New Methods For Cyclopentannulation

Frédèric Douelle

A Thesis submitted for the degree of
Doctor of Philosophy
The University of Edinburgh
June 2007

A ma famille

Maman, Papa
Karine, Guillaume
Stéphane, Sophie
Clément et Pauline

Declaration

This thesis was submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualifications at this, or any other university.

Frederic Douelle

Acknowledgments

I wish to use this acknowledgments part to thank people, which have been contributing at different scales of my last five years of postgraduate studies. I will not manage to mention all the people, whom I met and appreciated, but you will always be in my thought and memories.

The first person that I wish to thanks goes to Professor Branko Jursic, my supervisor and mentor when I carried out my Master degree at the University of New Orleans. Branko showed me the frustrating and enjoyable corners of organic synthesis in a laboratory, and most that perseverance is the key attitude in a research environment. Many faces come up to my mind, when I remember of my stay in "the big easy". I wish to express my gratitude to Celine, known as "la coloc de choc", for her addictive joy of life, and your trust on my spontaneous planned-less nightlife experiences. Jua, those mental Jazz gig tours were fantastic; you made me in love with New Orleans jazz music. You might not know it yet but you are the best jazz drum player on earth. Pascal, Pablo and Toshi, this introduction to the Mardi Gras celebrations are forever in my mind; you all know what is party all about. Tattoo and Julio, the Jazz Festival would have not been the same without you, beers, bikinis and sunshine, it's all we want isn't it. Kind thoughts to the Romanian community of UNO; this Cajun says was defined for you guys, "Laisse le bon temps roule". Eddy, I miss your crawfish-boil feasts; Courtney thanks to have given me a wee piece of your Cajun Heritage; I am sure that your devotion to the coastal restoration and hurricane protection of the state of Louisiana will pay off one day. Maria, I did not forget this priceless journey in your sweet home country Nicaragua for Christmas time. Thanks for the invitation to this cultural and human voyage with the most dedicated guide. Cyril, you made this crazy challenge possible, which pushed us to cover half of the North American continent in one-month. With twelve National Parks explored, a Death Valley excursion, that Las Vegas weekend and the Californian final treat, this trip will remain in my memories as one of the most enjoyable. Spicy thanks to Melissa and Monica for this weekend in L.A, which to me could have been a perfect

Cohen's Brother movie plot. To finish with my memories from the States, one of the lessons that I learned over these two years is that the interaction with people of different backgrounds, cultures and social classes, conducted me to a distance-less field of knowledge. Trying not to fall into a "cliché", I truly believe that everybody has something to share and give away, and a smile is unquestionably the answer to any situation.

Having lost tolerance for sweet potato pies and chicorée cafe, I decided to cross the ocean again to land in Scotland. It was clear that my main motivation was to carry on my education in organic Chemistry, but a significant aspect of the local culture called me out as well. Only one hint, it starts with W and finishes with Y.

The inevitable person that I want to mention here is my supervisor, which accompanied me through my PhD degree at the University of Edinburgh. I sincerely manifest my gratitude to you Mike, to have given me the opportunity of achieving my postgraduate research studies under your guidance. When I look back over the last three years, I feel really fortunate. This facility of leading students in a demanding but fair and enthusiastic directions creates a healthy and dynamic atmosphere in the group. Your dedication and passion to chemistry are highly inspiring; who made me surpassed my borders, and procured me a unique and rewarding experience. I want to especially thank James for the proofreading of some of my chapters, and all the members, past and present of Greaney's planet, which contributed to the enjoyable and educational spirit of the group. I also need to mention here the high quality of facilities carried out by the technical staff of the School of Chemistry, including the NMR spectroscopy service, orchestrated by John Millar, the Mass spectroscopy department and the X-ray diffraction service. The first-class research environment at the school of chemistry would not be what it is without the good vibes and the professionalism of the Store's Dream Team, featuring, Tim, Kenny, Raymond and Derek. I thank Derek again for those extra-jobs, which allowed me to treat my pasta with extra tomato sauce and local bacon at the end of my PhD. At last, I am deeply grateful to the JSPS program and CNRS to have selected me for three months research collaboration with a Japanese institution. Warm regards to Professor Sasai and his group (University of Osaka), which did welcome me so nicely in and out the laboratory. I largely express my gratitude to Tomomie, Pritie, Haruki, Hara, and Patil for their kindness and friendship. Haruki, Ume and the Dude, I loved so much these two weeks of camping and canoeing spent at Chikoku island with you all, thanks to have given me this Japan's unique flavour. This ultimate Japanese experience would not has been the same without the hospitality of my two very good mates, Toshi and Kaz, which transmitted me their fascination for the local culture and the fun that emanated from it. Toshi, you are a terrible Karaoke's singer, luckily Tannoe could balance out.

As you might know, the achievement of a PhD degree requires about eighty percent of your time and energy; therefore you try to enjoy the twenty remaining percent as hard as you can. I want to give it up for the "17 Mayfield road community", which has been my sweet home for the last three years and a half. I firstly feel to thank Donald and Stewart, the twin brother landlords, which have unceasingly been present, fixing and adjusting stuffs with sunny mood and more particularly for this comfortable deal at the end of my PhD. All the housemates that crossed my sleepers and contributed to this "roots" atmosphere; you have been my family and even more sometime. Vassili, Wiebke, Ameyline, Frank, Lale, Vale, Fabio, Lara, Leti, Joa, Marie, Mo, Gwang Chao, Erwan, Chan, Celia and Luisa, you will not get rid of me that easily. Vassili, I still have sore legs, even two years after this bicycle trip from France to your home country Crete. Even though, I am definitely ready for another mental experience under your wings. Once more, I want to give it up for Manu, which to me is one of the most inspiring body that I met as a person and a friend. He was the first to put me in a wetsuit and pushed me in this freezing ocean with a surfboard as only escape. I officially accuse him to be the cause of this addiction now on and will take revenge one day. But surfing would not provide me that state of wealth without the exaltation of Diego, Ed and Noel after a long and smooth ride, Joa's low diving show, or Luisa's smile after being washed by an aggressive Scottish wave. I thank you so much guys for those unique moments shared, over these numerous surfing-camping trips to every corners of this beautiful Scottish island. Irrational thanks to Arno and Benny, who are invariably willing to take off and flirt with the borderline of wildness. From bothy ultimate adventures to cheesy metal gypsy lesbian transsexual gigs, you are out there, showing the way around. Kind regards to Vale, which rendered me the fortuity to foresee the bambinita's power and be the friend that you are. Distinctive thoughts to Mourad, this lively mind in a Moroccan body, which brought me to different perspectives, and your computer skills, which often rescued my ignorance from distressing situation. Loud thanks to Joa and Marie, which demonstrated me that laughs and good vibes can be deadly communicative, if a Scottish "little miss sunshine" was recast, I would offer you the parts. I sincerely need to mention a person now, which has been playing a predominant role in my life for the last few months. Luisa, you procure me this balance and plenitude, which I rarely felt before. Although our routes may diverge to different horizons, I will keep these moments next to you as a gift.

Je voudrais aussi remercier les personnes que j'ai laissé derriere moi, une fois que j'ai commencé a voyager. Une pensée chargée de souvenirs pour mes amis d'enfance, Foun, Sarah, Dada, Emilie, Geraldine, Sammy, Alexandra, Babas, Pauline, Julien, Guismo, Simmon, Elise et Fred; vous me manquez tous.

Je désire conclure ce chapitre en remerciant ma famille entière pour avoir respecté les choix que j'ai pu faire à certain moments de ma vie et de votre impérissable soutien et encouragement. Merci à vous deux, Guillaume et Karine, d'étre le frère et la soeur que j'aime autant, mon amour pour vous est et restera sans frontière. Merci à toi Stephane de m'avoir démontré qu'un beau-frère pouvait etre une telle source d'inspiration, tu es en quelque sorte le grand frère que je n'ai jamais eu. Merci a toi Sophie pour ta joie de vivre et ta simplicité qui a envouté mon frérot à ma plus profonde satisfaction. Deux grosses poutouilles à vous, Clément et Pauline, qui me procurez cette divine fierté et bonheur d'étre votre tonton Frédèric. Il m'est difficile d'exprimer la chaleur de ma gratitude pour vous, Maman et Papa; l'amour que vous nous portez et les sacrifices que vous avez consenti afin de nous donner les moyens de nous réaliser signifient plus que tout pour moi. Vous nous avez tout donné sans rien demander en retour. C'est pourquoi, j'aimerai vous dédier cet ouvrage, ainsi qu'au reste de la famille.

Abstract

A non-exhaustive introduction to well-established synthetic approaches toward cyclopentannulation is illustrated, which relies on modern aspect reported in between 2003 to present year. Next, our investigations on the validity of novel stereoselective cyclopentannulation are outlined.

Preliminary studies on nucleophilic catalysis toward the synthesis of cyclopentenone conducted us to the discovery of a new reagent-free protocol for Nazarov cyclization that produces highly substituted cyclopentenones in good to excellent yields. These neutral reaction conditions may enable the extension of Nazarov methodology to acid-sensitive substrates that have been previously inaccessible.

We have also developed the intramolecular iodo-aldol cyclization of enoate aldehydes and ketones to afford quaternary centre containing hetero and carbocycles. The reaction transforms simple, pro-chiral starting materials into cyclic alcohols, containing *vicinal* quaternary and secondary/tertiary stereocentres, in good yields with excellent stereoselectivity. In addition, the products display a collection of orthogonal functional groups that may be further elaborated in the synthesis of complex natural product targets.

Finally, we have produced 5-monosubstituted tetronic acid derivatives through a simple and selective Pd-π-allyl-mediated cyclization. Although catalytic and asymmetric aspects of the reaction remain to be investigated, these preliminary may be incorporated into a racemic synthesis of the natural product vertinolide.

Contents

Chapter 1: Some Cyclopentannulation Strategies

Chapter 2: Reagent-free Nazarov Cyclizations

List of Abbreviations

Å	angstrom(s)
Ac	acetyl
Ac_2O	acetic anhydride
aq	aqueous
atm	atmosphere
Bn	benzyl
bz	benzoyl
bp	boiling point
°C	boiling point
CAN	ceric ammonium nitrate
Chex	cyclohexenyl
Chx	cyclohexyl
cm^{-1}	wavenumber(s)
cod	*cis*,*cis*-1,5-cyclooctadiene
COSY	correlation spectroscopy
d	doublet (spectral)
DABCO	1,4-diazobicyclo[2.2.2]octane
dba	*trans*,*trans*-dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidone
DMSO	dimethyl sulfoxide

dr	diastereomeric ratio
ee	enantiomeric excess
EPP	*N*-ethylpiperidine
eq	equivalent
ES	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HFIP	hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HMRS	high-resolution mass spectroscopy
$h\nu$	irradiation with light
Hz	hertz
IR	infrared
J	coupling constant
LA	lewis acid
m	multiplet (spectral)
M	molar (moles per litre)
Me	methyl
m/z	mass to charge ratio
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
M.p.	melting point
MS	mass spectroscopy

NMR	nuclear magnetic resonance
Nu	nucleophile
o.n	overnight
PCC	pyridinium chlorochromate
Pd	palladium
PDC	pyridinium dichromate
Ph	phenyl
PKR	Pauson-Khand reaction
PMP	*p*-methoxyphenyl
ppm	part(s) per million
PPTSA	pyridinium *p*-toluenesulfonate
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
s-Bu	*sec*-Butyl
t	triplet (spectral)
TBAF	tetra-*N*-butylammonium fluoride
t-Bu	*tert*-Butyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin-layer chromatography
TMM	trimethylenemethane
TMP	2,4,6-trimethoxyphenyl
TMS	trimethylsilyl
Tmtu	Tetramethylthiourea
Ts	*p*-toluenesulfonyl
UV	ultraviolet
W	watt

X	halogen

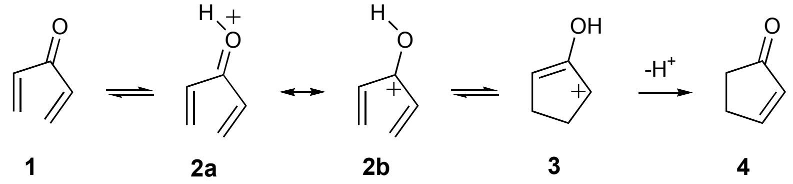
Chapter 1

Some Cyclopentannulation Strategies

The aim of this introduction is to give a non-exhaustive description of classic approaches toward cyclopentannulation. Hereby is reported some examples of Nazarov reaction, [3+2] cycloaddition, Pauson-Khand reaction, Fischer carbene complex chemistry and ring-closing metathesis reaction. The selected pieces of research showcase modern aspects of these strategies from 2003 to the present time.

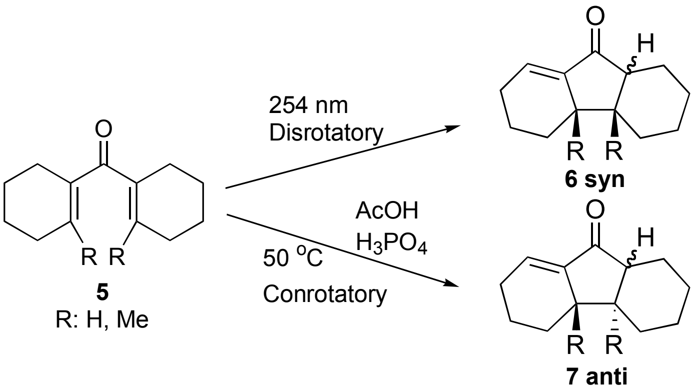
I-Nazarov Reaction

The Nazarov cyclization is named after the Russian chemist I. N. Nazarov (1900-1957), who initially formulated a direct acid-catalysed ring closure[1] of the divinyl ketones **1** and demonstrated the preparation of cyclopent-2-enone **4** (*Scheme 1.1*). The Nazarov reaction is classically described as a pericyclic reaction belonging to the class of 4π-electrocyclizations. Woodward et *al.* documented the pericyclic mechanism[2] through the complementary rotatory pathway for the thermal (conrotatory, **5** to **7**) and photochemical (disrotatory, **5** to **6**) cyclizations, in accordance with the conservation of orbital symmetry (*Scheme 1.2*).



Scheme 1.1: Nazarov Reaction

The pentadienyl cation **2**, which undergoes the 4π-electrocyclization is formed by protonation of the dienone **1** (*Scheme 1.1*). Following the cyclization, the intermediate allyl cation **3** exhibits proton loss to give the cyclopentenone **4**. Since the reaction proceeds through carbocationic intermediates, there is an opportunity to perform C-C bond forming reactions via cyclization[3]. It is sometimes the case that random Wagner-Meerwein rearrangements such as C-C migration of alkyl, aryl or hydride ions of the cyclic cation **3**, may frustrate synthetic planning.



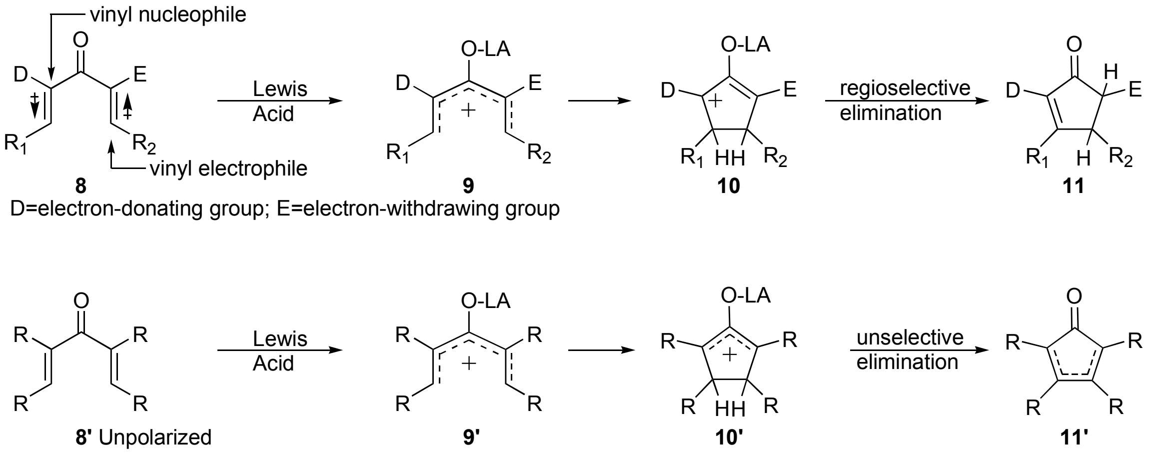
Scheme 1.2: Pericyclic mechanism of Nazarov cyclization

Although not relevant in the case of the symmetrical substrate (*Scheme 1.1*), it is often useful to be able to control the location of the α,β-unsaturation during the termination step.

I-1-Catalyzed Nazarov Reaction from Polarized Dienophile Substrates

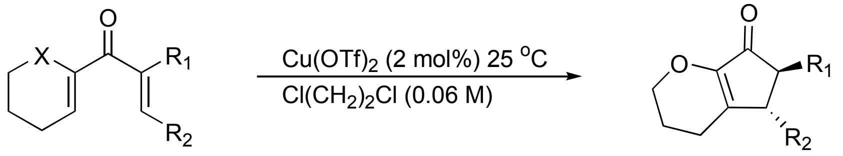
In general, the Nazarov reaction requires either the presence of protic acid or strong Lewis acid (e.g., BF_3, $SnCl_4$, $TiCl_4$, $AlCl_3$) to be promoted. One or more equivalents of Lewis acid is necessary for best results[4], and the regioselectivity of the elimination event can be poor, giving a mixture of cyclopentenone isomers[5].

In contrast, Diels-Alder, aldol, Michael and ene-like reactions can be effected using mild Lewis acids as catalysts[6]. These reaction types involve addition of an electron-rich π-system to an electron-poor π-system, a bond-forming process similar to the 4π Nazarov reaction. With that in mind, Frontier and coworkers[7] in 2003 designed divinyl ketones with a “vinyl nucleophile” and a “vinyl electrophile” (substrate **8**, *Scheme 1.3*).



Scheme 1.3: Effect of the Polarized Nazarov reaction on the Electrocyclization Process

It was found that Nazarov cyclization is facilitated by the presence of the electron-donating and withdrawing groups on the divinyl ketone that enhances the Lewis basicity of **8** (*Scheme 1.3*). The formation of carbocation **9** from **8** is expected to be more favourable than carbocation **9’** from the unpolarized divinyl ketone **8’** due to the π-system polarization of cation **9** relative to cation **9’**. Regioselectivity of the elimination of **10** is likely controlled by the position of the positive charge, localized adjacent to the stabilizing electron-donating group. In oxyallyl cation **10’**, the positive charge is fully delocalized and elimination is not expected to be regioselective (**11** *vs* **11’**). From a practical angle, dienones **12** readily undergo cyclization in chlorinated solvent at room temperature in air, catalized by copper triflate (2 mol%) affording excellent yields of cyclopentenones **13** (*Scheme 1.4*). In every case, substrates with α-unsubstituted vinyl electrophiles were less efficiently cyclized than the carbomethoxy substitution substrates (products **13b**, **13d**, **13f** and **13h**). In general, the more polarizing groups on the divinyl ketone, the more efficient the reaction. However, if polar substitution on the divinyl ketone was reduced to a minimum, reaction behaviour became complex and decomposition began to compete with cyclization (products **13d**, **13f** and **13h**).

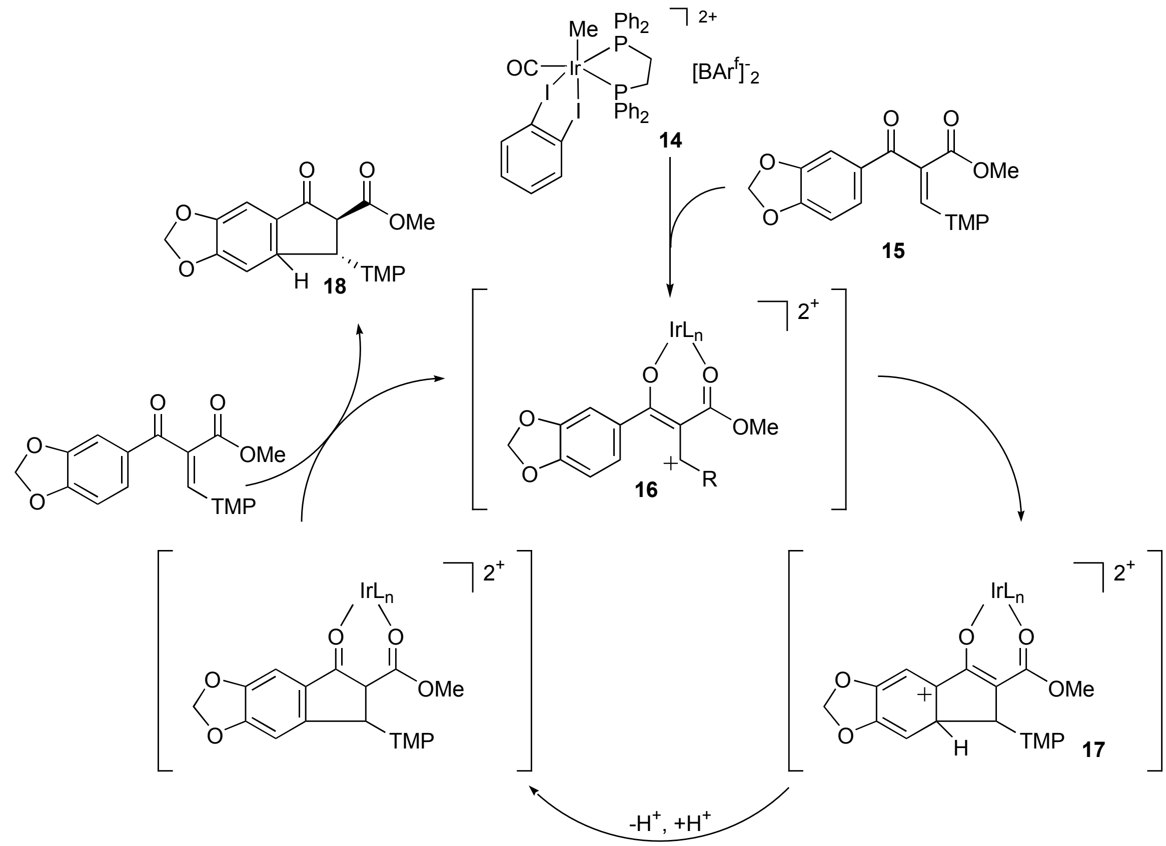


12a-h **13a-h**

X	R_1	R_2	Temp (T°C)	Time (h)	% yield (product)
O	CO_2Me	TMP	25	0.1	99 (**13a**)
O	H	TMP	25	0.33	86 (**13b**)
O	CO_2Me	Chx	55	2	99 (**13c**)
O	H	Chx	55	0.5	60 (**13d**)
C	CO_2Me	TMP	40	0.25	86 (**13e**)
C	H	TMP	40	5	35 (**13f**)
C	CO_2Me	Chx	65	14	70 (**13g**)
C	H	Chx	65	4	40 (**13h**)

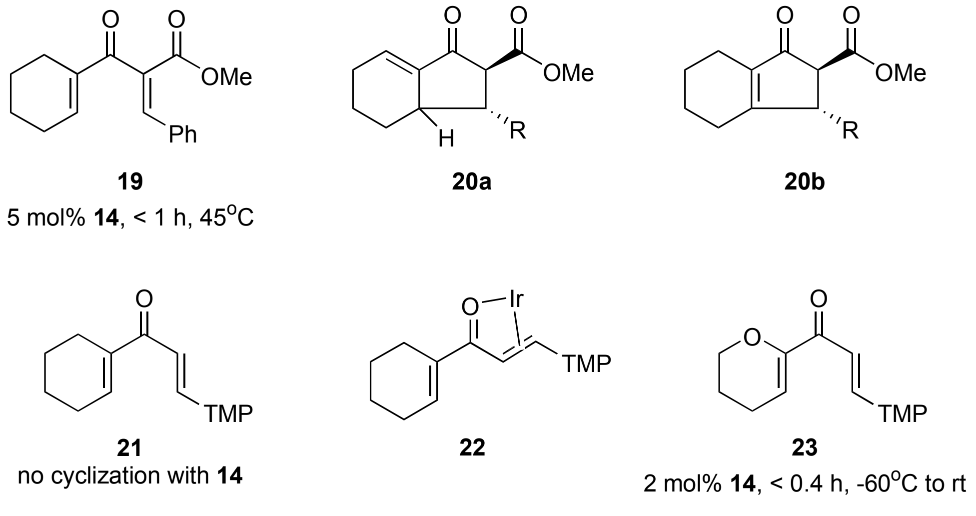
Scheme 1.4: Effect of Vinyl Electrophile α and substitution on Reactivity

With this powerful polarized dienone Nazarov cyclization methodology in hand (*Scheme 1.3*), in 2004 Frontier and coworkers reported even higher reaction rates for these same substrates[8] using the dicationic Ir(III) complex $[IrMe(CO)(dppe)\text{-}(DIB)](BARF)_2$ **14** where dppe=bis(diphenylphosphino)ethane, DIB=*o*-diiodobenzene and BARF=$[B(3,5\text{-}C_6H_3(CF_3)_2)_4]$ (*Scheme 1.5*). The weak coordinating ability of the DIB ligand provides adjacent labile sites in **14** that are found to play a crucial role in the observed electrocyclization. It was found by P^{31} NMR spectroscopy that the displacement of the DIB ligand by substrate **15** using the previous conditions is rapid and essentially complete at -10 °C. Whereas dienone **15** using the previous conditions (2 mol% $Cu(OTf)_2$, 53°C, 20 h) reacts to form cyclic compound **18** in 92% yield, the same reaction is quantitative in less than 20 min using 2 mol% of **14** at room temperature. A plausible mechanism for the process involves generation of the oxyallyl cation **16** (a resonance is shown), cyclization to generate intermediate **17**, re-aromatization, enolate protonation to give catalyst-bound product and substrate substitution to give free product **18** and **16**.



Scheme 1.5: Plausible mechanism of the process

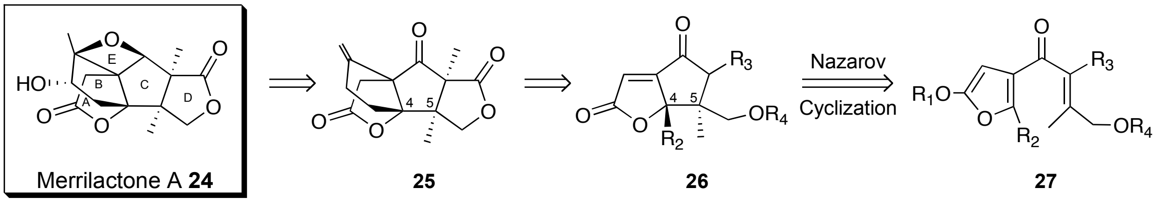
The importance of the adjacent labile binding sites of **14** and the nature of substrate chelation to **14** is illustrated by cyclization studies of specifically varied substrates (*Scheme 1.6*).



Scheme 1.6: Importance of the adjacent labile binding sites of **14** and the nature of substrates chelation to **14**

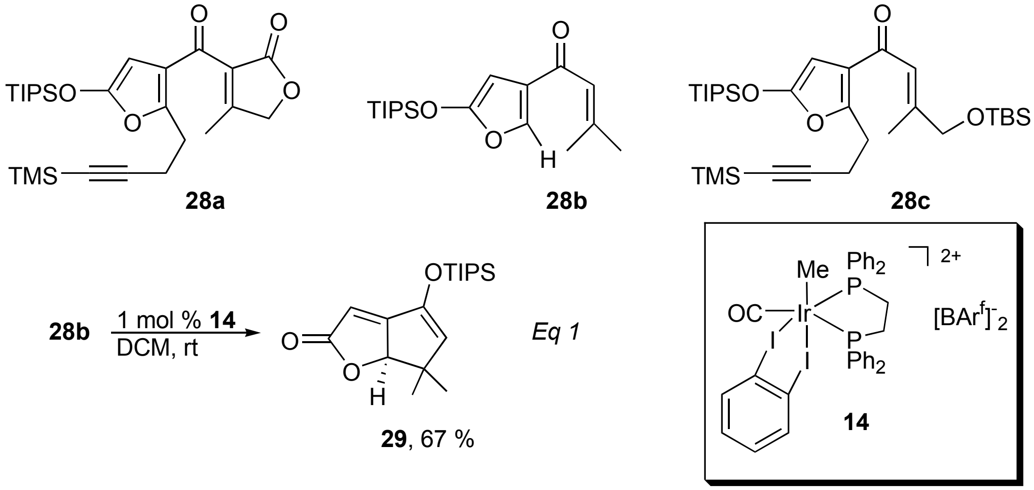
For instance, substrate **19** cyclizes smoothly (5 mol% **14**, 45°C, <1 h) to produce the cycloisomers **20a** and **20b**. However **21**, which undergoes smooth Nazarov cyclization with $Cu(OTf)_2$ (55°C, 9 h, 53%), does not cyclize with **14**. H^1 NMR Spectroscopy of the reaction solution reveals that **21** readily displaces the DIB chelate of **14**. The observation that **21** coordinates to **14** but does not cyclize suggests that in the absence of a second carbonyl the Ir(III) center may bind to an olefin of **21**, as shown in **22**. The two vinyl groups of **22** would be spacially separated and not in an orientation to allow for cyclization. Interestingly, **23** cyclizes in less than 20 min using 2 mol% of **14** upon warming to room temperature. In this case, it appears that the carbonyl and ether oxygen atoms bind to the catalyst, allowing the two vinyl groups to adopt the proper orientation for cyclization.

More recently, Frontier's group reported the first example of a stereoselective synthesis of (±)-merrilactone A, where complex **14** catalyst (*Scheme 1.5*) was used for the Nazarov cyclization key step[9]. The overall strategy used the compound **25** which Danishefsky and co-worker were able to convert into merrilactone A **24** in four steps[10,11] (*Scheme 1.7*).



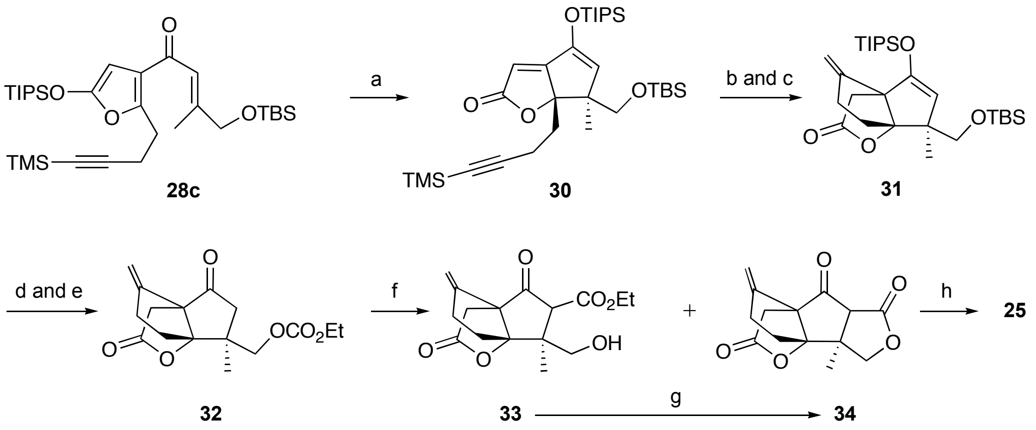
Scheme 1.7: Frontier's General Synthetic Strategy Targeting (±)-merrilactone A

It was thought that the adjacent stereocenters at C-4 and C-5 of the key intermediate **26** would be stereospecifically formed through the 4π- electrocyclization following the expected conrotatory pathway (*Scheme 1.7*). Initial experiments focused on the silyloxyfuran **28a**, which has an electron-rich aromatic donor and an electron-poor butenolide acceptor. Unfortunately, no cyclization of **28a** was observed upon exposure to a wide range of Lewis acid promoters. However it was found that the simplier ketone **28b** underwent smooth Nazarov cyclization catalyzed by the dicationic complex **14** (*Scheme 1.8*).



