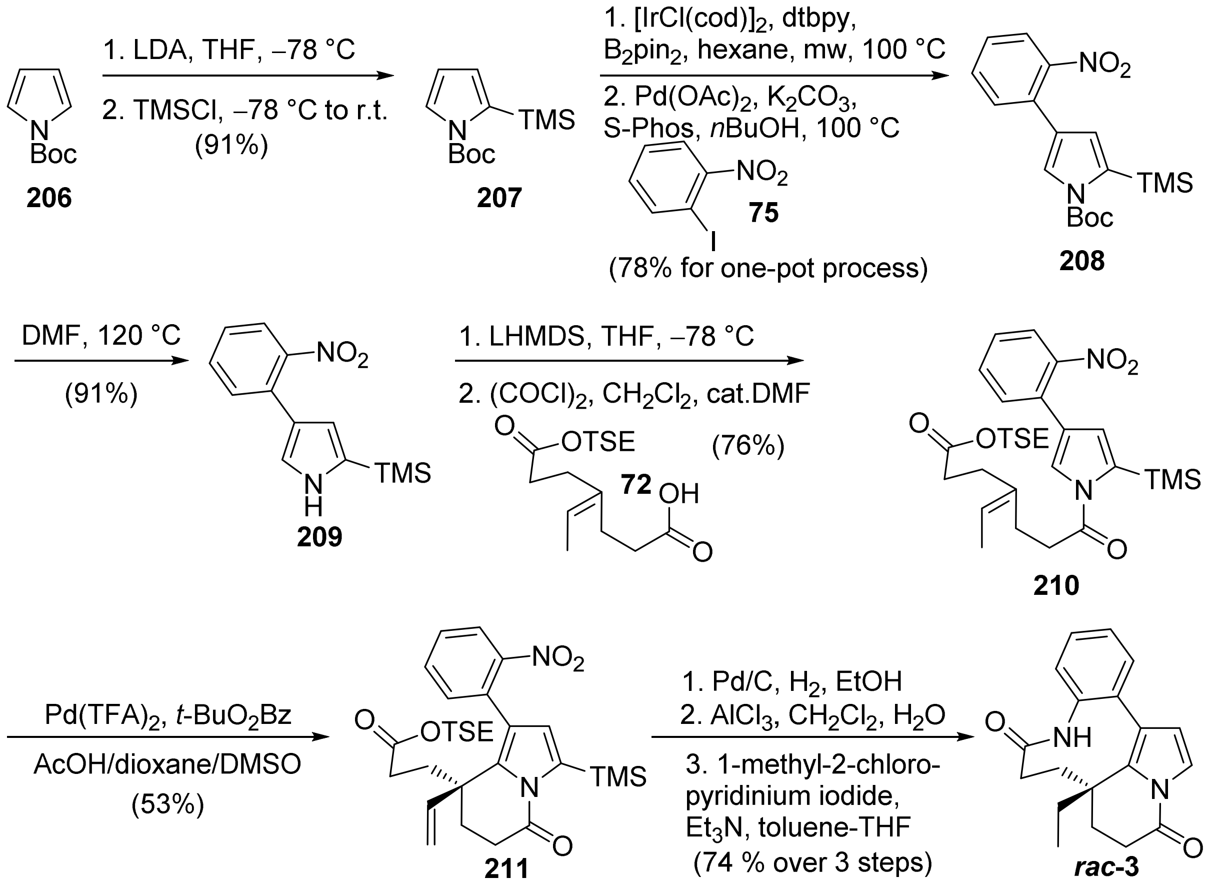
The selective reduction of the double bond using Crabtree's catalyst followed by hydrolysis of the ester yielded the corresponding acid **202** in excellent yield. Coupling of the acid **202** with

2-iodoaniline (**64**) under Mukaiyama's conditions provided the amide **203**,[55] which was protected as the methoxymethyl (MOM) key intermediate **204** in 75% yield. The B-ring was formed using 10 mol % of Buchwald's "DavePhos" ligand **67**[56] and $Pd(OAc)_2$ in the presence of potassium carbonate to produce the *N*-MOM rhazinal **205** in 43% yield. After removal of the MOM protecting group with a large excess of boron trichloride racemic *rac*-(±)-rhazinal (**10**) was obtained in 45% yield. The synthesis proceeds through thirteen steps in 1.3% overall yield (Method A) or through fourteen steps in 0.8% overall yield (Method B). We have calculated the yield starting from aldehyde **189** which is not commercial. The method used for the preparation of this aldehyde is not indicated.

1.4.2 Total syntheses of rhazinicine

Total synthesis of *rac*-rhazinicine by Gaunt

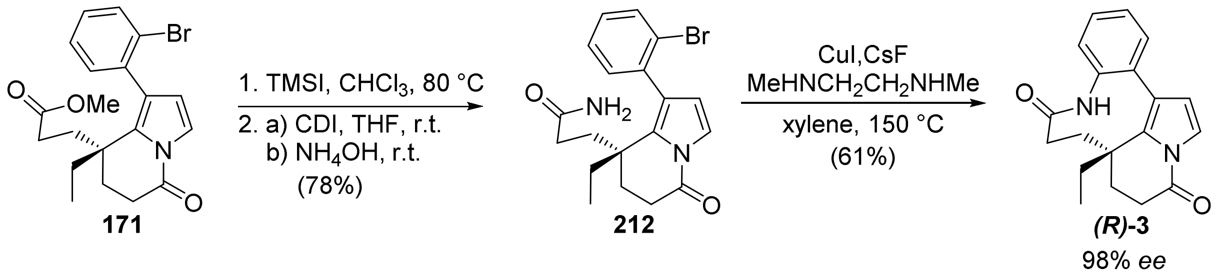
The first total synthesis of the *rac*-rhazinicine (**3**) was reported by Gaunt and co-workers in 2008.[59] The synthetic approach and pathway are similar to the synthesis of *rac*-rhazinilam described above. The A, C and D rings are constructed via metal-catalysed C-H bond functionalization. The synthesis started from a different pyrrole **206** (Scheme 1.21). For the preparation of the biaryl intermediate **209** containing the A-C rings Boc and TMS protecting groups had to be introduced to obtain the doubly protected precursor **207**. The one-pot Ir^{I}-catalysed borylation/Suzuki coupling[60-62] formed the 3-arylated pyrrole **208** in 78% yield. Removal of Boc-protecting group under heating afforded the pyrrole **209** containing the A-C rings of rhazinicine. Reacting the lithium anion of **209** with acid chloride of intermediate **72** the *N*-acylated pyrrole **210** was obtained in 76% yield (Scheme 1.14). The intermediate **210** contains all the carbons present in the target molecule. Treating **210** with $Pd(TFA)_2$ catalyst and *t*-butylperoxybenzoate resulted in the formation of cyclisation product **211** in 53% yield. The synthesis was achieved in a three steps sequence: simultaneous reduction of the nitro and alkene groups, $AlCl_3$-mediated removal of the silyl protecting groups and lactamisation under Mukaiyama conditions. The *rac*-rhazinicine **(3)** was obtained in eight steps starting from pyrrole **206** in 1.9% overall yield (in nine steps starting from diester **18** in 1.3% overall yield).



Scheme 1.21. Total synthesis of *rac*-rhazinicine (**3**) by Gaunt.

Total synthesis of (*R*)-(−)-rhazinicine by Tokuyama

The first total synthesis of the (*R*)-(−)-rhazinicine (**3**) was reported by and co-workers in 2013.[84] This protecting group free synthesis involved as a key step a gold-catalysed cascade cyclisation and follows the path depicted in Scheme 1.18 for the synthesis of (*R*)-(−)-rhazinilam (**1**) until the final stages. The divergence occurs after the preparation of indolizinone **171** (Scheme 1.22). The *N*-acyl pyrrole functionality was preserved. In contrast to (*R*)-(−)-rhazinilam (**1**), the synthesis of (*R*)-(−)-rhazinicine (**3**) was achieved in three steps sequence by the smooth conversion of methyl ester **171** into amide **212** and subsequent macrolactamisation carried out via a copper-mediated intramolecular amidation. The synthesis proceeds through fourteen steps starting from 2-ethylcyclohexanone (**156**) in good 7.7% overall yield and 98% *ee*.



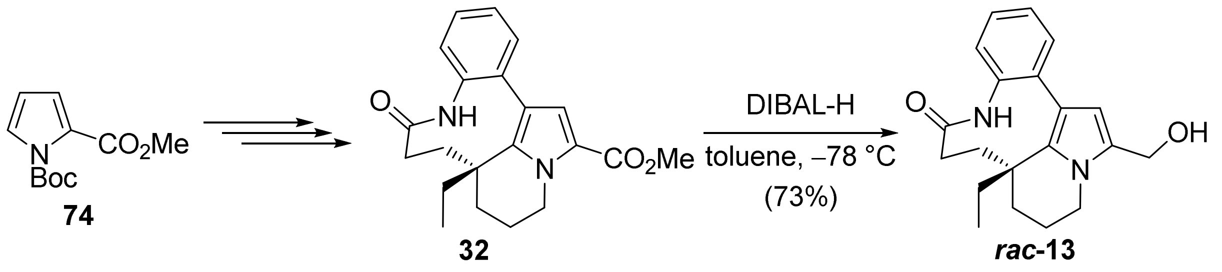
Scheme 1.22. Total synthesis of (*R*)-(−)-rhazinicine (**3**) by Tokuyama.

1.4.3 Total synthesis of leuconolam and epi-leuconolam by Banwell

Banwell and co-workers reported the first total syntheses of (−)-leuconolam (**6**) achieved in nineteen steps with 1.2% overall yield, and (+)-*epi*-leuconolam (**8**)[74] achieved in nineteen steps with 2.0% overall yield. Both syntheses involved as a key step an intramolecular Michael addition reaction. They were described in Scheme 1.14.

1.4.4 Total synthesis of rac-kopsiyunnanine C3 by Gaunt

The first total synthesis of the *rac*-kopsiyunnanine (**13**) was reported by Gaunt and co-workers in 2012.[58] The synthetic route follows the steps outlined previously for the synthesis of *rac*-rhazinilam in Scheme 1.8. The presence of ester group in intermediate **32** allowed applying the divergent endgame strategy and obtaining the *rac*-kopsiyunnanine C3 instead of *rac*-razhinilam by DIBAL-H reduction (Scheme 1.23). The synthesis proceeds through eight steps starting from pyrrole **74** in considerable 16.1% overall yield (through twelve steps starting from diester **18** in 8.7% overall yield).



Scheme 1.23. Total synthesis of *rac*-kopsiyunnanine (**13**) C3 by Gaunt.

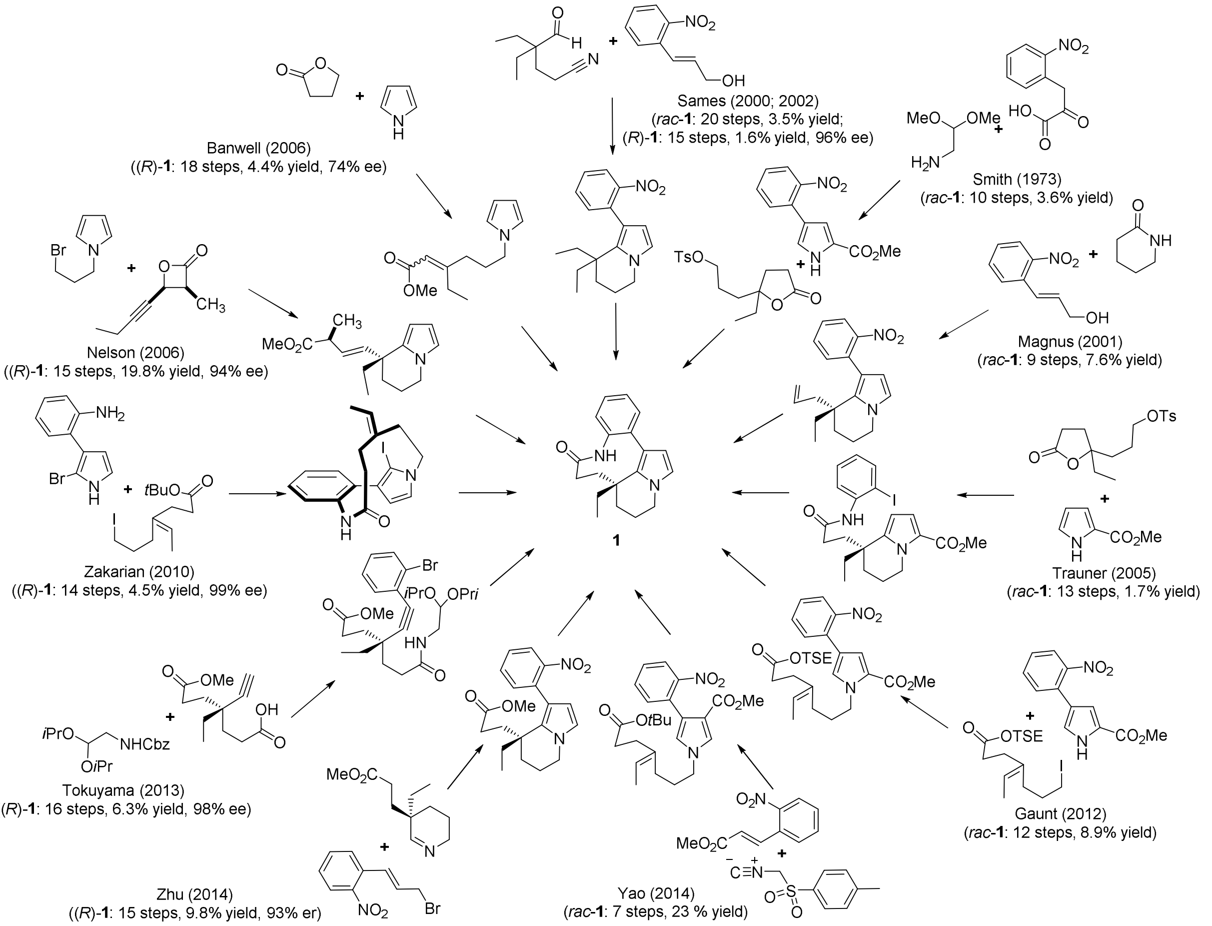
1.5 Comparison of the published rhazinilam syntheses

General remarks

The synthesis of rhazinilam has been studied for now almost 40 years. Twelve different syntheses have been reported so far: six of *rac*-rhazinilam and six of (*R*)-rhazinilam. Five analogues of rhazinilam have been synthesized by four different groups using four different approaches: *rac*-rhazinal, (*R*)-rhazinal, *rac*-rhazinicine, (*R*)-rhazinicine, (*R*)-leuconolam, (*R*)-*epi*-leuconolam and *rac*-kopsiyunnanine C3. The methods to construct the rhazinilam skeleton have changed over the years; however the retrosynthetic cuts for all these synthesis have stayed rather similar. The major difference between the different syntheses is the sequence of the synthetic steps forming the tetracyclic structure and the methods used to create the different rings of rhazinilam. Most of the recent studies reported the synthesis of the enantiomerically enriched natural product (*ee* between 74% and 99%). The research leading to the very first synthesis had clearly been started before the structure of (*R*)-rhazinilam had been ascertained by the structure determination of the crystal by X-ray diffraction. This initial synthesis project follows therefore the logic of structure determination by total synthesis. For almost 30 years no new academic synthesis was reported. The recent synthesis reported since 2000 have been designed around one or several key steps. The goal of these syntheses is to showcase the efficiency of these key steps applying them to a “real” synthetic goal. The use of transition metals for the forming of C-C and more recently of C-N bonds is illustrated in several of the recent total synthesis. Another important feature illustrating the latest development in organic synthesis is the application of organocatalysis for the asymmetric synthesis of a key intermediate.

Comparison of the number of synthetic steps and the overall yield

The development of synthetic methodologies since 1973 has been spectacular and it seems almost unfair to compare the first synthesis published in 1973 with the most recent synthesis published in 2014. If one wants to compare the overall yields and the number of synthetic steps from commercially available starting material for all ten syntheses we had in some cases to go back to the literature reports cited by the authors to identify the commercial starting materials. In these cases we assumed that the authors have used the reported procedure and that the authors had obtained the yields of the cited procedures.



Scheme 1.24. Comparison of the twelve total syntheses of rhazinilam reported during the last 40 years. Six syntheses yielded *rac*-(±)-rhazinilam and six syntheses gave (*R*)-(–)-rhazinilam.

The number of steps from commercial starting material varies from 9 to 20 steps (Scheme 1.24). The lowest overall yield is 1.6% and the best 23%. The average yield per step is more than 70% for all the synthesis reported. The highest yielding synthesis reports an impressive average yield of 90% over 15 steps. The short syntheses tend to be more efficient, but it is interesting to emphasize that six of the ten syntheses have an overall yield between 1.6 and 4.5%, despite the fact that the shortest of these syntheses needs only 10 steps whereas the longest needs 20 steps, twice as many compared with the shortest synthesis.

Looking at these syntheses from the standpoint of overall yield the first synthesis is surprisingly efficient. In comparing the five syntheses of *rac*-rhazinilam the shortest synthesis with only 9 steps has been reported by Magnus. In the Magnus synthesis no protecting group on the pyrrole ring was introduced, which shortens the synthetic pathway by at least two steps. The six enantioselective syntheses are all considerably longer, 14 to 18 steps. In two cases (Sames' and Tokuyama's syntheses) a chiral auxiliary had to be introduced and to be cleaved. The interesting strategy exploiting the axial chirality of the macrolactam ring had been applied in Zakarian's synthesis to create the quaternary chiral center. Perhaps, despite the absence of protecting group on the pyrrole ring, the number of steps and yield are comparable to other syntheses. In the enantioselective syntheses by Nelson and by Banwell an enantioselective catalytic process is applied. The overall length of these two syntheses is 15 respectively 18 steps. Based on the overall yield the synthesis reported by the Nelson group stands out with an overall yield, which is two time higher than the Gaunt synthesis and at least a factor of five better than most of the other syntheses.

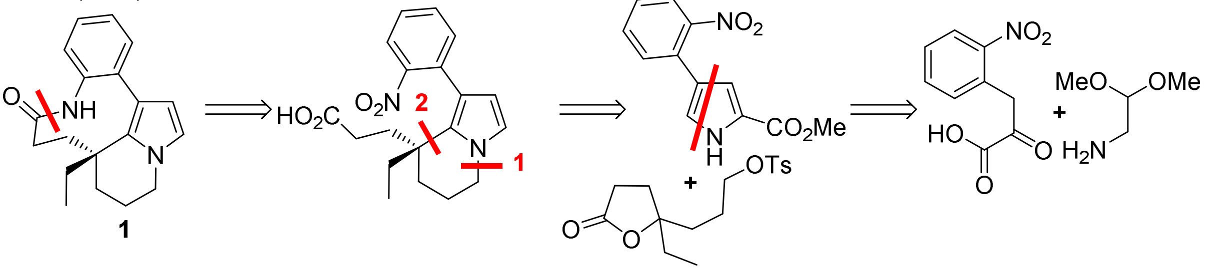
Comparison of the retrosynthetic analysis used

The summary of the retrosynthetic analysis used in the different total syntheses leads to some interesting conclusions (Scheme 1.25). In most of the syntheses the B-ring is formed last. Due to this common retrosynthetic analysis the end game of all syntheses is quite similar. In ten of the twelve syntheses the lactam formation is the last step finishing the construction of the skeleton of rhazinilam. In Trauner's and Zakarian's syntheses the B-ring is closed via a Heck type C-C coupling. One has however to mention that the Trauner synthesis is an inversion of the sequence used by Nelson and Banwell. In Trauner's synthesis the amide bond of the B-ring is formed first and the ring closure is achieved via the Heck type coupling second. In the syntheses of Nelson and Banwell the sequence is inverted. The particularity of the Zakarian synthesis is the simultaneous formation of B and D rings.

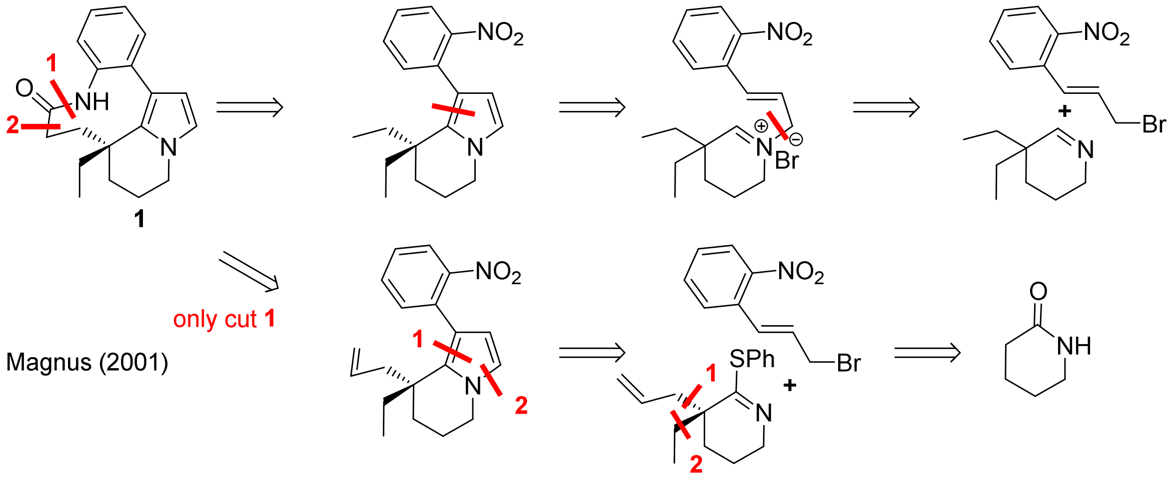
The other six syntheses propose the D-ring formation just before closing the lactam ring (ring B). In the two syntheses by Sames and the synthesis reported by Magnus the D-ring is part of the starting material and stays intact during the whole synthetic sequence. In Tokuyama synthesis the D ring is constructed together with the pyrrole ring in the one-pot reaction. In Zhu synthesis the D ring is prepared first bearing a chiral quaternary center.

In the recent syntheses the aromatic A ring is introduced by Suzuki coupling reaction (Banwell, Nelson, Trauner, Gaunt, Zakarian syntheses) or Sonogashira coupling reaction (Tokuyama synthesis).

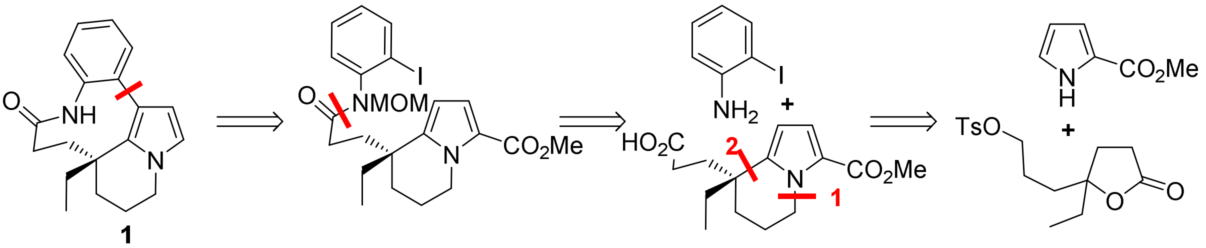
Smith (1973)



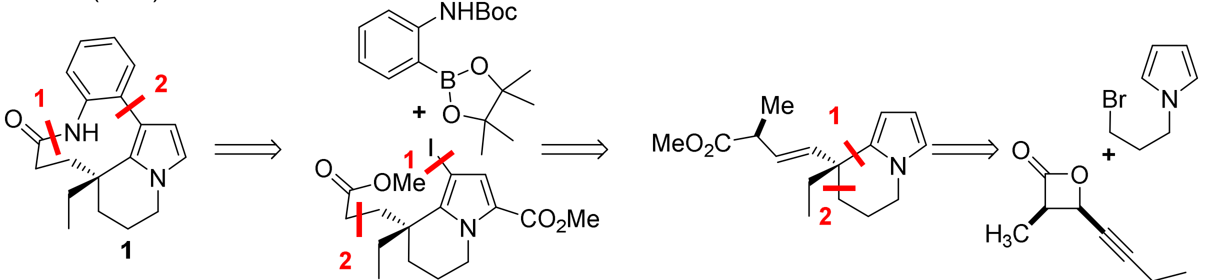
Sames (2000, 2002)



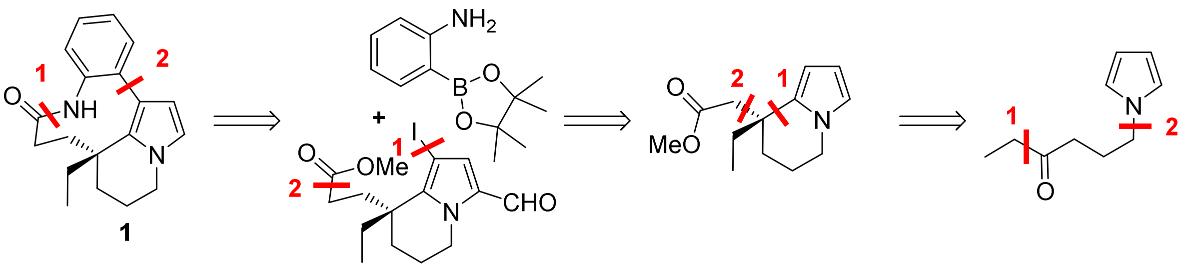
Trauner (2005)

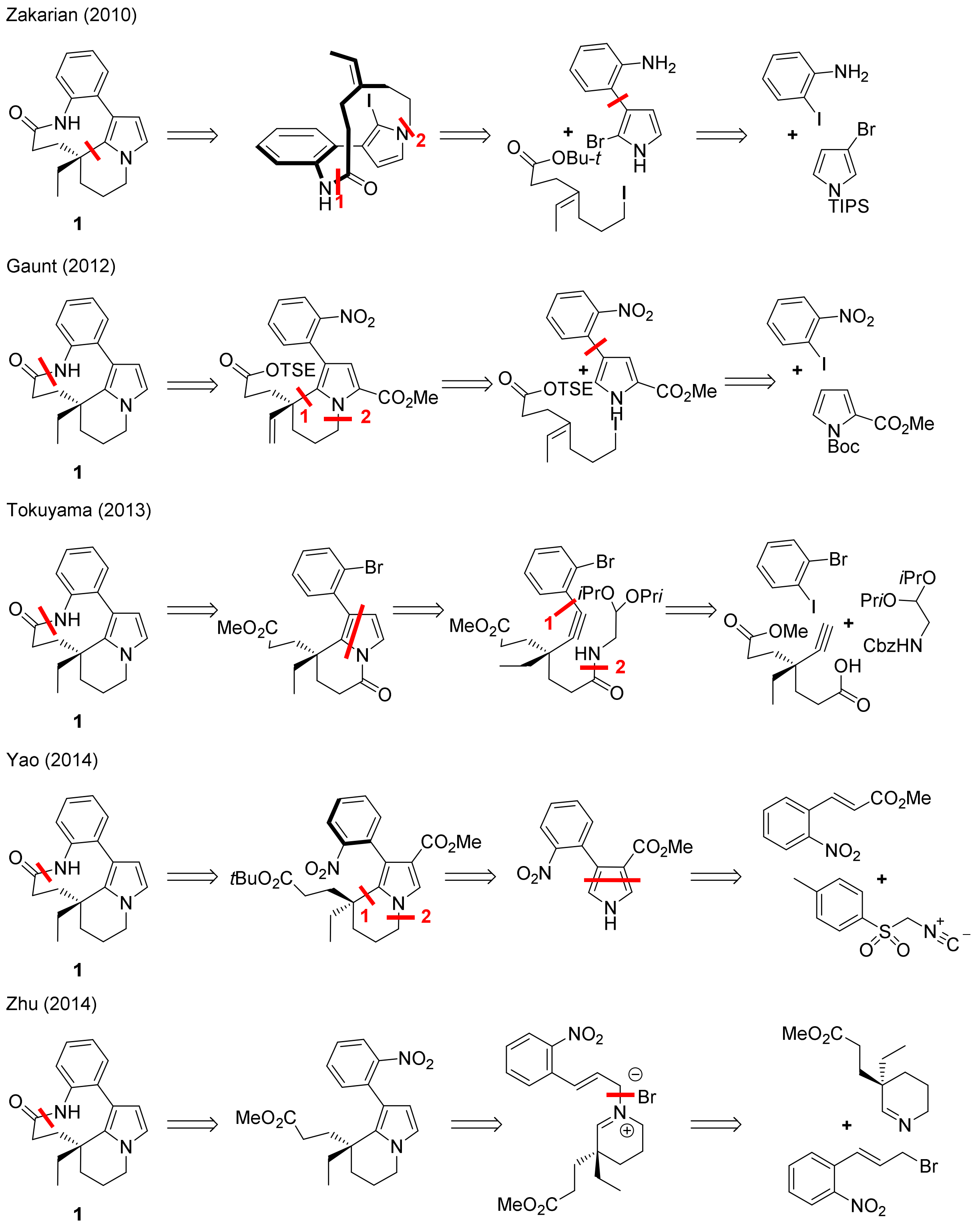


Nelson (2006)



Banwell (2006)





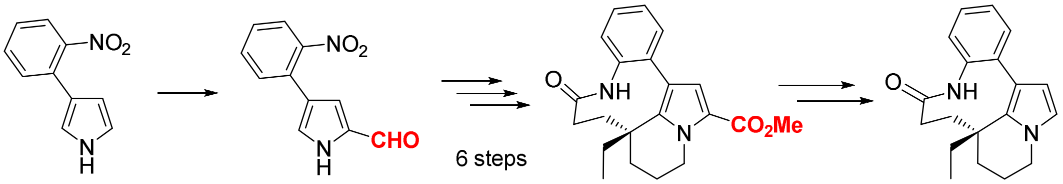
Scheme 1.25. Summary of the retrosynthetic analysis of the twelve total syntheses of rhazinilam reported during the last 40 years.

Five of the twelve syntheses use a commercial precursor containing the intact pyrrole ring (Banwell, Nelson, Trauner, Gaunt, Zakarian syntheses). The groups of Smith, Sames, Magnus and more recently of Tokuyama, Zhu and Yao have applied synthetic schemes, where the pyrrole ring is constructed during the preparation of rhazinilam. Smith uses a variant of a Knorr-type pyrrole synthesis whereas Sames, Magnus and Zhu use a Grigg-type 1,5-electrocyclization. In Tokuyama synthesis the pyrrole ring construction proceeded through an intramolecular gold catalysed cyclisation process whereas Yao group adopted a Barton-Zard-type pyrrole synthesis.

Another observation concerns the use of "protecting" or stabilizing group on the pyrrole ring (Scheme 1.26). With five exceptions, all syntheses have to introduce or to carry on an electron attracting substituent on the pyrrole ring. Most of the syntheses use an ester group in the α-position. The Banwell synthesis employs an aldehyde function as protecting group of the pyrrole. Very often two steps are needed to introduce the protecting group and one to two steps are again needed for the deprotection. The protecting group is in most of the syntheses carried along a good part of the synthetic sequence. In the Sames synthesis the ester protecting group is present during 14 steps. These substituents have to be removed towards the end of the synthesis. Even if it is not formally stated in most of the publications, their function is clearly to make the intermediates stable enough, that they can be manipulated. The exceptions are the more recent Magnus, Zakarian, Tokuyama, Zhu and Yao syntheses. Despite the fact that the Magnus' group uses an intermediate, which is identical with the one reported in the first synthesis of Sames, the Magnus group was able to avoid the use of electron attracting group on the pyrrole ring. Such a comment can be made about Zakarian synthesis, the first steps and starting materials of which are similar to the synthesis of Gaunt. Curiously, despite the absence of protecting group, the Zakarian synthesis is longer than synthesis of Gaunt, 11 steps and 8 steps respectively starting from the corresponding pyrroles. Regarding the Tokuyama synthesis, one can note that the pyrrole ring is formed at latest stage and the protecting group is not needed for the end-game sequence.

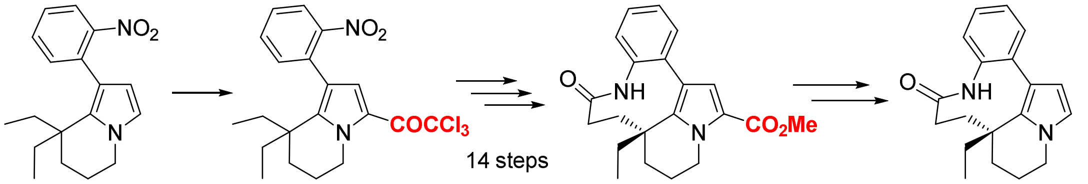
In summary the synthesis of rhazinilam is still a challenging synthetic problem. The syntheses reported are attractive and incorporate different interesting key steps. Despite the spectacular developments of organic synthesis even the very first reported synthesis is still a valid approach to this fascinating natural product.

Smith (1973)



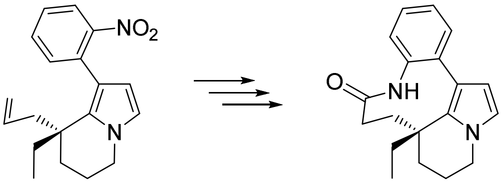
25 **26** **32** *rac*-**1**

Sames (2000, 2002)



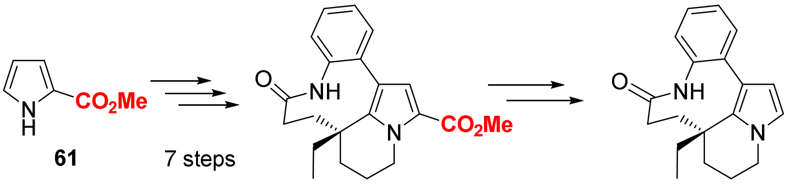
40 **41** **32** *rac*-**1** and (*R*)-**1**

Magnus (2001)



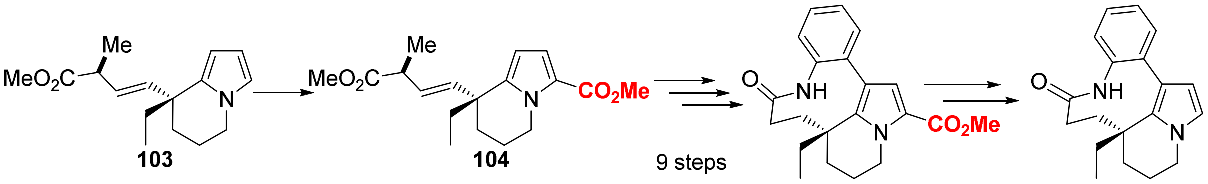
56 *rac*-**1**

Trauner (2005)



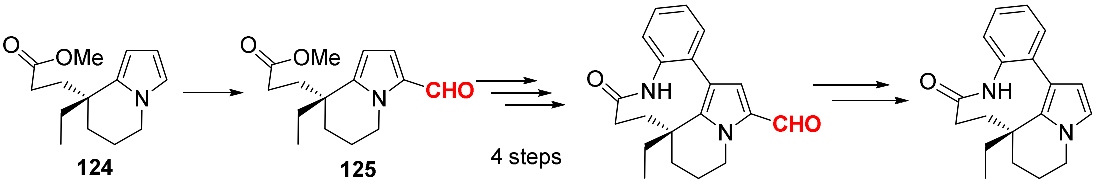
61 **32** *rac*-**1**

Nelson (2006)

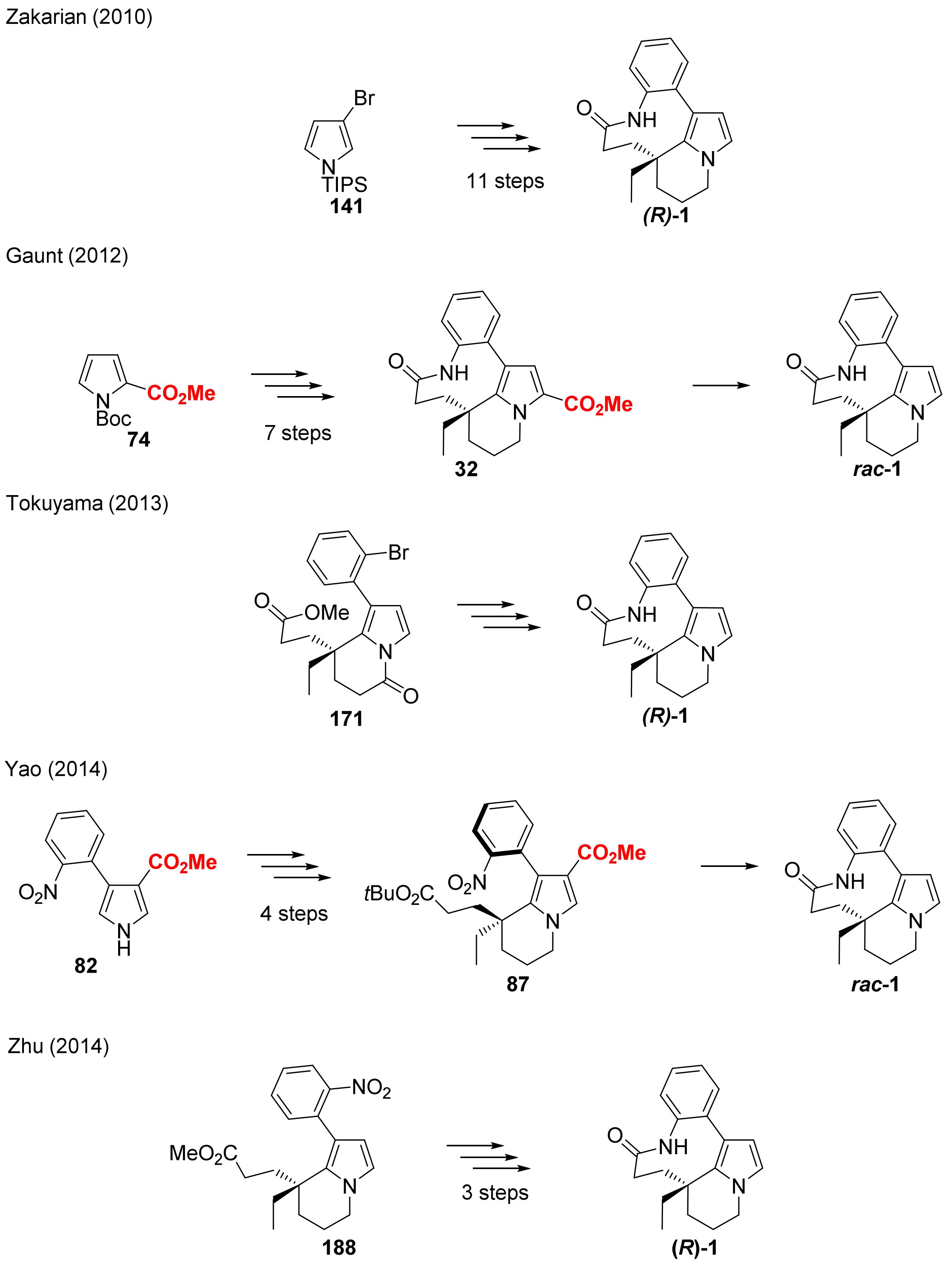


103 **104** **32** (*R*)-**1**

Banwell (2006)



124 **125** (*R*)-**10** (*R*)-**1**



Scheme 1.26. Protecting the α-position of the pyrrole C-ring introducing an electron attracting protecting group during the syntheses of rhazinilam.

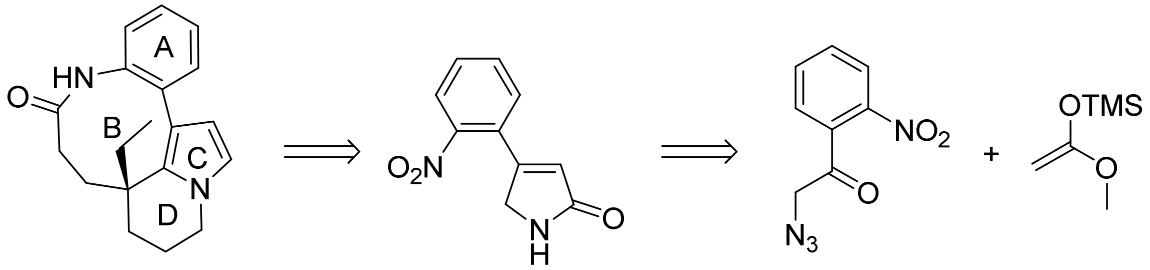
Chapter two

PREPARATION OF ADVANCED INTERMEDIATES FOR PYRROLINONE AND PYRROLE BASED RHAZINILAM ANALOGUES

2.1 Introduction

As previously discussed, (*R*)-(–)-rhazinilam **1** and some of its congeners have unique antimitotic properties and were identified as promising targets for developing of a new generation of anticancer agents. The scientific challenge of this relatively simple natural product is to understand and to explain in structural terms its activity. Transferring the knowledge from *in vitro* studies to *in vivo* experiments has proved to be quasi impossible.[94] The combination of the findings on the chemical reactivity, with the well-known sensitivity of rhazinilam towards oxidative metabolic transformations[95] was used as a guideline for proposing and designing novel rhazinilam analogues. The retrosynthetic approach chosen is conceived so as to avoid the notorious sensitivity of non-stabilized pyrroles towards oxidation and/or acid conditions avoiding protecting groups as much as possible.

Our group has developed a convergent synthesis of the phenyl-pyrrolic core of rhazinilam involving a tandem Mukaiyama aldol-type condensation − Staudinger cyclisation sequence[96-101] (Scheme 2.1).



(*R*)-(–)-Rhazinilam **1** **235** **214** **215**

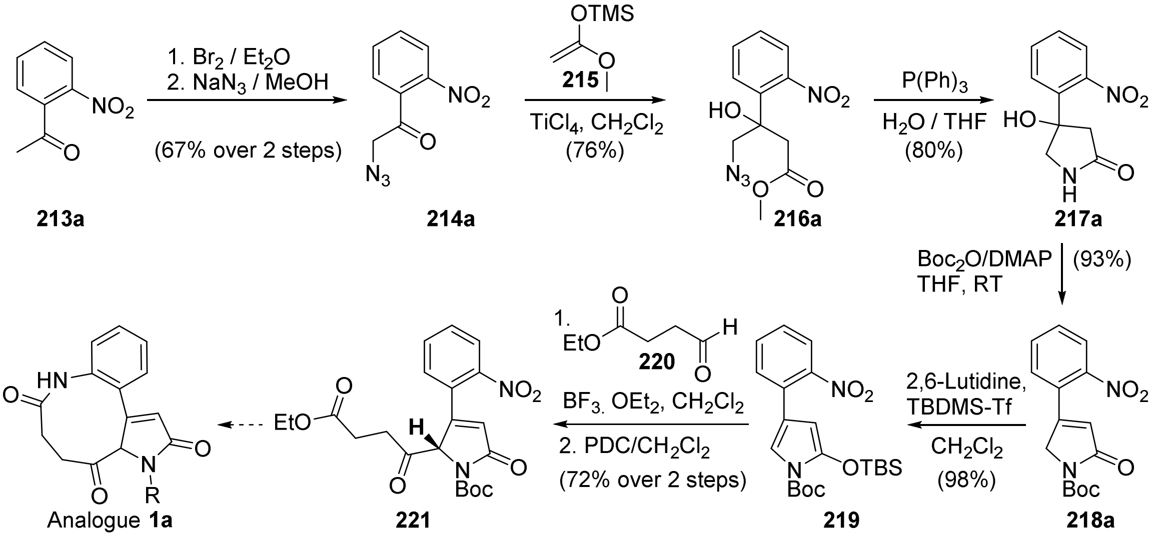
Scheme 2.1. Retrosynthetic analysis involving Mukaiyama – Staudinger tandem sequence.

The chosen convergent strategy allows the short and efficient synthesis of many derivatives. The new approach complements the classical Knorr pyrrole synthesis.[102] The key intermediate is the 3-pyrrolin-2-one **235** serving two goals: facilitating the introduction of the substituents needed for the construction of rings B and D and reducing the sensitivity the pyrrole ring precursor (ring C).

Having this key intermediate **218** in hand, the important challenges are to find good and efficient methodologies to introduce the B-ring and the D-ring.

2.2. Previous studies

The first advanced studies were pursuing the goal to introduce the side chain needed for the creation of the B-ring (Schema 2.2). The realisation of this goal would be the preparation of analogue **1a** of the general form depicted in the Scheme 2. Earlier structure activity studies had clearly indicated the importance of the B-ring,[29,95] whereas the D-ring seemed to influence the in vitro activity only slightly.[38,39,48]



Scheme 2.2. Synthetic pathway to the formation of lactam B-ring.[100,103]

The synthetic pathway exploited the protocols established for the preparation of 3-pyrrolin-2-one **218a** involving the Mukaiyama crossed aldol condensation – Staudinger cyclisation sequence as a key reaction.

The synthesis started with the commercially available 2-nitroacetophenone (**213a**) which is subsequently substituted with bromine and sodium azide to give the 2-azido-1-(2-nitrophenyl)-ethanone (**214a**). The key step has proved to be sensitive to temperature and quantity of Lewis acid. Indeed, at temperatures above –10 °C the starting materials and products were unstable. As a result, the reduction of the yield was observed. On the other hand, the use of large amount of the strong Lewis acid such as $TiCl_4$ which is needed to be neutralized during the work-up diminished the yield dramatically. Gratifyingly, treating the compound **214a** with 3 equiv. of ketene acetal **215** and 0.5 equiv. of $TiCl_4$ under the temperature keeping between –30 °C and –15 °C, the desired aldol product **216a** was obtained in very good 76% yield. The Staudinger cyclisation using 1.5 equiv. of triphenylphosphine proceeded smoothly to afford the pyrrolidinone **217a** in 80% yield. The subsequent elimination of the tertiary alcohol was achieved under treatment of pyrrolidinone **7** with 2.1 equiv. of Boc_2O in the presence of catalytic amount of DMAP and resulted in the formation of Boc-protected 3-pyrrolin-2-one **218a** in excellent yield. The side-chain was introduced into the compound **219** at C-5 position of 3-pyrrolin-2-one ring in a sequence of tree steps: silylation of **218a**, second Mukaiyma type aldol condensation of silylpyrrole **219** with aldehyde **220** and finally Swern oxidation of the resulting aldol product. The resulting compound **221** contains all the carbons required to form the nine-membered lactam ring B.

However, this intermediate has proved to be very sensitive to pH changes due to the acidic proton at C-5 of 3-pyrrolin-2-one ring. This proton can easily be deprotonated due to the keto-enol equilibrium between the pyrrolinone and the aromatic hydroxyl-pyrrole tautomeric form (Figure 2.1).

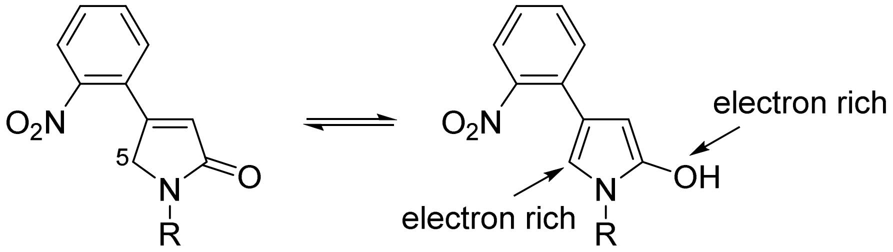


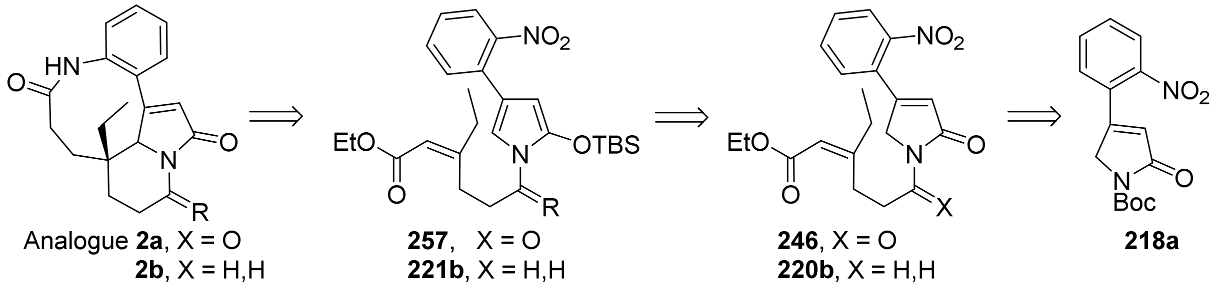
Figure 2.1. Keto-enol equilibrium in 3-pyrrolin-2-ones.

The ease of tautomerisation makes this position particularly sensitive to unwanted side reactions. As a result, all efforts to saponify or to reduce these intermediates and thereby to increase their stability have been non-conclusive or have failed.

Thus, alternative strategies avoiding or reducing the problem of stability of substituted 3-pyrrolin-2-one were necessary to develop. Inverting the proposed sequence by constructing the D ring the first might bring a solution to the observed problem. This matter is addressed in the following sections.

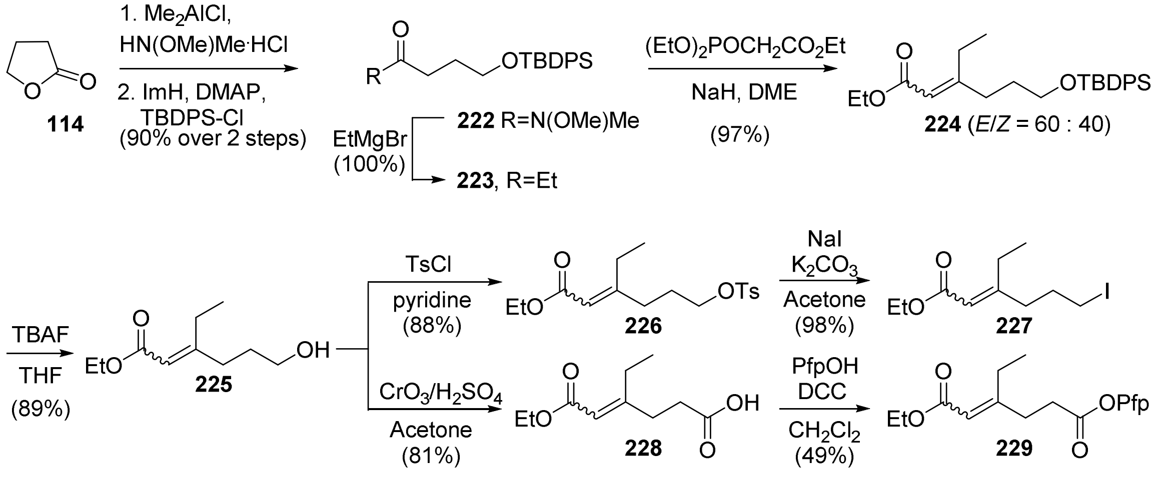
2.3. *N*-Alkylation vs *N*-Acylation

A strategy introducing a side chain containing all the carbon atoms of ring D and the appropriate functionality for the ring closure and the introduction of ring B on the 3-pyrrolin-2-one ring was chosen. The attractivity of this strategy was the fact that the intramolecular Michael addition reaction has been successfully applied[74] in former syntheses of rhazinilam. The activation of the pyrrole through the *O*-silyl group in the 2-position should facilitate the ring closing process (Scheme 2.3).



Scheme 2.3. Synthetic pathway to the formation of D-ring via intramolecular Michael addition reaction.

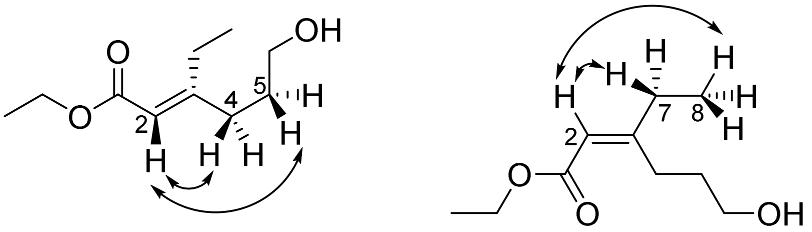
To realize this strategy the corresponding iodo acrylate **227** or the pentafluorophenylester **229** had to be prepared.



Scheme 2.4. Synthesis of acrylate **227** and **229**.

The synthesis of these acrylates started with commercially available γ-butyrolactone **114** which were converted into the Weinreb amide **222** according to the procedure described by Fukuda et al.[104,105] in 90% yield over the two steps (Scheme 2.4). Reaction of amide **222** with ethylmagnesium bromide afforded the alkynone **223**[106] in nearly quantitative yield. Compound **223** underwent a Wadswoth-Horner-Emmons (WHE)[74,107] olefination to give the unsaturated ester **224** as a 60:40 mixture of *E*/*Z*-isomers in excellent yield. After desilylation of **224** with TBAF, treatment of the resulting alcohol **225** with tosyl chloride produced the tosyl acrylate **226**[92] in 78% yield over the two steps. Finally **226** was converted into the desired iodo acrylate **227**[108] in excellent 67% overall yield over seven steps starting from the commercial lactone **114**.

The structure of **225** was determined by spectral analyses, and the stereochemistry was confirmed by NOE experiment (Figure 2.2).



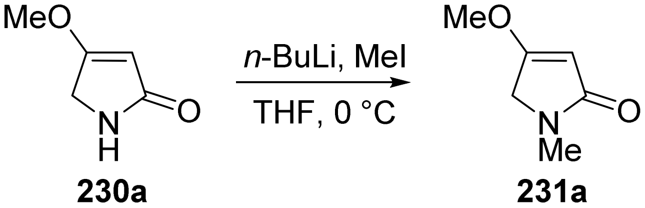
E-**225** *Z*-**225**

Figure 2.2. NOE experiments of (*E*)-**225** and (*Z*)-**225**.

In parallel, the alcohol **225** was oxidized with Jones' reagent[109,110] (1.9 M, acetone/H_2O, 0 °C) to provide the acid **228** in 81% yield. Activation of acid **228** using pentafluorophenol and *N*,*N'*-dicyclohexylcarbodiimide provided the pentafluorophenylester **229**[111] in moderate yield. However, the activated acrylate **229** could be obtained from the commercially available γ-butyrolactone **114** in seven-steps and in 31% overall yield.

2.3.1. *N*-alkylation of 4-(2-nitrophenyl)-1*H*-pyrrol-2(5*H*)-one (235)

In literature only few examples of *N*-alkylation of tetramates have been reported.[112,113]
Thus, Jones and Bates[112] accomplished the alkylation of NH-3-pyrrolin-2-one by two procedures. *N*-methylated 4-*O*-tetramate **231a** was obtained from 3-pyrrolin-2-one **230a** using a strong base such as *n*-BuLi under low temperature (Scheme 2.5).



Scheme 2.5. Reported *N*-alkylation of *O*-methyl tetramate **230a** using *n*-BuLi.[112]

However, the most effective, reported N-alkylation procedure used phase-transfer conditions (PTC) for promoting N-1 deprotonation and alkyl iodides or benzyl bromides as electrophiles (Table 2.1, entry 2,5,7). Under these conditions double alkylation products **25** were often co-isolated in minor amounts.

A more recent systematic study of the reaction of 4-*O*-methyl tetramate was reported by Jones and Patience.[113] The amount of N-1, C-5 or multiple alkylations could be influenced by the stoichiometry of the reagents (Table 1, entry 3,6,8-10). Di- and trialkyl derivatives were obtained using 10 mol equivalents of base and alkyl halide. In many cases increasing large excess of these reagents and/or longer reaction times led to extensive decomposition of 3-pyrrolin-2-one. In some cases even *O*-alkylated by-products were isolated. However, the normal sequence of deprotonation of tetramates was brought to light (Figure 2.3).

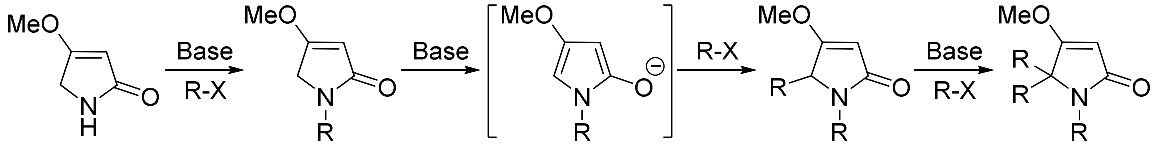
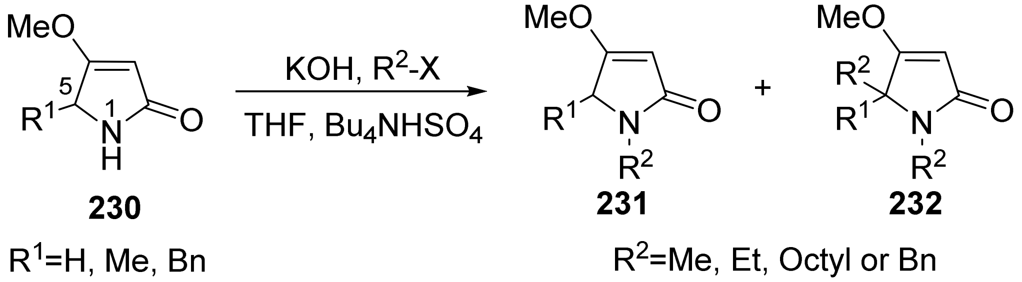


Figure 2.3. Sequence of deprotonation of 4-*O*-tetramate.

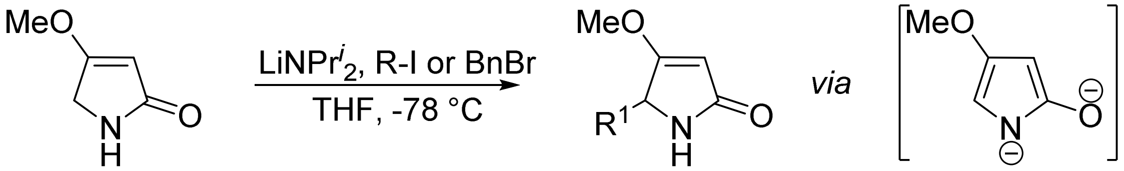
Table 2.1. Reported examples of *N*-alkylation of 4-*O*-methyl tetramates.[112,113]



Entry	Compound	Alkyl halide	Conditions	Product (yield)
1[112]	**230a** (R^1=H)	MeI	*n*-BuLi, 0°C	**231a**
2[112]	**230a** (R^1=H)	MeI	KOH, Bu_4NHSO_4, THF, 25 °C	**231a** (55%) + **232a**
3[113]	**230a** (R^1=H)	EtI (3 equiv.)	KOH (1.4 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**231b** (48%)
4[113]	**230a** (R^1=H)	EtI (10 equiv.)	KOH (10 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**232b** (69%)
5[112]	**230a** (R^1=H)	Octyl-I	KOH, Bu_4NHSO_4, THF, reflux	**231c** (43%) + **232c**
6[113]	**230a** (R^1=H)	BnBr (3 equiv.)	KOH (1.4 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**231d** (55%)
7[112]	**230a** (R^1=H)	BnBr	KOH, Bu_4NHSO_4, THF, 25 °C	**231d** (60%) + **232d**
8[113, [a]]	**230b** (R^1=Me)	MeI (10 equiv.)	KOH (10 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**232a + 232e**
9[113]	**230b** (R^1=Bn)	MeI (3 equiv.)	KOH (1.4 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**231e** (88%)
10[113]	**230b** (R^1=Bn)	BnBr (10 equiv.)	KOH (10 equiv.), Bu_4NHSO_4, THF, 25 °C, 20 h	**232f** (67%)

[a] Some *O*-alkylated materials were obtained as by-product

As an alternative the authors investigated the alkylation at C-5 of the *N*-unsubstituted tetramates using at least two equivalents of a strong base under low temperature conditions (Scheme 2.6). The resulting dianion of 4-*O*-methyl tetramate **233** underwent preferential *C*-alkylation in moderate to good yields using benzyl bromide or alkyl iodides as electrophiles.



230a

234a, R=Me
234b, R=Et
234c, R=Bn

233

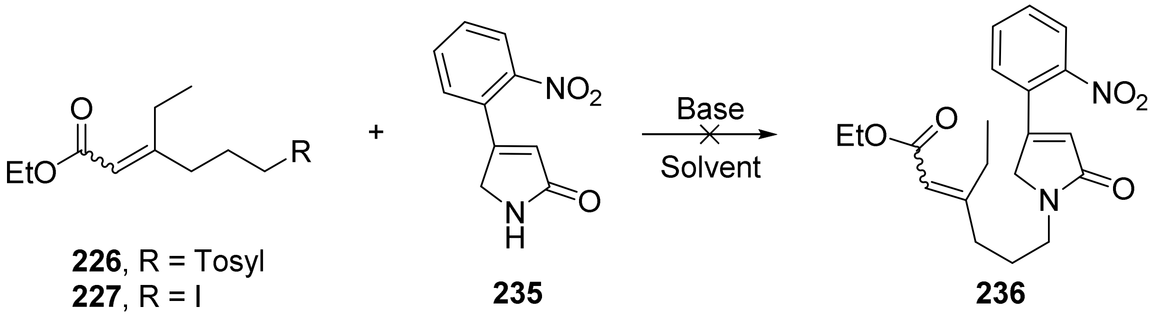
Scheme 2.6. Reported *C*-5-alkylation of the *N*-unsubstituted *O*-methyl tetramates via the intermediate dianion **233**.[113]

Based on the encouraging results reported in the literature, the further investigation was focused on the *N*-alkylation with alkyl iodide **227** of 3-pyrrolin-2-one **235** quantitatively prepared from compound **218** by deprotection using TFA. Disappointingly, despite numerous efforts varying the approach and the reaction parameters such as base, number of equivalents, temperature, reaction time, the *N*-alkylation of 3-pyrrolin-2-one **235** using olefin **227** could not be achieved (Table 2.2).

Often starting material could be re-isolated or degradation of 3-pyrrolin-2-one was observed as evidenced by the poor mass-balance after work-up and purification. Using *n*-BuLi as a strong base at low temperatures and then warming the solution to room temperature led to recovery of the iodide **227** whereas the 3-pyrrolin-2-one **235** was degraded (Entry 1). Using the different variants of the phase transfer alkylation did not lead to product formation either. Under these milder conditions both starting materials could be partially recovered (Entry 2 – 4). Using strong bases like potassium hexamethylsilazane (KHMDS) of sodium hydride in THF or in DMF did not allow detecting product formation (Entry 5 and 6 for KHMDS and 7 to 9 for NaH).

It seems that the nucleophilicity of the 3-pyrrolin-2-one substrate is not high enough for an optimal further transformation *via* *N*-alkylation. Obviously, such a proposal requires additional studies which are summarized in the following sections.

Table 2.2. Attempts to *N*-alkylate the 3-pyrrolin-2-one **235**.

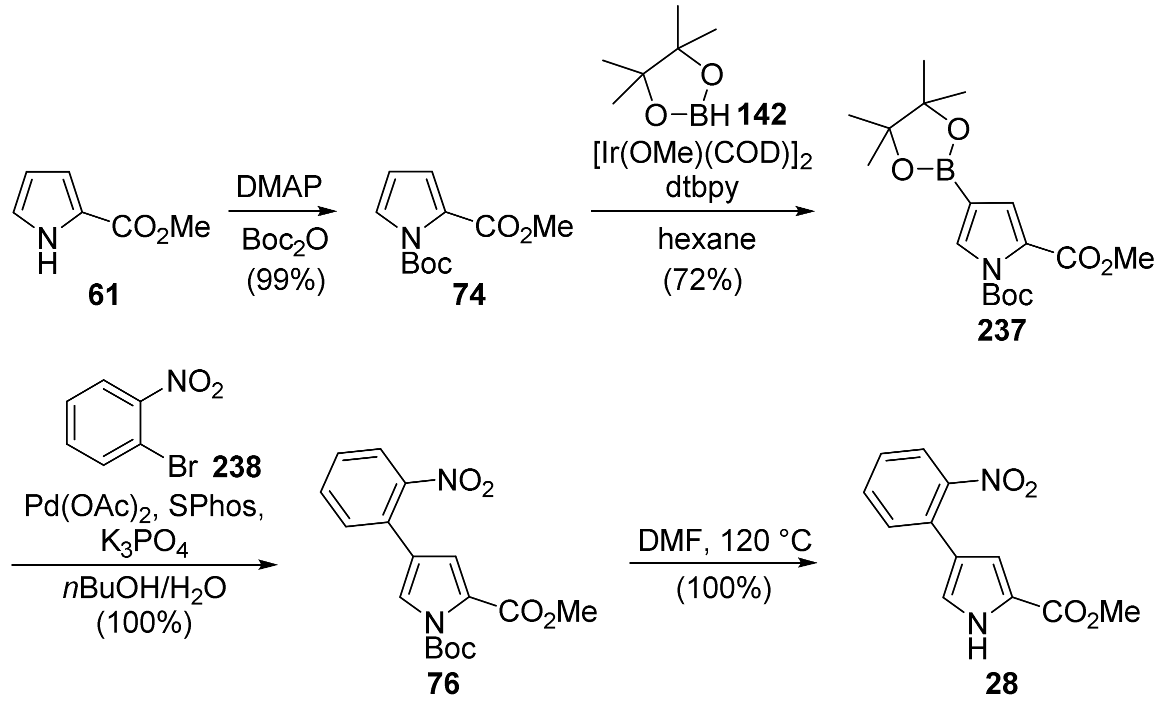


Entry	Electrophile (equiv.)	Base (equiv.)	PTS[a] (equiv.)	Solvent	T, °C	t, h	Product [b]
1[100,112]	**227** (1.13)	*n*-BuLi (1.12)	–	THF	0–20	3.5	**227**+ **235** decomposed
2[112,114]	**227** (1.25)	KOH (6.00)/ K_2CO_3 (1.25)	Bu_4NHSO_4 (0.10)	MePh	60	5	**227** + **235** decomposed
3[113]	**227** (3.00)	KOH (1.40)	Bu_4NHSO_4 (0.10)	THF	0–20	18	**227** + **235** decomposed
4[113 ,[c]]	**BnBr** (3.00)	KOH (1.40)	Bu_4NHSO_4 (0.10)	THF	0–20	18	**BnBr** + **235**
5[115]	**226** (1.1)	KHMDS (1.1)	–	THF	70	2	**226** + **235** decomposed
6[115]	**227** (1.1)	KHMDS (1.1)	–	THF	70	3	**227** + **235** decomposed
7[116]	**226** (1.10)	NaH (1.10)	TBAI (0.22)	THF DMF	20	27	**226** + **235** decomposed
8[55]	**227** (1.10)	NaH (1.10)	–	DMF	20	24	**227** + **235** decomposed
9[55]	**227** (1.10)	NaH (1.10)	–	DMF	0–20	24	**227** + **235** decomposed

[a] Phase transfer catalyst was added. [b] According to NMR and/or GC. [c] Benzyl bromide was used as electrophile.