Scheme 1.8: Dienone structures used for Nazarov key step cyclization

$Cu(OTf)_2$ did not catalyze the cyclization of **28b**, possibly due to its lack of reactivity in polarized Nazarov cyclizations[7]. Triisopropylsilyl triflate also did not catalyze the cyclization of **28b**, underlying the importance of the strong Lewis acid character of the Ir^{III} complex **14**. As hoped, Nazarov cyclization of **28c** proceeded cleanly with **14** in DCM to give a single diastereoisomeric product **30** (*Scheme 1.9*). Removal of the trimethylsilyl group of **30**, radical cyclization of the resulting exocyclic olefin **31**[12], fluoride-induced deprotection of **31** with further carbonation of the primary alcohol furnished **32**. Intramolecular nucleophilic lactonization[13] of **32** gives a 1:1 mixture of desired bislactone **34** and its open counterpart **33** which was refluxed with *p*-TsOH to deliver **34** in 90% overall yield from carbonate **32**[14]. α-Methylation of ketone **34** afforded **25** in almost quantitative yield[15]. Finally **25** was converted into merrilactone A following the known procedures[10].

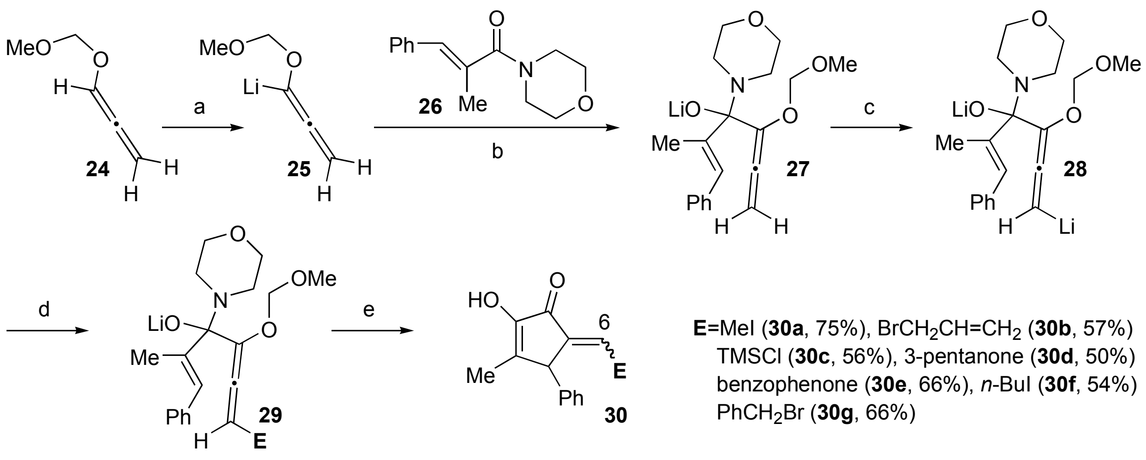


(a) **14** (2 mol%), DCM, 87%;(b) $AgNO_3$, KCN, THF/EtOH/H_2O, 83%; (c) AIBN, Bu_3SnH, benzene, reflux, then *p*-TsOH, rt, 91%; (d) TBAF, THF, rt, 99%; (e) pyridine, DMAP, ethylchloroformate, 95%; (f) NaH, THF, rt; (g) *p*-TsOH, benzene, reflux, 30 min, 90%; (h) NaH, MeI, HMPA, THF, rt, 97%

Scheme 1.9: Construction of ring B, C and D of Merrilactone A

I-2-Asymmetric Cyclization of Allene Ether Precursors

A variant of the Nazarov reaction in which one π electron pair is supplied by an allenyl ether has been a significant research interest for decades[16]. Tius and coworkers carried out detailed studies of cationic cyclopentannulation and have demonstrated very efficient construction of α-methylene-cyclopentanones[17]. In 2003, Tius et *al*. described a triply convergent cyclopentannulation process[18] involving an allene **24**, a morpholino amide **26** and an electrophile (*Scheme 1.10*). The addition of the lithiated allene **25** to the amide **26** produces the tetrahedral intermediate **27**, which after deprotonation leads to the O,C-dianion **28**. Exposure of **28** to electrophile **E** followed by quenching with acidic aqueous solution gave α,α'-hydroxy-methylene-cyclopentanones **30a**-**g** substituted at the C-6 position with various functionalities in good yields.

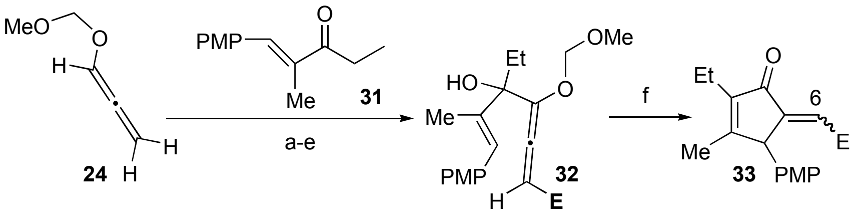


E=MeI (**30a**, 75%), $BrCH_2CH=CH_2$ (**30b**, 57%)
TMSCl (**30c**, 56%), 3-pentanone (**30d**, 50%)
benzophenone (**30e**, 66%), *n*-BuI (**30f**, 54%)
$PhCH_2Br$ (**30g**, 66%)

(a) n-BuLi (1.2 eq), THF, -78°C, 20 min; (b) **26** (1 eq), KCN, -78°C, 30 min; (c) *sec*-BuLi (1.7 eq), -78°C, 20 min; (d) **E** (3 eq), -78°C, 20 min and -40°C, 30 min; (e) aqueous HCl

Scheme 1.10: Triply convergent process toward α,α'-hydroxy-methylene-cyclopentanones

Furthermore, by differing the nature of the α,β-unsaturated electrophilic component such as amide (**26**, *Scheme 1.10*) with ketone (**31**, *Scheme 1.11*) or with nitrile (**34**, *Scheme 1.12*), α,α'-alkyl-methylene-cyclopentanones **33a-g**, *Scheme 1.11*) and α,α'-amino-methylene-cyclopentanones **36a-b**, *Scheme 1.12*) were readily accessible. When enone **31** was used, the intermediate alcohol **32** was isolated and then cyclized in a separate step (*Scheme 1.11*).

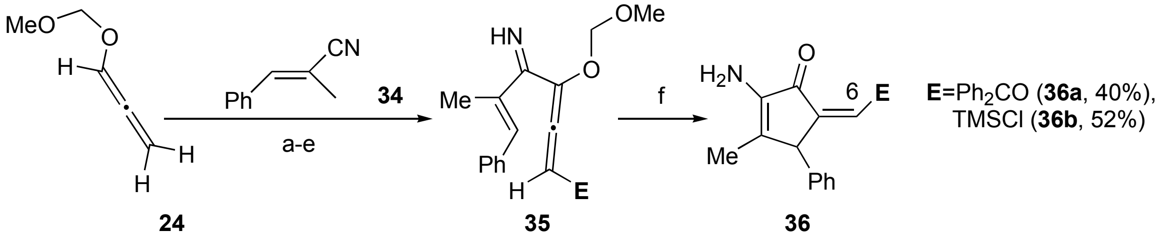


E=MeI (**33a**, 79%),
$BrCH_2CH=CH_2$ (**33b**, 65%)
TMSCl (**33c**, 65%)
EtOCOCN (**33d**, 55%),
n-BuI (**33f**, 67%),
$PhCH_2Br$ (**33g**, 73%)

(a) *n*-BuLi (1.2 eq), THF, -78°C, 20 min; (b) **31** (1 eq), -78°C, 30 min; (c) *sec*-BuLi (1.7 eq), -78°C, 20 min; (d) **E** (3 to 6 eq), -78 to -30°C, 15 to 150 min; (e) aqueous HCl; (f) $FeCl_3$, DCM

Scheme 1.11: Triply convergent process toward α,α'-alkyl-methylene-cyclopentanones

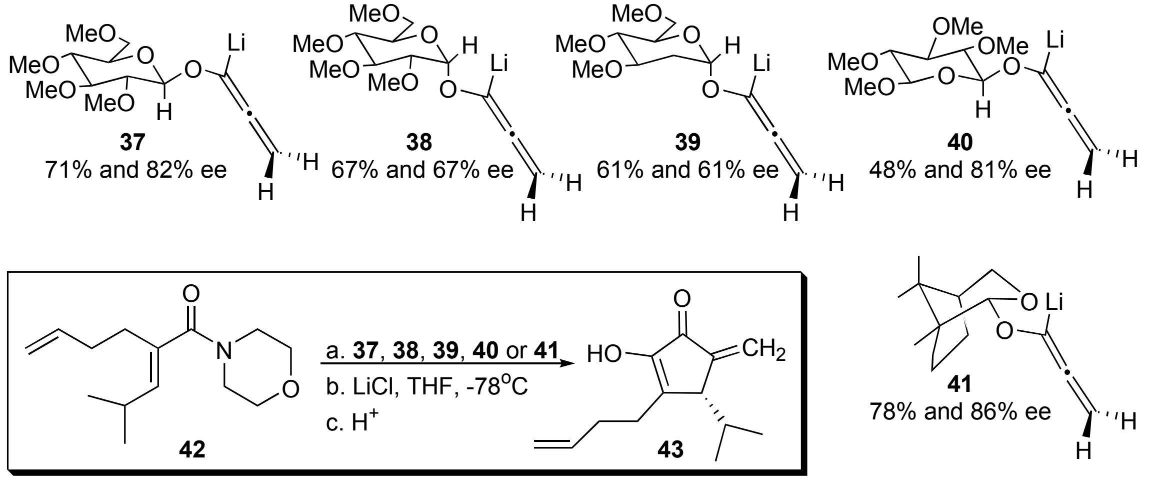
The cyclization could be affected by either trifluoroacetic anhydride/2,6-lutidine or $FeCl_3$ with moderate to good yields. Addition of **24** to α-methyl-cinnamonitrile **34** followed by γ-deprotonation of the intermediate, trapping of the dianion with either benzophenone or trimethylsilyl chloride and cyclization led to (*Z*) products **36a** (KH_2PO_4 quench) or **36b** ($FeCl_3$ quench) (*Scheme 1.12*).



(a) n-BuLi (1.2 eq), THF, -78°C, 20 min; (b) **34** (1 eq), -78°C, 30 min; (c) *sec*-BuLi (1.7 eq), -78°C, 20 min; (d) **E** (3 to 6 eq), -78 to -30°C, 15 to 150 min; (e) aqueous HCl; (f) $FeCl_3$, DCM or KH_2PO_4

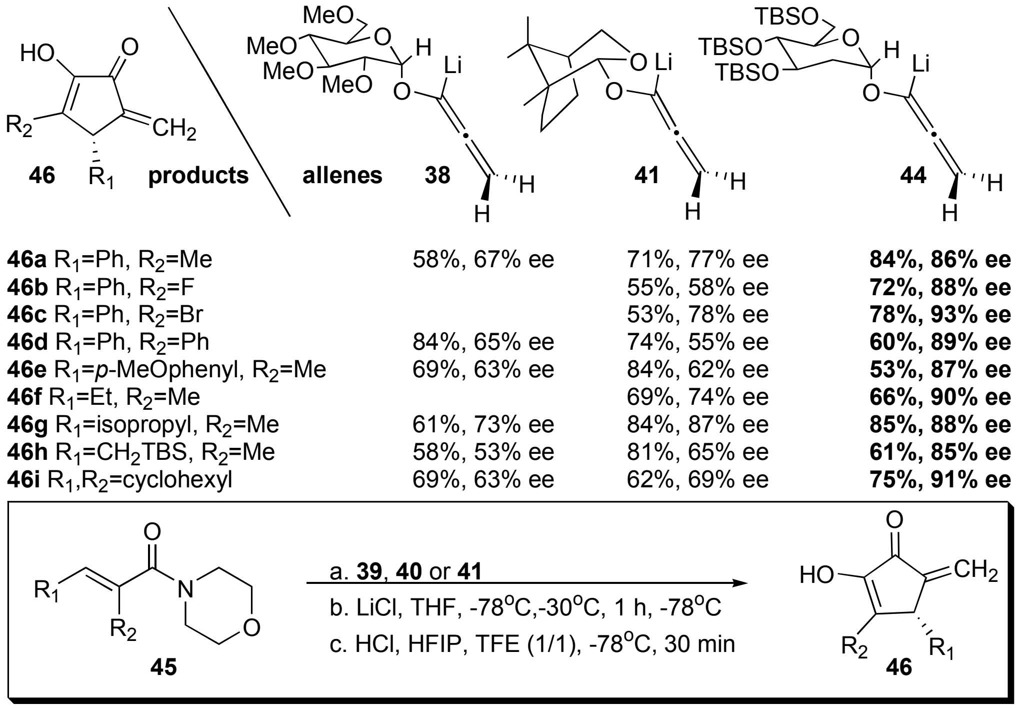
Scheme 1.12: Triply convergent process toward α,α'-amino-methylene-cyclopentanones

Having demonstrated the potential of the above methodology (*Scheme 1.10*) with the spontaneous cyclization of the allenyl vinyl ketone **29** upon workup, Tius et *al*. expected the reactive nature of **29** to converge on asymmetric catalysis of the synthesis of **30**. Since the $–CH_2OMe$ group (**35**, *Scheme 1.12*) on oxygen is lost (as a cation) during the cyclization, one option would be to use a chiral $–CH_2OR^*$ group as a traceless chiral auxiliary[19,20] such as β-D-glucose, α-D-glucose, α-2-deoxy- D-glucose, β-rhamnose and camphor (**37-41**, *Scheme 1.13*).



Scheme 1.13: First generation of chiral auxiliaries used in cationic cyclopentannulation

This work revealed several features based on the cyclization of **42** to **43**. First of all, it was noted that the absolute stereochemistry of the major cyclic product depends on the absolute stereochemistry of the anomeric carbon atom of the monosaccharide. The second feature was that the optical purity of product was higher from the β-anomeric compound **37** and **40** than from the α-anomeric **38** and **39**.It was demonstrated that the actual methoxy substituents at C-2 and C-6 expected to show the greatest influence on the stereochemical course of the reaction, in fact have only a small effect on the optical purity of the product (comparison in between **38** and **39** % ee, *Scheme 1.13*). The difference in the optical purity of the product is insignificant for allenyllithiums **37** and **40;** which are pseudoenantiomers and differ with respect to the presence or absence of the primary methoxy group. Camphor derived allenyllithium **41** had been the most effective reagent. One possible explanation is that chiral auxiliary **41**, seems to be more nucleophilic compared to the sugar-derived allenyllithium (**37-40**) containing more oxygen substituents. This is balanced out by the use of several equivalents of LiCl for optimal yields[21]. The role of LiCl is presumably to disrupt the aggregation of the allenyl anion leading to a more reactive nucleophile. It was hypothesized that replacing methoxy group in **39** by *tert*-butyldimethylsilyloxy (OTBS) would suppress aggregation of the allenyllithium, leading to a more reactive nucleophile (**44**, *Scheme 1.14*). Using these data, a comparison between the effectiveness of the allenyllithium **44**, camphor-derived **41** and the methoxy-substituted sugar **38** can be made (*Scheme 1.14*). Lithioallene **44** leads to products of much higher optical purity than **38** and **41** in all cases **46a-46i**. Even with noncoordinating OTBS groups, **44** required 7 equivalents of LiCl in order for the reaction with enamide **45** to proceed with good yields. Therefore, LiCl may be playing more than one role in the reaction. For instance, omitting it from the reaction of **44** with **45** and changing none of the other reaction parameters resulted in a significant attenuated yield of cyclopentenone **46a** (38% yield, 99% ee). The reason **44** is so much more effective than the other lithioallene studied (**38**, **39** and **41**) is not obvious and it seems unlikely that the C-6 OTBS group is alone responsible. Work on varying substituents and stereochemistry on the pyran will be required to further understand interactions between auxiliary and pentadienyl cation.

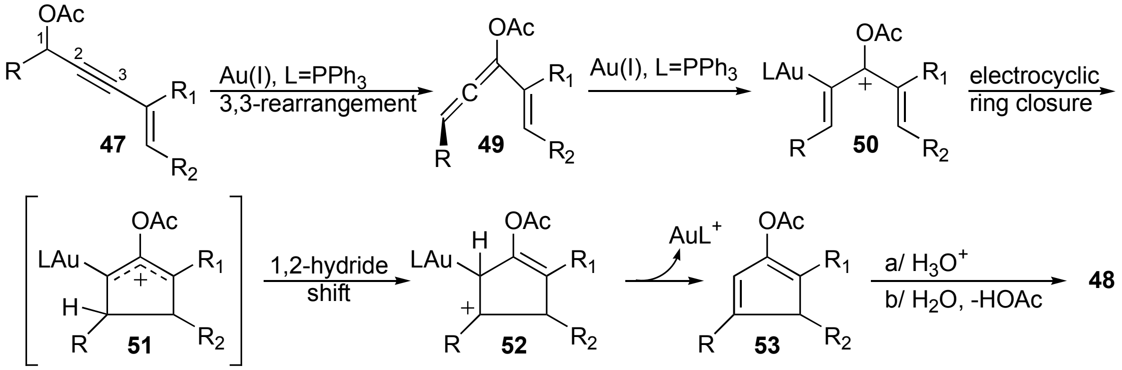


46 products \ allenes	38	41	44
46a R_1=Ph, R_2=Me	58%, 67% ee	71%, 77% ee	**84%, 86% ee**
46b R_1=Ph, R_2=F		55%, 58% ee	**72%, 88% ee**
46c R_1=Ph, R_2=Br		53%, 78% ee	**78%, 93% ee**
46d R_1=Ph, R_2=Ph	84%, 65% ee	74%, 55% ee	**60%, 89% ee**
46e R_1=*p*-MeOphenyl, R_2=Me	69%, 63% ee	84%, 62% ee	**53%, 87% ee**
46f R_1=Et, R_2=Me		69%, 74% ee	**66%, 90% ee**
46g R_1=isopropyl, R_2=Me	61%, 73% ee	84%, 87% ee	**85%, 88% ee**
46h R_1=CH_2TBS, R_2=Me	58%, 53% ee	81%, 65% ee	**61%, 85% ee**
46i R_1,R_2=cyclohexyl	69%, 63% ee	62%, 69% ee	**75%, 91% ee**

Scheme 1.14: Second generation of chiral auxiliaries used in cationic cyclopentannulation

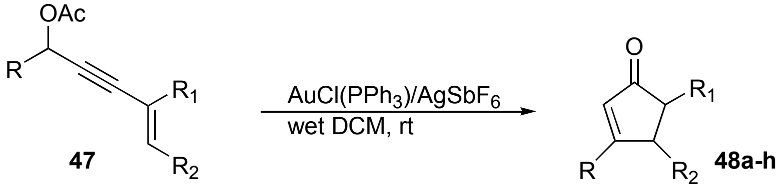
I-3-Tandem Reaction

The Nazarov reaction is generally carried out using divinyl ketone starting materials or equivalents prepared from convergent substrates containing a double bond, which limits the substrate scope and the utility of this reaction. Zhang and coworkers[22], reported in 2006 a Au(I)-catalyzed synthesis of cyclopentenones from readily available enyl esters *via* tandem 3,3-rearrangement and Nazarov reaction (*Scheme 1.15*). In this reaction, AuCl-(PPh_3)/$AgSbF_6$ plays a dual roles of activating both alkynes and allene. It was found that cationic Au(I) cationic complexes can not only catalyze 3,3-rearrangement of enyl acetate **47** but also activate the resulting allenylic acetate **49** in situ to give the pentadienyl cation **50**. Subsequent 4π-electrocyclization of **50** forms Au-containing cyclopentenylic cation **51**, which after regioselective 1,2-hydride shift and collapse of cation **52** yields selectively cyclopentadienylic acetate **53**. When R in **53** is an alkyl group, hydrolysis of the enol acetate moiety occurs and cyclopentenone **48** is formed as a final product.



Scheme 1.15: Proposed Mechanism for the Formation of Cyclopentenone

Attractive features of this reaction are the significant substrate flexibility allowed and the excellent control of the cyclopentenone double bond position (*Scheme 1.16*).

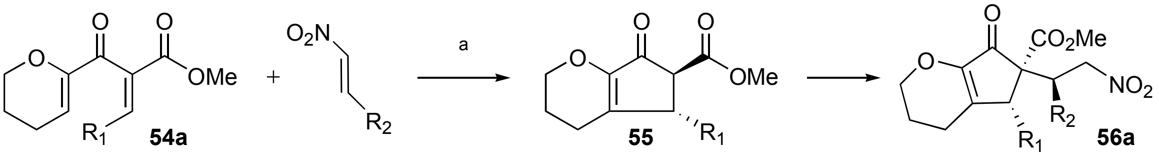


Enynyl acetate	Catalyst (mol%)	Time (min)	Yield (%)
47a R=cyclohexyl, R_1=Me, R_2=H	1	30	95
47b R=isopropyl, R_1=Me, R_2=H	1	30	88
47c R=pentyl, R_1=H, R_2=H	1	30	79
47d R=pentyl, R_1 and R_2=cyclopentyl	1	30	57
47e R=pentyl, R_1 and R_2=cyclohexyl	1	30	84
47f R=pentyl, R_1 and R_2=cycloheptyl	1	30	90
47g R=pentyl, R_1=Ph, R_2=H	5	60	74
47h R=pentyl, R_1=$(CH_2)_2$OTIPS, R_2=H	5	30	81

Scheme 1.16: AuCl-$(PPh_3)/AgSbF_6$-Catalyzed Formation of Cyclopentenones

Substrates **47a** and **47b** underwent smooth cyclization and the corresponding cyclopentenones **48a** and **48b** were isolated in excellent yields indicating steric tolerance at the propargylic position. Treatment of enyl acetates **47d-f** containing cyclopentene, cyclohexene and cycloheptene moieties respectively led to bicyclic cyclopentenones in fairly good to excellent yields. Phenyl substitution at the double bond was tolerated although a higher catalyst loading (5 mol%) was necessary (**47g**). Desilylation occurred during the cyclization of TIPS-protected acetate **47h** producing hydroxyl enone **48h** in 81% yield after treating the reaction mixture with TFA.

In 2006, Frontier et *al.* described a tandem Nazarov cyclization-Michael addition sequence[23] catalyzed by the [IrMe(CO)(dppe)-(DIB)](BARF)$_2$ complex **14** previously studied (*Scheme 1.5 and 1.8*). In their previous work, it was shown that dicationic complex **14** was able to catalytically cyclize polarized divinyl β-ketoester **54a** to the corresponding Nazarov product **55** (*Scheme 1.17*) in excellent yield[8]. It was found that combination of alkylidene β-ketoester **54a**, nitrostyrene, *N*-ethylpiperidine (EPP) and catalyst **14** reacted in a stepwise manner to give first the Nazarov product **55** and then the Michael adduct **56a** in high yield, creating three contiguous stereocenters with excellent diastereoselectivity (only two of four possible diastereomers were observed) (*Scheme 1.17*).

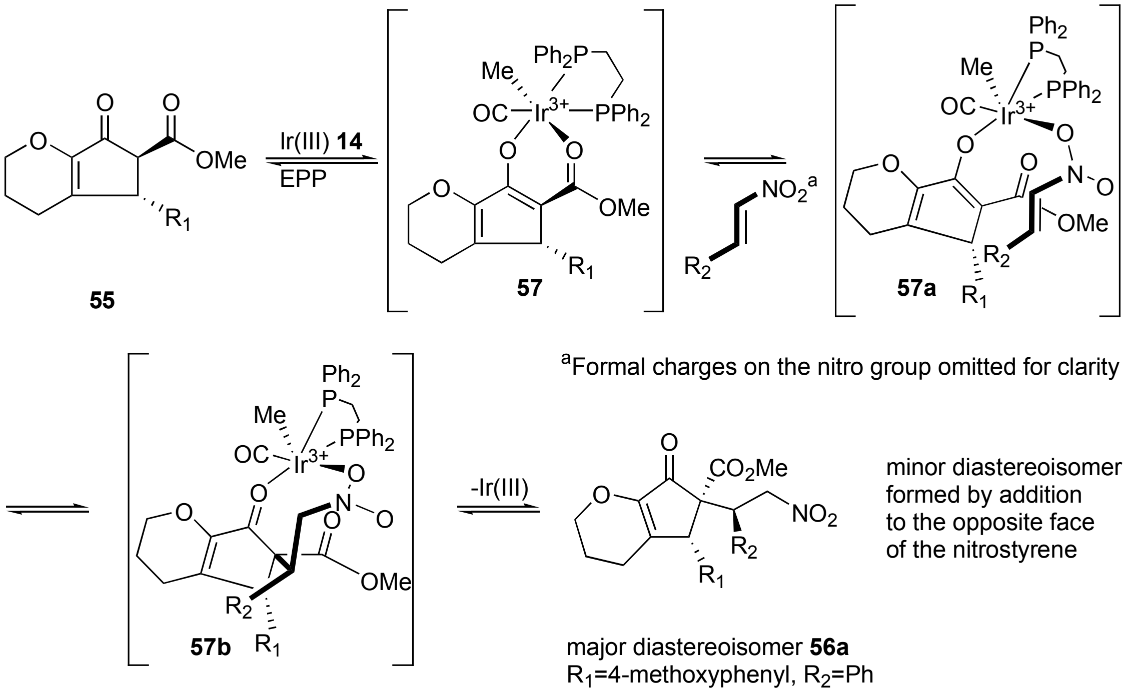


R_1=4-methoxyphenyl

[a] reaction conditions: Cl(CH$_2$)$_2$Cl (0.2 M), **14** (4 mol%), EPP (10 mol%), 40°C, 11.5h, 92% yield, dr 14:1

Scheme 1.17: Tandem Nazarov Cyclization-Michael Addition Sequence

While it is thought that the Michael addition step of the tandem chemistry occurs *via* attack of the enolate species **57** on the nitroalkene (*Scheme 1.18*), as suggested by previous report on conjugate addition reactions of transition metal-complexed enolates[24,25], the rapid rate of Michael addition suggests Lewis acid activation of the nitroalkene *via* formation of an enolate complex **57a** (*Scheme 1.18*). The proposed ligand exchange is consistent with the readily observed exchange chemistry seen for **14** with η^1 intermediates of bidentate ligand species and would provide a more reactive enolate nucleophile as well as a coordination site to activate the nitroalkene electrophile[26,27]. Either intramolecular (shown) or intermolecular alkylation could then occur to give the final product. It was demonstrated that the pathway that accounts for the thermodynamic equilibration of the product mixture is *via* reversible Michael addition. Furthermore, the observed mixture of diastereoisomers results from Michael addition to both faces of the nitroalkene from one face of the enolate.



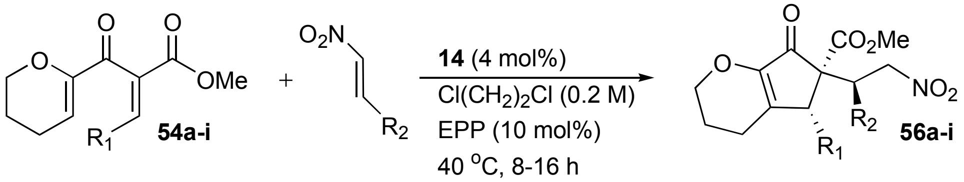
^{a}Formal charges on the nitro group omitted for clarity

minor diastereoisomer formed by addition to the opposite face of the nitrostyrene

major diastereoisomer **56a**
R_1=4-methoxyphenyl, R_2=Ph

Scheme 1.18: Proposed Mechanism of the Tandem Nazarov Cyclization-Michael Addition Sequence

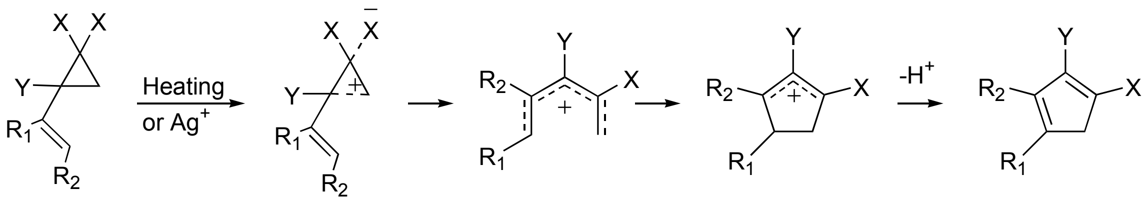
The reaction sequence showed similar efficiency and diastereo-selectivity for a range of alkylidene β-ketoesters and nitroalkenes (products **54a**-**i**) (*Scheme 1.19*). It is worth remarking that alkyl substitution on the nitroalkene does not significantly decrease the yield or selectivity of the reaction (shown with **56e**) and that alkylidene β-ketoester **54i** with alkenyl substitution also gave a good result.



R_1	R_2	yield (%)	dr
4-methoxyphenyl	Ph	**56a** (92)	14:1
4-methoxyphenyl	4-bromophenyl	**56b** (90)	15:1
4-methoxyphenyl	4-methoxyphenyl	**56c** (90)	13:1
4-methoxyphenyl	2-furyl	**56d** (91)	12:1
4-methoxyphenyl	n-C_3H_7	**56e** (85)	10:1
2-furyl	Ph	**56f** (89)	13:1
2-furyl	4-bromophenyl	**56g** (91)	15:1
2-furyl	4-methoxyphenyl	**56h** (86)	13:1
cinnamyl	Ph	**56i** (87)	8:1

Scheme 1.19: Scope of Tandem Nazarov-Michael Addition Sequence

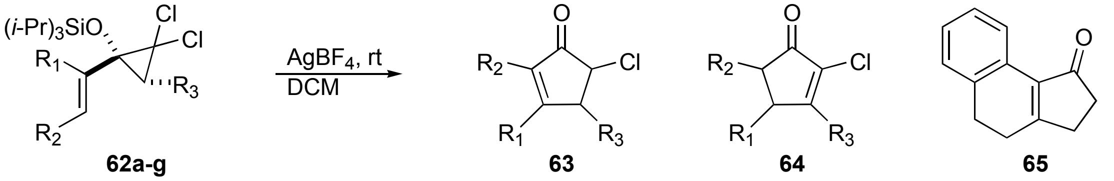
West's group have been focusing for the last decade on alternative methods for the generation of Nazarov-type pentadienyl systems and they have recently described the first examples of an apparent sequential 2π-electrocyclic opening then 4π-electrocyclic closure reaction[28]. The novel Nazarov process is based on the ring opening chemistry of alkenyl substituted dihalocyclopropanes **58** leading to pentadienyl cations **59** which can undergo 4π-electrocyclization (*Scheme 1.20*).



58 (X=Cl, Br;
Y=H, R, OR) **59** **60** **61**

Scheme 1.20: Approach to the Nazarov Reaction via Electrocyclic Ring Opening and Ring Closure

The design of substrate **58** resulted from a computational study that showed that the presence of an alkenyl substituent on C-2 of a 1,1-dihalocyclopropane should increase the rate of electrocyclic opening relative to hydrogen[29]. The presence of an oxygen-containing group on the same carbon (Y = OR) should also accelerate ring opening and would furnish a pentadienyl cation motif. Silyl ethers were chosen for initial investigation, as the cyclization products **61** would be expected to undergo facile desilylation to the corresponding cyclopentenone (*Scheme 21*).



substrate	R_1	R_2	R_3	yield (%)
62a	H	H	H	**64a** ([a])
62b	$(CH_3)_2CH$	H	H	**63b+64b** (57)
62c	Ph	Me	H	**63c** (70)
62d	$(CH_2)_4$	[b]/	H	**63d** (45)
62e	$(CH_2)_3$	[b]/	H	**63e** (74)
62f	Ph	Me	Pr	**63f+64f** (87)
62g	$Ph(CH_2)_2$	H	H	**65** (63)

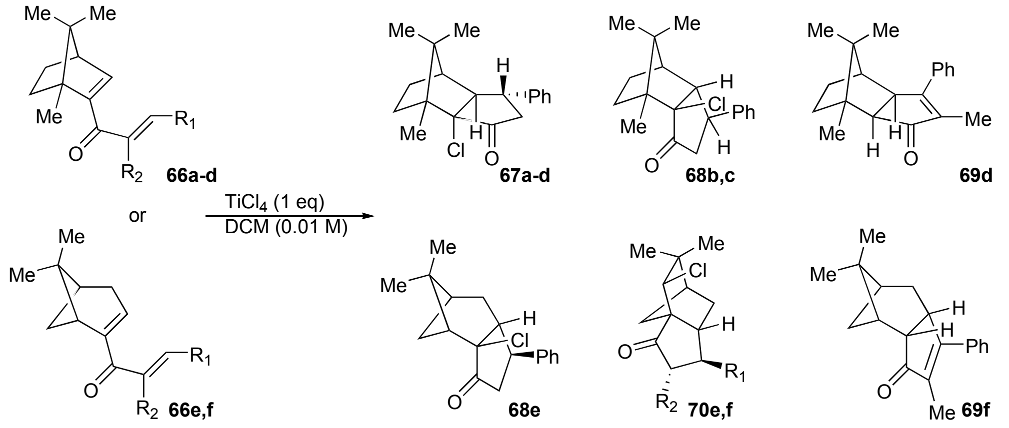
[a] compound **64a** was present in the crude reaction mixture, but decomposed during attempted chromatographic purification; [b] cyclic substituents.

Scheme 1.21: $AgBF_4$-Mediated Rearrangement of Cyclopropanes **62**

The presence of additional substituents on either the alkenyl moiety or the cyclopropane **62b-f** permitted clean conversion to the desired cyclopentenones **63** or **64**, which did not occur with unsubstituted dihalogenated vinylcyclopropane **62a**. For cyclopropanes **62b-e** lacking an additional alkyl substituent complete regioselectivity was seen in the elimination step in favor of the more substituted alkene product[30], except in the case of **62b**. The presence of an additional alkyl group on the cyclopropane **62f** led to a mixture of **63f** and **64f**. The behavior of phenethyl-substituted **62g** is especially notable as none of the expected cyclopentenone was isolated. Instead, tricyclic product **65** was obtained in good yield. This product is assumed to form *via* electrophilic aromatic substitution involving the 2-silyloxycyclopentenyl cation, formed upon electrocyclization[31]. Previous examples, of the arene-terminated interrupted Nazarov reaction required the presence of at least one electron-donating group on the aromatic trap. The eventual formation of the tetrasubstituted alkene presumably arises *via* elimination of HCl and C=C migration.

I-4-Interrupted Nazarov Reaction

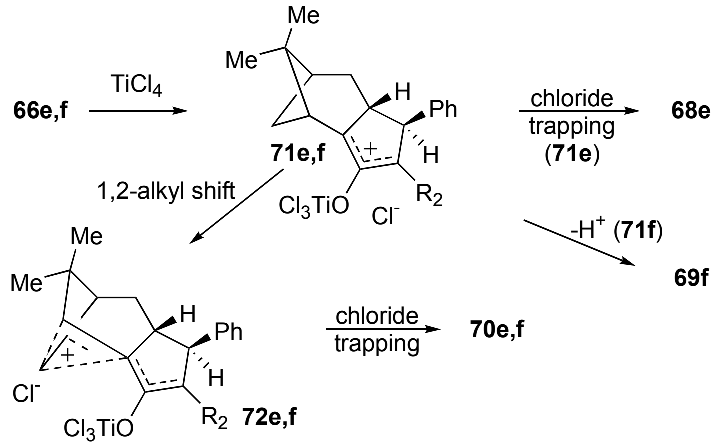
The potential for coupling a Nazarov reaction with additional C-C bond forming steps is illustrated by West's halide trapping of the Nazarov intermediate in strained polycyclic systems[32]. The novel halide trapping process occurs in preference to and often to the exclusion of the usual elimination step. Experiments showed that treatment of dienone **66a** with $TiCl_4$ at low temperature led to a single new product **67a** in which a chloride from the Lewis acid trapped the 2-oxidocyclopentenyl cation[33-35] formed after conrotatory electrocyclization (*Scheme 1.22*).



Dienone	R_1	R_2	Temperature	Time	Yield **67** (%)	Yield **68** (%)	Yield **69** (%)	Yield **70** (%)	Combined yield (%)
66a	Ph	H	-78°C to 0°C	5 h	87	/	/	/	87
66b	Me	H	-78°C to 0°C	2 h	59	7	/	/	66
66c	*t*-Bu	H	-78°C to 0°C	2 h	50	16	/	/	66
66d	Ph	Me	-78°C	10 min	25	/	25	/	50
66e	Ph	H	-78°C to -20°C	14 d	/	12	/	48	60
66f	Ph	Me	-78°C	10 min	/	/	29	33	62

Scheme 1.22: Nazarov Cyclization /Chloride Trapping of Dienones **66a-f**

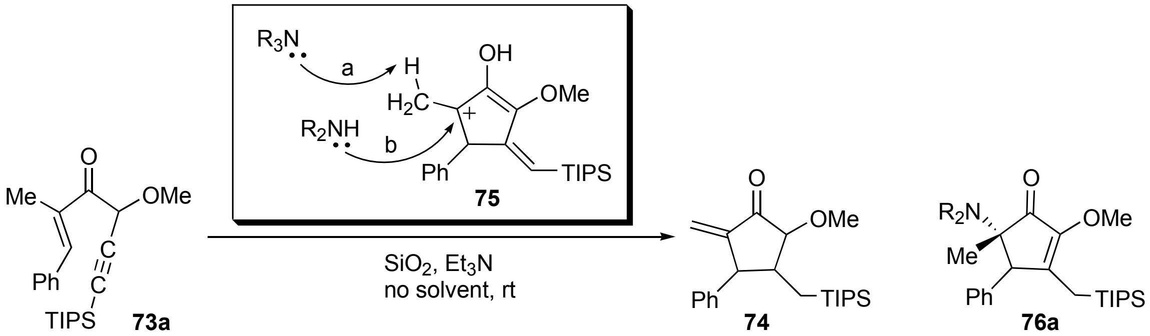
It is speculated that the high *exo* selectivity displayed by camphor-derived **66a** might be explained by facial preference such as torsional strain[36], non-equivalent orbital extension[37], alkene pyramidalization[38] or transition state allylic bond staggering[39]. Camphor-derived dienones **66b-d** all displayed the same *exo* cyclization preference as **66a**, although with reduced selectivity. The more heavily substituted dienone **66d** furnished a mixture of chlorine trapping product **67d** and simple elimination product **69d**. Nopinone-derived dienones **66e**,**f** underwent efficient cyclization, but in each case provided a mixture of two distinct products. **66e**,**f** minor products were furnished from cyclopentenyl carbocation **71e,f** where *endo* cyclization followed by chloride trapping yielded product **68e** and product **69f** was formed through the elimination pathway (*Scheme 1.23*).



Scheme 1.23: Scope of **66e**,**f** Cyclization Pathways

Major products **70e**,**f** seem to result from a 1,2-alkyl migration by the intermediate cyclopentenyl cation **72e**,**f**, with chloride trapping of the resulting secondary carbocation.

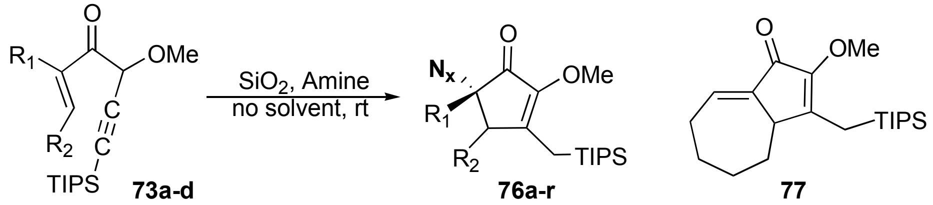
Tius et *al.* described the first example of a Nazarov reaction that is terminated by C-N bond formation[40]. Exposure of enone **73a** to activated dry silica gel[41] that had been thoroughly mixed with triethylamine (1.2 eq) led to enone **74** and aminocyclopentenone **76a** after 3 h at room temperature (*Scheme 1.24*).

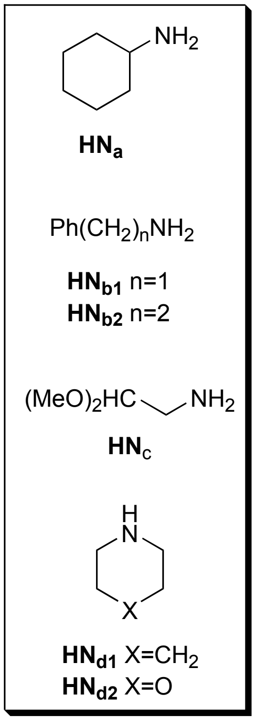


Scheme 1.24: Interrupted Nazarov Cyclization on Silica gel

Presumably, the isomerization of **73a** to the corresponding allenyl vinyl ketone by triethylamine had initiated a cascade of reactions through the generation of cation **75**. The process giving the enol to ketone conversion and alkene migration is terminated by proton loss according to pathway a. But when the presumed cationic intermediate **75** is trapped with nucleophilic primary or secondary amines according to pathway b, aminocyclopentenone **76a** would be formed.

Experiments suggest that the reaction with liquid aliphatic primary and secondary amines in the absence of solvent in all cases leads to good products yields (*Scheme 1.25*).





Substituents	**Amine (HN$_x$)**	**Product (yield %)**
73a R_1=Me, R_2=Ph	HN$_a$	**76a** (65)
R_1=Me, R_2=Ph	HN$_{b1}$	**76b** (60)
R_1=Me, R_2=Ph	HN$_{b2}$	**76c** (63)
R_1=Me, R_2=Ph	HN$_c$	**76d** (67)
R_1=Me, R_2=Ph	HN$_{d1}$	**76e** (58)
R_1=Me, R_2=Ph	HN$_{d2}$	**76f** (70)
73b R_1=Me, R_2=Me	HN$_a$	**76g** (63)
R_1=Me, R_2=Me	HN$_{b1}$	**76h** (64)
R_1=Me, R_2=Me	HN$_{b2}$	**76i** (55)
R_1=Me, R_2=Me	HN$_c$	**76j** (51)
R_1=Me, R_2=Me	HN$_{d2}$	**76k** (66)
[a]**73c** R_1,R_2=$(CH_2)_5$	HN$_a$	**76l+77** (68+13)
R_1,R_2=$(CH_2)_5$	HN$_{b1}$	**76m+77** (75+4)
R_1,R_2=$(CH_2)_5$	HN$_{b2}$	**76n+77** (71+4)
R_1,R_2=$(CH_2)_5$	HN$_c$	**76o+77** (60+10)
R_1,R_2=$(CH_2)_5$	HN$_{d1}$	**76p+77** (51+28)
R_1,R_2=$(CH_2)_5$	HN$_{d2}$	**76q+77** (61+20)
[a]**73d** R_1,R_2=$(CH_2)_4$	HN$_a$	**76p** (59)
R_1,R_2=$(CH_2)_4$	HN$_{b1}$	**76q** (60)
R_1,R_2=$(CH_2)_4$	HN$_{b2}$	**76r** (64)

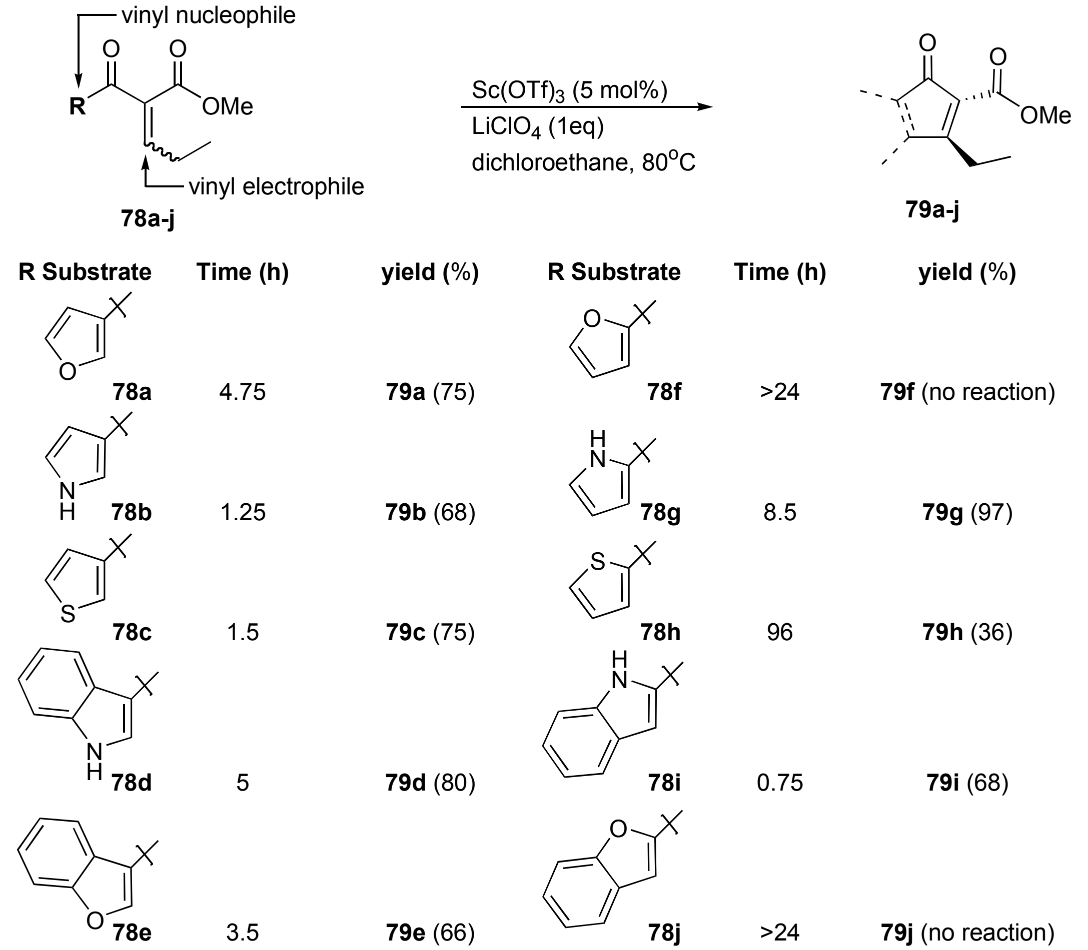
[a] R_1=R_2=cyclic substituent

Scheme 1.25: Scope of Nazarov Cyclization Terminated by C-N Bond Formation

It appeared that proton loss from the intermediate cation occurs more readily in the presence of solvent. Increasing the steric requirement of the α-substituent of the enone or of the amine can be predicted to favor reaction pathway a over b. The mild nature of the reaction conditions is also shown by the success of cyclization with 2,2-dimethoxyethyl-amine **HN$_c$**. No hydrolytic cleavage products of the acetal were detected under the reaction conditions. The reaction of **73a** with aromatic aniline (**HN$_{b1}$** and **HN$_{b2}$**) gave rise to multiple products including the anticipated the aminocyclopentenone **76a**, suggesting a competition between C-N bond formation and Friedel-Crafts alkylation[42]. Product stereochemistry in all cases is governed by approach of the amine nucleophile from the less hindered face of the cation (**75**, *Scheme 1.23*). Since highly reactive cation **75** has a number of decomposition pathways, nucleophilic trapping must take place more rapidly. Therefore, it seems likely that the close proximity of amine and propargyl ketone ensure the success of the nucleophilic addition as the reactive intermediate is only generated in the proximity of the amine. The great ease with which allenyl vinyl ketones undergo the Nazarov cyclization in the presence of even the weakest acid catalyst[43] makes it possible to use amine nucleophiles in the termination step.

I-5-Catalytic Method of Complex Heterocyclic Nazarov Products

Efforts from Frontier's laboratory have focused on the study of substrates that are favourably polarized[7]; divinyl ketone with appropriate design such as that containing an electron-rich and an electron-poor π-system would allow the 4π electrocyclization to proceed with a lower activation barrier (*Scheme 1.3*). This approach is demonstrated further by the development of a mild Lewis acid-catalyzed cyclization procedure for aromatic heterocycle-containing precursors seen as a relatively unreactive class of substrates[44] (*Scheme 1.26*).



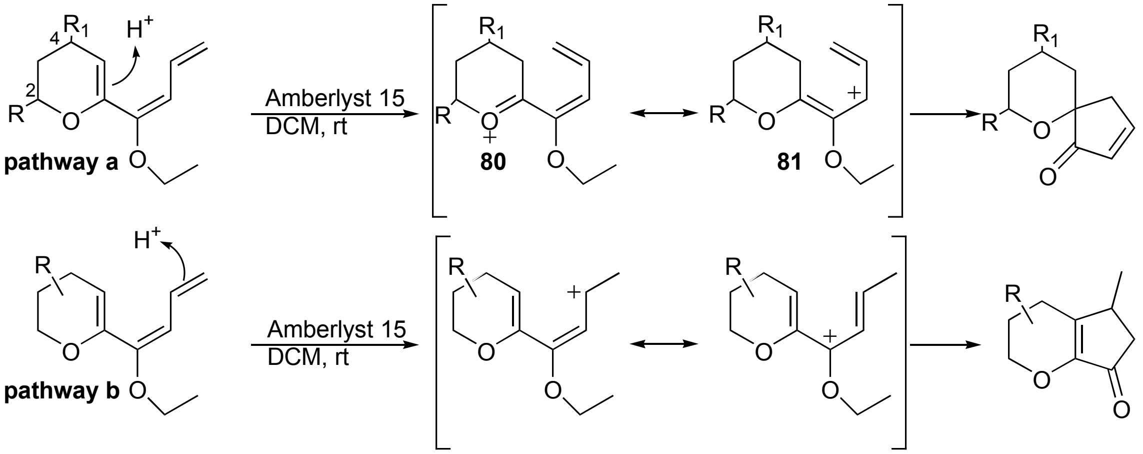
R Substrate	Time (h)	yield (%)	R Substrate	Time (h)	yield (%)
78a	4.75	**79a** (75)	**78f**	>24	**79f** (no reaction)
78b	1.25	**79b** (68)	**78g**	8.5	**79g** (97)
78c	1.5	**79c** (75)	**78h**	96	**79h** (36)
78d	5	**79d** (80)	**78i**	0.75	**79i** (68)
78e	3.5	**79e** (66)	**78j**	>24	**79j** (no reaction)

Scheme 1.26: Heteroaromatic Nazarov Cyclizations

Bearing in mind that Nazarov cyclization of aryl vinyl ketones can also be termed intramolecular vinylogous Friedel-Crafts acylations, Frontier et *al*. chose to use a range of Lewis acid catalysts combined with lithium perchlorate ($LiClO_4$), which is known to play an important role as an additive in Friedel-Crafts acylation. It was discovered that the presence of $LiClO_4$ (1 eq) as additive and scandium triflate ($Sc(OTf)_3$, 5 mol%) as Lewis acid gave the best result[45] relative to reactions achieved with Lewis acid only and different Lewis acid/$LiClO_4$ ratios.

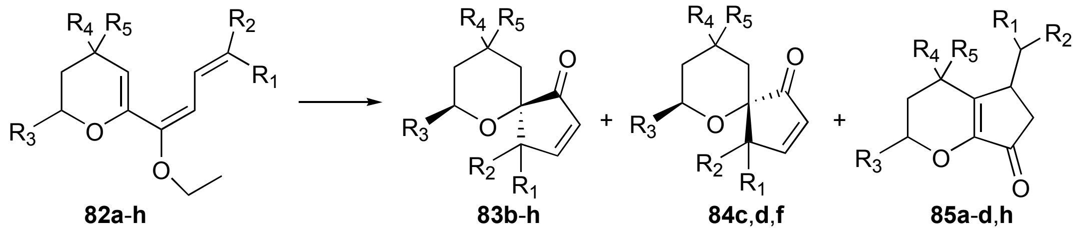
These heteroaromatic Nazarov cyclizations survey showed reaction rates and yields consistent with the expected reactivity of heteroaromatic systems[46], which here represents the electron-donating component of the polarized system. For furan, pyrrole, thiophene and benzofuran systems, reaction rates for ring closure at the 2-position (products **79a-c** and **79e**) are faster than their 2-substituted analogs (products **79f-h** and **79i**). Ring closure of the indole occurs faster at the 3-position than at the 2-position (product **79d** *vs* **79j**). The 2-substituted furan **78f** and benzofuran **78j** did not undergo Nazarov cyclization. In each case, only one diastereomer was isolated after column chromatography, which was assigned as the diastereomer with a *trans* relationship between the α-carbo-methoxy group and the β-alkyl group.

During the investigation by Occhiato's group on the Nazarov reaction toward the synthesis of cyclopenta-fused heterocycles[47], an unexpected concurrent Nazarov process was discovered that formed spirocyclic ketones as secondary products (pathway a, *Scheme 1.27*).



Scheme 1.27: Possible Nazarov Reaction Pathways

The relative amount of the spiro byproducts seemed dependent on the ring substitution, in particular 2- and 4-substituted dihydropyran derivatives gave spirocyclic ketones[48] whereas unsubstituted dihydropyrans reacted exclusively according to pathway b (*Scheme 1.27*). Occhiato et al. demonstrated[49] that it is possible to modulate the course of the acid-catalyzed cyclization of triene **82** derivatives in order to selectively obtain spirocyclic ketones (*Scheme 1.28*).

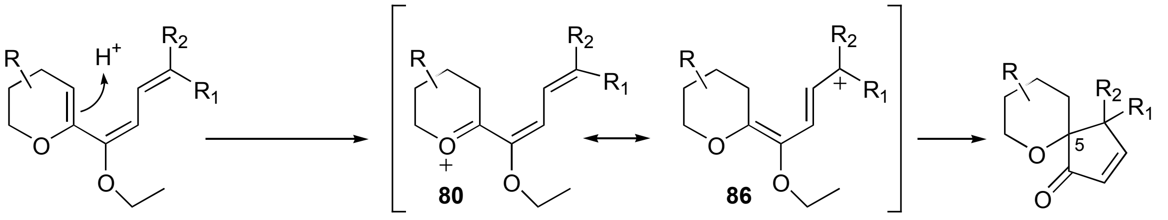


Substrate	**R$_1$**	**R$_2$**	**R$_3$**	**R$_4$**	**R$_5$**	**83**: **84**: **85**: (ratio)	**yield (%)**
82a	H	H	H	H	H	0:0:100	62
82b	H	H	Me	H	H	10:0:90	85
82c	H	H	H	Me	H	24[a]:76	88
82d	H	H	H	Me	Me	10[a]:90	69
82e	Me	Me	H	H	H	100:0:0	72
82f	Me	Me	H	Me	H	50:50:0	74
82g	Me	Me	Me	H	H	100:0:0	58
82h	H	Et	Me	H	H	75:0:25	66

[a] mixture of diastereoisomers **83** and **84**

Scheme 1.28: Possible Nazarov Cyclization of Ethoxytrienes **82a-h**

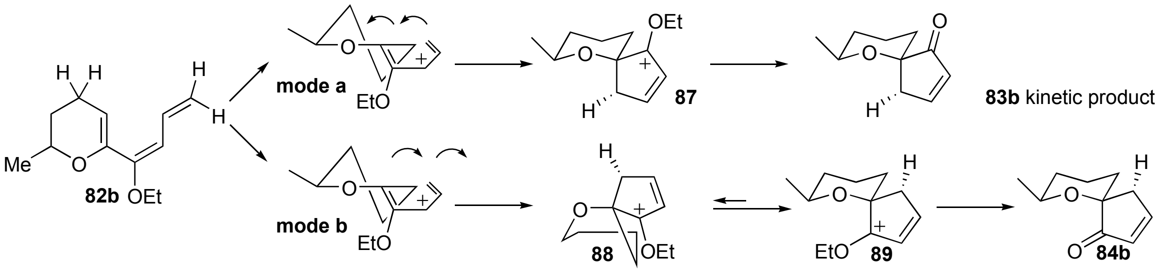
One or two alkyl substituents on the distal sp^2 carbon atom of the ethoxydiene moiety are in fact sufficient to favor the spirocyclization pathway. When trienes **82a-d**, unsubstituted on the ethoxydienol fragment, were subjected to mild acidic treatment, cyclopenta-fused ketones **85a-d** were the main products with only small amount of the spiro compound observed. When trienes **82e-g**, in which the dienyl moiety is *gem*-dimethyl-substituted, were treated with Amberlyst 15, the corresponding spiro-ketones **83e-g** and **84e-g** were the only products recovered as diastereopure compounds. A mixture of diastereopure spiro-adduct **83h** and fused-bicyclo system **85h** was finally obtained with monosubstituted triene **82h**. Results indicate that spiro-ketone formation could be favored by the stabilization of the positive charge by the heteroatom in the resonance structure **80** (*Scheme 1.29*).



Scheme 1.29: Effect of Distal Constituents on Cyclization

Furthermore, the presence of one or two substituents on the distal C atom of the diene moiety lead to a more competitive endocyclic protonation process as a result of the contribution of structure **86**. The results of the substitution start to be visible in the case of **82h** where a secondary carbocation is formed (*Scheme 1.28*). The effect is largest in the case of **82g** where the endocyclic protonation generates a tertiary carbocation. In this case, the spiro compound is the only observed product[49].

The conrotatory spirocyclization results in the generation of a new stereogenic center at C-5. Presumably, the electrocyclization process is triggered by the initial protonation of the endocyclic double bond with generation of the pentadienyl cation **80** (*Scheme 1.29*). In case of substituted dihydropyran derivatives such as **82b**, two rapidly equilibrating semi-chair conformations are possible, one of which would be thermodynamically less stable (because of the axial position of the methyl group on C-2) (*Scheme 1.30*).



Scheme 1.30: Conrotation Modes in Spirocyclization

It can then be assumed that the conformer in which the methyl group is equatorially oriented is involved in the electrocyclization[50]. The two possible conrotation modes, clockwise and counterclockwise, lead to the two different diastereomers. The counterclockwise conrotation (mode a) would imply a chair-like arrangement of the transition structure **87**, which maintains the methyl group equatorially orientated and delivers kinetic product **83b**. Alternatively, a clockwise conrotation (mode b) proceeds through a less favored twist-boat transition structure **88**. Intermediate **88** could then equilibrate with a less energetic intermediate 8**9** to furnish thermodynamically more stable product **84b**. The preferred chair-like conformation of the transition structure involved in mode a, in which the methyl group is equatorial, could explain the high diastereoselectivity observed in the formation of the diastereoisomer **83b**.

II-[3+2]-Cycloaddition

[3+2]-Cycloaddition reactions in organic chemistry are not only among the synthetically most useful reactions; the theoretical and mechanistic aspects of reactions are also fundamentally understood. When a metal is involved, there are three different ways in which a metal can interact in a cycloaddition reaction[51].

In metal-assisted cycloaddition reactions, carbo- and heterocycles are formed during the course of an organic reaction in which the metal is present in at least one of the reactants and possibly product, but not within the formed ring.

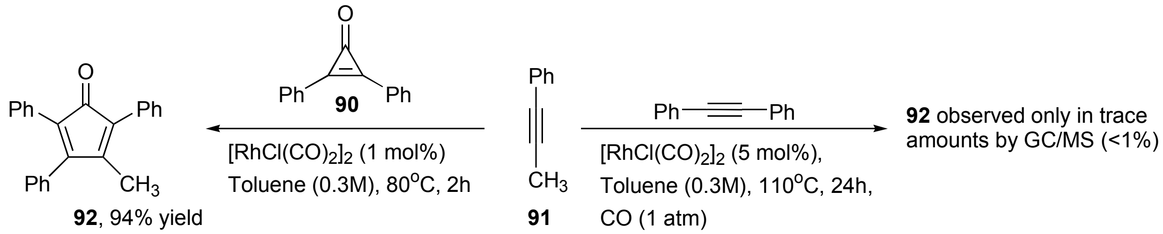
In organometallic cycloaddition reactions, an ML_n fragment forms an integral part of at least one of the reactants and the resulting initial products are metallaheterocycles. These initial metallaheterocycles are not necessarily the final products but can react further and undergo insertion and/or reductive elimination reactions.

In metal-catalyzed cycloaddition reactions, the metal fragment does not form stable complexes with either of the reactants or with the product. It is only present in reactive intermediates.

Metal-catalyzed and organometallic cycloaddition reactions constitute the driving-theme of this chapter focusing on [3+2] cycloaddition.