2.3.2. *N*-alkylation of substituted pyrrole 28

Having this hypothesis in mind, the use of more nucleophilic aryl-pyrrole **28** was envisaged (Scheme 2.7).



Scheme 2.7. Synthesis of biaryl **28**.

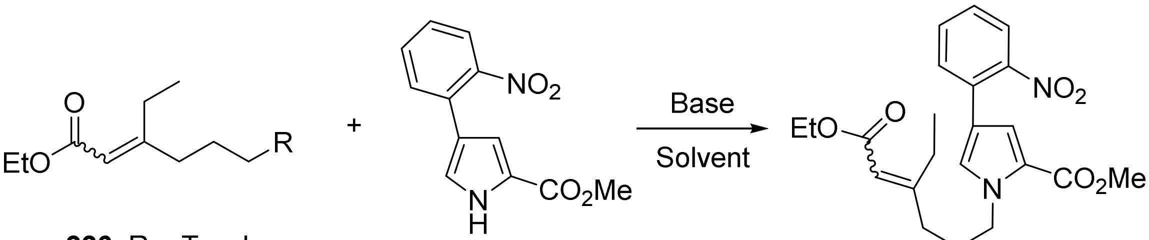
The synthesis started with a pyrrole **61** containing a temporary blocking group at C2 position. In most of the reported rhazinilam syntheses[117,118] a carboxymethyl group at the C2 position of the pyrrole ring had to be used as temporary protecting group. This protection probably prevents competing oxidative pyrrole dimerization reactions.

The key structural elements of **28** could be directly installed from a simple pyrrole nucleus by a metal-catalysed C-H bond arylation to produce the heterobiaryl framework.

Thus, the Ir^{I}-catalysed C-H borylation, developed by the groups of Smith–Malezcka and Hartwig–Miyaura, [60,61,119] was adopted to furnish the desired pyrrole nucleus and then performed a Suzuki coupling. The *tert*-butylcarboxy (Boc) group is known[120] to be a protector and director for Ir-catalysed borylations. The pyrrole **61** was converted into *N*-Boc-pyrrole **74** in excellent yield. Compound **74** underwent an Ir-catalysed borylation under Smith–Malezcka conditions[120] to yield a 4-borylated pyrrole **237** in 72% yield with complete regioselectivity at C-4. A Pd-catalysed Suzuki cross-coupling reaction of **237** with 2-bromo-nitrobenzene (**238**) was achieved quantitatively following the procedure described by Morrison and co-wokers.[82] Alternatively, the biaryl **76** could be obtained in 96% yield by one-pot Ir^{I}-catalysed C-H borylation and Suzuki coupling on **74** (see experimental part). Removal of the Boc group under thermal conditions[59,120,121] delivered quantitatively **28**.

Having sufficient quantities of the required aryl-pyrrole **28** available, we tested the alkylation reaction with the corresponding olefin (Table 2.3).

Table 2.3. *N*-alkylation of the pyrrole **28**.



226, R = Tosyl
227, R = I

28

239

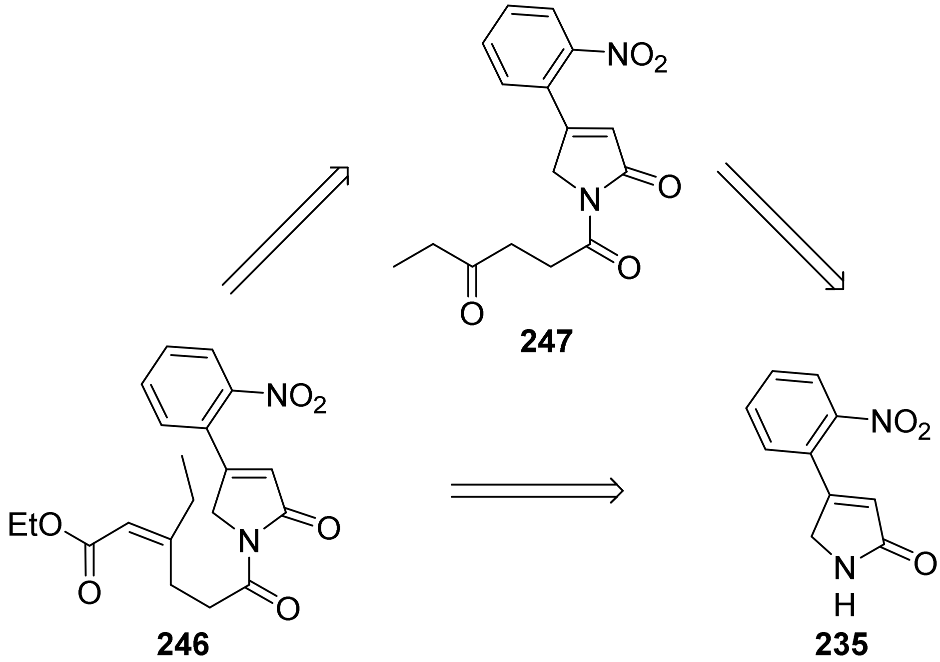
Entry	Electrophile (equiv.)	Base (equiv.)	Solvent	Temperature [°C]	Time [h]	Yield [%]
1[115]	**226** (1.1)	KHMDS (1.1)	THF	85	20	–[a]
2[55]	**226** (1.1)	NaH (1.1)	DMF	0 – 20	20	**63**[b]
3[55]	**227** (1.1)	NaH (1.1)	DMF	0 – 20	6	**Quant.**

[a] Only starting materials were recovered. [b] According to NMR data.

A nucleophilic substitution of the tosyl group by the potassium salt of pyrrole **28** was unsuccessful. The *N*-alkylated pyrrole **239** was isolated in moderated yield using the sodium salt of pyrrole precursor. Gratifyingly, *N*-alkylation of pyrrole **28** preceded smoothly and quantitatively using iodo-alkyl **227** as electrophile and NaH as a base.

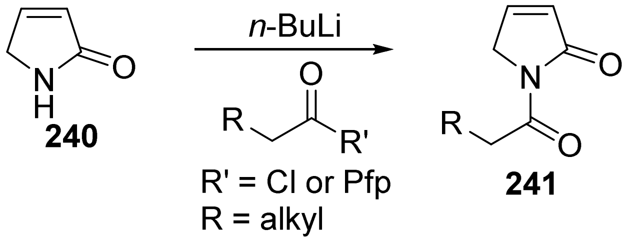
2.3.3. *N*-acylation of 3-pyrrolin-2-one 240

Given the poor nucleophilic nature of 3-pyrrolin-2-one substrate, it was decided to investigate the *N*-acylation instead of the *N*-alkylation on the model series involving sterically less demanding substrates (Schema 2.8). Two retrosynthetic pathways were envisaged and experimentally tested.



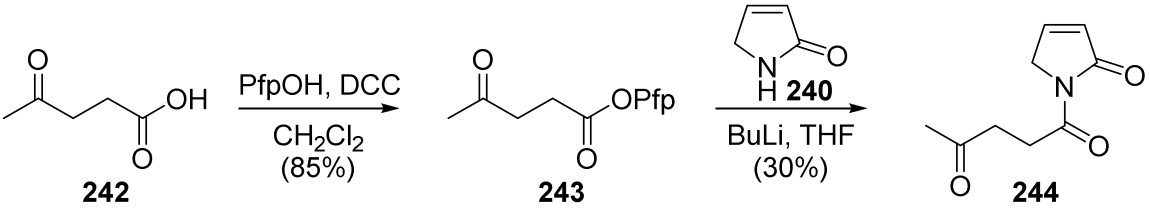
Scheme 2.8. Retrosynthetic pathways for synthesis of **246** *via* *N*-acylation of pyrrolinone **235**.

N-Acylation of sterically hindered chiral cyclic amides has previously been described; especially the oxazolidinones have attracted much interest due to their use as chiral auxiliaries.[122,123] Similar 3-pyrrolin-2-ones have been *N*-acylated using an *n*-BuLi protocol with electrophiles such as acid chlorides[124] and pentafluorophenyl (Pfp) esters (Scheme 2.9).[125-127]



Scheme 2.9. *N*-acylation of 3-pyrrolin-2-one **240**.

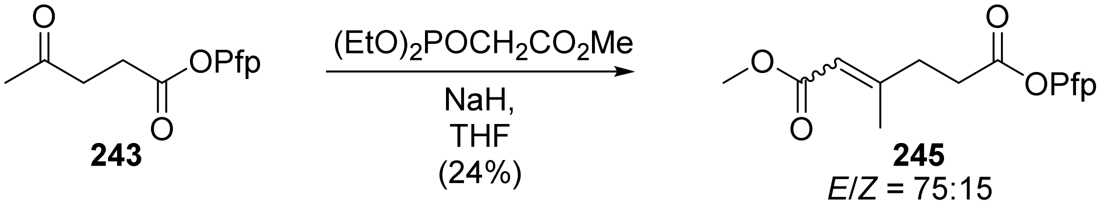
The first attempt to perform the *N*-acylation using the 1*H*-pyrrol-2(5*H*)-one **240**[101] and the active ester **243** derived from the levulinic acid (**242**) (Scheme 2.10) was successful. Thus, activation of the carboxylic functionality of **242** as its pentafluorophenol ester **243**, followed by condensation with the lithium salt of **240** afforded **244** in moderate 30% yield.



Scheme 2.10. *N*-acylation of 3-pyrrolin-2-one **240** with levulinic acid pentafluoroester **243**.

Unfortunately, all attempts to achieve WHE olefination of **244** using NaH (4 equiv.) and methyl diethylphosphonoacetate (3.52 equiv.) in dry THF were unsuccessful. Only starting materials and the products of hydrolysis of 3-pyrrolin-2-one **244**, levulinic acid **242** and 1*H*-pyrrole-2(5*H*)-one **240**, were recovered.

Given the failure to direct WHE olefination of **244**, it was deemed necessary to synthesize first a α,β-unsaturated carbonyl chain. Thus, the pentafluorophenol ester **243** was subjected to WHE olefination using the conditions described above. Under such conditions, the activated ester **243** underwent WHE olefination to afford in 24% yield the acrylate **245** as a 75**:**15 mixture of *E*- and *Z*-isomers (Scheme 2.11).

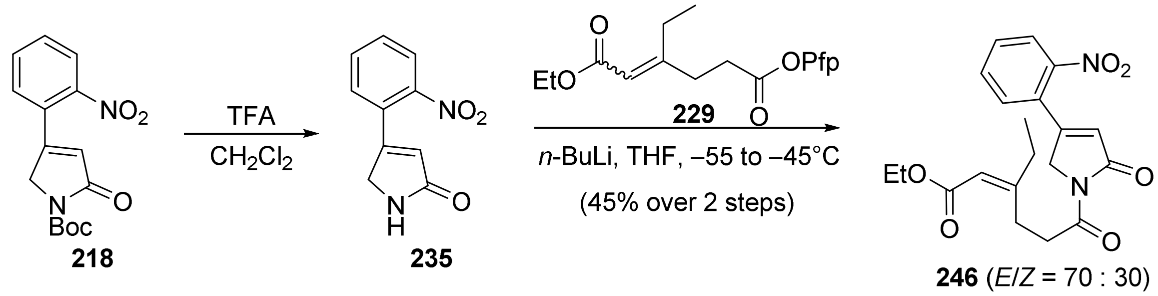


Scheme 2.11. Olefination of levulinic acid pentafluorophenylester **243**.

The low yield should be due to a partial hydrolysis of ester **243**. Nevertheless, the foregoing results demonstrated that the activated acrylate **245** could be obtained from the commercially available levulinic acid by two-step procedure and in 23% overall yield.

This was a very positive outcome as it provided an easy access to a broad range of intramolecular Michael addition substrates.

In light of these encouraging results, the *N*-acylation of more complex aryl-3-pyrrolin-2-one **235** was investigated (Scheme 2.12).

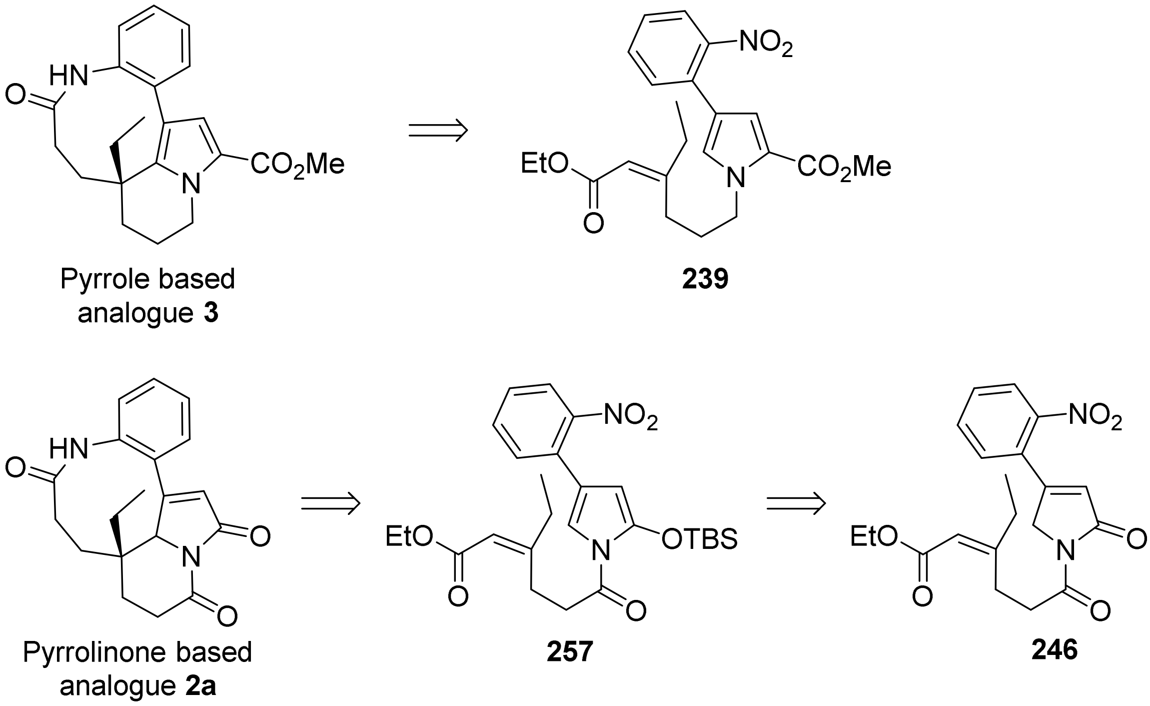


Scheme 2.12. *N*-Acylation of 3-pyrrolin-2-one **235**.

The first attempt to perform the *N*-acylation on the 3-pyrrolin-2-one **235** using the activated acrylate **229** and *n*-BuLi at low temperature was successful. Such a result enabled to better understand the reactivity of this compound and to obtain the coupling product **246**.

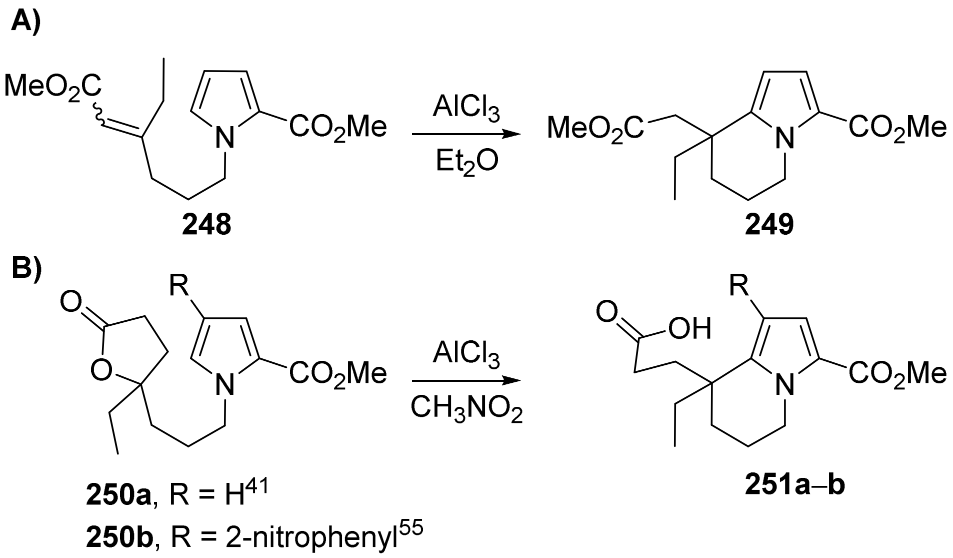
2.4. Preliminary investigation on the intramolecular Michael addition reaction of 239 and 246 to *N*-Tethered Acrylates

After a number of synthetic efforts, the compounds **239** and **246** have been obtained and considered as promising advanced intermediates for obtaining the different derivatives of rhazinilam (Scheme 2.13).



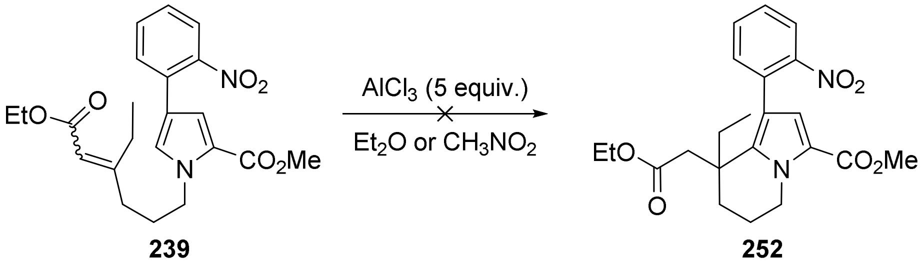
Scheme 2.13. Retrosynthetic pathway to formation of D-ring *via* intramolecular Michael addition reaction.

With the requisite functional handle in place, the stage was now set for the implementation of the key intramolecular Michael addition reaction. Smith,[17] Trauner[55] and Banwel[41] used the aluminium trichloride and the substituted pyrroles to achieve the itramolecular cyclisation (Scheme 2.14).



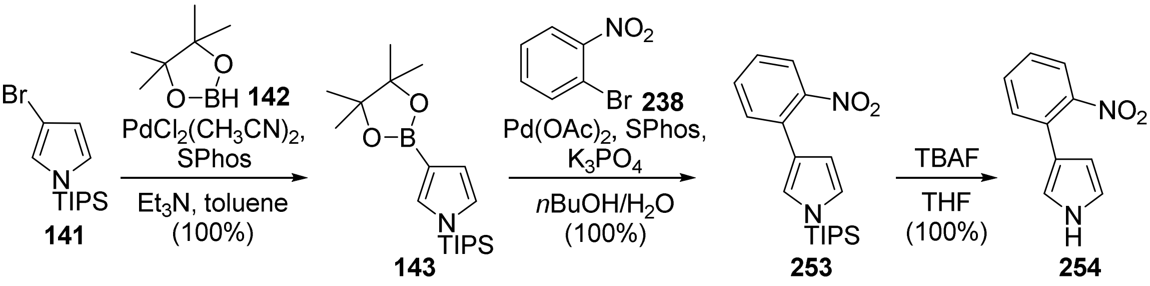
Scheme 2.14. Intramolecular cyclisations using $AlCl_3$ as a Lewis acid activator: A) *via* an intramolecular Michael addition reaction;[41] B) *via* an intramolecular Friedel-Crafts alkylation.[17,55]

Unfortunately, all attempts to obtain the cyclic adduct **252** from acrylate **239** using aluminium chloride in diethyl ether or nitromethane are failed (Scheme 2.15).



Scheme 2.15. Attempt to cyclicise the acrylate **239** into the tetrahydroindolizine **252**.

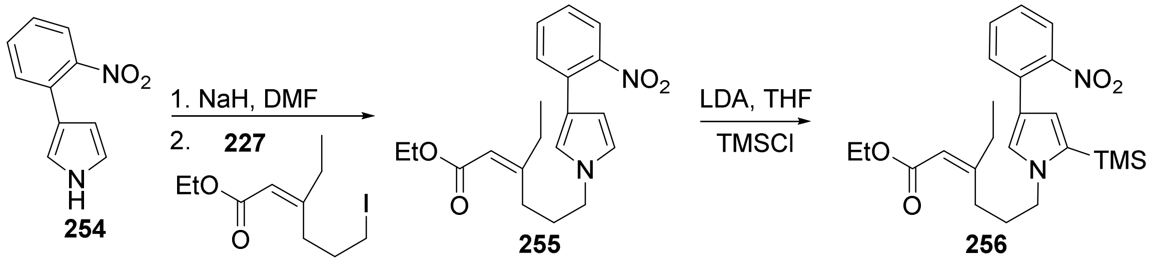
The presence of both methyl ester substituent on the pyrrole ring and 2-nitro group on the phenyl rings deactivates the pyrrole ring sufficiently preventing Michael addition reaction. The synthesis of the more nucleophilic pyrrole **254** was a logic solution overcoming this problem (Scheme 2.16).



Scheme 2.16. Synthesis of biaryl **254**.

The synthetic pathway started with the commercially available triisopropylsilyl-3-bromopyrrole **141** which was easily converted into the pinacolboronate ester **143** *via* Pd-catalysed carbon-boron bond formation using the procedure of Billingsley and Buchwald.[128] Pd-catalysed Suzuki-Miyaura cross-coupling of **143** and 2-bromo-nitrobenzene (**238**) was achieved quantitatively following the procedure described by Morrison and co-wokers.[82] Fluoro-desilylation of resulting biaryl **253** proceeded smoothly to yield the 3-(2-nitrophenyl)-1*H*-pyrrole **254** in excellent yield.

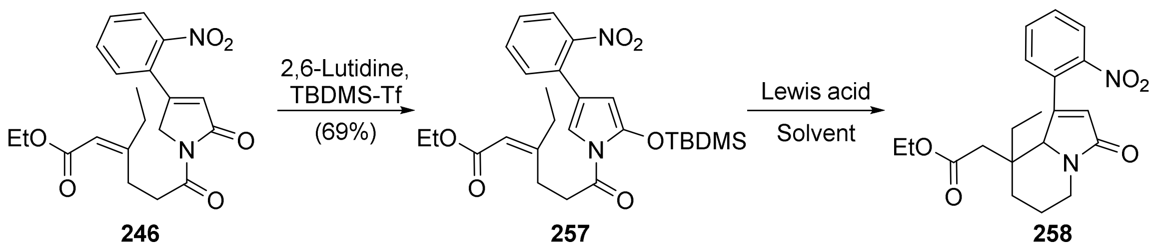
The next logical step was the *N*-alkylation of "more activated nucleophile" such us aryl pyrrole **254** using the procedure described above. The installation of a temporary blocking group for the C5 position[59] of **255** should provide a handle for controlling the regioselectivity of the Michael addition reaction (Scheme 2.17).



Scheme 2.17. Presumptive synthesis of precursor **256**.

Unfortunately, during the preparation of these intermediates, a total enantiospecific concise synthesis of rhazinilam was published by Professor Zakarian research group.[64] The synthetic pathway required very similar steps for the construction of a target biaryl core. Thus we decided not to pursue this approach.

Thereby, it was reasonable to turn the attention back to the studies of 3-pyrrolin-2-one chemistry. Thus, the activation of 3-pyrrolin-2-one **246** with *tert*-butyldimethylsilyl triflate could be easily performed and afforded the silyloxypyrrole **257** in good 69% yield (Scheme 2.18).



Scheme 2.18. Presumptive synthesis of precursor **258** *via* silyloxypyrrole **257**.

However, the first trail to perform the intramolecular Michael addition using a Lewis acid such as $BF_3{\cdot}Et_2O$ at −90 °C failed. Only the desilylated product **246** was recovered. The screening of the reaction conditions needed for the formation of the desired Michael product **258** has not been achieved yet.

2.5. Summery.

In summary, this project achieved the aims proposed at the outset. The *N*-alkylation and *N*-acylation of 3-pyrrolin-2-one derivatives were investigated. This process was attractive because the products could contain all the atoms and the functionality needed for the formation of the D-ring via Michael addition. In this process the substituent for the elaboration of ring B could be introduced simultaneously. This building block, acrylates **227** and **229**, was prepared in remarkable yields.

The introduction of a side chain by nucleophilic *N*-alkylation on 3-pyrrolin-2-one derivative could not be achieved whilst the reaction with a more nucleophilic pyrrole afforded in good yield the intermediate **239** for the further synthesis of pyrrole based rhazinilam analogues. Alternatively, the *N*-acylation on 3-pyrrolin-2-one derivatives was successfully performed. The advanced intermediates **246** and **257** contain all essential elements needed for the construction of pyrrolinone based rhazinilam analogues *via* a simple homologation step.

Unfortunately, due to time constraints, it was not possible to continue the investigation of the intramolecular Michael addition reaction on the activated pyrrole **257**. This compound is still to be a suitable substrate for further investigations.

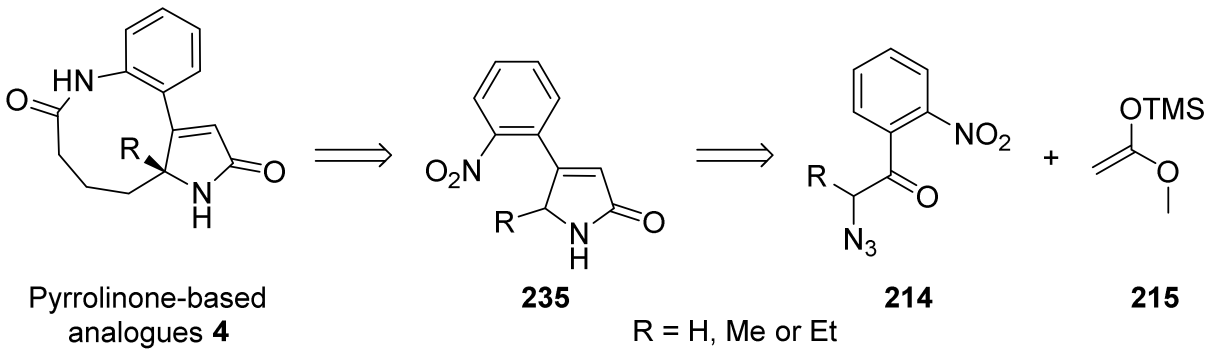
Chapter three

MUKAIYAMA CROSSED ALDOL REACTION METHODOLOGY

3.1 Introduction

The recent metabolism studies were conducted in order to investigate the reasons for the *in vivo* lack of activity of (−)-rhazinilam.[129] They revealed that rhazinilam is easily oxidized at positions 3 and 5 by human liver microsomes leading to the formation of metabolites, including leuconolam, which are much less active than rhazinilam or inactive *in vitro* and probably more rapidly eliminated. The isolated metabolites are mostly pyrrolinone containing derivatives of rhazinilam such as leuconolam. Our previous studies have shown that these products are also quite unstable.[103,130] The introduction of a blocking group at the C-5 should overcome the problem of further oxidation.

This observation led us to propose a new synthetic route to the phenyl-pyrrolidinone core of pyrrolinone-based analogues of rhazinilam. The process involves a tandem Mukaiyama aldol-type condensation - Staudinger cyclisation sequence[96-101] (Scheme 3.1). The chosen convergent strategy allows the short and efficient synthesis of more sterically hindered derivatives.



Scheme 3.1. Retrosynthetic analysis involving Mukaiyama – Staudinger tandem sequence.

3.2 Results and discussion

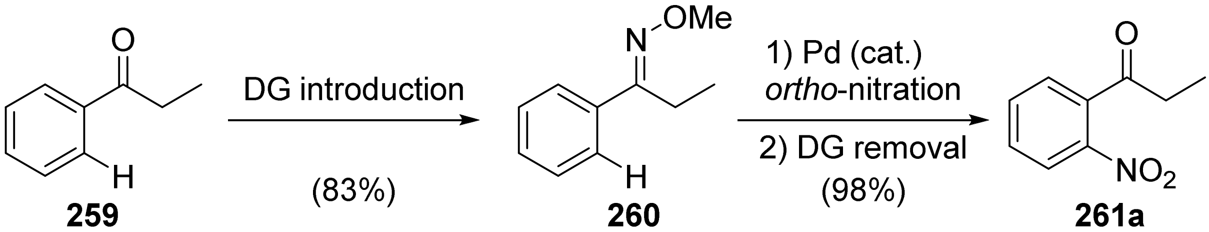
3.2.1. Preparation of 1-(2-nitrophenyl) alkyl ketones.

To synthesize the *o*-nitro-substituted phenyl pyrrolidinones using the approach reported above, it was essential to develop a flexible and efficient method for the preparation of the nitro-substituted alkyl phenyl ketone substrates.

Indeed, the formation of such a substrate is not trivial. A literature review of relevant studies shows that there are only a few synthetic routes to the *ortho*-nitro substituted alkyl phenyl ketones which can be divided into three major strategies.

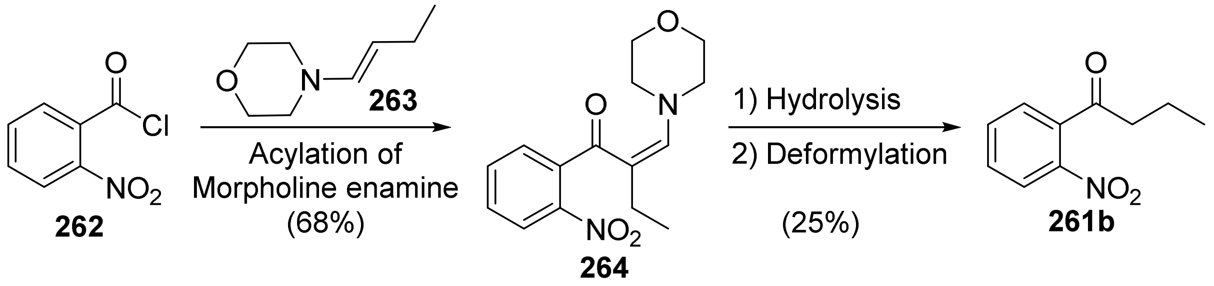
The most common approach is the nitration of the corresponding aryl ketones.[131,132] Since Mitscherlich[133,134] reported the first nitration of benzene with fuming nitric acid in 1834, the nitrating agent-involved electrophilic aromatic substitution has long been the most common approach for the preparation of nitroarenes.[135,136] However, the traditional electrophilic nitration processes are usually associated with several persistent disadvantages including poor regioselectivity,[137,138] poor chemoselectivity arising from overnitration, imperfect functional group and/or substrate compatibility under acidic conditions, nitration sites significantly depending on the directing effect of the different functional groups, and the use of environmentally harmful acid reagents.

In the last decades, a more attractive method for the regiospecific synthesis of nitroarenes has been developed *via* the transition-metal-catalysed (Cu or Pd) *ipso*-nitration.[139,140] Despite several characteristic advantages of these methods including improved regiospecificity for the *ortho*-substitution independent of the orientation rules, mononitration selectivity, broad functional group and substrate tolerance under neutral conditions, they suffer from the necessity to use prefunctionalized starting materials such as aryl halides, pseudohalides, triflates, nonaflates or aryl boronic acids[141-145] or they require the introduction of directing groups (Scheme 3.2).[146]



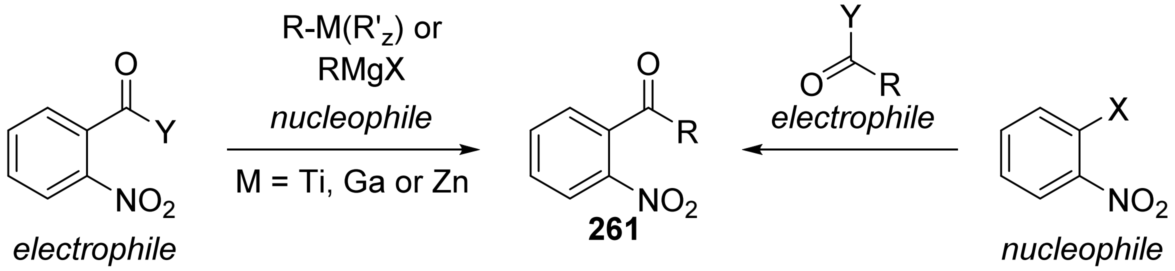
Scheme 3.2. The site regiospecific nitration free from the effect of orientation rules involving the directing group (DG) installation.[146]

An alternative strategy to *ortho*-nitro substituted alkyl phenyl ketones **261** was demonstrated by Kamath and co-workers.[147] In this approach, nitro substituted alkyl phenyl ketones have been synthesized by reacting nitro substituted benzoyl chlorides (**262**) with morpholine enamines of aliphatic aldehydes **263**. The resulting acylated enamines on hydrolysis afforded the desired products. However, 2-nitro and 2,4-dinitro substituted enamines on hydrolysis furnish the β-keto aldehydes which can be converted into the corresponding ketones by additional treatment with aqueous sodium bicarbonate (Scheme 3.3). Nevertheless, this approach was found to be sensitive and afforded the desired product in unsatisfactory yield.



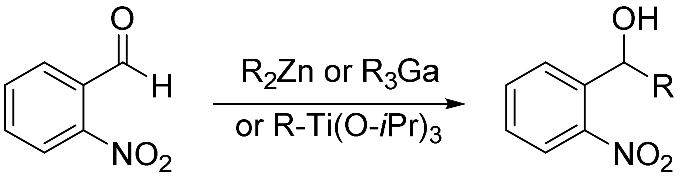
Scheme 3.3. Synthesis of *ortho*-nitro substituted alkyl phenyl ketones *via* morpholine enamines formation, hydrolysis and deformylation.[147]

The development of organometallic chemistry has seen major advances in the past half century. The nucleophilic addition of organometallic reagents to carbonyl compounds is a well-known reaction, which represents a powerful tool for the construction of carbon-carbon bonds.[148] However, literature survey has revealed only few examples of the synthesis of *ortho*-nitro substituted alkyl phenyl ketones **261** *via* nucleophilic addition of organometallic reagents followed by oxidation of resulted alcohol. These approaches available for achieving the nucleophilic addition can be divided into one of two categories depicted in Scheme 3.4.



Scheme 3.4. Synthesis of *ortho*-nitro substituted alkyl phenyl ketones **261** *via* nucleophilic addition of organometallic reagents.[148]

Since the first reports on the alkyl groups transfer from organotitanium compounds to aromatic aldehydes,[149,150] new methodologies using organozinc[151-153] and organogallium[154,155] substrates have been developed in last 5 years (Scheme 3.5).



265 **266**

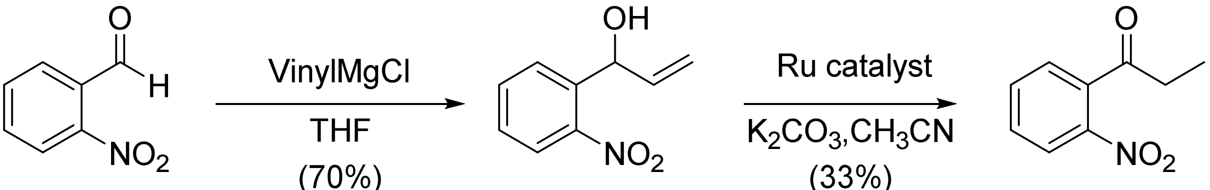
Scheme 3.5. Synthesis of *ortho*-nitro substituted phenyl alkyl alcohols using organozinc, gallium and titanium compounds.[149-155]

Despite the attractiveness of these methods including the good yields, these organometallic compounds are expensive and sometimes difficult to handle due to their air- and moisture-sensitivity. These facts limit their accessibility and, ultimately, the diversity of compounds that will be crucial for further investigation in this project.

Reports on direct addition of Grignard reagents such as EtMgBr or MeMgBr to *o*-nitrobenzoylchloride[156] or *o*-nitrobenzaldehyde respectively[157] are extremely rare and give the unsatisfactory yield.

The replacement of alkyl by less nucleophilic vinyl magnesium bromide or chloride is most common way to deal with this issue.[158-161]

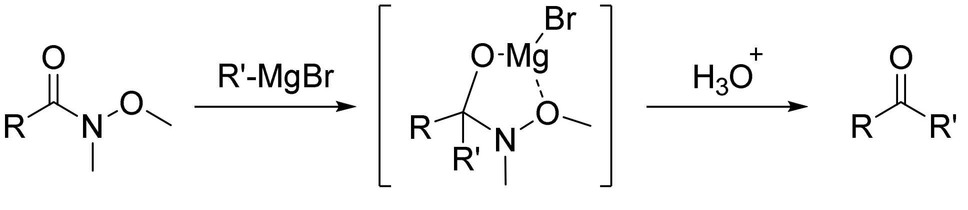
Recently, Bouziane and co-workers proposed an interesting approach to the preparation of various aromatic ketones from the corresponding allylic alcohols by Ru-catalysed redox isomerization.[162] However, the yield of *ortho*-nitro substituted phenyl ketone **261** was poor. The coordination of the nitro group to the ruthenium catalyst was invoked to explain the decreased reactivity (Scheme 3.6).



265 **267** **261a**

Scheme 3.6. Synthesis of *ortho*-nitro substituted alkyl phenyl ketones *via* Grignard reaction followed by Ru-catalysed redox isomerization.[162]

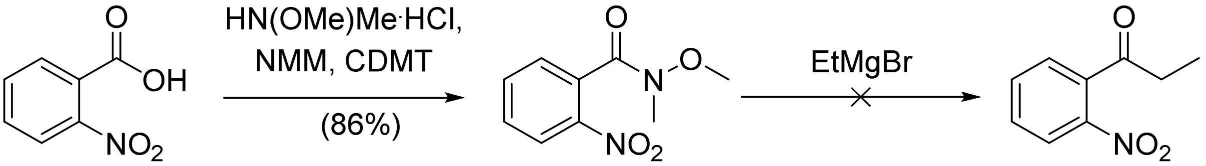
One of the possible reasons of inefficiency of Grignard reaction could be a well-known propensity of reactive Grignard and organolithium reagents to overadd to the substrate in the carboxylic acid oxidation state, producing a tertiary alcohol. Among the methods to solve this problem, the use of Weinreb amide is especially convenient and attractive.[163] Normally, no over-addition occurs due to formation of a very stable tetrahedral chelate **268** involving the –OMe group of the substrate amide with the metal cation which prevents further reaction with the organometallic reagent (Scheme 3.7). This intermediate could be converted into the desired carbonyl compounds by treatment with acid.[163-165]



268

Scheme 3.7. Formation of carbonyl compounds using Weinreb amide.[163]

Indeed, a review of the literature shows that diverse aryl substituted *N*-methoxy-*N*-methylamides (Weinreb amides) have been successfully converted into their corresponding ketones *via* modified Grignard reaction.[166-171] Encouraged by these examples, our first attempt was focused on trying to employ the originally described conditions,[168] involving addition of EtMgBr to the known[172-174] Weinreb amide **270** (Scheme 3.8). Thus, *N*-methoxy-*N*-methyl-2-nitrobenzamide **270** was prepared in 86% yield from *ortho*-nitrobenzoic acide(**269**) and *N*,*O*-dimethylhydroxylamine hydrochloride using *N*-methylmorpholine (NMM) and 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT) as a coupling agent under conditions defined by de Luca.[173]



269 **270** **261a**

Scheme 3.8. Attempted synthesis of 1-(2-nitrophenyl)propan-1-one (**261a**) *via* Weinreb amide.

However, the subsequent addition of 2 equiv. of EtMgBr at 0 °C resulted in decomposition of the starting material. It has been suggested that 1,2-and/or 1,6- conjugate addition[175] to the phenyl ring activated by nitro-group may take place rather than substitution of *N*-methoxy-*N*-methylamide functionality. This hypothesis is in accordance with studies conducted by several groups on the mechanism of reaction between Grignard reagents and nitroarenes.[175-179]

It was demonstrated that the reaction between nitroarenes and Grignard reagents may proceed through two different pathways (Figure 3.1), i.e. conjugate addition (path A) and reductive 1,2-addition (path B). The nature of the carbanionic moiety is crucial: alkyl Grignard reagents yielded ring-alkylated products almost exclusively while PhMgX follow path B.

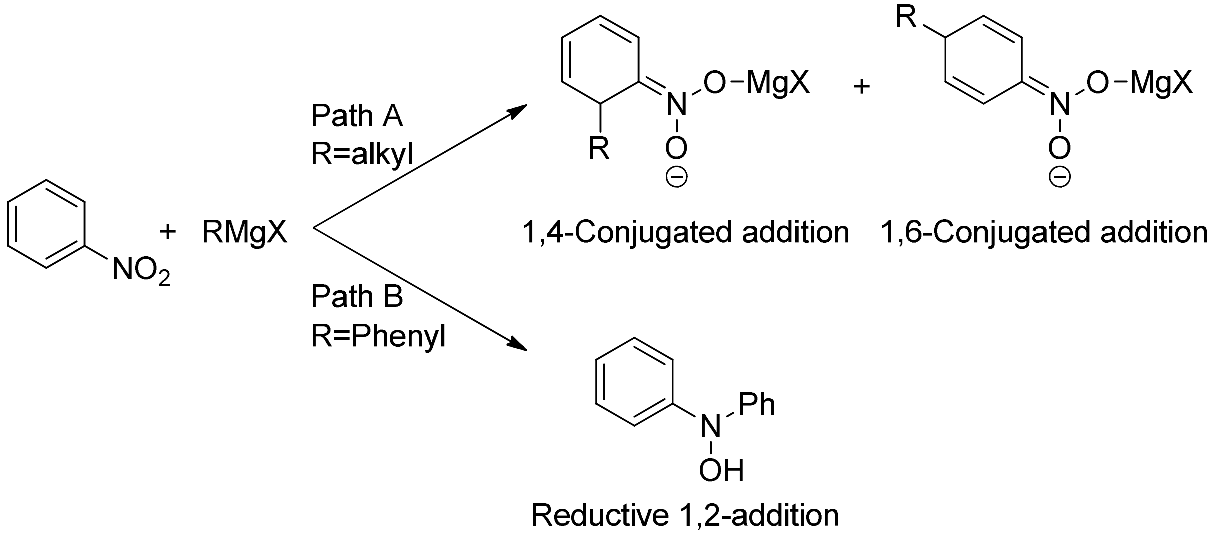


Figure 3.1. Mechanism of the reaction between nitroarenes and Grignard reagents.[175]

Even if nucleophilic substitution of the amine functionality of **270** were to occur, the role of methoxyamine segment in the post-reaction mixture seems to be not fully explored. Recent publications[180,181] reported the substitution of Weinreb amide **270** with vinylmagnesium bromide followed by Michael addition reaction of the extruded *N*-methoxy-*N*-methylamine to form β-aminoketone **271** (Figure 3.2).

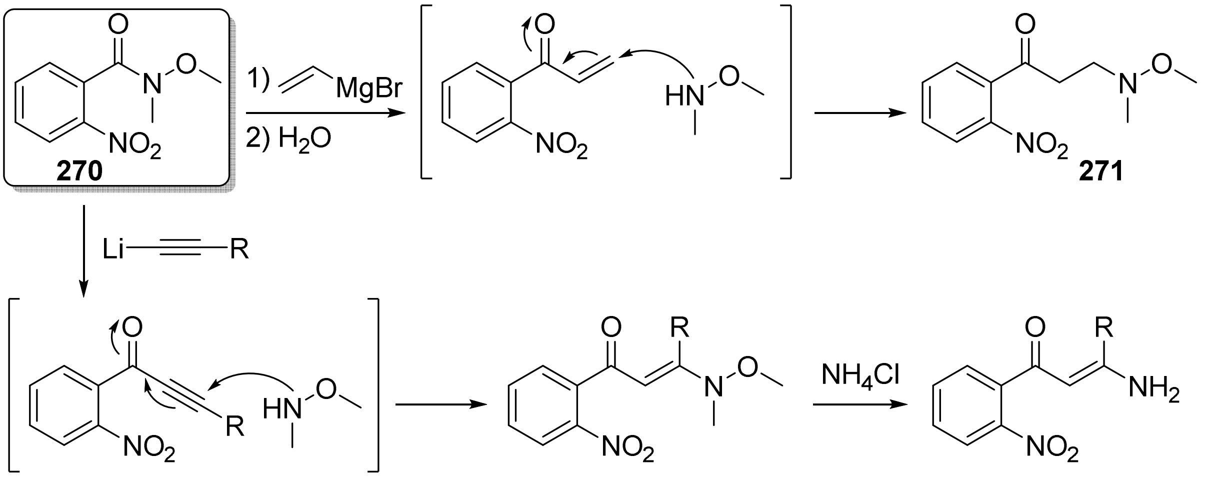


Figure 3.2. Sequential nucleophilic substitution/Michael reaction of Weinreb amide **270**.[180,181]

The above experimental results and literature review suggested that the addition of Grignard reagents to nitro-substituted aryl carbonyl derivatives was not the optimal approach towards *ortho*-nitro substituted alkyl phenyl ketones. A change of strategy was then proposed, where the nitro-substituted aryl derivative may act as a nucleophile towards aliphatic aldehydes. Although reports on nucleophilic substitution reactions involving nitro-substituted aryl organometallic species are extremely rare, an interesting approach was proposed by Knochel group.[182] In this approach, the aryl Grignard reagents with an *ortho*-nitro substituent have been prepared from 2-iodonitroaryl compounds through an I-Mg exchange reaction with PhMgCl (Figure 3.3).

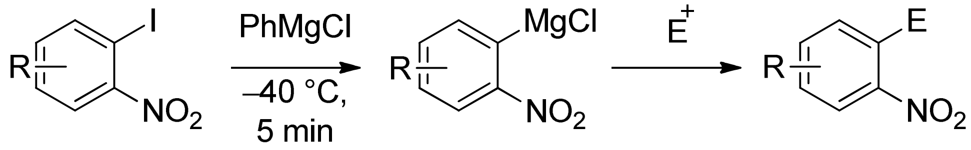
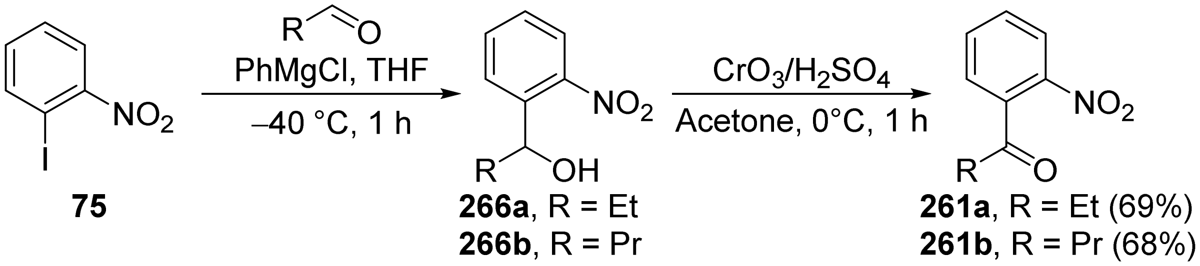


Figure 3.3. Preparation of *o*-nirtomagnesium halides through I-Mg exchange.[182]

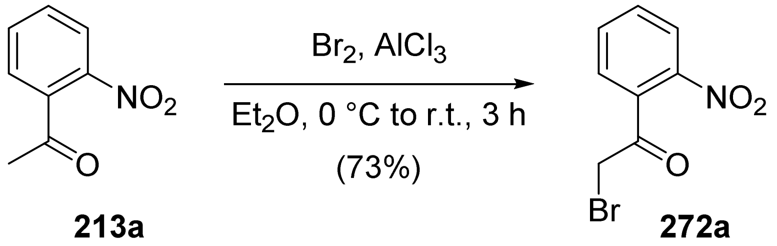
Interestingly, two observations were made: the use of more reactive Grignard reagents led to complex reaction mixtures suggesting the reaction of organometallic reagents with the nitro group, and the inductive and chelation effect of nitro group should favour the *ortho*-iodine–magnesium exchange. Whilst the electrophiles in the original paper were cyclohexyl and phenyl aldehyde, it was decided to extend[183] these conditions to aliphatic aldehydes. Fortunately, all aldehydes react smoothly with nitro-substituted Grignard reagent generated *in situ* from 2-iodonitrobenzene (**75**) to afford the corresponding alcohols **266a–b**. After extraction of the reaction mixture and ^1H NMR analysis of the product, it was found that the crude material was sufficiently clean to use without further purification. Thus, crude alcohols were oxidized to the corresponding ketones **261a–b** using Jones reagent[109,110] (1.9 M, acetone/H_2O, 0 °C) (Scheme 3.9).



Scheme 3.9. Synthesis of *ortho*-nitro substituted phenyl alkyl ketones **261a–b**.

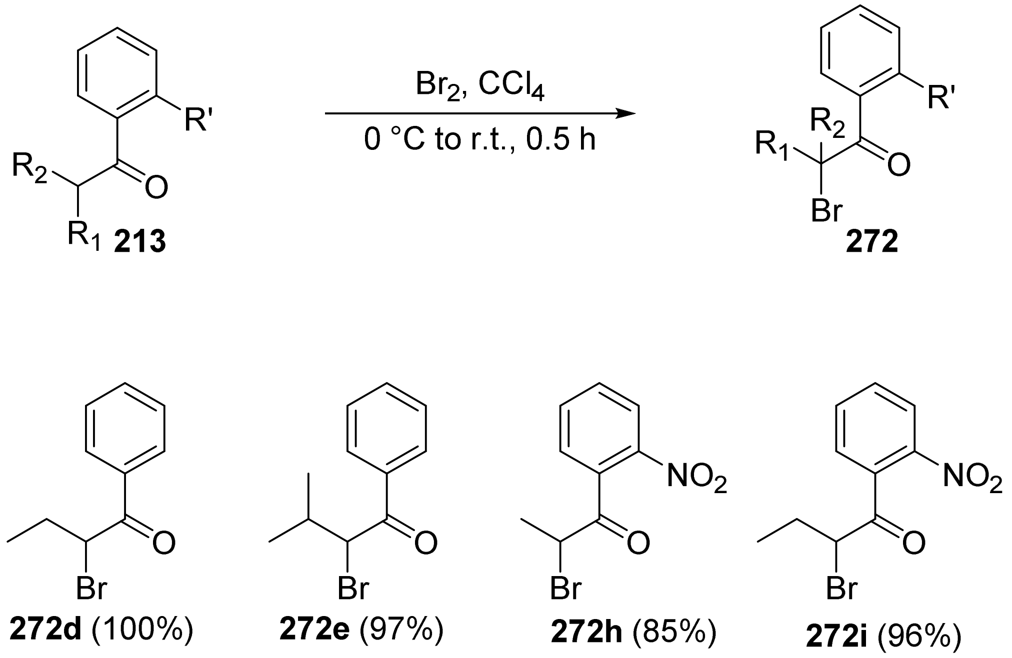
3.2.2. Preparation of α-bromoketones and α-azidoketones.

The strategy of employing the Mukaiyama aldol reaction previously developed in our group required the α-azidoketone substrates. They were prepared by addition of bromine to the phenyl alkyl ketones followed by substitution of bromine with sodium azide. Some of the α-bromoketones such as 2-bromoacetophenone **272b**, 2-bromopropiophenone **272c**, 2-bromoisobutyrophenone **272f** and 2-bromo-1-(4-nitrophenyl)ethanone **272g** were commercially available. 2-Brom-2'-nitroacetophenone **272a** was synthesized as described in previous work of our group (Scheme 3.10).[100,101]



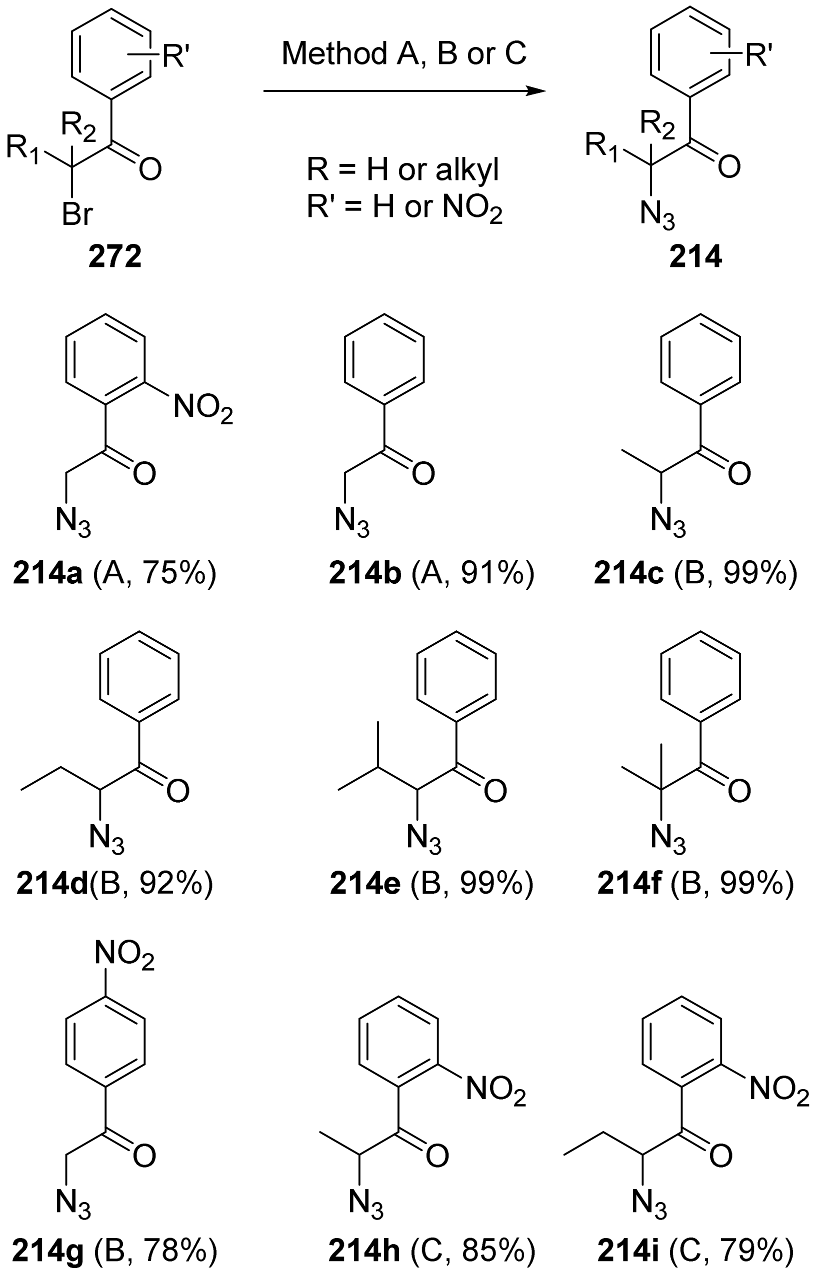
Scheme 3.10. Synthesis of 2-brom-2'-nitroacetophenone (**272a**)

The procedure for the preparation of other α-bromoketones was slightly modified aiming to improve the reaction time and yields of bromination reaction.[100,101] Thus, the reaction was completed within 0.5 h and afforded the brominated products in near quantitative yields using carbon tetrachloride[184,185] instead of diethyl ether in absence of Lewis acid (Scheme 3.11).



Scheme 3.11. Synthesis of α-bromoketones **272d–e** and **272h–i**

Substitution of α-bromoketones **272a−b** with sodium azide was previously performed by our group. Whilst yields of these products were good, the reaction time was long, 48 h and 15 h respectively (Scheme 3.12, Method A: NaN_3, $MeOH/H_2O$, 15 h or 48 h, 4 °C). Fortunately, the change of the solvent system from protic $MeOH/H_2O$ to aprotic, polar DMSO decreased considerably the reaction time (from 15 h to 20 min) and the reaction could be performed at room temperature (Method B: NaN_3, DMSO, 20 min, r.t.).[186]



Scheme 3.12. Synthesis of α-azidoketones **214a−i**. Reaction conditions: Method A: NaN_3, $MeOH/H_2O$, 15 h or 48 h, 4 °C; Method B: NaN_3, DMSO, 20 min, r.t.; Method C: NaN_3, Acetone, 18 h, r.t.

Although the phenyl substituted α-azidoketones **214c−f** were obtained in high yields under these conditions, the application of this protocol to *ortho*-nitro substituted α-bromoketones **272h−i** led to decomposition of the substrate and/or the products. Interestingly, the *para*-nirtophenacyl bromide **272g** reacted smoothly with sodium azide to give the *para*-nirtophenacyl azide **214g** in 78% yield. This result was in accordance with data reported by Gong and co-workers for synthesis of *para*-and *meta*-nirtophenacyl azides.[187] A successful alternative was found in conditions described by Zhao, employing acetone as aprotic solvent (Method C: NaN_3, Acetone, 18 h, r.t.).[188] Reaction of *ortho*-nitro substituted α-bromoketones **272h−i** with sodium azide under these conditions at room temperature afforded the desired α-azidoketones **214h−i** in good yields. This method is more suitable for the preparation of *ortho*-nitro substituted α-azidoketones than previous group procedure (Method A) for two reasons: shorter reaction time (18 h instead of 48 h) and optimal temperature (no practical complications of maintaining the reaction at 4 °C for extended periods).

3.2.3. Synthesis of Pyrrolidinones via the Tandem Mukaiyama cross Aldol-Staudinger-type reductive cyclisation process.

Subsequent to the formation of the α-azidoketones is the Mukaiyama crossed aldol reaction. This is a key step in the synthesis, as it involves the C-C bond formation between the phenyl and pyrrolidinone rings of the final compounds. The Mukaiyama crossed-aldol reaction typically involves the addition of silyl enol ether[189-192] or more nucleophilic silyl ketene acetal[193,194] (nucleophile) to an aldehyde or ketone (electrophile) in the presence of a Lewis acid catalyst such as $TiCl_4$. (Figure 3.4).[195]

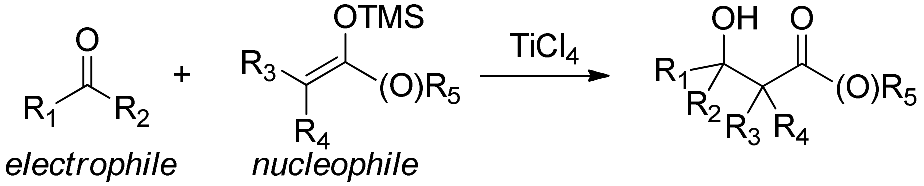


Figure 3.4. Mukaiyama crossed aldol reaction.[195]

The reaction mechanism has not been completely elucidated yet.[196,197] The known facts are that a) Lewis acid enolates are not involved in this reaction:[198] no transmetalation occurs;[199,200] b) the Lewis acids coordinate with the carbonyl function leading to its activation,[201-205] and c) the Si-O bond is cleaved by the nucleophilic attack of the anionic species, generally halide, on silicon.[196] Two possible mechanisms were proposed involving the stabilization of the aldol adducts by their intramolecular chelation with a titanium center **277**[195,206] (Figure 3.5) or by their conversion into silyl ethers **281**[195,207,208] (Figure 3.6).

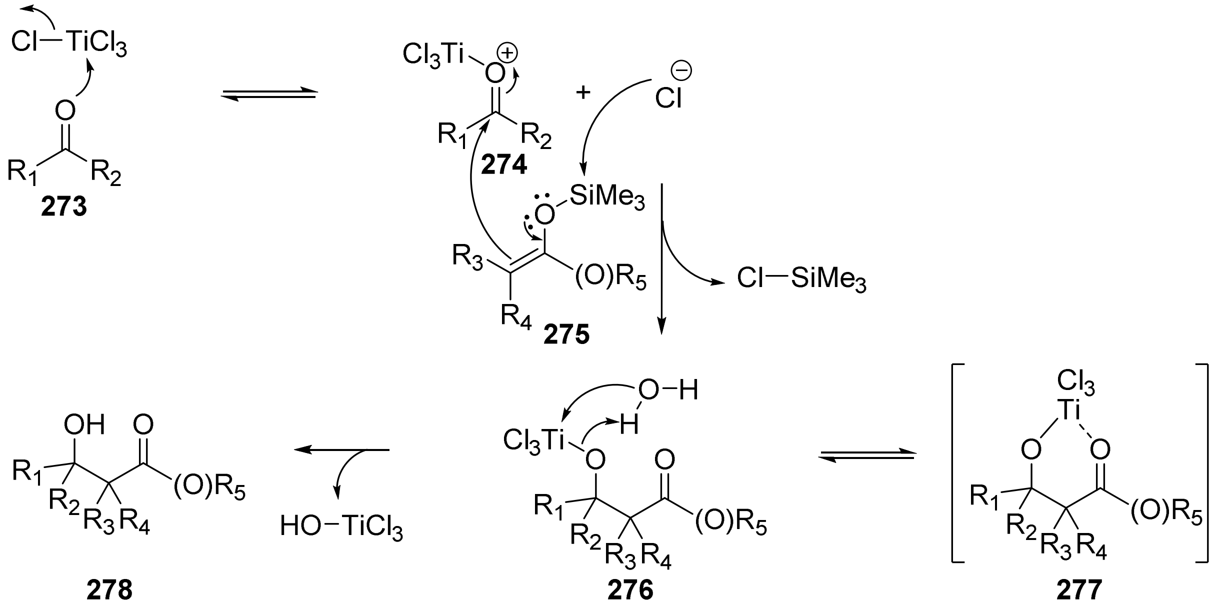


Figure 3.5. Proposed mechanism of Mukaiyama aldol reaction *via* intramolecular chelation with titanium center.[195,206]

Both mechanisms started with the coordination of the carbonyl's oxygen of **273** to titanium leading to the activation of the carbonyl for attack while also releasing a chloride ion. Accordingly to the first mechanism (Figure 3.5), the attack of the chloride on the silicon of the silyl ketene acetal **275** leads to the release of TMSCl followed by the addition of enolate to the activated carbonyl **274**. The desilylated aldol adduct **276** could be stabilized by chelation with titanium **277**.The subsequent aqueous work-up provides the final β-hydroxy ester **278**.[191,192]

An alternative mechanism suggests the formation of intermediate **279** followed by the chloride attack at the latest stages (Figure 3.6). The presumed product before hydrolysis is the silylated aldol adduct **281** which can be formed either by a quasi-concerted path, **A**, or by a nonconcerted process, **B**.[208] Path **A** involves the intramolecular transfer of the silyl group from the ketonic oxygen atom to the bound alkoxide oxygen in chelated intermediate **280**, resulting in the formation of the silylated aldol adduct **281** and the release of the catalyst. The nonconcerted path **B** leads to the formation of the aldolate intermediate **276** and TMSCl. For this pathway to occur the TMSCl is required to remove the titanium from intermediate **276** by an intermolecular process.

The combination of a strong Lewis acid, such as $TiCl_4$, with the labile trimethylsilyl protecting group, which could be easily and reversibly coordinated to the oxygen atoms, opens up several pathways which may occur simultaneously.