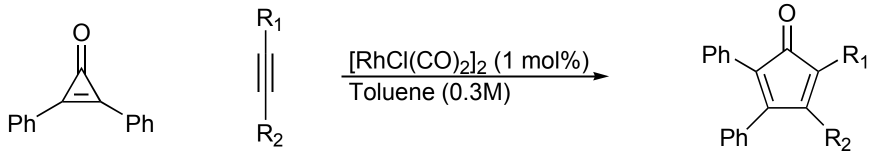
II-[3+2] Metal Catalyzed and Organometallic Cycloaddition

Cyclopentadienones are members of diverse class of fascinating compounds that can be highly valuable due to their broad potential in synthesis, biology, materials science and nanotechnology[52]. The synthesis of cyclopentadienones has been achieved in various ways; one of the most notorious being the metal mediated or catalyzed formal [2+2+1] cycloaddition of two equivalents of alkyne and carbon monoxide[53]. The use of two different components in the catalyzed three-component process is very rare as such reactions suffer of severe chemo- and regioselectivity problems. However, Pearson et *al.* have simplified the issue by the use of temporary silicon tethers[54]. Boger and Nakamura have reported that cyclopropenones ketals, either thermally (*via* dipolar cycloaddition)[55] or with a $Pd(OAc)_2$ catalyst[56], undergo cycloaddition with various π-system to provide cyclopentadienones after ketal hydrolysis. More recently, Wender et *al.* demonstrated that cyclopropenones serve as excellent 3-carbon components[57] in Rh(I)-catalyzed [3+2] cycloaddition (*Scheme 2.1*).



Scheme 2.1: The [3+2] and [2+2+1] Cycloaddition to form Cyclopentadienones

It was found that when diphenylcyclopropene **90** and alkyne **91** were heated in toluene in the presence of $[RhCl(CO)_2]_2$ (1 mol%), one regioisomer **92** is obtained in 94% yield. In contrast, attempt to produce **92** through a [2+2+1] cycloaddition by heating alkyne **91**, diphenylcycloacetylene **90** and Rh(I) catalyst (5 mol%) in toluene under an atmosphere of CO for a prolonged time at higher temperature, produced only trace amounts of **92**. The above mentioned Rh(I)-catalyzed [3+2] cycloaddition tolerates a broad range of functionalized-aryl alkyne substituents (*Scheme 2.2*). The electron-rich alkyne **93a** selectively provides **94a** in 94% yield. Similarly, electron-deficient alkynes **93b-d** afford cycloadducts **94b-d** in high yields. It is noteworthy that ortho-substituted aryl alkynes **93d** and **93e** are well tolerated. Importantly, the reaction is not limited to aryl alkynes. Enynes, heteroaryl alkynes, benzyne and 4-octyne all undergo selective [3+2] cycloaddition (products **94f-j**).



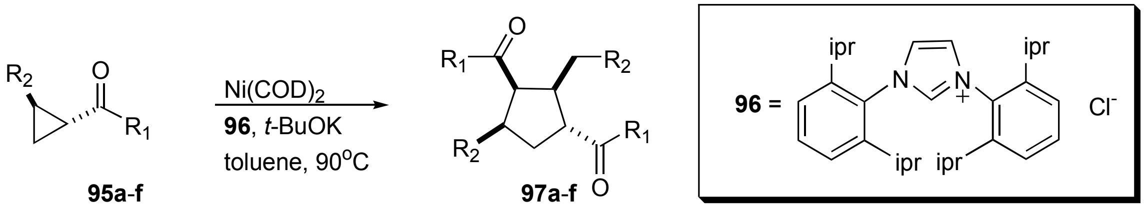
90 **93a-j** **94a-j**

93 R_1, R_2	**Temp (T°C)**	**Time (h)**	**% yield (product)**
p-OCH_3-Ph, CH_3	80	2.5	94 (**94a**)
p-C(O)CH_3-Ph, CH_2OCH_3	110	5	78 (**94b**)
p-CF_3-Ph, CH_3	110	6.5	91 (**94c**)
o-F-Ph, CH_3	80	20	77 (**94d**)
o-CH_3-Ph, CH_3	110	5	98 (**94e**)
Chex, CH_3	80	3	88 (**94f**)
3-furan, CH_2OCH_3	110	17.5	52 (**94g**)
2-pyridine, CH_2OCH_3	80	20	52 (**94h**)
n-C_3H_7, *n*-C_3H_7	80	7.5	65 (**94i**)
[a]$(CH)_4$	120	3.5	69 (**94j**)

[a] R_1=R_2=cyclic substituent

Scheme 2.2: [3+2] Cycloaddition of **90** with different alkynes **93a-j**

Cyclopropanes that lack exomethylene[58] or vinyl substituents[59] have received relatively little attention as useful precursors in metal catalyzed cycloaddition processes. Donor-acceptor cyclopropanes are highly versatile substrates in five membered-ring synthesis via Lewis acid catalysis[60]. However, Lewis acid-promoted [3+2] cycloaddition of simple cyclopropyl ketones are typically not efficient. Montgomery et *al.* recently developed a new organo-nickel catalyzed cycloaddition process involving simple cyclopropyl ketones[61]. By reacting the cyclopropyl ketone **95a** with a catalyst derived from Ni(COD)$_2$, imidazolium chloride **96** and potassium *tert*-butoxide[62], **95a** undergoes an efficient and highly diastereoselective dimerization to trisubstituted cyclopentane **97a** in 85% yield (*Scheme 2.3*).

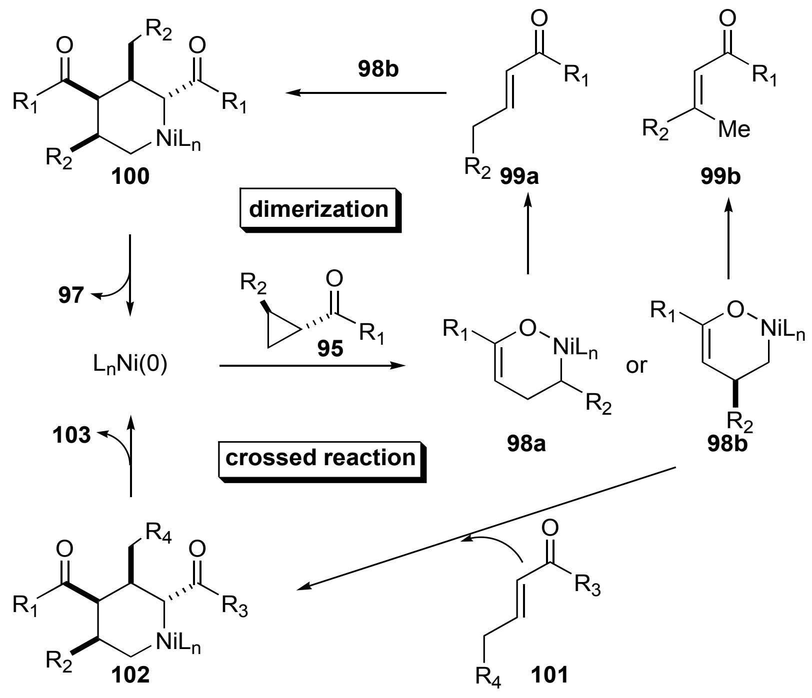


substrate	R_1	R_2	product (% yield, dr)
95a	Ph	H	**97a** (85, 98:2)
95b	*p*-CH_3O-Ph	H	**97b** (90, 99:1)
95c	*p*-F-Ph	H	**97c** (85, 98:2)
95d	thiophen-2-yl	H	**97d** (88, 99:1)
95e	furan-2-yl	H	**97e** (83, 90:10)
95f	CH_3	CH_3	**97f** (24)[a]

[a] 3-Methyl-1-phenylbut-2-en-1-one was obtained in 66% yield

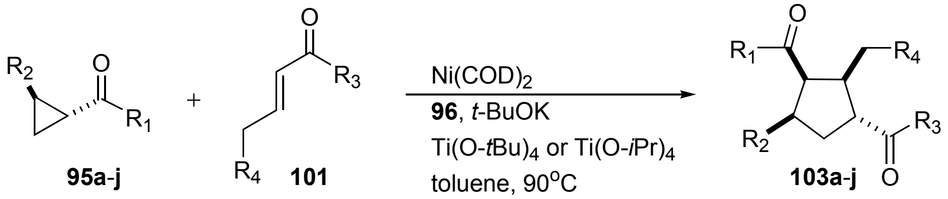
Scheme 2.3: Cyclopropyl Ketone Dimerizations

A variety of aromatic ketones undergo the process efficiently (products **97a-e**) but aliphatic ketones were significantly less reactive in the process (product **97f**). It was reasoned that the transformation is likely to involve the oxidative addition of Ni(0) to **95** to afford metallacycle **98a** or **98b**, which undergoes a sequence involving β-hydride elimination to afford enone **99a** or **99b**, along with regeneration of Ni(0) (*Scheme 2.4*).



Scheme 2.4: Proposed Mechanism

Enone **99a** then undergoes addition to another equivalent of **98b** to afford [3+2] cycloaddition product **97** through the organo-nickel intermediate **100** (alkene stereochemistry arbitrarily shown). When the crossed reactions of differentially substituted cyclopropyl ketones and enones were attempted, yields were typically modest to good and the cyclopropyl ketone dimer **97** was nearly always observed as a component of the reaction mixture (*Scheme 2.5*).



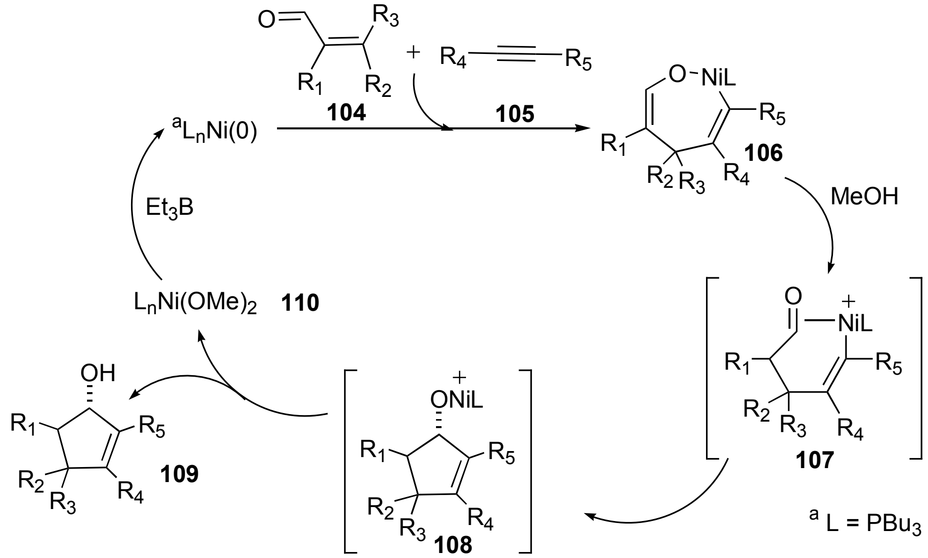
R_1	R_2	R_3	R_4	product (% yield, dr)
p-F-Ph	H	Ph	Me	**103a** (77, 94:6)
thiophen-2-yl	H	Ph	Me	**103b** (59, 97:3)
Ph	H	furan-2-yl	Me	**103c** (58, 96:4)
furan-2-yl	H	Ph	Me	**103d** (42, 90:10)
p-F-Ph	H	Ph	C_6H_{13}	**103e** (66, 93:7)
p-F-Ph	H	Ph	Ph	**103f** (59, 39:61)[a]
Ph	H	Ph	$SiMe_3$	**103g** (41, >97:3)
Me	H	Ph	Me	**103h** (47, 93:7)
Ph	Me	Ph	Me	**103i** (52, 75:25)
Ph	Me	furan-2-yl	Me	**103j** (41, 88:12)

[a] The major product is the trans/trans isomer of **103**

Scheme 2.5: Crossed Reactions of Cyclopropyl Ketones and Enones

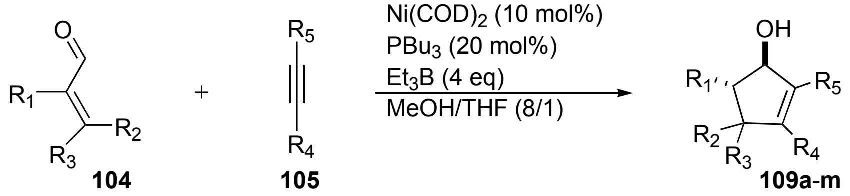
While not strictly required for reaction to take place, the use of Ti(O-*i*Pr)$_4$ or Ti(O-*t*Bu)$_4$ as additives leads to improved yields and increased reaction rates. The crossed reactions of differentially substituted cyclopropyl ketones **95** and enones **101** that both possess aromatic substitution at the carbonyl proceed efficiently (products **103a-d**). Whereas dimerization of cyclopropyl methyl ketone was inefficient (product **97f**, *Scheme 2.3*), a crossed reaction involving this substrate did proceed with modest yield (product **103h**, *Scheme 2.5*). Use of disubstituted cyclopropanes allows the generation of tetrasubstituted cyclopentanes (products **103i** and **103j**).

Following this work, Montgomery's group has studied a nickel catalyzed [3+2] cycloaddition process by the development of an intramolecular nickel-catalyzed three-component coupling of enals alkynes and triethyl borane in protic solvents. It was demonstrated that a Ni(0) catalyst promotes the oxidative cyclization of conjugated aldehyde **104** and alkyne **105** to metallacycle **106** (*Scheme 2.6*).



Scheme 2.6: Intermolecular Nickel-Catalyzed Three-Component Coupling [3+2] Cycloaddition Cycle

The addition of methanol (Brønsted acid) to a solution of **106** presumably allows protonation of the enolate to afford vinyl nickel species **107**. The addition of the alkenyl nickel bond to the resulting carbonyl affords nickel alkoxide **108**, which undergoes further protonation to afford product **109**. Et_3B reducing agent converts Ni(II) alkoxide **110** back to Ni(0). The resulting catalytic process involving tributylphosphine as ligand and a methanol/THF cosolvent system allowed desired reductive cycloadditions. A wide range of conjugated enals underwent catalytic, diastereoselective and regioselective [3+2] cycloadditions with 1-phenylpropyne (*Scheme 2.7*). The reaction tolerates α and β monosubstituted enals (products **109a-c**). α,β-disubstitution was tolerated with both alkyl and aryl substitution patterns (products **109d** and **109e**). A bicyclic compound was prepared by a participation of a cyclic enal in the process (product **109f**). Silyl alkynes (products **109g-i**), terminal alkyne (product **109j**), diaryl alkynes (products **109k and 109l**) and dialkyl alkynes (product **109m**) were suitable patterns in the reaction.

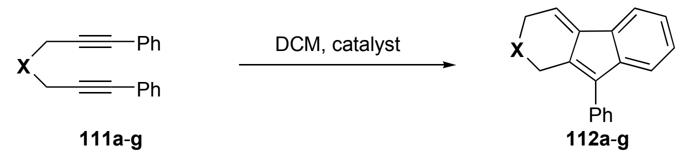


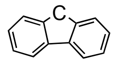
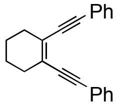
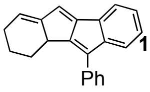
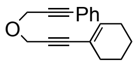
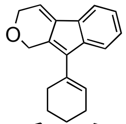
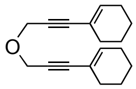
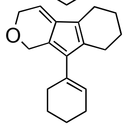
R_1	R_2	R_3	R_4	R_5	product (% yield, dr)
H	H	Ph	Me	Ph	**109a** (56, 81:19)
H	H	propyl	Me	Ph	**109b** (85, 87:13)
Me	H	H	Me	Ph	**109c** (80, 90:10)
Me	H	Ph	Me	Ph	**109d** (57, 81:11:8)
Me	H	Me	Me	Ph	**109e** (75, 71:17:12)
$^{a}(CH_2)_4$	H	/	Me	Ph	**109f** (68, 87:13)
Me	H	H	TMS	Ph	**109g** (60, 82:18)
Me	H	H	TMS	PMP	**109h** (69, 90:10)
H	H	propyl	TMS	PMP	**109i** (78, 92:8)
H	Me	Me	H	Ph	**109j** (60)
Me	H	H	Ph	Ph	**109k** (30, 84:16)
H	H	propyl	Ph	Ph	**109l** (74, 82:18)
H	H	propyl	Et	Et	**109m** (64, 63:37)

[a] R_1=R_3=Cyclic substituent

Scheme 2.7: Scope of Enal and Alkyne Structure in [3+2] Cycloaddition

Liu et *al.* recently reported the discovery of a new intramolecular [3+2] cycloaddition of unactivated arenyne-yne (or enyne-yne) functionalities with gold catalysts[63]. Most reactions were achieved with PPh_3AuSbF_6 (2 mol%) in DCM at room temperature except substrates **111h** and **111j** for which $PtCl_2$ (5 mol%) and PPh_3AuOTf (5 mol%) were used respectively (*Scheme 2.8)*. Diynes **111a-g** bearing functional groups such as tosylamide, ester, ketone, phenylsulfonyl, methylene and fluorenyl produced [4.3.0]-cycloadducts in satisfactory yields (products **112a-g**). This methodology allowed the construction of strained bicyclic [3.3.0] framework **112h** in 64% yield *via* $PtCl_2$-catalyzed cycloaddition of **111h**. Bicyclic [4.3.0] products **112i** and **112j** were obtained in 73% and 51% yields respectively.

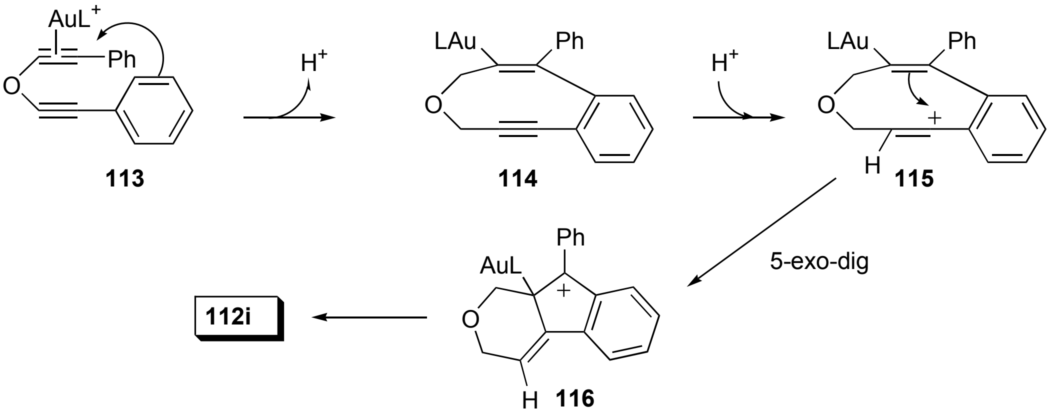


Diynes (111a-m)	time	temperature (T°C)	catalyst	product (% yield)
X=NTs	3	23	[a][AuPPh$_3$]SbF$_6$	**112a** (61)
X=C(CO$_2$Me)$_2$	3	23	[AuPPh$_3$]SbF$_6$	**112b** (90)
X=C(COMe)(CO$_2$Et)	3	23	[AuPPh$_3$]SbF$_6$	**112c** (81)
X=C(COPh)(CO$_2$Et)	3	23	[AuPPh$_3$]SbF$_6$	**112d** (78)
X=C(SO$_2$Ph)$_2$	12	23	[AuPPh$_3$]SbF$_6$	**112e** (81)
X=CH$_2$	5	23	[AuPPh$_3$]SbF$_6$	**112f** (72)
X= 	0.5	23	[AuPPh$_3$]SbF$_6$	**112g** (80)
 **111h**	5	100	[b]PtCl$_2$	 **112h** (64)
 **111i**	3	23	[AuPPh$_3$]SbF$_6$	 **112i** (73)
 **111j**	23	100	[c][AuPPh$_3$]OTf	 **112j** (51)

catalyst loading with L=PPh$_3$: [a] 2 mol% of LAuCl/AgSbF$_6$ (DCM), [b] 5 mol% of PtCl$_2$ (toluene), [c] 5 mol% of LAuCl/AgOTf (dioxane)

Scheme 2.8: Catalytic Intramolecular [3+2] Cycloaddition of Diynes

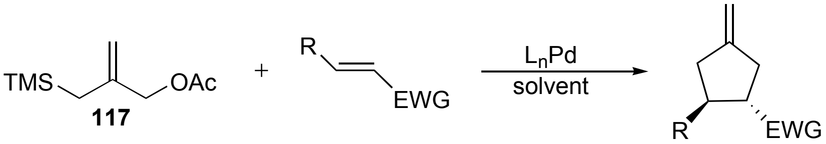
Liu and coworkers speculated a mechanistic study showing the preferable [3+2] pathway of the gold-based catalysis (*Scheme 2.9*).



Scheme 2.9: [3+2] Cycloaddition Pathways the Gold-Based Catalysis

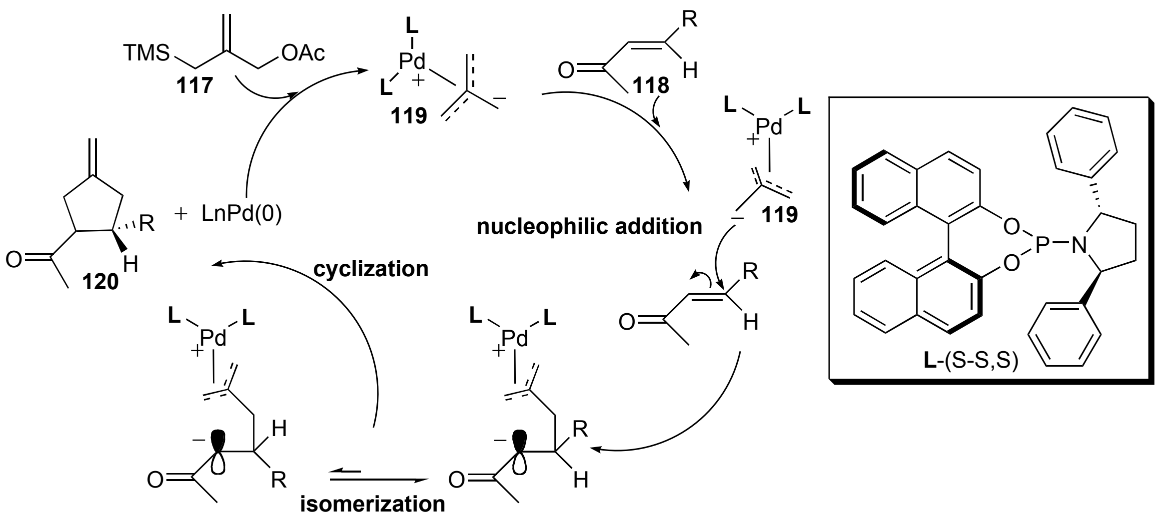
It appeared that formation of product **112i** from suggests that this cyclization is initiated by nucleophilic attack of the aromatic substitutent of intermediate **113** at its Au(I)-activated π-alkyne moiety. This would produce vinyl-gold(I) intermediate **114** with loss of a proton. It was proposed that the electron-rich AuL fragment of species **114** greatly favors protonation at the alkyne functionality to generate vinyl-cationic intermediate **115**. Such cationic resonance leads to a 5-*exo-dig* cyclization of species **115** to give diphenyl carbocation **116**, ultimately leading to formation of major isomer **112i**.

In 1979, Trost et *al.* first reported[64] that Pd-trimethylenemethane (TMM) complexes generated from 3-acetoxy-2-trimethylsilyl-methyl-1-propene **117** and catalytic palladium react with electron-deficient olefins to produce *exo*-methylene-cyclopentanes (*Scheme 2.10*).



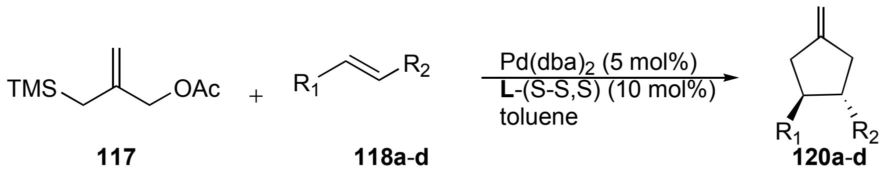
Scheme 2.10: Palladium-Catalyzed [3+2] Cycloaddition of *exo*-Methylene-Cyclopentanes

It was shown that this palladium-catalyzed [3+2] TMM cycloaddition reaction is highly chemo-, regio- and diastereo-selective process[65,66]. However, the formation of stereogenic centers in the cycloadducts produced in this chemistry has mainly been limited to the use of chiral auxiliaries[67]. In 2006, Trost's group suggested a palladium-catalyzed asymmetric [3+2] TMM cycloaddition reactions[68] illustrated in the proposed mechanism (*Scheme 2.11*). The formation of the zwitterionic intermediate **119** is generated by insertion of L_nPd into the C-O bond **117** followed by attack of the displaced acetate anion onto the trimethylsilyl group, which deposits its electrons onto TMM fragment[69]. The enantiodetermining step is most likely the initial nucleophilic attack. This step occurs distal to the set of coordinated chiral phosphoramidites **L**-(S-S,S).



Scheme 2.11: Palladium-Catalyzed Asymmetric [3+2] Cycloaddition Mechanism

Using the optimized catalytic conditions, scope of the TMM accepting olefin was examined (*Scheme 2.12*).



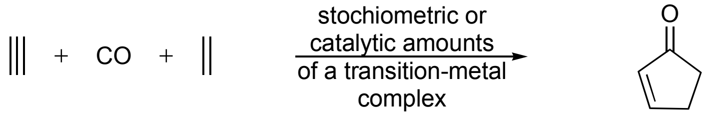
R_1	R_2	temperature (°C)	product (% yield)	ee (%)
Ph	CO_2Me	23	**120a** (81)	58
Ph	CO_2Me	0	**120a** (80)	62
Ph	COMe	23	**120b** (76)	72
Ph	COMe	-25	**120b** (63)	82
$(CH_2)_4CH_3$	COMe	23	**120c** (72)	73
$(CH_2)_4CH_3$	COMe	-25	**120c**(79)	84
Ph	CN	0	**120d** (78)	58

Scheme 2.12: Scope of Palladium-Catalyzed [3+2] TMM Cycloaddition Reactions

All cyclopentane products **120a-d** were formed in >19:1 *trans*:*cis* selectivity. The reaction of methyl cinnamate **118a** with **117** at 0 °C rather than 23 °C increased the enantioselectivity from 58 to 62%. Cooling the reaction to -25 °C failed to produce more than 5% of **120a**. Employing the more reactive (*E*)-benzalacetone **118b** allowed the reaction to be performed at -25 °C, which increased selectivity to 82% ee. Lowering the reaction temperature to -50 °C failed to produce any noticeable product. The selectivity of this reaction does not rely on the presence of the phenyl group as *trans*-nonenone **118c** reacts with yields and enantiomeric excesses that are comparable to those of benzalacetone **118b**. Nitriles **118d** were compatible functionalities and gave enantioselectivities comparable to those of ester **118a**.

III-Pauson-Khand Reaction

The Pauson-Khand reaction (PKR) is a transition-metal-mediated carbon-carbon bond forming reaction that converts an alkyne, alkene and carbon monoxide into a cyclopentenone (Scheme 3.1).

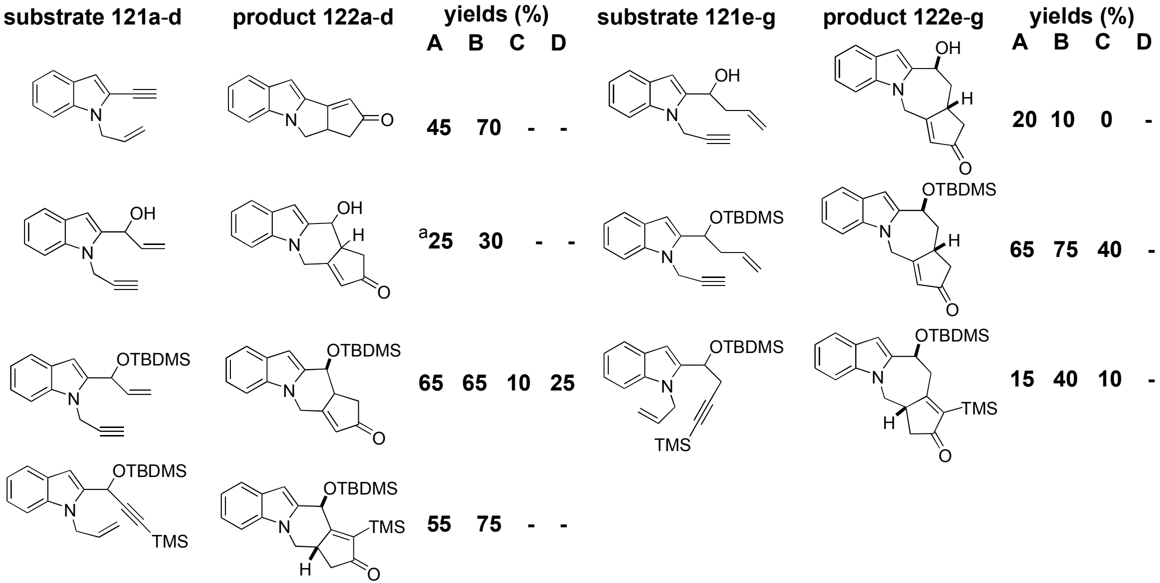


Scheme 3.1: The Pauson-Khand Reaction

PKR has become an important tool in the synthesis of natural products containing cyclopentenones[70]. In the past years, extensive studies have widened the scope of this reaction to many substrates. Skeletons derived from 1-hepten-6-yne and 1-octen-7-yne are well-known substrates, and several aromatic enynes have also given good results[71]. This improvement in scope is due, in part, to gains in reactivity both in the catalytic[72] and the stochiometric process with the introduction of new promoters and reaction conditions[73]. Among the promoters of this reaction, amine *N*-oxides and cyclohexylamine are the most popular. Recently, Zeolites have also been introduced as efficient promoters for catalytic and stochiometric versions of Pauson-Khand reactions[74]. New metal catalysts, such as $Co_4(CO)_{12}$[75] and different complexes including metals such as ruthenium[76], titanium[77], iridium[78], rhodium[72] and even palladium[79] have been used with success.

III-1-Stochiometric Version

Perez-Castells et *al.* have focused their research on the use of aromatic substrates in PKR. They recently described the first stoichiometric version of PKR adapted to indole chemistry[80]. Using 1,2-enyno-indoles **132a-g** as starting materials, construction of 5, 6 and 7 membered tetracyclic products **133a-g** was achieved (*Scheme 3.2*).