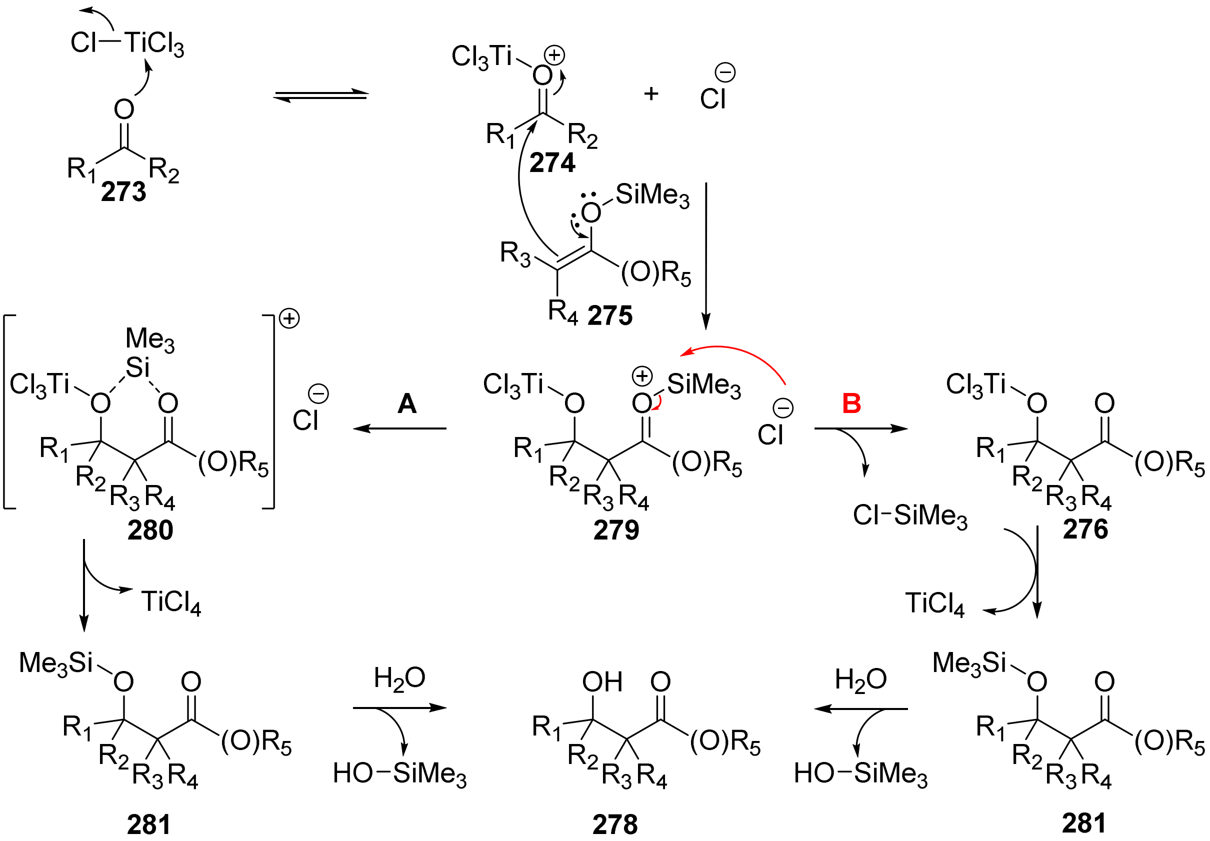
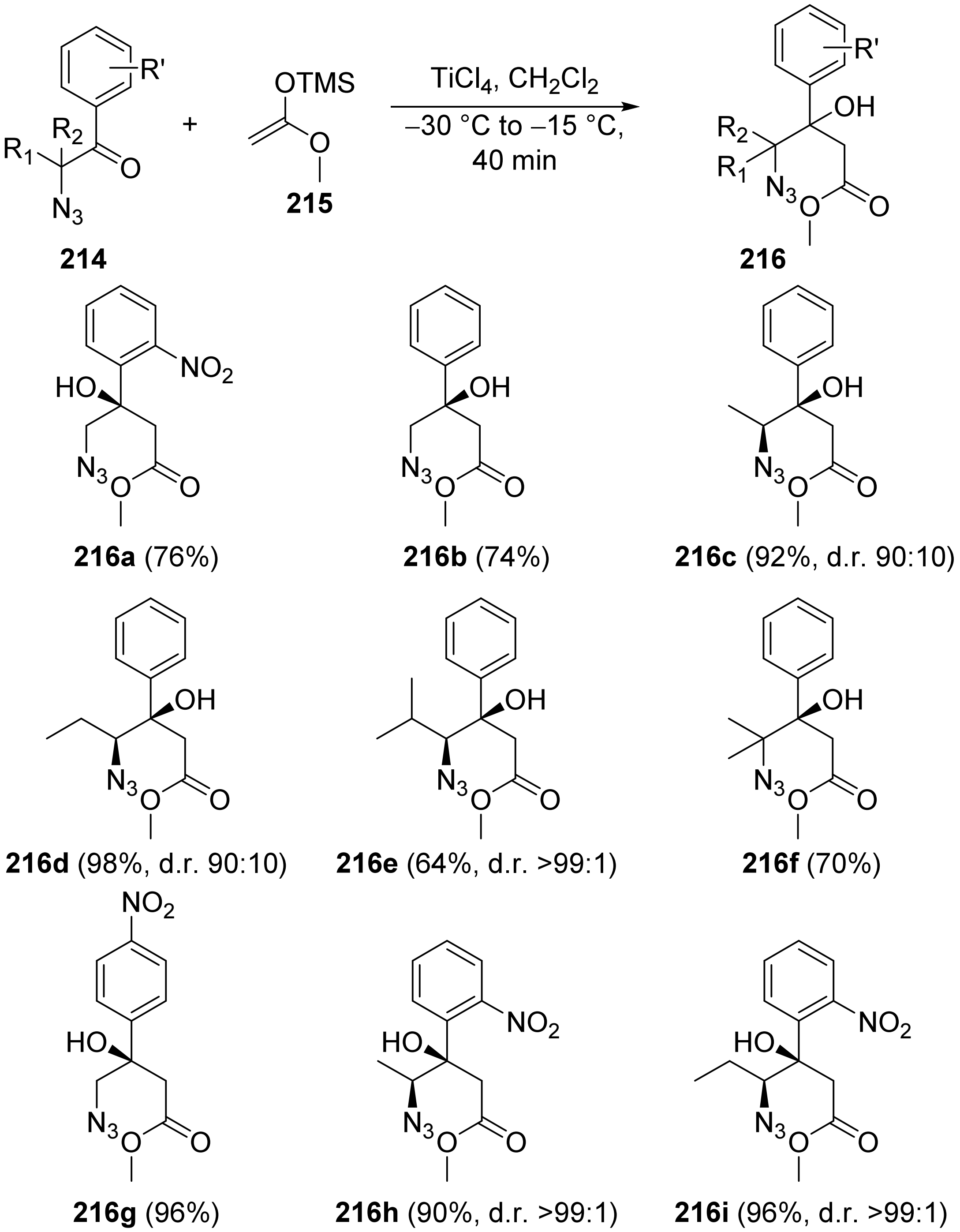


Figure 3.6. Proposed mechanism of Mukaiyama aldol reaction *via* transfer of silyl group.[195,207,208]

Previous research in the group has focused on the development and optimization of the reaction conditions of the Mukaiyama aldol reaction between the acetophenone or its *o*-nitro-substituted analogue and the silyl ketene acetal **215**. It was found that the amount of reagent, the sequence of their addition and the temperature play a crucial role for the outcome. Optimized conditions employed silyl ketene acetal **215** (3 equiv.) and freshly distilled $TiCl_4$ (0.3 equiv.) to give compounds **216a** and **216b** in 76% and 74% yield respectively. The reaction was initiated at −30 °C and quenched at −15 °C However, under these conditions, the substituted β-hydroxy ester **216c** could only be observed in a modest 40–60% yield after 7 h, as judged from the TLC and ^{1}H NMR analyses. This might be due to the increased substitution of α-azido ketones **216c** when compared to previous reactions. The tested ketones **214c−i** have greater steric hindrance at the α-position to the carbonyl group. This steric effect may lead to reduced reaction rates. In an attempt to accelerate the reaction, the use of 5 equiv.

of silyl ketene acetal **215** and 0.5 equiv. of $TiCl_4$ was tested. The hypothesis being that an increased amount of silyl enolate and activated carbonyl present in the reaction would lead to greater conversion and shorter reaction times. Under these modified conditions, the reaction proceeded smoothly affording the desired substituted β-hydroxy ester **216c–i** in good to excellent yields (Scheme 3.13).



Scheme 3.13. $TiCl_4$-catalyzed Mukaiyama aldol reaction for aldol products **216a–i** detailing the yields and diastereoselectivity.

Not surprisingly, the reaction of the more sterically hindered α-azido ketones such as **214e** and **214f** with silyl ketene acetal **215** led to reduced yields. With ketones bearing a substituent in α to carbonyl group this reaction proceeded in diastereoselective manner. The diastereomeric ratios were determined by by ^{1}H NMR analysis of the crude reaction mixture, and confirmed by GC-MS analysis.

The factors determining the diastereoselectivity of Mukaiyama aldol reaction have not been fully rationalized. Different types of transition-states were proposed.[196,197,209] It was presumed that the stereoselectivity of Mukaiyama aldol reaction cannot be explained by classical "closed" six-membered transition-state models, such as Zimmermann-Traxler models,[210] and the less organized open transition state models with no direct contact between the silyl enolate and the Lewis acid provides a model in good agreement with the experimental results.[211,212]
In our case, we have to deal with a π-facial selectivity[196,197] of azido ketones imposed by the presence of a chiral center in the α position to the carbonyl group. The stereochemical outcome and the problems arising from the 1,2-asymmetric induction has often be rationalized and predicted by the Felkin-Anh model.[213-215] One of the first models used for the explanation of the observed selectivities is the Cram-model. Despite the fact, that the rationale behind the explanation is distinctly different between the Cram-model and the Felkin-Anh-model the terms are quite often used as synonyms for the description of the selectivity obtained by a diastereoselective addition to a carbonyl group. The main concept of the Felkin-Anh transition state model is that the substituent L exhibiting an electron-withdrawing effect (independently of its steric bulk) is placed orthogonal to the carbonyl group, allowing the nucleophile to attack *anti* to L following a Dunitz-Bürgi trajectory,[216,217] thus most effectively avoiding steric repulsion.[218] Following this model, the azido group should be aligned *anti* to the forming bond due to stereoelectronic reasons (Figure 3.7). A nucleophile would now preferentially attack from the side of the small substituent H, leading to the so-called Felkin-Anh product.

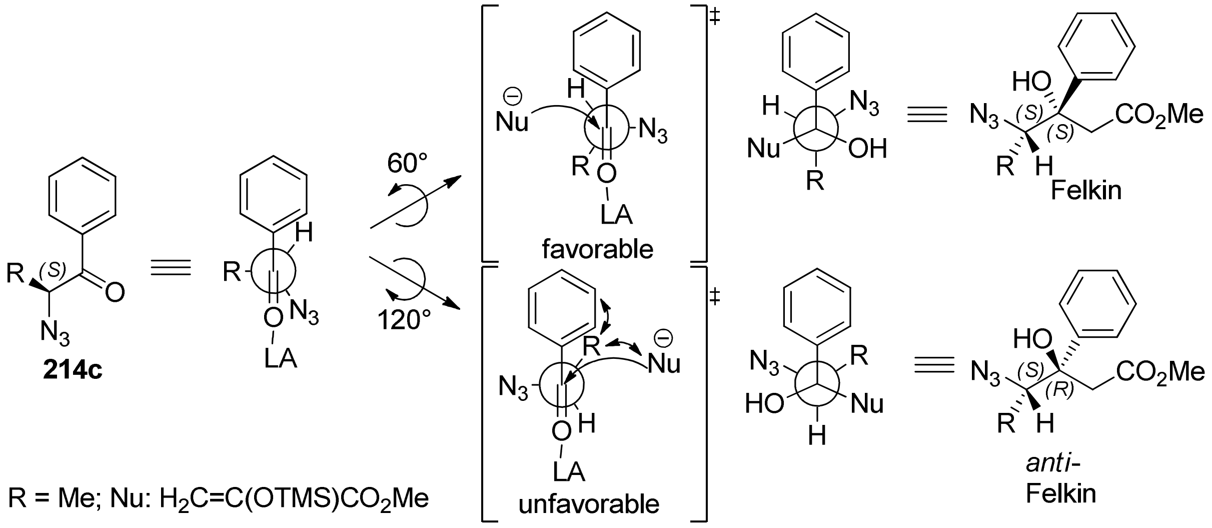


Figure 3.7. Felkin-Anh model for 1,2-assymetric induction applied to the synthesis of aldol product **214c**.[219]

The cases where the opposite selectivity is observed are called anit-Felkin-Anh selectivities or Cram chelate control. Our results are consistent with the Cram chelate control or the anti-Felkin-Anh model. A high level of *anti*-Felkin-diastereoselectivity was observed for β-hydroxy esters **216c** and **216d**. The relative configuration of the major diastereomer of **216c** was confirmed by X-ray analysis (Figure 3.8). The major diastereomer (*R*/*S*) was obtained in a diastereomeric ratio 90:10. The enhanced diastereoselectivity as observed for compound **216e** can be rationalized by taking into account the increased bulk of the isopropyl substituent. Compounds **216h** and **216i** showed an even higher (almost perfect) level of diastereoselectivity may be due to the presence of the *ortho* nitro group increasing the steric bulk and thereby increasing the allylic strain.

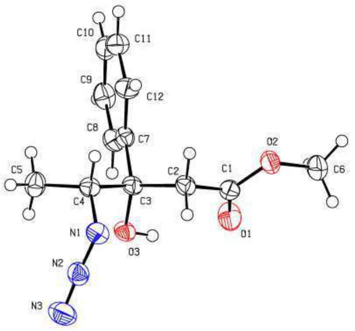


Figure 3.8. Anisotropic displacement ellipsoid plot of compound **216c** showing the relative (*S*,*R*) configuration.

These results are in accordance with the Cram chelate rule.[220-223] This model suggests the chelation between the carbonyl group and azido group facilitated by a Lewis acid. In this way, the substrate is locked into the chelated conformation (Figure 3.9). The remaining two substituents are placed on different sides of the carbonyl group. A nucleophile can attack the carbonyl group from the side of the small substituent H leading to the major product, which is generally called the Cram-chelate or *anti*-Felkin product.

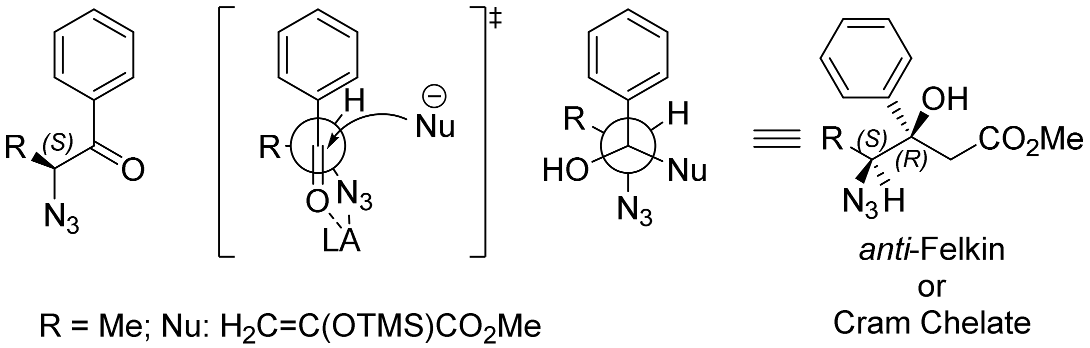


Figure 3.9. Cram chelate model for 1,2-assymetric induction applied to the synthesis of aldol product **214c**.[218,220]

Evidence of chelation might be accessible using specific NMR experiments. Complexing the α-azido ester with $TiCl_4$ the postulated interaction between nitrogen and titanium should be observable by ^{14}N NMR.

The next step for investigation was to test the feasibility of the previously described Staudinger-type reductive cyclisation involving the more sterically hindered β-hydroxy esters. The transformation first reported by Staudinger and Meyer[224] proceeds through a formation of iminophosphorane **282a** with concomitant loss of nitrogen (Figure 3.10).[225,226] This intermediate can undergo a number of reactions but in aqueous media it is hydrolysed to the amine and phosphane oxide.[225,227] Vaultier and co-workers[228,229] reported the synthesis of lactam from the azido esters which proceeds through a formation of the free amine **283** first followed by the nucleophilic attack on the carbonyl of the ester (Mechanism 1). However, iminophosphorane can react with the carbonyl electrophile to give intermediate **284**, especially if the electrophilic attack proceeds in an intramolecular fashion.[230-232] In this case the new amide bond is formed prior to hydrolysis (Mechanism 2).

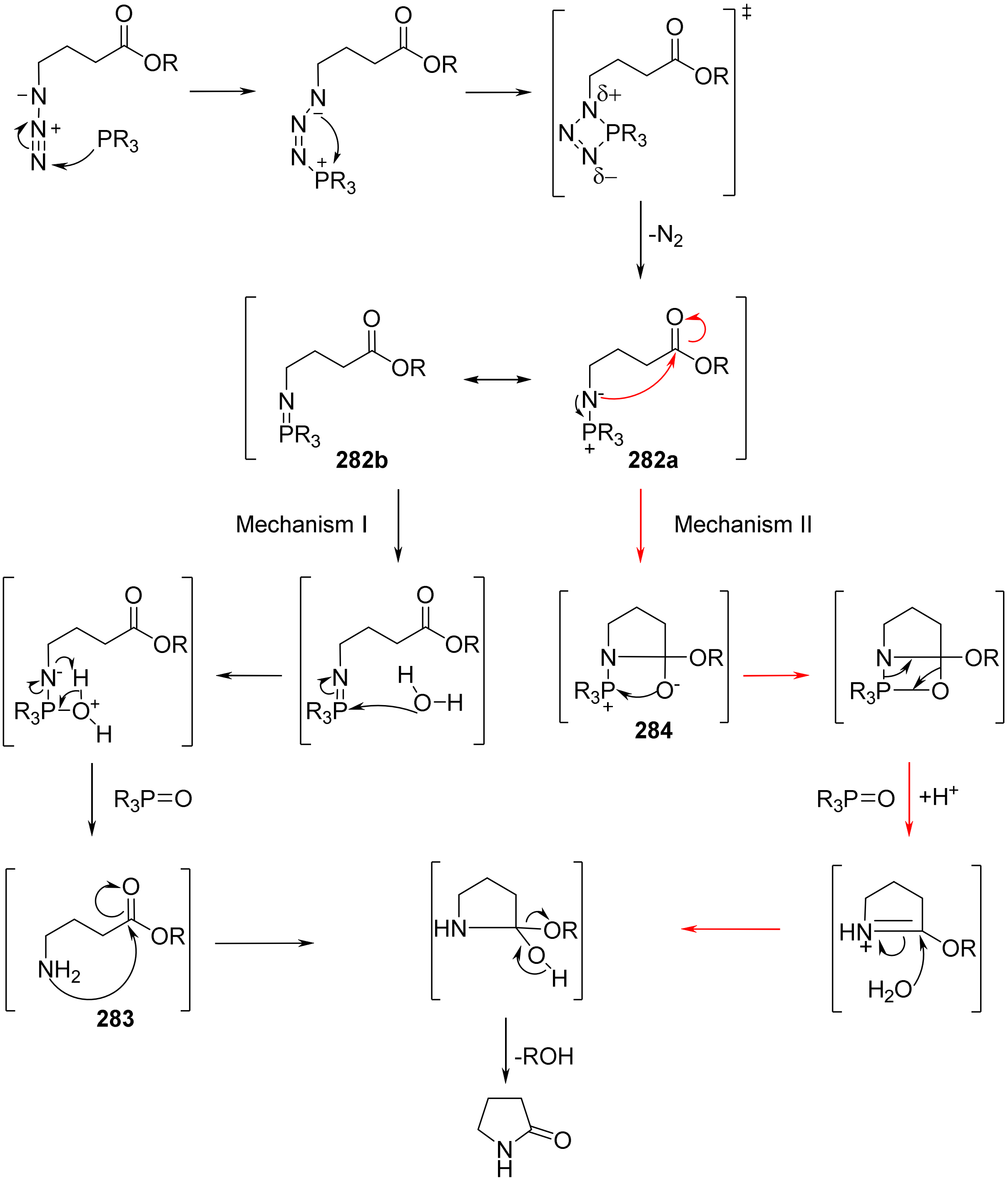
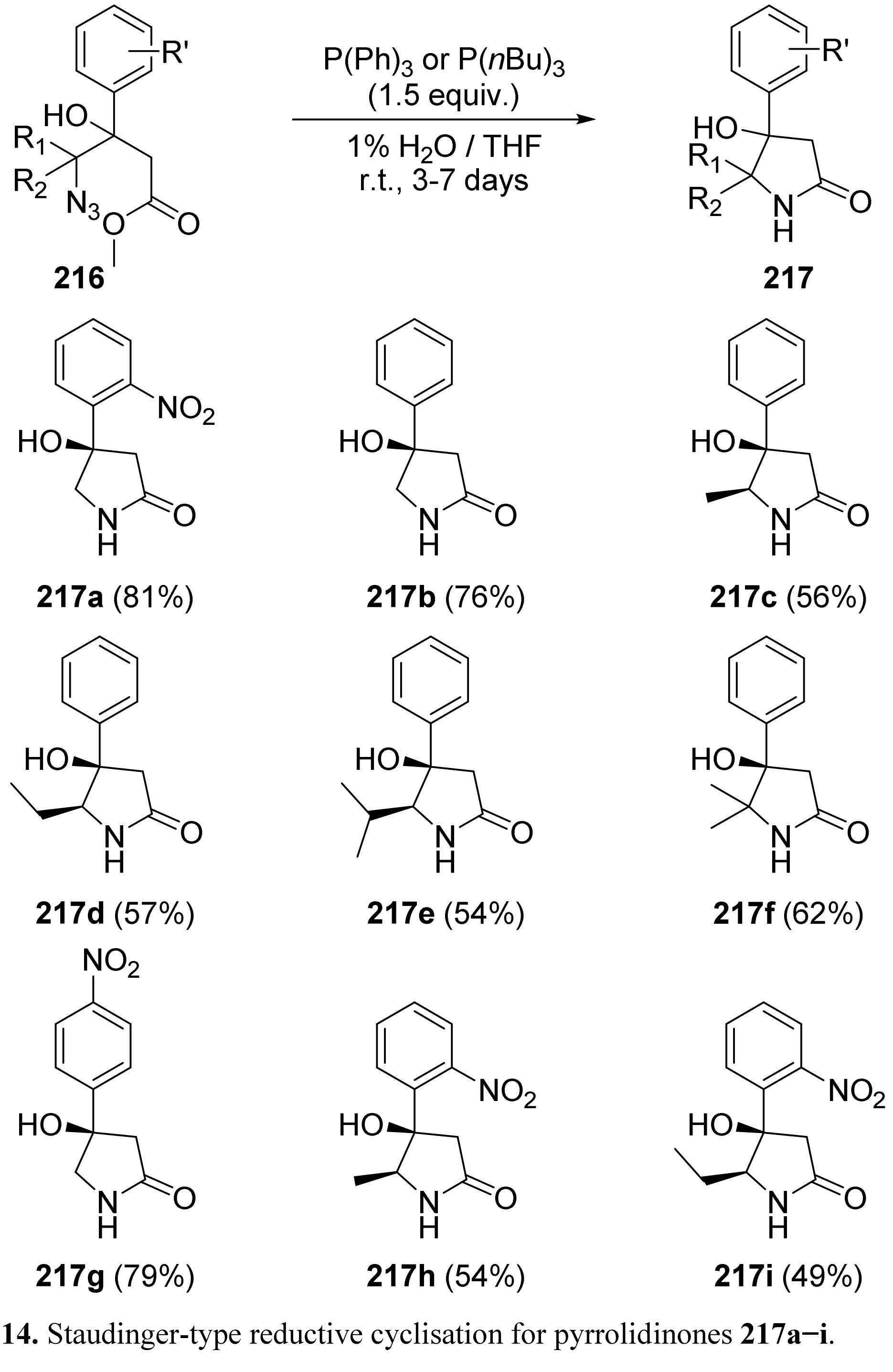


Figure 3.10. Plausible mechanisms of Staudinger-type reductive cyclisation.[229,232]

The preferred procedure used in our group this transformation involves a treatment of azido esters **216a–i** with 1.5 equiv. of triphenylphosphine (PPh_3) or tributylphosphine ($P(nBu)_3$) in THF in presence of 1% water. The choice of the phosphine was determined by the efficiency of the work-up which followed the reaction. Whilst the nitro-phenyl substituted products precipitated during the reaction with PPh_3 and could be purified by crystallization. Without the nitro group we could not purify the phenyl-substituted products by simple crystallization.

Purification had to be done by flash chromatography on silica gel. Triphenylphosphine oxide notoriously creates major problems in this type of separation and the product contaminated with the phosphine oxide was obtained. Changing PPh_3 to $P(nBu)_3$, the phenyl substituted products were obtained in good yields after chromatography due to the water solubility of the tributylphosphine oxide (Scheme 14).



216

217

217a (81%)
217b (76%)
217c (56%)
217d (57%)
217e (54%)
217f (62%)
217g (79%)
217h (54%)
217i (49%)

Scheme 3.14. Staudinger-type reductive cyclisation for pyrrolidinones **217a–i**.

Table 3.1. Reaction conditions for Staudinger-type reductive cyclisation.

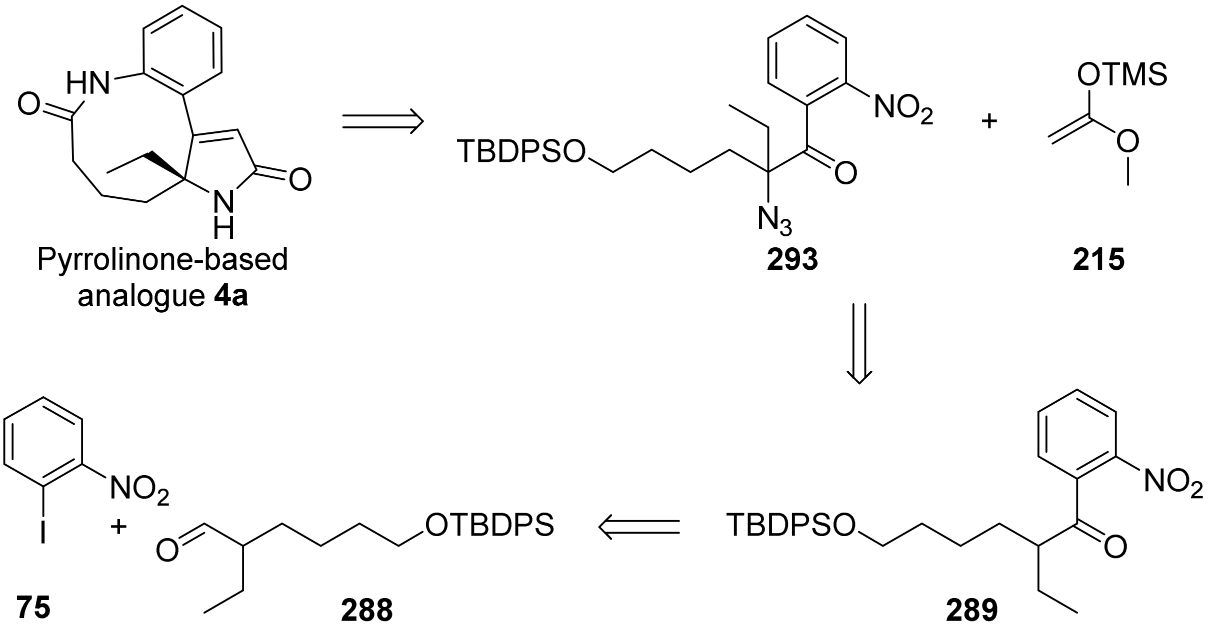
Entry	Azido ester	Phosphine	Time [days]	Product	Yield [%]
1	**216a**	P(Ph)$_{33}$	3	**217a**	81
2	**216b**	P(nBu)$_3$	3	**217b**	76
3	**216c**	P(nBu)$_3$	3	**217c**	56
4	**216d**	P(nBu)$_3$	3	**217d**	57
5	**216e**	P(nBu)$_3$	6	**217e**	54
6	**216f**	P(nBu)$_3$	4	**217f**	62
7	**216g**	P(Ph)$_3$	7	**217g**	79
8	**216h**	P(Ph)$_3$	6	**217h**	54
9	**216i**	P(Ph)$_3$	7	**217i**	49

We were able to obtain the X-ray structures of the new compounds **217c–h** which confirmed the structure attribution. The major diastereomers have *R*/*S* relative configuration (see Appendix).

While the reaction time was much longer than in the cases studied before, all products were obtained in good to satisfactory yields. The following observations can be made. The steric hindrance on the azido esters diminished the yields (Table 3.1, Entry 3-6 and 8-9). Monitoring by TLC showed a very slow progress of the reaction. The comparison between the yields of the products **217c** and **217h** or **217d** and **217i** (Entry 3, 8 and 4, 9) with similar steric bulk, led to the conclusion that extending reaction times would not be an effective solution to increase the yield. However, the given strategy allowed synthesizing a variety of highly substituted pyrrolidinones.

3.2.4. Synthesis of intermediate 290

These results demonstrated that even the azido ketones with bulky substituents in α to carbonyl can be subjected to the tandem Mukaiyama cross-aldol – Staudinger cyclization sequences giving access to highly substituted pyrrolidinones. The next logical step was to obtain a cyclisation precursor containing all atoms necessary to the construction of pyrrolinone-based rhazinilam analogues (Scheme 3.15). The route previously described for the synthesis of *ortho*-nitro substituted phenyl ketones should be used to form the intermediate **289**, followed by investigations of bromination in the α-position to the ketone, substitution of the bromine with azide and tandem Mukaiyama aldol reaction – Staudinger reductive cyclisation. This approach seemed attractive as the majority of the route was well developed, and the bromination and substitution with azide were expected to be standard transformation, allowing focusing the attention on the critical azido ester formation-cyclisation step.

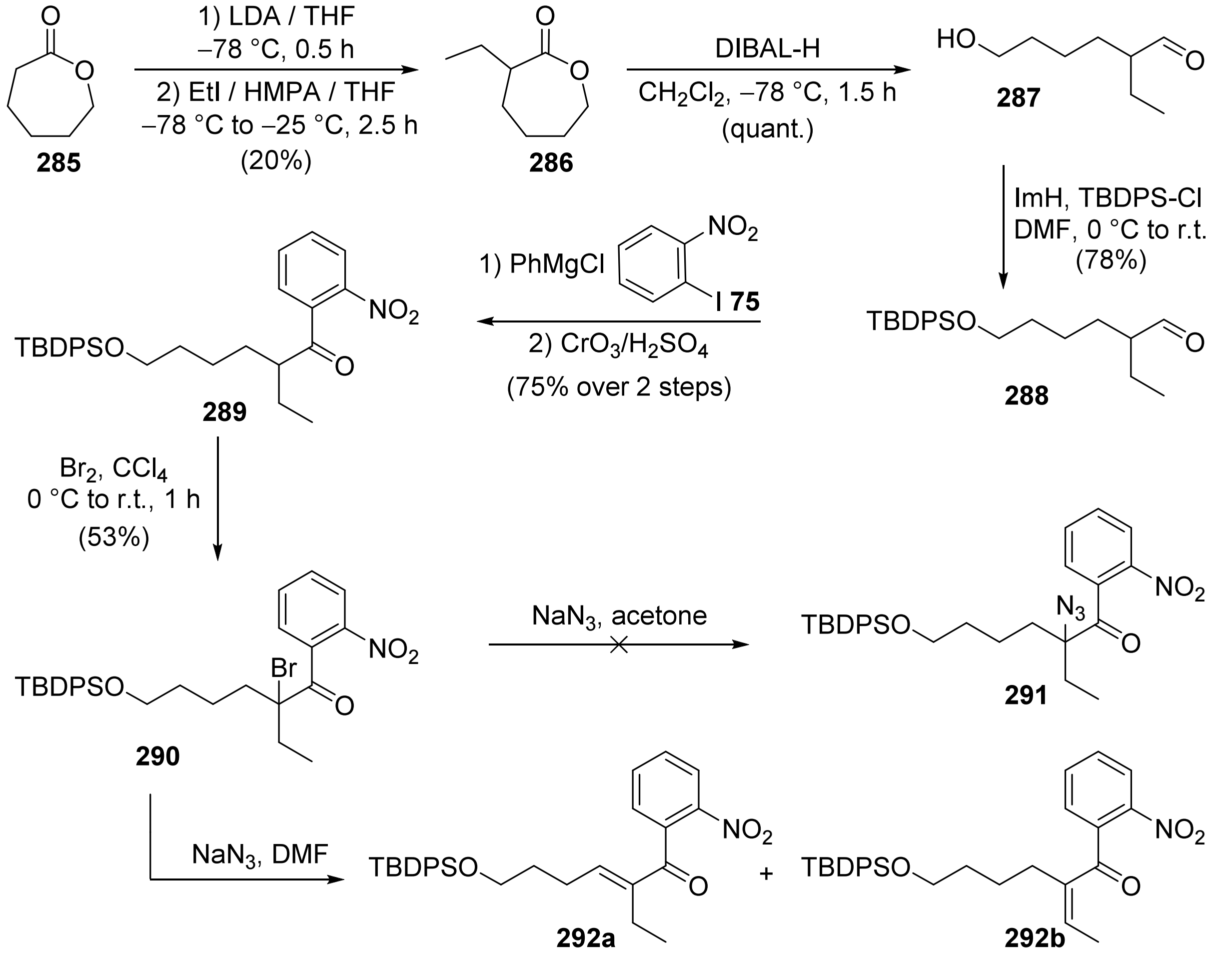


Scheme 3.15. Retrosynthetic pathway for the synthesis of pyrrolinone-based analogue **4a**.

The route began with the preparation of 2-ethyl ε-caprolactone (**286**) by alkylation of ε-caprolactone (**285**) with ethyl iodide using procedure defined by Nicolaou and co-workers[233] (Scheme 3.16). Subjecting the lactone **286** to DIBAL reduction followed by silylation afforded the aldehyde **288** in 78% overall yield. Treatment of aldehyde **288** with the Grignard reagent generated *in situ* from 2-iodonitrobenzene (**75**) by I-Mg exchange[182] and subsequent oxidation with Jones' reagent give the corresponding ketone **289** in 75% overall yield.

Bromination of **289** using aforementioned conditions produced the α-bromo ketone **290** in 53% yield. The challenge, then, was to form the α-azido ketone **291**. The previous approach using sodium azide in acetone was tried, but no reaction was observed under these conditions after 24 h and only the starting material was recovered. The reaction was repeated in DMF. After 2 h at room temperature, no conversion was detected by ^{1}H NMR and the reaction mixture was allowed to stir at room temperature overnight. However, only the product of the unwanted bromo elimination **292a** and **292b** were recovered in 1:2 ratio and 86% overall yield.

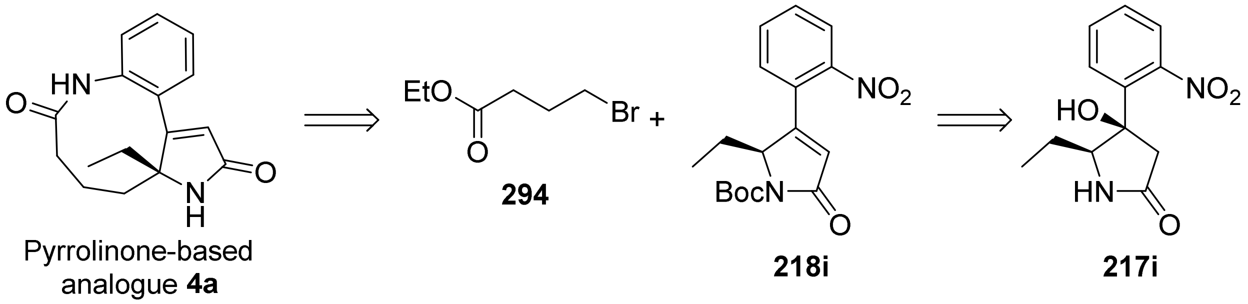
This result demonstrated that in DMF elimination is favoured. Other reaction conditions have to be tried (e.g. changing the solvent and the temperature) hopefully giving preference to the substitution. Due to time reasons the transformation of α-bromo ketone **290** into the corresponding α-azido ketone **291** was not investigated further.



Scheme 3.16. Attempted synthesis of azido ketone **291**.

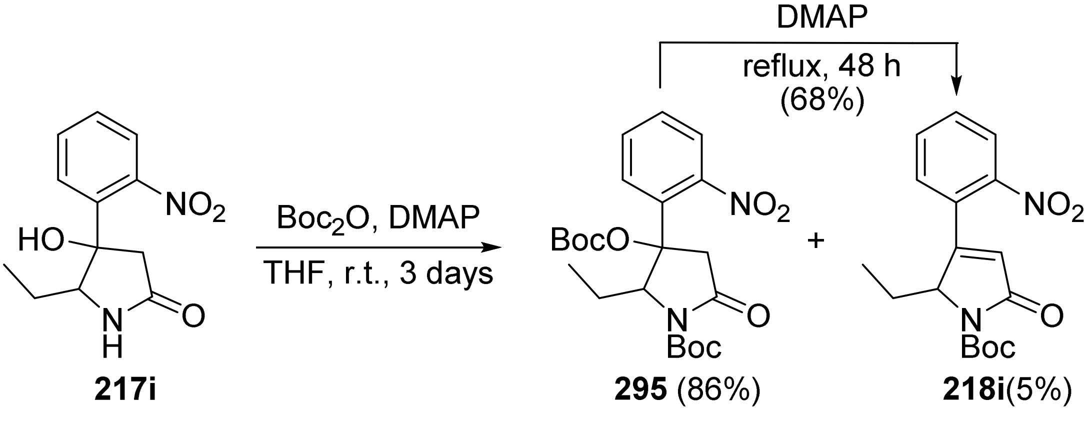
3.2.5. Dehydration of pyrrolidinone 217i

An alternative approach to pyrrolinone-based analogue **4a** was envisaged *via* the reaction of activated pyrrolinone **296** with the bromoester **294** by an alkylation followed by subsequent macrolactamisation (Scheme 3.17). Intermediate **296** should be obtained from **217i** by hydroxy group elimination.



Scheme 3.17. Retrosynthetic pathway for the synthesis of analogue **4a** via intermediate **218i**.

The previous research demonstrated that pyrrolidinone **217a** and **217b**[103] can be converted into 3-pyrrolin-2-one **218a** and **218b** at room temperature by hydroxy group elimination using 2.1 equiv. of Boc_2O and 0.4 equiv. of DMAP (Scheme 2.2). The reaction times were 2 h for nitrophenyl substituted pyrrolidinone and 24 h for its phenyl analogue. These conditions were applied to the pyrrolidinone **217i** (Scheme 3.18). However, the major product which was recovered in 86% yield after 3 days was a di-boc substituted pyrrolidinones **295**. Only a minor amount (5 % from ^1H NMR analysis of the crude mixture) of hydroxyl-elimination product **218i** was recovered.

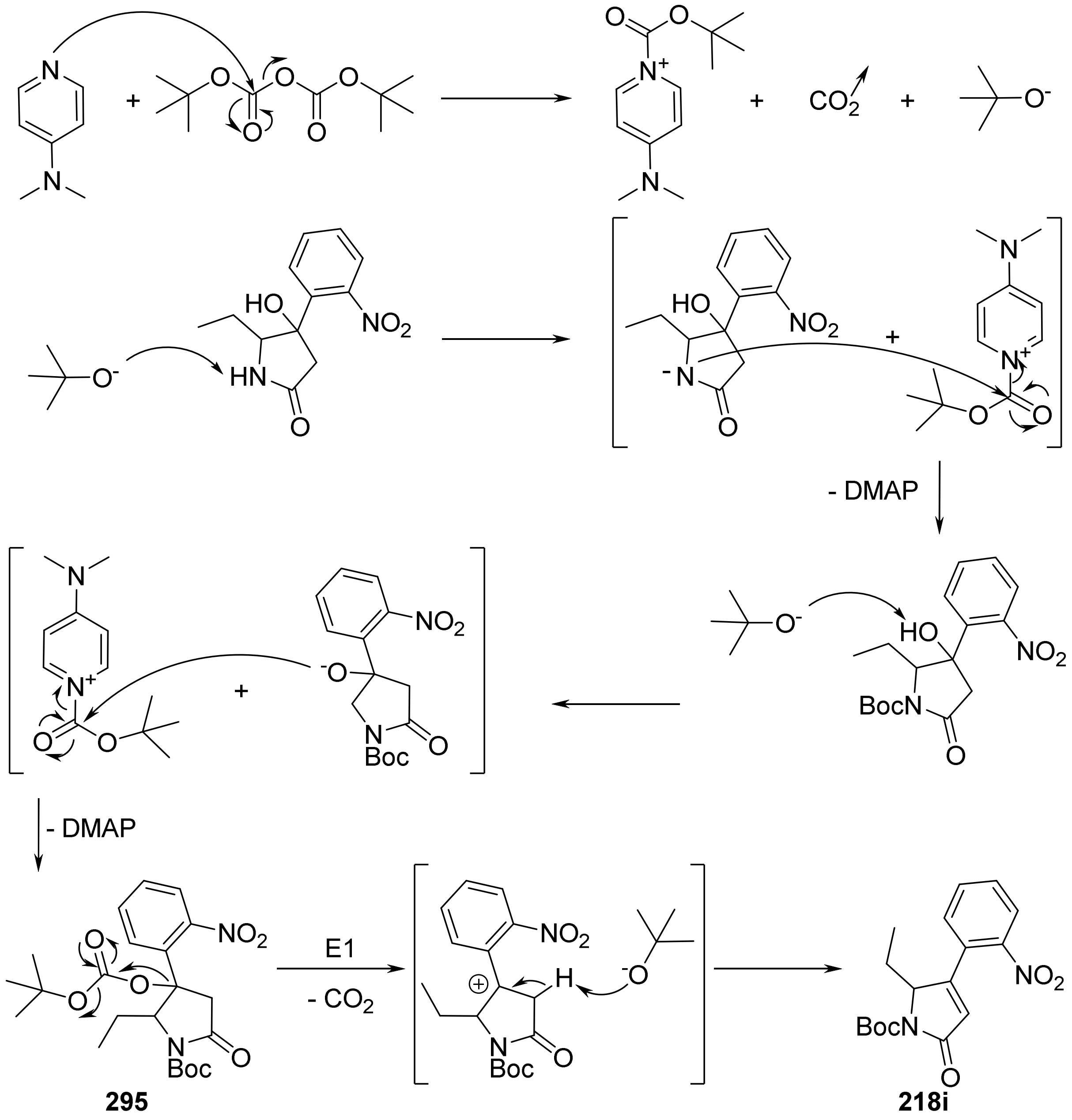


Scheme 3.18. Synthesis of 3-pyrrolin-2-one **218i**.

In an attempt to accelerate the elimination the temperature was increased. Heating the pyrrolidinone **295** under reflux in the presence of 0.5 equiv. of DMAP afforded 70% conversion to 3-pyrroline-2-one **218i** after 48 hours. The separation by column chromatography of the product **218i** from the unreacted compound **295** proved to be difficult. Product **295** was isolated and fully characterized whereas **218i** was partially characterized using the best fractions from the column.

The formation of compounds **295** and **218i** could be explained by the mechanism of Boc-protection and tertiary alcohol elimination (Scheme 3.19). DMAP plays a dual role in this process: generates the more reactive specie reacting with Boc_2O and releases the *tert*-butanoate allowing the deprotonation of amide and hydroxyl groups. This previous study[100] suggests that the first step is the *N*-bocylation followed by the *O*-bocylation. Ethyl substituent in α to hydroxy could make the *O*-bocylation more difficult due to the steric hindrance. However, this process takes place and the di-boc intermediate **295** is isolated in excellent yield. The elimination of carbonate should be a crucial step for formation of 3-pyrrolin2-one **218i**. The structure of di-boc protected pyrrolidinone **295** was confirmed by X-Ray analysis (Figure 3.11).

Carbonate is not a good leaving group. Nevertheless, this process must be irreversible and thermodynamically favoured due to CO_2 removal from the reaction mixture. Moreover, the *tert*-butyl carbonate group is bulky and induces an important steric hindrance on a quaternary carbon. The loss of carbonate results in the formation of stable carbocation. From these points of view the mechanism E1 should be favoured. However, without heating, the desired product was observed in insignificant yield. This is possibly due to the increased substitution of compound **217i** when compared to previous alcohol intermediates **217a** prepared in the group. The increased steric hindrance surrounding the hydroxyl group may lead to the observed lower reaction rates.



Scheme 3.19. Proposed mechanism of Boc-protection and elimination.

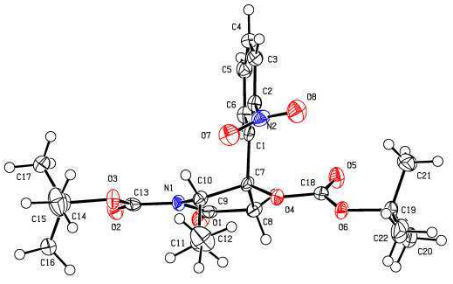


Figure 3.11. Anisotropic displacement ellipsoid plot of compound **295**.

3.3. Summery.

In summary, this project achieved the aims proposed at the outset. Two key transformations were investigated using the sterically hindered starting materials. First, a $TiCl_4$ promoted Mukaiyama crossed aldol addition of silyl ketene acetal to α-substituted azidoketones was employed to produce a library of aldol products with considerable diastereoselectivity. The modified reaction conditions afforded these products in improved yields. The bulky substituent in α to carbonyl seems to have a relatively small impact on the reaction outcome. Second, the Staudinger reductive cyclization was a critical step in the formation of the highly substituted lactam rings present in the target compounds. Bulkier substituents bearing the azido group have a slightly negative impact on this transformation.

Unfortunately, due to time constraints, it was not possible to continue the investigation of the project beyond this point. The procedure for preparation of sterically hindered ketones possessing a fully substituted carbon in the α-position and tandem Mukaiyama aldol – Staudinger reaction sequences could be applied to the synthesis of advanced intermediates. The investigations of the elimination of the tertiary alcohol proofed the optimization of the reaction conditions are crucial. Optimization of the steps needed for the formation of the desired 3-pyrrolin-2-ones has not been achieved yet.

Chapter four

CONCLUSIONS

Conclusions

In summary, this research programme consisted of two distinct projects, which will be considered in turn below.

The aim of the first project was a synthesis of advanced intermediates of rhazinilam analogues. The retrosynthetic approach focused on the synthesis of the heterobiarylic core, attaching the chains and functional groups needed for the formation of rings B and D in a later stage. Building on the known sensitivity of pyrrole rings lacking electronic or steric stabilization, the synthetic intermediates were designed to contain at least one stabilizing element: either the well-known methoxycarbonyl ester group or the novel pyrrolinone element.

The *N*-alkylation and *N*-acylation of the 3-pyrrolin-2-ones derivatives, as discussed above, received a particular attention. Thus, the intramolecular Michael addition of activated pyrrolinone to *N*-tethered acrylate was envisaged in order to obtain the indolizine–type cyclisation product. Starting from the previously described Staudinger cyclisation product, *N*-acylation and *N*-alkylation were applied towards the synthesis of a model system. Under the conditions reported in the literature and under the conditions tested in our laboratory, the introduction of a side chain on 3-pyrroline-2-one by nucleophilic *N*-alkylation could not be achieved. In contrast, the use of more nucleophilic aryl-pyrrole synthesized for this proposal from a simple pyrrole nucleus by a metal-catalysed C-H bond arylation afforded the desired *N*-alkylated biaryl intermediate.

Given the poor nucleophilic nature of 3-pyrrolin-2-one substrate, the *N*-acylation was investigated instead of the *N*-alkylation on the model series involving sterically less demanding substrates. The optimized conditions were then successfully applied to the more complex aryl-3-pyrroline-2-one.

Whilst this project achieved its primary aims and two advanced intermediates were obtained for the further synthesis of the pyrrole or pyrrolinone based rhazinilam analogues there are a number of avenues that could be investigated. The screening of the reaction conditions needed for the formation of the desired Michael products has not been achieved yet.

The aim of the second project was to expand the scope of the tandem Mukaiyama cross aldol − Staudinger reaction to the preparation of highly substituted phenyl-pyrrolinones having a blocking group at the C-5. The attractivity of this approach was the synthesis of chemically stable intermediates which not undergo the further oxidation process and undesirable side reactions.

There are several attractive facets of the developed methodology. Two key transformations were investigated using the sterically hindered starting materials. Whilst, the bulky substituent in α to carbonyl seems to have a relatively small impact on the Mukaiyama reaction outcome, the Staudinger reductive cyclization was a critical step. Bulkier substituents bearing the azido group had a slightly negative impact on this transformation. However, an important library of highly substituted pyrrolidinones with considerable diastereoselectivity was prepared.

In addition, an efficient methodology for the synthesis of *ortho*-nitro phenyl substituted ketones with long alkyl chain was developed. Moreover, the modified reaction conditions for bromination and subsequent substitution offers improved yields, fewer synthetic manipulations, and compared to previous work are advantageous in terms of time economy.

Finally, the procedure for preparation of sterically hindered ketones possessing a fully substituted carbon in the α-position and tandem Mukaiyama aldol – Staudinger reaction sequences could be applied to the synthesis of advanced intermediates. The investigations of the elimination of the tertiary alcohol proofed the optimization of the reaction conditions are crucial. Optimization of the steps needed for the formation of the desired 3-pyrrolin-2-ones has not been achieved yet.

Chapter five

EXPERIMENTAL SECTION

5.1. General Remarks

Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen or argon.

5.1.1. Chromatography

Thin layer chromatography

Thin layer chromatography (TLC) was conducted on glass-backed 0.2 mm thick silica-gel plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with a potassium permanganate dip (2.5 g $KMnO_4$, 2.5 g K_2CO_3, 250 mL water) or a Ehrlich reagent dip (2 g dimethylaminoacetaldehyde, 20 mL perchloric acid diluted to 50 mL with acetic acid) followed by heating. All mixed solvent systems were reported as v/v solutions. The retardation factor (Rf) quoted is rounded to the nearest 0.1.

Column chromatography

Flash column chromatography was performed on silica gel silica gel (Silica 32-63, 60 Å; Chemie Brunschwig AG, Basel, Switzerland) as the stationary phase in conjunction with the analytical reagent (AR) grade solvents indicated.

Gas chromatography

Gas chromatography (GC) was performed on Agilent 6850 Series chromatograph using high resolution gas chromatography HP-5 column (30 m × 0.32 mm × 0.25 μm). Polymer nature: polysiloxane (crosslinked 5% Ph, Me siloxane), gas vecteur : He, 1.1 mL/min. Injection temperature : 245 °C, detector temperature (FID) : 300 °C. The two following temperature programs were employed: 1) IZ: 100 °C (3 min)/ 15 °C/min/ 280 °C/ 280 °C (4 min); 2) AG: 220 °C (2 min)/ 5 °C/min/ 300 °C/ 300 °C (10 min). Spectra were treated by ChemStation program.

5.1.2. Infrared Spectroscopy (IR)

Infrared spectra were obtained with a Perkin–Elmer Spectrum One version B FT-IR unit with the resolution of 2 cm^{-1}. Software used: Spectrum version 5.0.1. The solid substances and thick oil like substances were analysed by KBr (Fluka puriss., p.a.) pressed films. Liquid samples were analysed using KBr plates. The absorption bands between 4000 and 400 cm^{-1} were measured. Absorption maxima (υ_{max}) are reported in wave numbers (cm^{-1}). The intensity of spectrum was divided into five equal parts for the abbreviations *vs* (very strong – the maximum intensity), *s* (strong), *m* (medium), *w* (weak), *vw* (very weak) and *br* (broad).

5.1.3. Nuclear Magnetic Spectroscopy (NMR)

All reported NMR spectra were recorded on Bruker Avance-400 spectrometer at 400 (^{1}H NMR), 376 (^{19}F NMR) or 100 (^{13}C NMR) at 298 K. The NMR solvents were purchased from Cambridge Isotope Laboratories. Chemical shifts are reported as δ values relative to TMS, defined as δ = 0.00 ppm (^{1}H NMR) or δ = 0.0 ppm (^{13}C NMR) and are referenced to the risidual protonated NMR solvent, defined as δ = 7.26 ppm (^{1}H NMR) or δ = 77.00 ppm (^{13}C NMR) for $CHCl_3$, δ = 3.31 ppm (^{1}H NMR) or δ = 49.00 ppm (^{13}C NMR) for CH_3OH, δ = 2.50 ppm (^{1}H NMR) or δ = 39.52 ppm (^{13}C NMR) for DMSO-d_6, δ = 2.05 ppm (^{1}H NMR) or δ = 29.84 and 206.26 ppm (^{13}C NMR) for acetone-d_6. The ^{13}C spactra were measured by decoupling from ^{1}H. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, number of protons, coupling constant(s) *J* (Hz) and assignment (where possible)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; br = broad; m = multiplet or combinations of the above. The sign "≈" denotes for the average value of *J* varying from 0.2 to 0.4 Hz.

5.1.4. Mass Sectrometry

GC-MS analyses were performed by EI (electron impact) (70 eV) on a ThermoFinnigan PolarisQ instrument equipped with a Trace GC gas chromatograph and PolarisQ mass spectrometer. Software used : *X*calibur version 1.2. The following temperature program was employed: 60 °C (1min)/ 10 °C/min/ 250 °C/ 250 °C (60 min). The mass spectra for ESI (electro-spray ionisation) or APCI (atmospheric pressure chemical ionisation) were recorded on a ThermoFinnigan LCQ instrument (San Jose, California, USA). Software: Tune Plus version 1.2. The values given are average mass of ion with precision of ±0.1. The nature of ion pattern is specified in parentheses with intensity. Only the mass corresponding to the highest abundant isotope is indicated.

The high resolution mass spectrometry (HR-MS) was made at University of Fribourg (Switzerland) in the group of Professor Gossauer and recorded on a Brücker BioAPEX II Daltonics instrument by ESI unless otherwise specified.

5.1.5. Glass Apparatus

For reactions under inert atmosphere (Ar or N_2), the glass apparatus were oven-dried at 150 °C for at least 2 h. The apparatus were assembled and cooled to ambient temperature under Ar or N_2 atmosphere. For reactions at low temperature, salt – ice bath (0 °C to –10 °C) and acetone/liquid nitrogen bath (down to –80 °C) were used. For extended periods of low temperature reactions (2 days), cryostat was used. For heating reactions, polyethylene glycol (PEG) bath was used. The reaction temperatures were measured *in situ*.

5.1.6. Melting points

Melting points were determined in open capillaries with a Gallenkamp melting point apparatus without correction.

5.1.7. Elemental analysis

The elemental analyses (CHN) were made at ETH Zurich (Switzerland) in the group of Professor Pretsch.

5.1.8. Solvents

Standard solvents

For the purpose of chromatography and extractions, technical grade solvents were distilled over drying agent.

Solvent	Abbreviation used	Drying agent
Chloroform	$CHCl_3$	$CaCl_2$
Cyclohexane	Cyclohexane	Molecular sieve 0.4nm
Dichloromethane	CH_2Cl_2	$CaCl_2$
Diethyl ether	Et_2O	$CaCl_2$
Ethyl acetate	AcOEt	K_2CO_3
Hexane	Hexane	$CaCl_2$
Methanol	MeOH	CaO
Petrolium ether	Petrolium ether	$CaCl_2$

Solvents for reactions with distillation

Solvent	Abbreviation used	Drying agent
Carbon tetrachloride	CCl_4	P_2O_3
Dichloromethane	CH_2Cl_2	P_2O_5
Diethyl ether	Et_2O	$LiAlH_4$
Pentane	Pentane	P_2O_5
Tetrahydrofuran	THF	Sodium (benzophenone)

Solvents for reactions without distillation

Solvent	Abbreviation used	Quality
Acetic acid glacial	AcOH	Carlo Erba, for analysis
Acetone	Acetone	Aldrich, CHROMASOLV ® Plus, for HPLC, ≥99.9%
Acetonitrile	ACN	Aldrich, sealed-bottle over molecular sieve (H_2O ≤0.01%), ≥99.5% (GC).
n-Butanol	*n*BuOH	Aldrich, anhydrous, 99.8%
Chloroform	$CHCl_3$	Aldrich, anhydrous, contains amylenes as stabilizer, ≥99%
Dichloromethane	CH_2Cl_2	Acros, 99.8%, extra dry over molecular sieve
1,2-Dimethoxyethane	DME	Aldrich, puriss., dried over molecular sieve (H2O ≤0.005%), ≥99.5% (GC)
Dimethyl formamide	DMF	Aldrich, puriss., absolute, over molecular sieve (H_2O ≤0.005%), ≥99.5% (GC)
Dimethyl sulfoxyde	DMSO	Aldrich, puriss., absolute, over

		molecular sieve (H_2O ≤0.01%), ≥99.5% (GC)
Isopropanol	^{i}PrOH	Aldrichanhydrous, 99.5%
Methanol	MeOH	Fluka, puriss. abs., ≥99.5% over molecular sieve (H_2O ≤0.01%)
Pyridine	Pyridine	Fluka, puriss., ≥99.5% (with crown cap)
Tetrahydrofuran	THF	Aldrich, sealed-bottle over molecular sieve (H_2O ≤0.005%), contains ~0.025% 2,6-di-tert-butyl-4- methylphenol as stabilizer, ≥99.5% (GC)
Toluene	Toluene	Aldrich, absolute, over molecular sieve (H_2O ≤0.005%), ≥99.7% (GC)

5.1.9. Reagents and products

Reagents

Reagent	Abbreviation used	Quality
Aluminium chloride	$AlCl_3$	Fluka, puriss. p.a.99%
Ammonium carbonate	$(NH_4)_2CO_3$	Acros
Ammonium chloride	NH_4Cl	Fluka, purum p.a.
Argon	Ar	Carbagas, tech.
Bis(acetonitrile) dichloropalladium(II)	$PdCl_2(CH_3CN)_2$	Aldrich, 99%
Boron trifluoride diethyl etherate	$BF_3 \cdot OEt_2$	Fluka, purum
Bromine	Br_2	Acros p.a.
2-Bromoacetophenone	–	Fluka, puriss >99.0%
2-Bromoisobutyrophenone	–	Aldrich, 98%
2-Bromo-2'-nitroacetophenone	–	Aldrich, 99%
2-Bromo-4′-nitroacetophenone	–	Aldrich, 95%
1-Bromo-2-nitrobenzene	–	Aldrich, 98%
2-Bromopropiophenone	–	Aldrich, 97%
3-Bromo-1(triisopropysilyl)pyrrole	–	Aldrich, 97%
tert-Butyldimethylsilyl trifluoromethanesulfonate	TBSOTf	Acros, 98%
tert-Butyldiphenylsilyl chloride	TBDPS-Cl	Aldrich, 98%
n-Butyllithium solution	*n*BuLi	Aldrich, 2.0 M in cyclohexane
Butyraldehyde	–	Aldrich, ≥99.0%, dry

γ-Butyrolactone	–	Aldrich, ≥99%
Butyrophenone	–	Aldrich, ≥99%
ε-Caprolactone	–	Aldrich, 97%
Celite 535	–	Fluka, 10-40mm
Chlorotrimethylsilane	TMSCl	Fluka, puriss., ≥99.0% (GC)
Chromium (VI) oxide	CrO_3	Fluka, purum p.a., ≥99.0% (RT)
1,5-Cyclooctadiene(methoxy)iridium(I) dimer	$[Ir(OMe)(COD)]_2$	Aldrich
N,N′-Dicyclohexylcarbodiimide	DCC	Fluka, puriss., ≥99.0% (GC)
2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl	SPhos	Aldrich, 97%
Diisobutylaluminum hydride solution	DIBALH	Acros, 1.0 M in hexane
Dimethyl sulfoxyde	DMSO	Aldrich, anhydrous, ≥99.9
Dimethylaluminum chloride	Me_2AlCl	Aldrich, 1.0 M in hexanes
4-(Dimethylamino)pyridine	DMAP	Fluka, purum >98%
N,*O*-Dimethylhydroxylamine hydrochloride	HN(OMe)·HCl	Aldrich, 98%
Di-*tert*-butyl dicarbonate	Boc_2O	Acros, 99%
4,4'-Di-*tert*-butyl-2,2'-dipyridine	dtbpy	Aldrich, 98%
Ethylmagnesium bromide	EtMgBr	Aldrich, 1.0 M in THF
Hexamethylphosphoramide	HMPA	Aldrich, absolute, over molecular sieve (H2O ≤0.01%), ≥98.0%
Hydrochloric acid	HCl	Prochimie, 32%
Imidazole	ImH	Fluka, puriss.., ≥99%
Iodoethane	EtI	Aldrich, 99%
1-Iodo-2-nitrobenzene	–	Aldrich, 97%
Isovalerophenone	–	Aldrich, ≥98.0% (GC)
Levulinic acid	–	Aldrich, 98%
Lithium bis(trimethylsilyl)amide solution	LHMDS	Alldrich, 1.0 M in THF
Lithium diisopropylamide	LDA	Aldrich, 2.0 M in THF
2,6-Lutidine	–	Fluka, puriss p.a. >99.7
Magnesium sulfate	$MgSO_4$	Aldrich, puriss. p.a., drying agent, anhydrous, ≥98.0% (KT), powder (very fine)
Methyl 2-pyrrolecarboxylate	–	Aldrich, 97%
Methyl acetate	–	Fluka, puriss p.a. >99%
Methyl diethylphosphonoacetate	$(EtO)_2POCH_2CO_2Me$	Aldrich, 97%

Molecular sieve 4A	–	Fluka, powder
2'-Nitroacetophenone	–	Aldrich, 95%
Nitogen	N_2	Carbagas, tech.
Nitric acid	HNO_3	Fluka, fuming >99.5%
Palladium(II) acetate	$Pd(OAc)_2$	Fluka, 98%
Pentafluorophenol	PfpOH	Aldrich, ≥99%
Phenylmagnesium chloride	PhMgCl	Aldrich, 2.0 M in THF
Pinacolborane	HBpin	Aldrich, 97%
Poly(4-vinylpyridine)	–	Fluka, purum
Potassium	K	Fluka, purum
Potassium carbonate	K_2CO_3	Fluka, purum p.a., anhydrous, ≥99.0%
Potassium phosphate	K_3PO_4	Aldrich, 97%
Propionaldehyde	–	Aldrich, ≥97%
p-Toluenesulfonyl chloride	Ts-Cl	Fluka, puriss.
Sodium azide	NaN_3	Fluka, purum ≥ 99.0%
Sodium carbonate	$NaCO_3$	Fluka
Sodium chloride	NaCl	Prochimie
Sodium dihydrogen phosphate	NaH_2PO_4	Fluka, purum, ≥99%
Sodium hydride	NaH	Aldrich, dry, 95%
Sodium hydrogen carbonate	$NaHCO_3$	Fluka, purum p.a., ≥99.0%
Sodium hydroxyde	NaOH	Fluka, puriss., p.a.
Sodium iodide	NaI	Fluka, purum p.a., ≥99.0%
Sodium sulfate	Na_2SO_4	Fluka, anhydrous, powder
Sodium thiosulfate	$Na_2S_2O_3$	Aldrich, purum p.a., anhydrous, ≥98.0% (RT)
Sulfuric acid	H_2SO_4	Prochimie, 96%
Tetrabutylammonium floride	TBAF	Fluka, 1.0 M in THF
Titanium tetrachloride	$TiCl_4$	Fluka, purum, ≥98.0% and then distilled over poly vinyl pyridine
Tributyl phosphine	$P(nBu)_3$	Fluka, techn. >99%
Triethyl phosphonoacetate	$(EtO)_2POCH_2CO_2Et$	Aldrich, 98%
Triethylamine	Et_3N	Fluka, puriss. p.a. ≥99.5%
Trifluoroacetic acid	TFA	Fluka, puriss p.a. >99%
Triphenylphosphine	PPh_3	Fluka, puriss. ≥98.5 %
Zinc	Zn	Fluka, p.a. > 99.0%

Destruction of sodium azide

All the aqueous phases coming from the extraction of azido products and containing NaN_3 were stored separately for treating the solution with freshly prepared nitrous acid and then were discarded.

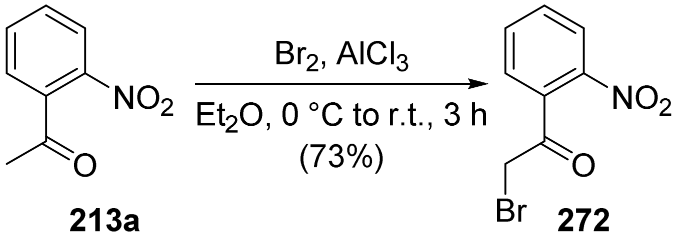
$$2\ NaNO_2 + H_2SO_4 \rightarrow 2\ HNO_2 + Na_2SO_4$$

$$2\ NaN_3 + 2\ HNO_2 \rightarrow 3N_2 + 2\ NO + 2\ NaOH$$

Treatment: The treatment is performed in a hood due to the formation of nitric oxide. The aqueous solution containing NaN_3 was put into a three-necked flask equiped a stirrer, a dropping funnel, and an outlet for gas. The sodium nitrite aqueous solution (7.5 g of $NaNO_2$ in 38 mL of water for 5 g of NaN_3) was added dropwise under vigorous stirring, followed by a slow addition of 20% H_2SO_4 until the reaction mixture is acidic to pH paper. When the evolution of nitrogen oxides is over, the acidic solution was tested with starch-iodide paper. The color change from white to blue means that excess nitrite is present and decomposition is complete. The solution was neutralized with dilute NaOH solution to pH 6-9 prior to discharge and was washed down the drain.