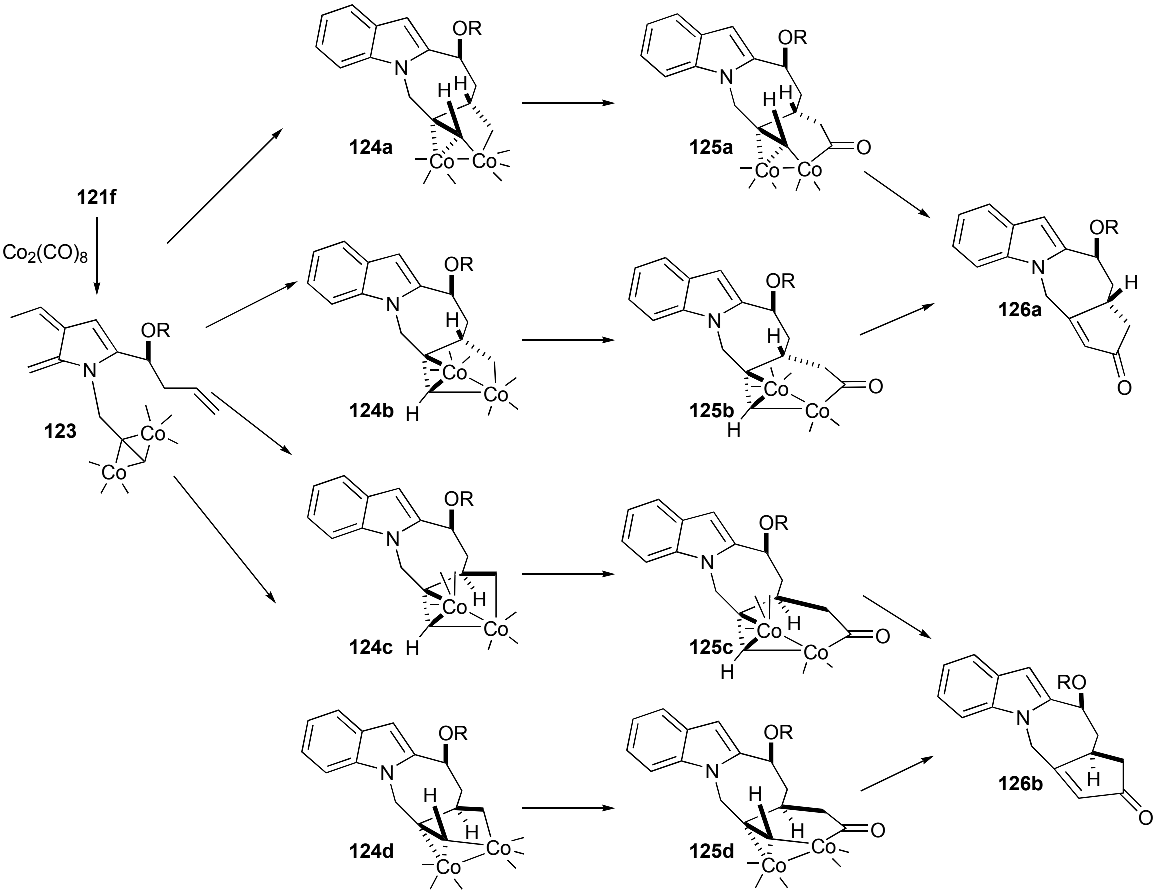


^{a} 1:1 ratio of diastereomers **122b** and **122b'** (*Scheme 3.4*) with method **A** and **B**

condition	promoter	$Co_2(CO)_8$ (eq)	temperature (^oC)
A	Me_3NO/4 Å mol. sieves	1.1	0
B	4 Å mol. sieves	1.1	110
C	/	1.1	110
D	Me_3NO	1.1	0

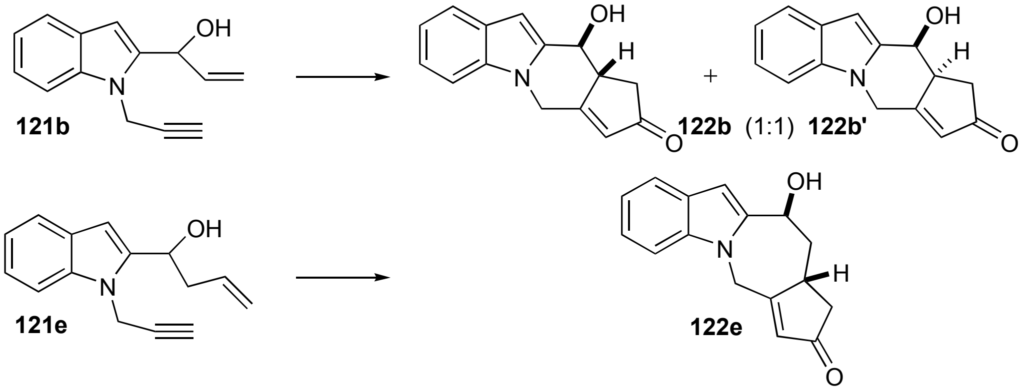
Scheme 3.2: Synthesis of 1,2-Fused Tetracyclic Indole Derivatives

The stochiometric conditions A and B use molecular sieves as promoters. Conditions C and D are used in some cases for comparison purposes with A and B respectively. Preliminary result with compound **121a** gave the cyclopenta-indole **122a** in good yield (condition B). Substrate **121b** only gave a moderate yield of Pauson-Khand product **122b** that was obtained as a 1:1 mixture of diastereomers **122b** and **122b'**. But when **121b** was converted into its TBDMS derivative **121c**, this compound gave readily the polycyclic structure **122c** in good yield (conditions A and B) and moderate yields (conditions C and D), thus underlining the positive effect of molecular sieves in this reaction. TMS Substituted alkyne of 1,2-enyno-indole **121d** gave similar product yield than unsubstituted alkyne **121c**. Compound **121e** reacted with very low yield to give only one diastereomer of the cyclohepta-indole **122e**. Conversely, TBDMS protected alcohol **121f** gave the desired product **122f** with the best yield. Both the planarity of the indole nucleus and the buttressing effect of the OTBDMS group are probably responsible for this result. TMS substituted cyclohepta-indole **122g** was obtained in a much lower yield than cyclohexa-indole **122d**. Note that any substrates with bulky TBDMS group always produced a single diastereomer in which this group is at the same side as the hydrogen at the fusion. In an effort to rationalize the diastereoselectivity of this methodology, Pericas et *al.* depicted the possible intermediates[81] in the formation of cycloadduct **121f** (*Scheme 3.3*).



Scheme 3.3: Possible Intermediate of **121f**

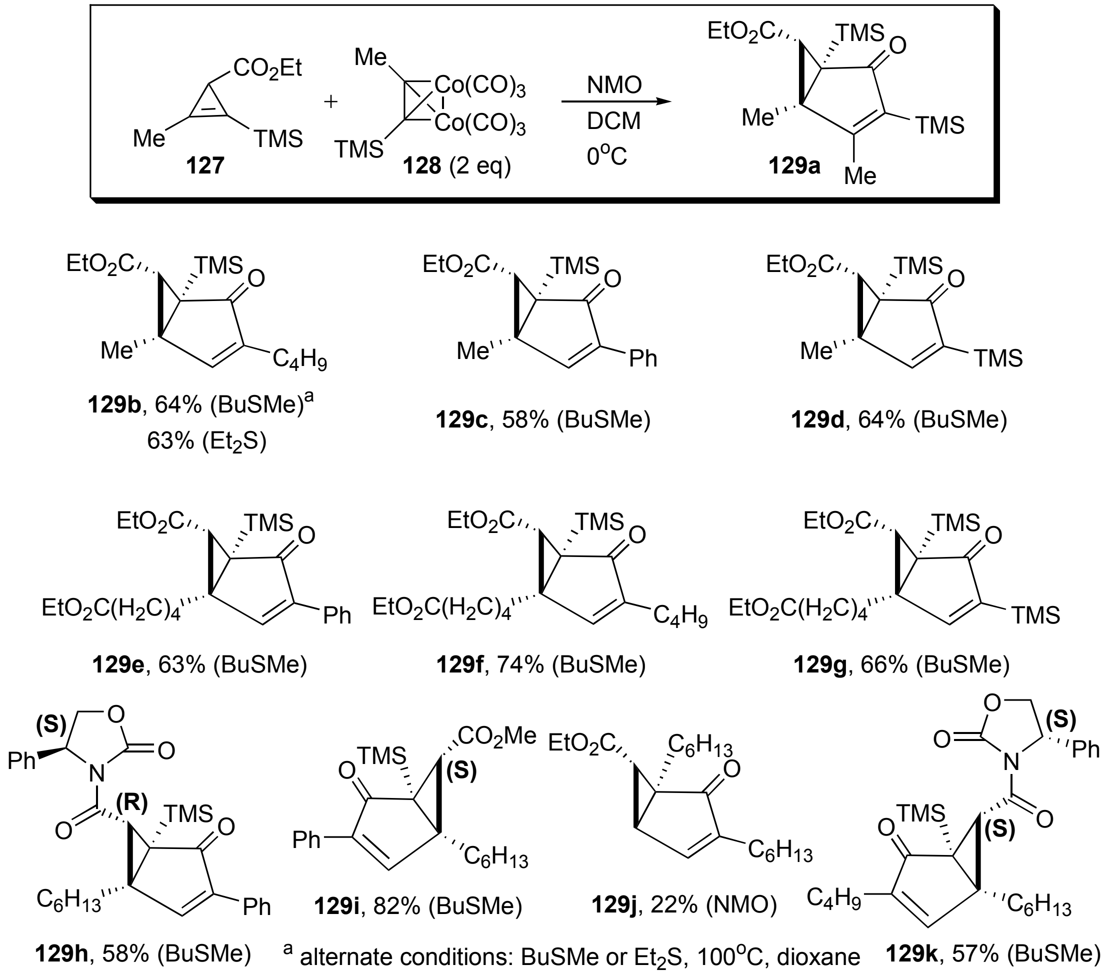
The complex **123** can give, upon insertion of the olefin fragment, intermediates **124a-d**. Insertion of CO would give complexes **125a-d**. Intermediates **125a** and **125b** and **125c** and **125d** would lead respectively to isomers **126a** and **126b**. Complex **124a**, which minimizes the interaction of the substituent OR with the metalacycle, would be the most stable, giving the observed product **126a**. This diastereoselection may have its origin in the bulky protecting group used, as it does not happen with the parent alcohol. Other effects such as the coordination of lone pairs of the oxygen with the metal cannot be discarded. If the stereochemical result of the reaction of **121b** and **121e** are compared, the hydroxy group present in these two substrates may act as directing group as in the directed PKR (*Scheme 3.4*).



Scheme 3.4: Comparison on the diastereoselectivity of **121b** and **121e**

In the case of **121e**, the distance for the interaction of the hydroxy would be adequate to give a more rigid intermediate that would enhance the diastereoselectivity. In **121b**, this distance is too short to allow simultaneous coordination of the olefin and the hydroxyl group[81].

It was recognized shortly after the discovery of the PKR that strained alkenes were usually “the best substrates” for the reaction. Possessing a remarkable strain energy (55 kCal/mol)[82] and unusual reactivity, cyclopropenes seem to be excellent substrates for intermolecular PKRs, but few examples are in the literature[83-85]. Fox et *al.* reported a diastereoselective intermolecular PKR of chiral cyclopropenes where reactions proceed with exceptional efficiency[86] in the presence of sulfide[87] or *N*-oxide[88,89] promoters. The well-defined chiral environment of cyclopropenes has a powerful influence on diastereoselectivity such that a single *exo*-diastereomer-cyclopentenone was isolated in each of the reactions (*Scheme 3.5*).



127 + **128** (2 eq) → **129a**

129b, 64% (BuSMe)[a] 63% (Et_2S)

129c, 58% (BuSMe)

129d, 64% (BuSMe)

129e, 63% (BuSMe)

129f, 74% (BuSMe)

129g, 66% (BuSMe)

129h, 58% (BuSMe)

129i, 82% (BuSMe)

129j, 22% (NMO)

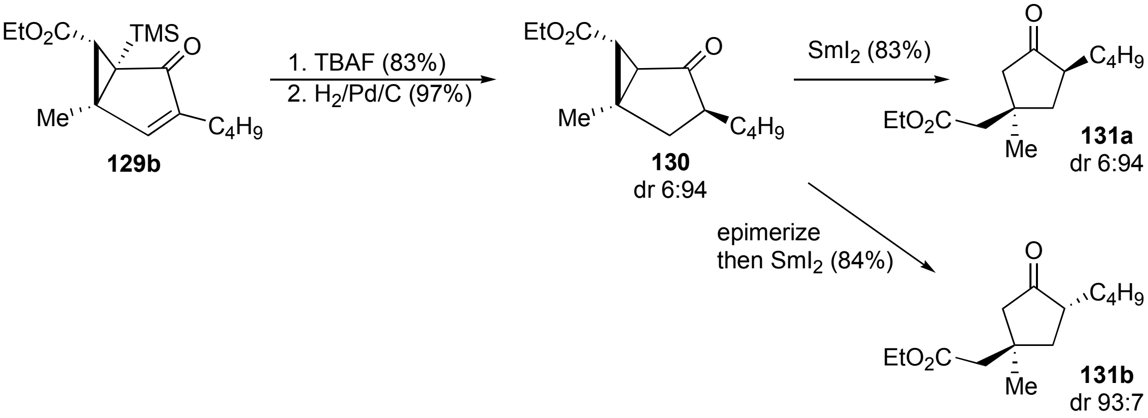
129k, 57% (BuSMe)

[a] alternate conditions: BuSMe or Et_2S, 100^oC, dioxane

Scheme 3.5: PKR of Chiral Cyclopropenes

2-Silyl-3-alkyl cyclopropene-1-carboxylate cyclo-products **129a-j** gave good yields for the Pauson-Khand chemistry. Ethyl 2-hexylcyclopropene-1-carboxylate gives the complementary product **129k** but the reaction was less efficient (22% isolated yield). The best results were obtained when a large excess of promoter was utilized and while BuSEt was the promoter for most studies. While most of the reactions were carried out with racemic materials, enones **129h**, **129i** and **129k** were prepared in enantiomerically enriched form from readily available, enantiopure starting materials.

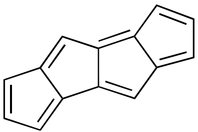
Cyclopropene PKRs provides straightforward access to complex cyclopentenones, the three-membered ring strongly influences the stereochemistry of subsequent reactions of the enone and can be cleaved under mild conditions. For example, desilylation and hydrogenation provides **130** with high diastereoselectivity (*Scheme 3.6*).



Scheme 3.6: Diastereoselective Synthesis of Cyclopentenones

Reductive ring cleavage[85] gives cyclopentanone **131a**, which bears all carbon-quaternary and -tertiary stereocenters. The complementary diastereomer **131b** can be obtained by epimerizing **130** prior to SmI_2 reduction.

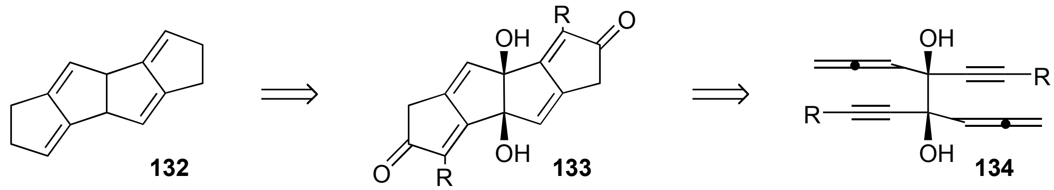
Dicyclopenta[a,f]pentalene **132** is an highly unstable compound whose synthesis has never been reported, but has been discussed only from a computational point of view (*Scheme 3.7*).



132

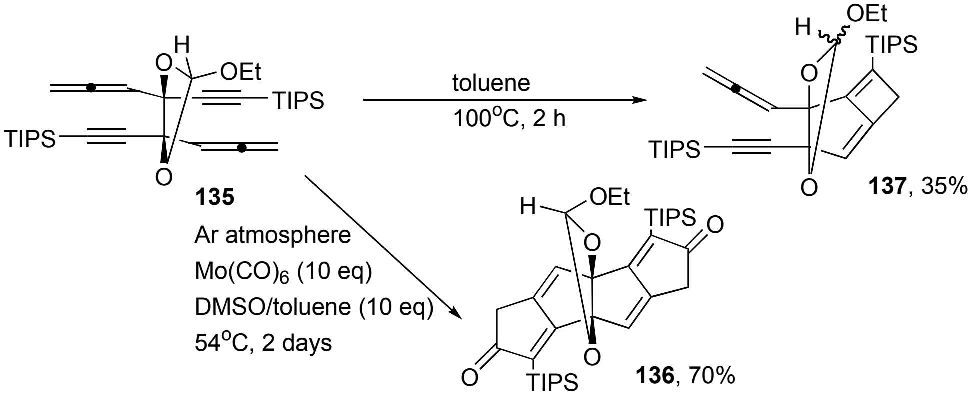
Scheme 3.7: Dicyclopenta[a,f]pentalene **132**

Controversy exists as to whether this 14π cross linked annulenes is delocalized, exhibit aromatic “Hückel” type stability, or exists as nonalternant hydrocarbons that behave as highly reactive olefins. If cyclopentapentalenes such as **132** exhibit aromatic character as postulated, the resonance energy of **132** has been computed to be 1.2 kcal/mol. Cook et *al.* proposed a synthesis for the 14π-system **132** based on a molybdenum carbonyl mediated tandem allenic PKR[90] of bisallene-bisalkyne **134** which would form the [5.5.5.5] tetracyclic species **133** (*Scheme 3.8*).



Scheme 3.8: Retrosynthetic Analysis *via* bisallene **134**

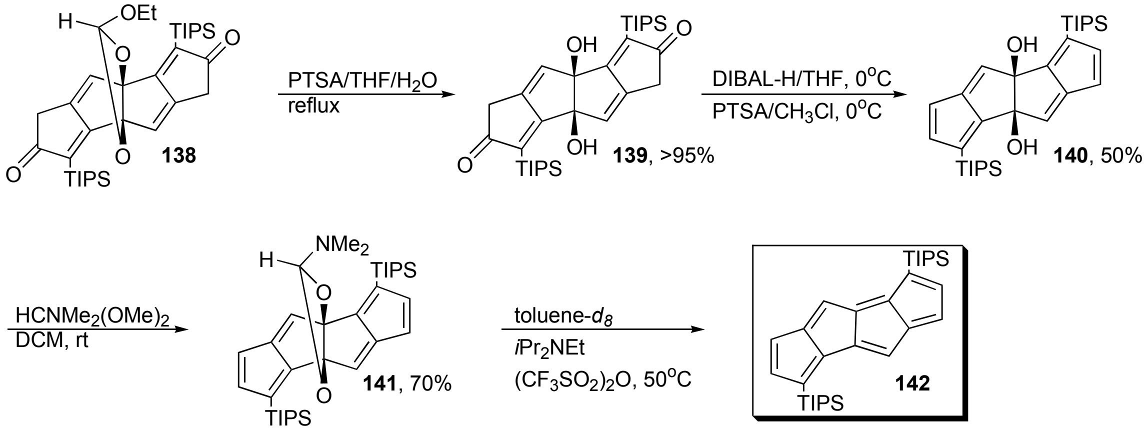
Preliminary results on the key Pauson Khand step reaction have shown that when bisallene **146** was heated at 100 ºC in toluene for a few hours in the absence of $Mo(CO)_6$, a thermally mediated [2+2] cycloaddition occurred (*Scheme 3.9*).



Scheme 3.9: $Mo(CO)_6$ Mediated Tandem Allenic PKR of **135**

The monocyclized four-membered ring bicycle **137** was the major product formed (35% yield) and species **136** was not detected. To promote the tandem PKR at the expense of the thermal [2+2] process, a large excess of $Mo(CO)_6$ was heated in toluene at lower temperature (54 ºC) to form a saturated solution, which provided a higher concentration of Mo-alkyne complex. These optimized conditions gave the desired tetracycle **136** in

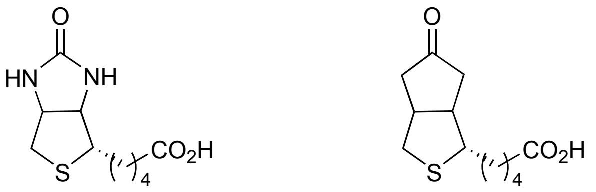
70% yield and species **137** was not detected. Cyclic ortho ester acetal **138** was heated in aqueous THF solution to a gentle reflux to provide the tetracyclic diol **139** almost quantitatively (*Scheme 3.10*).



Scheme 3.10: Synthesis of 14π cross-linked annulenes **142**

Reduction of the two ketones in **139** to alcohol by DIBAL-H, which followed by an elimination process under acidic media produced species **140** in 50% yield. Due to stability issue, diol **140** was immediately converted into the amino-acetal **141**, which when mixed with diisopropyl ethylamine and trifluoromethane sulfonic anhydride in toluene-d_8 provided the desired 14π cross-linked annulenes **142**. To date, this 14π system **142** has survived only in solution. However, analysis indicated that species **142** demonstrated aromatic delocalization.

Ting et *al.* recently reported the synthesis[91] of a ketone analogue of biotin, ketone biotin **143b** (*Scheme 3.11*).

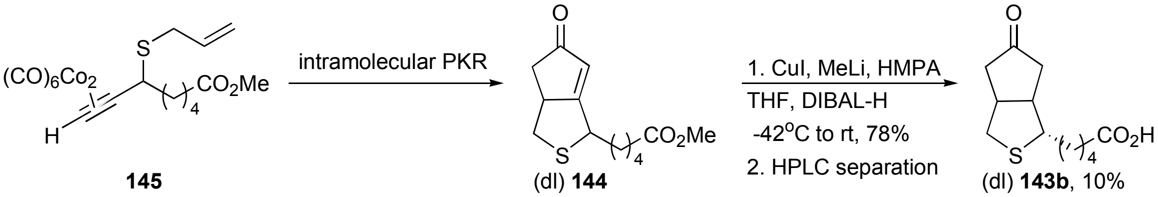


biotin

(dl) **ketone biotin 143b**

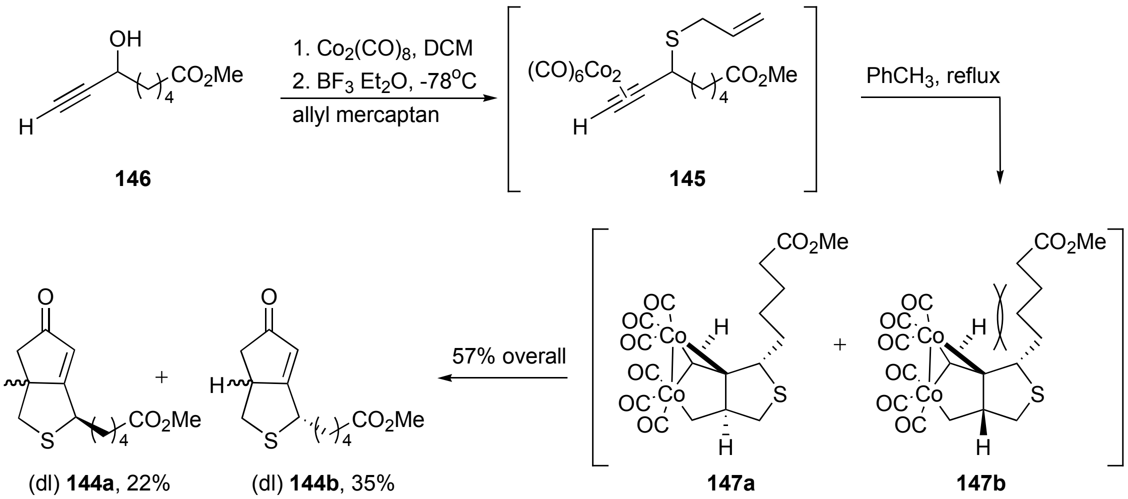
Scheme 3.11: Biotin and Ketone Biotin **143b**

This compound is ligated site specifically to a 15-amino acid receptor peptide (AP) by the *Escherichia coli* enzyme biotin ligase (BirA)[92]. Through this ketone, AP-tagged cell surface proteins can be labeled with hydrazide or hydroxylamine bearing biophysical probes in a two-step process. The synthetic approach of the ketone biotin **143b** is based on the intramolecular PKR of **145** that gives the α,β-unsaturated bicyclic ketone **144**. Reduction of the alkene with an *in-situ* generated copper hydride complex provided the ketone biotin **143b** in 10% yield after HPLC separation (*Scheme 3.12*).



Scheme 3.12: Synthetic Route of **143b**

The synthesis of the Pauson-Khand precursor **145** takes place in three distinct steps. First is the formation of the hexa-carbonyl-dicobalt complex of **146** by reaction with octa-carbonyl-dicobalt in DCM (*Scheme 3.13*).

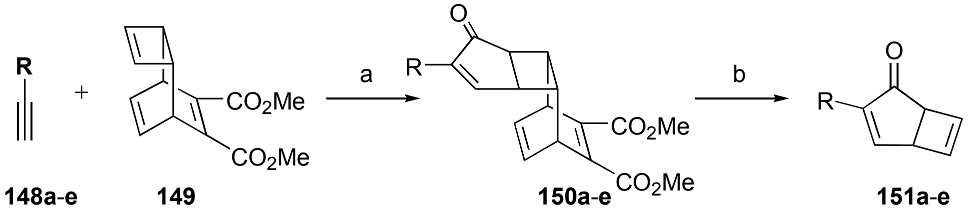


Scheme 3.13: Synthesis of Ketone Biotin **144b**

Next is the complexation of the alcohol to BF_3 Et_2O, finally followed by nucleophilic displacement with allyl mercaptan. Pauson-Khand cyclization precursor **145** was not isolated due to air stability issue. The optimized refluxed Pauson-Khand reaction in toluene provides 57% overall yield of a mixture of diastereomers **144a** (22% yield) and **144b** (35% yield). The cobaltacyclic Pauson-Khand intermediate **147b** that places the valeric acid side chain on the more sterically congested concave face of the bicyclic ring structure is disfavoured at 70 °C compared to **147a**. However, increase of the reaction temperature enhances the formation of **147b** (35% yield) over **147a** (22% yield). The reduction of the alkene was performed on the above mixture providing 10% yield of ketone biotin **147b** after HPLC separation (*Scheme 3.12*).

III-2-Catalytic Version

Good progress has been made in the last three to five years in the fields of catalysis and asymmetric catalysis of PKR using a variety of transition metal and ligand, almost all the work reported has been based on intramolecular substrates. Traditionally, the intermolecular PKR has been dominated by strained alkenes[93,94] such as norbornene, norbornadiene[83] and cyclopropene[86] used as precursor with various alkynes. Gibson et *al.* recently reported[95] a new catalytic intermolecular PKR where cyclobutadiene the protected **149** and alkynes **148** give PK products **150**, which under retro-Diels-Alder reaction produce highly functionalized bicyclic products **151** (*Scheme 3.14*). The use of 1.5 equivalents of **149a-d** and alkyne **148a-d** (1 eq) considerably raised the yields of the PKR products **150a-e** from moderate to good compared to the equimolar reaction. Protected cyclobutadiene **149e** (10 eq) and **148e** (1 eq) were required to reach good yield of bicyclic product **150e**. Reactions occurred selectively at the most strained double bond and work-up led to the isolation of a single diastereomer (products **150a-e**). The thermal retro-Diels-Alder reaction of **150a-e** was achieved at 205 °C under a vacuum of 6 Torr for 1h to give 3-substituted bicyclo[3.2.0]hepta-3,6-diene-ones **151a-e** in very good yields.



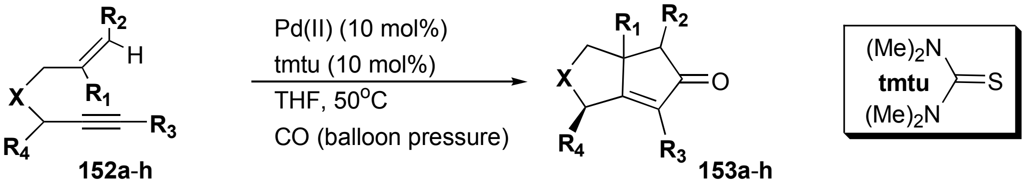
148a-e **149** **150a-e** **151a-e**

alkyne, R	**149** (eq)	**PK product** **150 yield (%)**	**Retro-Diels-Alder product** **151 yield (%)**
148a R=Ph	1.5	77	92
148b R=hex	1.5	85	90
148c R=CH_2OTBDMS	1.5	60	90
148d R=CH_2NHBoc	1.5	75	90
148e R=TMS	10.0	86	85

^{a} $Co_2(CO)_8$ (5 mol%), CO (1 atm), DME, 75°C, 4h, **148** (0.5 mmol); ^{b} 205°C, 6 Torr, 1h, **150** (0.35 mmol)

Scheme 3.14: Catalytic Intermolecular PKR of **149** with Alkynes **148** and thermolysis of PK products **150**

In view of a lack of any precedents in the utilization of palladium as a catalyst in the PKR, Yang et al. recently reported the use of thiourea derivative tmtu as ligand in the Pd-catalyzed intramolecular PKR[79]. The optimized 1:1 ratio of $PdCl_2$: tmtu-catalyzed reaction was applied to a broad range of substrates in THF at 50 °C (*Scheme 3.15*).



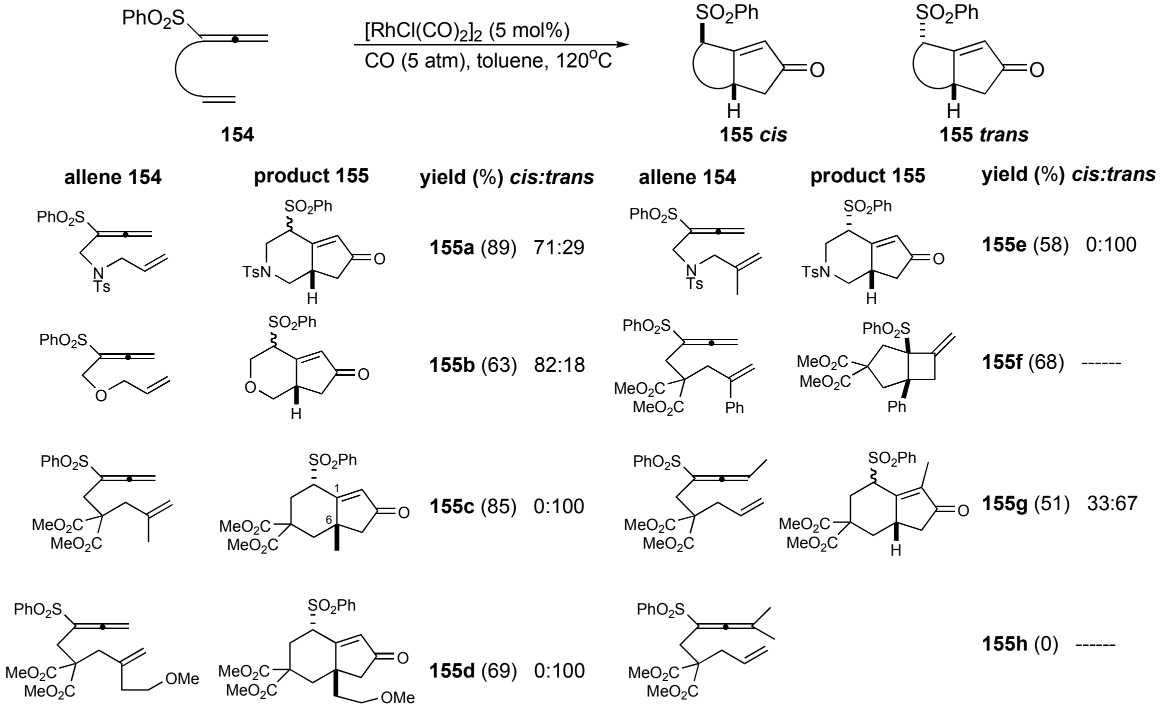
152a-h **153a-h**

substrate R_1	R_2	R_3	R_4	X	time (h)	**153 yield** (%)
Me	H	H	H	$C(CO_2Me)_2$	48	**153a** (NR)
H	H	Ph	H	$C(CO_2Me)_2$	24	**153b** (24)
H	CH_2OBn	H	H	O	48	**153c** (31)
H	Ph	H	H	O	/	**153d** (SM decomposed)
H	H	CH_2OTPS	H	NTs	36	**153e** (89)
H	H	Ph	H	NTs	48	**153f** (58)
H	CH_2OBn	C_5H_4-4-NO_2	H	NTs	48	**153g** (80)
H	H	C_5H_4-4-NO_2	n-C_5H_{11}	NTs	36	**153h** (96)

Scheme 3.15: Pd-tmtu-Catalyzed Intramolecular PKR

To this end, allylpropargyl malonates **152a** and **152b** were found to be either non-reactive or to suffer from low conversion under the conditions used. When allylpropargyl ethers **152c** and **152d** were investigated, a similar trend of reactivity was observed. However, allylpropargyl amines **152e-h**, bearing substituents on the alkyne, the alkene moieties and/or α- of the amine functionality gave good to excellent yields (products **153e-h**). As these substrates are fairly stable under the reaction conditions, the desired coupling yields could be improved by increasing the reaction time. Importantly, contrary to popular thought[96], the alkynes **152g** and **152h** bearing an electron-deficient substituent gave better results than other members of the family. Last, it is notable that when substrates **152g** and **152h** were employed in the cyclization, only one diastereomer was obtained. Although the thiourea-Pd complex can significantly accelerate the course of PKR, its catalytic mechanism is unclear. Based on the available structural information for Pt-tmtu[97], it is speculated that catalysis is taking place with the ligand bound to the metal centre in consideration of the required 1:1 ratio of $PdCl_2$ with tmtu.