5.2. Experimental procedures and characterization data associated with compounds described in Chapter Two

5.2.1. 2-Bromo-1-(2-nitrophenyl)ethanone (272a)

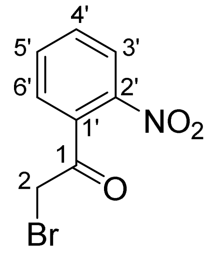


213a
$C_8H_7NO_3$
165.15

272
$C_8H_6BrNO_3$
244.04

To a stirred mixture of 2′-nitroacetophenone (**213a**) (20 g, 121 mmol) and $AlCl_3$ (500 mg, 3.75 mmol) in dry ether (600 mL) at 0 °C and under argon was added dropwise bromine (6.2 mL, 121 mmol) over 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h (reaction progress monitored by TLC). The organic layer was washed with water (3 x 200 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 70:30) to afford 31.7 g of **272** as a yellow solid. The product was crystallised from MeOH to give 26.1 g (73%) of pure **272** as colourless micro-needles.

Analytical Data for **272**:

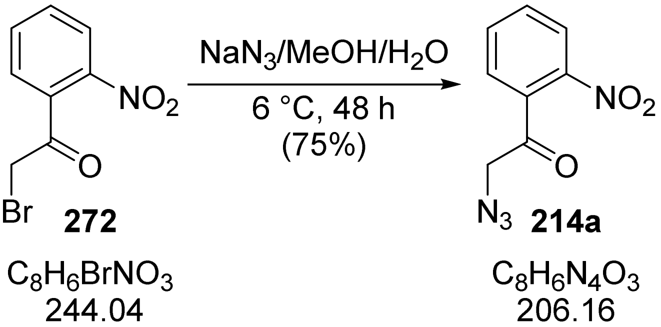


TLC: R_f (CH_2Cl_2/petroleum ether, 70:30) = 0.37

^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.21 (dd, $^3J_{\mathrm{H3',H4'}}$ = 8.1 Hz, $^4J_{\mathrm{H3',H5'}}$ = 1.2 Hz, 1 H, H$^{3'}$), 7.79 (td, $^3J_{\mathrm{H5',H6'}}$ = $^3J_{\mathrm{H5',H4'}}$ = 7.5 Hz, $^4J_{\mathrm{H5',H3'}}$ = 1.3 Hz, 1 H, H$^{5'}$), 7.68 (ddd, $^3J_{\mathrm{H4',H3'}}$ = 8.1 Hz, $^3J_{\mathrm{H4',H5'}}$ = 7.5 Hz, $^4J_{\mathrm{H4',H6'}}$ = 1.6 Hz, 1 H, H$^{4'}$), 7.50 (dd, $^3J_{\mathrm{H6',H5'}}$ = 7.5 Hz, $^4J_{\mathrm{H6',H4'}}$ = 1.6 Hz, 1 H, H^{11}), 4.30 (s, 2 H, H^2)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 194.3 (C^1), 145.4 (C$^{2'}$), 134.9 (C$^{1'}$), 134.8 (C$^{5'}$), 131.3 (C$^{4'}$), 129.1 (C$^{6'}$), 124.5 (C$^{3'}$), 33.9 (C^2)

5.2.2. 2-Azido-1-(2-nitrophenyl)ethanone (214a)

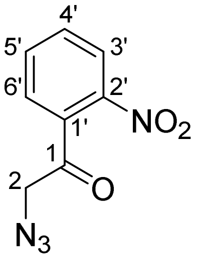


272 $C_8H_6BrNO_3$ 244.04

214a $C_8H_6N_4O_3$ 206.16

To a mechanically stirred solution of sodium azide (3.68 g, 56.55 mmol) in water (55 mL) at 6 °C was added a solution of 2-bromo-2′-nitroacetophenone (**272**) (9.20 g, 37.70 mmol) in MeOH (190 mL). The reaction mixture was stirred for 48 h at 6 °C and then extracted with Et_2O (4 x 200 mL). The organic layer was washed with water (1 x 200 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford 6.17 g of **214a** as a brown solid. The product was crystallised from Et_2O/hexane to give 5.83 g (75%) of pure **214a** as yellow-brown micro-needles.

Analytical Data for **214a**:

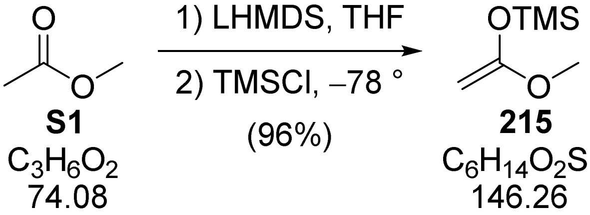


TLC: R_f (CH_2Cl_2, 100%) = 0.47

^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.23 (dd, $^3J_{H3',H4'} = 8.0$ Hz, $^4J_{H3',H5'} = 1.5$ Hz, 1 H, $H^{3'}$), 7.80 (td, $^3J_{H5',H6'} = {}^3J_{H5',H4'} = 7.4$ Hz, $^4J_{H5',H3'} = 1.5$ Hz, 1 H, $H^{5'}$), 7.70 (ddd, $^3J_{H4',H3'} = 8.0$ Hz, $^3J_{H4',H5'} = 7.4$ Hz, $^4J_{H4',H6'} = 1.6$ Hz, 1 H, $H^{4'}$), 7.43 (dd, $^3J_{H6',H5'} = 7.4$ Hz, $^4J_{H6',H4'} = 1.6$ Hz, 1 H, H^{11}), 4.32 (s, 2 H, H^2)

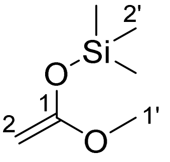
^{13}C-NMR (100 MHz, CDCl$_3$): δ 197.2 (C^1), 145.9 ($C^{2'}$), 135.2 ($C^{1'}$), 135.0 ($C^{5'}$), 131.5 ($C^{4'}$), 127.9 ($C^{6'}$), 124.6 ($C^{3'}$), 57.8 (C^2)

5.2.3. ((1-Methoxyvinyl)oxy)trimethylsilane (215)



To a stirred solution of LHMDS (1.0 M in THF, 100 mL, 100 mmol) in dry THF (30 mL) was added dropwise a solution of methyl acetate (**S1**) (6.17 g, 83.33 mmol) in dry THF (37 mL) at −78 °C and under argon. After 30 min at −78 °C, TMSCl (10.86 g, 100 mmol) was added dropwise over 20 min. The mixture was allowed to stir at −78 °C for 1.5 h. The solvent was removed in vacuo and the excess salts were precipitated by the addition of dry pentane (30 mL). After filtration through a plug of Celite and evaporation of solvent, the residue was purified by distillation (P = 45 mmHg, T = 48-50 °C) to afford 11.68 g (96%) of **S4** as a clear, colourless oil.

Analytical Data for **215**:

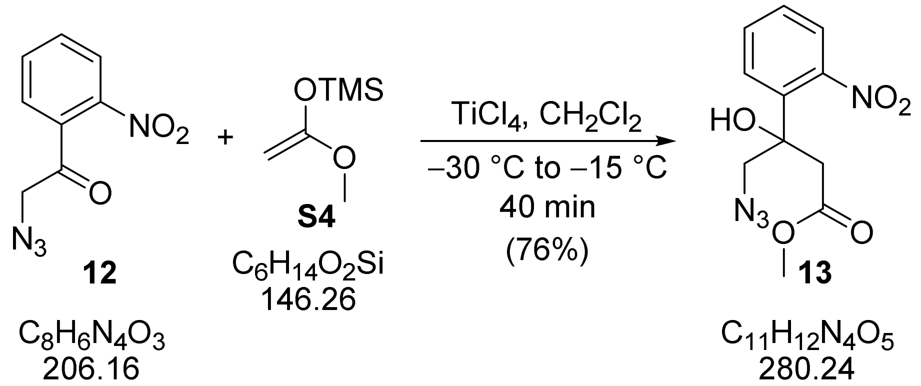


TLC: R_f (CH_2Cl_2, 100%) = 0.35

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.55 (s, 3 H, $H^{1'}$), 3.22 and 3.11 (2 x d, AB system, $^2J_{H2a,H2b}$ = 2.6 Hz, 2 H, H^{2a} and H^{2b}), 0.25 (s, 9 H, $H^{2'}$)

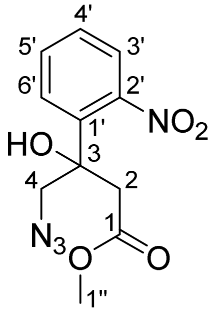
^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.1 (C^1), 59.9 (C^2), 55.1 ($C^{1'}$), 2.5 ($C^{2'}$)

5.2.4. Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)butanoate (216a)



2-Azido-1-(2-nitrophenyl)-ethanone (**214a**) (3.0 g, 14.55 mmol) was added portionwise to a stirred solution of ((1-methoxyvinyl)oxy)trimethylsilane **215** (6.39 g, 43.66 mmol, 3 equiv.) in dry CH_2Cl_2 (60 mL) at −30 °C and under argon. A solution of freshly distilled $TiCl_4$ (0.84 mL, 7.28 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 15 min. The resulting mixture was stirred stirred at −30 °C for 15 min and then allowed to reach −15 °C over a period of 30 min. The dark red solution was quenched with NaOH (2.0 M, 15 mL) and extracted with $CHCl_3$ (4 x 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent to afford 3.39 g of **216a** as a clear, slightly yellowish oil which solidified on standing. The product was crystallised from Et_2O/hexane to give 3.10 g (76%) of pure **216a** as white solid.

Analytical Data for **216a**:



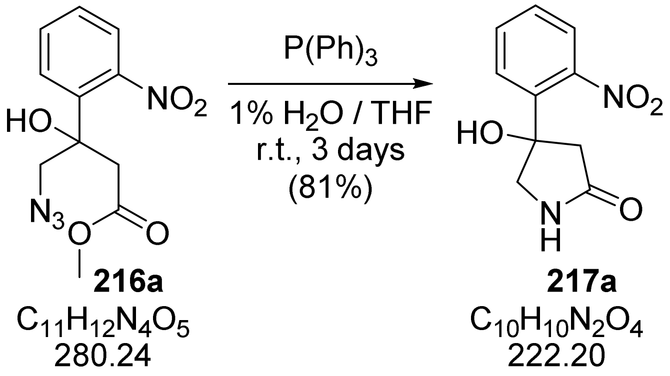
TLC: *R*f (CH2Cl2, 100%) = 0.30

MP: 77 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-7.52 (m, 4 H, $H^{3'}$, $H^{4'}$, $H^{5'}$ and $H^{6'}$), 4.83 (s, 1 H, OH), 3.66 (s, 3 H, $H^{1''}$), 3.80 and 3.59 (2 x d AB system, $^2J_{H4a,H4b}$ = 12.7 Hz, 2 H, H^{4a} and H^{4b}), 3.17 and 3.06 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.7 Hz, 2 H, H^{2a} and H^{2b})

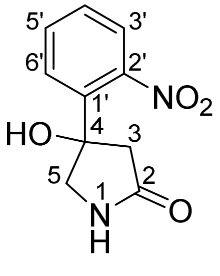
^{13}C-NMR (100 MHz, CDCl$_3$): δ 172.8 (C^{1}), 150.4 (C$^{2'}$), 134.6 (C$^{1'}$), 131.1 (C$^{5'}$), 129.4 (C$^{4'}$), 128.1 (C$^{3'}$), 124.5 (C$^{6'}$), 76.2 (C^{3}), 59.2 (C^{4}), 52.5 (C$^{1''}$), 41.0 (C^{2})

5.2.5 4-Hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (217a)



Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)butanoate (**216a**) (8.42 g, 30.05 mmol) and triphenylphosphine (12.00 g, 45.07 mmol) were dissolved in THF (126 mL) at room temperature. After 30 min, deionized water (1%, 1.26 mL) was added. The resulting mixture was stirred at room temperature for 3 days and then the solvents were evaporated in vacuo. The crude product was crystallised from MeOH and washed with EtOAc to give 5.43 g (81%) of pure **217a** as white solid.

Analytical Data for **217a**:



MP: 223 °C

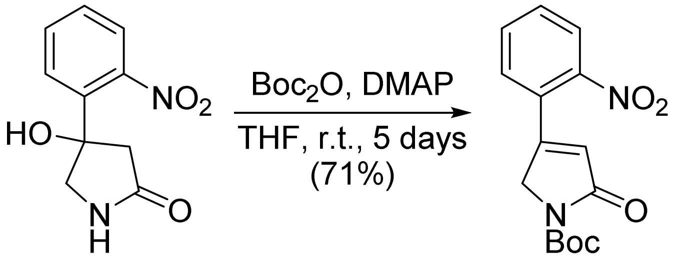
^{1}H-NMR (400 MHz, DMSO-d6): δ 7.77 (br s, 1 H, H^{1}), 7.66 (dd, $^{3}J_{H3',H4'} = 7.8$ Hz, $^{4}J_{H3',H5'} = 1.4$ Hz, 1 H, H$^{3'}$), 7.65 (dd, $^{3}J_{H6',H5'} = 7.9$ Hz, $^{4}J_{H6',H4'} = 1.4$ Hz, 1 H, H$^{6'}$), 7.59 (m (partially solved), $^{3}J_{H5',H6'} = 7.9$ Hz, $^{3}J_{H5',H4'} = 7.3$ Hz, $^{4}J_{H5',H3'} = 1.4$ Hz, 1 H, H$^{5'}$), 7.50 (m (partially solved), $^{3}J_{H4',H3'}$ =7.8 Hz, $^{3}J_{H4',H5'}$ = 7.3 Hz, $^{4}J_{H4',H6'}$ = 1.4 Hz, 1 H, $H^{4'}$), 6.06 (s, 1 H, OH), 3.65 and 3.46 (2 x d AB system, $^{2}J_{H5a,H5b}$ = 10.6 Hz, 2 H, H^{5a} and H^{5b}), 2.96 and 2.42 (2 x d AB system, $^{2}J_{H3a,H3b}$ = 16.6 Hz, 2 H, H^{3a} and H^{3b})

^{13}C-NMR (100 MHz, DMSO-d6): δ 173.8 (C^{2}), 150.1 ($C^{2'}$), 137.0 ($C^{1'}$), 131.2 ($C^{5'}$), 128.7 ($C^{4'}$), 127.4 ($C^{6'}$), 123.9 ($C^{3'}$), 76.3 (C^{4}), 55.4 (C^{5}), 45.7 (C^{3})

MS-ESI: 245.2 (100, $[M+Na]^{+}$)

IR (KBr): ν = 3403 (s), 3227 (m), 1673 (vs), 1525 (s), 1481 (w), 1441 (w), 1405 (w), 1373 (s), 1321 (w), 1243 (m), 1204 (w), 1104 (m), 1050 (w), 985 (w), 957 (vw), 931 (vw), 912 (vw), 855 (w), 796 (vw), 781 (w), 751 (w), 725 (w), 681 (vw), 645 (m), 632 (s), 567 (w), 547 (w), 508 (vw) cm^{-1}

5.2.6. tert-Butyl 4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (218a)

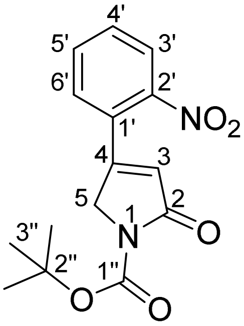


217a
$C_{10}H_{10}N_2O_4$
222.20

218a
$C_{15}H_{16}N_2O_5$
304.30

To a stirred suspension of pyrrolidinone **217a** (1.0 g, 4.50 mmol) in dry THF (100 mL) at room temperature and under argon was added DMAP (222 mg, 1.80 mmol) followed by Boc_2O (2.06 g, 9.45 mmol). The resulting solution was stirred at room temperature for 5 days, then was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to afford 1.39 g (100%) of Boc-protected pyrrolinone **218a** as a viscous, brownish red oil. The product was crystallised from Et_2O/petroleum ether to give 0.97 g (71%) of pure **218a** as white solid.

Analytical Data for **218a**:



TLC: R_f (CH$_2$Cl$_2$/MeOH, 99:1= 0.16

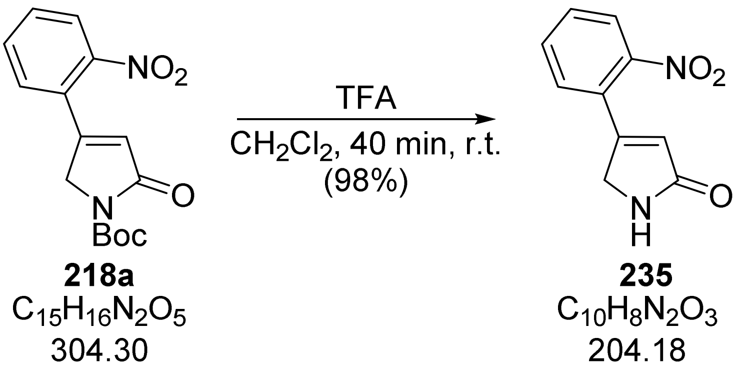
^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.12 (dd, $^3J_{H3',H4'}$ = 8.1 Hz, $^4J_{H3',H5'}$ = 1.2 Hz, 1 H, H$^{3'}$), 7.74 (td, $^3J_{H5',H6'}$ = $^3J_{H5',H4'}$ = 7.5 Hz, $^4J_{H5',H3'}$ = 1.1 Hz, 1 H, H$^{5'}$), 7.65 (td, $^3J_{H4',H3'}$ = $^3J_{H4',H5'}$ = 7.7 Hz, $^4J_{H4',H6'}$ = 1.4 Hz, 1 H, H$^{4'}$), 7.43 (dd, $^3J_{H6',H5'}$ = 7.5 Hz, $^4J_{H6',H4'}$ = 1.4 Hz, 1 H, H$^{6'}$), 6.15 (t, $^4J_{H3,H5}$ = 1.5 Hz, 1 H, H^3), 4.56 (d, $^4J_{H5,H3}$ = 1.5 Hz, 2 H, H^5), 1.58 (s, 9 H, H$^{3''}$)

^{13}C-NMR (400 MHz, CDCl$_3$): δ 168.4 (C^2), 155.7 (C$^{1''}$), 149.6 (C$^{2'}$), 147.8 (C^4), 134.0 (C$^{5'}$), 131.1 (C$^{4'}$), 130.7 (C$^{6'}$), 128.7 (C$^{1'}$), 125.4 (C$^{3'}$), 125.3 (C^3), 83.7 (C$^{2''}$), 53.4 (C^5), 28.5 (C$^{3''}$)

MS-ESI: 326.9 (100, [M+Na]$^+$)

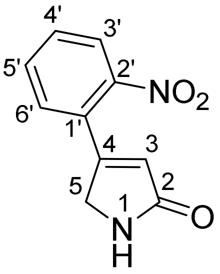
IR (KBr): ν = 3105 (vw), 2981 (w), 2924 (w), 1781 (vs), 1693 (m), 1604 (w), 1571 (w), 1520 (vs), 1477 (w), 1448 (m), 1368 (s), 1357 (vs), 1339 (vs), 1322 (s), 1289 (vs), 1261 (m), 1225 (w), 1204 (w), 1158 (s), 1072 (s), 877 (w), 863 (m), 847 (m), 796 (w), 774 (w), 761 (m), 748 (w), 739 (m), 693 (w), 639 (vw), 579 (vw), 531 (vw), 490 (vw), 457 (vw) cm^{-1}

5.2.7. 4-(2-Nitrophenyl)-1H-pyrrol-2(5H)-one (235)



Trifluoroacetic acid (1.60 mL) was added dropwise to a solution of Boc-protected pyrrolinone **218a** (200 mg, 0.66 mmol) in dry CH_2Cl_2 (8.0 mL) at room temperature. The mixture was stirred at room temperature for 40 min (reaction progress monitored by TLC) and then quenched with a saturated aqueous $NaHCO_3$ (30 mL). The organic and aqueous layers were separated and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated. 131 mg (98%) of deprotected pyrrolinone **235** were recovered as a yellow solid.

Analytical Data for **235**:



TLC: R_f (EtOAc, 100%) = 0.29

GC (method IZ): t_R = 15.71 min

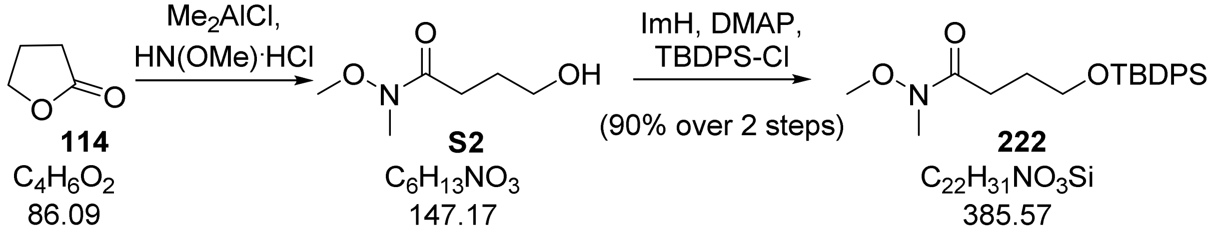
^{1}H-NMR (400 MHz, CD_3OD): δ 8.03 (dd, $^3J_{H3',H4'}$ = 8.1 Hz, $^4J_{H3',H5'}$ = 1.3 Hz, 1 H, $H^{3'}$), 7.76 (td, $^3J_{H5',H6'}$ = $^3J_{H5',H4'}$ = 7.5 Hz, $^4J_{H5',H3'}$ = 1.3 Hz, 1 H, $H^{5'}$), 7.66 (td, $^3J_{H4',H3'}$ = $^3J_{H4',H5'}$ = 7.5 Hz, $^4J_{H4',H6'}$ = 1.3 Hz, 1 H, $H^{4'}$), 7.59 (dd, $^3J_{H6',H5'}$ = 7.6 Hz, $^4J_{H6',H4'}$ = 1.5 Hz, 1 H, $H^{6'}$), 6.12 (t, $^4J_{H3,H5}$ = 1.6 Hz, 1 H, H^3), 4.35 (d, $^4J_{H5,H3}$ = 1.6 Hz, 2 H, H^5)

^{13}C-NMR (100 MHz, CD_3OD): δ 176.0 (C^2), 158.3 (C^4), 149.6 ($C^{2'}$), 134.4 ($C^{5'}$), 131.6 ($C^{4'}$), 131.6 ($C^{6'}$), 129.4 ($C^{1'}$), 126.6 ($C^{3'}$), 125.3 (C^3), 51.6 (C^5)

MS-ESI: 227.2 (100, $[M+Na]^+$)

HR-MS (ESI): 227.04317 ($[M+Na]^+$; $C_{10}H_8N_2O_3Na^+$; calc. 227.04326)

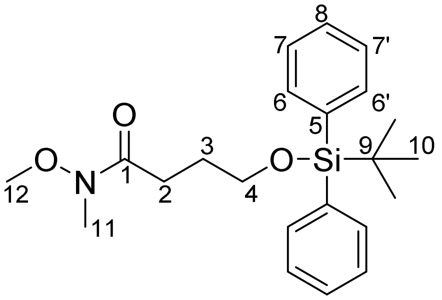
5.2.8. 4-Hydroxy-*N*-methoxy-*N*-methylbutanamide (S2) and 4-(*tert*-butyldiphenylsilyloxy)-*N*-methoxy-*N*-methylbutanamide (222)[24]



N, *O*-dimethylhydroxylamine hydrochloride (1.03 g, 10.31 mmol) was dissolved in dry CH_2Cl_2 (50 mL) under argon. The solution was cooled to 0 °C and Me_2AlCl (1.0 M solution in *n*-hexane, 10.3 mL, 10.31 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. Neat γ–butyrolactone (0.72 mL, 93.8 mmol) was then added slowly and the resulting mixture was stirred at room temperature for 21 h. The reaction mixture was quenched with water (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). Aqueous phase was diluted with a saturated Rochelle's salt (10 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford 1.42 g of the crude alcohol **S2** as a clear, colourless oil. R_f (CH_2Cl_2/MeOH, 95:5) = 0.23. GC (method IZ): t_R = 6.67 min.

Under argon, imidazole (728 mg, 10.69 mmol) was added to a solution of the crude alcohol **S2** in dry CH_2Cl_2 (50 mL) and the solution was cooled to 0 °C. *tert*-Butyldiphenylchlorosilane (2.32 mL, 9.75 mmol) and 4-DMAP (58 mg, 0.47 mmol) were added and the resulting mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with water (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 70:30) to afford 3.25 g (90%) of **222** as a clear, colourless oil.

Analytical Data for **222**:



TLC: R_f (Petroleum ether/EtOAc, 50:50) = 0.58

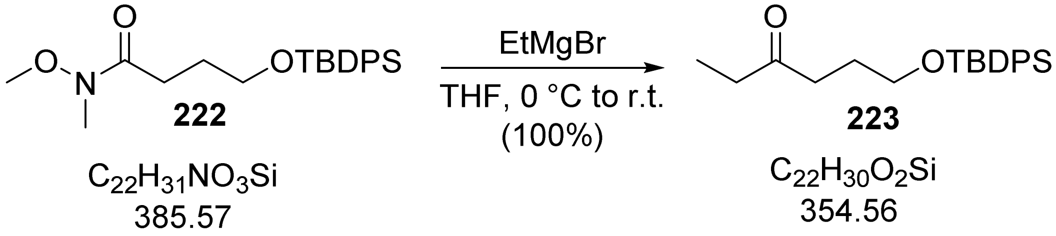
GC (method IZ): t_R = 16.28 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.66 (≈ td, $^3J_{H6,H7\ obs.}$ = 6.1 Hz, $^4J_{H6,H8\ obs.}$ = $^4J_{H6,H6'\ obs.}$ = 1.5 Hz, 4 H, H^6, $H^{6'}$), 7.44-7.35 (m, 6 H, H^7, $H^{7'}$, H^8), 3.73 (t, $^3J_{H4,H3}$ = 6.1 Hz, 2 H, H^4), 3.67 (s, 3 H, H^{12}), 3.18 (s, 3 H, H^{11}), 2.56 (t, $^3J_{H2,H3}$ = 7.5 Hz, 2 H, H^2), 1.89 (tt, $^3J_{H3,H2}$ = 7.5 Hz, $^3J_{H3,H4}$ = 6.1 Hz, 2 H, H^3), 1.05 (s, 9 H, H^{10})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 174.4 (C^1) visible on HMBC spectrum, 135.5 (C^6, $C^{6'}$), 133.9 (C^5), 129.6 (C^8), 127.6 (C^7, $C^{7'}$), 63.2 (C^4), 61.2 (C^{12}), 32.3 (C^{11}), 28.4 (C^3), 27.6 (C^2), 26.9 (C^{10}), 19.2 (C^9)

MS-ESI: 408.5 (100, $[M+Na]^+$)

5.2.9. 6-(tert-Butyldiphenylsilyloxy)hexan-3-one (223)[52]



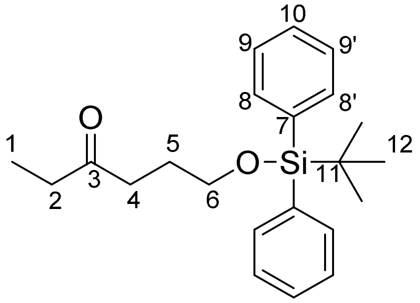
222
$C_{22}H_{31}NO_3Si$
385.57

223
$C_{22}H_{30}O_2Si$
354.56

Weinreb amide **222** (3.25 g, 8.41 mmol) was dissolved in dry THF (17 mL) under argon. The solution was cooled to 0 °C and ethyl magnesiumbromide (1.0 M solution in THF, 16.83 mL, 16.83 mmol) was added dropwise. The resulting mixture was stirred at room temperature for

45 min and quenched with a saturated aqueous NH_4Cl (40 mL). The mixture was poured into Et_2O (60 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The solvent was removed in vacuo to afford 2.98 g (100%) of a pure ketone **223** as a clear, colourless oil. The crude product was engaged in the next step without further purification.

Analytical Data for **223**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.62

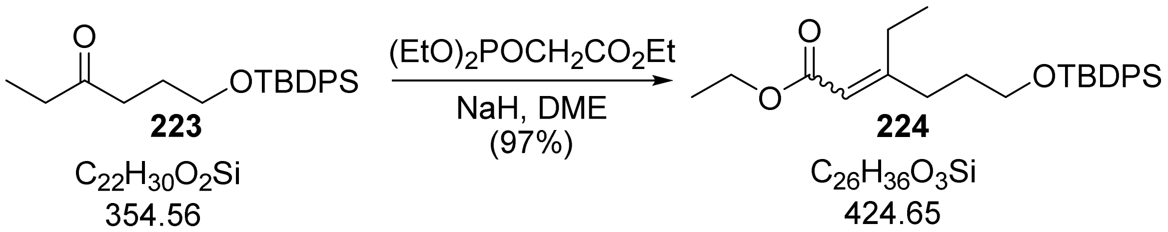
GC (method IZ): t_R = 15.01 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.65 (≈ td, $^3J_{H8,H9\ obs.}$ = 6.1 Hz, $^4J_{H8,H10\ obs.}$ = $^4J_{H6,H8'\ obs.}$ = 1.5 Hz, 4 H, H^8, $H^{8'}$), 7.45-7.35 (m, 6 H, H^9, $H^{9'}$, H^{10}), 3.66 (t, $^3J_{H6,H5}$ = 6.1 Hz, 2 H, H^6), 2.52 (t, $^3J_{H4,H5}$ = 7.4 Hz, 2 H, H^4), 2.41 (q, $^3J_{H2,H1}$ = 7.3 Hz, 2 H, H^2), 1.83 (tt, $^3J_{H5,H4}$ = 7.4 Hz, $^3J_{H5,H6}$ = 6.1 Hz, 2 H, H^5), 1.04 (t, $^3J_{H1,H2}$ = 7.3 Hz, 3 H, H^1), 1.04 (s, 9 H, H^{12})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 211.5 (C^3), 135.5 (C^8, $C^{8'}$), 133.8 (C^7), 129.6 (C^{10}), 127.6 (C^9, $C^{9'}$), 63.1 (C^6), 38.7 (C^4), 35.9 (C^2), 26.9 (C^{12}), 26.7 (C^5), 19.2 (C^{11}), 7.8 (C^1)

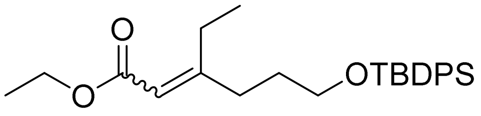
MS-ESI: 377.6 (100, $[M+Na]^+$)

5.2.10. (*E*/*Z*)-Ethyl 6-(*tert*-butyldiphenylsilyloxy)-3-ethylhex-2-enoate (224)[24]



A flame-dried 250 mL two-necked round bottom flask was charged with NaH (864 mg of 95%, 34.21 mmol) and 100 mL of dry DME. Neat triethyl phosphonoacetate (7.62 mL, 37.25 mmol) was then added slowly to the suspension at room temperature. After the addition was completed (~15 min), a solution of the ketone **223** (2.70 g, 7.60 mmol) in dry DME (25 mL) was added. The homogeneous mixture was refluxed overnight then cooled to room temperature. The reaction mixture was diluted with 70 mL of water and 100 mL of EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 99:1 to 96:4) to afford 3.13 g (97%) of *E*/*Z* mixture (60:40) of **224** as a clear, slightly yellowish oil.

Analytical Data for **224**:



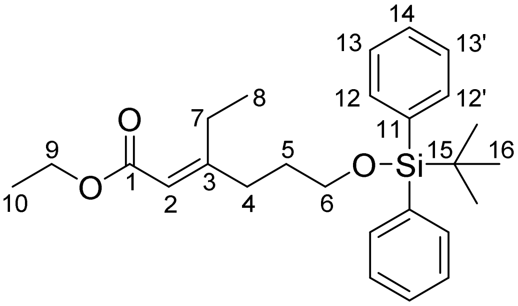
TLC: R_f (Petroleum ether/EtOAc, 95:5) = 0.24

MS-ESI: 447.6 (100, $[M+Na]^+$)

HR-MS (ESI): 447.23192 ($[M+Na]^+$; $C_{26}H_{36}O_3SiNa^+$; calc. 447.23259)

IR (KBr, film): ν = 3072 (w), 3050 (w), 2959 (s), 2933 (vs), 2897 (s), 2859 (s), 1960 (vw), 1890 (vw), 1741 (m), 1716 (vs), 1645 (s), 1590 (vw), 1473 (m), 1463 (m), 1428 (s), 1390 (m), 1305 (w), 1272 (m), 1240 (m), 1207 (s), 1180 (s), 1147 (vs), 1111 (vs), 1041 (s), 1008 (w), 998 (w), 974 (w), 940 (w), 868 (w), 824 (m), 741 (m), 702 (vs), 688 (m), 614 (m), 506 (s) cm^{-1}

Analytical Data for **(*E*)-224**:

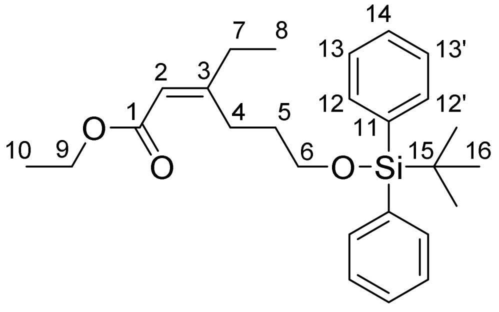


^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.66 (ddd, $^{3}J_{\mathrm{H12,H13}}$ = 7.7 Hz, $^{4}J_{\mathrm{H12,H14}}$ = 2.7 Hz, $^{4}J_{\mathrm{H12,H12'}}$ = 1.5 Hz, 4 H, A$_2$B$_2$, H^{12}, H$^{12'}$), 7.35-7.446 (m, 6 H, A$_2$B$_2$, H^{13}, H$^{13'}$, H^{14}), 5.61 (s, 1 H, H^{2}), 4.14 (q, $^{3}J_{\mathrm{H9,H10}}$ = 7.2 Hz, 2 H, H^{9}), 3.67 (t, $^{3}J_{\mathrm{H6,H5}}$ = 6.2 Hz, 2 H, H^{6}), 2.60 (q, $^{3}J_{\mathrm{H7,H8}}$ = 7.5 Hz, 2 H, H^{7}), 2.25 (≈t, $^{3}J_{\mathrm{H4,H5}}$ = 7.3 Hz, 2 H, H^{4}), 1.72 (≈quint, $^{3}J_{\mathrm{H5,H4}}$ = $^{3}J_{\mathrm{H5,H6}}$ = 6.2 Hz, 2 H, H^{5}), 1.28 (t, $^{3}J_{\mathrm{H10,H9}}$ = 7.2 Hz, 3 H, H^{10}), 1.06 (t, $^{3}J_{\mathrm{H8,H7}}$ = 7.5 Hz, 3 H, H^{8}), 1.05 (s, 9 H, H^{16})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.6 (C^{1}), 165.7 (C^{3}), 135.7 (C^{12}, C$^{12'}$), 134.0 (C^{11}), 129.8 (C^{14}), 127.8 (C^{13}, C$^{13'}$), 115.0 (C^{2}), 63.4 (C^{6}), 59.6 (C^{9}), 34.4 (C^{4}), 30.8 (C^{5}), 27.0 (C^{16}), 25.4 (C^{7}), 19.4 (C^{15}), 14.5 (C^{10}), 13.1 (C^{8})

GC (method IZ): t_{R} = 17.33 min

Analytical Data for **(*Z*)-224**:

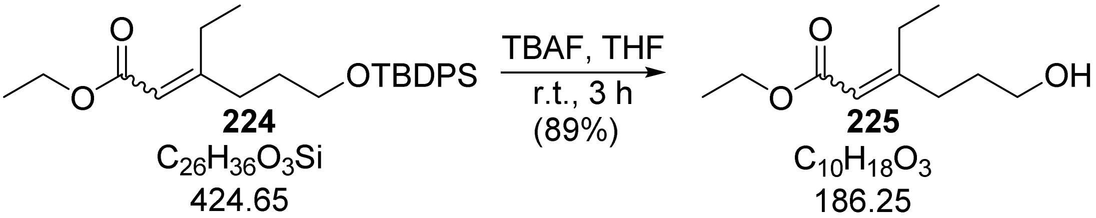


^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.66 (ddd, $^{3}J_{\mathrm{H12,H13}}$ = 7.7 Hz, $^{4}J_{\mathrm{H12,H14}}$ = 2.7 Hz, $^{4}J_{\mathrm{H12,H12'}}$ = 1.5 Hz, 4 H, A$_2$B$_2$, H^{12}, H$^{12'}$), 7.35-7.446 (m, 6 H, A$_2$B$_2$, H^{13}, H$^{13'}$, H^{14}), 5.61 (s, 1 H, H^{2}), 4.11 (q, $^{3}J_{\mathrm{H9,H10}}$ = 7.1 Hz, 2 H, H^{9}), 3.71 (t, $^{3}J_{\mathrm{H6,H5}}$ = 6.4 Hz, 2 H, H^{6}), 2.67 (≈t, $^{3}J_{\mathrm{H4,H5}}$ = 7.8 Hz, 2 H, H^{4}), 2.17 (dq, $^{3}J_{\mathrm{H7,H8}}$ = 7.4 Hz, $^{4}J_{\mathrm{H7,H2}}$ = 1.0 Hz, 2 H, H^{7}), 1.70 (≈quint, $^{3}J_{\mathrm{H5,H4}}$ = $^{3}J_{\mathrm{H5,H6}}$ = 6.2 Hz, 2 H, H^{5}), 1.25 (t, $^{3}J_{\mathrm{H10,H9}}$ = 7.1 Hz, 3 H, H^{10}), 1.05 (t, $^{3}J_{\mathrm{H8,H7}}$ = 7.3 Hz, 3 H, H^{8}), 1.05 (s, 9 H, H^{16})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.7 (C^1), 165.6 (C^3), 135.8 (C^{12}, C$^{12'}$), 134.2 (C^{11}), 129.7 (C^{14}), 127.7 (C^{13}, C$^{13'}$), 114.6 (C^2), 64.1 (C^6), 59.6 (C^9), 31.8 (C^7), 31.4 (C^5), 28.9 (C^4), 27.0 (C^{16}), 19.4 (C^{15}), 14.5 (C^{10}), 12.2 (C^8)

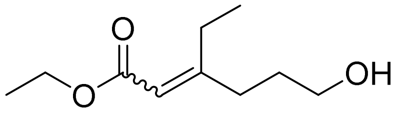
GC (method IZ): t_R = 17.06 min

5.2.11. (E/Z)- Ethyl 3-ethyl-6-hydroxyhex-2-enoate (225)[24]



At 0° C and under argon, TBAF (1.0 M solution in THF, 6.65 mL, 6.65 mmol) was added to a solution of acrylate **224** (2.57 g, 6.04 mmol) in 35 mL of dry THF. The resulting solution was stirred at room temperature for 3 h then concentrated. The residue was diluted with water (40 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) to afford 1.00 g (89%) of *E*/*Z* mixture (60:40) of **225** as a clear, slightly yellowish oil. The relative stereochemistry was determined by NOESY experiment.

Analytical Data for **225**:



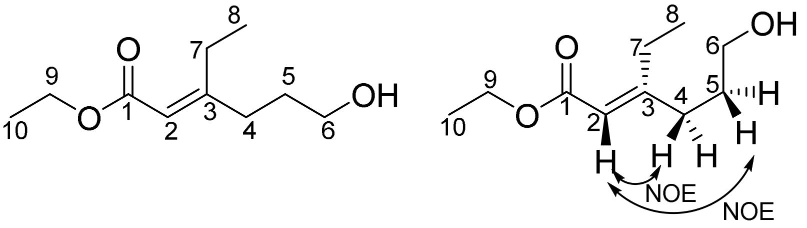
TLC: R_f (Petroleum ether/EtOAc, 50:50) = 0.40

MS-ESI: 209.3 (100, [M+Na]$^+$)

HR-MS (ESI): 209.11464 ([M+Na]$^+$; $C_{10}H_{18}O_3Na^+$; calc. 209.11536)

IR (KBr, film): ν = 3415 (br s), 2938 (vs), 2876 (s), 1715 (vs), 1644 (s), 1463 (s), 1421 (m), 1380 (s), 1304 (s), 1275 (s), 1209 (vs), 1148 (vs), 1097 (s), 1038 (vs), 920 (w), 870 (m), 809 (vw), 736 (w), 628 (w) cm^{-1}

Analytical Data for ***(E)*-225**:



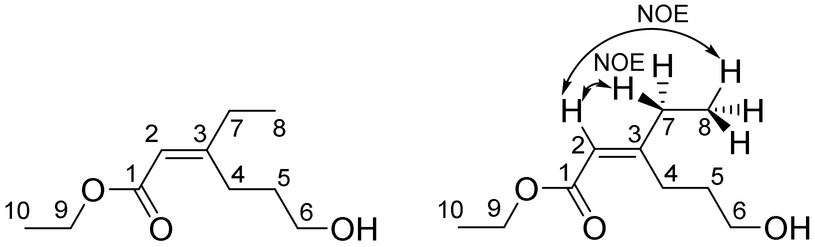
^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.63 (s, 1 H, H^2), 4.14 (q, $^3J_{H9,H10}$ = 7.0 Hz, 2 H, H^9), 3.67 (t, $^3J_{H6,H5}$ = 6.4 Hz, 2 H, H^6), 2.62 (q, $^3J_{H7,H8}$ = 7.5 Hz, 2 H, H^7), 2.24 (≈t, $^3J_{H4,H5}$ = 7.2 Hz, 2 H, H^4), 1.77-1.70 (m (partial solved), $^3J_{H5,H4}$ = 7.2 Hz, $^3J_{H5,H6}$ = 6.4 Hz, 2 H, H^5), 1.27 (t, $^3J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.08 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

^{1}H, NOE diff: irrad H^2 (5.63) → enh H^4 (2.24) and H^5 (1.77-1.70)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.4 (C^1), 165.0 (C^3), 115.1 (C^2), 62.2 (C^6), 59.5 (C^9), 34.1 (C^4), 30.5 (C^5), 25.3 (C^7), 14.3 (C^{10}), 13.0 (C^8)

GC-MS (EI, 70 eV): t_R = 13.21 min; m/z (%) = 187.0 (1, $[M+H]^+$), 157.1 (84, $[M-29]^+$), 125.1 (49, $[M-61]^+$), 111.1 (100, $[M-75]^+$), 109.1 (34, $[M-77]^+$), 96.1 (41, $[M-90]^+$), 95.1 (50, $[M-91]^+$), 81.1 (72, $[M-105]^+$), 79.1 (94, $[M-107]^+$), 69.1 (75, $[M-117]^+$), 67.1 (88, $[M-119]^+$)

Analytical Data for ***(Z)*-225**:



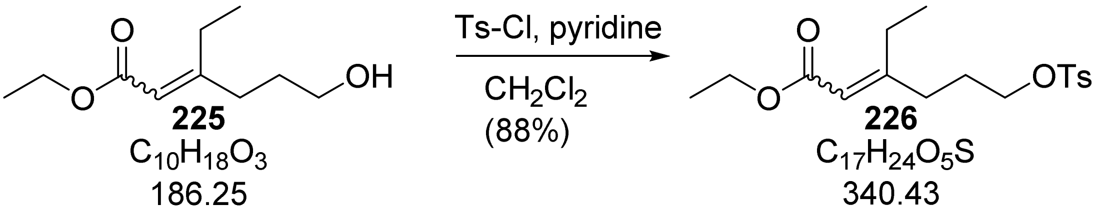
^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.74 (s, 1 H, H^2), 4.15 (q, $^3J_{H9,H10}$ = 7.0 Hz, 2 H, H^9), 3.56 (t, $^3J_{H6,H5}$ = 5.6 Hz, 2 H, H^6), 2.71 (t, $^3J_{H4,H5}$ = 7.0 Hz, 2 H, H^4), 2.18 (dq, $^3J_{H7,H8}$ = 7.4 Hz, $^4J_{H7,H2}$ = 1.0 Hz, 2 H, H^7), 1.77-1.70 (m (partial solved), $^3J_{H5,H4}$ = 7.2 Hz, $^3J_{H5,H6}$ = 5.7 Hz, 2 H, H^5), 1.28 (t, $^3J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.08 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

^{1}H, NOE diff: irrad H^2 (5.74) → enh H^7 (2.18) and H^8 (1.08)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.4 (C^1), 164.9 (C^3), 115.5 (C^2), 60.7 (C^6), 60.0 (C^9), 30.6 (C^7), 30.5 (C^5), 27.7 (C^4), 14.2 (C^{10}), 12.1 (C^8)

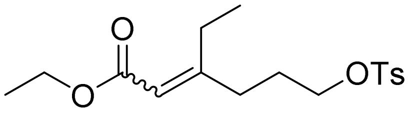
GC-MS (EI, 70 eV): t_R = 12.72 min; m/z (%) = 187.1 (1, $[M+H]^+$), 157.1 (56, $[M-29]^+$), 125.1 (31, $[M-61]^+$), 111.1 (100, $[M-75]^+$), 109.2 (41, $[M-77]^+$), 95.1 (50, $[M-91]^+$), 81.1 (66, $[M-105]^+$), 79.1 (75, $[M-107]^+$), 69.1 (50, $[M-117]^+$), 67.2 (62, $[M-119]^+$)

5.2.12. (*E*/*Z*)- Ethyl 3-ethyl-6-(tosyloxy)hex-2-enoate (226)[53]



To a solution of alcohol **225** (1.00 g, 5.37 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C and under argon was added *p*-toluene sulfonyl chloride (1.56 g, 8.16 mmol), followed by pyridine (0.93 mL, 11.60 mmol). The reaction mixture was stirred at room temperature overnight then diluted with 50 mL of water and 50 mL of Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 80:20) to afford 1.60 g (88%) of *E*/*Z* mixture (60:40) of **226** as a clear, colourless oil.

Analytical Data for **226**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.32

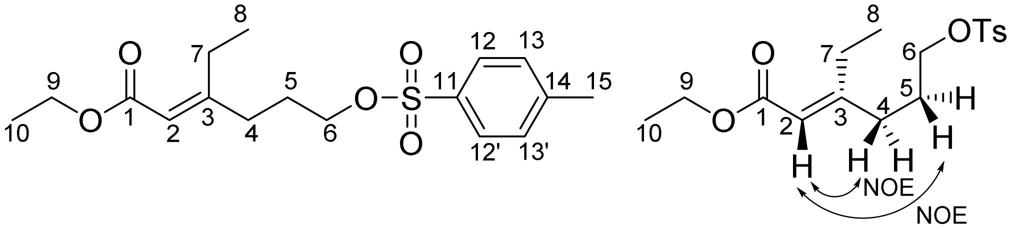
GC (method IZ): t_R = 15.70 min

MS-ESI: 363.3 (100, $[M+Na]^+$)

HR-MS (ESI): 363.12288 ([M+Na]$^+$; $C_{17}H_{24}O_5SNa^+$; calc. 363.12421)

IR (KBr, film): ν = 2974 (m), 2934 (m), 1713 (vs), 1645 (m), 1599 (w), 1496 (vw), 1463 (m), 1363 (vs), 1308 (w), 1274 (w), 1209 (s), 1189 (vs), 1177 (vs), 1149 (s), 1098 (m), 1037 (m), 1009 (w), 967 (m), 929 (s), 870 (w), 836 (m), 816 (m), 785 (w), 738 (w), 706 (vw), 690 (vw), 665 (s), 577 (w), 555 (s) cm^{-1}

Analytical Data for **(*E*)-226**:

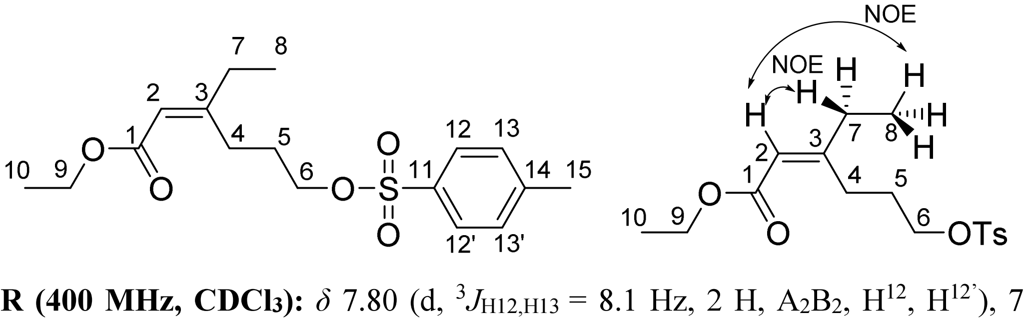


^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.80 (d, $^3J_{\mathrm{H12,H13}}$ = 8.1 Hz, 2 H, A_2B_2, H^{12}, H$^{12'}$), 7.35 (d, $^3J_{\mathrm{H13,H12}}$ = 8.1 Hz, 2 H, A_2B_2, H^{13}, H$^{13'}$), 5.51 (s, 1 H, H^2), 4.13 (q, $^3J_{\mathrm{H9,H10}}$ = 7.1 Hz, 2 H, H^9), 4.04 (t, $^3J_{\mathrm{H6,H5}}$ = 6.2 Hz, 2 H, H^6), 2.54 (q, $^3J_{\mathrm{H7,H8}}$ = 7.5 Hz, 2 H, H^7), 2.45 (s, 3 H, H^{15}), 2.17 (≈t, $^3J_{\mathrm{H4,H5}}$ = 7.3 Hz, 2 H, H^4), 1.84 (≈quint, $^3J_{\mathrm{H5,H4}}$ = $^3J_{\mathrm{H5,H6}}$ = 6.2 Hz, 2 H, H^5), 1.27 (t, $^3J_{\mathrm{H10,H9}}$ = 7.1 Hz, 3 H, H^{10}), 1.02 (t, $^3J_{\mathrm{H8,H7}}$ = 7.5 Hz, 3 H, H^8)

^{1}H, NOE diff: irrad H^2 (5.51) → enh H^6 (4.04), H^4 (2.17) and H^5 (1.84)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.1 (C^1), 163.2 (C^3), 144.8 (C^{11}), 133.1 (C^{14}), 129.9 (C^{13}), 127.9 (C^{12}), 115.7 (C^2), 69.6 (C^6), 59.6 (C^9), 33.3 (C^4), 26.9 (C^5), 25.1 (C^7), 21.6 (C^{15}), 14.3 (C^{10}), 12.9 (C^8)

Analytical Data for **(*Z*)-226**:



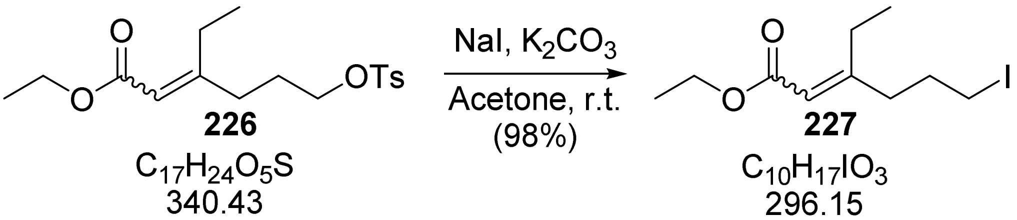
^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.80 (d, $^3J_{\mathrm{H12,H13}}$ = 8.1 Hz, 2 H, A_2B_2, H^{12}, H$^{12'}$), 7.34 (d, $^3J_{\mathrm{H13,H12}}$ = 8.1 Hz, 2 H, A_2B_2, H^{13}, H$^{13'}$), 5.63 (s, 1 H, H^2), 4.11 (q, $^3J_{\mathrm{H9,H10}}$ = 7.1 Hz, 2 H, H^9), 4.06 (t, $^3J_{\mathrm{H6,H5}}$ = 6.4 Hz, 2 H, H^6), 2.58 (≈t, $^3J_{\mathrm{H4,H5}}$ = 7.8 Hz, 2 H, H^4), 2.45 (s, 3 H, H^{15}), 2.13

(dq, ${}^3J_{H7,H8}$ = 7.4 Hz, ${}^4J_{H7,H2}$ = 1.3 Hz, 2 H, H^7), 1.80 (≈quint, ${}^3J_{H5,H4}$ = ${}^3J_{H5,H6}$ = 6.2 Hz, 2 H, H^5), 1.25 (t, ${}^3J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.04 (t, ${}^3J_{H8,H7}$ = 7.4 Hz, 3 H, H^8)

^{1}H, NOE diff: irrad H^2 (5.63) → enh H^7 (2.13) and H^8 (1.04)

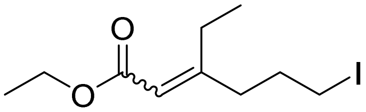
^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.4 (C^1), 163.7 (C^3), 144.7 (C^{11}), 133.2 (C^{14}), 129.8 (C^{13}), 127.9 (C^{12}), 115.3 (C^2), 70.5 (C^6), 59.6 (C^9), 31.2 (C^7), 28.4 (C^4), 27.9 (C^5), 21.6 (C^{15}), 14.3 (C^{10}), 11.9 (C^8)

5.2.13. (E/Z)- Ethyl 3-ethyl-6-iodohex-2-enoate (227)[54]



To a solution of tosylate **226** (700 mg, 2.06 mmol) in acetone (70 mL) was added sodium iodide (925 mg, 6.17 mmol), followed by K_2CO_3 (853 mg, 6.17 mmol). The reaction mixture was refluxed for 5 h then concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to afford 594 mg (98%) of *E*/*Z* mixture (60:40) of **227** as a clear, colourless oil.

Analytical Data for **227**:



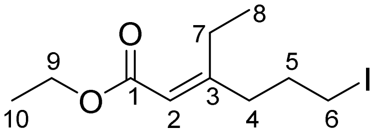
TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.59

MS-ESI: 353.4 (10, [M+K+H$_2$O]$^+$), 319.1 (100, [M+Na]$^+$), 304.5 (33, [(M+Na)-15]$^+$)

HR-MS (ESI): 319.01666 ([M+Na]$^+$; $C_{10}H_{17}IO_2Na^+$; calc. 319.01654)

IR (KBr, film): ν = 2964 (s), 2929 (s), 2873 (m), 1715 (vs), 1645 (s), 1460 (m), 1379 (m), 1314 (m), 1272 (m), 1205 (vs), 1151 (vs), 1096 (w), 1078 (w), 1037 (m), 948 (vw), 870 (w), 810 (vw), 726 (vw), 594 (vw), 502 (vw) cm^{-1}

Analytical Data for **(*E*)-227**:

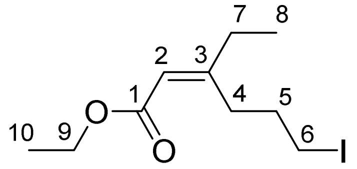


^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.63 (s, 1 H, H^2), 4.14 (q, $^3J_{H9,H10}$ = 7.1 Hz, 2 H, H^9), 3.18 (t, $^3J_{H6,H5}$ = 6.9 Hz, 2 H, H^6), 2.61 (q, $^3J_{H7,H8}$ = 7.5 Hz, 2 H, H^7), 2.27 (≈t, $^3J_{H4,H5}$ = 6.9 Hz, 2 H, H^4), 1.99 (≈quint, $^3J_{H5,H4}$ = $^3J_{H5,H6}$ = 6.9 Hz, 2 H, H^5), 1.28 (t, $^3J_{H10,H9}$ = 7.2 Hz, 3 H, H^{10}), 1.08 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.4 (C^1), 163.4 (C^3), 116.0 (C^2), 59.8 (C^9), 38.5 (C^4), 31.3 (C^5), 25.3 (C^7), 14.5 (C^{10}), 13.1 (C^8), 5.8 (C^6)

GC (method IZ): t_R = 10.10 min

Analytical Data for **(*Z*)-227**:

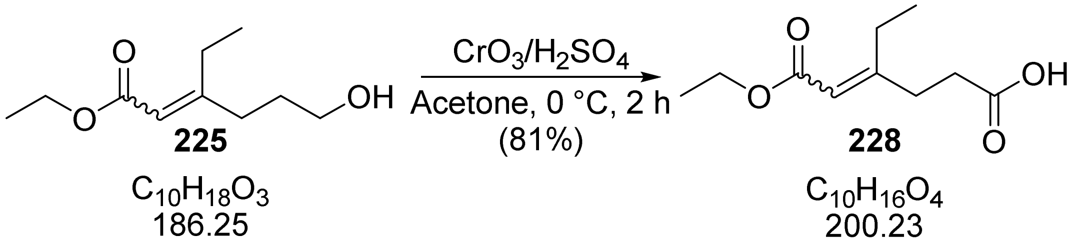


^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.67 (s, 1 H, H^2), 4.14 (q, $^3J_{H9,H10}$ = 7.1 Hz, 2 H, H^9), 3.22 (t, $^3J_{H6,H5}$ = 7.2 Hz, 2 H, H^6), 2.68 (≈t, $^3J_{H4,H5}$ = 7.7 Hz, 2 H, H^4), 2.19 (dq, $^3J_{H7,H8}$ = 7.4 Hz, $^4J_{H7,H2}$ = 1.2 Hz, 2 H, H^7), 1.99 (≈quint, $^3J_{H5,H4}$ = $^3J_{H5,H6}$ = 6.9 Hz, 2 H, H^5), 1.28 (t, $^3J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.08 (t, $^3J_{H8,H7}$ = 7.4 Hz, 3 H, H^8)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.6 (C^1), 163.6 (C^3), 115.5 (C^2), 59.8 (C^9), 33.6 (C^4), 32.8 (C^5), 31.5 (C^7), 14.4 (C^{10}), 12.1 (C^8), 6.4 (C^6)

GC (method IZ): t_R = 9.89 min

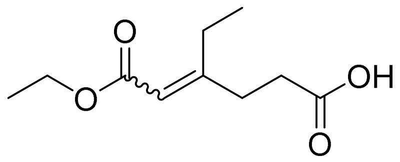
5.2.14. (E/Z)- 6-Ethoxy-4-ethyl-6-oxohex-4-enoic acid (228)[51]



Preparation of Jones' reagent 1.9 M CrO_3 in 2.95 M H_2SO_4 (4 mL): Water (3.34 mL) was added dropwise to a solution of CrO_3 (760 mg, 7.6 mmol) in 0.66 mL of 96% H_2SO_4 at 0 °C.

To a stirred solution of alcohol **225** (200 mg, 1.07 mmol) in acetone (4.5 mL) at 0 °C was added dropwise a freshly prepared Jones' reagent (1.9 M, *ca.* 2 mL). The addition of the oxidant was continued until the starting material was consumed as determined by TLC analysis (*ca.* 0.5 h). The resulting yellow-brown reaction mixture was stirred for an additional 2 h at 0 °C, before it was quenched with ^{i}PrOH (2 mL) and warmed to room temperature for 10 min. The crude reaction mixture was then filtered through a plug of Celite (eluting with 30 mL of Et_2O) and concentrated in vacuo. The organic residue was taken up in Et_2O (100 mL) and washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 50:50) to afford 175 mg (81%) of *E*/*Z* mixture (60:40) of **228** as a clear, slightly yellowish oil.

Analytical Data for **228**:



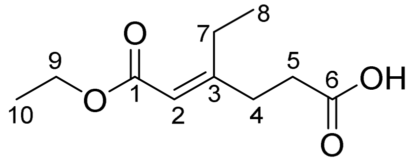
TLC: R_f (Petroleum ether/EtOAc, 50:50) = 0.20

MS-ESI: 223.1 (100, $[M+Na]^+$)

HR-MS (ESI): 223.09407 ($[M+Na]^+$; $C_{10}H_{16}O_4Na^+$; calc. 223.09463)

IR (KBr, film): ν = 2976 (vs), 2934 (vs), 1715 (vs), 1646 (vs), 1447 (s), 1422 (s), 1381 (s), 1276 (vs), 1209 (vs), 1148 (vs), 1096 (m), 1040 (s), 920 (m), 870 (s), 759 (w), 666 (w) cm^{-1}

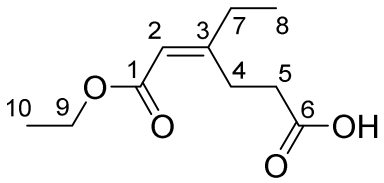
Analytical Data for ***(E)*-228**:



^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.61 (s, 1 H, H^{2}), 4.15 (q, $^{3}J_{H9,H10}$ = 7.1 Hz, 2 H, H^{9}), 2.63 (q, $^{3}J_{H7,H8}$ = 7.5 Hz, 2 H, H^{7}), 2.58-2.48 (m, 2 H, H^{5}), 2.53 (≈t, $^{3}J_{H4,H5}$ = 6.7 Hz, 2 H, H^{4}), 1.27 (t, $^{3}J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.09 (t, $^{3}J_{H8,H7}$ = 7.5 Hz, 3 H, H^{8})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 177.6 (C^{6}), 166.2 (C^{1}), 162.7 (C^{3}), 115.4 (C^{2}), 59.7 (C^{9}), 32.2 (C^{5}), 31.7 (C^{4}), 25.4 (C^{7}), 14.3 (C^{10}), 12.9 (C^{8})

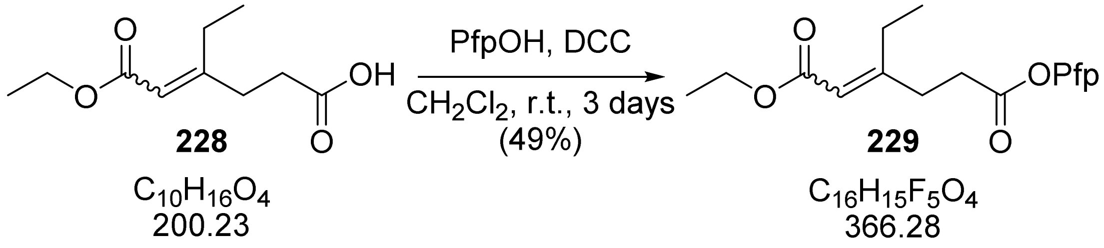
Analytical Data for ***(Z)*-228**:



^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.69 (s, 1 H, H^{2}), 4.16 (q, $^{3}J_{H9,H10}$ = 7.2 Hz, 2 H, H^{9}), 2.88 (≈t, $^{3}J_{H4,H5}$ = 7.6 Hz, 2 H, H^{4}), 2.58-2.48 (m, 2 H, H^{5}), 2.21 (dq, $^{3}J_{H7,H8}$ = 7.4 Hz, $^{4}J_{H7,H2}$ = 1.3 Hz, 2 H, H^{7}), 1.28 (t, $^{3}J_{H10,H9}$ = 7.2 Hz, 3 H, H^{10}), 1.08 (t, $^{3}J_{H8,H7}$ = 7.4 Hz, 3 H, H^{8})

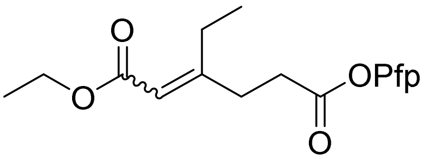
^{13}C-NMR (100 MHz, CDCl$_3$): δ 177.9 (C^{6}), 166.4 (C^{1}), 162.9 (C^{3}), 115.7 (C^{2}), 59.8 (C^{9}), 32.8 (C^{5}), 31.4 (C^{7}), 27.5 (C^{4}), 14.1 (C^{10}), 11.9 (C^{8})

5.2.15. (*E*/*Z*)- 1-Ethyl 6-perfluorophenyl 3-ethylhex-2-enedioate (229)[56]



To a stirred solution of acid **228** (110 mg, 0.55 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C and under argon was added pentafluorophenol (111 mg, 0.60 mmol) followed by N,N'-dicyclohexylcarbodiimide (127 mg, 0.62 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 days, then was filtered through a plug of Celite (eluting with 40 mL of CH_2Cl_2) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to afford 98 mg (49%) of *E*/*Z* mixture (60:40) of **229** as a clear, slightly yellowish oil.

Analytical Data for **229**:



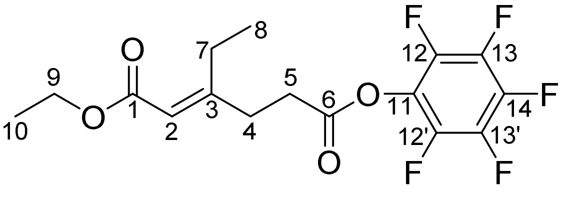
TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.56

MS-ESI: 389.1 (100, $[M+Na]^+$)

HR-MS (ESI): 389.07832 ($[M+Na]^+$; $C_{16}H_{15}F_5O_4Na^+$; calc. 389.07882)

IR (KBr, film): ν = 2932 (s), 2857 (m), 2669 (vw), 2461 (vw), 2120 (m), 1791 (vs), 1717 (vs), 1649 (s), 1521 (vs), 1466 (m), 1380 (m), 1314 (m), 1275 (m), 1207 (vs), 1150 (vs), 1100 (vs), 1042 (s), 1004 (vs), 873 (m), 741 (m), 729 (vw), 618 (vw), 553 (vw) cm^{-1}

Analytical Data for **(*E*)-229**:

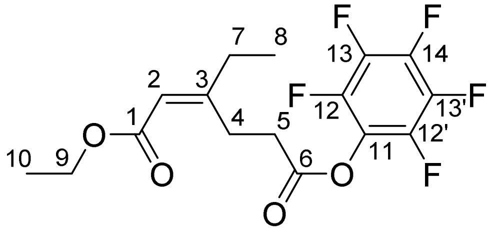


^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.67 (s, 1 H, H^2), 4.16 (q, $^3J_{H9,H10}$ = 7.1 Hz, 2 H, H^9), 2.86 (≈t, $^3J_{H4,H5}$ = 8.0 Hz, 2 H, H^4), 2.67 (q, $^3J_{H7,H8}$ = 7.5 Hz, 2 H, H^7), 2.63 (t, $^3J_{H5,H4}$ = 7.8 Hz, 2 H, H^5), 1.28 (t, $^3J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.12 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 168.4 (C^{6}), 165.9 (C^{1}), 165.9 (2 x ar.), 161.5 (C^{3}), 142.4 (ar.), 139.8 (ar.), 138.9 (ar.), 125.0 (ar.), 116.0 (C^{2}), 59.7 (C^{9}), 32.1 (C^{5}), 31.3 (C^{4}), 25.3 (C^{7}), 14.2 (C^{10}), 12.9 (C^{8})

^{19}F-NMR (376 MHz, CDCl$_3$): δ -151.5 (d, $^{3}J_{F12,F13} = {}^{3}J_{F12',F13'}$ = 19.4 Hz, 2 F, A$_2$B$_2$, F^{12}, F$^{12'}$), -156.7 (≈t, $^{3}J_{F14,F13} = {}^{3}J_{F14,F13'}$ = 19.1 Hz, 1 F, A$_2$B$_2$, F^{14}), -161.1 (≈t, $^{3}J_{F13,F14} = {}^{3}J_{F13,F12} = {}^{3}J_{F13',F14'} = {}^{3}J_{F13',F12'}$ = 20.1 Hz, 2 F, A$_2$B$_2$, F^{13}, F$^{13'}$)

Analytical Data for **(*Z*)-229**:

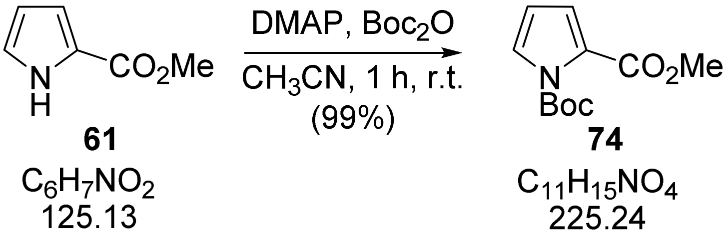


^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.75 (s, 1 H, H^{2}), 4.17 (q, $^{3}J_{H9,H10}$ = 7.1 Hz, 2 H, H^{9}), 3.01 (t, $^{3}J_{H4,H5}$ = 8.0 Hz, 2 H, H^{4}), 2.88 (≈t, $^{3}J_{H5,H4}$ = 8.0 Hz, 2 H, H^{5}), 2.26 (dq, $^{3}J_{H7,H8}$ = 7.4 Hz, $^{4}J_{H7,H2}$ = 1.4 Hz, 2 H, H^{7}), 1.29 (t, $^{3}J_{H10,H9}$ = 7.1 Hz, 3 H, H^{10}), 1.11 (t, $^{3}J_{H8,H7}$ = 7.4 Hz, 3 H, H^{8})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 168.9 (C^{6}), 166.2 (C^{1}), 165.9 (2 x ar.), 161.8 (C^{3}), 142.3 (ar.), 139.8 (ar.), 138.9 (ar.), 125.0 (ar.), 116.3 (C^{2}), 59.9 (C^{9}), 32.1 (C^{5}), 31.4 (C^{7}), 27.5 (C^{4}), 14.2 (C^{10}), 11.9 (C^{8})

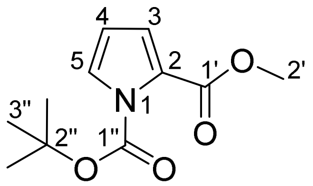
^{19}F-NMR (376 MHz, CDCl$_3$): δ -151.5 (d, $^{3}J_{F12,F13} = {}^{3}J_{F12',F13'}$ = 17.4 Hz, 2 F, A$_2$B$_2$, F^{12}, F$^{12'}$), -157.1 (≈t, $^{3}J_{F14,F13} = {}^{3}J_{F14,F13'}$ = 19.0 Hz, 1 F, A$_2$B$_2$, F^{14}), -161.4 (≈t, $^{3}J_{F13,F14} = {}^{3}J_{F13,F12} = {}^{3}J_{F13',F14} = {}^{3}J_{F13',F12'}$ = 20.7 Hz, 2 F, A$_2$B$_2$, F^{13}, F$^{13'}$)

5.2.16. 1-tert-Butyl 2-methyl 1H-pyrrole-1,2-dicarboxylate (74)[55]



At room temperature and under argon, $(Boc)_2O$ (1.92 g, 8.79 mmol) was added to a solution of a pyrrole (**61**) (1.0 g, 8.00 mmol) and DMAP (49 mg, 0.40 mmol) in dry CH_3CN (2.6 ml). The resulting mixture was stirred at room temperature for 1 h then diluted with 20 mL of water and 30 mL of EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give 1.78 g (99%) of **74** as a clear, colourless oil.

Analytical Data for **74**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.46

GC (method IZ): t_R = 8.87 min

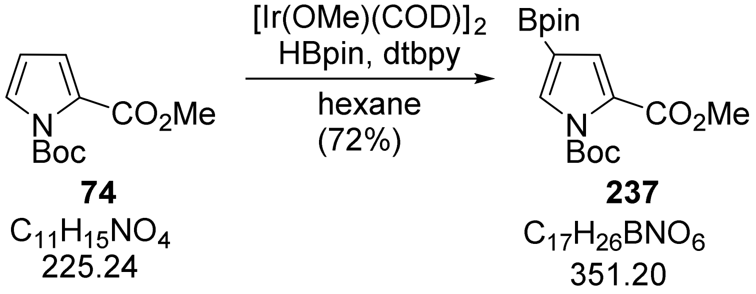
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, $^3J_{H5,H4}$ = 3.1 Hz, $^4J_{H5,H3}$ = 1.7 Hz, 1 H, H^5), 6.83 (dd, $^3J_{H3,H4}$ = 3.4 Hz, $^4J_{H3,H5}$ = 1.7 Hz, 1 H, H^3), 6.17 (t, $^3J_{H4,H3}$ = $^3J_{H4,H5}$ = 3.3 Hz, 1 H, H^3), 3.84 (s, 3 H, $H^{2'}$), 1.58 (s, 9 H, $H^{3''}$)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.3 ($C^{1'}$), 148.4 ($C^{1''}$), 126.7 (C^5), 125.2 (C^2), 120.8 (C^3), 110.1 (C^4), 84.8 ($C^{2''}$), 51.9 ($C^{2'}$), 27.7 ($C^{3''}$)

MS-ESI: 473.0 (100, $[2M+Na]^+$), 248.1 (88, $[M+Na]^+$), 192.0 (46, [M-33])

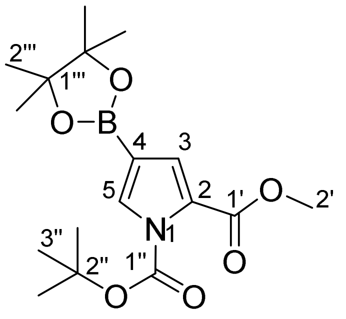
IR (KBr, film): ν = 3132 (vw), 2983 (m), 2953 (m), 1752 (vs), 1729 (vs), 1549 (w), 1451 (vs), 1414 (s), 1396 (m), 1371 (vs), 1358 (s), 1319 (vs), 1272 (vs), 1216 (vs), 1196 (vs), 1159 (vs), 1097 (vs), 1064 (s), 1021 (w), 949 (m), 887 (w), 848 (s), 797 (m), 775 (s), 759 (s), 746 (s), 646 (vw), 600 (vw), 569 (vw), 494 (vw), 450 (vw), 417 (vw) cm^{-1}

5.2.17. 1-*tert*-Butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-1,2-dicarboxylate (237)[36]



A glass microwave tube was initially charged with $[Ir(OMe)(COD)]_2$ (20 mg, 0.03 mmol, 3 mol % Ir) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (16 mg, 0.06 mmol, 3 mol %). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. 3 mL of dry and degased hexane were added at room temperature. To a resulting mixture were added dropwise pinacolborane (0.35 mL, 2.40 mmol) followed by pyrrole **74** (450 mg, 2.00 mmol). The resulting mixture were heated at 80 °C for 6 h, and then stirred at room temperature overnight. The reaction solution was filtered through a thin pad of Celite (eluting with 50 mL of EtOAc), and the eluent was concentrated under reduced pressure. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 50:50) to afford 508 mg (72%) of **237** as a white solid.

Analytical Data for **237**:



TLC: R_f (Petroleum ether/EtOAc, 95:5) = 0.12

GC (method IZ): t_R = 11.70 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.68 (d, $^4J_{H5,H3}$ = 1.7 Hz, 1 H, H^5), 7.12 (d, $^4J_{H3,H5}$ = 1.7 Hz, 1 H, H^3), 3.82 (s, 3 H, H$^{2'}$), 1.57 (s, 9 H, H$^{3''}$), 1.31 (s, 12 H, H$^{2'''}$)

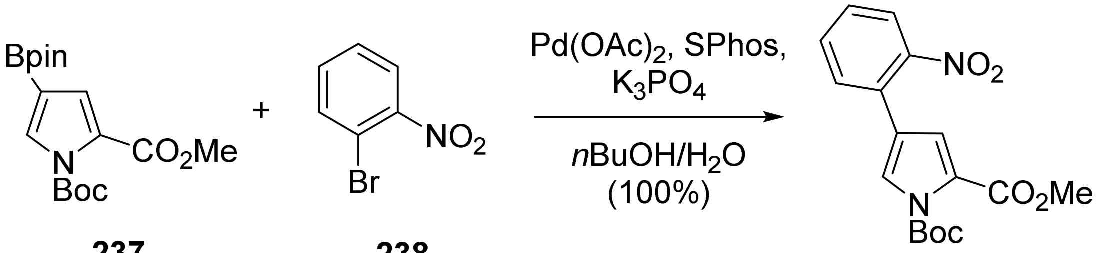
^{13}C-NMR (100 MHz, CDCl$_3$): δ 161.2 (C$^{1'}$), 148.0 (C$^{1''}$), 134.8 (C^5), 126.0 (C^2), 125.7 (C^3), 110.9 (C^4), 85.0 (C$^{2''}$), 83.6 (C$^{1'''}$), 51.8 (C$^{2'}$), 27.7 (C$^{3''}$), 24.8 (C$^{2'''}$)

MS-ESI: 374.2 (100, [M+Na]$^+$)

HR-MS (ESI): 374.17396 ([M+Na]$^+$; $C_{17}H_{26}BNO_6Na^+$; calc. 374.17509)

5.2.18. 1-tert-Butyl 2-methyl 4-(2-nitrophenyl)-1H-pyrrole-1,2-dicarboxylate (76)

Method A:[37]



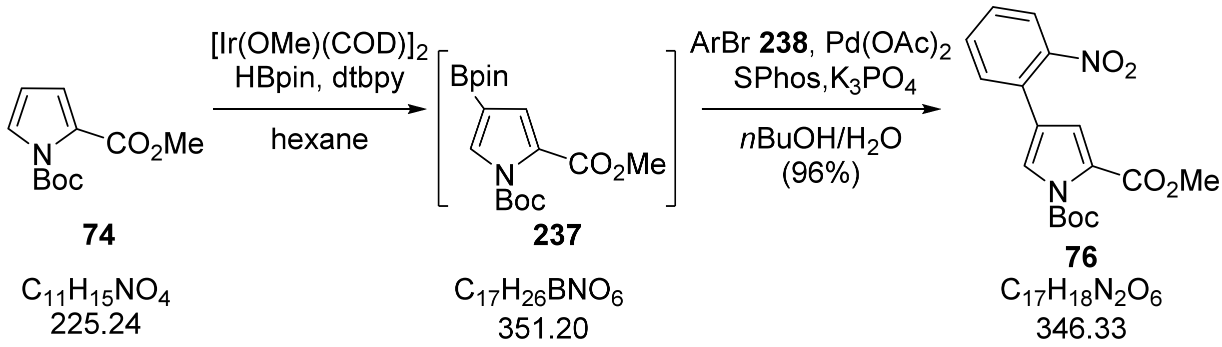
237 $C_{17}H_{26}BNO_6$ 351.20

238 $C_6H_4BrNO_2$ 202.01

76 $C_{17}H_{18}N_2O_6$ 346.33

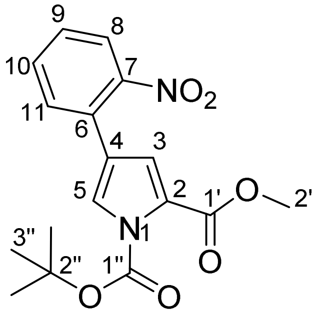
In an over-dried glass microwave flask, the solid starting materials were combined: *N*-(Boc)pyrrole pinacol boronate **237** (450 mg, 1.28 mmol), 2-bromo-nitrobenzene (**238**) (216 mg, 1.07 mmol), palladium acetate (12 mg, 0.05 mmol), 2-dicyclohexyl-phosphino-2′,6′-dimethoxybiphenyl (44 mg, 0.11 mmol), and K_3PO_4 (453 mg, 2.14 mmol). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. The solvent system (2.56 mL, 2.0 mL/mmol 2-bromo-nitrobenzene), consisting of degassed *n*-butanol (1.83 mL) and degassed deionized water (0.73 mL) in the ratio of 2.5:1 was added. The resulting mixture was heated at 35 °C for 16 h. The crude reaction mixture was then filtered through a plug of silica gel (eluting with 35 mL of EtOAc) and concentrated in vacuo. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 90:10) to provide 380 mg (100%) of desired Boc-protected phenylpyrrole **76** as a yellow oil.

Method B (one-pot synthesis):



A glass microwave flask was initially charged with [Ir(OMe)(COD)]$_2$ (20 mg, 0.03 mmol, 3 mol % Ir) and 4,4'-di*tert*butyl-2,2'-bipyridine (16 mg, 0.06 mmol, 3 mol %). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. 3 mL of dry and degased hexane were added at room temperature. To a resulting mixture were added dropwise pinacolborane (0.35 mL, 2.40 mmol) followed by pyrrole **74** (450 mg, 2.00 mmol). The resulting mixture were heated at 80 °C for 6 h, and then stirred at room temperature overnight. The screw cap was removed and the solid starting materials were added to a crude mixture: 2-bromo-nitrobenzene (**238**) (403 mg, 2.00 mmol), palladium acetate (19 mg, 0.04 mmol), SPhos (68 mg, 0.08 mmol), and K_3PO_4 (706 mg, 1.66 mmol). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. The solvent system (2.56 mL, 1.0 mL/mmol 2-bromo-nitrobenzene), consisting of degassed *n*-butanol (1.83 mL) and degassed deionized water (0.73 mL) in the ratio of 2.5:1 was added. The resulting mixture was heated at 35 °C for 16 h. The crude reaction mixture was then filtered through a plug of silica gel (eluting with 30 mL of EtOAc) and concentrated in vacuo. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 90:10) to give 661 mg (96% starting from pyrrole **74**) of desired Boc-protected phenylpyrrole **76** as a yellow oil.

Analytical Data for **76**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.30

^{1}H-NMR (400 MHz, acetone-d_6): δ 7.87 (dd, $^{3}J_{H8,H9}$ = 8.1 Hz, $^{4}J_{H8,H10}$ = 1.0 Hz, 1 H, H^{8}), 7.72 (ddd, $^{3}J_{H10,H11}$ = 7.9 Hz, $^{3}J_{H10,H9}$ = 6.9, $^{4}J_{H10,H8}$ = 1.2 Hz, 1 H, H^{10}), 7.68 (dd, $^{3}J_{H11,H10}$ = 7.7 Hz, $^{4}J_{H11,H9}$ = 1.8 Hz, 1 H, H^{11}), 7.60 (d, $^{4}J_{H5,H3}$ = 1.9 Hz, 1 H, H^{5}), 7.59 (ddd, $^{3}J_{H9,H8}$ = 8.0 Hz, $^{3}J_{H9,H10}$ = 6.9 Hz, $^{4}J_{H9,H11}$ = 1.9 Hz, 1 H, H^{9}), 6.90 (d, $^{4}J_{H3,H5}$ = 1.9 Hz, 1 H, H^{3}), 3.84 (s, 3 H, $H^{2'}$), 1.60 (s, 9 H, $H^{3''}$)

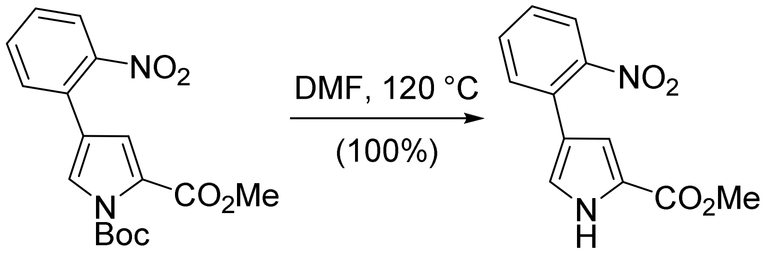
^{13}C-NMR (100 MHz, acetone-d_6): δ 161.4 ($C^{1'}$), 150.1 ($C^{1''}$), 148.9 (C^{7}), 133.2 (C^{9}), 132.3 (C^{11}), 129.4 (C^{10}), 128.0 (C^{6}), 126.8 (C^{4}), 125.2 (C^{5}), 124.6 (C^{8}), 121.8 (C^{2}), 119.9 (C^{3}), 86.3 ($C^{2''}$), 52.4 ($C^{2'}$), 27.7 ($C^{3''}$)

MS-ESI: 369.3 (100, $[M+Na]^+$), 269.2 (17, [M-77])

HR-MS (ESI): 369.10566 ($[M+Na]^+$; $C_{17}H_{18}N_2O_6Na^+$; calc. 369.10626)

IR (KBr, film): ν = 3134 (w), 2983 (m), 2954 (m), 1732 (vs), 1613 (m), 1569 (m), 1529 (vs), 1459 (s), 1436 (s), 1395 (vs), 1371 (vs), 1344 (vs), 1284 (vs), 1246 (m), 1155 (vs), 1078 (vs), 1037 (w), 954 (m), 929 (w), 849 (vs), 802 (m), 776 (vs), 748 (vs), 704 (w), 648 (w), 634 (w), 596 (vw), 527 (vw) cm^{-1}

5.2.19. Methyl 4-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate (28)[39]

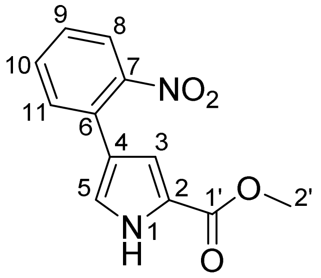


76 $C_{17}H_{18}N_2O_6$ 346.33

28 $C_{12}H_{10}N_2O_4$ 246.22

Under argon, a solution of Boc-protected phenylpyrrole **76** (330 mg, 0.95 mmol) in dry DMF (3 mL) was heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and poured into water (100 mL). The aqueous layer was extracted with EtOAc (3 x 60 mL). Combined organic extracts were washed with water (2 x 50 mL), brine (60 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 70:30) to afford 243 mg (100%) of deprotected phenylpyrrole **28** as a yellow solid.

Analytical Data for **28**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.15

GC (method IZ): t_R = 14.04 min

^{1}H-NMR (400 MHz, acetone-d$_6$): δ 11.28 (br s, 1 H, NH), 7.75 (dd, $^3J_{H8,H9}$ = 7.9 Hz, $^4J_{H8,H10}$ = 0.9 Hz, 1 H, H^8), 7.68 (dd, $^3J_{H11,H10}$ = 7.6 Hz, $^4J_{H11,H9}$ = 1.8 Hz, 1 H, H^{11}), 7.65 (ddd, $^3J_{H10,H11}$ = 7.8 Hz, $^3J_{H10,H9}$ = 6.6, $^4J_{H10,H8}$ = 1.2 Hz, 1 H, H^{10}), 7.49 (ddd, $^3J_{H9,H8}$ = 8.1 Hz, $^3J_{H9,H10}$ = 6.8 Hz, $^4J_{H9,H11}$ = 1.9 Hz, 1 H, H^9), 7.30 (dd, $^3J_{H5,H1}$ = 3.0 Hz, $^4J_{H5,H3}$ = 1.8 Hz, 1 H, H^5), 6.93 (t, $^4J_{H3,H5}$ = $^4J_{H3,H1}$ = 1.9 Hz, 1 H, H^3), 3.81 (s, 3 H, $H^{2'}$)

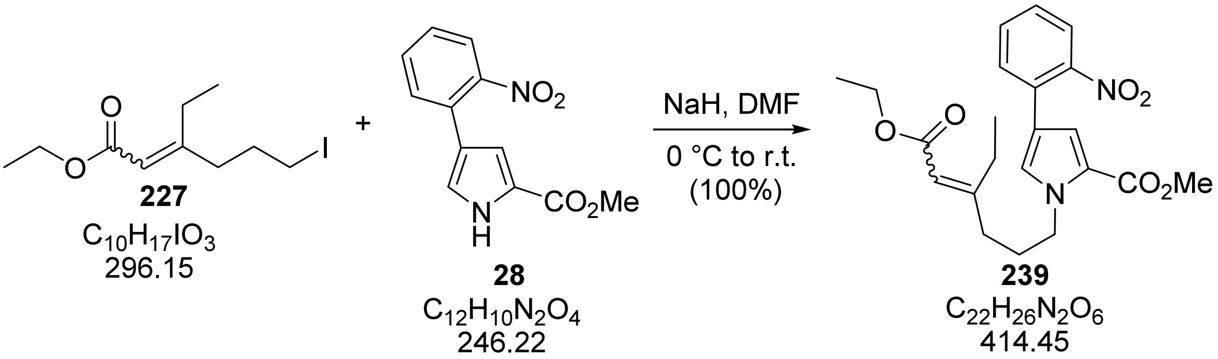
^{13}C-NMR (100 MHz, acetone-d$_6$): δ 161.5 (C$^{1'}$), 150.3 (C^{7}), 132.7 (C^{10}), 131.7 (C^{11}), 129.1 (C^{6}), 128.3 (C^{9}), 124.5 (C^{2}), 124.1 (C^{8}), 123.1 (C^{5}), 121.1 (C^{4}), 114.6 (C^{3}), 51.6 (C$^{2'}$)

MS-ESI: 245.3 (100, [M-H]$^-$)

HR-MS (ESI): 269.05355 ([M+Na]$^+$; $C_{12}H_{10}N_2O_4Na^+$; calc. 269.05383)

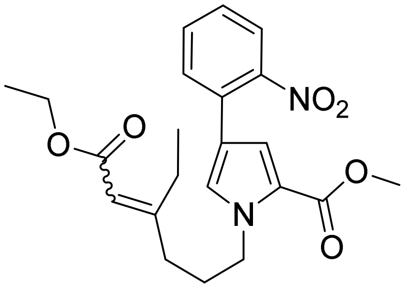
IR (KBr): ν = 3282 (vs), 3128 (w), 2956 (m), 2925 (s), 2855 (m), 1967 (vw), 1926 (vw), 1697 (vs), 1608 (s), 1568 (m), 1516 (vs), 1438 (s), 1393 (s), 1367 (s), 1309 (s), 1292 (s), 1251 (m), 1217 (s), 1174 (m), 1151 (s), 1048 (w), 992 (m), 943 (w), 929 (w), 854 (m), 834 (s), 807 (vw), 764 (vs), 741 (vs), 703 (m), 648 (m), 611 (w), 543 (w), 503 (w), 459 (vw), 438 (vw), 419 (vw) cm^{-1}

5.2.20. (E/Z) - Methyl 1-(6-ethoxy-4-ethyl-6-oxohex-4-enyl)-4-(2-nitrophenyl)-1H-pyrrole-2-carboxylate (239)



To a solution of phenylpyrrole **28** (20 g, 0.08 mmol) in dry DMF (0.3 mL) at 0 °C was added 95% NaH (2 mg, 0.09 mmol) under argon. After 10 min at 0 °C, the solution was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, and a solution of iodo acrylate **227** (26 mg, 0.09 mmol) in dry DMF (0.1 mL) was added dropwise. The flask containing **227** was rinsed with an additional 0.2 mL of dry DMF. The resulting solution was stirred at room temperature for 6 h, and then poured into water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (petroleum ether and then petroleum ether/EtOAc, 90:10) to afford 36 mg (100%) of *E*/*Z* mixture (70:30) of **239** as a yellowish oil.

Analytical Data for **239**:



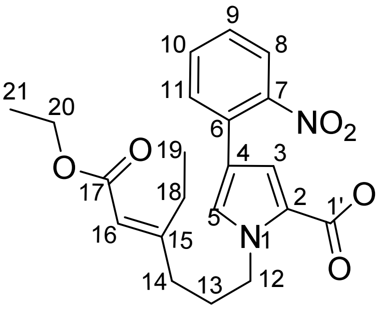
TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.33

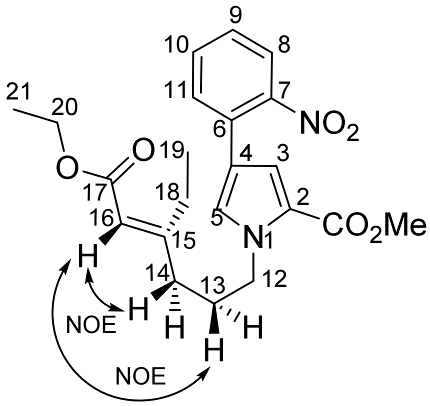
MS-ESI: 437.5 (100, $[M+Na]^+$), 453.3 (13, $[M+K]^+$)

HR-MS (ESI): 437.16802 ($[M+Na]^+$; $C_{22}H_{26}N_2O_6Na^+$; calc. 437.16886)

IR (KBr, film): ν = 3065 (w), 2956 (s), 2874 (m), 1713 (vs), 1645 (s), 1609 (s), 1563 (s), 1531 (vs), 1495 (s), 1476 (s), 1446 (vs), 1394 (vs), 1368 (vs), 1259 (vs), 1206 (vs), 1148 (vs), 1105 (vs), 1038 (s), 959 (w), 933 (m), 853 (s), 812 (w), 779 (m), 749 (vs), 696 (m), 674 (vw), 651 (w), 561 (vw), 509 (vw), 445 (vw) cm^{-1}

Analytical Data for **(*E*)-239**:





^{1}H-NMR (400 MHz, acetone-d$_6$): δ 7.75 (dd, $^3J_{H8,H9}$ = 7.9 Hz, $^4J_{H8,H10}$ = 2.4 Hz, 1 H, H^8), 7.68-7.62 (m, 2 H, H^{10}, H^{11}), 7.49 (ddd, $^3J_{H9,H10}$ = 8.8 Hz, $^3J_{H9,H8}$ = 8.1 Hz, $^4J_{H9,H11}$ = 4.3 Hz, 1 H, H^9), 7.35 (d, $^4J_{H5,H3}$ = 2.1 Hz, 1 H, H^5), 6.99 (d, $^4J_{H3,H5}$ = 2.1 Hz, 1 H, H^3), 5.63 (s, 1 H, H^{16}), 4.45 (t, $^3J_{H12,H13}$ = 7.1 Hz, 2 H, H^{12}), 4.08 (q, $^3J_{H20,H21}$ = 7.1 Hz, 2 H, H^{20}), 3.81 (s, 3 H, $H^{2'}$), 2.64 (q, $^3J_{H18,H19}$ = 7.5 Hz, 2 H, H^{18}), 2.23 (≈t, $^3J_{H14,H13}$ = 7.5 Hz, 2 H, H^{14}), 2.00 (≈quint,

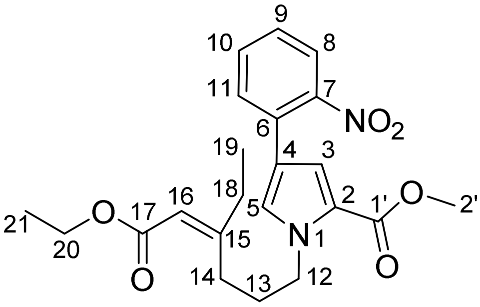
${}^{3}J_{H13,H14} = {}^{3}J_{H13,H12} = 7.3$ Hz, 2 H, H^{13}), 1.21 (t, ${}^{3}J_{H21,H20} = 7.1$ Hz, 3 H, H^{21}), 1.03 (t, ${}^{3}J_{H19,H18} =$ 7.5 Hz, 3 H, H^{19})

^{1}H, NOE diff: irrad H^{16} (5.63) → enh H^{14} (2.23) and H^{13} (2.00)

^{13}C-NMR (100 MHz, acetone-d$_6$): δ 166.4 (C^{17}), 165.1 (C^{15}), 161.6 ($C^{1'}$), 150.2 (C^{7}), 132.7 (C^{10}), 131.6 (C^{11}), 128.9 (C^{6}), 128.6 (C^{5}), 128.3 (C^{9}), 124.2 (C^{8}), 123.3 (C^{2}), 119.0 (C^{4}), 117.5 (C^{3}), 116.0 (C^{16}), 59.8 (C^{20}), 51.5 ($C^{2'}$), 49.5 (C^{12}), 35.2 (C^{14}), 30.2 (C^{13}), 25.3 (C^{18}), 14.6 (C^{21}), 13.3 (C^{19})

GC (method IZ): $t_R = 21.27$ min

Analytical Data for **(*Z*)-239**:

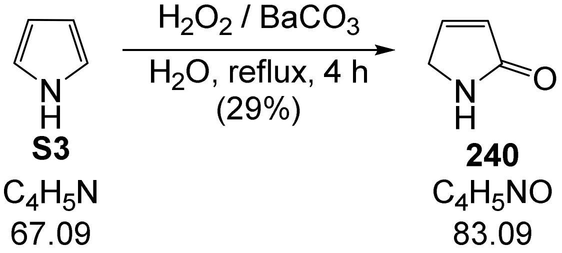


^{1}H-NMR (400 MHz, acetone-d$_6$): δ 7.75 (dd, ${}^{3}J_{H8,H9} = 7.9$ Hz, ${}^{4}J_{H8,H10} = 2.4$ Hz, 1 H, H^{8}), 7.68-7.62 (m, 2 H, H^{10}, H^{11}), 7.49 (ddd, ${}^{3}J_{H9,H10} = 8.8$ Hz, ${}^{3}J_{H9,H8} = 8.1$ Hz, ${}^{4}J_{H9,H11} = 4.3$ Hz, 1 H, H^{9}), 7.37 (d, ${}^{4}J_{H5,H3} = 2.1$ Hz, 1 H, H^{5}), 6.98 (d, ${}^{4}J_{H3,H5} = 2.1$ Hz, 1 H, H^{3}), 5.66 (s, 1 H, H^{16}), 4.44 (t, ${}^{3}J_{H12,H13} = 7.2$ Hz, 2 H, H^{12}), 4.10 (q, ${}^{3}J_{H20,H21} = 7.0$ Hz, 2 H, H^{20}), 3.80 (s, 3 H, $H^{2'}$), 2.67 (≈t, ${}^{3}J_{H14,H13} = 7.7$ Hz, 2 H, H^{14}), 2.22 (dq, ${}^{3}J_{H18,H19} = 7.5$ Hz, ${}^{4}J_{H18,H16} = 1.2$ Hz, 2 H, H^{18}), 1.97 (≈quint, ${}^{3}J_{H13,H14} = {}^{3}J_{H13,H12} = 7.4$ Hz, 2 H, H^{13}), 1.22 (t, ${}^{3}J_{H21,H20} = 7.1$ Hz, 3 H, H^{21}), 1.05 (t, ${}^{3}J_{H19,H18} = 7.4$ Hz, 3 H, H^{19})

^{13}C-NMR (100 MHz, acetone-d$_6$): δ 166.4 (C^{17}), 164.9 (C^{15}), 161.6 ($C^{1'}$), 150.2 (C^{7}), 132.7 (C^{10}), 131.6 (C^{11}), 128.9 (C^{6}), 128.6 (C^{5}), 128.2 (C^{9}), 124.2 (C^{8}), 123.3 (C^{2}), 118.9 (C^{4}), 117.4 (C^{3}), 115.8 (C^{16}), 60.0 (C^{20}), 51.5 ($C^{2'}$), 49.9 (C^{12}), 31.5 (C^{18}), 30.9 (C^{13}), 29.6 (C^{14}), 14.3 (C^{21}), 12.3 (C^{19})

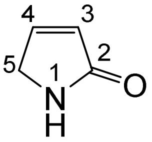
GC (method IZ): $t_R = 20.55$ min

5.2.21. 1H-Pyrrole-2(5H)-one (240)



To a solution of pyrrole **S3** (5.00 g, 74.5 mmol) in water (450 mL) were added H_2O_2 (35%, 6.18 mL, 74.5 mmol) and $BaCO_3$ (1.50 g, 7.6 mmol). The resulting mixture was stirred at reflux for 4 h. The excess of oxidant was destroyed with small quantity of PbO_2, the inorganic salts were filtered through Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (T=100-130 °C), P=0.5 mmHg) to give 1.8 g (29%) of **240** as a light yellow oil.

Analytical Data for **240**:



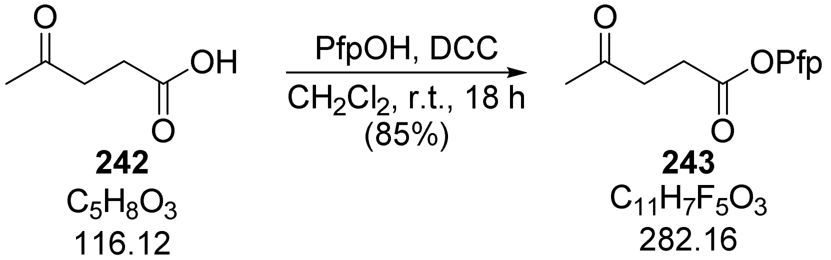
^{1}H-NMR (400 MHz, CDCl$_3$): δ 6.91 (dq, $^3J_{H3,H4} = 5.6$ Hz, $^4J_{H3,H5} = {}^4J_{H3,H1} = 1.7$ Hz, 1 H, H^3), 5.85 (≈dq, $^3J_{H4,H3} = 5.6$ Hz, $^3J_{H4,H5} = {}^4J_{H4,H1} \approx 1.9$ Hz, 1 H, H^4), 3.78 (≈q, $^3J_{H5,H1} \approx {}^3J_{H5,H4} \approx {}^4J_{H5,H3} \approx 1.8$ Hz, 2 H, H^5)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 175.9 (C^2), 146.5 (C^3), 127.6 (C^4), 49.3 (C^5)

MS-ESI: 84.1 (100, $[M+H]^+$)

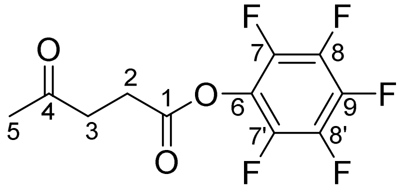
IR (KBr, film): ν = 3271 (m), 1672 (vs), 1583(w), 1449 (w), 1245 (w), 1101 (vw), 1055 (vw), 943 (vw), 807 (m), 692 (w), 485 (vw) cm^{-1}

5.2.22. Perfluorophenyl 4-oxopentanoate (243)[56]



To a stirred solution of levulinic acid (**242**) (0.96 mL, 9.38 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C and under argon was added pentafluorophenol (1.90 g, 10.32 mmol) followed by N,N'-dicyclohexylcarbodiimide (2.17 g, 10.51 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h, then was filtered through a plug of Celite (eluting with 40 mL of CH_2Cl_2) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent to afford 2.90 g (85%) of **243** as a colourless oil which solidifies upon cooling in a refrigerator overnight.

Analytical Data for **243**:



TLC: R_f (CH_2Cl_2) = 0.43

MS-ESI: 304.9 (100, $[M+Na]^+$), 301.1 (86, $[M+H_2O+H]^+$)

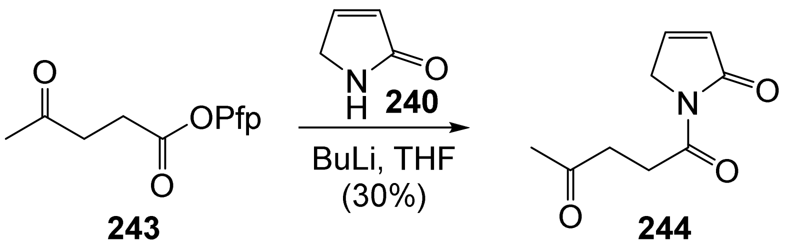
^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.96-2.88 (m, 4 H, H^2, H^3), 2.23 (s, 3 H, H^5)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 205.3 (C^4), 168.9 (C^1), 142.3 (ar.), 139.9 (ar.), 139.1 (ar.), 138.2 (ar.), 136.6 (ar.), 125.0 (ar.), 37.7 (C^3), 29.7 (C^5), 27.2 (C^2)

^{19}F-NMR (376 MHz, $CDCl_3$): δ -153.5 (d, $^3J_{F7,F8} = {}^3J_{F7',H8'}$ = 18.2 Hz, 2 F, A_2B_2, F^7, $F^{7'}$), -159.0 (t, $^3J_{F9,F8} = {}^3J_{F9,F8'}$ = 21.7 Hz, 1 F, A_2B_2, F^9), -163.4 (≈t, $^3J_{F8,F7} = {}^3J_{F8,F9} = {}^3J_{F8',F7'} = {}^3J_{F8',F9}$ = 19.9 Hz, 2 F, A_2B_2, F^8, $F^{8'}$)

IR (KBr, film): ν = 3556 (vw), 3419 (vw), 2953 (m), 2669 (w), 2461 (w), 2141 (w), 2097 (w), 1783 (vs), 1717 (vs), 1657 (m), 1521 (vs), 1470 (m), 1418 (vs), 1365 (s), 1346 (m), 1317 (vs), 1302 (vs), 1154 (vs), 1118 (vs), 1077 (vs), 1039 (s), 991 (vs), 913 (s), 839 (m), 753 (m), 701 (vw), 622 (m), 580 (s), 488 (w), 428 (m) cm^{-1}

5.2.23. 1-(2-Oxo-2,5-dihydro-1H-pyrrol-1-yl)pentane-1,4-dione (244)

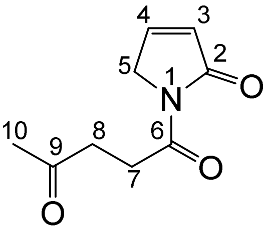


243
$C_{11}H_7F_5O_3$
282.17

244
$C_9H_{11}NO_3$
181.19

To a solution of pyrrol-2-one **240** (0.5 g, 6.02 mmol) in dry THF (80 mL) was added dropwise BuLi (1.6 M in cyclohexane, 4.21 mL, 6.74 mmol) at 0 °C and under argon. After 1.5 h at 0 °C, a solution of activated ester **243** (1.92 g, 6.80 mmol) in dry THF (30 mL) was added dropwise over 15 min. The mixture was allowed to stir for an additional 30 min at 0 °C, then 3 h at room temperature. The resulting mixture was quenched with a solution of saturated NH_4Cl (20 mL) and extracted with $CHCl_3$ (3 x 40 mL). The combined organic phases dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to afford 332 mg (30%) of **244** as an orange oil.

Analytical Data for **244**:

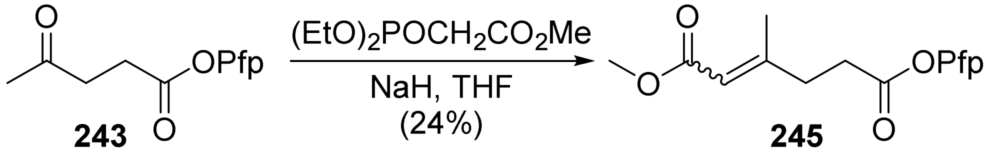


TLC: R_f (CH_2Cl_2/MeOH, 9:1) = 0.56

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.30 (m, 1 H, H^3), 6.19-6.18 (m, 1 H, H^4), 4.40-4.39 (m, 2 H, H^5), 3.25-3.22 (m, 2 H, H^7), 2.83-2.80.71 (m, 2 H, H^8), 2.23 (s, 3 H, H^{10})

^{13}C-NMR (100 MHz, $CDCl_3$): δ 207.2 (C^9), 172.2 (C^6), 170.2 (C^2), 146.8 (C^3), 127.8 (C^4), 50.7 (C^5), 37.1 (C^8), 30.8 (C7), 30.1 (C^{10})

5.2.24. (E/Z)- 1-Methyl 6-perfluorophenyl 3-methylhex-2-enedioate (245)

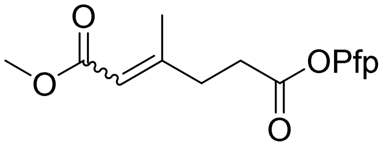


243 $C_{11}H_7F_5O_3$ 286.16

245 $C_{14}H_{11}F_5O_4$ 338.23

A flame-dried 25 mL two-necked round bottom flask was charged with NaH (333 mg of 95%, 13.88 mmol) and 10 mL of dry THF. Neat methyl diethylphosphonoacetate (2.24 mL, 12.20 mmol) was then added slowly (in 5 min.) to the suspension at 0 °C. The resulting mixture was stirred at room temperature for 45 min and a solution of the ketone **243** (0.50 g, 1.77 mmol) in dry THF (5 mL) was added. The homogeneous mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with brine (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to afford 140 mg (24%) of *E*/*Z* mixture (70:30) of **245** as a clear, slightly yellowish oil.

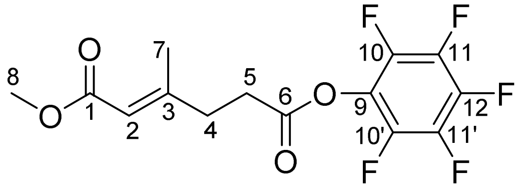
Analytical Data for **245**:

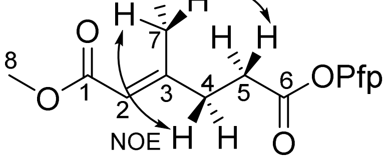


TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.51

MS (EI, 70 eV): 395.2 (88, $[M+K+H_2O]^+$), 209.1 (100)

Analytical Data for **(*E*)-245**:





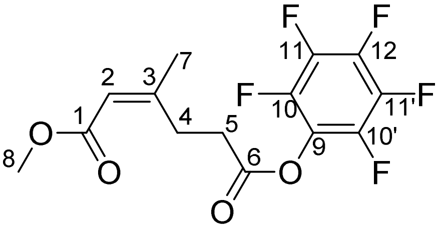
¹H-NMR (400 MHz, CDCl₃): δ 5.67 (≈q, $^4J_{H2,H7}$ = 1.3 Hz, 1 H, H^2), 3.69 (s, 3 H, H^8), 2.50-2.47 (m, 4 H, H^4, H^5), 2.16 (d, $^4J_{H7,H2}$ = 1.3 Hz, 3 H, H^7)

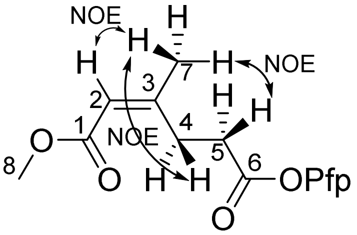
¹H, NOE diff: irrad H^7 (2.61) → enh H^4 and H^5 (2.50-2.47)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 173.1 (C^{6}), 167.1 (C^{1}), 157.8 (C^{3}), 139.2 (2 x ar.), 136.7 (2 x ar.), 134.0 (ar.), 131.3 (ar.), 115.8 (C^{2}), 51.0 (C^{8}), 35.5 (C^{4}), 31.9 (C^{5}), 18.7 (C^{7})

^{19}F-NMR (376 MHz, CDCl$_3$): δ -164.2 (dd, $^{3}J_{F10,F11} = {}^{3}J_{F10',F11'}$ = 17.5 Hz, $^{4}J_{F10,F12} = {}^{4}J_{F10',F12}$ = 5.5 Hz, 2 F, A$_2$B$_2$, F^{10}, F$^{10'}$), -164.9 (≈dt, $^{3}J_{F11,F12} = {}^{3}J_{F11',F12} = {}^{3}J_{F11,F10'} = {}^{3}J_{F11',F10'}$ = 21.8 Hz, $^{4}J_{F11,F11'} = {}^{4}J_{F11',F11}$ = 4.3 Hz, 2 F, A$_2$B$_2$, F^{11}, F$^{11'}$), -169.8 (tt, $^{3}J_{F12,F11} = {}^{3}J_{F12,F11'}$ = 22.0 Hz, $^{4}J_{F12,F10} = {}^{4}J_{F12,F10'}$ = 5.5 Hz, 2 F, A$_2$B$_2$, F^{13}, F$^{13'}$)

Analytical Data for **(*Z*)-245**:





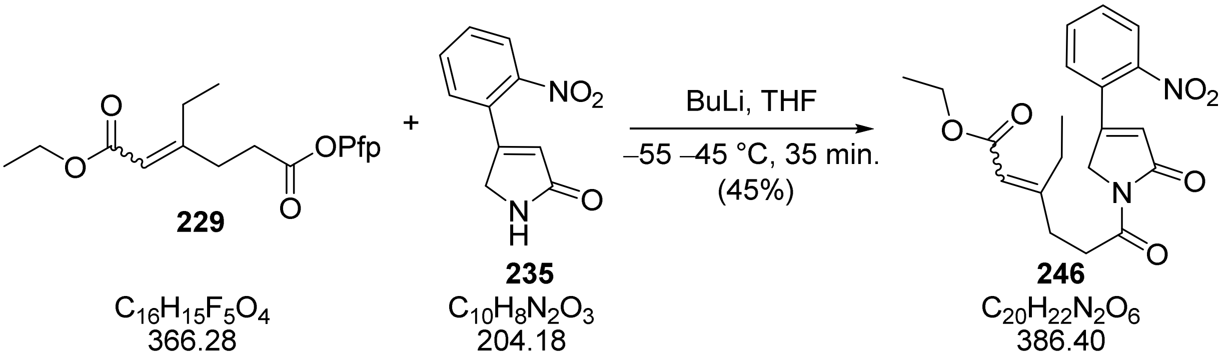
^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.71 (≈tq, $^{4}J_{H2,H7}$ = 1.4 Hz, $^{4}J_{H2,H4}$ = 0.6 Hz, 1 H, H^{2}), 3.68 (s, 3 H, H^{8}), 2.91 (≈t, $^{3}J_{H4,H5}$ = 7.6 Hz, 2 H, H^{4}), 2.53-2.51 (m, 2 H, H^{5}), 1.91 (d, $^{4}J_{H7,H2}$ = 1.4 Hz, 3 H, H^{7})

^{1}H, NOE diff: irrad H^{7} (1.91) → enh H^{2} (5.71), H^{4} (2.91) and H^{5} (2.53-2.51)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 173.5 (C^{6}), 166.6 (C^{1}), 158.4 (C^{3}), 139.2 (2 x ar.), 136.7 (2 x ar.), 134.0 (ar.), 131.3 (ar.), 116.9 (C^{2}), 51.8 (C^{8}), 32.4 (C^{5}), 28.7 (C^{4}), 25.1 (C^{7})

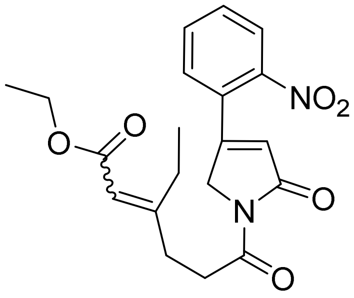
^{19}F-NMR (376 MHz, CDCl$_3$): δ -164.2 (dd, $^{3}J_{F10,F11} = {}^{3}J_{F10',F11'}$ = 17.5 Hz, $^{4}J_{F10,F12} = {}^{4}J_{F10',F12}$ = 5.5 Hz, 2 F, A$_2$B$_2$, F^{10}, F$^{10'}$), -164.9 (≈dt, $^{3}J_{F11,F12} = {}^{3}J_{F11',F12} = {}^{3}J_{F11,F10'} = {}^{3}J_{F11',F10'}$ = 21.8 Hz, $^{4}J_{F11,F11'} = {}^{4}J_{F11',F11}$ = 4.3 Hz, 2 F, A$_2$B$_2$, F^{11}, F$^{11'}$), -169.8 (tt, $^{3}J_{F12,F11} = {}^{3}J_{F12,F11'}$ = 22.0 Hz, $^{4}J_{F12,F10} = {}^{4}J_{F12,F10'}$ = 5.5 Hz, 2 F, A$_2$B$_2$, F^{13}, F$^{13'}$)

5.2.25. (E/Z)-Ethyl 3-ethyl-6-(4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-6-oxohex-2-enoate (246)



To a solution of pyrrolinone **235** (50 mg, 0.25 mmol) in dry THF (3.0 mL) was added dropwise BuLi (2.0 M in cyclohexane, 0.13 mL, 0.25 mmol) at -55 °C and under argon. After 10 min at -54 °C, a solution of activated ester **229** (98 mg, 0.27 mmol) in dry THF (2.0 mL) was added dropwise over 15 min. The mixture was allowed to stir for an additional 5 min. Over this 30 min period, the temperature had been allowed to reach -45 °C. The mixture was quenched with AcOH (0.1 mL) and evaporated with 5 mL of silica. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 70:30 to 50:50) to afford 43 mg (45%) of *E*/*Z* mixture (70:30) of **246** as an orange oil.

Analytical Data for **246**:



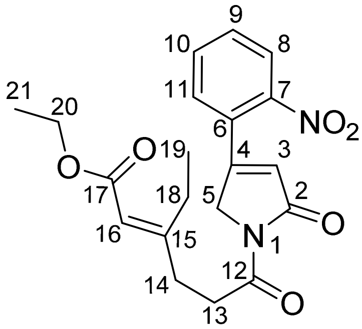
TLC: R_f (Petroleum ether/EtOAc, 50:50) = 0.45

HPLC-MS (EI, 70 eV): t_R = 6.94 min ((***E***)-**57**); 7.08 min ((***Z***)-**57**); m/z (%) = 425.1 (11, [M+K]$^+$), 409.2 (100, [M+Na]$^+$), 387.2 (14, [M+H]$^+$)

HR-MS (ESI): 409.13695 ([M+Na]$^+$; $C_{20}H_{22}N_2O_6Na^+$; calc. 409.13756)

IR (KBr, film): ν = 3079 (vw), 2979 (w), 2924 (w), 1744 (s), 1713 (vs), 1683 (s), 1646 (s), 1601 (w), 1570 (w), 1531 (s), 1478 (w), 1446 (m), 1373 (m), 1349 (s), 1319 (s), 1259 (m), 1239 (s), 1208 (s), 1190 (s), 1172 (s), 1152 (s), 1085 (w), 1048 (m), 984 (w), 897 (w), 882 (w), 866 (m), 796 (w), 755 (m), 726 (w), 697 (w), 688 (w), 646 (vw), 629 (vw), 574 (vw), 533 (vw) cm^{-1}

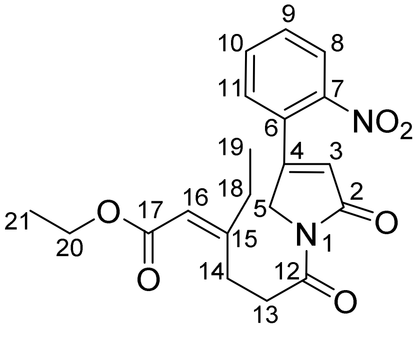
Analytical Data for ***(E)*-246**:



^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.11-8.08 (m, 1 H, H^8), 7.73 (td, $^3J_{H10,H11}$ = $^3J_{H10,H9obs.}$ = 7.3 Hz, $^4J_{H10,H8obs.}$ = 2.4 Hz, 1 H, H^{10}), 7.67-7.62 (m, 1 H, H^9), 7.41 (dd, $^3J_{H11,H10}$ = 7.2 Hz, $^4J_{H11,H9obs.}$ = 2.3 Hz, 1 H, H^{11}), 6.15 (t, $^4J_{H3,H5}$ = 1.5 Hz, 1 H, H^3), 5.71 (s, 1 H, H^{16}), 4.64 (d, $^4J_{H5,H3}$ = 1.5 Hz, 2 H, H^5), 4.15 (q, $^3J_{H20,H21}$ = 7.1 Hz, 2 H, H^{20}), 3.21-3.13 (m, 2 H, H^{13}), 2.68 (q, $^3J_{H18,H19}$ = 7.5 Hz, 2 H, H^{18}), 2.23 (td, $^3J_{H14,H13}$ = 7.6 Hz, $^4J_{H14,H16}$ = 0.8 Hz, 2 H, H^{14}), 1.28 (t, $^3J_{H21,H20}$ = 7.1 Hz, 3 H, H^{21}), 1.12 (t, $^3J_{H19,H18}$ = 7.5 Hz, 3 H, H^{19})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 171.8 (C^{12}), 168.7 (C^2), 166.3 (C^{17}), 163.5 (C^{15}), 156.8 (C^4), 147.6 (C^7), 133.6 (C^{10}), 130.9 (C^9), 130.1 (C^{11}), 128.0 (C^6), 125.1 (C^8), 124.5 (C^3), 115.5 (C^{16}), 59.6 (C^{20}), 52.3 (C^5), 34.7 (C^{13}), 31.8 (C^{14}), 25.5 (C^{18}), 14.3 (C^{21}), 13.0 (C^{19})

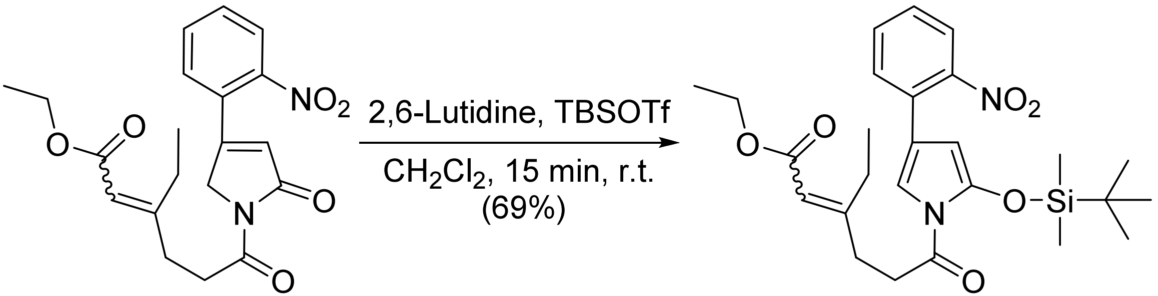
Analytical Data for ***(Z)*-246**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.11-8.08 (m, 1 H, H^{8}), 7.73 (td, $^{3}J_{\mathrm{H10,H11}}$ = $^{3}J_{\mathrm{H10,H9}\mathit{obs.}}$ = 7.3 Hz, $^{4}J_{\mathrm{H10,H8}\mathit{obs.}}$ = 2.4 Hz, 1 H, H^{10}), 7.67-7.62 (m, 1 H, H^{9}), 7.41 (dd, $^{3}J_{\mathrm{H11,H10}}$ = 7.2 Hz, $^{4}J_{\mathrm{H11,H9}\mathit{obs.}}$ = 2.3 Hz, 1 H, H^{11}), 6.13 (t, $^{4}J_{\mathrm{H3,H5}}$ = 1.5 Hz, 1 H, H^{3}), 5.69 (s, 1 H, H^{16}), 4.64 (d, $^{4}J_{\mathrm{H5,H3}}$ = 1.5 Hz, 2 H, H^{5}), 4.14 (q, $^{3}J_{\mathrm{H20,H21}}$ = 7.1 Hz, 2 H, H^{20}), 3.21-3.13 (m, 2 H, H^{13}), 2.97 (≈t, $^{3}J_{\mathrm{H14,H13}}$ = 7.9 Hz, 2 H, H^{14}), 2.26 (q, $^{3}J_{\mathrm{H18,H19}}$ = 7.3 Hz, 2 H, H^{18}), 1.27 (t, $^{3}J_{\mathrm{H21,H20}}$ = 7.1 Hz, 3 H, H^{21}), 1.11 (t, $^{3}J_{\mathrm{H19,H18}}$ = 7.3 Hz, 3 H, H^{19})

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2 (C^{12}), 168.7 (C^{2}), 166.4 (C^{17}), 163.5 (C^{15}), 156.5 (C^{4}), 147.6 (C^{7}), 133.5 (C^{10}), 130.8 (C^{9}), 130.1 (C^{11}), 128.1 (C^{6}), 125.0 (C^{8}), 124.6 (C^{3}), 115.6 (C^{16}), 59.6 (C^{20}), 52.3 (C^{5}), 35.4 (C^{13}), 31.4 (C^{18}), 26.9 (C^{14}), 14.3 (C^{21}), 11.9 (C^{19})

5.2.26. (E/Z)- Ethyl 6-(2-((tert-butyldimethylsilyl)oxy)-4-(2-nitrophenyl)-1H-pyrrol-1-yl)-3-ethyl-6-oxohex-2-enoate (257)

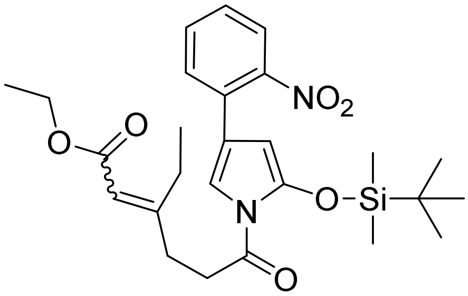


246
$C_{20}H_{22}N_2O_6$
386.40

257
$C_{26}H_{36}N_2O_6Si$
500.66

To a stirred solution of pyrrolinone **246** (40 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) at room temperature and under argon was added 2,6-lutidine (0.04 g, 0.31 mmol) followed by TBSOTf (0.02 mL, 0.11 mmol). The reaction mixture was stirred at room temperature for 15 min (reaction progress monitored by TLC) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 90:10) to afford 36 mg (69%) of *E*/*Z* mixture (60:40) of **257** as a yellow oil.

Analytical Data for **257**:

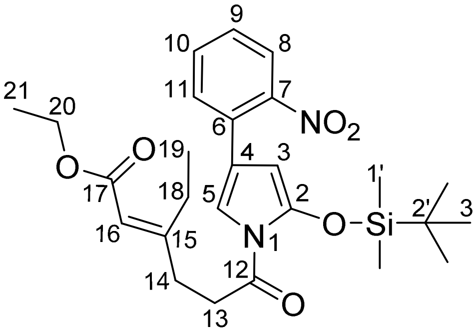


TLC: R_f (Cyclohexane/EtOAc, 90:10) = 0.39

MS-ESI: 539.4 (7, [M+K]$^+$), 423.5 (100, [M+Na]$^+$), 501.5 (8, [M+H]$^+$)

HR-MS (ESI): 523.22399 ([M+Na]$^+$; $C_{26}H_{36}N_2O_6SiNa^+$; calc. 523.22403)

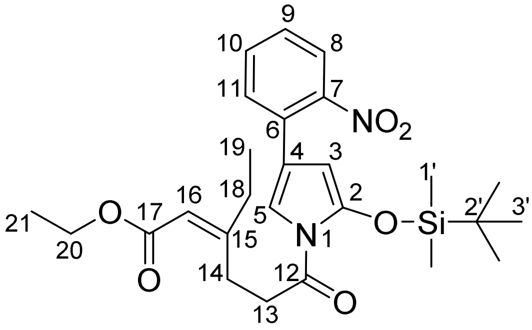
Analytical Data for **(*E*)-257**:



H-NMR (400 MHz, CDCl$_3$): δ 7.70 (ddd, $^3J_{H8,H9}$ = 8.0 Hz, $^4J_{H8,H10}$ = 4.2 Hz, $^5J_{H8,H11}$ = 1.2 Hz, 1 H, H^8), 7.54 (ddd, $^3J_{H11,H10}$ = 7.8 Hz, $^4J_{H11,H9obs.}$ = 2.7 Hz, $^5J_{H11,H8}$ = 1.2 Hz, 1 H, H^{11}), 7.51-7.47 (m (partially solved), $^3J_{H10,H11}$ = 7.8 Hz, $^4J_{H10,H8}$ = 4.2 Hz, 1 H, H^{10}), 7.40-7.35 (m (partially solved), $^3J_{H9,H8}$ = 8.0 Hz, 1 H, H^9), 7.17 (d, $^4J_{H5,H3}$ = 2.3 Hz, 1 H, H^5), 5.66 (s, 1 H, H^{16}), 5.28 (d, $^4J_{H3,H5}$ = 2.3 Hz, 1 H, H^3), 4.15 (q, $^3J_{H20,H21}$ = 7.2 Hz, 2 H, H^{20}), 3.13-3.08 (m, 2 H, H^{13}), 2.66 (q, $^3J_{H18,H19}$ = 7.5 Hz, 2 H, H^{18}), 2.62 (dd, $^3J_{H14,H13a}$ = 7.7 Hz, $^3J_{H14,H13b}$ = 6.4 Hz, 2 H, H^{14}), 1.28 (t, $^3J_{H21,H20}$ = 7.2 Hz, 3 H, H^{21}), 1.11 (t, $^3J_{H19,H18}$ = 7.5 Hz, 3 H, H^{19}), 1.00 (s, 9 H, H$^{3'}$), 0.32 (s, 6 H, H$^{1'}$)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 169.9 (C^{12}), 166.1 (C^{17}), 163.4 (C^{15}), 149.0 (C^7), 143.0 (C^2), 132.1 (C^{11}), 130.8 (C^{10}), 129.0 (C^6), 127.7 (C^9), 123.8 (C^8), 120.4 (C^4), 115.6 (C^{16}), 109.7 (C^5), 91.8 (C^3), 59.6 (C^{20}), 35.3 (C^{13}), 31.7 (C^{14}), 25.7 (C$^{3'}$), 25.6 (C^{18}), 18.3 (C$^{2'}$), 14.3 (C^{21}), 13.0 (C^{19})

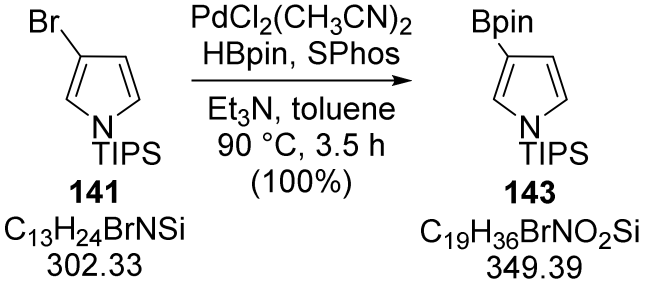
Analytical Data for ***(Z)*****-257**:



^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.70 (ddd, $^{3}J_{H8,H9}$ = 8.0 Hz, $^{4}J_{H8,H10}$ = 4.2 Hz, $^{5}J_{H8,H11}$ = 1.2 Hz, 1 H, H^{8}), 7.54 (ddd, $^{3}J_{H11,H10}$ = 7.8 Hz, $^{4}J_{H11,H9\,obs.}$ = 2.7 Hz, $^{5}J_{H11,H8}$ = 1.2 Hz, 1 H, H^{11}), 7.51-7.47 (m (partially solved), $^{3}J_{H10,H11}$ = 7.8 Hz, $^{4}J_{H10,H8}$ = 4.2 Hz, 1 H, H^{10}), 7.40-7.35 (m (partially solved), $^{3}J_{H9,H8}$ = 8.0 Hz, 1 H, H^{9}), 7.20 (d, $^{4}J_{H5,H3}$ = 2.3 Hz, 1 H, H^{5}), 5.71 (s, 1 H, H^{16}), 5.25 (d, $^{4}J_{H3,H5}$ = 2.3 Hz, 1 H, H^{3}), 4.13 (q, $^{3}J_{H20,H21}$ = 7.1 Hz, 2 H, H^{20}), 3.13-3.08 (m, 2 H, H^{13}), 2.96 (dd, $^{3}J_{H14,H13a}$ = 9.0 Hz, $^{3}J_{H14,H13b}$ = 6.7 Hz, 2 H, H^{14}), 2.23 (qd, $^{3}J_{H18,H19}$ = 7.4 Hz, $^{4}J_{H18,H16\,obs.}$ = 1.3 Hz, 2 H, H^{18}), 1.26 (t, $^{3}J_{H21,H20}$ = 7.1 Hz, 3 H, H^{21}), 1.10 (t, $^{3}J_{H19,H18}$ = 7.4 Hz, 3 H, H^{19}), 0.95 (s, 9 H, $H^{3'}$), 0.28 (s, 6 H, $H^{1'}$)

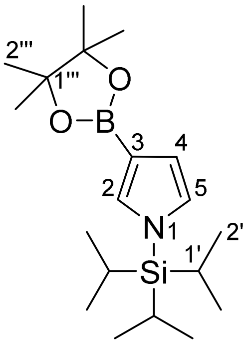
^{13}C-NMR (100 MHz, CDCl$_3$): δ 170.4 (C^{12}), 166.2 (C^{17}), 163.8 (C^{15}), 149.1 (C^{7}), 143.1 (C^{2}), 132.0 (C^{11}), 130.8 (C^{10}), 129.2 (C^{6}), 127.5 (C^{9}), 123.7 (C^{8}), 120.1 (C^{4}), 115.6 (C^{16}), 109.7 (C^{5}), 91.5 (C^{3}), 59.7 (C^{20}), 36.4 (C^{13}), 31.8 (C^{18}), 27.1 (C^{14}), 25.7 ($C^{3'}$), 18.1 ($C^{2'}$), 14.1 (C^{21}), 12.0 (C^{19})

5.2.27. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (143)[43]



A glass microwave tube was initially charged with $PdCl_2(CH_3CN)_2$ (6 mg, 0.02 mmol, 3 mol %) and SPhos (28 mg, 0.07 mmol, 9 mol %). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. 1.5 mL of dry and degased toluene were added at room temperature. To a resulting mixture were added dropwise 3-bromo-1-(triisopropyl-silanyl)-1*H*-pyrrole (**141**) (0.2 mL, 0.75 mmol) followed by triethylamine (0.26 mL, 1.88 mmol) and pinacolborane (0.13 mL, 0.90 mmol). The resulting mixture was heated at 90 °C for 3.5 h, and then allowed to cool to room temperature. The reaction solution was filtered through a thin pad of Al_2O_3 (eluting with 35 mL of EtOAc), and the eluent was concentrated under reduced pressure. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc, 20:1) to afford 262 mg (100 %) of **143** as a yellow solid.