Mukai et al. recently described the novel $[RhCl(CO)_2]_2$-catalyzed intramolecular PKR[98] of 3-phenylsulfonyl-1,2,7-octatrienes **154** leading to the formation of the bicyclo[4.3.0]non-1(9)-en-8-one **155**, in which the distal double-bond of the allenyl moiety exclusively served as a π component (*Scheme 3.16*). The scope of the catalyzed ring closing reaction was investigated with $[RhCl(CO)_2]_2$ (5 mol%), under CO (5 atm) and at 120 °C in toluene for several 1,2,7-octatrienes **154**. The allenenes **154a** and **154b**, having a heteroatom on the alkyl tether, consistently produced the corresponding bicyclic compound **155a** and **155b** in good yields. The 6-alkyl-bicyclo[4.3.0]nonenone skeletons **154c-e** could be constructed from **154c-e** in acceptable yields. Similarly, trisubstituted allenyl moiety **154g** produced **155g** in 51% yield. In contrast, phenyl derivative **154f** was transformed into the unexpected bicyclo[3.2.0]heptane derivative **155f** in 68% yield. Based on Padwa's work[99], the formation of **155f** would be interpreted by the thermal [2+2] cycloaddition between the proximal π-bond of the allenyl moiety and the terminal olefin. In fact, compound **155f** was obtained by simply heating in toluene without the Rh(I)-catalyst. Last, the tetrasubstituted allene derivative **154h** was found to be an inadequate substrate for this PKR and the starting material was recovered in 50% yield.



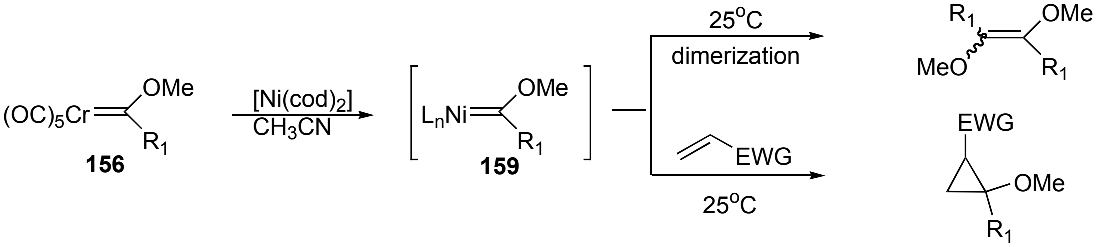
Scheme 3.16: $[RhCl(CO)_2]_2$-Catalyzed PKR of 1,2,7-Trienes **154**

IV-Fischer Carbene Complex

The preparation of the first carbene complex was reported by E. O. Fischer[100] in 1964. Complexes of this kind with a metal-carbon double bond containing a central metal in a low oxidation state and hetero-atom(s) on the carbene carbon have since been described as Fischer carbene complexes. One of the most important features[101] of Fischer carbenes is the pronounced electron-deficiency on the carbene carbon atom due to the strongly electron-withdrawing pentacarbonylmetal fragment. This enhances the C-H acidity of an alkyl adjacent to the carbene carbon even beyond that of the α-C-H acidity in standard carbonyl compounds. Along the same lines, α,β-unsaturated, alkenyl and alkynyl-substituted Fischer carbene complexes are much more reactive towards any kind of nucleophile compared to α,β-unsaturated carbonyls, amides and thioesters. With these characteristics, Fischer carbene complexes have become important tools in the methodology of organometallics for organic synthesis.

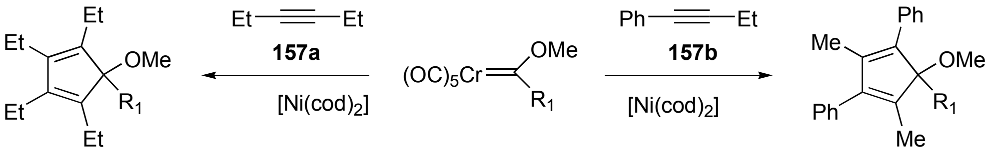
IV-1-[2+2+1] Cycloaddition

Barluenga's group and others have recently studied the transmetalation reaction[102] that is a simple transfer of a carbene ligand from one metal centre to another. This process appears as a convient route to access new carbene complexes of late transition metals such as Cu(I)[103], Pd(0) [104] and Rh(I)[105]. This methodology also proved to be useful for the generation of nickel(0) alkoxycarbene complexes **159** from the corresponding chromium complexes **156** and [Ni(cod)$_2$] (*Scheme 4.1*).



Scheme 4.1: Nickel(0) Alcoxycarbene complex **159**

The existence of the species **159** is validated by the room temperature thermal dimerization of the carbene ligand and its capability to cyclopropanate electron-poor alkenes also at room temperature[106]. Barluenga et al. reported that the reaction of chromium carbene complexes **156** with internal alkynes in the presence of [Ni(cod)$_2$] proceeds *via* a new [2+2+1] cycloaddition pathway[107]. It is worthwhile noting that the mode of assembling of both alkyne units into the resulting cyclopentadiene depends primarily on the electronic demand of the alkyne. Chronium carbene complex **156**, alkynes **157** and [Ni(cod)$_2$] were mixed in a 1:2.5:1 ratio and formed the three-component [2+2+1] cycloadducts **158** in good yields - a single isomer was isolated in each case (*Scheme 4.2*).



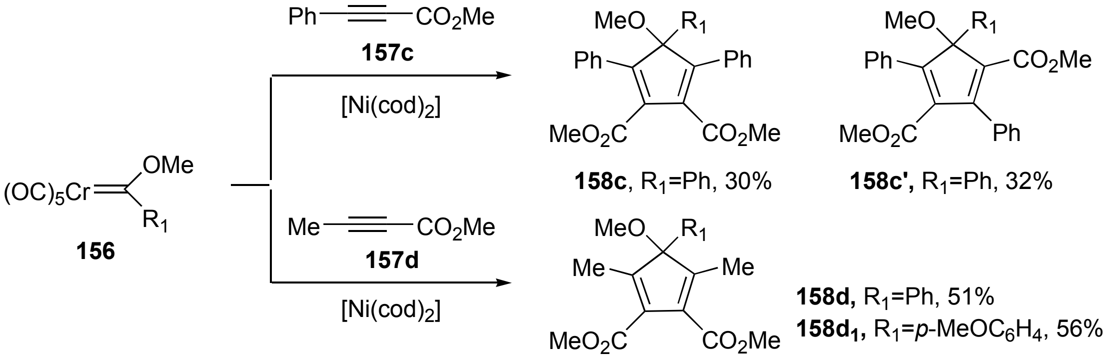
158a, R_1=Me, 52%

156

158b, R_1=Ph, 48%
158b$_1$, R_1=2-furyl, 51%

Scheme 4.2: [2+2+1] Cycloaddition of Cr-Carbene complex **156** with internal alkynes **157a** and **157b** in the presence of [Ni(cod)$_2$]

The cyclization of the carbene complex **156** and methyl phenylpropynoate **157c** resulted in the formation of a mixture of symmetrical and unsymmetrical cyclopentadienes **158c** and **158c'** in 62% yield (*Scheme 4.3*).



156

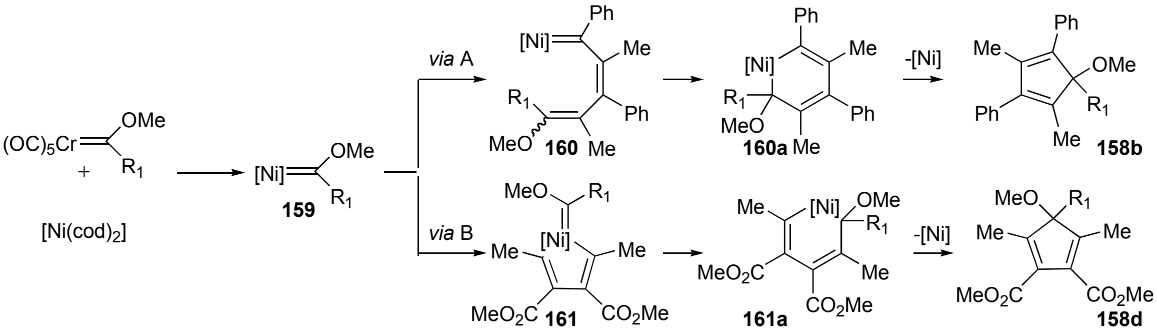
158c, R_1=Ph, 30%

158c', R_1=Ph, 32%

158d, R_1=Ph, 51%
158d$_1$, R_1=*p*-MeOC$_6$H$_4$, 56%

Scheme 4.3: [2+2+1] Cycloaddition of Cr-Carbene complex **156** with internal alkynes **157c** and **157d** in the presence of [Ni(cod)$_2$]

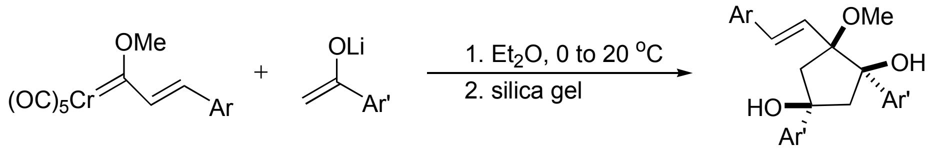
Cyclization between **156** and methyl 2-butynoate **157d** resulted in the regioselective formation of the cycloadducts **158d** and **158d$_1$**. Since a divergent regioselectivity is observed depending on the nature of the alkyne **157**, a common mechanism cannot operate (cyclopentadienes **158b** *vs* **158d**). However, a tentative rationale for alkynes **157b** and **157d** is outlined (*Scheme 4.4*).



Scheme 4.4: Postulated [2+2+1] Cycloaddition Mechanism

The chromium-nickel exchange to form the nickel carbene species **159** is assumed to be the common initial step. Two consecutive regioselective insertion reactions of **157b** (*Scheme 4.2*) into the nickel-carbon double bond would generate the 1-nickela-1,3,6-haxatriene **160**, which would produce the final cycloadduct **158b** upon cyclization to the nickelacycle **160a** and Ni(0) reductive elimination (*via* A). However, the symmetrical structure of **158d** makes this mechanism unsatisfactory. Based on Montgomery's proposal[108], it is postulated that the formation of the symmetrical product **158d** begins with the oxidative co-cyclization of nickel carbene complex **159** with two alkyne units to form regioselectively the nickelacyclo-pentadiene **161** (*via* B). Then, carbene insertion into the nickel-carbon bond would allow formation of nickelacyclohexadiene **161a**, which would provide product **158d** by reductive elimination.

Over the years, stabilized Group 6 alkenylcarbene complexes have been recognized as valuable buiding-blocks as the C_3 component for the preparation of five-membered carbocycles by a formal [3+2] cycloaddition process with various alkynes and 1,3-dienes[109]. In 2003, Barluenga's group reported a novel formal [3+2] cycloaddition using α,β-substituted (alkenyl)(methoxy)carbene complexes and methyl ketone lithium enolates as a C_2 component[110]. In 2005, the same group described[111] the reaction of β-substituted alkenyl chromium carbene complexes **162** acting as a C_2 component with aryl methyl ketone lithium enolates **163a-c** acting as both C_1 and C_2 components successively (*Scheme 4.5*).



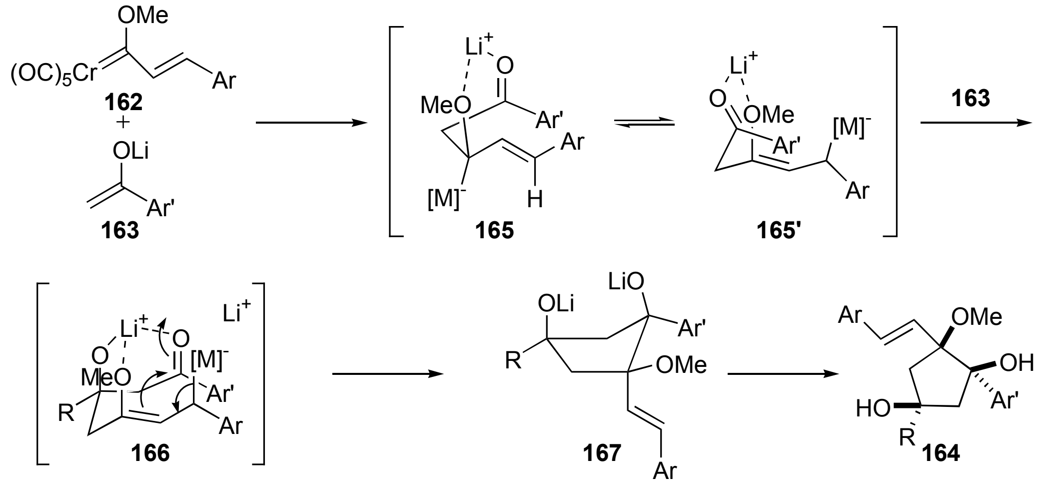
162a-b **163a-c** **164a-e**

carbene complex, Ar	^{a}**enolate, Ar'**	**product yield (%)**
162a Ar=Ph	**163a** Ar'=Ph	**164a** (51)
162a Ar=Ph	**163b** Ar'=4-MeOC_6H_4	**164b** (55)
162a Ar=Ph	**163c** Ar'=2-furyl	**164c** (28)
162b Ar=2-furyl	**163a** Ar'=Ph	**164d** (52)
162b Ar=2-furyl	**163b** Ar'=4-MeOC_6H_4	**164e** (42)

[a] enolates **163** were generated by reaction of the corresponding silyl enol ether with BuLi at 0 °C.

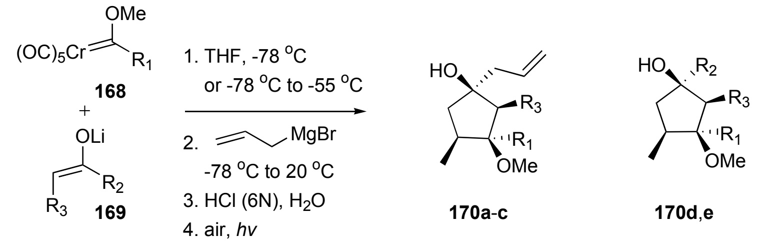
Scheme 4.5: Reaction of Carbene Complexe **162** with Aryl Methyl Ketone Lithium Enolates **163a-c** to Give 1,3-Cyclopentanediol Derivatives **164a-e**

When chromium carbene complexes **162a-b** were treated with two equivalents of aryl methyl ketone lithium enolates **163a-c**, 1,3-cyclopentanediol derivatives **164a-e** were obtained after hydrolysis with silica gel in moderate yields and as single diastereoisomers. Compounds **164a-e** can be considered as the result of a three-component formal [2+2+1] carbocyclization reaction, in which three quaternary stereogenic centers have been generated with complete diastereoselectivity. A tentative mechanism to rationalize the [2+2+1] cycloaddition of β-substituted alkenyl chromium carbene complexes **162** with methyl ketone enolates **163** has been presented (*Scheme 4.6*). It was assumed that a 1,2-addition of the lithium enolates **163** to the carbene complexes **162** occurs first to form intermediate **165**, which could be in equilibrium with **165'** derived from 1,3-migration of the pentacarbonylmetal. The lithium atom could coordinate to the oxygen atoms of the carbonyl and methoxy groups increasing the rigidity of intermediate **165** and **165'** and the electrophilic character of the carbonyl group. Next is the addition of a second lithium enolate species **163** to the carbonyl group of **165** or **165'**, giving the new intermediate **166**. A nucleophilic attack of the γ-carbon atom of the allyl-pentacarbonyl-metallate on the carbonyl group in intermediate **166** would lead to the cyclic system **167**, which after hydrolysis, would give rise to the 1,3-cyclopentadiol derivatives **164**.



Scheme 4.6: Mechanistic Proposal for the Formation of Compound **164**

During the exploration of multi-component Fischer carbene complex reactions applied to five-membered ring formation, Barluenga et *al.* reported[112] a novel one-pot diastereoselective synthesis of highly substituted cyclopentanols from three simple precursors. The successive reaction of chromium carbene complexes **168** with β-substituted lithium enolates **169** and then with allyl magnesium bromide led after hydrolysis with acid and decoordination of the metal center, to 1,2,3,3,4-pentasubstituted cyclopentanols **170**, which were obtained in each case as a single diastereomer (*Scheme 4.7*).

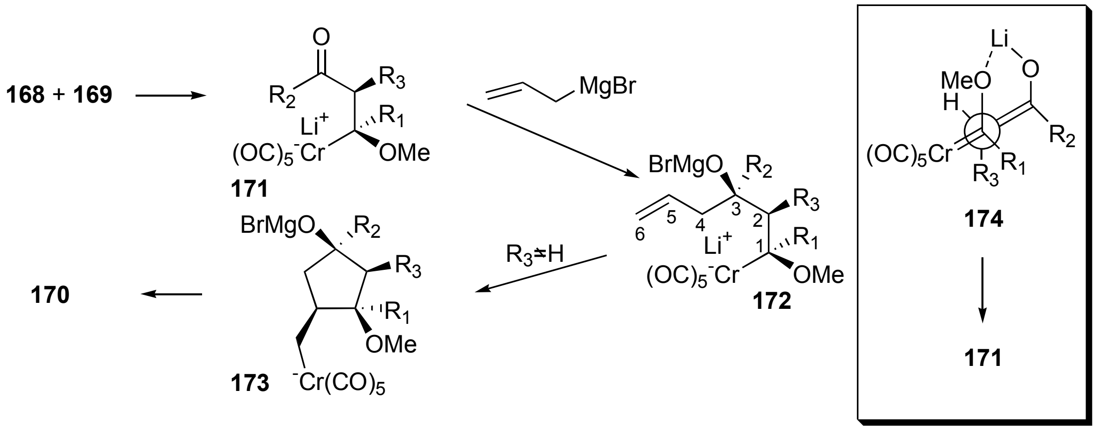


Fischer carbene, R_1	**enolate, R_2, R_3**	**method**[a]	**product yield (%)**
168a, 2-naphtyl	**169a**, MeO, Me	A	**170a** (79)
168b, 2-furyl	**169a**, MeO, Me	A	**170b** (73)
168c, cyclopentyl	**169a**, MeO, Me	A	**170c** (87)
168d, Ph	**169b**, Et, Me	B	**170d** (80)
168a, 2-naphtyl	**169c**, $(CH_2)_4$	B	**170e** (78)

[a] reaction conditions: method A: **169a** (1.2 eq), -78 °C, 15 min, CH_2=$CHCH_2MgBr$ (2.5 eq), -78°C, 30 min; then 20 °C, 20 min. method B: **169b,c** (1.2 eq), -78 °C to -55 °C, 45 min, CH_2=$CHCH_2MgBr$ (1.5 eq), -78 °C, 30 min; then 20 °C, 20 min.

Scheme 4.7: 1,2,3,3,4-Pentasubstituted Cyclopentanols **170** Prepared by One-Pot Three or Four-Component Coupling of **168**, **169** and Allyl Magnesium Bromide

1-Allyl-cyclopentanols **170a-c** were formed when ester lithium enolate **169a** was used in the process that involves four reacting components and the formation of four new C-C bonds. Other 1-substituted cyclopentanols **170d** and **170e** were isolated from the reaction with ketone lithium enolates **169b** and **169c**, which represents the coupling of three reacting components with the formation of three new C-C bonds. This sequential one-pot synthesis of cyclopentanols proceeded successfully with aryl and heteroaryl carbene complexes **168a**, **168d** and **168b** respectively, and even with alkyl carbene complex **168c**, which contains an acidic hydrogen atom at the tertiary center α to the carbene carbon atom. A plausible mechanism to explain the formation of **170** proceeds with an initial 1,2-addition of the enolate **169** to carbene complex **168**, which then generates intermediate **171** (*Scheme 4.8*).

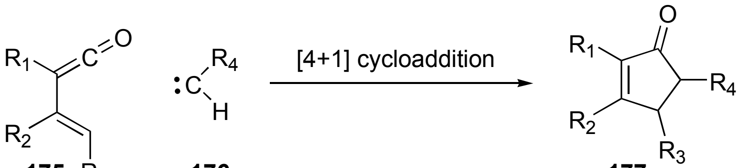


Scheme 4.8: Proposed Mechanism for the formation of **170**

Subsequent addition of the organomagnesium reagent at low temperature to the corresponding ester or ketone functional group produces 5-hexenylchromate intermediate **172**. Complexes **172** undergo an intramolecular carbometalation reaction to give the cyclopentylmethylchromate derivatives **173**, which finally furnish cyclopentanols **170** upon protonation. The observed diastereoselectivity in the first reaction step can be explained in terms of approach topology **174**, which is favored by coordination of the lithium center to the oxygen atom of the methoxy group.

IV-2-[4+1] Cycloaddition

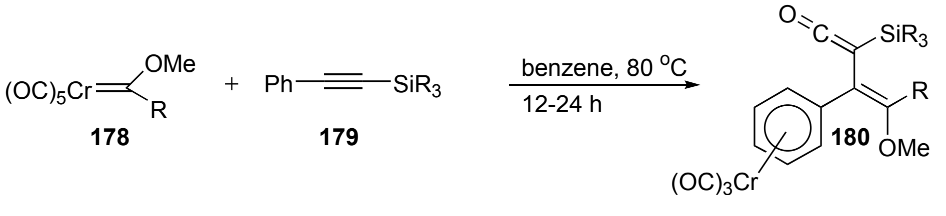
[4+1] Cycloaddition has been recognized as a very attractive approach for the formation of cyclopentenone ring system since regiochemical difficulties are avoided compared to methods such as the Pauson-Khand reaction[113]. The combination of vinylketene **175** and a carbenoid unit **176** would appear to represent a very direct approach to cyclopentenones (*Scheme 4.9*).



175 **176** **177**

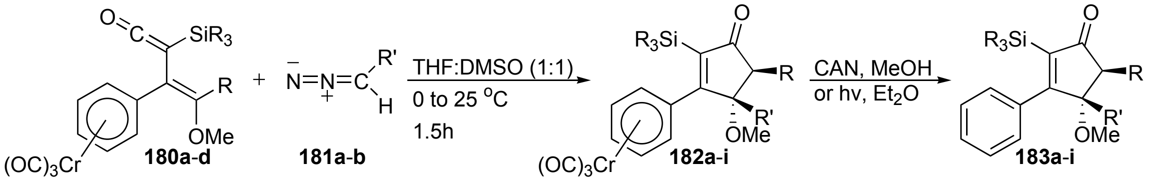
Scheme 4.9: [4+1] Cycloaddition Toward Cyclopentenones **177**

However, despite the ability of vinylketenes to serve as versatile four-carbon building blocks, their use in [4+1] cycloaddition reactions is rendered difficult by their characteristic instability and a preference to undergo dimerization and/or [2+2] cycloaddition reactions instead[114]. In contrast, silyl vinylketenes have been demonstrated as viable precursors to cyclopentenones[115,116] such that the silyl substituent provides significant stabilization to the ketene moiety and suppresses the dimerization pathway[117]. Moser et *al.* recently reported the stereoselective construction of functionalized cyclopentenones from [4+1] cycloaddition of silyl vinylketenes derived from Fischer carbene complexes with carbenoid reagents[118]. Silyl vinylketenes **190** were prepared from chromium carbene complexes **178** and silyl alkynes **179** under the reaction conditions described, affording yellow crystalline compounds as the major products in good yields (*Scheme 4.10*).



Scheme 4.10: [4+1] Synthesis of Silyl Vinylketenes **180**

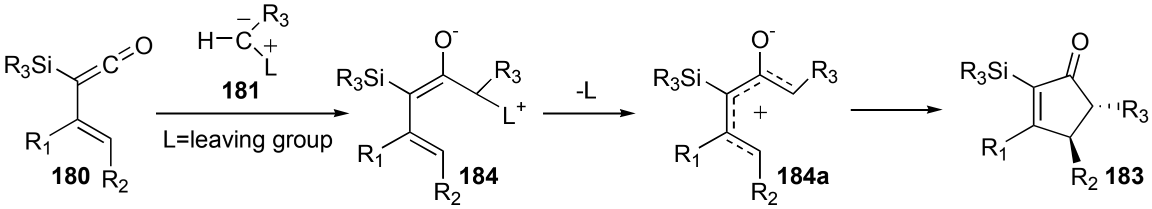
The use of silyl substituted phenylacetylenes **180** is notable such that it promotes capture of the chromium fragment by the phenyl ring and affords access to the silyl vinylketenes as arene complexes that display excellent thermal stability[119]. When stabilized silyl vinylketenes **180a-d** were mixed with diazomethane derivatives **181a** or **181b** (carbenoid reagents), [4+1] products **182a-i** were produced in good to excellent yields (*Scheme 4.11*).



silyl vinyl ketene, SiR_3, R	**carbenoid, R'**	**[4+1] product yield (%)**	**cyclopentenones** in quantitative yield
180a, TIPS, Me	**181a**, TMS	**182a** (93)	**183a**
180b, TIPS, n-Bu	**181a**, TMS	**182b** (79)	**183b**
180c, TIPS, Ph	**181a**, TMS	**182c** (62)	**183c**
180c, TIPS, Ph	**181a**, TMS	**182d** (86)	**183d**
180a, TIPS, Me	**181b**, Ph	**182e** (80)	**183e**
180b, TIPS, n-Bu	**181b**, Ph	**182f** (83)	**183f**
180c, TIPS, Ph	**181b**, Ph	**182g** (73)	**183g**
180d, TIPS, 4-MeOPh	**181b**, Ph	**182h** (77)	**183h**
180c, TIPS, Ph	**181b**, Ph	**182i** (76)	**183i**

Scheme 4.11: Stereoselective [4+1] Annulation Reactions

Notably, only one diastereomer was isolated after the reactions in each case, the products **182** containing two contiguous stereogenic centers with a *cis* relationship between the R and R' substituents. In all cases, the chromium tricarbonyl is readily removed from the [4+1] cycloadducts **182** by treatment with ceric ammonium nitrate (CAN), providing cyclopentenones **183a-i** in quantitative yields. The construction of cyclopentenones **183** can be considered as a formal [2+1+1+1] annulation process in which the five cyclic carbons are derived from the two carbons of the alkyne **179**, the carbene complex carbon **178**, carbon monoxide and the carbon of the carbenoid reagent **181**. The wide range of substituents that can be incorporated by variation of those four components suggests that the method will provide broad access to cyclopentanoid products. On the basis of previous models[120], one interpretation of the mechanistic pathway followed by the formal [4+1] annulation can involve initial stereoselective addition of carbenoid reagent **181** to provide *Z*-enolate **184** (*Scheme 4.12*).

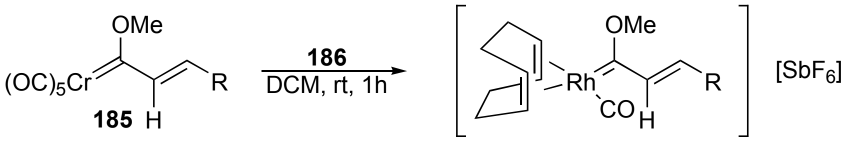


Scheme 4.12: Possible annulation mechanism

This is followed by ionization of the leaving group to generate 2-oxidopentadienylcation **184a** as the sterically favored intermediate. A concerted 4π-electrocyclic ring closure would preserve the original alkene geometry and provide the observed diastereomer of the cyclopentenone **183**.

IV-3-Rh-Catalyzed Transmetalation [3+2] Cycloaddition

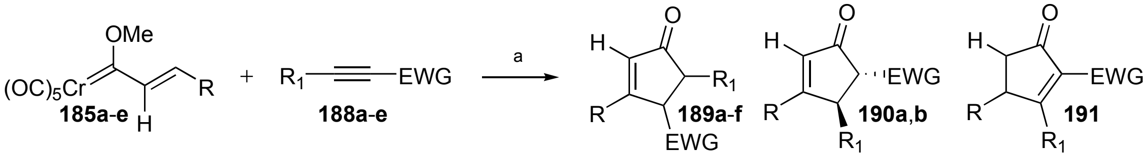
Inspired by the first example of Aumann et *al.*, in which a rhodium transition-metal catalyst had been successfully applied to enhance the reactivity of a Fischer carbene complex[121,122], Barluenga et *al.* reported[105] the preparation of novel cationic rhodium(I) alkoxycarbene complexes **187** (*Scheme 4.13*).



186=[(naphthalene)Rh(cod)][SbF_6] **carbonyl Rh(I) carbene complexes, yield (%)**
187a, R=Ph (60)
187b, R=4-MeOPh (70)
187c, R=2-furyl (65%)
187d, R=ferrocenyl (72)

Scheme 4.13: Synthesis of cationic Carbonyl Rh(I) Carbene Complexes **187**

The simultaneous transfer of two ligands (carbene and CO) observed when readily available rhodium complex **186** and Cr-methoxycarbene complexes **185** represents a rare process[123]. The reactivity of the novel Rh complexes **187** toward electrophilic alkynes was investigated, since the reaction of these systems with group 6 carbenes complexes presents severe limitations[124] (*Scheme 4.14*).