Analytical Data for **143**:



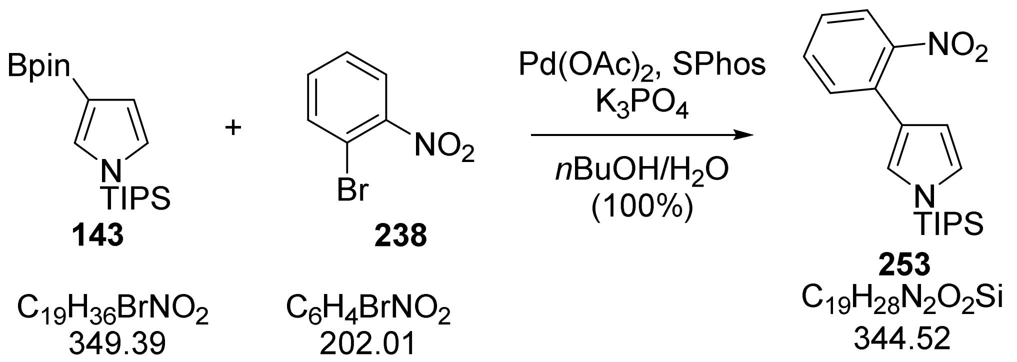
TLC: R_f (Petroleum ether/EtOAc, 95:5) = 0.28

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23 (t, $^4J_{H2,H4} = {}^4J_{H2,H5} = 1.4$ Hz, 1 H, H^2), 6.81 (t, $^3J_{H5,H4} = 2.4$ Hz, 1 H, H^5), 6.62 (dd, $^3J_{H4,H5} = 2.5$ Hz, $^4J_{H4,H2} = 1.2$ Hz, 1 H, H^4), 1.46 (sept, $^3J_{H1',H2'} = 7.5$ Hz, 3 H, $H^{1'}$), 1.32 (s, 12 H, $H^{2'''}$), 1.09 (d, $^3J_{H2',H1'} = 7.5$ Hz, 18 H, $H^{2'}$)

^{13}C-NMR (100 MHz, CDCl$_3$): *δ* 133.7 (C^{2}), 125.0 (C^{5}), 115.6 (C^{4}), 82.7 (C^{3}), 24.9 (C$^{2''}$), 17.8 (C$^{2'}$), 11.7 (C$^{1'}$)

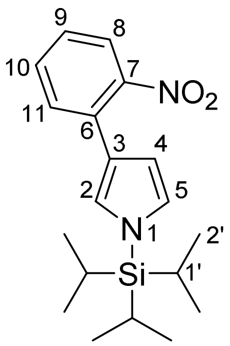
MS-ESI: 350.3 (100, [M+Na]$^{+}$)

5.2.28. 3-(2-Nitrophenyl)-1-(triisopropylsilyl)-1*H*-pyrrole (44)[37]



In an over-dried glass microwave flask, the solid starting materials were combined: N-(TIPS)pyrrole pinacol boronate **143** (230 mg, 0.66 mmol), 2-bromo-nitrobenzene (**238**) (111 mg, 0.55 mmol), palladium acetate (6 mg, 0.03 mmol), 2-dicyclohexyl-phosphino-2′,6′-dimethoxybiphenyl (23 mg, 0.06 mmol), and K_3PO_4 (233 mg, 1.10 mmol). The vial was sealed with a Teflon-coated screw cap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. The solvent system (1.10 mL, 2.0 mL/mmol 2-bromo-nitrobenzene), consisting of degassed *n*-butanol (0.78 mL) and degassed deionized water (0.32 mL) in the ratio of 2.5:1 was added. The resulting mixture was heated at 35 °C for 16 h. The crude reaction mixture was then filtered through a plug of silica gel (eluting with 30 mL of EtOAc) and concentrated in vacuo. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 20:1) to provide 189 mg (100%) of desired TIPS-protected phenylpyrrole **253** as a yellow oil.

Analytical Data for **253**:



TLC: R_f (Petroleum ether/EtOAc, 95:5) = 0.32

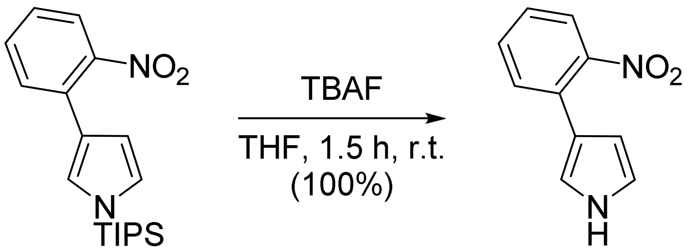
^{1}H-NMR (400 MHz, acetone-d$_6$): δ 7.66 (dd, $^3J_{H11,H10}$ = 7.8 Hz, $^4J_{H11,H9}$ = 1.3 Hz, 1 H, H^{11}), 7.65 (dd, $^3J_{H8,H9}$ = 8.1 Hz, $^4J_{H8,H10}$ = 1.2 Hz, 1 H, H^8), 7.58 (dt, $^3J_{H10,H11}$ = $^3J_{H10,H9}$ = 7.6 Hz, $^4J_{H10,H8}$ = 1.3 Hz, 1 H, H^{10}), 7.40 (ddd, $^3J_{H9,H8}$ = 8.0 Hz, $^3J_{H9,H10}$ = 7.4 Hz, $^4J_{H9,H11}$ = 1.3 Hz, 1 H, H^9), 7.05 (t, $^4J_{H2,H4}$ = $^4J_{H2,H5}$ = 1.7 Hz, 1 H, H^2), 6.92 (≈t, $^3J_{H5,H4}$ = 2.6 Hz, 1 H, H^5), 6.41 (dd, $^3J_{H4,H5}$ = 2.8 Hz, $^4J_{H4,H2}$ = 1.5 Hz, 1 H, H^4), 1.55 (sept, $^3J_{H1',H2'}$ = 7.5 Hz, 3 H, H$^{1'}$), 1.13 (d, $^3J_{H2',H1'}$ = 7.5 Hz, 18 H, H$^{2'}$)

^{13}C-NMR (100 MHz, acetone-d$_6$): δ 150.3 (C^7), 132.2 (C^{10}), 131.3 (C^{11}), 130.0 (C^6), 127.3 (C^9), 126.2 (C^5), 123.8 (C^8), 123.7 (C^2), 121.8 (C^3), 111.0 (C^4), 18.1 (C$^{2'}$), 12.7 (C$^{1'}$)

HPLC-MS (EI, 70 eV): t_R = 17.1 min; m/z (%) = 345.4 (100, [M+H]$^+$)

HR-MS (ESI): 367.18132 ([M+Na]$^+$; $C_{19}H_{28}N_2O_2SiNa^+$; calc. 367.18177)

5.2.29. 3-(2-Nitrophenyl)-1*H*-pyrrole (45)[37]

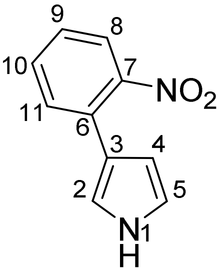


253
$C_{19}H_{28}N_2O_2Si$
344.52

254
$C_{10}H_8N_2O_2$
188.18

Tetrabutylammonium fluoride (1.0 M in THF, 1.03 mL, 1.03 mmol) was added dropwise to a solution of TIPS-protected phenylpyrrole **253** (177 mg, 0.51 mmol) in dry THF (1.0 mL) at room temperature and under argon. The reaction vessel was covered in aluminium foil to minimize light exposure; the mixture was stirred at room temperature for 1.5 h (reaction progress monitored by TLC). The reaction mixture was quenched with a saturated aqueous NH_4Cl (10 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). Combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 80:20) to afford 97 mg (100%) of deprotected phenylpyrrole **254** as a yellow oil.

Analytical Data for **254**:



TLC: R_f (Petroleum ether/EtOAc, 80:20) = 0.22

GC (method IZ): t_R = 11.88 min

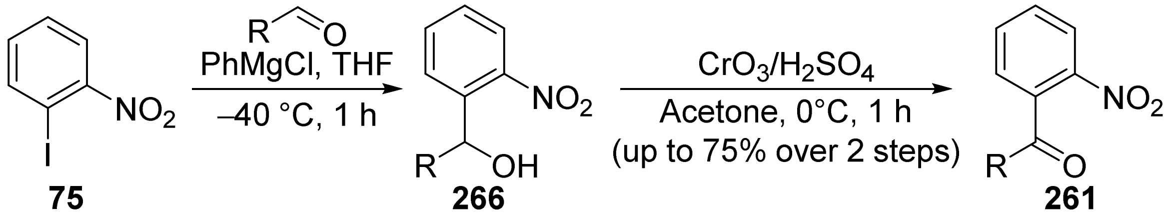
^{1}H-NMR (400 MHz, acetone-d_6): δ 10.37 (br s, 1 H, NH), 7.64-7.62 (m, 2 H, H^{11}, H^8), 7.57 (ddd, $^3J_{H10,H11\ obs.}$ = 8.1 Hz, $^3J_{H10,H9\ obs.}$ = 7.2 Hz, $^4J_{H10,H8}$ = 1.2 Hz, 1 H, H^{10}), 7.38 (ddd, $^3J_{H9,H8}$ = 7.9 Hz, $^3J_{H9,H10}$ = 7.2 Hz, $^4J_{H9,H11}$ = 1.6 Hz, 1 H, H^9), 7.05 (td, $^3J_{H2,H1}$ = 2.8 Hz, $^4J_{H2,H4}$ = $^4J_{H2,H5}$ = 1.7 Hz, 1 H, H^2), 6.87 (dt, $^3J_{H5,H4}$ = $^3J_{H5,H1}$ = 2.7 Hz, $^4J_{H5,H2}$ = 2.0 Hz, 1 H, H^5), 6.26 (dt, $^3J_{H4,H5}$ = 2.6 Hz, $^4J_{H4,H2}$ = $^4J_{H4,H1}$ = 1.7 Hz, 1 H, H^4)

^{13}C-NMR (100 MHz, acetone-d_6): δ 150.3 (C^7), 132.2 (C^{10}), 131.3 (C^{11}), 130.4 (C^6), 127.0 (C^9), 123.7 (C^8), 120.0 (C^5), 119.1 (C^3), 117.8 (C^2), 108.1 (C^4)

MS-ESI: 205.1 (100, $[M-H+H_2O]^-$), 287.2 (66, $[M-H]^-$)

5.3. Experimental procedures and characterization data associated with compounds described in Chapter Three

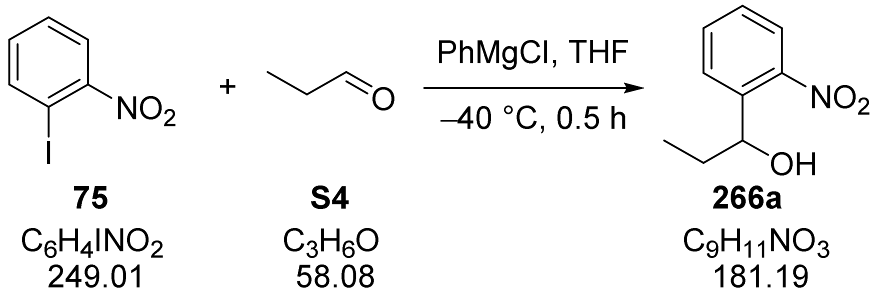
5.3.1. Preparation of 1-(2-nitrophenyl)ketones: General Procedure:



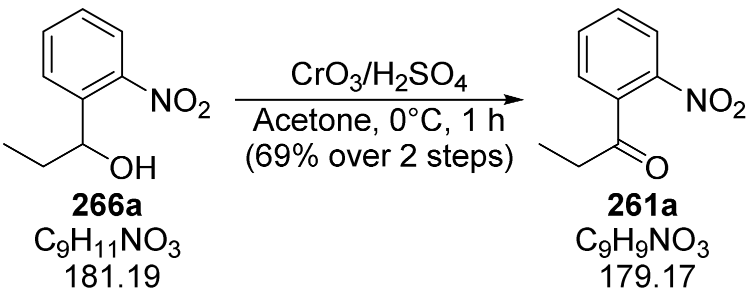
To a solution of the 2-iodonitrobenzene (8.03 mmol, 1.0 equiv.) in dry THF (56 mL, 0.14 M) phenylmagnesium chloride (2.0 M in THF, 8.84 mmol, 1.1 equiv.) was added dropwise over a period of 10 min at −40 °C and under argon. The red solution was stirred for another 10 min, and then the corresponding aldehyde (9.64 mmol, 1.2 equiv.) was added dropwise over a period of 5 min. The reaction mixture was stirred for 0.5 h at −40 °C, and then quenched with a saturated aqueous NH_4Cl (10 mL) and poured into water (100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude alcohol was engaged in the next step without further purification.

Preparation of Jones' reagent 2.67 M CrO_3 in 4.14 M H_2SO_4 (6.5 mL): Water (5.0 mL) was added dropwise to a solution of CrO_3 (1.72 g, 17.18 mmol) in 1.5 mL of 98% H_2SO_4 at 0 °C. To a stirred solution of the corresponding alcohol (8.03 mmol, 1.0 equiv.) in acetone (13 mL, 0.6 M) at 0 °C was added dropwise a freshly prepared Jones' reagent (2.67 M, 6.5 mL, *ca.* 2.1 equiv.). The resulting yellow-brown reaction mixture was stirred at 0 °C for 1 h (reaction progress monitored by TLC), before it was quenched with ^{i}PrOH (15 mL) and warmed to room temperature for 10 min. The crude reaction mixture was then filtered through a plug of Celite (eluting with 100 mL of Et_2O) and concentrated in vacuo. The organic residue was taken up in Et_2O (100 mL) and washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude ketone was purified by flash chromatography on silica gel.

5.3.2. 1-(2-Nitrophenyl)propan-1-one (261a)

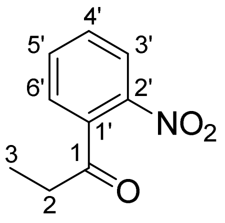


1-(2-Nitrophenyl)propan-1-ol (**266a**) was prepared from 2-iodonitrobenzene (**75**) (2.0 g, 8.03 mmol), phenylmagnesium chloride (2.0 M in THF, 4.42 mL, 8.84 mmol) and propanal (**S4**) (0.75 mL, 9.64 mmol) in dry THF (56 mL). The crude alcohol was engaged in the next step without further purification. *R*f (CH_2Cl_2, 100%) = 0.34. GC (method IZ): *t*R = 9.42 min.



1-(2-Nitrophenyl)propan-1-one (**261a**) was prepared from the crude 1-(2-nitrophenyl)propan-1-ol (**266a**) (2.0 g, 8.03 mmol) and Jone's reagent (2.67 M in H_2SO_4, 6.5 mL) in acetone (13 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 70:30. The product was isolated in 69% yield (0.99 g) over the two steps as a yellow oil.

Analytical Data for **261a**:



TLC: *R*f (Cyclohexane/CH_2Cl_2, 50:50) = 0.27

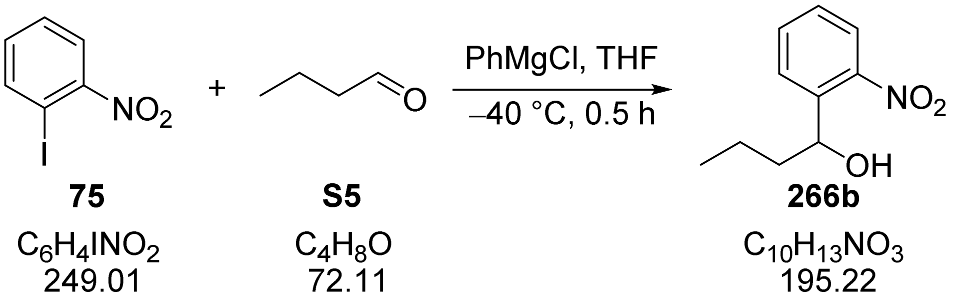
GC (method IZ): *t*R = 9.32 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.13 (dd, $^3J_{H3',H4'}$ = 8.2 Hz, $^4J_{H3',H5'}$ = 1.2 Hz, 1 H, H$^{3'}$), 7.72 (td, $^3J_{H5',H6'}$ = $^3J_{H5',H4'}$ = 7.5 Hz, $^4J_{H5',H3'}$ = 1.2 Hz, 1 H, H$^{5'}$), 7.60 (ddd, $^3J_{H4',H3'}$ = 8.2 Hz, $^3J_{H4',H5'}$ = 7.5 Hz, $^4J_{H4',H6'}$ = 1.4 Hz, 1 H, H$^{4'}$), 7.38 (dd, $^3J_{H6',H5'}$ = 7.5 Hz, $^4J_{H6',H4'}$ = 1.4 Hz, $^5J_{H6',H3'}$ = 0.3 Hz, 1 H, H$^{6'}$), 2.79 (q, $^3J_{H2,H3}$ = 7.2 Hz, 2 H, H^2), 1.26 (t, $^3J_{H3,H2}$ = 7.2 Hz, 3 H, H^3)

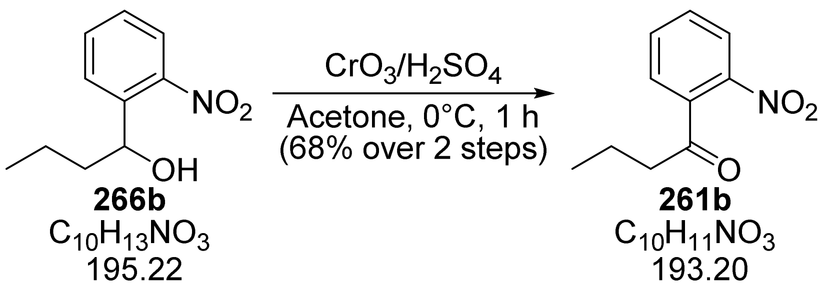
^{13}C-NMR (100 MHz, CDCl$_3$): δ 203.3 (C^1), 145.6 (C$^{2'}$), 138.3 (C$^{1'}$), 134.3 (C$^{5'}$), 130.3 (C$^{4'}$), 127.3 (C$^{6'}$), 124.4 (C$^{3'}$), 36.4 (C^2), 8.2 (C^3)

MS-EI (70 eV): 180.0 (100, [M+H]$^+$), 150.0 (53, [M-CH$_3$CH$_2$]$^+$), 120.1 (36), 92.1 (19), 51.1 (31)

5.3.3. 1-(2-Nitrophenyl)butan-1-one (261b)

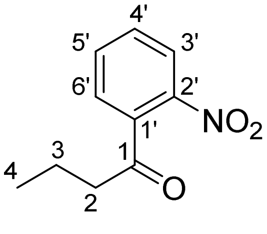


1-(2-Nitrophenyl)butan-1-ol (**266b**) was prepared from 2-iodonitrobenzene (**75**) (4.0 g, 16.06 mmol), phenylmagnesium chloride (2.0 M in THF, 8.83 mL, 17.67 mmol) and butanal (**S5**) (1.76 mL, 19.28 mmol) in dry THF (110 mL). The crude alcohol was engaged in the next step without further purification. R_f (CH$_2$Cl$_2$, 100%) = 0.30. GC (method IZ): t_R = 10.17 min.



1-(2-nitrophenyl)butan-1-one (**261b**) was prepared from the crude 1-(2-nitrophenyl)butan-1-ol (**266b**) (2.0 g, 8.03 mmol) and Jone's reagent (2.67 M in H$_2$SO$_4$, 13.0 mL) in acetone (26 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 70:30. The product was isolated in 68% yield (2.12 g) over the two steps as a yellow oil.

Analytical Data for **266b**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.27

GC (method IZ): t_R = 10.09 min

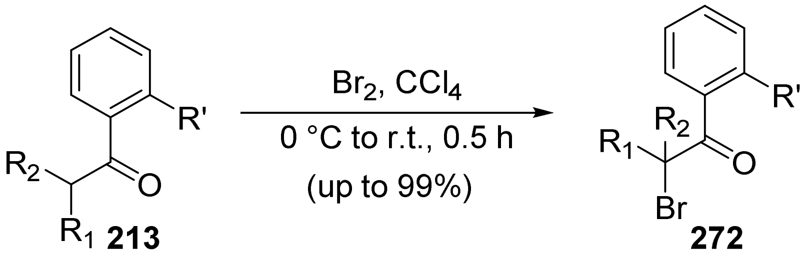
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, $^3J_{H3',H4'}$ = 8.2 Hz, $^4J_{H3',H5'}$ = 1.2 Hz, 1 H, $H^{3'}$), 7.71 (td, $^3J_{H5',H6'}$ = $^3J_{H5',H4'}$ = 7.5 Hz, $^4J_{H5',H3'}$ = 1.2 Hz, 1 H, $H^{5'}$), 7.58 (ddd, $^3J_{H4',H3'}$ = 8.2 Hz, $^3J_{H4',H5'}$ = 7.5 Hz, $^4J_{H4',H6'}$ = 1.4 Hz, 1 H, $H^{4'}$), 7.37 (dd, $^3J_{H6',H5'}$ = 7.5 Hz, $^4J_{H6',H4'}$ = 1.4 Hz, 1 H, $H^{6'}$), 2.75 (t, $^3J_{H2,H3}$ = 7.4 Hz, 2 H, H^2), 1.77 (sext, $^3J_{H3,H4}$ = $^3J_{H3,H2}$ = 7.4 Hz, 2 H, H^3), 1.00 (t, $^3J_{H4,H3}$ = 7.4 Hz, 3 H, H^4)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.5 (C^1), 145.6 ($C^{2'}$), 138.2 ($C^{1'}$), 134.2 ($C^{5'}$), 130.3 ($C^{4'}$), 127.3 ($C^{6'}$), 124.3 ($C^{3'}$), 44.8 (C^2), 17.3 (C^3), 13.5 (C^4)

HR-MS (ESI): 216.06290 ($[M+Na]^+$; $C_{10}H_{11}NO_3Na^+$; calc. 216.06366)

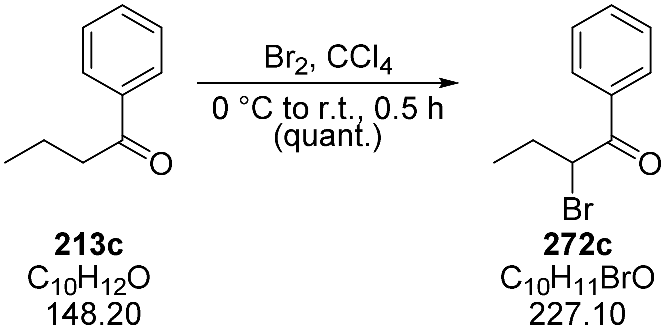
IR (KBr): ν = 3071 (vw), 2966 (s), 2936 (m), 2877 (m), 2378 (vw), 1708 (vs), 1604 (w), 1575 (m), 1530 (vs), 1465 (m), 1442 (w), 1402 (m), 1348 (vs), 1309 (m), 1277 (w), 1211 (s), 1166 (vw), 1147 (vw), 1112 (vw), 1087 (vw), 1051 (vw), 1004 (w), 991 (w), 962 (vw), 900 (vw), 854 (m), 822 (vw), 789 (s), 752 (m), 729 (m), 702 (m), 641 (vw), 556 (vw), 409 (vw) cm^{-1}

5.3.4. Preparation of α-bromoketones: General Procedure:



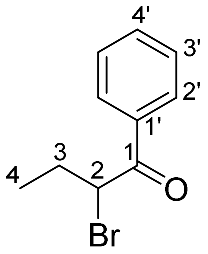
To an ice-cooled solution of the ketone **213** (40 mmol, 1.0 equiv.) in CCl_4 (100 mL) bromine (40 mmol, 1.0 equiv.) was added dropwise at such a rate as to obtain a continuous discoloration. The almost colourless solution was stirred for another 15 min at room temperature (reaction progress monitored by TLC), and then the reaction was quenched with a saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with $Na_2S_2O_3$ (0.1 M, 80 mL), dried over Na_2SO_4, filtered and concentrated. The α-bromoketone **272** was purified by flash chromatography (in some batches we observed 1-2% 2,2-dibromoketone).

5.3.5. 2-Bromo-1-phenylbutan-1-one (272c)



Prepared from butyrophenone **213c** (6.0 g, 40.5 mmol) and bromine (2.08 mL, 40.5 mmol) in CCl_4 (120 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 50:50. The product was isolated quantitatively (9.19 g) as a slightly yellow oil.

Analytical Data for **272c**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.37

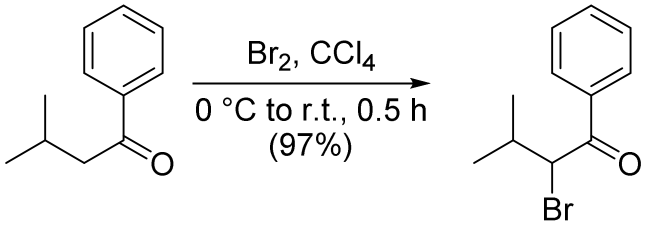
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02-8.00 (m (partially solved), $^3J_{H2',H3'obs.}$ = 8.4 Hz, $^4J_{H2',H4'}$ = 2.0 Hz, 2 H, $H^{2'}$), 7.60 (t, $^3J_{H4',H3'obs.}$ = 7.4 Hz, $^4J_{H4',H2'}$ = 2.0 Hz, 1 H, $H^{4'}$), 7.52-7.47 (m, 2 H, $H^{3'}$), 5.08 (dd, $^3J_{H2,H3b}$ = 7.8 Hz, $^3J_{H2,H3a}$ = 6.4 Hz, 1 H, H^2), 2.25 (quint d, $^3J_{H3a,H4}$ = $^2J_{H3a,H3b}$ = 7.3 Hz, $^3J_{H3a,H2}$ = 6.4 Hz, 1 H, H^{3a}), 2.14 (sext, $^3J_{H3b,H4}$ = $^3J_{H3b,H2}$ = $^2J_{H3b,H3a}$ = 7.3 Hz, 1 H, H^{3b}), 1.09 (t, $^3J_{H4,H3}$ = 7.3 Hz, 3 H, H^4)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.2 (C^1), 134.5 ($C^{1'}$), 133.6 ($C^{4'}$), 128.8 and 128.7 ($C^{2'}$ and $C^{3'}$), 49.0 (C^2), 26.9 (C^3), 12.2 (C^4)

MS-ESI: 248.8 (96, [M (^{79}Br)+Na]$^+$), 250.7 (100, [M (^{81}Br)+Na]$^+$)

IR (KBr, film): ν = 3063 (w), 2973 (s), 2937 (m), 2877 (w), 1966 (vw), 1904 (vw), 1814 (vw), 1686 (vs), 1597 (m), 1580 (m), 1449 (s), 1381 (m), 1365 (m), 1319 (m), 1295 (m), 1271 (s), 1225 (vs), 1196 (w), 1160 (m), 1110 (w), 1084 (vw), 1028 (vw), 1003 (m), 930 (vw), 899 (m), 835 (w), 819 (w), 801 (m), 777 (vw), 722 (m), 704 (s), 686 (s), 658 (m), 646 (w), 618 (vw), 546 (vw), 485 (vw) cm^{-1}

5.3.6. 2-Bromo-3-methyl-1-phenylbutan-1-one (272d)

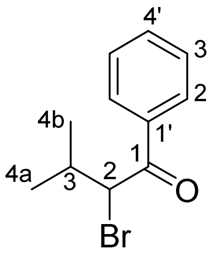


213d
$C_{11}H_{14}O$
162.23

272d
$C_{11}H_{13}BrO$
241.12

Prepared from isovalerophenone (**213d**) (6.0 g, 36.98 mmol) and bromine (1.90 mL, 36.98 mmol) in CCl_4 (110 mL, 0.34 M). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 70:30 to 50:50. The product was isolated in 97% yield (8.66 g) as a slightly yellow oil which solidified on standing.

Analytical Data for **272d**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 70:30) = 0.21

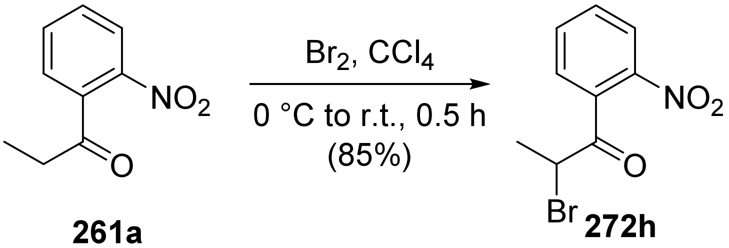
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (d, $^3J_{H2',H3'}$ = 7.4 Hz, 2 H, $H^{2'}$), 7.60 (t, $^3J_{H4',H3'}$ = 7.4 Hz, 1 H, $H^{4'}$), 7.49 (t, $^3J_{H3',H2'}$ = $^3J_{H3',H4'}$ = 7.5 Hz, 2 H, $H^{3'}$), 4.94 (d, $^3J_{H2,H3obs.}$ = 8.6 Hz, 1 H, H^2), 2.54-2.42 (m (partially solved), $^3J_{H3,H4a}$ = $^3J_{H3,H4b}$ = 6.6 Hz 1 H, H^3), 1.21 (d, $^3J_{H4a,H3}$ = 6.6 Hz, 3 H, H^{4a}), 1.03 (d, $^3J_{H4b,H3}$ = 6.6 Hz, 3 H, H^{4b})

^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.6 (C^1), 135.0 ($C^{1'}$), 133.6 ($C^{4'}$), 128.8 and 128.7 ($C^{2'}$ and $C^{3'}$), 55.9 (C^2), 31.0 (C^3), 20.7 (C^{4b}), 20.4 (C^{4a})

MS-ESI: 262.9 (99, [M (^{79}Br)+Na]$^+$), 265.0 (100, [M (^{81}Br)+Na]$^+$)

IR (KBr): ν = 3089 (w), 3064 (w), 3042 (w), 2967 (vs), 2930 (s), 2873 (s), 2341 (w), 1967 (w), 1908 (vw), 1813 (vw), 1776 (vw), 1678 (vs), 1596 (s), 1579 (s), 1465 (s), 1447 (vs), 1385 (m), 1369 (vs), 1307 (s), 1289 (vs), 1236 (vs), 1171 (vs), 1124 (m), 1103 (m), 1076 (m), 1028 (vw), 1011 (s), 1011 (m), 961 (w), 928 (vs), 847 (s), 811 (s), 796 (s), 718 (vs), 684 (vs), 659 (vs), 606 (vs), 493 (m), 417 (vw) cm^{-1}

5.3.7. 2-Bromo-1-(2-nitrophenyl)propan-1-one (272h)



261a

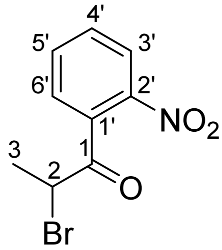
$C_9H_9NO_3$
179.17

272h

$C_9H_8BrNO_3$
258.07

Prepared from 1-(2-nitrophenyl)propan-1-one (**261a**) (187 mg, 1.04 mmol) and bromine (0.05 mL, 1.04 mmol) in CCl_4 (3.0 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 50:50. The product was isolated in 85% yield (228 mg) as a slightly yellow oil which solidified on standing.

Analytical Data for **272h**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.33

GC (method IZ): t_R = 10.76 min

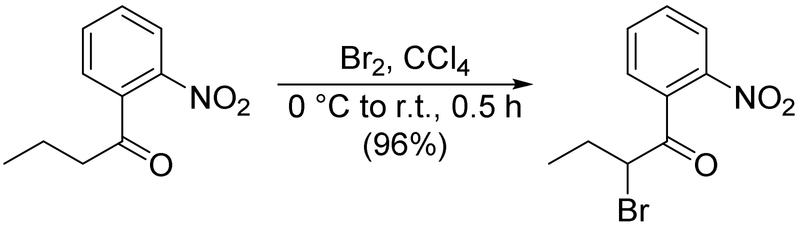
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.23 (ddd, ${}^3J_{H3',H4'}$ = 8.2 Hz, ${}^4J_{H3',H5'}$ = 1.2 Hz, ${}^5J_{H3',H6'}$ = 0.3 Hz, 1 H, $H^{3'}$), 7.78 (td, ${}^3J_{H5',H6'}$ = ${}^3J_{H5',H4'}$ = 7.5 Hz, ${}^4J_{H5',H3'}$ = 1.2 Hz, 1 H, $H^{5'}$), 7.66 (ddd, ${}^3J_{H4',H3'}$ = 8.2 Hz, ${}^3J_{H4',H5'}$ = 7.5 Hz, ${}^4J_{H4',H6'}$ = 1.5 Hz, 1 H, $H^{4'}$), 7.63 (ddd, ${}^3J_{H6',H5'}$ = 7.5 Hz, ${}^4J_{H6',H4'}$ = 1.5 Hz, ${}^5J_{H6',H3'}$ = 0.3 Hz, 1 H, $H^{6'}$), 4.74 (q, ${}^3J_{H2,H3}$ = 6.7 Hz, 1 H, H^2), 2.01 (d, ${}^3J_{H3,H2}$ = 6.7 Hz, 3 H, H^3)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.1 (C^1), 145.0 ($C^{2'}$), 135.5 ($C^{1'}$), 134.7 ($C^{5'}$), 131.0 ($C^{4'}$), 130.9 ($C^{6'}$), 124.3 ($C^{3'}$), 47.1 (C^2), 20.1 (C^3)

MS-EI (70 eV): 259.9 (15, [M (^{81}Br)]$^+$), 257.9 (13, [M (^{79}Br)]$^+$), 178.0 (15, [M-Br]$^+$), 162.0 (28), 151.0 (43), 150.0 (50), 134.0 (100), 121.1 (58), 104.1 (55), 93.0 (25), 78.1 (28), 76.0 (48), 65.1 (40), 51.0 (99), 50.0 (48)

IR (KBr): ν = 3103 (vw), 3016 (vw), 3001 (w), 2936 (vw), 2862 (vw), 1703 (vs), 1614 (vw), 1569 (w), 1531 (vs), 1473 (w), 1449 (m), 1439 (m), 1374 (w), 1342 (vs), 1272 (w), 1225 (s), 1186 (m), 1145 (w), 1101 (w), 1068 (w), 1040 (vw), 996 (m), 963 (w), 951 (m), 857 (m), 788 (m), 768 (w), 727 (s), 693 (m), 679 (w), 639 (w), 572 (w), 500 (w), 416 (vw) cm^{-1}

5.3.8. 2-Bromo-1-(2-nitrophenyl)butan-1-one (272i)

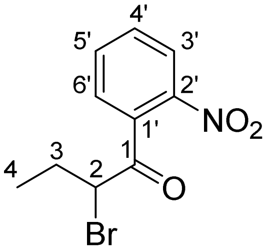


261b
$C_{10}H_{11}NO_3$
193.20

272i
$C_{10}H_{10}BrNO_3$
272.10

Prepared from 1-(2-nitrophenyl)butan-1-one (**261b**)(1.80 g, 9.30 mmol) and bromine (0.48 mL, 9.30 mmol) in CCl_4 (27 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 70:30. The product was isolated in 96% yield (2.44 g) as a slightly yellow oil which solidified on standing.

Analytical Data for **272i**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.28

GC (method IZ): t_R = 11.50 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.21 (ddd, $^3J_{H3',H4'}$ = 8.5 Hz, $^4J_{H3',H5'}$ = 1.2 Hz, $^5J_{H3',H6'}$ = 0.6 Hz, 1 H, $H^{3'}$), 7.77 (ddd, $^3J_{H5',H6'}$ = 8.0 Hz, $^3J_{H5',H4'}$ = 7.4 Hz, $^4J_{H5',H3'}$ = 1.2 Hz, 1 H, $H^{5'}$), 7.65 (ddd, $^3J_{H4',H3'}$ = 8.5 Hz, $^3J_{H4',H5'}$ = 7.5 Hz, $^4J_{H4',H6'}$ = 1.5 Hz, 1 H, $H^{4'}$), 7.64 (ddd, $^3J_{H6',H5'}$ = 8.0 Hz, $^4J_{H6',H4'}$ = 1.5 Hz, $^5J_{H6',H3'}$ = 0.6 Hz, 1 H, $H^{6'}$), 4.55 (dd, $^3J_{H2,H3b}$ = 9.2 Hz, $^3J_{H2,H3a}$ = 4.5 Hz, 1 H, H^2), 2.36 (dqd, $^2J_{H3a,H3b}$ = 14.6 Hz, $^3J_{H3a,H4}$ = 7.3 Hz, $^3J_{H3a,H2}$ = 4.5 Hz, 1 H, H^{3a}), 2.36 (ddq, $^2J_{H3b,H3a}$ = 14.6 Hz, $^3J_{H3b,H2}$ = 9.2 Hz, $^3J_{H3b,H4}$ = 7.3 Hz, 1 H, H^{3b}), 1.16 (t, $^3J_{H4,H3a}$ = $^3J_{H4,H3b}$ = 7.3 Hz, 3 H, H^4)

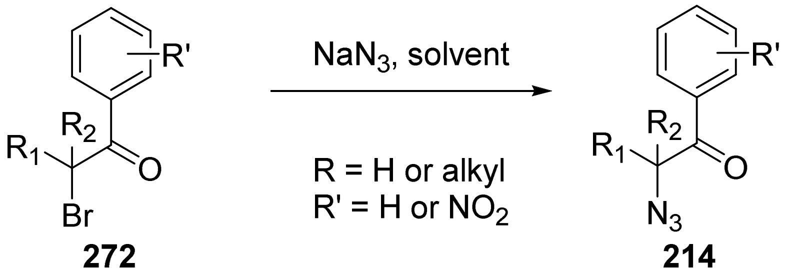
^{13}C-NMR (100 MHz, CDCl$_3$): δ 195.9 (C^1), 145.0 ($C^{2'}$), 135.6 ($C^{1'}$), 134.6 ($C^{5'}$), 131.1 ($C^{4'}$), 130.9 ($C^{6'}$), 124.2 ($C^{3'}$), 55.4 (C^2), 26.4 (C^3), 11.8 (C^4)

MS-EI (70 eV): 273.8 (16, [M (^{81}Br)]$^+$), 271.8 (20, [M (^{79}Br)]$^+$), 192.0 (13, [M-Br]$^+$), 176.0 (42), 151.0 (64), 150.0 (68), 134.0 (78), 121.1 (100), 104.1 (28), 93.1 (27), 92.1 (16), 78.1 (13), 76.1 (35), 65.1 (46), 51.0 (41)

HR-MS (ESI): 293.97384 ([M (^{79}Br)+Na]$^+$; $C_{10}H_{10}{}^{79}BrNO_3Na^+$; calc. 293.97418), 295.97136 ([M (^{81}Br)+Na]$^+$; $C_{10}H_{10}{}^{81}BrNO_3Na^+$; calc. 295.97213)

IR (KBr): ν = 3079 (vw), 2974 (w), 1705 (vs), 1572 (w), 1524 (vs), 1370 (m), 1346 (vs), 1302 (m), 1212 (m), 1010 (w), 903 (w), 860 (w), 789 (w), 761 (w), 728 (w), 700 (m), 572 (w), 502 (vw) cm^{-1}

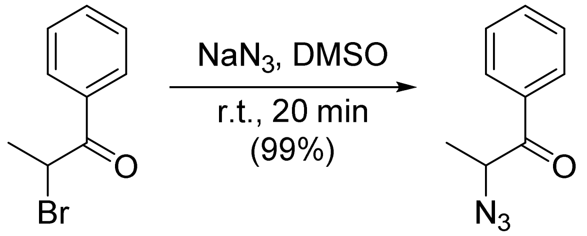
5.3.9. Preparation of α-azidoketones: General Procedures:



Method A: To a stirred solution of sodium azide (79.26 mmol, 3.0 equiv.) in DMSO (130 mL) was added the corresponding α-bromoketone (26.42 mmol, 1.0 equiv.) at room temperature. After 20 min of vigorous stirring, the mixture was poured onto ice-water (200 mL) and extracted with ether (3 x 100 mL). The combined organic phases were washed with water (4 x 300 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The α-azidoketone was obtained mostly quantitatively and engaged in the next step without further purification. In some cases, the DMSO was still present, and the product was purified by flash chromatography.

Method B: To a stirred solution of sodium azide (6.51 mmol, 3.0 equiv.) in acetone (8 mL) was added the corresponding α-bromoketone (2.17 mmol, 1.0 equiv.) at room temperature. After 18 h of vigorous stirring, the mixture was filtered to remove inorganic salts and the filtrate was concentrated carefully under reduced pressure. The product was purified by flash chromatography.

5.3.10. 2-Azido-1-phenylpropan-1-one (214c)

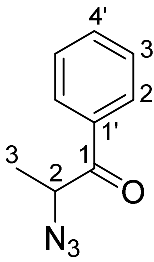


272c C_9H_9BrO 213.07

214c $C_9H_9N_3O$ 175.18

Prepared from 2-bromopropiophenone (**272c**) (1.81 g, 8.51 mmol) and sodium azide (2.02 g, 31.07 mmol) in DMSO (50 mL) following method A. The product was isolated quantitatively (1.49 g) as a slightly yellow oil.

Analytical Data for **214c**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 70:30) = 0.27

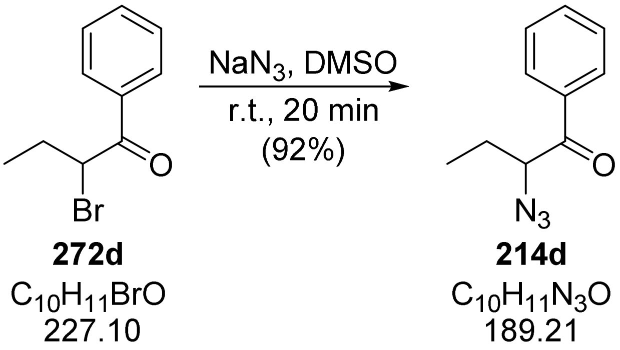
GC (method IZ): t_R = 8.74 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96-7.93 (m (partially solved), $^3J_{H2',H3'obs.}$ = 8.2 Hz, 2 H, $H^{2'}$), 6.12(tt, $^3J_{H4',H3'obs.}$ = 7.4 Hz, $^4J_{H4',H2'}$ = 1.2 Hz, 1 H, $H^{4'}$), 7.52-7.48 (m, 2 H, $H^{3'}$), 4.71 (q, $^3J_{H2,H3}$ = 7.0 Hz, 1 H, H^2), 1.57 (d, $^3J_{H3,H2}$ = 7.0 Hz, 3 H, H^3)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.7 (C^1), 134.3 ($C^{1'}$), 133.9 ($C^{4'}$), 128.9 and 128.6 ($C^{2'}$ and $C^{3'}$), 58.4 (C^2), 16.5 (C^3)

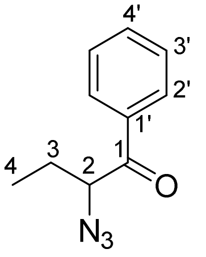
MS-EI (70 eV): 176.0 (17, $[M+H]^+$), 148.0 (5, $[M-N_2+H]^+$), 147.0 (2, $[M-N_2]^+$), 105.0 (100, $[M-CH_3CHN_3]^+$), 77.2 (44), 51.2 (13)

5.3.11. 2-Azido-1-phenylbutan-1-one (214d)



Prepared from 2-bromo-1-phenylbutan-1-one (**272d**) (6.0 g, 26.42 mmol) and sodium azide (5.15 g, 79.26 mmol) in DMSO (130 mL) following method A. Solvent system for chromatography: CH_2Cl_2, 100%. The product was isolated in 92% yield (4.58 g) as a slightly yellow oil.

Analytical Data for **214d**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.43

GC (method IZ): t_R = 9.44 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.93 (d, $^3J_{H2',H3.}$ = 8.0 Hz, 2 H, H$^{2'}$), 7.62 (t, $^3J_{H4',H3'}$ = 7.7 Hz, 1 H, H$^{4'}$), 7.50 (t, $^3J_{H3',H4'}$ = $^3J_{H3',H2'}$ = 7.7 Hz, 2 H, H$^{3'}$), 4.53 (dd, $^3J_{H2,H3b\ obs.}$ = 8.2 Hz, $^3J_{H2,H3a\ obs.}$ = 5.1 Hz, 1 H, H^2), 2.05-1.82 (m, 2 H, H^{3a} and H^{3b}), 1.08 (t, $^3J_{H4,H3}$ = 7.4 Hz, 3 H, H^4)

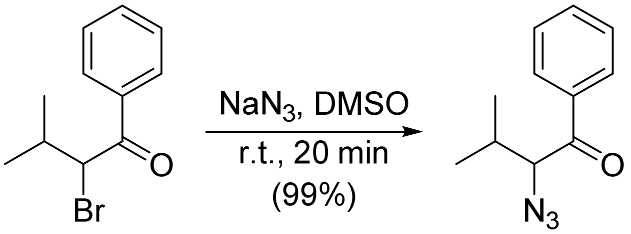
^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.7 (C^1), 134.9 (C$^{1'}$), 133.8 (C$^{4'}$), 128.9 (C$^{3'}$), 128.5 (C$^{2'}$), 64.6 (C^2), 24.8 (C^3), 10.6 (C^4)

MS-ESI: 212.0 (100, $[M+Na]^+$)

HR-MS (ESI): 212.07942 ($[M+Na]^+$; $C_{10}H_{11}N_3ONa^+$; calc. 212.07998)

IR (KBr, film): ν = 3065 (vw), 2974 (m), 2937 (w), 2879 (w), 2503 (vw), 2104 (vs), 1690 (vs), 1597 (m), 1460(m), 1449 (s), 1384 (w), 1364 (w), 1339 (w), 1266 (m), 1235 (s), 1214 (vs), 1183 (w), 1160 (vw), 1116 (vw), 1002 (m), 989 (m), 940 (w), 893 (vw), 862 (w), 787 (w), 761 (w), 694 (s), 637 (w), 557 (vw), 507 (vw) cm^{-1}

5.3.12. 2-Azido-3-methyl-1-phenylbutan-1-one (214e)

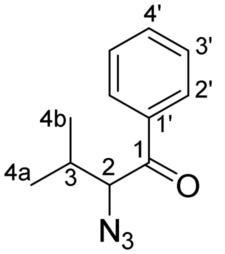


272e
$C_{11}H_{13}BrO$
241.12

214e
$C_{11}H_{13}N_3O$
203.24

Prepared from 2-bromo-3-methyl-1-phenylbutan-1-one (**272e**) (6.0 g, 24.88 mmol) and sodium azide (4.85 g, 74.65 mmol) in DMSO (125 mL) following method A. The product was isolated in 99% yield (5.02 g) as a slightly yellow oil.

Analytical Data for **214e**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 70:30) = 0.26

GC (method IZ): t_R = 9.83 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.94 (d, $^3J_{H2',H3'} = 8.1$ Hz, 2 H, $H^{2'}$), 7.62 (t, $^3J_{H4',H3'} = 7.3$ Hz, 1 H, $H^{4'}$), 7.52-7.48 (m, 2 H, $H^{3'}$), 4.40 (d, $^3J_{H2,H3\,obs.} = 6.9$ Hz, 1 H, H^2), 2.34 (oct, $^3J_{H3,H4a} = {}^3J_{H3,H4b} = {}^3J_{H3,H2} = 7.0$ Hz 1 H, H^3), 1.03 (d, $^3J_{H4a,H3} = 7.1$ Hz, 3 H, H^{4a}), 1.01 (d, $^3J_{H4b,H3} = 7.1$ Hz, 3 H, H^{4b})

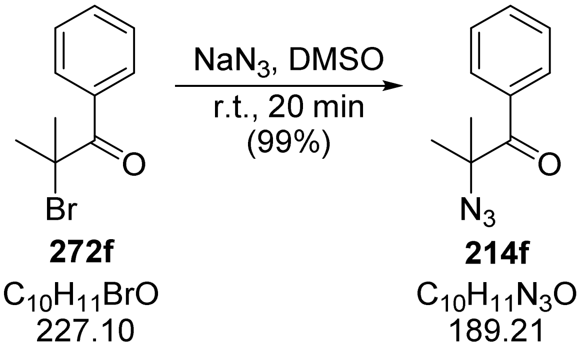
^{13}C-NMR (100 MHz, CDCl$_3$): δ 196.8 (C^1), 135.6 (C$^{1'}$), 133.8 (C$^{4'}$), 128.9 (C$^{3'}$), 128.5 (C$^{2'}$), 69.1 (C^2), 30.9 (C^3), 19.9 (C^{4b}), 18.1 (C^{4a})

MS-ESI: 226.1 (100, [M+Na]$^+$)

HR-MS (ESI): 226.09515 ([M+Na]$^+$; $C_{11}H_{13}N_3ONa^+$; calc. 226.09563)

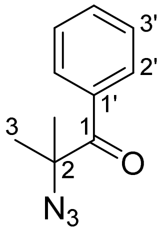
IR (KBr, film): ν = 3065 (vw), 2969 (s), 2933 (w), 2876 (w), 2104 (vs), 1687 (vs), 1597 (w), 1580 (w), 1466 (w), 1449 (m), 1389 (w), 1370 (w), 1327 (w), 1281 (m), 1246 (m), 1216 (vs), 1183 (w), 1127 (vw), 1003 (w), 976 (vw), 949 (vw), 931 (vw), 911 (w), 892 (vw), 837 (w), 785 (vw), 762 (w), 725 (w), 693 (s), 646 (w), 629 (w), 556 (vw) cm^{-1}

5.3.13. 2-Azido-2-methyl-1-phenylpropan-1-one (214f)



Prepared from 2-bromoisobutyrophenone (**272f**) (2.11 g, 9.27 mmol) and sodium azide (1.81 g, 27.82 mmol) in DMSO (50 mL) following method A. The product was isolated quantitatively (1.75 g) as a slightly yellow oil.

Analytical Data for **214f**:



TLC: *R*f (Cyclohexane/CH$_2$Cl$_2$, 70:30) = 0.31

^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.12-8.09 (m (partially solved), $^{3}J_{\mathrm{H2',H3'}\,obs.}$ = 7.4 Hz, 2 H, H$^{2'}$), 7.56 (tt, $^{3}J_{\mathrm{H4',H3'}\,obs.}$ = 7.4 Hz, $^{4}J_{\mathrm{H4',H2'}\,obs.}$ = 1.3 Hz, 1 H, H$^{4'}$), 7.48-7.44 (m, 2 H, $^{3}J_{\mathrm{H3',H4'}\,obs.}$ = 7.4 Hz, H$^{3'}$), 1.62 (s, 6 H, H^{3})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 199.4 (C^{1}), 134.5 (C$^{1'}$), 132.9 (C$^{4'}$), 129.7 (C$^{2'}$), 128.3 (C$^{3'}$), 67.6 (C^{2}), 24.9 (C^{3})

HR-MS (ESI): 212.07940 ([M+Na]$^{+}$; $C_{10}H_{11}N_3ONa^{+}$; calc. 212.07998)

IR (KBr, film): ν = 3065 (w), 2984 (w), 2938 (w), 2478 (vw), 2106 (vs), 1683 (vs), 1597 (w), 1464 (m), 1447 (m), 1387 (w), 1370 (w), 1251 (vs), 1170 (s), 1149 (s), 1078 (vw), 1002 (w), 981 (m), 954 (w), 935 (w), 908 (w), 794 (w), 714 (s), 690 (m), 666 (w), 560 (w), 445 (vw) cm^{-1}

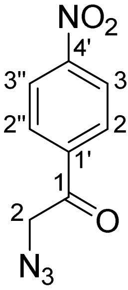
5.3.14. 2-Azido-1-(4-nitrophenyl)ethanone (214g)

272g
$C_8H_6BrNO_3$
244.04

214g
$C_8H_6N_4O_3$
206.16

Prepared from 2-bromo-1-(4-nitrophenyl)ethanone (**272g**) (1.0 g, 4.10 mmol, 1 equiv.) and sodium azide (0.29 g, 4.52 mmol, 1.1 equiv.) in DMSO (16 mL, 0.26 M) following modified method A. Solvent system for chromatography: CH_2Cl_2, 100%. The product was isolated in 78% yield (0.66 g) as a yellow solid.

Analytical Data for **214g**:



TLC: R_f (CH_2Cl_2, 100%) = 0.46

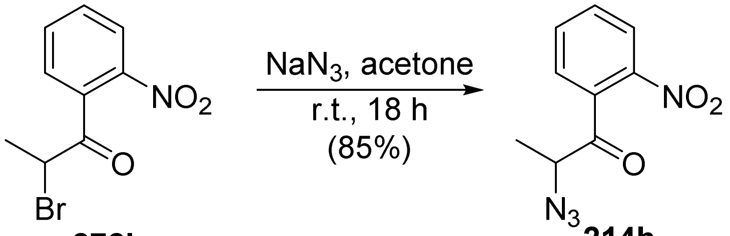
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.36 (dt, $^3J_{H3',H2'}$ = 9.2 Hz, $^4J_{H3',H3''}$ = 2.1 Hz, 2 H, H$^{3'}$ and H$^{3''}$), 8.09 (dt, $^3J_{H2',H3'}$ = 9.2 Hz, $^4J_{H2',H2''}$ = 2.1 Hz, 2 H, H$^{2'}$ and H$^{2''}$), 4.61 (s, 2 H, H^2)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 191.9 (C^1), 150.8 (C$^{4'}$), 138.7 (C$^{1'}$), 129.1 (C$^{2'}$ and C$^{2''}$), 124.2 (C$^{3'}$ and C$^{3''}$), 55.2 (C^2)

MS-EI (70 eV): 207.1 (7, $[M+H]^+$), 164.0 (85, $[M-N_3]^+$), 150.0 (100, $[M-CH_2N_3]^+$), 134.1 (34), 120.1 (57), 104.2 (21, $[M-CH_2N_3-NO_2]^+$), 92.1 (84), 76.1 (25), 50.0 (13)

IR (KBr): ν = 2897 (w), 2152 (m), 2113 (vs), 1705 (s), 1602 (w), 1524 (vs), 1346 (vs), 1319 (s), 1213 (vs), 1006 (w), 916 (m), 855 (s), 750 (w), 690 (w), 640 (w), 552 (w), 502 (vw) cm^{-1}

5.3.15. 2-Azido-1-(2-nitrophenyl)propan-1-one (214h)

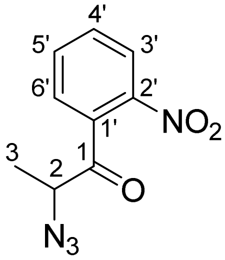


272h
$C_9H_8BrNO_3$
258.07

214h
$C_9H_8N_4O_3$
220.18

Prepared from 2-bromo-1-(2-nitrophenyl)propan-1-one (**272h**) (560 mg, 2.17 mmol) and sodium azide (423 mg, 6.51 mmol) in acetone (8 mL) following method B. Solvent system for chromatography: cyclohexane/CH_2Cl_2, 50:50. The product was isolated in 85% yield (410 mg) as an orange oil.

Analytical Data for **214h**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.31

GC (method IZ): t_R = 10.86 min

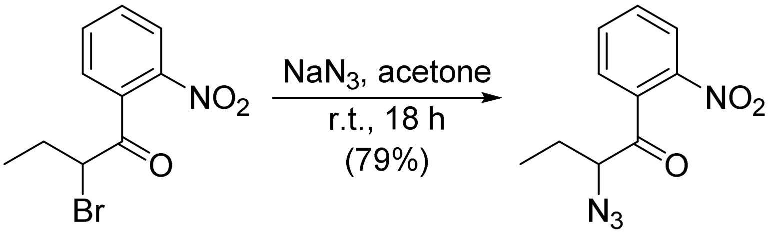
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $^{3}J_{H3',H4'}$ = 8.3 Hz, $^{4}J_{H3',H5'}$ = 1.1 Hz, 1 H, $H^{3'}$), 7.78 (td, $^{3}J_{H5',H6'}$ = $^{3}J_{H5',H4'}$ = 7.5 Hz, $^{4}J_{H5',H3'}$ = 1.1 Hz, 1 H, $H^{5'}$), 7.67 (ddd, $^{3}J_{H4',H3'}$ = 8.3 Hz, $^{3}J_{H4',H5'}$ = 7.5 Hz, $^{4}J_{H4',H6'}$ = 1.4 Hz, 1 H, $H^{4'}$), 7.39 (dd, $^{3}J_{H6',H5'}$ = 7.5 Hz, $^{4}J_{H6',H4'}$ = 1.4 Hz, 1 H, $H^{6'}$), 4.37 (q, $^{3}J_{H2,H3}$ = 7.0 Hz, 1 H, H^{2}), 1.61 (d, $^{3}J_{H3,H2}$ = 7.0 Hz, 3 H, H^{3})

^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.0 (C^{1}), 145.7 ($C^{2'}$), 135.5 ($C^{1'}$), 134.7 ($C^{5'}$), 131.0 ($C^{4'}$), 127.9 ($C^{6'}$), 124.3 ($C^{3'}$), 63.2 (C^{2}), 16.1 (C^{3})

MS-EI (70 eV): 221.1 (4, $[M+H]^+$), 151.0 (67, $[M-CH_3CHN_3+H]^+$), 121.0 (100), 107.1 (11), 93.0 (66), 76.0 (43), 74.1 (21), 65.1 (89), 50.0 (54)

IR (KBr, film): ν = 3107 (vw), 2990 (vw), 2938 (vw), 2871 (vw), 2105 (vs), 1717 (vs), 1613 (vw), 1574 (w), 1530 (vs), 1476 (vw), 1450 (w), 1375 (vs), 1313 (w), 1258 (m), 1230 (m), 1174 (vw), 1148 (vw), 1081 (vw), 1018 (vw), 969 (w), 911 (vw), 857 (w), 791 (w), 757 (w), 717 (w), 699 (w), 649 (vw), 622 (vw), 555 (vw) cm^{-1}

5.3.16. 2-Azido-1-(2-nitrophenyl)butan-1-one (214i)

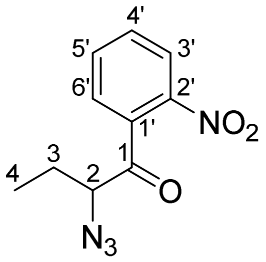


272i
$C_{10}H_{10}BrNO_3$
272.10

214i
$C_{10}H_{10}N_4O_3$
234.21

Prepared from 2-bromo-1-(2-nitrophenyl)butan-1-one (**272i**) (1.0 g, 3.68 mmol) and sodium azide (717 mg, 11.03 mmol) in acetone (14 mL) following method B. Solvent system for chromatography: cyclohexane/CH_2Cl_2, 70:30. The product was isolated in 79% yield (680 mg) as an orange oil.

Analytical Data for **214i**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.27

GC (method IZ): t_R = 11.50 min

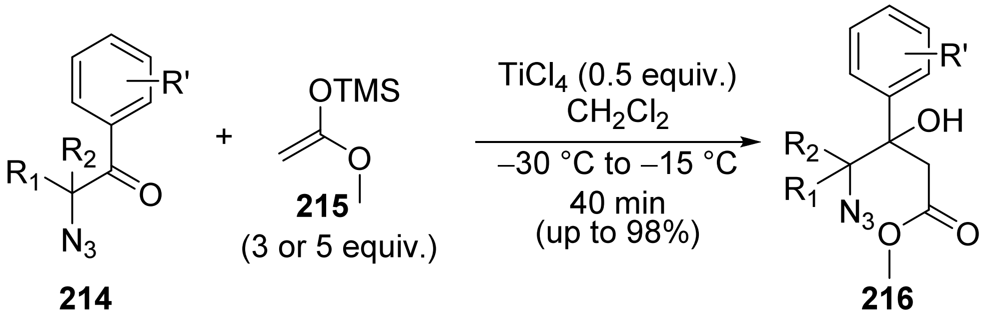
^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.22 (dd, ${}^{3}J_{H3',H4'}$ = 8.3 Hz, ${}^{4}J_{H3',H5'}$ = 1.1 Hz, 1 H, H$^{3'}$), 7.78 (td, ${}^{3}J_{H5',H6'}$ = ${}^{3}J_{H5',H4'}$ = 7.5 Hz, ${}^{4}J_{H5',H3'}$ = 1.1 Hz, 1 H, H$^{5'}$), 7.67 (ddd, ${}^{3}J_{H4',H3'}$ = 8.3 Hz, ${}^{3}J_{H4',H5'}$ = 7.5 Hz, ${}^{4}J_{H4',H6'}$ = 1.4 Hz, 1 H, H$^{4'}$), 7.38 (dd, ${}^{3}J_{H6',H5'}$ = 7.5 Hz, ${}^{4}J_{H6',H4'}$ = 1.4 Hz, 1 H, H$^{6'}$), 4.21 (dd, ${}^{3}J_{H2,H3b}$ = 8.9 Hz, ${}^{3}J_{H2,H3a}$ = 4.3 Hz, 1 H, H^{2}), 2.06 (dqd, ${}^{2}J_{H3a,H3b}$ = 14.4 Hz, ${}^{3}J_{H3a,H4}$ = 7.4 Hz, ${}^{3}J_{H3a,H2}$ = 4.3 Hz, 1 H, H^{3a}), 1.87 (ddq, ${}^{2}J_{H3b,H3a}$ = 14.4 Hz, ${}^{3}J_{H3b,H2}$ = 8.9 Hz, ${}^{3}J_{H3b,H4}$ = 7.4 Hz, 1 H, H^{3b}), 1.10 (t, ${}^{3}J_{H4,H3a}$ = ${}^{3}J_{H4,H3b}$ = 7.4 Hz, 3 H, H^{4})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 199.7 (C^{1}), 145.7 (C$^{2'}$), 135.8 (C$^{1'}$), 134.67 (C$^{5'}$), 131.0 (C$^{4'}$), 128.0 (C$^{6'}$), 124.3 (C$^{3'}$), 69.5 (C^{2}), 24.6 (C^{3}), 10.5 (C^{4})

MS-ESI: 257.3 (43, $[M+Na]^+$), 229.3 (14, $[M-N_2+Na]^+$), 207.2 (100, $[M-N_2+H]^+$)

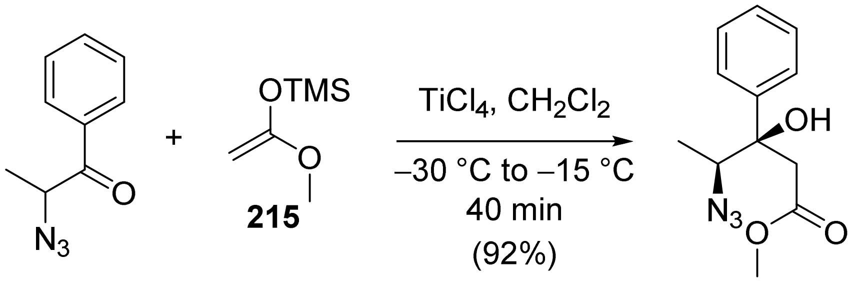
IR (KBr, film): ν = 3106 (vw), 2976 (w), 2939 (w), 2880 (w), 2495 (vw), 2108 (vs), 1716 (vs), 1574 (w), 1530 (vs), 1462 (w), 1442 (w), 1347 (vs), 1314 (m), 1239 (m), 1148 (vw), 1085 (vw), 993 (w), 963 (vw), 941 (vw), 858 (w), 790 (m), 757 (m), 714 (m), 646 (vw), 555 (vw) cm^{-1}

5.3.17. Preparation of azidoesters by Mukaiyama aldol reaction: General Procedures:



To a stirred solution of ((1-methoxyvinyl)oxy)trimethylsilane **S4** (43.66 mmol, 3.0 or 5.0 equiv.) in dry CH_2Cl_2 (60 mL, 0.26 M) was added the corresponding α-azidoketone (14.55 mmol, 1.0 equiv.) at -30 °C and under argon. A solution of freshly distilled $TiCl_4$ (7.28 mmol, 0.5 equiv.) in dry CH_2Cl_2 (10 mL, 0.73 M) was added dropwise over 15 min. The resulting mixture was stirred at -30 °C for 15 min and then allowed to reach -15 °C over a period of 30 min. The dark red solution was quenched with NaOH (2.0 M, 15 mL) and extracted with $CHCl_3$ (4 x 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography and in the some cases crystallised from the appropriate solvent.

5.3.18. Methyl 4-azido-3-hydroxy-3-phenylpentanoate (216c)



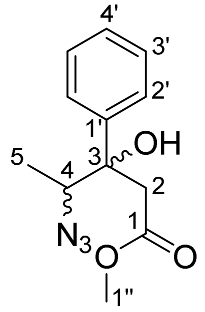
214c
$C_9H_9N_3O$
175.18

$C_6H_{14}O_2Si$
146.26

216c
$C_{12}H_{15}N_3O_3$
249.27

Prepared from 2-azido-1-phenylpropan-1-one (**214c**) (0.94 g, 5.39 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (4.25 g, 29.06 mmol, 5.0 equiv.) and titanium tetrachloride (0.32 mL, 2.90 mmol) in dry CH_2Cl_2 (33 mL). Solvent system for chromatography: cyclohexane/EtOAc, 95:5. The product was isolated in 92% yield (1.23 g) as a slightly yellow oil and as a mixture of two pairs of diastereomers in 90:10 ratio. The oil could be crystallised from EtOAc/petroleum ether to give the product as white solid and as a major diastereomer.

Analytical Data for **216c**:



TLC: R_f (Cyclohexane/EtOAc, 95:5) = 0.28

MP: 64-65 °C

GC (method IZ): t_R = 11.17 min (minor isomer, 10%), t_R = 11.28 min (major isomer, 90%)

GC-MS (EI, 70 eV): t_R = 14.75 min (minor isomer, 10%), t_R = 14.88 min (major isomer, 90%); m/z (%) = 249.9 (1, $[M]^+$), 179.0 (27), 105.0 (100), 77.1 (41), 51.0 (10)

MS-ESI: 272.3 (100, $[M+Na]^+$)

HR-MS (ESI): 272.10062 ($[M+Na]^+$; $C_{12}H_{15}N_3O_3Na^+$; calc. 272.10111)

IR (KBr): ν = 3463 (s), 3088 (w), 2985 (w), 2955 (m), 2487 (vw), 2100 (vs), 2067 (vs), 1709 (vs), 1489 (w), 1443 (s), 1421 (m), 1374 (vs), 1364 (vs), 1309 (m), 1247 (vs), 1207 (vs), 1174 (vs), 1114 (s), 1078 (m), 1054 (m), 1028 (m), 1005 (m), 996 (m), 960 (vs), 869 (w), 833 (vw), 773 (m), 753 (s), 731 (w), 702 (s), 642 (w), 615 (m), 579 (m), 501 (m), 459 (vw) cm^{-1}

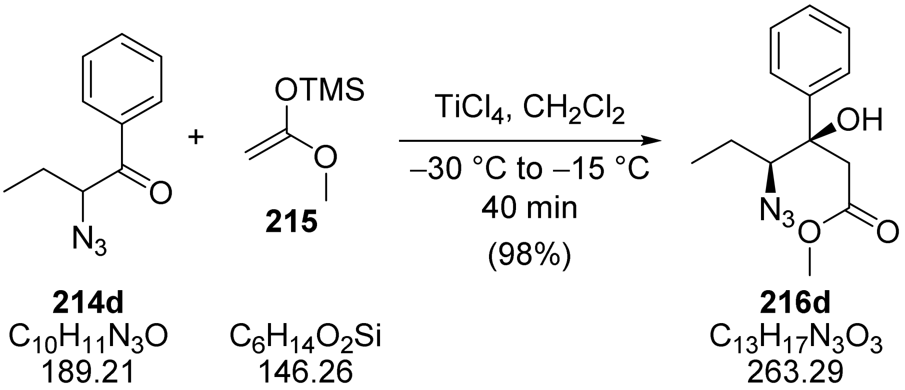
CHN: calc.: C: 57.82; H: 6.07; N: 16.86; found: C: 58.11; H: 6.07; N: 16.47

Major diastereomer (*R*/*S*, *S*/*R*, 90 %):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 4 H, $H^{2'}$ and $H^{3'}$), 7.29-7.25 (m, 1 H, $H^{4'}$), 4.66 (br s, 1 H, OH), 3.54 (s, 3 H, $H^{1''}$), 3.38 (q, $^3J_{H4,H5}$ = 6.7 Hz, 1 H, H^4), 3.17 and 2.94 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.0 Hz, 2 H, H^{2a} and H^{2b}), 1.12 (d, $^3J_{H5,H4}$ = 6.7 Hz, 3 H, H^5)

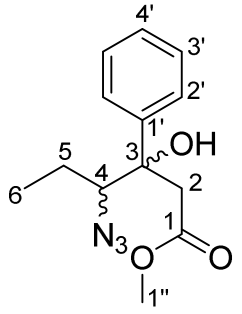
^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.4 (C^1), 142.6 ($C^{1'}$), 128.4 ($C^{3'}$), 127.5 ($C^{4'}$), 125.2 ($C^{2'}$), 76.7 (C^3), 64.1 (C^4), 51.9 ($C^{1''}$), 42.3 (C^2), 12.6 (C^5)

5.3.18. Methyl 4-azido-3-hydroxy-3-phenylhexanoate (216d)



Prepared from 2-azido-1-phenylbutan-1-one (**214d**) (1.0 g, 5.29 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (3.92 g, 26.77 mmol, 5.0 equiv.) and titanium tetrachloride (0.29 mL, 2.64 mmol) in dry CH_2Cl_2 (33 mL). Solvent system for chromatography: cyclohexane/CH_2Cl_2, 50:50 to CH_2Cl_2, 100%. The product was isolated in 98% yield (1.37 g) as a slightly yellow oil and as a mixture of two pairs of diastereomers in 90:10 ratio.

Analytical Data for **216d**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 50:50) = 0.23

GC (method IZ): t_R = 11.68 min (minor isomer, 10%), t_R = 11.71 min (major isomer, 90%)

MS-ESI: 286.5 (100, $[M+Na]^+$)

HR-MS (ESI): 286.11607 ($[M+Na]^+$; $C_{13}H_{17}N_3O_3Na^+$; calc. 286.11676)

IR (KBr, film): ν = 3480 (w), 3061 (vw), 3029 (vw), 2971 (m), 2880 (w), 2105 (vs), 1715 (s), 1602 (vw), 1495 (w), 1439 (m), 1359 (s), 1299 (m), 1267 (m), 1233 (s), 1210 (s), 1168 (s), 1068 (w), 1029 (w), 1005 (w), 937 (w), 903 (vw), 883 (w), 849 (vw), 808 (vw), 768 (w), 703 (s), 645 (vw), 573 (w), 560 (w), 503 (vw) cm^{-1}

Major diastereomer (*R*/*S*, *S*/*R*, 90 %):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 4 H, $H^{2'}$ and $H^{3'}$), 7.29-7.25 (m, 1 H, $H^{4'}$), 4.67 (br s, 1 H, OH), 3.55 (s, 3 H, $H^{1''}$), 3.16 and 2.97 (2 x d AB system, $^2J_{H2a,H2b}$ = 15.9 Hz, 2 H, H^{2a} and H^{2b}), 3.03 (dd, $^3J_{H4,H5b}$ = 2.5 Hz, $^3J_{H4,H5a}$ = 11.2 Hz, 1 H, H^4), 1.65 (ddq, $^2J_{H5a,H5b}$ = 14.7 Hz, $^3J_{H5a,H4}$ = 11.2 Hz, $^3J_{H5a,H6}$ = 7.4 Hz, 1 H, H^{5a}), 1.33 (dqd, $^2J_{H5b,H5a}$ = 14.7 Hz, $^3J_{Hb5,H6}$ = 7.4 Hz, $^3J_{H5b,H4}$ = 2.5 Hz, 1 H, H^{5b}), 0.92 (t, $^3J_{H6,H5a}$ = $^3J_{H6,H5b}$ = 7.4 Hz, 3 H, H^6)

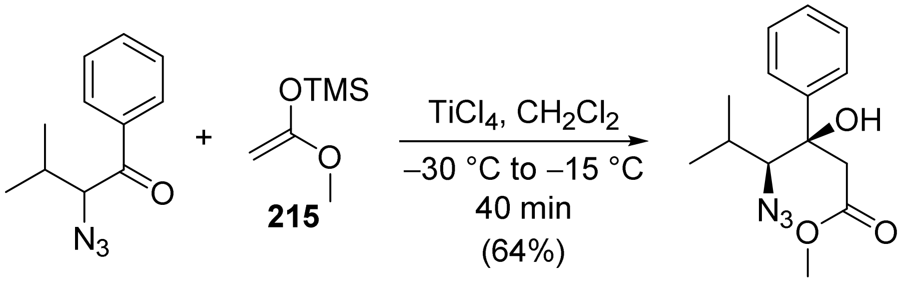
^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.4 (C^1), 142.9 ($C^{1'}$), 128.4 ($C^{3'}$), 127.5 ($C^{4'}$), 125.2 ($C^{2'}$), 78.4 (C^3), 71.5 (C^4), 51.9 ($C^{1''}$), 42.5 (C^2), 20.6 (C^5), 11.5 (C^6)

Some distinct signals of the **minor diastereomer (*R*/*R*, *S*/*S*, 10 %)** were observed.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.46-7.44 (m, 2 H, H$^{2'}$), 3.63 (s, 3 H, H$^{1''}$), 3.34 (dd, $^{3}J_{H4,H5b}$ = 2.4 Hz, $^{3}J_{H4,H5a}$ = 11.1 Hz, 1 H, H^{4}), 3.15 and 2.97 (2 x d AB system, $^{2}J_{H2a,H2b}$ = 16.5 Hz, 2 H, H^{2a} and H^{2b}), 1.49 (dqd, $^{2}J_{H5b,H5a}$ = 14.8 Hz, $^{3}J_{Hb5,H6}$ = 7.4 Hz, $^{3}J_{H5b,H4}$ = 2.4 Hz, 1 H, H^{5b}), 1.12-0.99 (m, 1 H, H^{5a})

^{13}C-NMR (100 MHz, CDCl$_3$): δ 173.5 (C^{1}), 142.2 (C$^{1'}$), 128.3 (C$^{3'}$), 127.7 (C$^{4'}$), 125.9 (C$^{2'}$), 77.9 (C^{3}), 72.8 (C^{4}), 52.0 (C$^{1''}$), 39.6 (C^{2}), 22.1 (C^{5}), 11.7 (C^{6})

5.3.19. Methyl 4-azido-3-hydroxy-5-methyl-3-phenylhexanoate (216e)



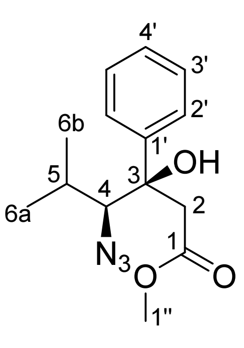
214e $C_{11}H_{13}N_3O$ 203.24

215 $C_6H_{14}O_2Si$ 146.26

216e $C_{14}H_{19}N_3O_3$ 277.32

Prepared from 2-azido-3-methyl-1-phenylbutan-1-one (**214e**) (1.0 g, 4.92 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (3.6 g, 24.60 mmol, 5.0 equiv.) and titanium tetrachloride (0.27 mL, 2.46 mmol) in dry CH$_2$Cl$_2$ (30 mL). Solvent system for chromatography: cyclohexane/EtOAc, 95:5. The product was isolated in 64% yield (0.87 g) as a slightly yellow oil and as a pair of enantiomers.

Analytical Data for **216e**:



TLC: R_f (cyclohexane/EtOAc, 95:5) = 0.27

GC (method IZ): t_R = 12.06 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.43-7.40 (m, 2 H, $H^{2'}$), 7.38-7.33 (m, 2 H, $H^{3'}$), 7.29-7.25 (m, 1 H, $H^{4'}$), 4.51 (d, $^4J_{OH,H4}$ = 1.0 Hz, 1 H, OH), 3.55 (s, 3 H, $H^{1''}$), 3.27 (dd, $^3J_{H4,H5}$ = 3.0 Hz, $^4J_{H4,OH}$ = 1.0 Hz, 1 H, H^4), 3.13 and 2.96 (2 x d AB system, $^2J_{H2a,H2b}$ = 15.5 Hz, 2 H, H^{2a} and H^{2b}), 1.80 (sept d, $^3J_{H5,H6}$ = 6.8 Hz, $^3J_{H5,H4}$ = 3.0 Hz, 1 H, H^5), 1.00 (d, $^3J_{H6a,H5}$ = 6.8 Hz, 3 H, H^{6a}), 0.88 (d, $^3J_{H6b,H5}$ = 6.8 Hz, 3 H, H^{6b})

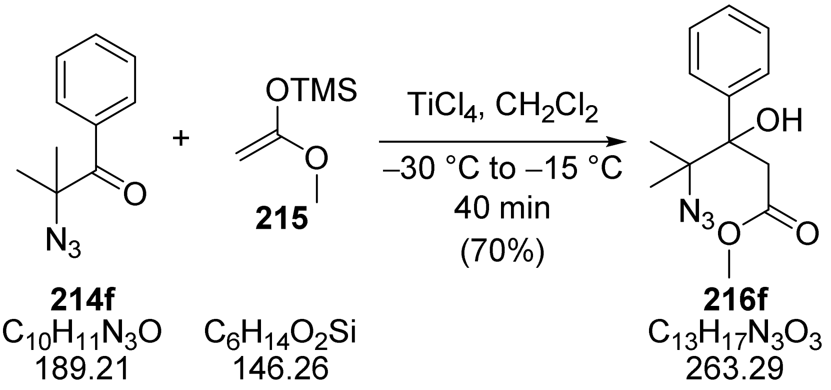
^{13}C-NMR (100 MHz, CDCl$_3$): δ 173.0 (C^1), 143.1 ($C^{1'}$), 128.5 ($C^{3'}$), 127.5 ($C^{4'}$), 125.2 ($C^{2'}$), 78.7 (C^3), 75.4 (C^4), 51.9 ($C^{1''}$), 43.8 (C^2), 29.8 (C^5), 23.1 (C^{6b}), 17.6 (C^{6a})

MS-ESI: 300.3 (100, $[M+Na]^+$)

HR-MS (ESI): 300.13144 ($[M+Na]^+$; $C_{14}H_{19}N_3O_3Na^+$; calc. 300.13241)

IR (KBr, film): ν = 3480 (w), 3062 (vw), 2962 (m), 2875 (w), 2103 (vs), 1716 (s), 1496 (vw), 1439 (m), 1346 (m), 1265 (m), 1210 (s), 1169 (m), 1104 (vw), 1071 (w), 1003 (w), 965 (vw), 909 (vw), 890 (vw), 821 (vw), 768 (vw), 703 (m), 644 (vw), 559 (vw) cm^{-1}

5.3.20. Methyl 4-azido-3-hydroxy-4-methyl-3-phenylpentanoate (216f)



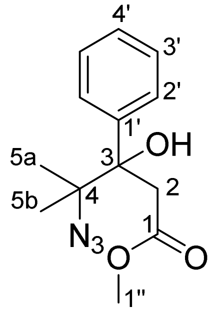
214f $C_{10}H_{11}N_3O$ 189.21

215 $C_6H_{14}O_2Si$ 146.26

216f $C_{13}H_{17}N_3O_3$ 263.29

Prepared from 2-azido-2-methyl-1-phenylpropan-1-one (**214f**) (0.40 g, 2.11 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (1.55 g, 10.57 mmol, 5.0 equiv.) and titanium tetrachloride (0.12 g, 1.06 mmol) in dry CH_2Cl_2 (18 mL). Solvent system for chromatography: cyclohexane/EtOAc, 95:5. The product was isolated in 70% yield (0.39 g) as a slightly yellow oil and as a a pair of enantiomers.

Analytical Data for **216f**:



TLC: R_f (cyclohexane/EtOAc, 95:5) = 0.31

GC (method IZ): t_R = 11.54 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.49 (d, $^3J_{H2',H3'obs.}$ = 7.3 Hz, 2 H, H$^{2'}$), 7.34-7.30 (m, 2 H, H$^{3'}$), 7.27 (tt, $^3J_{H4',H3'obs.}$ = 7.3 Hz, $^4J_{H4',H2'obs.}$ = 1.4 Hz, 1 H, H$^{4'}$), 4.67 (br s, 1 H, OH), 3.53 (s, 3 H, H$^{1''}$), 3.30 and 3.03 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.1 Hz, 2 H, H^{2a} and H^{2b}), 1.33 (s, 3 H, H^{5a}), 1.12 (s, 3 H, H^{5b})

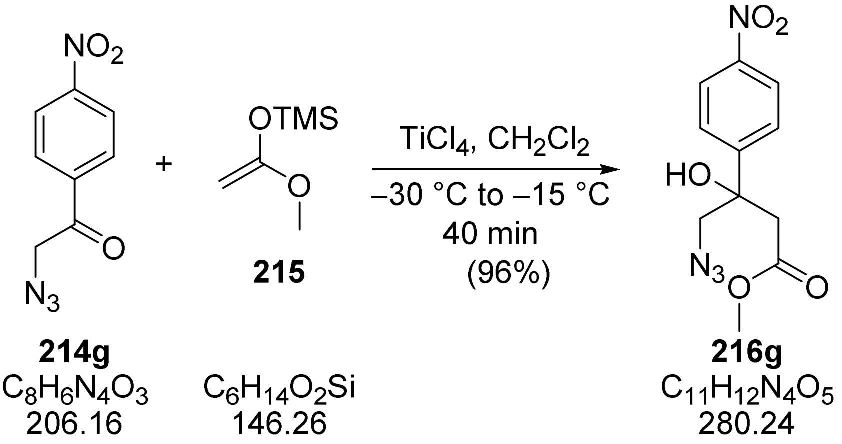
^{13}C-NMR (100 MHz, CDCl$_3$): δ 173.9 (C^1), 141.8 (C$^{1'}$), 127.7 (C$^{3'}$), 127.5 (C$^{4'}$), 127.1 (C$^{2'}$), 79.5 (C^3), 66.2 (C^4), 51.9 (C$^{1''}$), 39.4 (C^2), 22.4 (C^{5b}), 21.4 (C^{5a})

MS-EI (70 eV): 263.9 (12, [M]$^+$), 221.0 (5, [M-N$_3$]$^+$), 203.0 (10), 179.0 (40), 158.1 (15), 119.1 (51), 105.1 (100), 91.2 (7), 77.1 (20), 58.1 (8)

HR-MS (ESI): 286.11697 ([M+Na]$^+$; C$_{13}$H$_{17}$N$_3$O$_3$Na$^+$; calc. 286.11676)

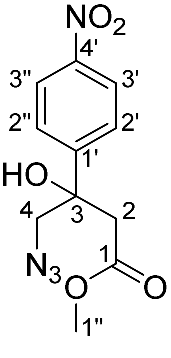
IR (KBr, film): ν = 3479 (m), 3060 (vw), 2982 (w), 2954 (w), 2504 (vw), 2111 (vs), 2066 (m), 1716 (vs), 1602 (vw), 1494 (w), 1439 (s), 1388 (m), 1369 (s), 1344 (s), 1267 (s), 1216 (s), 1153 (vs), 1108 (w), 1071 (w), 1045 (w), 1025 (m), 1005 (m), 916 (vw), 899 (vw), 857 (vw), 799 (vw), 764 (m), 705 (s), 661 (w), 630 (vw), 578 (w), 559 (w) cm^{-1}

5.3.21. Methyl 4-azido-3-hydroxy-3-(4-nitrophenyl)butanoate (216g)



Prepared from 2-azido-1-(4-nitrophenyl)ethanone (**214g**) (500 mg, 2.43 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (1.77 g, 12.13 mmol, 5.0 equiv.) and titanium tetrachloride (0.14 mL, 1.21 mmol) in dry CH_2Cl_2 (18 mL). Solvent system for chromatography: CH_2Cl_2, 100%. The product was isolated in 96% yield (656 mg) as a slightly yellow oil and as a pair of enantiomers.

Analytical Data for **216g**:



TLC: R_f (CH_2Cl_2, 100%) = 0.36

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.23 (dt, $^3J_{H3',H2'}$ = 9.4 Hz, $^4J_{H3',H3''}$ = $^5J_{H3',H2''}$ = 2.3 Hz, 2 H, $H^{3'}$), 7.65 (dt, $^3J_{H2',H3'}$ = 9.4 Hz, $^4J_{H2',H2''}$ = $^5J_{H2',H3''}$ = 2.3 Hz, 2 H, $H^{2'}$), 4.81 (d, $^4J_{OH,H4b}$ = 1.0 Hz, 1 H, OH), 3.63 (s, 3 H, $H^{1''}$), 3.50 (d AB system, $^2J_{H4a,H4b}$ = 12.7 Hz, 1 H, H^{4a}), 3.32 (dd AB system, $^2J_{H4b,H4a}$ = 12.7 Hz, $^4J_{H4b,OH}$ = 1.0 Hz, 1 H, H^{4b}), 3.11 and 3.00 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.5 Hz, 2 H, H^{2a} and H^{2b})

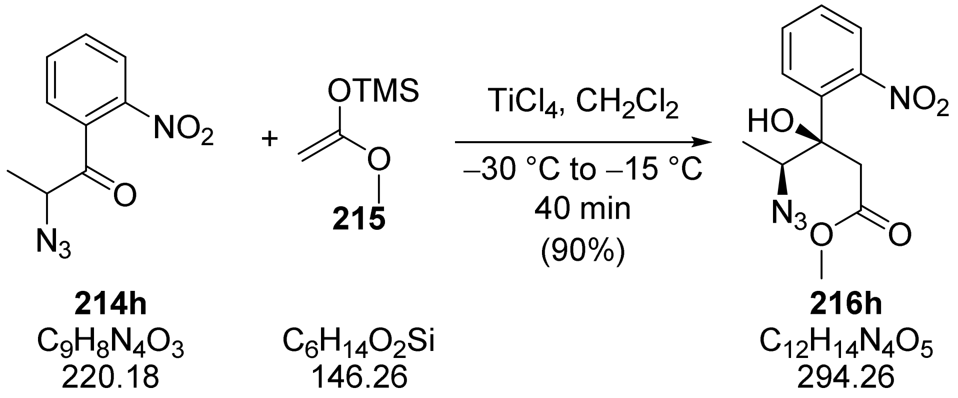
^{13}C-NMR (100 MHz, CDCl$_3$): δ 172.6 (C^{1}), 150.0 (C$^{1'}$), 147.6 (C$^{4'}$), 126.3 (C$^{2'}$), 123.8 (C$^{3'}$), 75.7 (C^{3}), 60.1 (C^{4}), 52.3 (C$^{1''}$), 41.1 (C^{2})

MS-ESI: 303.2 (100, [M+Na]$^+$)

HR-MS (ESI): 303.06908 ([M+Na]$^+$; $C_{11}H_{12}N_4O_5Na^+$; calc. 303.07054)

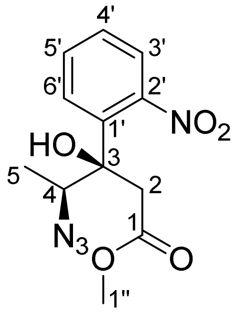
IR (KBr, film): ν = 3479 (m), 3113 (vw), 3080 (vw), 2956 (w), 2459 (vw), 2108 (vs), 1717 (vs), 1606 (m), 1522 (vs), 1494 (w), 1439 (s), 1414 (m), 1351 (vs), 1288 (s), 1209 (vs), 1111 (m), 1059 (m), 1012 (m), 949 (w), 915 (w), 855 (s), 756 (m), 702 (m), 642 (vw), 557 (w) cm^{-1}

5.3.22. Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)pentanoate (216h)



Prepared from 2-azido-1-(2-nitrophenyl)propan-1-one (**214h**) (375 mg, 1.70 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (1.25 g, 8.52 mmol, 5.0 equiv.) and titanium tetrachloride (0.10 mL, 0.85 mmol) in dry CH_2Cl_2 (11 mL). Solvent system for chromatography: CH_2Cl_2, 100%. The product was isolated in 90% yield (453 mg) as a yellow oil and as a pair of enantiomers.

Analytical Data for **216h**:



TLC: R_f (CH_2Cl_2, 100%) = 0.40

GC (method IZ): t_R = 13.18 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2 H, H$^{6'}$ and H$^{5'}$), 7.44-7.39 (m, 2 H, H$^{3'}$ and H$^{4'}$), 4.86 (br s, 1 H, OH), 3.88 (q, $^3J_{H4,H5}$ = 6.7 Hz, 1 H, H^4), 3.61 (s, 3 H, H$^{1''}$), 3.09 and 3.04 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.4 Hz, 2 H, H^{2a} and H^{2b}), 1.26 (d, $^3J_{H5,H4}$ = 6.7 Hz, 3 H, H^4)

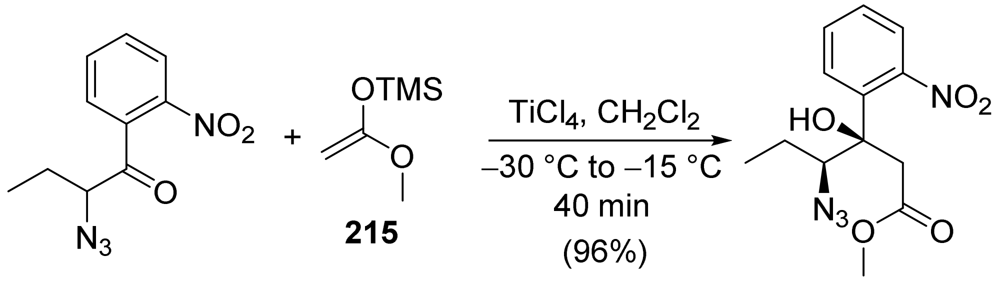
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 173.0 (C^1), 150.1 (C$^{2'}$), 134.6 (C$^{1'}$), 130.6 (C$^{5'}$), 129.0 (C$^{4'}$), 128.6 (C$^{6'}$), 124.1 (C$^{3'}$), 77.9 (C^3), 62.8 (C^4), 52.3 (C$^{1''}$), 40.3 (C^2), 13.2 (C^5)

MS-EI (70 eV): 294.9 (4, [M]$^+$), 224.0 (11), 192.0 (73), 150.0 (100), 135.1 (20), 104.1 (17), 77.1 (24), 51.0 (42)

HR-MS (ESI): 317.08597 ([M+Na]$^+$; $C_{12}H_{14}N_4O_5Na^+$; calc. 317.08619)

IR (KBr, film): ν = 3457 (m), 2990 (w), 2956 (w), 2488 (vw), 2120 (vs), 1713 (vs), 1604 (vw), 1539 (vs), 1486 (w), 1440 (s), 1379 (vs), 1250 (s), 1213 (vs), 1175 (s), 1116 (m), 1092 (w), 1036 (m), 997 (m), 968 (w), 911 (vw), 872 (w), 855 (m), 774 (s), 736 (m), 673 (w), 649 (vw), 584 (w), 562 (w), 508 (vw) cm^{-1}

5.3.23. Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)hexanoate (216i)



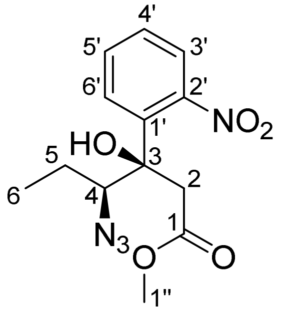
214i
$C_{10}H_{10}N_4O_3$
234.21

215
$C_6H_{14}O_2Si$
146.26

216i
$C_{13}H_{16}N_4O_5$
308.29

Prepared from 2-azido-1-(2-nitrophenyl)butan-1-one (**214i**) (500 mg, 2.14 mmol), ((1-methoxyvinyl)oxy)trimethylsilane **215** (1.56 g, 10.67 mmol, 5.0 equiv.) and titanium tetrachloride (0.12 mL, 1.07 mmol) in dry CH_2Cl_2 (14 mL). Solvent system for chromatography: CH_2Cl_2, 100%. The product was isolated in 96% yield (632 mg) as a slightly yellow oil and as a pair of enantiomers. The oil could be crystallised from THF/cyclohexane to give the product as white solid.

Analytical Data for **216i**:



TLC: R_f (CH_2Cl_2, 100%) = 0.50

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, $^3J_{H6',H5'}$ = 8.0 Hz, $^4J_{H6',H4'obs.}$ = 2.2 Hz, 1 H, $H^{6'}$), 7.50 (td, $^3J_{H5',H6'}$ = $^3J_{H5',H4'obs.}$ = 8.0 Hz, $^4J_{H5',H3'obs.}$ = 2.3 Hz, 1 H, $H^{5'}$), 7.44-7.38 (m, 2 H, $H^{3'}$ and $H^{4'}$), 4.89 (br s, 1 H, OH), 3.61 (s, 3 H, $H^{1''}$), 3.53 (dd, $^3J_{H4,H5a}$ = 10.5 Hz, $^3J_{H4,H5b}$ = 3.0 Hz, 1 H, H^4), 3.11 and 3.03 (2 x d AB system, $^2J_{H2a,H2b}$ = 16.3 Hz, 2 H, H^{2a} and H^{2b}), 1.64 (ddq, $^2J_{H5a,H5b}$ = 14.6 Hz, $^3J_{H5a,H4}$ = 10.5 Hz, $^3J_{H5a,H6}$ = 7.4 Hz, 1 H, H^{5a}), 1.57 (dqd, $^2J_{H5b,H5a}$ = 14.6 Hz, $^3J_{H5b,H6}$ = 7.4 Hz, $^3J_{H5b,H4}$ = 3.0 Hz, 1 H, H^{5b}), 1.01 (t, $^3J_{H6,H5a}$ = $^3J_{H6,H5b}$ = 7.4 Hz, 3 H, H^6)

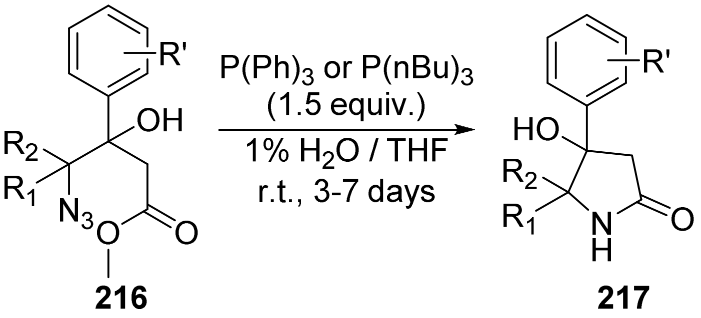
^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0 (C^1), 150.1 ($C^{2'}$), 134.9 ($C^{1'}$), 130.7 ($C^{5'}$), 129.0 ($C^{4'}$), 128.4 ($C^{6'}$), 124.1 ($C^{3'}$), 78.6 (C^3), 70.2 (C^4), 52.3 ($C^{1''}$), 40.6 (C^2), 21.5 (C^5), 11.5 (C^6)

MS-ESI: 331.2 (100, $[M+Na]^+$)

HR-MS (ESI): 331.10166 ($[M+Na]^+$; $C_{13}H_{16}N_4O_5Na^+$; calc. 331.10184)

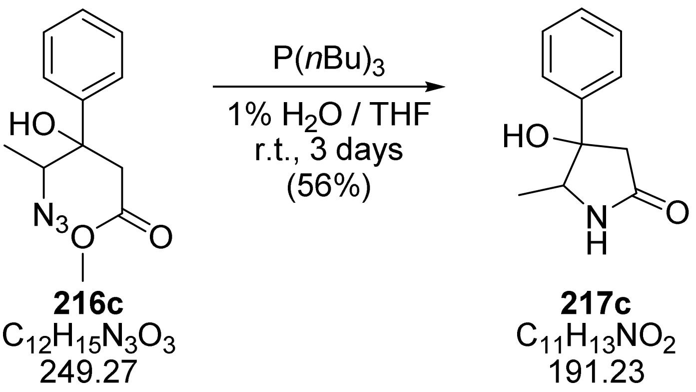
IR (KBr, film): ν = 3457 (m), 2972 (s), 2881 (w), 2497 (vw), 2107 (vs), 1713 (vs), 1604 (vw), 1537 (vs), 1486 (m), 1440 (vs), 1378 (vs), 1302 (s), 1211 (vs), 1172 (vs), 1112 (m), 1046 (m), 1004 (m), 936 (w), 905 (w), 888 (w), 850 (s), 775 (s), 742 (w), 703 (w), 673 (w), 646 (w), 585 (w), 559 (w) cm^{-1}

5.3.24. Preparation of pyrrolidinones by Staudinger cyclisation: General Procedures:



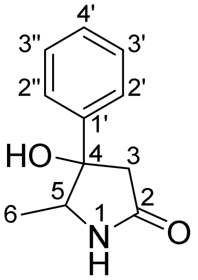
To a stirred solution of the corresponding azidoester **216** (30.05 mmol, 1 equiv.) in THF (126 mL, 0.24 M) was added triphenylphosphine or tributylphosphine (45.07 mmol, 1.5 equiv.) at room temperature. After 30 min, deionized water (1%, 1.26 mL) was added. The resulting mixture was stirred at room temperature for at least 3 days. The solvents were removed in vacuo and the crude product **217** was purified by crystallisation from the appropriate solvent and/or by flash chromatography in the some cases.

5.3.25. 4-Hydroxy-5-methyl-4-phenylpyrrolidin-2-one (217c)



Prepared from methyl 4-azido-3-hydroxy-3-phenylpentanoate (**216c**) (1.23 g, 4.94 mmol) and tributylphosphine (1.85 mL, 7.41 mmol) in THF (18 mL)/water (0.18 mL). Solvent system for chromatography: CH_2Cl_2/MeOH, 96:4. The product was crystallised from EtOAc to give 474 mg (56%) of pure pyrrolidinone as a white solid.

Analytical Data for **217c**:



TLC: R_f (CH_2Cl_2/MeOH, 96:4) = 0.25

MP: 186 °C

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.70 (br s, 1 H, H^1), 7.55 (ddd, $^3J_{H2',H3'}$ = 8.4 Hz, $^4J_{H2',H2''obs.}$ = 2.7 Hz, $^4J_{H2',H4'}$ = 1.2 Hz, 2 H, $H^{2'}$), 7.36-7.31 (m (partially solved), $^3J_{H3',H2'}$ = 8.4 Hz, $^3J_{H3',H4'}$ = 7.2 Hz, $^4J_{H3',H3''obs.}$ = 2.0 Hz, $^5J_{H3',H2''obs.}$ = 1.5 Hz, 2 H, $H^{3'}$), 7.24 (tt, $^3J_{H4',H3'}$ = 7.2 Hz, $^4J_{H4',H2'}$ = 1.2 Hz, 1 H, $H^{4'}$), 5.44 (br s, 1 H, OH), 3.71 (q, $^3J_{H5,H6}$ = 6.5 Hz, 1 H, H^5), 2.88 and 2.30 (2 x d AB system, $^2J_{H3a,H3b}$ = 16.4 Hz, 2 H, H^{3a} and H^{3b}), 0.95 (d, $^3J_{H6,H5}$ = 6.5 Hz, 3 H, H^6)

^{13}C-NMR (400 MHz, DMSO-d6): δ 173.8 (C^2), 144.3 ($C^{1'}$), 127.9 ($C^{3'}$), 127.7 ($C^{4'}$), 125.6 ($C^{2'}$), 77.8 (C^4), 60.2 (C^5), 47.7 (C^3), 12.6 (C^6)

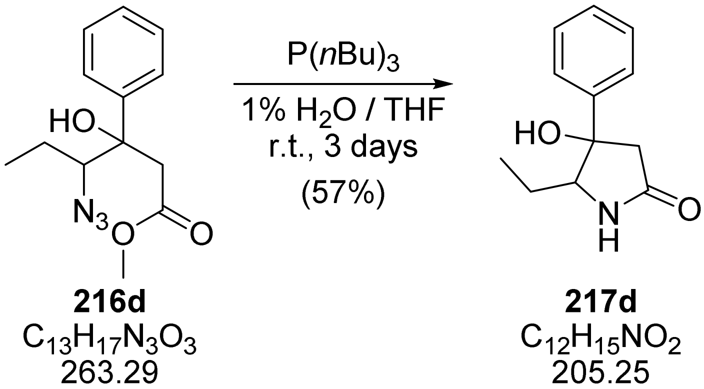
MS-ESI: 214.1 (100, $[M+Na]^+$)

HR-MS (ESI): 214.08360 ($[M+Na]^+$; $C_{11}H_{13}NO_2Na^+$; calc. 214.08440)

IR (KBr): ν = 3195 (vs), 3080 (s), 2991 (m), 2931 (m), 2876 (m), 1958 (vw), 1705 (vs), 1669 (vs), 1495 (m), 1444 (s), 1400 (s), 1376 (s), 1333 (m), 1311 (m), 1291 (w), 1266 (m), 1221 (s), 1186 (w), 1140 (vw), 1095 (m), 1072 (w), 1032 (vw), 1006 (m), 999 (m), 956 (w), 918 (w), 900 (w), 876 (w), 769 (s), 741 (s), 699 (vs), 659 (m), 601 (w), 565 (vw), 529 (w), 518 (w), 492 (m), 409 (vw) cm^{-1}

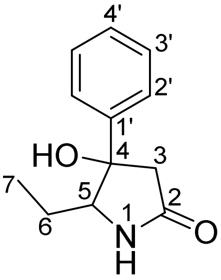
CHN: calc.: C: 69.09; H: 6.85; N: 7.32; found: C: 68.94; H: 6.85; N: 7.29

5.3.26. 5-Ethyl-4-hydroxy-4-phenylpyrrolidin-2-one (217d)



Prepared from methyl 4-azido-3-hydroxy-3-phenylhexanoate (**216d**) (1.01 g, 3.84 mmol) and tributylphosphine (1.44 mL, 5.75 mmol) in THF (15 mL)/water (0.15 mL). The product was crystallised from EtOAc/pentane to give 364 mg (45%) of pure pyrrolidinone. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to afford 260 mg of yellow solid which was crystallised from MeOH/pentane to give 84 mg (11%) of pure pyrrolidinone. The product was isolated in 57% total yield (448 mg) as a white solid.

Analytical Data for **217d**:



TLC: R_f (CH_2Cl_2/MeOH, 98:2) = 0.20

MP: 225 °C

GC (method IZ): t_R = 12.77 min

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.90 (br s, 1 H, H^1), 7.57-7.55 (m (partially solved), $^3J_{H2',H3'obs.}$ = 8.5 Hz, , $^4J_{H2',H4'obs.}$ = 1.2 Hz, 2 H, $H^{2'}$), 7.36-7.31 (m (partially solved), $^3J_{H3',H4'}$ = 7.3 Hz, 2 H, $H^{3'}$), 7.23 (t, $^3J_{H4',H3'}$ = 7.3 Hz, 1 H, $H^{4'}$), 5.46 (br s, 1 H, OH), 3.52 (t, $^3J_{H5,H6}$ = 6.6 Hz, 1 H, H^5), 2.83 and 2.31 (2 x d AB system, $^2J_{H3a,H3b}$ = 16.5 Hz, 2 H, H^{3a} and H^{3b}), 1.45-1.38 (m (partially solved), $^3J_{H6,H7}$ = 7.5 Hz, 2 H, H^6), 0.72 (t, $^3J_{H7,H6}$ = 7.5 Hz, 3 H, H^7)

^{13}C-NMR (400 MHz, DMSO-d6): δ 174.0 (C^2), 145.0 ($C^{1'}$), 127.8 ($C^{3'}$), 126.6 ($C^{4'}$), 125.5 ($C^{2'}$), 77.7 (C^4), 66.9 (C^5), 48.6 (C^3), 21.2 (C^6), 11.2 (C^7)

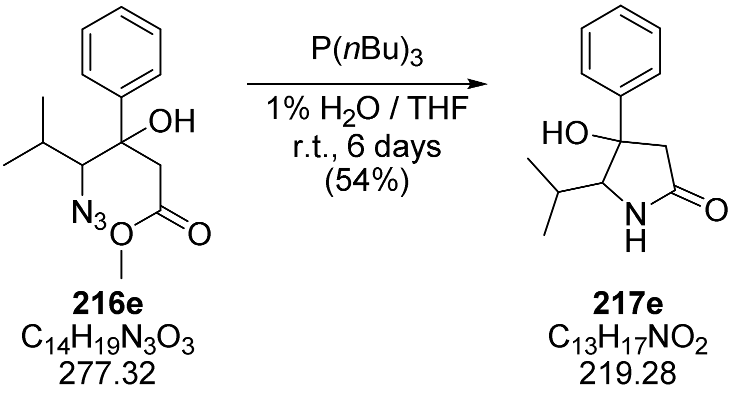
MS-EI (70 eV): 205.1 (12, $[M]^+$), 187.1 (9, $[M-H_2O]^+$), 158.1 (9, $[M-H_2O-CH_3CH_2]^+$), 120.1 (12), 105.0 (56), 91.1 (12), 78.1 (21), 77.1 (35), 58.1 (100)

HR-MS (ESI): 228.09953 ($[M+Na]^+$; $C_{12}H_{15}NO_2Na^+$; calc. 228.10005)

IR (KBr): ν = 3285 (s), 3199 (vs), 3081 (m), 3029 (m), 2963 (m), 2923 (w), 2875 (m), 1954 (vw), 1693 (vs), 1669 (vs), 1494 (w), 1462 (w), 1447 (m), 1405 (s), 1389 (s), 1357 (w), 1317 (s), 1293 (m), 1257 (w), 1222 (s), 1186 (w), 1138 (vw), 1097 (w), 1074 (m), 1048 (w), 1001 (vw), 976 (w), 939 (vw), 912 (vw), 902 (vw), 860 (vw), 827 (w), 788 (w), 758 (s), 697 (vs), 660 (m), 498 (m), 472 (vw), 425 (w) cm^{-1}

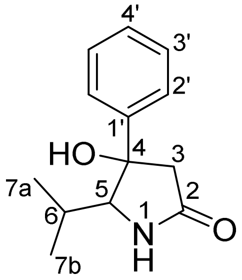
CHN: calc.: C: 70.22; H: 7.37; N: 6.82; found: C: 69.95; H: 7.38; N: 6.67

5.3.27. 4-Hydroxy-5-isopropyl-4-phenylpyrrolidin-2-one (217e)



Prepared from methyl 4-azido-3-hydroxy-5-methyl-3-phenylhexanoate (**216e**) (680 mg, 2.45 mmol) and tributylphosphine (0.92 mL, 3.68 mmol) in THF (9 mL)/water (0.09 mL). The product was crystallised from MeOH to give 279 mg (52%) of pure pyrrolidinone. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 96:4) to afford 143 mg of yellow solid which was crystallised from MeOH to give 10 mg (2%) of pure pyrrolidinone. The product was isolated in 54% total yield (289 mg) as a white solid.

Analytical Data for **217e**:



TLC: R_f (CH_2Cl_2/MeOH, 96:4) = 0.28

MP: 252 °C

GC (method IZ): t_R = 13.07 min

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.87 (br s, 1 H, H^1), 7.56 (d, $^3J_{H2',H3'}$= 7.3 Hz, 2 H, H$^{2'}$), 7.32 (t, $^3J_{H3',H4'}$ = $^3J_{H3',H2'}$ = 7.3 Hz, 2 H, H$^{3'}$), 7.20 (t, $^3J_{H4',H3'}$ = 7.3 Hz, 1 H, H$^{4'}$), 5.58 (br s, 1 H, OH), 3.45 (t, $^3J_{H5,H6\,obs.}$ = 8.1 Hz, 1 H, H^5), 2.68 and 2.34 (2 x d AB system, $^2J_{H3a,H3b}$ = 16.6 Hz, 2 H, H^{3a} and H^{3b}), 1.96-1.88 (m (partially solved), $^3J_{H6,H7a}$ = $^3J_{H6,H7b}$ = 6.7 Hz, 1 H, H^6), 0.91 (d, $^3J_{H7a,H6}$ = 6.7 Hz, 3 H, H^{7a}), 0.48 (d, $^3J_{H7b,H6}$ = 6.7 Hz, 3 H, H^{7b})

^{13}C-NMR (400 MHz, DMSO-d6): δ 174.4 (C^2), 147.2 (C$^{1'}$), 128.3 (C$^{3'}$), 126.8 (C$^{4'}$), 125.8 (C$^{2'}$), 78.3 (C^4), 71.3 (C^5), 50.8 (C^3), 28.7 (C^6), 20.9 and 20.8 (C^{7a} and C^{7b})

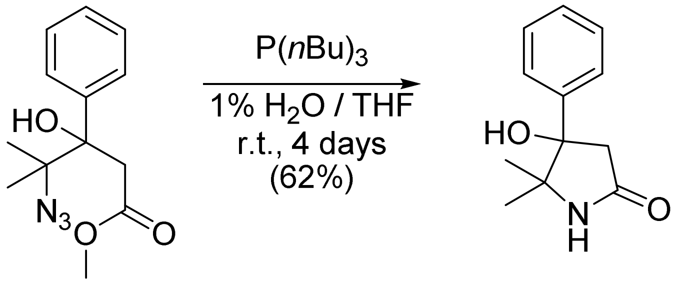
MS-ESI: 242.1 (100, [M+Na]$^+$), 239.1 (67), 183.0 (67), 143.0 (83)

HR-MS (ESI): 242.11509 ([M+Na]$^+$; $C_{13}H_{17}NO_2Na^+$; calc. 242.11570)

IR (KBr): ν = 3292 (vs), 3215 (vs), 3086 (s), 3034 (m), 2984 (m), 2954 (m), 2871 (s), 1950 (vw), 1697 (vs), 1671 (vs), 1601 (w), 1494 (w), 1446 (s), 1409 (s), 1393 (s), 1353 (m), 1323 (w), 1302 (s), 1277 (m), 1260 (m), 1221 (s), 1180 (m), 1145 (w), 1087 (w), 1064 (s), 1031 (w), 980 (w), 961 (w), 917 (w), 906 (w), 852 (vw), 808 (w), 760 (vs), 699 (vs), 660 (m), 499 (m), 439 (w) cm^{-1}

CHN: calc.: C: 71.21; H: 7.81; N: 6.39; found: C: 71.06; H: 7.80; N: 6.36

5.3.28. 4-Hydroxy-5,5-dimethyl-4-phenylpyrrolidin-2-one (217f)

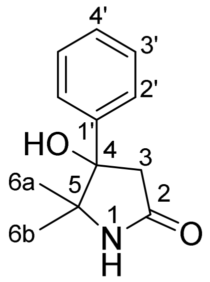


216f
$C_{13}H_{17}N_3O_3$
263.29

217f
$C_{12}H_{15}NO_2$
205.25

Prepared from methyl 4-azido-3-hydroxy-4-methyl-3-phenylpentanoate (**216f**) (205 mg, 0.78 mmol) and tributylphosphine (0.29 mL, 1.17 mmol) in THF (3 mL)/water (0.03 mL). The product was crystallised from MeOH to give 83 mg (62%) of pure pyrrolidinone as a white solid.

Analytical Data for **217f**:



MP: 234-235 °C

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.67 (br s, 1 H, H^1), 7.54-7.51 (m, 2 H, H$^{2'}$), 7.36-7.31 (m (partially solved), $^3J_{H3',H4'}$ = 7.3 Hz, 2 H, H$^{3'}$), 7.27 (tt, $^3J_{H4',H3'}$ = 7.3 Hz, $^4J_{H4',H2'obs.}$ = 1.2 Hz, 1 H, H$^{4'}$), 5.45 (br s, 1 H, OH), 3.30 and 2.22 (2 x d AB system, $^2J_{H3a,H3b}$ = 16.3 Hz, 2 H, H^{3a} and H^{3b}), 1.18 (s, 3 H, H^{6a}), 0.67 (s, 3 H, H^{7b})

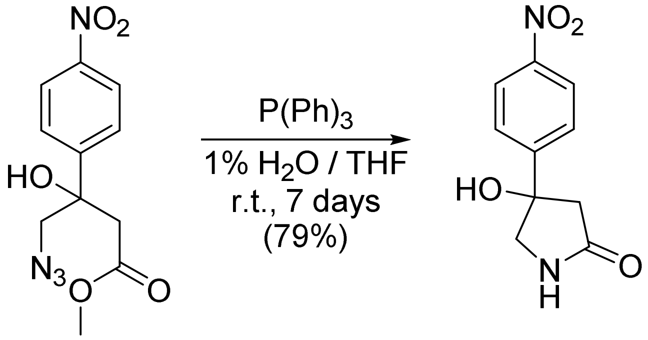
^{13}C-NMR (400 MHz, DMSO-d6): δ 173.2 (C^2), 142.6 (C$^{1'}$), 127.7 (C$^{3'}$), 127.0 (C$^{4'}$), 126.5 (C$^{2'}$), 79.9 (C^4), 62.3 (C^5), 43.5 (C^3), 27.1 (C^{6b}), 20.9 (C^{6a})

MS-EI (70 eV): 207.1 (7, [M+2H]$^+$), 205.1 (8, [M]$^+$), 187.1 (4, [M-H$_2$O]$^+$), 172.1 (19, [M-H$_2$O-CH$_3$]$^+$), 144.1 (15), 105.0 (31), 91.1 (8), 78.1 (15), 77.1 (20), 58.1 (100)
HR-MS (ESI): 228.09947 ([M+Na]$^+$; $C_{12}H_{15}NO_2Na^+$; calc. 228.10005)

IR (KBr): ν = 3298 (vs), 3184 (vs), 3061 (vs), 3003 (s), 2975 (s), 2934 (s), 1958 (vw), 1683 (vs), 1495 (m), 1446 (s), 1432 (s), 1386 (vs), 1288 (w), 1227 (m), 1190 (vs), 1159 (s), 1099 (w), 1068 (s), 1046 (s), 1033 (m), 997 (w), 953 (m), 917 (w), 895 (m), 862 (w), 765 (vs), 703 (vs), 661 (m), 619 (w), 604 (w), 570 (w), 534 (m), 506 (s), 453 (vw), 423 (w) cm^{-1}

CHN: calc.: C: 70.22; H: 7.37; N: 6.82; found: C: 69.93; H: 7.36; N: 6.77

5.3.29. 4-Hydroxy-4-(4-nitrophenyl)pyrrolidin-2-one (217g)

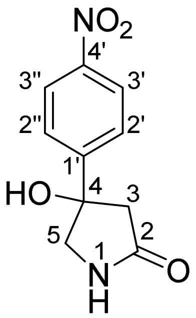


216g
$C_{11}H_{12}N_4O_5$
280.24

217g
$C_{10}H_{10}N_2O_4$
222.20

Prepared from methyl 4-azido-3-hydroxy-3-(4-nitrophenyl)butanoate (**216g**) (407 mg, 1.45 mmol) and triphenylphosphine (571 mg, 2.18 mmol) in THF (6 mL)/water (0.06 mL). The product was crystallised from MeOH to give 255 mg (79%) of pure pyrrolidinone as a white solid.

Analytical Data for **217g**:



MP: 203-204 °C

^{1}H-NMR (400 MHz, DMSO-d6): δ 8.21 (dt, $^3J_{H3',H2'}$ = 9.5 Hz, $^4J_{H3',H3''}$ = $^5J_{H3',H2''}$ = 2.3 Hz, 2 H, $H^{3'}$), 7.84 (br s, 1 H, H^1), 7.81 (dt, $^3J_{H2',H3'}$ = 9.5 Hz, $^4J_{H2',H2''}$ = $^5J_{H2',H3''}$ = 2.3 Hz, 2 H, $H^{2'}$), 6.00 (br s, 1 H, OH), 3.56 and 3.38 (2 x d AB system, $^2J_{H5a,H5b}$ = 10.4 Hz, 2 H, H^{5a} and H^{5b}), 2.79 and 2.36 (2 x d AB system, $^2J_{H3a,H3b}$ = 16.4 Hz, 2 H, H^{3a} and H^{3b})

^{13}C-NMR (400 MHz, DMSO-d6): δ 174.3 (C^2), 152.8 ($C^{1'}$), 146.5 ($C^{4'}$), 126.8 ($C^{2'}$), 123.2 ($C^{3'}$), 76.7 (C^4), 56.1 (C^5), 46.5 (C^3)

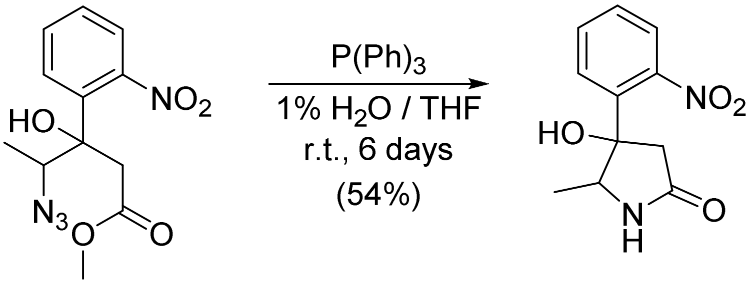
MS-ESI: 245.2 (100, $[M+Na]^+$)

HR-MS (ESI): 245.05299 ($[M+Na]^+$; $C_{10}H_{10}N_2O_4Na^+$; calc. 245.05383)

IR (KBr): ν = 3372 (vs), 2951 (w), 1696 (vs), 1600 (m), 1512 (vs), 1474 (s), 1406 (m), 1343 (vs), 1288 (s), 1235 (s), 1105 (m), 1069 (m), 1049 (m), 1012 (w), 978 (w), 929 (w), 907 (vw), 876 (w), 855 (s), 797 (vw), 753 (w), 717 (w), 700 (m), 681 (m), 560 (w), 483 (w), 420 (w) cm^{-1}

CHN: calc.: C: 54.05; H: 4.54; N: 12.61; found: C: 53.78; H: 4.69; N: 12.62

5.3.30. 4-Hydroxy-5-methyl-4-(2-nitrophenyl)pyrrolidin-2-one (217h)

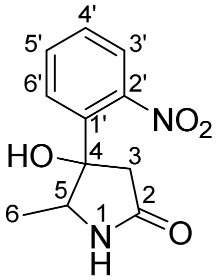


216h
$C_{12}H_{14}N_4O_5$
294.26

217h
$C_{11}H_{12}N_2O_4$
236.22

Prepared from methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)pentanoate (**216h**) (396 mg, 1.35 mmol) and triphenylphosphine (530 mg, 2.02 mmol) in THF (6 mL)/water (0.06 mL). Solvent system for chromatography: CH_2Cl_2/MeOH, 90:10. The product was isolated in 54% yield (172 mg) as a white powder.

Analytical Data for **217h**:



TLC: R_f (CH_2Cl_2/MeOH, 90:10) = 0.46

MP: 215-216 °C

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.84 (br s, 1 H, H^{1}), 7.61 (dd, $^{3}J_{H3',H4'}$ = 7.7 Hz, $^{4}J_{H3',H5'}$ = 1.3 Hz, 1 H, H$^{3'}$), 7.58 (ddd, $^{3}J_{H5',H6'}$ = 8.0 Hz, $^{3}J_{H5',H4'}$ = 7.1 Hz, $^{4}J_{H5',H3'}$ = 1.3 Hz, 1 H, H$^{5'}$), 7.54 (dd, $^{3}J_{H6',H5'}$ = 8.0 Hz, $^{4}J_{H6',H4'}$ = 1.5 Hz, 1 H, H$^{6'}$), 7.48 (ddd, $^{3}J_{H4',H3'}$ = 7.7 Hz, $^{3}J_{H4',H5'}$ = 7.1 Hz, $^{4}J_{H4',H6'}$ = 1.5 Hz, 1 H, H$^{4'}$), 5.97 (br s, 1 H, OH), 3.95 (q, $^{3}J_{H5,H6}$ = 6.4 Hz, 1 H, H^{5}), 2.73 and 2.62 (2 x d AB system, $^{2}J_{H3a,H3b}$ = 16.8 Hz, 2 H, H^{3a} and H^{3b}), 1.06 (d, $^{3}J_{H6,H5}$ = 64 Hz, 3 H, H^{6})

^{13}C-NMR (400 MHz, DMSO-d6): δ 172.7 (C^{2}), 150.0 (C$^{2'}$), 137.3 (C$^{1'}$), 130.9 (C$^{5'}$), 128.5 (C$^{4'}$), 127.2 (C$^{6'}$), 123.9 (C$^{3'}$), 76.9 (C^{4}), 58.9 (C^{5}), 46.1 (C^{3}), 14.7 (C^{6})

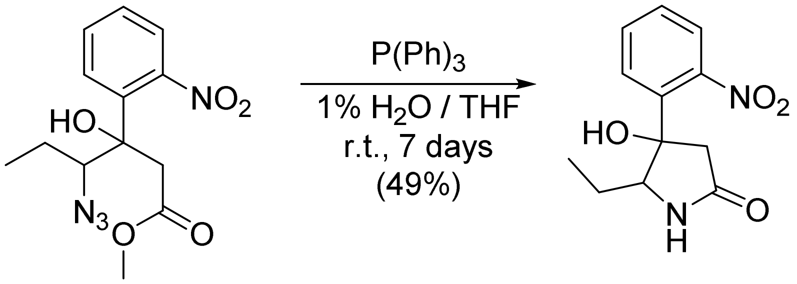
MS-ESI: 259.3 (100, $[M+Na]^+$), 237.2 (3, $[M+H]^+$)

HR-MS (ESI): 259.06859 ($[M+Na]^+$; $C_{11}H_{12}N_2O_4Na^+$; calc. 259.06948)

IR (KBr): ν = 3427 (s), 3311 (vs), 3045 (w), 2987 (w), 2943 (w), 1689 (vs), 1528 (vs), 1375 (vs), 1258 (m), 1211 (m), 1128 (w), 1084 (m), 1057 (m), 1036 (m), 1009 (m), 961 (w), 902 (vw), 851 (vw), 777 (m), 708 (m), 642 (m), 606 (s), 523 (m), 496 (m) cm^{-1}

CHN: calc.: C: 55.93; H: 5.12; N: 11.86; found: C: 55.66; H: 5.23; N: 11.64

5.3.31. 5-Ethyl-4-hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (217i)

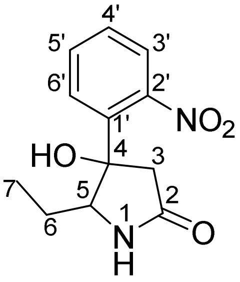


216i
$C_{13}H_{16}N_4O_5$
308.29

217i
$C_{12}H_{14}N_2O_4$
250.25

Prepared from methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)hexanoate (**216i**) (482 mg, 1.56 mmol) and triphenylphosphine (615 mg, 2.35 mmol) in THF (7 mL)/water (0.07 mL). Solvent system for chromatography: CH_2Cl_2/MeOH, 98:2. The product was isolated in 49% yield (190 mg) as a white powder.

Analytical Data for **217i**



TLC: R_f (CH_2Cl_2/MeOH, 98:2) = 0.17

GC (method IZ): t_R = 16.10 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (d, $^3J_{H3',H4'}$ = 8.1 Hz, 1 H, $H^{3'}$), 7.58-7.52 (m, 2 H, $H^{5'}$ and $H^{6'}$), 7.47-7.43 (m (partially solved), $^3J_{H4',H3'}$ = 8.1 Hz, 1 H, $H^{4'}$), 6.36 (br s, 1 H, H^1), 3.99 (dd, $^3J_{H5,H6b}$ = 9.5 Hz, $^3J_{H5,H6a}$ = 4.2 Hz, 1 H, H^5), 3.00 and 2.87 (2 x d AB system, $^2J_{H3a,H3b}$ = 17.4 Hz, 2 H, H^{3a} and H^{3b}), 2.75 (br s, 1 H, OH), 1.83 (dqd, $^2J_{H6a,H6b}$ = 14.5 Hz, $^3J_{H6a,H7}$ = 7.4 Hz, $^3J_{H6a,H5}$ = 4.2 Hz, 1 H, H^{6a}), 1.62 (ddq, $^2J_{H6b,H6a}$ = 14.5 Hz, $^3J_{H6b,H5}$ = 9.5 Hz, $^3J_{H6b,H7}$ = 7.4 Hz, 1 H, H^{6b}), 0.97 (t, $^3J_{H7,H6a}$ = $^3J_{H7,H6b}$ = 7.4 Hz, 3 H, H^6)

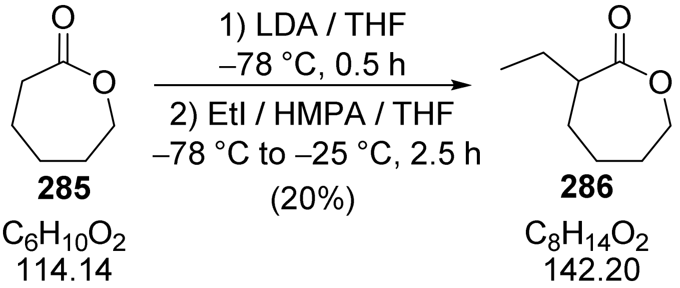
MS-ESI: 249.1 (100, $[M-H]^-$)

HR-MS (ESI): 273.08450 ($[M+Na]^+$; $C_{12}H_{14}N_2O_4Na^+$; calc. 273.08513)

IR (KBr): ν = 3456 (m), 3402 (m), 3046 (w), 2958 (m), 2873 (w), 1739 (vs), 1573 (vw), 1526 (vs), 1482 (w), 1458 (w), 1434 (s), 1365 (s), 1315 (w), 1242 (m), 1206 (s), 1167 (s), 1134 (m), 1116 (m), 1093 (m), 1080 (m), 1051 (m), 1025 (m), 996 (w), 908 (w), 851 (w), 784 (w), 739 (s), 720 (s), 699 (vs), 668 (m), 639 (w), 624 (w), 607 (m), 551 (s), 533 (s), 452 (m) cm^{-1}

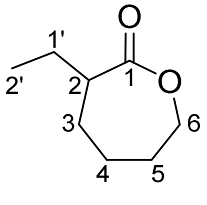
5.3.32. Preparation of intermediate (290)

5.3.33. 3-Ethyloxepan-2-one (286)



To a stirred solution of ε-caprolactone (**285**) (5.0 g, 43.81 mmol, 1 equiv.) in dry THF (40 mL) was added dropwise a solution of LDA (2.0 M in THF, 26.3 mL, 52.57 mmol, 1.2 equiv.) at −78 °C and under argon. After 30 min at −78 °C, ethyl iodide (7.0 mL, 87.61 mmol, 2 equiv.) dissolved in anhydrous HMPA (16.86 mL, 96.37 mmol, 2.2 equiv.) was added dropwise over 10 min. The mixture was allowed to stir at −78 °C for 1 h, and then was warmed to –25 ºC over a period of 1 h. Quenching of the reaction with saturated aqueous NH_4Cl solution (50 mL) at -–25 ºC followed by warm-up and extraction of the mixture with $CHCl_3$ (3 x 150 mL), washing of the combined organic phase with water (200 mL), saturated aqueous $NaHCO_3$ solution (200 mL), and brine (100 mL), drying ($MgSO_4$), filtration, and concentration gave an oily residue. The product was purified by flash chromatography on silica gel (cyclohexane/Et_2O, 50:50) to afford 1.25 g (20%) of 2-ethyl-ε-caprolactone (**286**) as a clear, slightly yellowish oil.