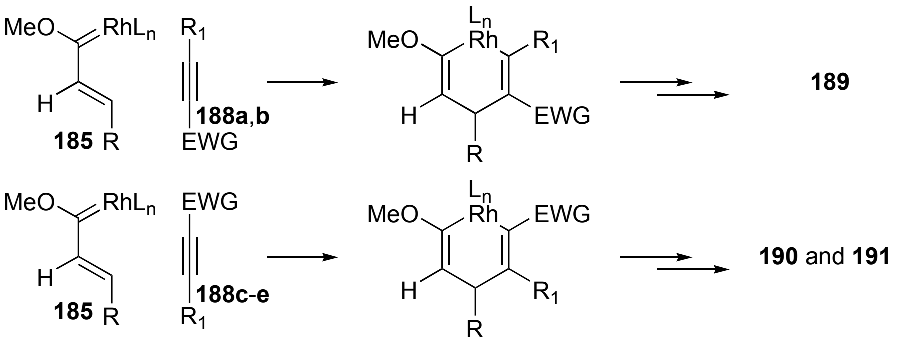


Cr methoxy-carbene complexes, R	alkyne, R_1	[3+2] product, EWG, yield (%)
185a, Ph	**188a**, H	**189a**, **CO_2Me**, (75)
185b, 4-MeOPh	**188a**, H	**189b**, **CO_2Me**, (81)
185c, 2-furyl	**188a**, H	**189c**, **CO_2Me**, (88)
185d, ferrocenyl	**188a**, H	**189d**, **CO_2Me**, (71)
185e, *n*-Butyl	**188a**, H	**189e**, **CO_2Me**, (70)
185c, 2-furyl	**188b**, H	**189f**, **COMe**, (64)
185c, 2-furyl	**188c**, Ph	**190a**, **CO_2Et**, (75)
185c, 2-furyl	**188d**, 1-cyclohexenyl	**190b**, **CO_2Me**, (85)
185c, 2-furyl	**188e**, Me	**191**, **CO_2Me**, (81)

[a] reaction conditions: [(naphtalene)Rh(cod)][SbF_6] **186** (10 mol%), DCM, 25 °C, 12-36 h

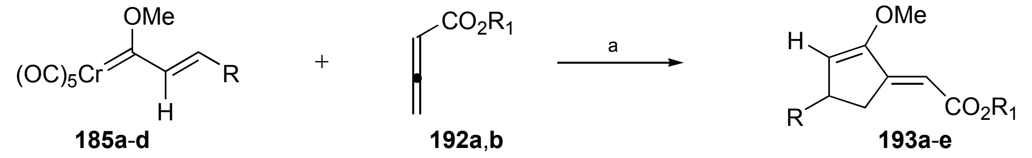
Scheme 4.14: Rh-Catalyzed [3+2] Cycloaddition of Cr-Carbene Complexes **185** and Electron-Poor Alkynes **188**

In this case, rhodium-catalyzed reaction was found very effective - terminal electron-poor alkynes ester **188a** or ketone **188b** reacted with chromium carbene complexes **185a**-**e** and **186** (10 mol%) to yield cyclopentenone derivatives **189a**-**f** with complete regioselectivity. Electron-poor internal alkynes **188c**-**e** also underwent efficiently the [3+2] cyclization with reversal of regiochemistry, affording **190** or **191** depending on the nature of the alkyne. On the basis of metalla-Diels-Alder reaction models[125], a speculative mechanistic proposal explaining the behavior of these new rhodium systems has been described (*Scheme 4.15*). The regiochemistry observed in the case of terminal electron-poor alkynes **188a** and **188b** giving rise to cycloadducts **189**, can be simply dictated by steric discrimination, the larger alkyne substituent being placed away from rhodium. In the case of internal electron-poor alkynes **188c**-**e**, the steric differentiation is not so large and electronic factors, which favor the interaction between the electrophilic metal center and the nucleophilic Cα-alkyne, would dominate, leading to cycloadducts **190** and **191** with opposite stereochemistry.



Scheme 4.15: Proposed Mechanism for the [3+2] Cycloaddition

The transmetalation reaction of group 6 carbene complexes has become a unique tool to access transition-metal carbenes of groups 9-11[102], but unexpectedly, studies concerning the reactivity of these metal complexes with allenes are rather limited, although the latter have demonstrated great potential in the field of transition-metal-catalyzed organic synthesis during the past years[126]. Barluenga et *al.* recently reported[127] the rhodium(I)-catalyzed reaction of electron-poor allenes with chromium carbene complexes. The process results in a facile and selective access to functionalized alkylidenecyclopentenones **193** using carbene complexes **185** and deactivated allenes **192** (*Scheme 4.16*). The reaction of carbene complexes **185a**-**d** and monosubstituted allenes **192a** or **192b** using 10 mol% of [(naphthalene)Rh(cod)][SbF6] **186** under the conditions shown afforded exclusively the cyclopentenes **193a**-**e** in 48-72% yields with complete chemo-and regioselectivity. The reaction proved to be totally stereoselective such that *E*-configurated isomer was uniquely obtained.

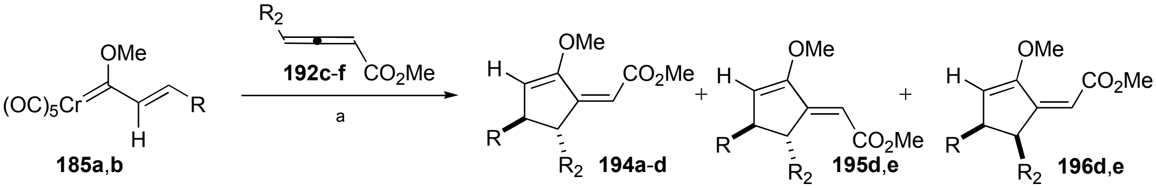


Cr methoxy-carbene complexes, R	**allene, R_1**	**[3+2] product, yield (%)**
185a, 4-MeOPh	**192a**, CH_3	**193a**, (72)
185b, Ph	**192a**, CH_3	**193b**, (66)
185c, 4-ClPh	**192a**, CH_3	**193c**, (62)
185d, ferrocenyl	**192a**, CH_3	**193d**, (48)
185a, 4-MeOPh	**192b**, CH_2Ph	**193e**, (56)

[a] reaction conditions: [(naphtalene)Rh(cod)][SbF_6] **186** (10 mol%), CO (1 mbar), DCM, rt

Scheme 4.16: [3+2] Cycloaddition of Alkenyl Carbene Complexes **185a-d** and Allenes **192a**,**b**

The influence of a substituent at the C-γ of the buta-2,3-dienoate framework on the cyclization reaction was also evaluated (*Scheme 4.17*).

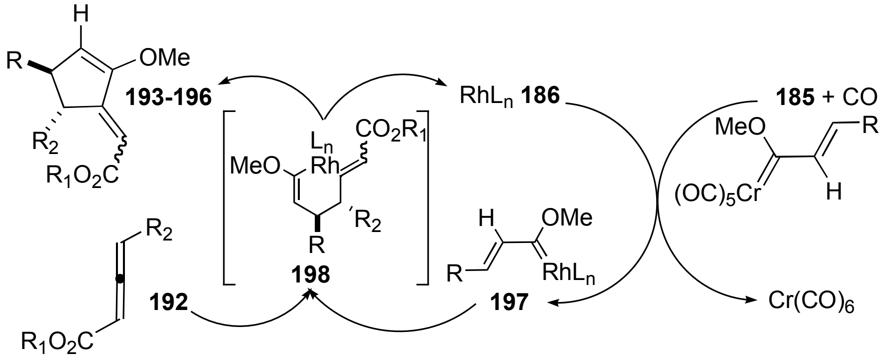


Cr methoxy-carbene complexes, R	**allene, R_2**	**[3+2] product, yield (%)**
185a, 4-MeOPh	**192c**, C_6H_5	**194a**, (70)
185b, Ph	**192c**, C_6H_5	**194b**, (66)
185a, 4-MeOPh	**192d**, $C(CH_3)_3$	**194c**, (66)
185a, 4-MeOPh	**192e**, $CH(CH_3)_2$	**194d**, **195d** and **196d** (68, 5 and 5)
185b, Ph	**192f**, CH_3	**195e** and **196e** (50 and 10)

[a] reaction conditions: [(naphtalene)Rh(cod)][SbF_6] **186** (10 mol%), CO (1 mbar), DCM, rt

Scheme 4.17: [3+2] Cycloaddition of Alkenyl Carbene Complexes **185a**,**b** and Allenes **192c-f**

The reaction of disubstituted allenes **192c-f** with carbene complexes **185a** or **185b** resulted in the exclusive formation of the 5-methoxycarbonylmethylidene-cyclopentene ring compounds **194-196**. This means that neither the chemoselectivity nor the regioselectivity are affected by the presence of a substituent, as large as the *tert*-butyl group, at the γ-position of the allene (product **194c**). However, the stereoselectivity was found to depend on the nature and the bulkiness of R_2 substituent. A tentative mechanistic pathway is outlined where the overall catalytic process is initiated by the Cr(0)-Rh(I) exchange[121], which produces the active rhodium carbene complex **197** and $Cr(CO)_6$ (*Scheme 4.18*).

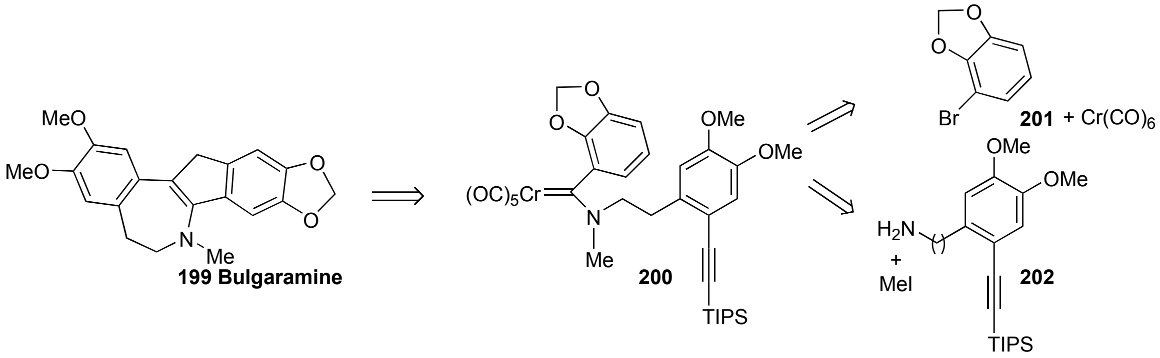


Scheme 4.18: Proposed Mechanism for the [3+2] Cycloaddition of Cr-Carbene Complexes **185** and Allenes **192**

Note that the two-fold role of CO is shown to have not only improved the efficiency of the catalytic reaction, probably by favoring the transmetalation step, but also allows almost quantitative recovery of the chromium material. Based on control experiments, it is thought that the active catalytic species L_nM is likely to be $[Rh(cod)(CO)]^+$. The carbocyclization between the rhodium species **197** and the allene **192** involves the nonactivated C-C double bond formation of the metalacyclohexene intermediate **198**, which after catalyst regeneration gives the cyclopentenes **193-196**.

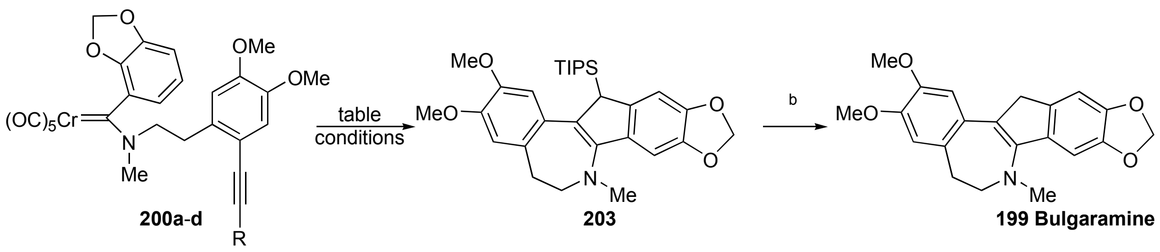
IV-4-Fischer Amino Carbene Complex

Utilized in several Asian and eastern European countries as folk medicines for its antipyretic, analgesic and diuretic properties[128], Bulgaramine has received the attention of chemistry community toward the development of new synthetic methodologies[129]. Moser and Giese recently proposed[130] a total synthesis of bulgaramine **199** with a longest linear sequence of eight steps and an overall yield of 23% from amine **202** and aryl bromide **201** (*Scheme 4.19*).



Scheme 4.19: Retrosynthetic Route Toward Bulgaramine **199**

A thermal intramolecular cyclopentannulation reaction of a Fischer amino-carbene complex **200** provides the key step and occurred under significantly milder conditions and higher yields than those of other reported examples of this reaction types[131]. A variety of factors including temperature, solvent, concentration, additives and alkyne substituents are known to affect the course of the thermal reactions between Fischer amino-carbene complexes and alkynes **200** leading to either a cyclopentannulation or a benzannulation pathway (*Scheme 4.20*). The benzannulation process takes place when a fragment of the carbene complex, alkyne and a carbon monoxide ligand join together to form a new phenolic product, which is commonly referred to the Dötz reaction. The polar and/or coordinating solvent DMF is known to favor 5-membered ring closure system, whereas less polar solvent such as benzene favors 6-membered ring formation as the predominant pathway. However, the desired pentannulation transformation of amino-carbene **200a** proceeds best in refluxed THF, showing that the relatively low reaction temperature is sufficient for the decarbonylation step. Even non-coordinating solvent such as chloroform at its reflux temperature resulted in no product formation. Although the desired product **203** was the major component, the latter was produced in a poor yield of 24%, along with multiple by-products. Reduction of the alkyne **200a** concentration modestly increased the product conversion up to 32%, favoring the cyclopentannulation pathway due to a minimization of the intermolecular cyclizations.

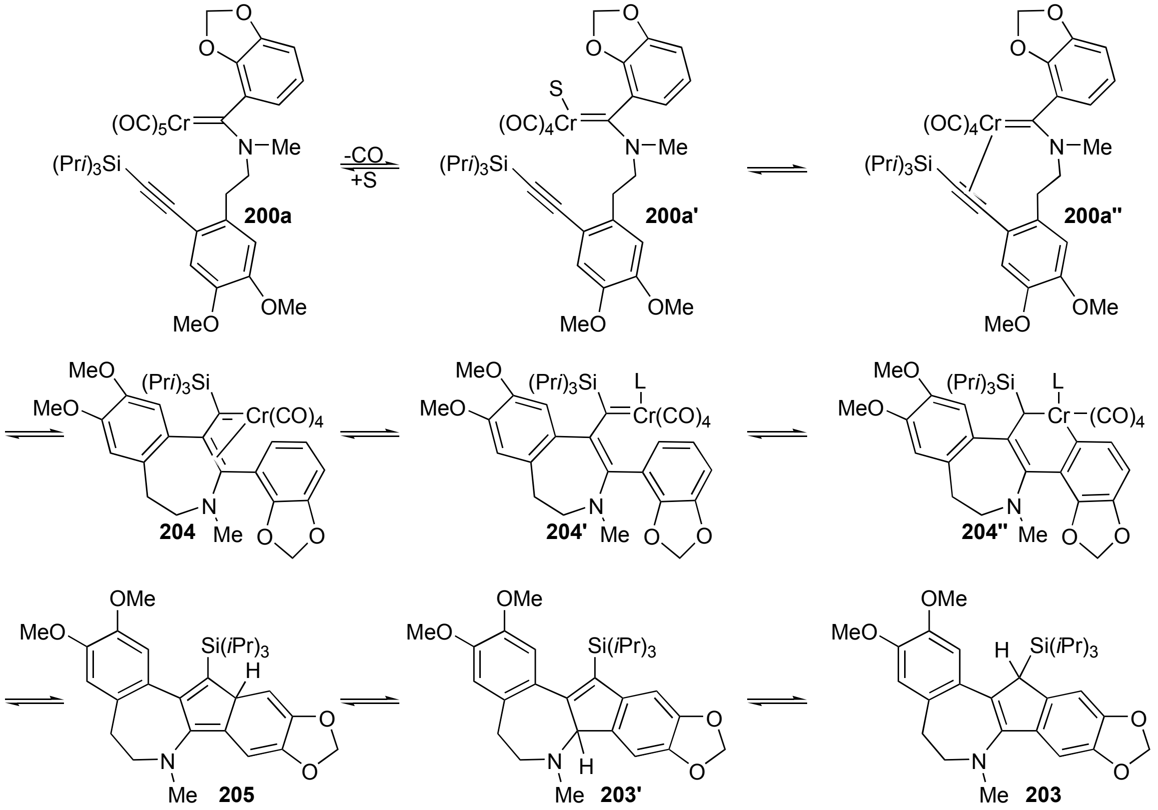


Cr amino-carbene complexes, R	**solvent**	**temperature** (°C)	**time** (h)	**M** (mol.L^{-1})	**additive** (eq)	**yield (%)**
200a, TIPS	benzene	80	24	0.022	none	**203**, (no reaction)
200a, TIPS	DMF	120	20	0.022	none	**203**, (trace)
200a, TIPS	DMF	152	24	0.022	none	**203**, (decomp)
200a, TIPS	$CDCl_3$	62	4	0.022	none	**203**, (no reaction)
200a, TIPS	pyridine	66	8	0.022	none	**203**, (no reaction)
200a, TIPS	pyridine	80	18	0.022	none	**203**, (decomp)
200a, TIPS	THF	66	8	0.022	none	**203**, (24)
200a, TIPS	THF	66	8	0.008	none	**203**, (32)
200a, TIPS	THF	66	8	0.008	PBu_3 (1)	**203**, (62)
200a, TIPS	THF	66	20	0.008	PBu_3 (1)	**203**, (67)
200b, H	THF	66	6	0.008	PBu_3 (1)	**203**, (38)
200c, TMS	THF	66	20	0.008	PBu_3 (1)	**203**, (56)
200d, TES	THF	66	20		PBu_3 (1)	**203**, (37)

[b] reaction conditions: 1. 10% HBr/HOAc, DCM; 2. 10% KOH, 1/1 $EtOH/H_2O$, reflux, 5 min, 80%

Scheme 4.20: Cyclopentannulation of Amino-Carbene Complexes **200**

Moreover, the use of ligating reagent such as tri-*n*-butyl phosphine resulted in an increase of the selectivity for the cyclopentannulated product **203** with 62% yield and a complete suppression of by-products. When TIPS substituted alkyne **200a** was changed for terminal alkyne **200b**, substituted TMS and TES alkynes **200c** and **200d** respectively, a rapid disappearance of the amino-carbene species and the selective formation of **203** were observed, but isolation of the products proved to be difficult and analytically pure samples could not be isolated. Taken together, these results are consistent with the following mechanism (*Scheme 4.21*). Reversible decarbonylation of **200a** to yield tetracarbonyl complex **200a'** occurs at an uncharacteristically low temperature for amino-carbene complexes and appears to be aided by the presence of the solvent as a donor species. Intramolecular displacement of the solvent by the alkyne provides intermediate **200a''**, which would insert the alkyne to yield the 18-electron chelate complex **204**. Coordination of the two-electron donor phosphine ligand dechelates the alkyene moiety to give the 18-electron vinyl carbene complex **204'**, which induces chromacycle **204''** formation and reductive elimination to afford cyclopentadiene **205**. Rearomatization could occur to yield isomers allylamine **203'** and enamine **203**.

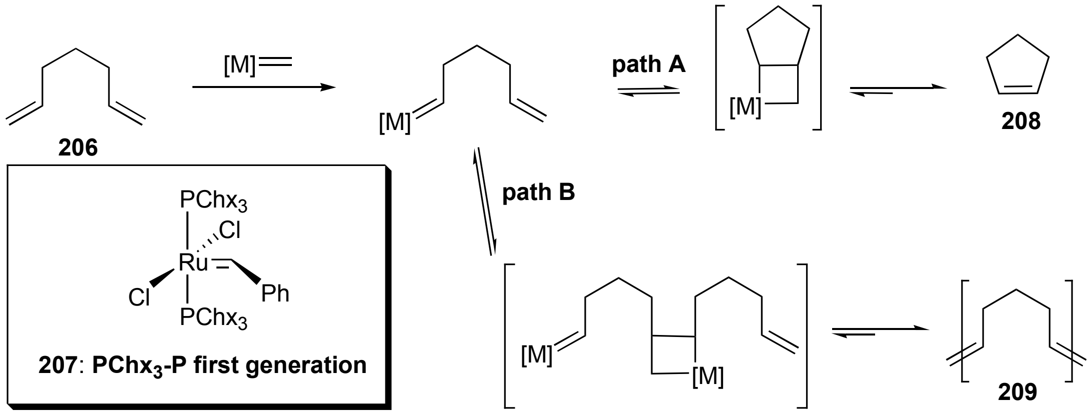


Scheme 4.21: Proposed Mechanism For the Optimized Cyclopentannulation Reaction

V-Ring-Closing Metathesis

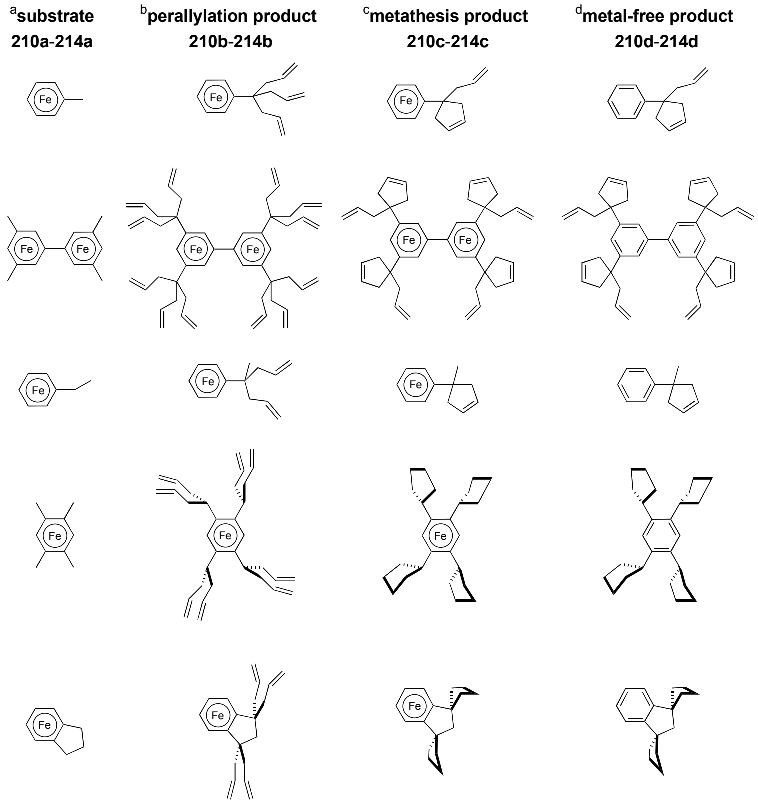
V-1-Ruthenium Ring-Closing Metathesis with Diene Substrates

Ring-closing metathesis (RCM) is commonly defined[132] as the treatment of a diene **206** with metal alkylidene, which leads to two competing reaction pathways (*Scheme 5.1*). [2+2] Cycloaddition occurs between the metal alkylidene and the diene substrate, which leads to the RCM cycloadduct **208** (path A), or intermolecular reaction occurs to form polymeric adduct **209** (path B). The reaction is also complicated by the possibility of ring-opening metathesis polymerization. Thermodynamic and kinetic parameters favour one or the other product. In the early 1990s, Grubbs and Fu demonstrated that the Schrock molybdenum catalysts[133,134] were effective for a number of important organic transformations, particularly those involving ring-closing reactions.



Scheme 5.1: RCM of Diene **206** using Metal Alkylidene

Shortly after, they reported a newly prepared ruthenium system derived from **207**, which could perform the same transformations without the use of glove-box (without exclusion of H_2O and O_2) allowing previously unreactive substrates to undergo ruthenium-catalyzed RCM in high yields[135]. Since then, the large functional group tolerance, the high catalyst activity and the simple use of ruthenium based alkylidene **207** led to its commercialization[136] and open up the use of this powerful and convenient tool to the wider synthetic community[137,138]. Among the myriad of publications applying the first generation of ruthenium catalyst **207** to 5-membered ring closing metathesis, Astruc et *al.* reported in 2002, a general and facile synthetic method[139] leading to sophisticated polycyclic cyclopentenyl aryl derivatives **210d**-**214d** (*Scheme 5.2*). Both the temporary π complexation of the arene substrates with iron, to give complexed compounds **210a**-**214a**, and the final decomplexation step of the metathesis products **210c**-**214c** are carried out in quantitative yields[140]. The first step reaction is the $CpFe^+$ induced perallylation **a**↦**b** at the benzylic position of alkyl arenes, which provides high selectivity and high yields in all cases. RCM is the second reaction using Grubb's commercial first generation catalyst **207**, which readily yields cyclopentenyl aryl derivatives in their sandwich complexes $[\mathrm{Fe}(\eta_5\text{-}C_5H_5)(\eta_6\text{-arene})]^+$ **210c-214c**. This reaction was carried out at room temperature in NMR tube using $CDCl_3$ or in DCM in Schlenk tubes. The authors noted that the presence of $CpFe^+$ enhances solubility of the metathesis starting material and selectivity of the metathesis reaction.

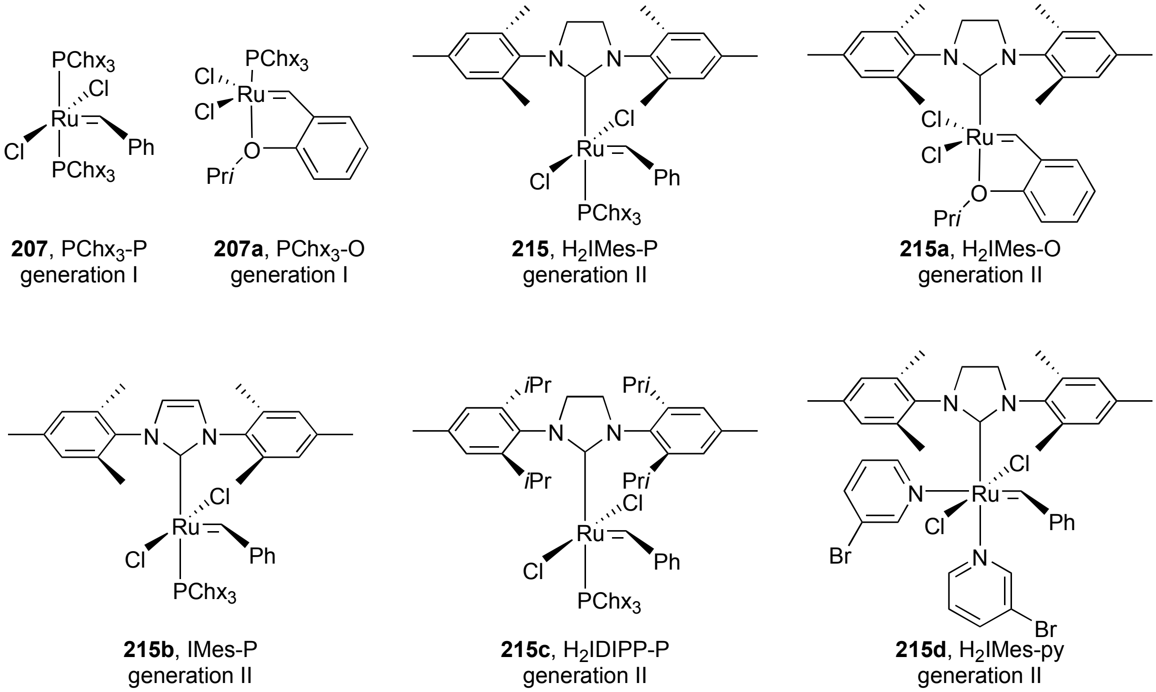


time (h)	yield (%)
210b (72) **210c** (4) **210d** (1)	**210b** (77) **210c** (65) **210d** (quant)
211b (72) **211c** (8) **211d** (1)	**211b** (59) **211c** (70) **211d** (quant)
212b (72) **212c** (4) **212d** (1)	**212b** (85) **212c** (65) **212d** (quant)
213b (48) **213c** (4) **213d** (1)	**213b** (72) **213c** (70) **213d** (quant)
214b (96) **214c** (4) **214d** (1)	**214b** (67) **214c** (76) **214d** (quant)

[a] FE=$[n^5\text{-CpFe}]^+PF_6^-$; reaction conditions: arene, ferrocene, Al_2Cl_6, overnight, reflux, 100°C, quantitative yields; [b] reaction conditions: CH_2CHCH_2Br, KOH, THF, rt; [c] reaction conditions: Ru-catalyst $[Ru(=CHPh)Cl_2(PChx_3)_2]$ **207**, DCM, rt; [d] reaction conditions: photolysis using visible light, MeCN, PPh_3.

Scheme 5.2: Synthesis of Free Aromatic Derivatives **210d-214d** from Successive Perallylation and Metathesis Reactions

A few years after the design of the second generation of Grubb's catalysts **215**, Grubbs et *al.* reported a study, which offered a concise method[141] for the comparison of ruthenium-based olefin metathesis catalysts under specific reaction conditions. This method was a valuable tool for the development of new catalysts (*Scheme 5.3*). The illustrated complexes **207**, **207a** and **215a-d** are among the most commonly used ruthenium catalysts for RCM[142]. The formation of tri- and tetrasubstituted olefins was investigated by plotting the product conversion over the time.



207, $PChx_3$-P generation I

207a, $PChx_3$-O generation I

215, H_2IMes-P generation II

215a, H_2IMes-O generation II

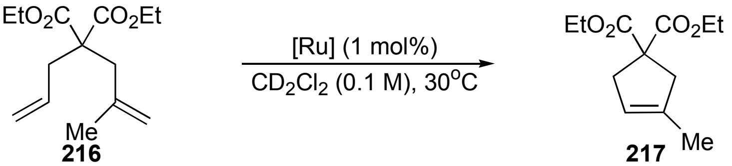
215b, IMes-P generation II

215c, H_2IDIPP-P generation II

215d, H_2IMes-py generation II

Scheme 5.3: Ruthenium Based-Catalyzed Used in This Study

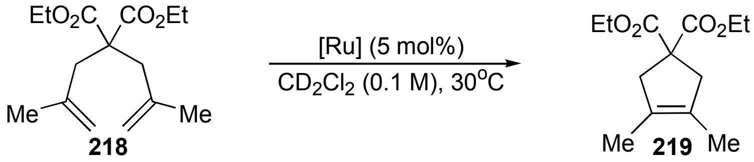
When the challenging reaction of trisubstituted olefin **216** was carried out, a large distinction between the phosphine-based first generation catalysts **$PChx_3$-P** and **$PChx_3$-O** and the second generation such as NHC-based catalysts was observed (*Scheme 5.4*).



216 **217**

Scheme 5.4: Conversion to Trisubstituted Olefin Product **217** Using Selected Catalysts

Although **$PChx_3$-P** and **$PChx_3$-O** are both capable of catalyzing the reaction to completion, the time required is significantly longer than observed with the NHC-based catalysts. **H_2IDIPP-P** and **H_2IMes-py** were the only catalysts that did not catalyzed the reaction to completion. This is formally explained by their lack of stability observed over the course of the reaction. When the reaction of tetrasubstituted olefin **218** was performed (which can be classified as an example of a currently unsolved problem in ruthenium-catalyzed olefin metathesis), the first generation catalysts did not catalyze the reaction even under an enhanced catalyst loading (5 mol%) and an increase of the reaction time (4 days) (*Scheme 5.5*).