Analytical Data for **286**:



TLC: R_f (cyclohexane/Et_2O, 50:50) = 0.37

GC (method IZ): t_R = 7.19 min

^{1}H-NMR (400 MHz, CDCl$_3$): δ 4.30-4.20 (m, 2 H, H^6), 2.47-2.41 (m, 1 H, H^2), 2.00-1.89 (m, 2 H, H^{5a} and H$^{1'a}$), 1.87-1.76 (m, 2 H, H^{3a} and H^{5b}), 1.74-1.54 (m, 2 H, H^{4a} and H^{4b}), 1.49-1.36 (m, 2 H, H^{3b} and H$^{1'b}$), 0.95 (t, $^3J_{H2',H1'}$ = 7.4 Hz, 3 H, H$^{2'}$)

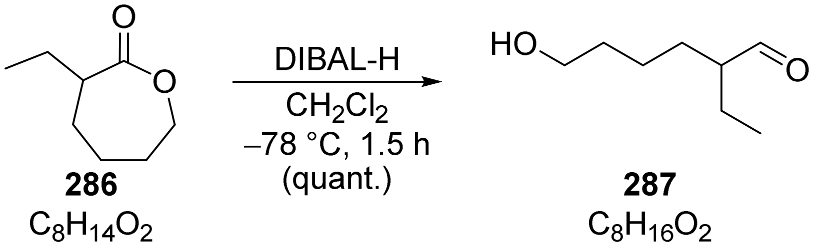
^{13}C-NMR (400 MHz, CDCl$_3$): δ 177.5 (C^1), 68.2 (C^6), 44.5 (C^2), 29.7 (C^3), 28.8 (C^5), 28.3 (C^4), 25.6 (C$^{1'}$), 11.9 (C$^{2'}$)

MS-ESI: 307.3 (16, [2M+Na]$^+$), 165.2 (100, [M+Na]$^+$)

HR-MS (ESI): 165.08876 ([M+Na]$^+$; $C_8H_{14}O_2Na^+$; calc. 165.08915)

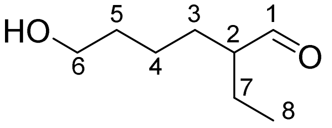
IR (KBr): ν = 2935 (vs), 2878 (m), 2252 (vw), 1734 (vs), 1457 (m), 1394 (m), 1374 (w), 1306 (w), 1289 (m), 1264 (w), 1248 (m), 1228 (w), 1178 (vs), 1119 (m), 1104 (s), 1094 (s), 1078 (m), 1055 (s), 1008 (w), 989 (w), 939 (w), 921 (w), 873 (w), 842 (vw), 797 (vw), 733 (m), 647 (vw), 576 (vw), 548 (vw) cm^{-1}

5.3.34. 2-Ethyl-6-hydroxyhexanal (287)



To a stirred solution of 2-ethyl-ε-caprolactone **(286)** (957 mg, 6.73 mmol, 1 equiv.) in dry CH_2Cl_2 (14 mL) was added dropwise a solution of DIBAL (1.0 M in hexane, 7.07 mL, 7.07 mmol, 1.05 equiv.) at -78 °C and under argon. After 1.5 h at -78 °C, the reaction mixture was quenched by the addition of CH_3OH (0.29 mL, 7.07 mmol, 1.05 equiv.) and then allowed to reach 25 °C. The resulting solution was diluted with EtOAc (100 mL), and then poured into a saturated solution of sodium potassium tartrate (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **287** as an oily residue (971 mg, 100% yield) pure enough for the next step.

Analytical Data for **287**:



TLC: R_f (cyclohexane/Et_2O, 50:50) = 0.26

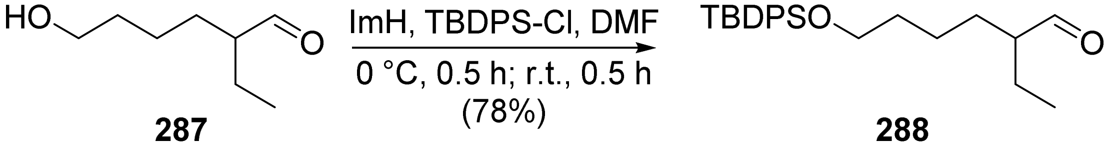
GC (method IZ): t_R = 6.88 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.57 (d, $^3J_{H1,H2}$ = 2.9 Hz, 1 H, H^1), 3.64 (t, $^3J_{H6,H5}$ = 6.5 Hz, 2 H, H^6), 2.23-2.15 (m (partially solved), $^3J_{H2,H1}$ = 2.9 Hz, 1 H, H^2), 1.72-1.43 (m, 6 H, H^3, H^5 and H^7), 1.40-1.32 (m, 2 H, H^4), 0.91 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

MS-ESI: 199.3 (70, $[M+Na+MeOH]^+$), 183.3 (21, $[M+K]^+$), 167.3 (100, $[M+Na]^+$)

IR (KBr): ν = 3392 (br m), 2936 (vs), 2865 (s), 2714 (vw), 1724 (vs), 1460 (m), 1383 (w), 1247 (w), 1054 (m), 917 (w), 770 (vw), 734 (m), 647 (vw) cm^{-1}

5.3.35. 6-((*tert*-Butyldiphenylsilyl)oxy)-2-ethylhexanal (288)

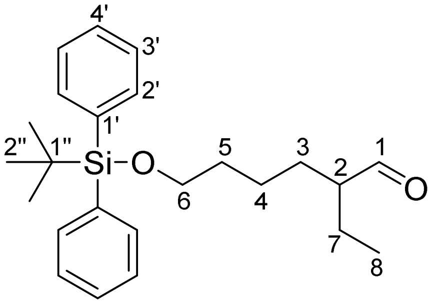


287
$C_8H_{16}O_2$
144.21

288
$C_{24}H_{34}O_2Si$
382.23

To a stirred solution of the crude aldehyde **287** (971 mg, 6.73 mmol, 1 equiv.) in dry DMF (9 mL) was added imidazole (688 mg, 10.10 mmol, 1.5 equiv.) followed by *tert*-butyldiphenylsilyl chloride (1.9 mL, 7.41 mmol, 1.1 equiv.) at 0 °C and under argon. After 30 min stirring at 0 °C, the reaction mixture was allowed to reach room temperature and stirred for additional 30 min. The resulting solution was diluted with Et_2O (100 mL), washed with water (2 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give an oily residue. The product was purified by flash chromatography on silica gel (cyclohexane/Et_2O, 95:5) to afford 2.00 g (78%) of aldehyde **288** as a clear, colourless oil.

Analytical Data for **288**:



TLC: R_f (cyclohexane/Et_2O, 95:5) = 0.38

GC (method IZ): t_R = 16.47 min

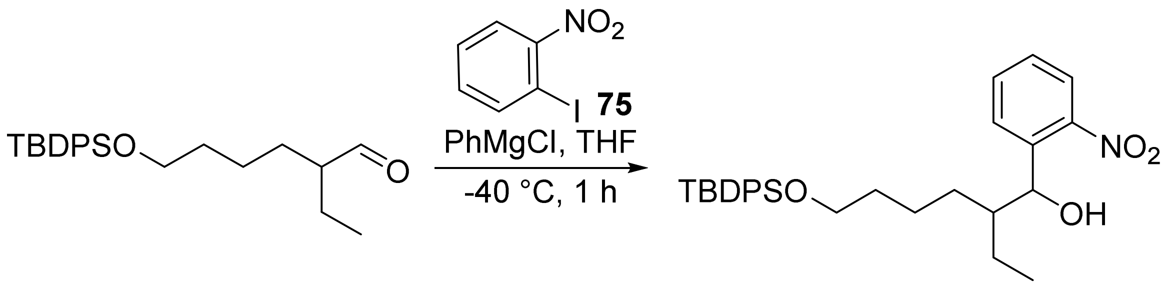
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.55 (d, $^3J_{H1,H2}$ = 2.9 Hz, 1 H, H^1), 7.68-7.67 (m, 4 H, $H^{2'}$), 7.45-7.36 (m, 6 H, $H^{3'}$ and $H^{4'}$), 3.65 (t, $^3J_{H6,H5}$ = 6.4 Hz, 2 H, H^6), 2.16 (ttd, $^3J_{H2,H1}$ = 2.9 Hz, $^3J_{H2,H7\mathit{obs.}}$ = 5.3 Hz, $^3J_{H2,H3\mathit{obs.}}$ = 10.5 Hz, 1 H, H^2), 1.70-1.52 (m, 5 H, H^{3a}, H^5 and H^7), 1.51-1.42 (m, 1 H, H^{3b}), 1.40-1.33 (m, 2 H, H^4), 1.05 (s, 9 H, $H^{2''}$), 0.91 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

^{13}C-NMR (400 MHz, $CDCl_3$): δ 205.5 (C^1), 135.6 ($C^{2'}$), 134.0 ($C^{1'}$), 129.5 ($C^{4'}$), 127.6 ($C^{3'}$), 63.5 (C^6), 53.3 (C^2), 32.5 (C^5), 28.2 (C^3), 26.9 ($C^{2''}$), 23.3 (C^4), 21.8 (C^7), 19.2 ($C^{1''}$), 11.4 (C^8)

HR-MS (ESI): 405.22191 ($[M+Na]^+$; $C_{24}H_{34}O_2SiNa^+$; calc. 405.22258)

IR (KBr): ν = 3071 (m), 3050 (w), 2999 (w), 2933 (vs), 2859 (vs), 2707 (w), 1960 (vw), 1890 (vw), 1824 (vw), 1727 (vs), 1589 (vw), 1473 (m), 1462 (m), 1428 (m), 1389 (m), 1362 (w), 1306 (vw), 1245 (vw), 1188 (w), 1111 (vs), 1008 (w), 939 (w), 823 (m), 741 (s), 703 (vs), 688 (m), 614 (m), 505 (vs), 428 (vw) cm^{-1}

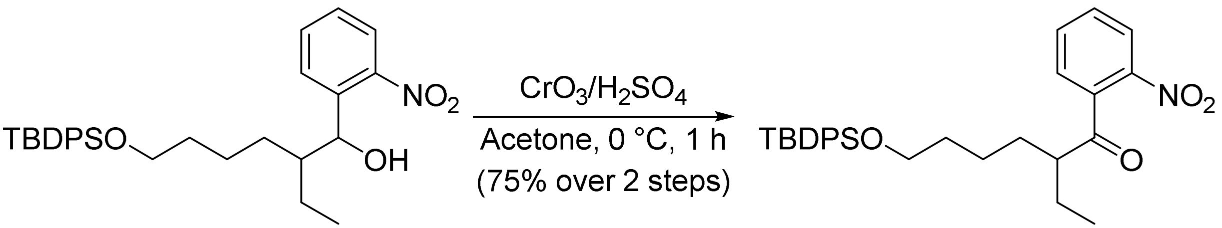
5.3.36. 6-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-one (289)



288
$C_{24}H_{34}O_2Si$
382.23

S6
$C_{30}H_{39}NO_4Si$
505.72

6-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-ol (**S6**) was prepared following the general procedure from 2-iodonitrobenzene (**75**) (1.0 g, 4.02 mmol), phenylmagnesium chloride (2.0 M in THF, 2.2 mL, 4.42 mmol) and aldehyde **288** (1.84 g, 4.82 mmol) in dry THF (28 mL). The crude alcohol was engaged in the next step without further purification. *R*f (cyclohexane/Et_2O, 75:25= 0.44. GC (method AG): *t*R = 22.77 min (minor diastereomer, 45 %), *t*R = 22.98 min (major diastereomer, 55 %).

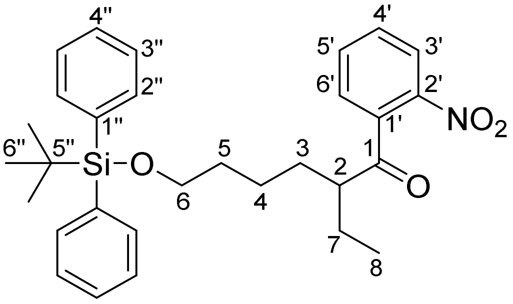


S6
$C_{30}H_{39}NO_4Si$
505.72

289
$C_{30}H_{37}NO_4Si$
503.70

6-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-one (**289**) was prepared from the crude 6-((*tert*-butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-ol (**S6**) (2.03 g, 4.02 mmol) and Jone's reagent (2.67 M in H_2SO_4, 3.25 mL) in acetone (7 mL). Solvent system for chromatography: cyclohexane/Et_2O, 95:5. The product was isolated in 75% yield (1.51 g) over the two steps as an orange oil.

Analytical Data for **289**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 75:25) = 0.42

GC (method AG): t_R = 23.07 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, $^3J_{H3',H4'}$ = 8.1 Hz, $^4J_{H3',H5'obs.}$ = 1.1 Hz, 1 H, $H^{3'}$), 7.68-7.64 (m, 5 H, $H^{2''}$ and $H^{5'}$), 7.58 (ddd, $^3J_{H4',H3'}$ = 8.1 Hz, $^3J_{H4',H5'obs.}$ = 7.5 Hz, $^4J_{H4',H6'obs.}$ = 1.5 Hz, 1 H, $H^{4'}$), 7.44-7.35 (m, 7 H, $H^{3''}$, $H^{4''}$ and $H^{6'}$), 3.64 (t, $^3J_{H6,H5}$ = 6.4 Hz, 2 H, H^6), 2.79 (quint, $^3J_{H2,H7obs.}$ = $^3J_{H2,H3obs.}$ = 6.1 Hz, 1 H, H^2), 1.84-1.70 (m, 2 H, H^{7a} and H^{3a}), 1.61-1.47 (m, 4 H, H^{7b}, H^5 and H^{3b}), 1.45-1.37 (m, 2 H, H^4), 1.04 (s, 9 H, $H^{6''}$), 0.93 (t, $^3J_{H8,H7}$ = 7.5 Hz, 3 H, H^8)

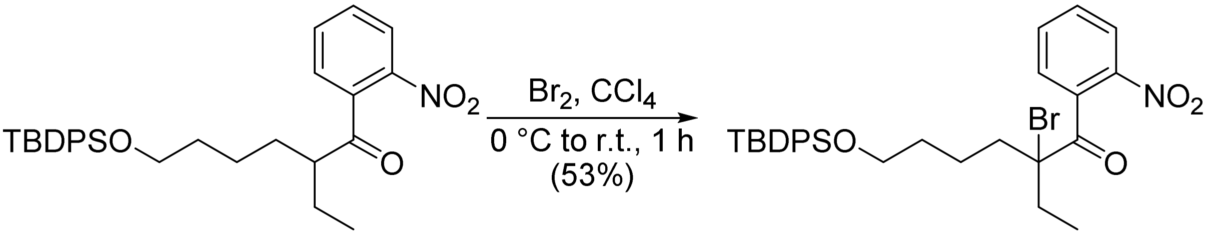
^{13}C-NMR (100 MHz, $CDCl_3$): δ 204.6 (C^1), 146.5 ($C^{2'}$), 137.5 ($C^{1'}$), 135.5 ($C^{2''}$), 134.0 ($C^{1''}$), 133.7 ($C^{5'}$), 130.6 ($C^{4'}$), 129.5 ($C^{4''}$), 128.4 ($C^{6'}$), 127.6 ($C^{3''}$), 124.4 ($C^{3'}$), 63.6 (C^6), 52.1 (C^2), 32.7 (C^5), 29.4 (C^3), 26.8 ($C^{6''}$), 23.0 and 22.9 (C^4 and C^7), 19.2 ($C^{5''}$), 11.0 (C^8)

MS-ESI: 526.7 (100, $[M+Na]^+$)

HR-MS (ESI): 526.23872 ($[M+Na]^+$; $C_{30}H_{37}NO_4SiNa^+$; calc. 526.23895)

IR (KBr): ν = 3071 (w), 2932 (vs), 2859 (s), 1830 (vw), 1701 (s), 1574 (w), 1531 (vs), 1473 (m), 1428 (m), 1347 (s), 1309 (w), 1264 (w), 1216 (m), 1111 (vs), 998 (m), 855 (w), 823 (m), 759 (s), 742 (s), 706 (vs), 614 (w), 505 (s) cm^{-1}

5.3.37. 2-Bromo-6-((*tert*-butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-one (290)

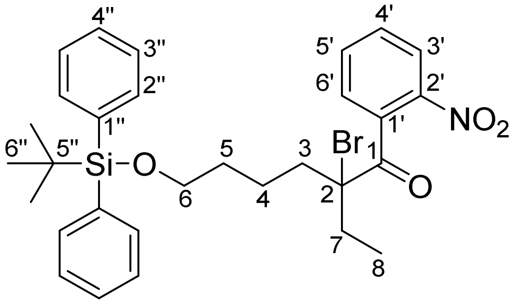


289
$C_{30}H_{37}NO_4Si$
503.70

290
$C_{30}H_{36}BrNO_4Si$
582.60

Prepared from 6-((*tert*-butyldiphenylsilyl)oxy)-2-ethyl-1-(2-nitrophenyl)hexan-1-one (**289**) (1.48 g, 2.93 mmol) and bromine (0.15 mL, 2.93 mmol) in CCl_4 (9 mL) following the general procedure. Solvent system for chromatography: cyclohexane/Et_2O, 95:5. The product was isolated in 53% yield (901 mg) as a viscous yellow oil.

Analytical Data for **290**:



TLC: R_f (Cyclohexane/CH_2Cl_2, 75:25) = 0.52

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, $^3J_{H3',H4'}$ = 8.2 Hz, $^4J_{H3',H5'obs.}$ = 1.0 Hz, 1 H, $H^{3'}$), 7.76 (dd, $^3J_{H6',H5'obs.}$ = 7.6 Hz, $^4J_{H6',H4'}$ = 1.4 Hz, 1 H, $H^{6'}$), 7.73-7.69 (m, 1 H, $H^{5'}$), 7.69-7.66 (m, 4 H, $H^{2''}$), 7.60 (ddd, $^3J_{H4',H3'}$ = 8.2 Hz, $^3J_{H4',H5'obs.}$ = 7.4 Hz, $^4J_{H4',H6'}$ = 1.4 Hz, 1 H, $H^{4'}$), 7.44-7.36 (m, 6 H, $H^{3''}$ and $H^{4''}$), 3.68 (t, $^3J_{H6,H5}$ = 5.7 Hz, 2 H, H^6), 2.40-2.31 (m, 1 H, H^{3a}), 2.35 (dq, $^2J_{H7a,H7b}$ = 14.5 Hz, $^3J_{H7a,H8}$ = 7.4 Hz, 1 H, H^{7a}), 2.13-2.04 (m, 1 H, H^{3b}), 2.11 (dq, $^2J_{H7b,H7a}$ = 14.5 Hz, $^3J_{H7b,H8}$ = 7.4 Hz, 1 H, H^{7b}), 1.64-1.55 (m, 4 H, H^4 and H^5), 1.07 (t, $^3J_{H8,H7a}$ = $^3J_{H8,H7b}$ = 7.4 Hz, 3 H, H^8), 1.04 (s, 9 H, $H^{6''}$)

^{13}C-NMR (100 MHz, CDCl$_3$): δ 198.5 (C^{1}), 146.0 ($C^{2'}$), 135.7 ($C^{1'}$), 135.6 ($C^{2''}$), 134.1 ($C^{5'}$), 134.0 ($C^{1''}$), 130.1 ($C^{4'}$), 129.7 ($C^{4''}$), 129.6 ($C^{6'}$), 127.6 ($C^{3''}$), 124.4 ($C^{3'}$), 75.7 (C^{2}), 63.4 (C^{6}), 37.2 (C^{3}), 32.5 (C^{5}), 30.8 (C^{7}), 26.8 ($C^{6''}$), 21.5 (C^{4}), 19.2 ($C^{5''}$), 9.7 (C^{8})

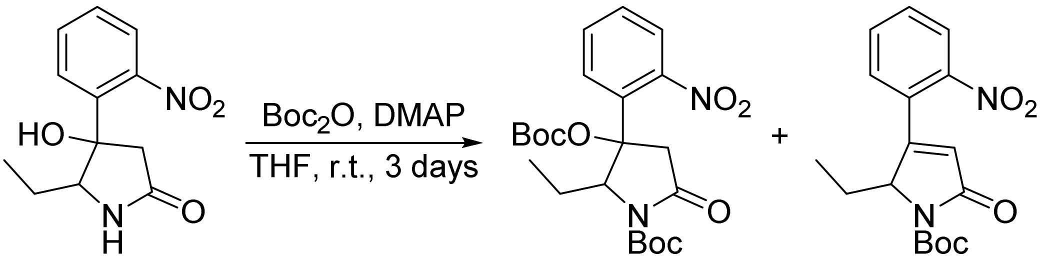
MS-ESI: 605.2 (100, [M (^{79}Br)+Na]$^+$), 206.4 (99, [M (^{81}Br)+Na]$^+$)

HR-MS (ESI): 604.14845 ([M (^{79}Br)+Na]$^+$; $C_{30}H_{36}{}^{79}BrNO_4SiNa^+$; calc. 604.14947), 606.14653 ([M (^{81}Br)+Na]$^+$; $C_{30}H_{36}{}^{81}BrNO_4SiNa^+$; calc. 606.14742)

IR (KBr): ν = 3071 (w), 3050 (w), 2931 (vs), 2858 (s), 1959 (vw), 1890 (vw), 1829 (vw), 1703 (vs), 1589 (w), 1574 (w), 1532 (vs), 1472 (m), 1461 (m), 1428 (m), 1389 (w), 1348 (vs), 1308 (w), 1228 (m), 1191 (w), 1111 (vs), 1008 (m), 939 (vw), 856 (m), 823 (m), 788 (m), 758 (vs), 743 (s), 703 (vs), 614 (m), 505 (s), 430 (vw) cm^{-1}

5.3.38. Dehydration of hydroxy lactam 217i

5.3.39. tert-Butyl 3-(tert-butoxycarbonyloxy)-2-ethyl-3-(2-nitrophenyl)-5-oxopyrrolidine-1-carboxylate (295)



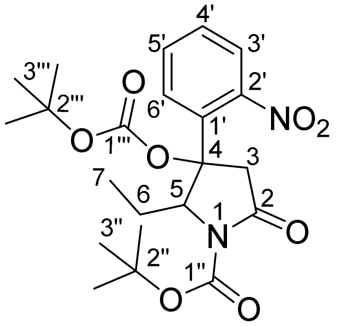
217i $C_{12}H_{14}N_2O_4$ 250.25

295 $C_{22}H_{30}N_2O_8$ 450.48

218i $C_{17}H_{20}N_2O_5$ 332.35

To a stirred suspension of hydroxyl pyrrolidinone **217i** (128 mg, 0.51 mmol) in dry THF (10 mL) at room temperature and under argon was added DMAP (25 mg, 0.21 mmol) followed by Boc$_2$O (234 mg, 1.07 mmol). The resulting solution was stirred at room temperature for 3 days, and then was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH, 99:1) to afford two fractions. The first fraction contained di-boc-protected compound **295** (123 mg, 0.27 mmol, 53%). The second fraction showed to be a complex mixture (83 mg, **295/218i**, 90:10) which corresponded to **295** (74.7 mg, 0.17 mmol, 33%) and **218i** (8.3 mg, 0.03 mmol, 5%).

Analytical Data for **295**:



TLC: R_f (CH_2Cl_2/MeOH, 90:10) = 0.18

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56-7.45 (m, (partially solved), $^3J_{H5',H6'}$ = 7.8 Hz, 3 H, $H^{3'}$, $H^{5'}$ and $H^{6'}$), 7.32 (d, $^3J_{H6',H5'}$ = 7.8 Hz, 1 H, $H^{6'}$), 4.87 (br s, 1 H, H^5), 3.58 and 3.14 (2 x d AB system, $^2J_{H3a,H3b}$ = 17.9 Hz, 2 H, H^{3a} and H^{3b}), 2.05 (br s, 1 H, H^{6a}), 1.62 (quint, $^3J_{H6b,H5}$ = $^3J_{H6b,H7}$ = 7.3 Hz, 1 H, H^{6b}), 1.50 (s, 9 H, $H^{3'''}$), 1.38 (s, 9 H, $H^{3''}$), 1.06 (t, $^3J_{H7,H6a}$ = $^3J_{H7,H6b}$ = 7.4 Hz, 3 H, H^6)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.3 ($C^{1'''}$), 149.4 ($C^{1''}$), 148.6 ($C^{2'}$), 134.7 ($C^{1'}$), 131.7 ($C^{5'}$), 129.4 ($C^{4'}$), 126.0 ($C^{6'}$), 124.6 ($C^{3'}$), 83.9 and 83.8 ($C^{2'''}$ and $C^{2''}$), 79.6 (C^4), 66.8 (C^5), 44.7 (C^3), 27.9 ($C^{3'''}$), 27.4 ($C^{3''}$), 23.5 (C^6), 10.2 (C^7)

MS-ESI: 473.5 (100, $[M +Na]^+$)

References and notes

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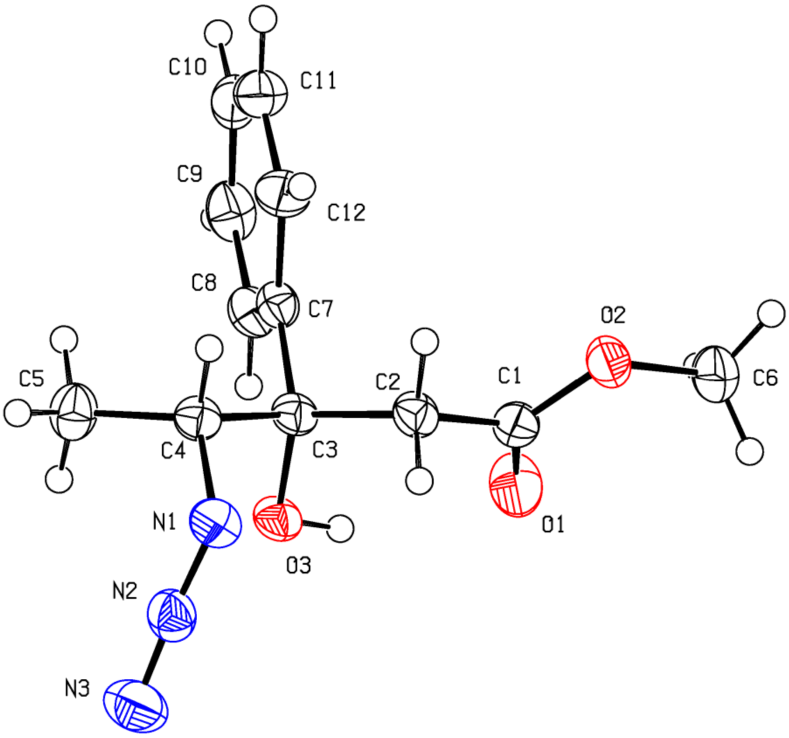
Appendices

Crystallographic studies

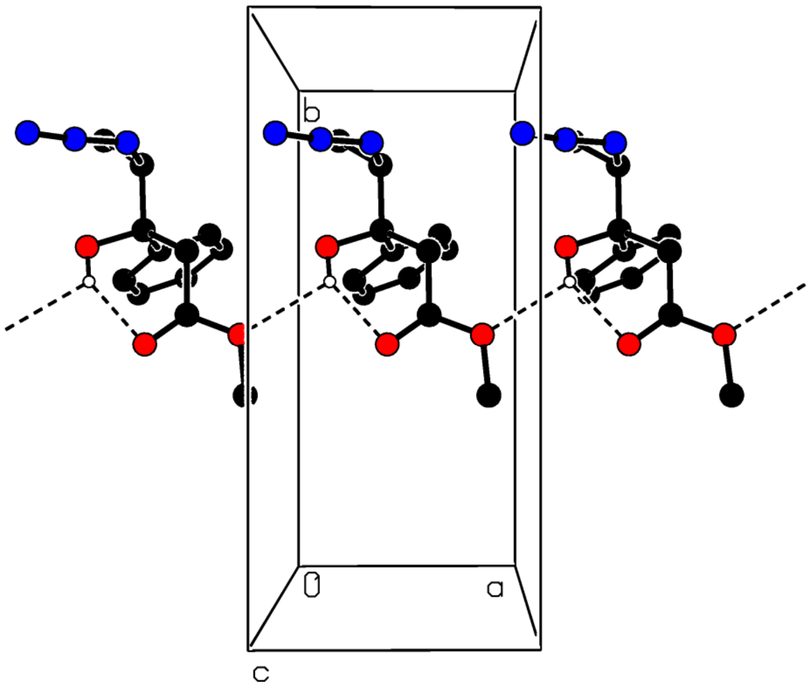
1. X-Ray crystallographic analysis of compounds 216c.

Anisotropic displacement ellipsoid plot of compound **216c**.



A view of the molecular structure and crystallographic numbering scheme of the title molecule, with displacement ellipsoids drawn at the 50% probability level.

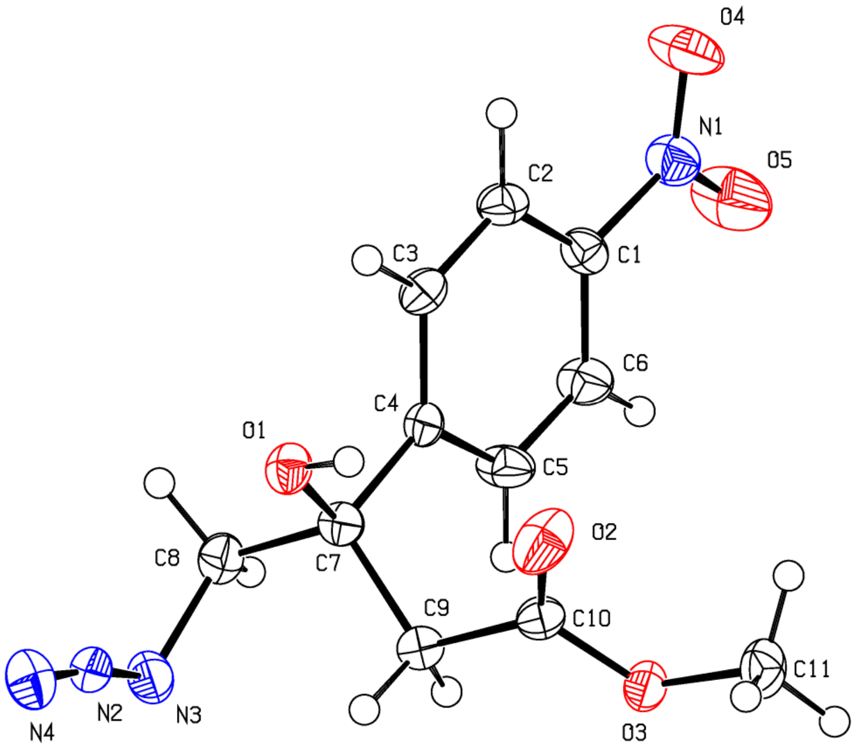
ORTEP unit-cell plot of compound **216c**.



A partial view of the crystal packing of the title compound **216c**, viewed along the c-axis, showing the formation of the O−H···O hydrogen bonded chain propagating in the direction of the a-axis. H-atoms not involved in this interaction have been omitted for clarity; hydrogen bonds shown as dashed lines.

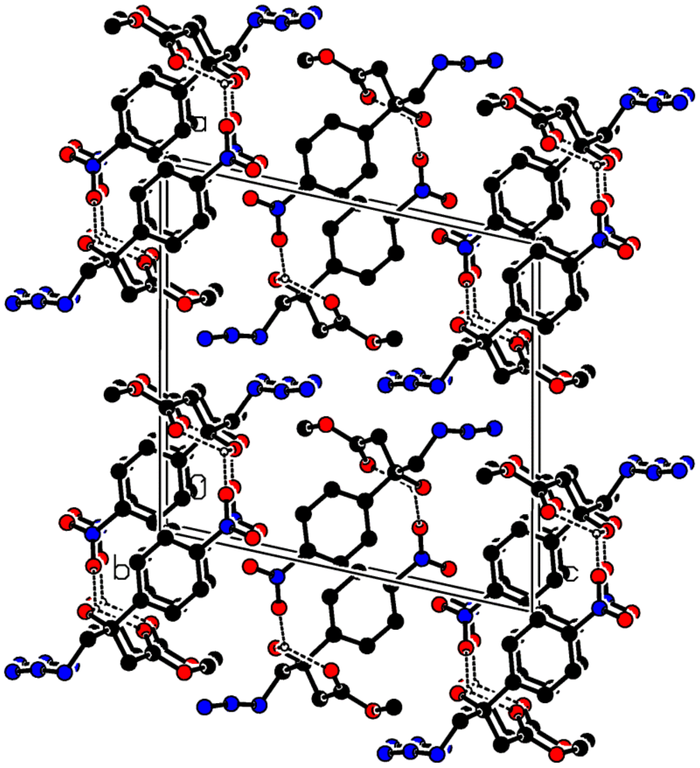
2. X-Ray crystallographic analysis of compounds 216g

Anisotropic displacement ellipsoid plot of compound **216g**.



A view of the molecular structure and crystallographic numbering scheme of the title compound **216g**, with displacement ellipsoids drawn at the 50% probability level.

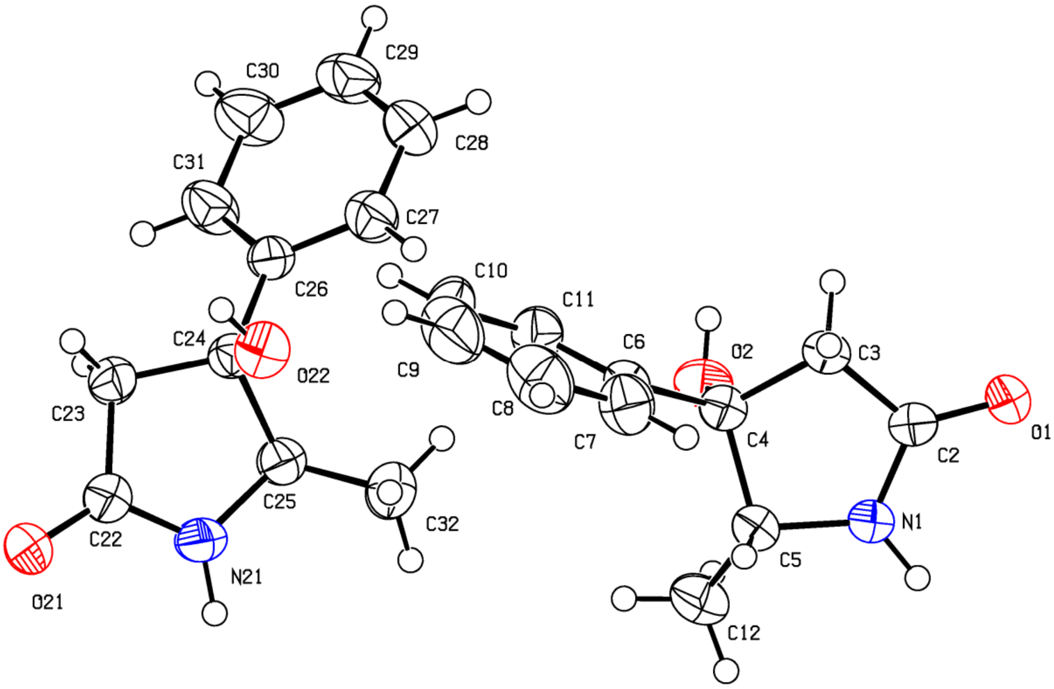
ORTEP unit-cell plot of compound **216g**.



The crystal packing of the title compound **216g**, viewed along the b-axis. The O−H···O and N−H···O hydrogen bonds are shown as dashed cyan lines. H-atoms not involved in these interactions have been omitted for clarity.

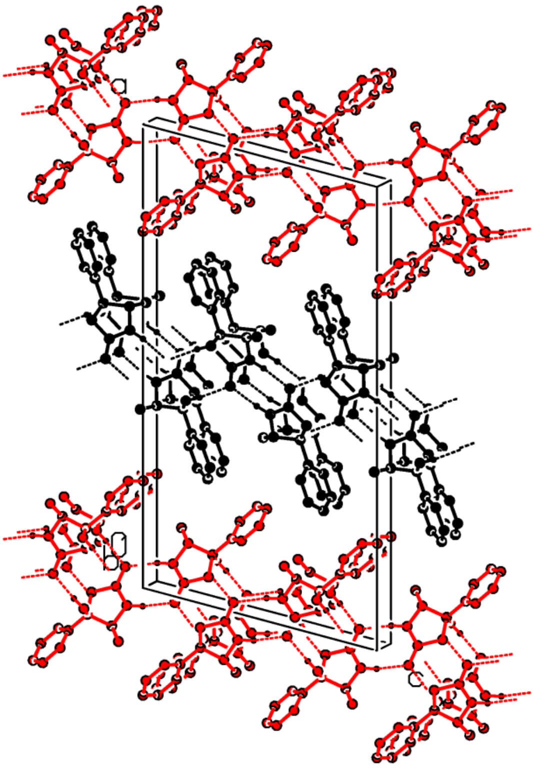
3. X-Ray crystallographic analysis of compounds 217c.

Anisotropic displacement ellipsoid plot of compound **217c**.



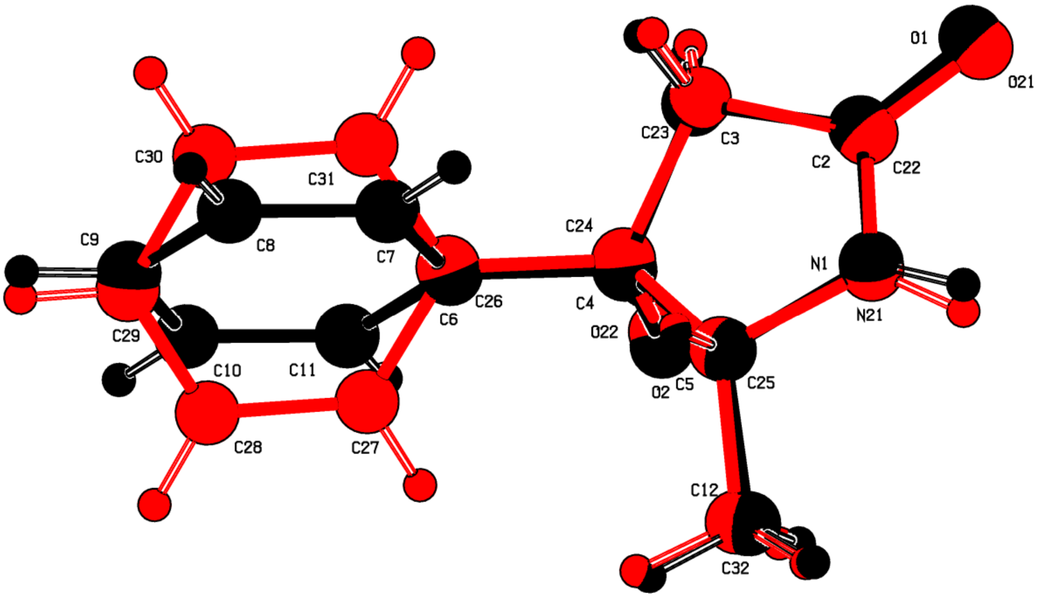
The molecular structure of the two independent molecules (A involving atoms N1,O1 and O2 and B involving atoms N21,O21 and O22) of compound **217c**, showing the numbering scheme and the displacement ellipsoids drawn at the 50% probability level.

ORTEP unit-cell plot of compound **217c**.



A view along the b-axis of the crystal packing of compound **217c**, showing the intermolecular N−H···O and O−H···N hydrogen bonds (dashed lines) leading to the formation of the two-dimenssional networks of the individual molecules (A black; B red) lying parallel to plane. The H-atoms not involved in the hydrogen bonding have been removed for clarity.

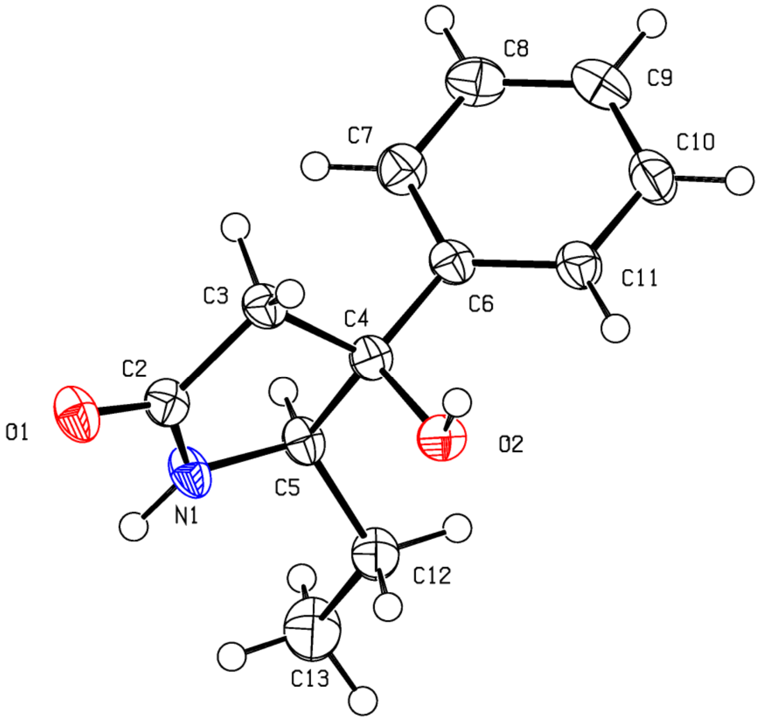
The compound crystallized with two independent molecules (A and B) per asymmetric unit. They differ only in the orientation of the phenyl ring with respect to the rest of the molecule.



A view of the automatic overalp of the two independent molecules (A black; B red) of compound **217c**.

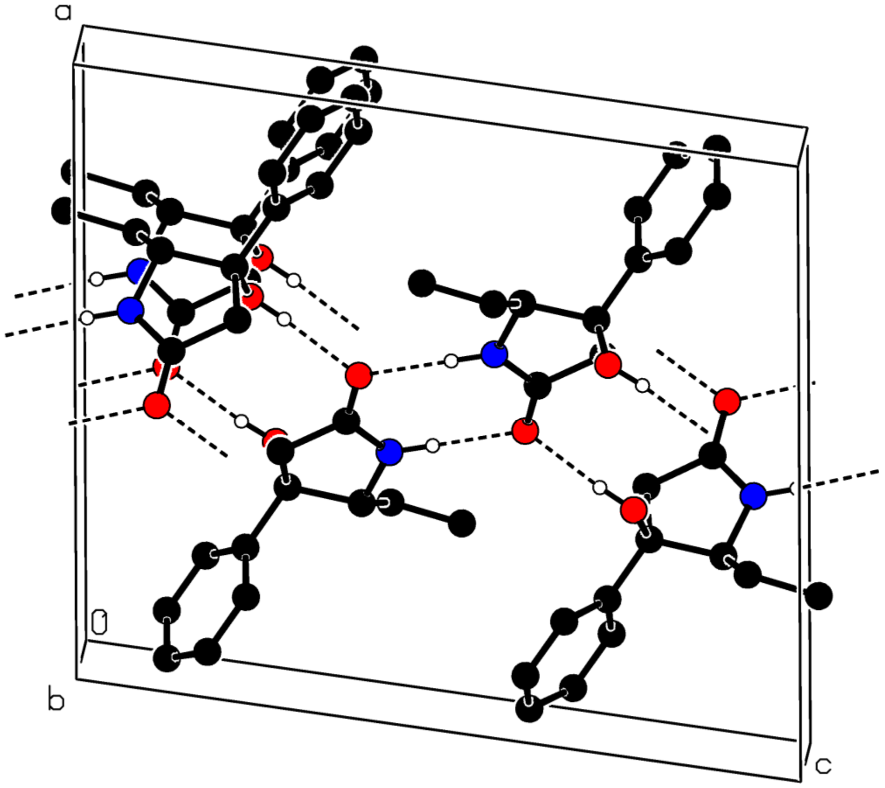
4. X-Ray crystallographic analysis of compounds 217d.

Anisotropic displacement ellipsoid plot of compound **217d**.



A view of the molecular structure and crystallographic numbering scheme of the title compound **217d**, with displacement ellipsoids drawn at the 50% probability level.

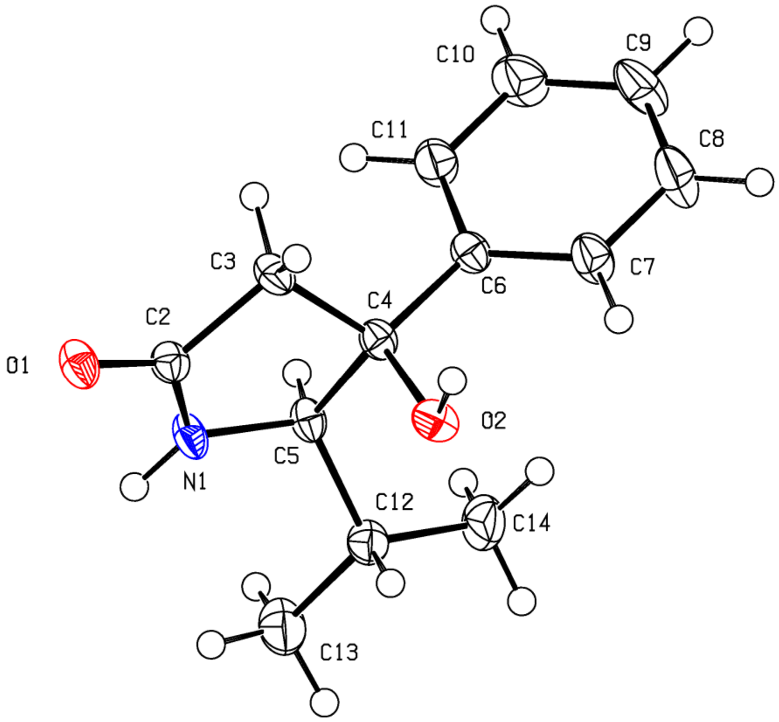
ORTEP unit-cell plot of compound **217d**.



The crystal packing of the title compound **217d**, viewed along the b-axis. The O−H···O and N−H···O hydrogen bonds are shown as dashed cyan lines. H-atoms not involved in these interactions have been omitted for clarity.

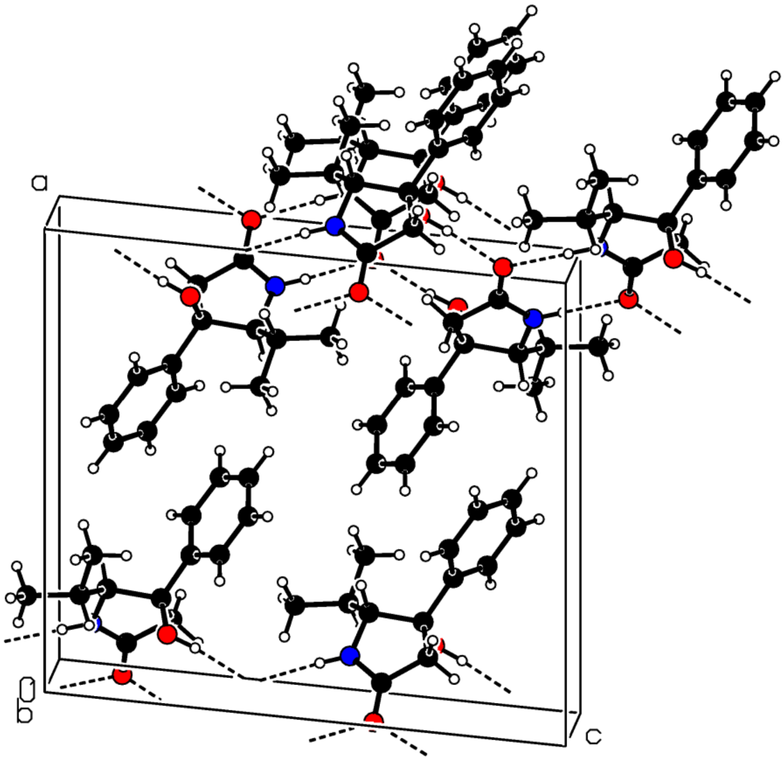
5. X-Ray crystallographic analysis of compounds 217e.

Anisotropic displacement ellipsoid plot of compound **217e**.



A view of the molecular structure and crystallographic numbering scheme of the title compound **217e**, with displacement ellipsoids drawn at the 50% probability level.

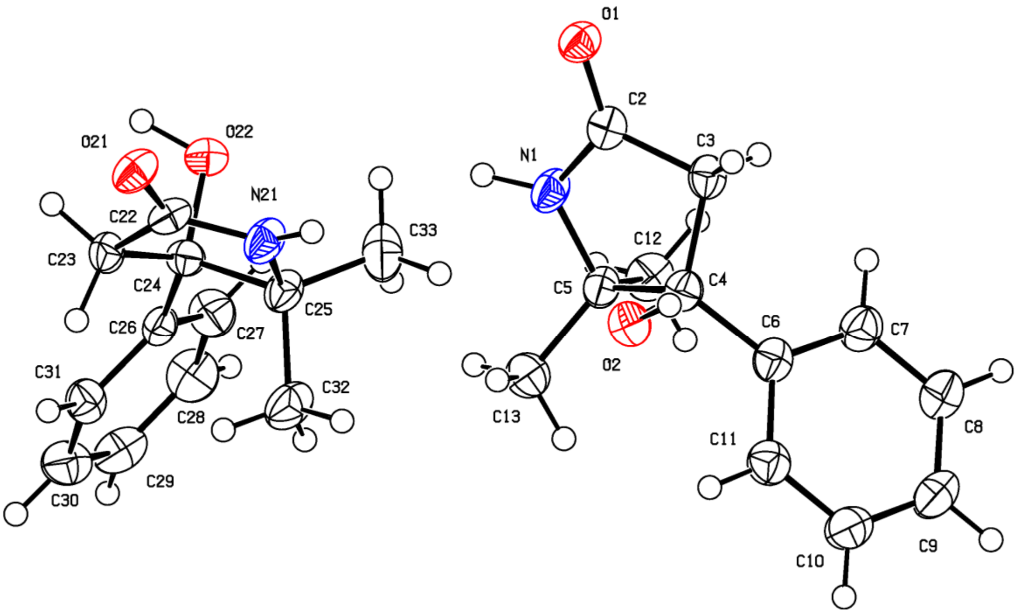
ORTEP unit-cell plot of compound **217e**.



The crystal packing of the title compound **217e**, viewed along the b-axis. The O−H···O and N···H···O hydrogen bonds are shown as dashed cyan lines. H-atoms not involved in these interactions have been omitted for clarity.

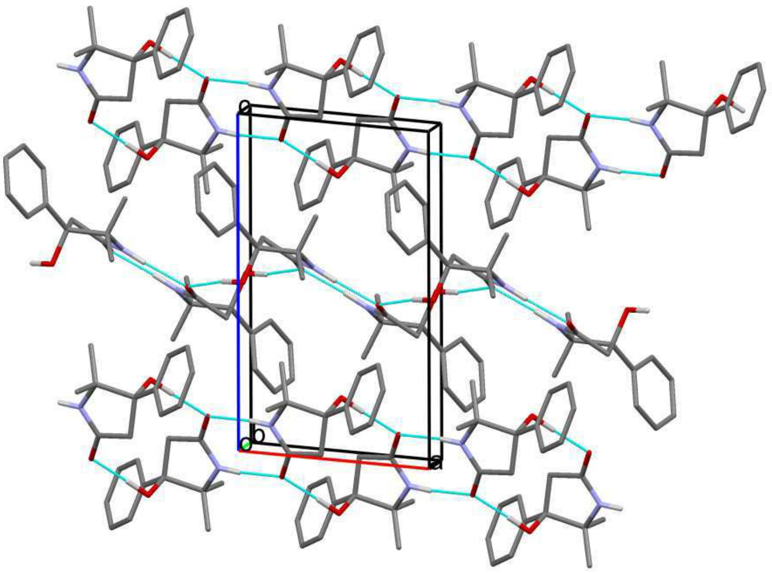
6. X-Ray crystallographic analysis of compounds 217f.

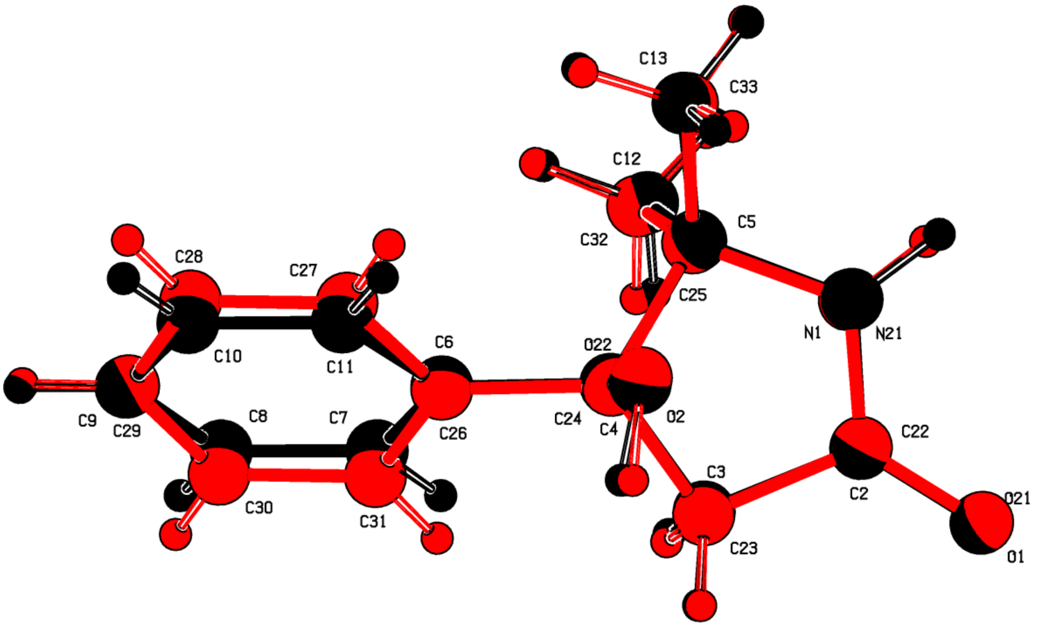
Anisotropic displacement ellipsoid plot of compound **217f**.



A view of the molecular structure and crystallographic numbering scheme of the title compound **217f**, with displacement ellipsoids drawn at the 50% probability level.

ORTEP unit-cell plot of compound **217f**.

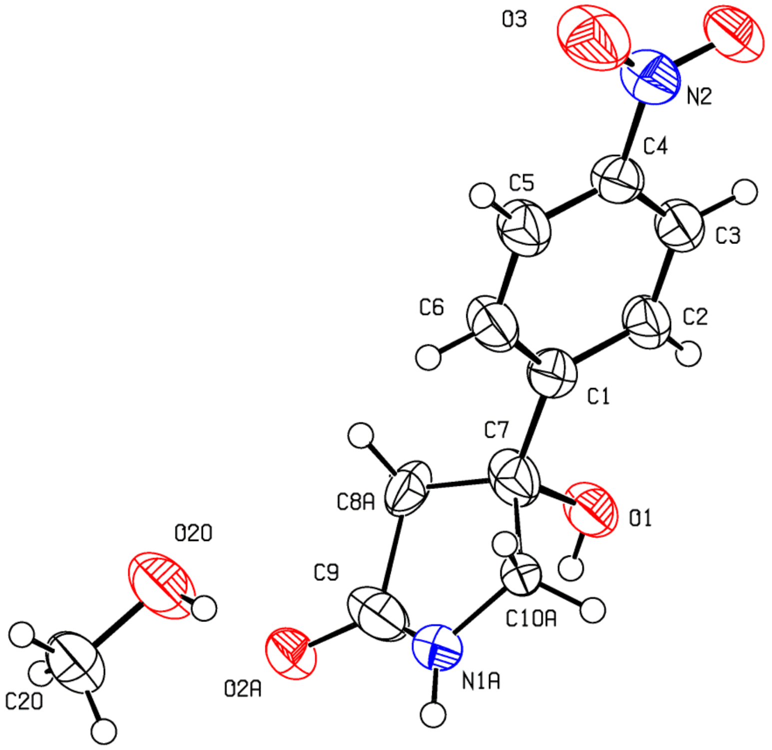




A view of the automatic overalp of the two independent molecules (A black; B red) of compound **217f**.

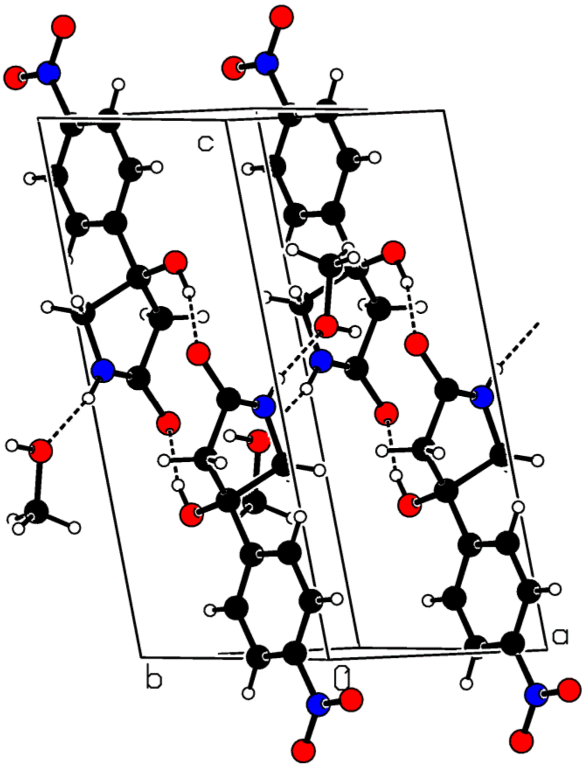
7. X-Ray crystallographic analysis of compounds 217g.

Anisotropic displacement ellipsoid plot of compound **217g**.



A view of the molecular structure and crystallographic numbering scheme of the two independent molecules of the title compound **217g**, with displacement ellipsoids drawn at the 50% probability level. Only the major component of the disordered atoms is shown.

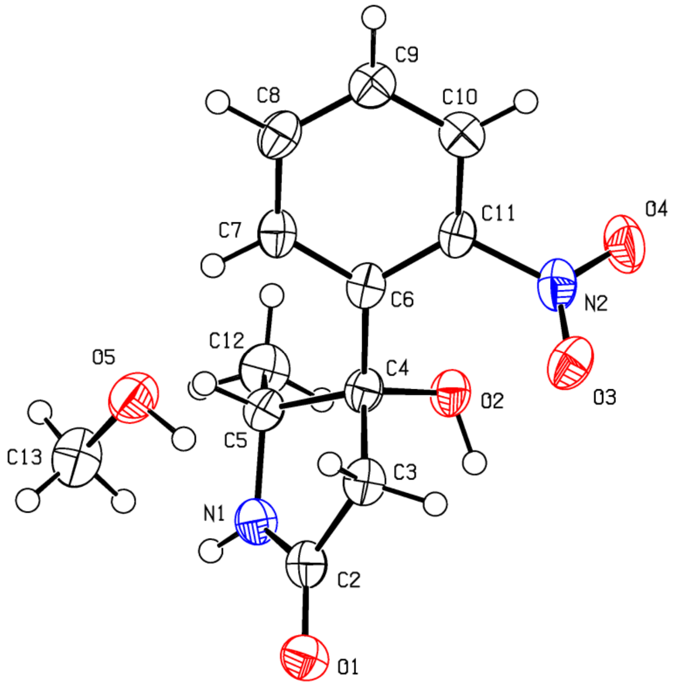
ORTEP unit-cell plot of compound **217g**.



The crystal packing of the title compound **217g**, with the O−H···O and N−H···O hydrogen bonds shown as dashed lines. H-atoms not involved in these short contacts have been omitted for clarity. Only the major component of the disordered atoms is shown.

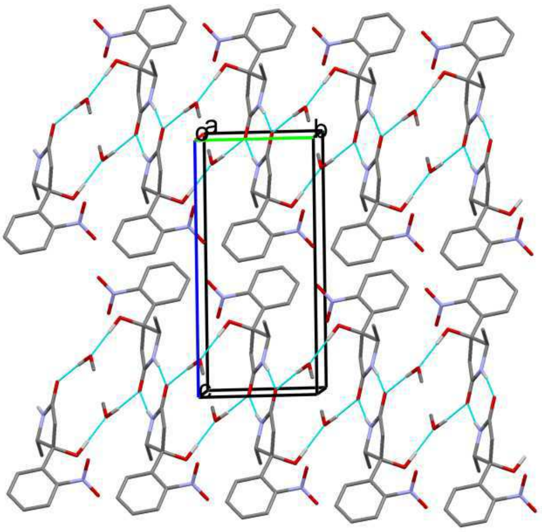
8. X-Ray crystallographic analysis of compounds 217h.

Anisotropic displacement ellipsoid plot of compound **217h**.



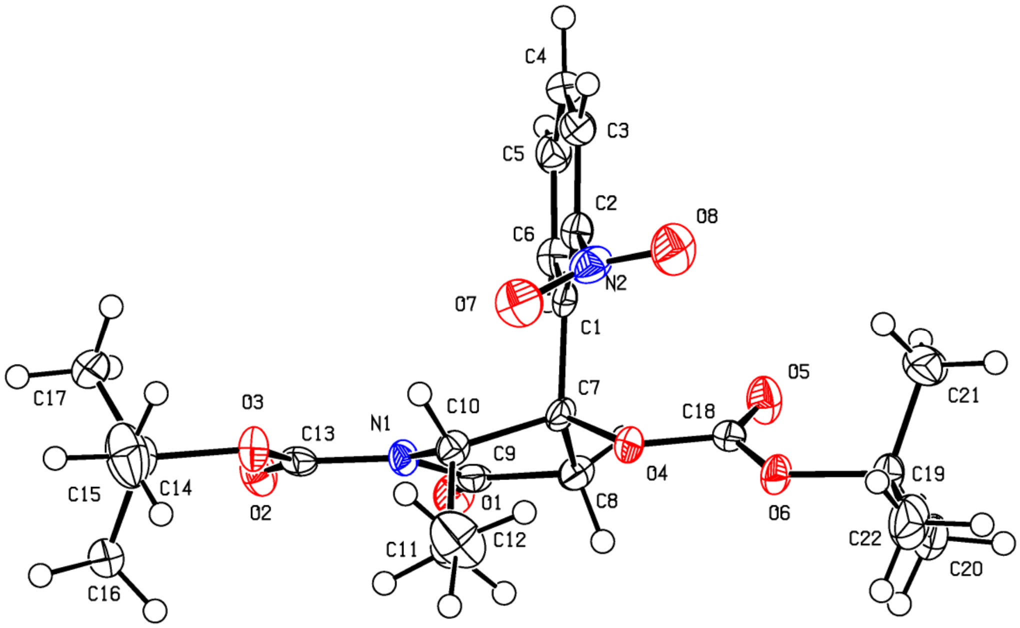
A view of the molecular structure and crystallographic numbering scheme of the title compound **217h**, with displacement ellipsoids drawn at the 50% probability level.

ORTEP unit-cell plot of compound **217h**.



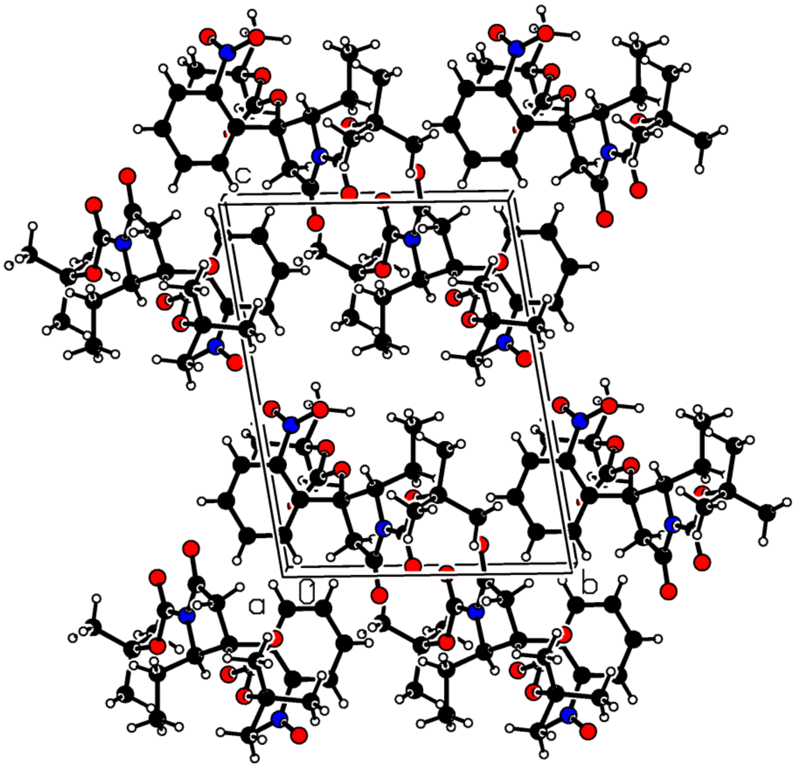
9. X-Ray crystallographic analysis of compounds 295.

Anisotropic displacement ellipsoid plot of compound **295**.



A view of the molecular structure and crystallographic numbering scheme of the two independent molecules of the title compound **295**, with displacement ellipsoids drawn at the 50% probability level.

ORTEP unit-cell plot of compound **295**.



The crystal packing of the title compound **295**, viewed along the a-axis [H-atoms have been omitted for clarity.