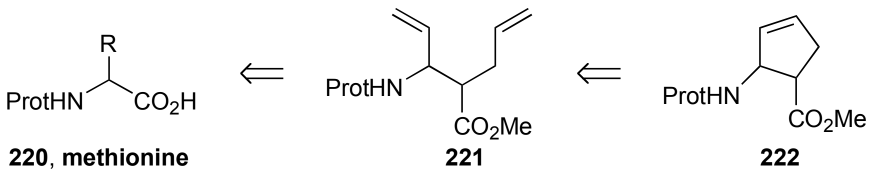


catalyst	**conversion (%)**
207 $PChx_3$-P	0
207a $PChx_3$-O	0
215 H_2IMes-P	17
215a H_2IMes-O	6
215b IMes-P	31
215c H_2IDIPP-P	0
215d H_2IMes-py	10

Scheme 5.5: Observed Conversions in the RCM of **219** After 4 Days

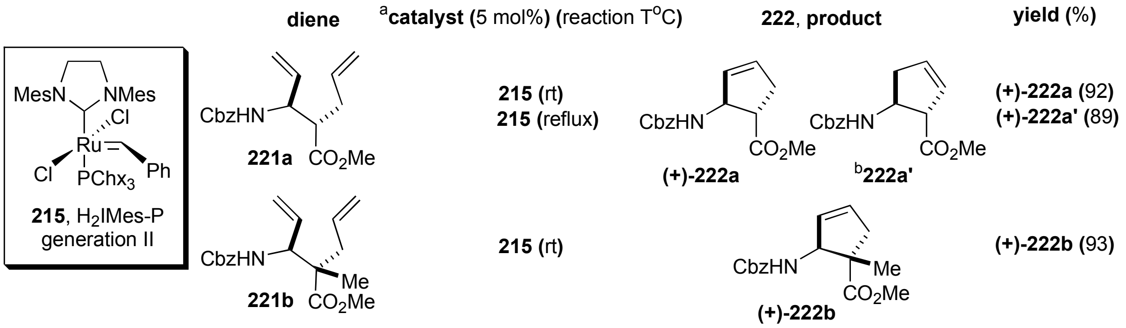
As in the case of the trisubstituted olefin reaction, **H_2IMes-py** catalyst was shown to be totally inefficient for this transformation. However, in the same situation, **H_2IDIPP-P** exhibits a timid activity for the formation of **219**. **IMes-P** was less efficient than **H_2IMes-P** in the RCM of trisubstituted olefin, whereas this unsaturated NHC catalyst **IMes-P** is the most efficient in the tetrasubstituted olefin conversion. It was concluded that highly active catalyst for easy RCM of unhindered olefins were readily available. However, catalyst stability and catalyst reactivity for more challenging tetrasubstituted double bond RCMs needs to be enhanced.

As an example of the application of second generation Grubb's catalyst **215** in methodology, Abell et *al.* in 2004 reported a versatile method[143] for the preparation of a range of functionalized cyclic β-amino esters **222** from the simple and readily available building-block methionine **220** (*Scheme 5.6*).



Scheme 5.6: Retrosynthetic Analysis of Carbocyclic β-Amino esters **222**

The key to the strategy is the diastereoselective preparation of dienes of type **221**, which cyclize in the presence of catalyst **215** to give cyclopentenyl-based β-amino esters **222** (*Scheme 5.7*).

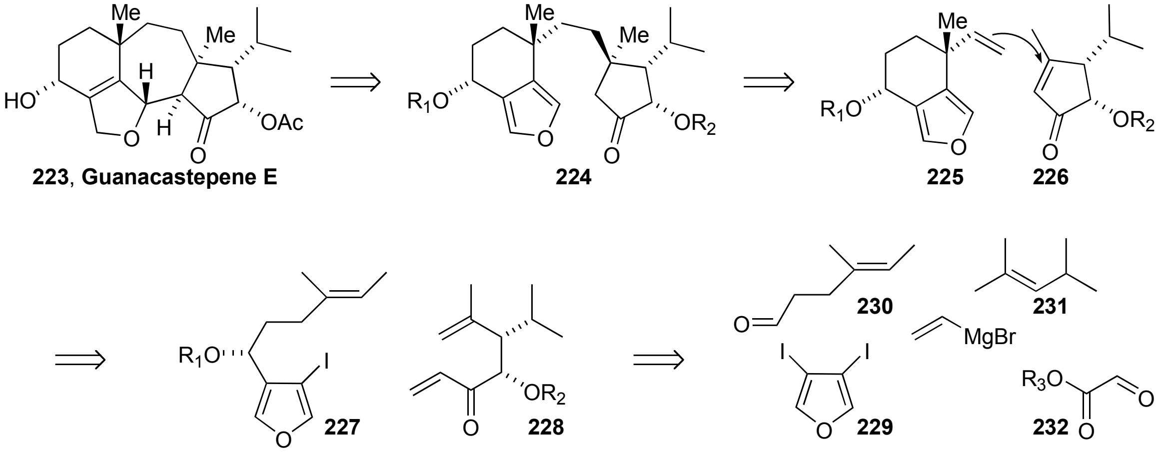


[a] all reactions were carried out in benzene; [b] 1.5:1 ratio of **(+)-222a/(+)-222a'** was observed on ^1H NMR when **221a** was refluxed

Scheme 5.7: RCM Reaction of Cyclic β-Amino Esters **222**

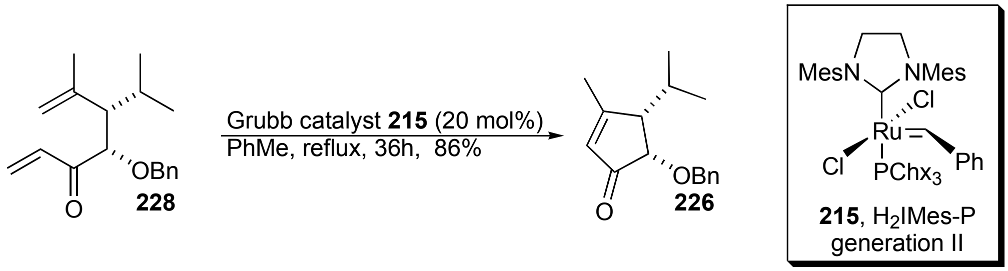
Initially, when a RCM reaction was carried out on the unsubstituted diene **221a** at room temperature for 2h, the ring-closed product was obtained in 92% yield. However when diene **221a** was refluxed in benzene for 2h, isomerization of the double bond of **(+)222a** was observed with the isolation of compound **222a'**. To minimize the double bond isomerization of **(+)222a**, the substituted diene **221b** was subject to the RCM at room temperature for 4 h. Carbocyclic product **(+)222b** was obtained in high yield with no evidence of double bond isomerization. The mild conditions applied to this RCM imply a good overall efficiency of the catalyst including a good selectivity, activity and stability.

As an example of the application of second generation Grubb's catalyst **215** in natural product synthesis, Trauner et *al.* in 2006 reported the total synthesis of (-)-guanacastepene E[144]. In light of its attractive structure and interesting biological activities, guanacastepene E has proven to be a fertile ground for total syntheses[145]. The retrosynthetic analysis of guanacastepene E **225** begins by disconnecting the central seven-membered ring to arrive at furyl ketone **226** (*Scheme 5.8*).



Scheme 5.8: Retrosynthetic Analysis of Guanacastepene E

In the forward direction, oxidative coupling of the furan and ketone functionalities in **224** would close the ring. Further disconnection of **224** yields the left-hand building-block **225** and the right-hand building-block **226**. These components would be joined by formal hydrometallation of **225**, followed by a diastereoselective conjugate addition to cyclopentenone **226**. Compounds **224** and **235** could be tracked back to iodofuran **227** and dienone **228** through an intramolecular Heck reaction and RCM respectively. Finally, those components could be fully disconnected to known starting materials: diiodofuran **229**, aldehyde **230**, vinyl magnesium bromide, pentene **231** and chiral glyoxylate **232**. The RCM reaction of diene **228** was carried out with second generation of Grubb's catalyst **215** (*Scheme 5.9*).

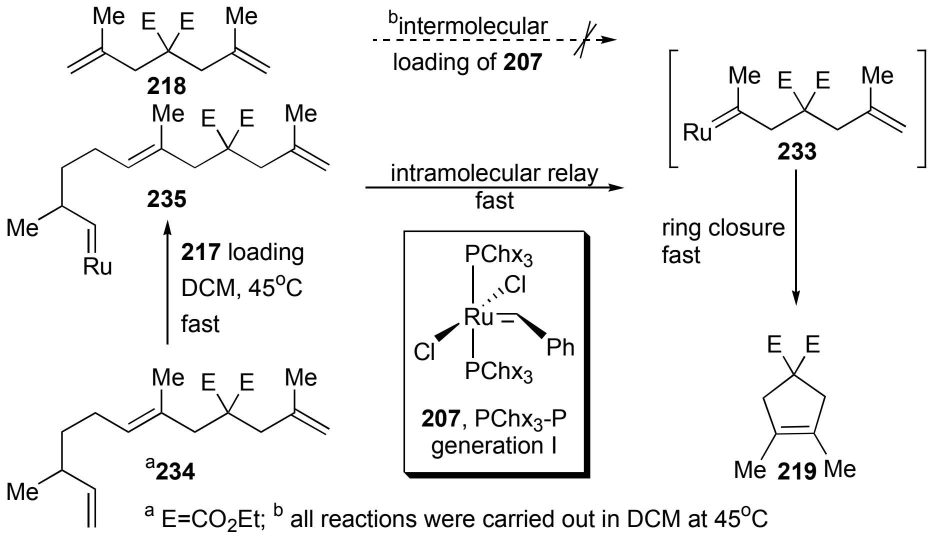


Scheme 5.9: RCM Reaction of Diene **228** with Grubb catalyst **215**

Reaction conditions were fairly harsh - diene **228** was refluxed in toluene for 36h with a catalyst loading of 20 mol% to afford enantiomerically pure cyclopentenone **226**. Although, an excellent yield was obtained, a lack of activity for catalyst **215** is observed using this type of substrate as shown by the extended reaction time.

V-2-Ruthenium Relay Ring-Closure Metathesis with Dienes and Enynes Substrates

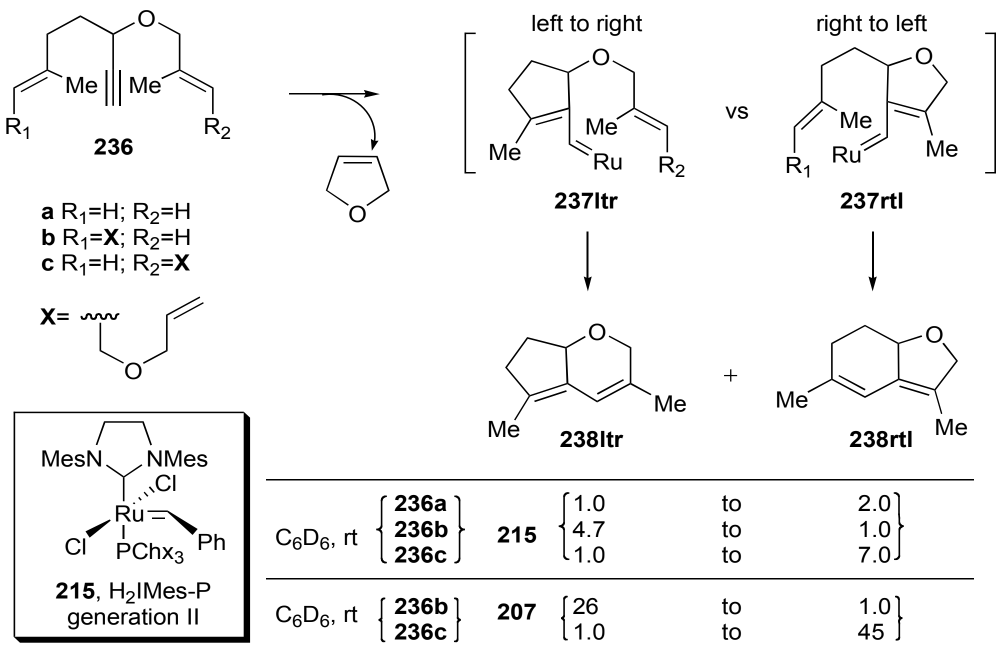
The past decade has seen the establishment of RCM as a powerful and generally applicable method for construction of carbocycles. However, even with the remarkable successes emanating from literally thousands of laboratories, the applicability of RCM is not universal. Limitations are most often encountered as users attempt to apply the technology to the construction of increasingly complex molecular targets. RCM can fail when substrate alkenes are either sterically hindered or electronically deactivated[146]. To overcome these types of problems, Hoye et al. have developed the concept of *relay* ring-closure metathesis (RRCM) [147]. This involves the design of substrates that permit a control of the sequence of metathesis events by manoeuvring the Ru metal atom through the individual steps of the RCM cascade[148,149]. RRCM permits the cyclization of many types of recalcitrant alkene substrates by solving reactivity or selectivity issues. The first example of RRCM involves the cyclization of diene (**218**, *Scheme 5.5*) bearing two 1,1-disubstituted ethylene moieties, which is known to be unreactive toward the first generation of Grubb's catalyst **207** (*Scheme 5.10*). In contrast, exposure of the modified relay substrate **234** to **207** (26 mol%) resulted in smooth cyclization to the cyclopentene derivative **219** (66% yield). Thus, introduction of the remote terminal alkene in **234** opened a pathway to access **233** by route of **235**. This is the only example of tetrasubstituted alkenes formed by first generation Grubb's catalyst **207**-mediated RCM of a simple α,ω-diene. Although this first success clearly demonstrated the RRCM concept, Grubb's catalyst second generation IMes-P **215b** (5 mol%) was also shown to catalyze the RCM of substrate **218** in a 31% yield (*Scheme 5.5*).



^{a} E=CO_2Et; ^{b} all reactions were carried out in DCM at 45°C

Scheme 5.10: Formation of Cyclopentene **219** *via* RRCM of diene **234**

However, another more striking example constitutes a definitive case in which RRCM provides a level of control that is not available with traditional RCM. Tandem enyne metathesis of substrate **236** can cyclize with either a *left-to-right* or *right-to-left* endedness to give isomeric dienes **238ltr** (*via* **237ltr**) or **238rtl** (*via* **237rtl**) (*Scheme 5.11*). Closure of diene **236a** with second generation **215** provided the ratio value 1.0:2.0 for the products **238ltr**:**238rtl**. The related relay substrates **236b** vs **236c** provided improved but imperfect selectivity. RRCM closure of each with **215** gave 1.0:7.0 vs 4.7:1.0 ratios of **238ltr** to **238rtl** respectively. Thus, **215** may not be highly discriminating of the two termini in **236b** and **236c**. If true, the less reactive first generation **207** should be superior. Consistent with this analysis, relay substrate **236b**, when treated with **207**, gave the bicyclic diene **238ltr** very selectively (26:1.0). Analogous treatment with isomeric **236c** was highly complementary, giving **238rtl** nearly exclusively (1.0:45). From these two examples, one can see that RRCM is complementary to RCM. It might be predicted that many applications will emerge as investigators contemplate their own uses of RRCM.



C_6D_6, rt	**236a**	**215**	1.0	to	2.0
	236b		4.7	to	1.0
	236c		1.0	to	7.0
C_6D_6, rt	**236b**	**207**	26	to	1.0
	236c		1.0	to	45

Scheme 5.11: Tandem Enyne Metathesis of Substrate **236**

VI-References

(1) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1941**, 211.

(2) Woodward, R. B. *Chem. Soc.* **1967**, *21*, 237.

(3) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193.

(4) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377.

(5) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642.

(6) Ojima, I. *Wiley-VCH: Weinheim, Germany* **2000**, *2nd ed.*

(7) He, W.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278.

(8) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864.

(9) He, W.; Huang, J.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498.

(10) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080.

(11) Meng, Z. Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 1511.

(12) Shanmugam, P.; Srinivasan, R.; Rajagopalan, K. *Tetrahedron* **1997**, *53*, 6085.

(13) Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358.

(14) Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257.

(15) Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202.

(16) Nagao, Y.; Lee, W. S.; Komaki, Y.; Sano, S.; Shiro, M. *Chemistry Letters* **1994**, 597.

(17) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1984**, *25*, 1539.

(18) Bee, C.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1681.

(19) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091.

(20) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579.

(21) Seebach, D.; Stucky, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1351.

(22) Zhang, L. M.; Wang, S. Z. *J. Am. Chem. Soc.* **2006**, *128*, 1442.

(23) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312.

(24) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958.

(25) Comelles, J.; Moreno-Manas, M.; Perez, E.; Roglans, A.; Sebastian, R. M.; Vallribera, A. *J. Org. Chem.* **2004**, *69*, 6834.

(26) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(27) Mccooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 6367.

(28) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348.

(29) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* **2004**, *69*, 9002.

(30) Ichikawa *J. Pure Appl. Chem.* **2000**, *72*.

(31) Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033.

(32) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629.

(33) Bremner, J. B.; Coates, J. A.; Coghlan, D. R.; David, D. M.; Keller, P. A.; Pyne, S. G. *New Journal of Chemistry* **2002**, *26*, 1549.

(34) Browder, C. C.; West, F. G. *Synlett* **1999**, 1363.

(35) Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860.

(36) Schleyer, P. V. *J. Am. Chem. Soc.* **1967**, *89*, 699.

(37) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054.

(38) Rondan, N. G.; Paddonrow, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436.

(39) Rondan, N. G.; Paddonrow, M. N.; Caramella, P.; Mareda, J.; Mueller, P. H.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4974.

(40) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472.

(41) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941.

(42) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443.

(43) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219.

(44) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661.

(45) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773.

(46) Fleming, I. *Frontier Orbital and Organic Chemical* reactions; John Wiley & Sons, Ltd.: New York, **1976**, 57.

(47) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728.

(48) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705.

(49) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345.

(50) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542.

(51) Fruhauf, H. W. *Coord. Chem. Rev.* **2002**, *230*, 79.

(52) Ogliarus.Ma; Romanell.Mg; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261.

(53) Shibata, T.; Yamashita, K.; Ishida, H.; Takagi, K. *Org. Lett.* **2001**, *3*, 1217.

(54) Pearson, A. J.; Kim, J. B. *Org. Lett.* **2002**, *4*, 2837.

(55) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

(56) Isobe, H.; Sato, S.; Tanaka, T.; Tokuyama, H.; Nakamura, E. *Org. Lett.* **2004**, *6*, 3569.

(57) Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814.

(58) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597.

(59) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573.

(60) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014.

(61) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348.

(62) Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1291.

(63) Lian, J. J.; Chen, P. C.; Lin, Y. P.; Ting, H. C.; Liu, R. S. *J. Am. Chem. Soc.* **2006**, *128*, 11372.

(64) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432.

(65) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615.

(66) Trost, B. M.; Nanninga, T. N.; Satoh, T. *J. Am. Chem. Soc.* **1985**, *107*, 721.

(67) Trost, B. M.; Yang, B. W.; Miller, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 6482.

(68) Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schworer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328.

(69) Su, C. C.; Chen, J. T.; Lee, G. H.; Wang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4999.

(70) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32.

(71) Lovely, C. J.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607.

(72) Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *67*, 7446.

(73) Krafft, M. E.; Bonaga, L. V. R.; Wright, J. A.; Hirosawa, C. *J. Org. Chem.* **2002**, *67*, 1233.

(74) Dominguez, G.; Casarubios, L.; Perez-Serano, L.; Perez-Castells, J. *Org. Lett.* **1999**, *1*.

(75) Gibson, S. E.; Johnstone, C.; Stevenazzi, A. *Tetrahedron* **2002**, *58*, 4937.

(76) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762.

(77) Sturla, S. J.; Buchwald, S. L. *Organometallics* **2002**, *21*, 739.

(78) Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*.

(79) Tang, Y. F.; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J. H.; Yang, Z. *Org. Lett.* **2005**, *7*, 1657.

(80) Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413.

(81) Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 6541.

(82) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444.

(83) Fox, J. M.; Yan, N. *Current Organic Chemistry* **2005**, *9*, 719.

(84) Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714.

(85) Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2001**, *3*, 3193.

(86) Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593.

(87) Sugihara, T.; Yamada, M.; Yamagushi, M.; Nishiizawa, M. *Synlett* **1991**, 771.

(88) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

(89) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204.

(90) Cao, H.; Van Ornum, S. G.; Deschamps, J.; Flippen-Anderson, J.; Laib, F.; Cook, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 933.

(91) Mcneill, E.; Chen, I.; Ting, A. Y. *Org. Lett.* **2006**, *8*, 4593.

(92) Chen, I.; Howarth, M.; Lin, W. Y.; Ting, A. Y. *Nature Methods* **2005**, *2*, 99.

(93) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379.

(94) Rivero, M. R.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992.

(95) Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 5680.

(96) Rivero, M. R.; Adrio, J.; Carretero, J. C. *Eur. J. Org. Chem.* **2002**, 2881.

(97) Gosavi, R. K.; Agarwala, U.; Rao, C. N. R. *J. Am. Chem. Soc.* **1967**, *89*, 235.

(98) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217.

(99) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. J. *J. Am. Chem. Soc.* **1995**, *117*, 7071.

(100) Fischer, E. O.; Maasbol, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

(101) Wu, Y.; Kurahashi, T.; de Meijere, A. *J. Organomet. Chem.* **2005**, *690*, 5900.

(102) Gomez-Gallego, M.; Mancheno, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44.

(103) Barluenga, J.; Lopez, L. A.; Lober, O.; Tomas, M.; Garcia-Granda, S.; Alvarez-Rua, C.; Borge, J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3392.

(104) Albeniz, A. C.; Espinet, P.; Manrique, R.; Perez-Mateo, A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2363.

(105) Barluenga, J.; Vicente, R.; Lopez, L. A.; Rubio, E.; Tomas, M.; Alvarez-Rua, C. *J. Am. Chem. Soc.* **2004**, *126*, 470.

(106) Barluenga, J.; Barrio, P.; Lopez, L. A.; Tomas, M.; Garcia-Granda, S.; Alvarez-Rua, C. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3008.

(107) Barluenga, J.; Barrio, P.; Riesoro, L.; Lopez, L. A.; Tomas, M. *Tetrahedron* **2006**, *62*, 7547.

(108) Ni, Y. K.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 11162.

(109) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3964.

(110) Barluenga, J.; Alonso, J.; Fananas, F. J. *J. Am. Chem. Soc.* **2003**, *125*, 2610.

(111) Barluenga, J.; Alonso, J.; Fananas, F. J. *Chem. Eur. J.* **2005**, *11*, 4995.

(112) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2406.

(113) Murakami, M.; Amii, H.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1476.

(114) Gibson, S. E.; Peplow, M. A. *Adv. Organomet. Chem.* **1999**, *44*, 275.

(115) Davie, C. P.; Danheiser, R. L. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 5867.

(116) Rigby, J. H.; Wang, Z. Q. *Org. Lett.* **2003**, *5*, 263.

(117) Huang, W. W.; Tidwell, T. T. *Synthesis* **2000**, 457.

(118) Moser, W. H.; Feltes, L. A.; Sun, L. D.; Giese, M. W.; Farrell, R. W. *J. Org. Chem.* **2006**, *71*, 6542.

(119) Moser, W. H.; Sun, L. D.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389.

(120) Dalton, A. M.; Zhang, Y. J.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465.

(121) Gottker-Schnetmann, I.; Aumann, R. *Organometallics* **2001**, *20*, 346.

(122) Gottker-Schnetmann, I.; Aumann, R.; Bergander, K. *Organometallics* **2001**, *20*, 3574.

(123) Ku, R. Z.; Huang, J. C.; Cho, J. Y.; Kiang, F. M.; Reddy, K. R.; Chen, Y. C.; Lee, K. J.; Lee, J. H.; Lee, G. H.; Peng, S. M.; Liu, S. T. *Organometallics* **1999**, *18*, 2145.

(124) Waters, M. L.; Brandvold, T. A.; Isaacs, L.; Wulff, W. D.; Rheingold, A. L. *Organometallics* **1998**, *17*, 4298.

(125) Padwa, A. *J. Organomet. Chem.* **2001**, *617*, 3.

(126) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(127) Barluenga, J.; Vicente, R.; Lopez, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2006**, *128*, 7050.

(128) Blasko, G.; Brossi, A. *In the alkaloids*; Ed. Academic Press Inc.: New York, **1990**, *157*, 111.

(129) Fidalgo, J.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1993**, *34*, 7317.

(130) Giese, M. W.; Moser, W. H. *J. Org. Chem.* **2005**, *70*, 6222.

(131) Bouaucheau, C.; Parlier, A.; Rudler, H. *J. Org. Chem.* **1997**, *62*, 7247.

(132) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(133) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

(134) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; Oregan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(135) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

(136) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(137) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(138) Grubbs, R. H. *Handbook of Metathesis*; (Ed.: R. H. Grubbs) Wiley-VCH: Weinheim, **2003**, 22.

(139) Martinez, V.; Blais, J. C.; Astruc, D. *Org. Lett.* **2002**, *4*, 651.

(140) Nesmeyanov, A. N.; Volkenau, N. A.; Bolesova, I. N. *Tetrahedron Lett.* **1963**, 1725.

(141) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740.

(142) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(143) Gardiner, J.; Anderson, K. H.; Downard, A.; Abell, A. D. *J. Org. Chem.* **2004**, *69*, 3375.

(144) Miller, A. K.; Chambers, C. H.; Kennedy-Smith, J. J.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057.

(145) Hiersemann, M. *Nachr. Chem.* **2006**, *54*, 29.

(146) Wallace, D. J. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 1912.

(147) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J. Z.; Zhao, H. Y. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

(148) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 3601.

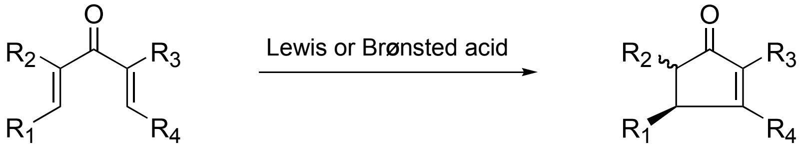
(149) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035.

Chapter 2

Reagent-free Nazarov Cyclizations

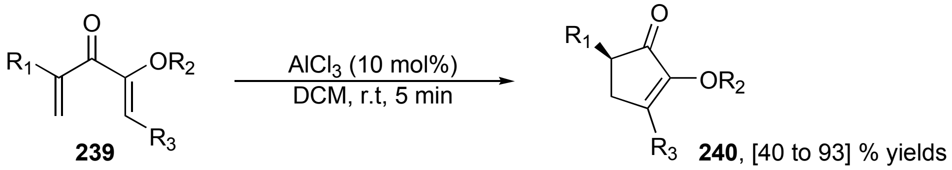
I-Introduction

The Nazarov cyclization of dienones to produce 2-cyclopentenones has become one of the most powerful methods for cyclopentannulation in recent years[1-5] (*Scheme 2.1*).



Scheme 2.1: Nazarov Cyclization Catalyzed by an Acid Source

Since its discovery in 1941[6], the reaction has been subject to a steady stream of innovations. The dienone substrates are easy to synthesize and the mechanistic picture that underpins the reaction permits the accurate prediction of substituent effects. The development of progressively milder acid promoters has played an important role in the evolution of the Nazarov cyclization as a versatile synthetic methodology. Strong Lewis acids such as $AlCl_3$, $SnCl_4$ and $FeCl_3$ largely surperceyuiopded the original harsh, mineral acid promoters. Although generally effective, they were necessarily restricted to robust sustrates that could tolerate the stoichiometric amounts of reagent that were usually required for complete reaction[1]. Recent reports in this area have described catalytic protocols for the cyclization, as well as milder Lewis acid with non-nucleophilic counter-ions[7-13]. In this respect, Trauner et *al.* described in 2003, the Lewis acid catalyzed electrocyclization of substrates **251** (*Scheme 2.2*).



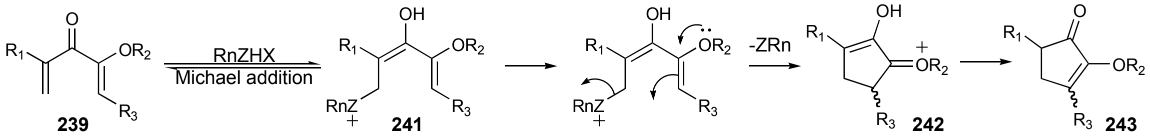
Scheme 2.2: Catalytic Nazarov Reaction of substrate **239**

Alkoxy cyclopentenones **240** were smoothly produced in good to excellent yields. All substrates underwent the Nazarov cyclization with complete regioselectivity, usually placing the double bond on the side of the alkoxy substituents.

II-Results and Discussion

II-1-Preliminary Results

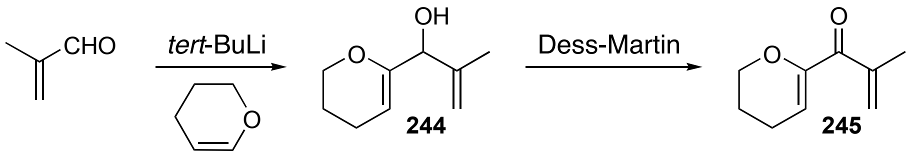
Catalytic asymmetric synthesis is providing chemists with new and powerful tools for the efficient synthesis of complex molecules. While many of the most notable catalytic systems are metal-based[14] and rely on chiral Lewis acid and organometallic redox-based catalyst, increasing numbers of asymmetric reactions are catalyzed by chiral nucleophiles[15-17]. However, there is a significant lack in the literature of such methodology utilized toward 5-membered ring formation. In this respect, we evaluated that nucleophilic catalysis could be employed as an elegant catalytic route toward the synthesis of cyclopentanoids. Hereby is described a concerted Michael addition and 5-*endo* cyclization reaction (*Scheme 2.3*).



Scheme 2.3: Concerned Michael Addition and 5-*Endo* Cyclization Reaction

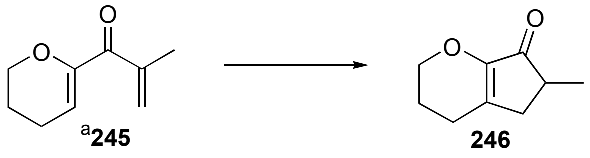
The aim of this project underpins the postulation that a preliminary Michael addition on the α,β-unsaturated ketone **249** with a suitable nucleophile would readily produce the cationic enolate intermediate **241**. Although the latter exhibits a *5-enolendo-exo-tet* intermediate, 5-membered ring closure may occur to produce cationic cyclic species **242** and finally cyclopentenone **243**.

We started by exploring the validity of this strategy with dienone **245**, which bears an α-alkoxy substituent to the ketone, depicting a straightforward and well-documented synthesis (*Scheme 2.4*).



Scheme 2.4: Synthesis of Substrate **245**

Following Trauner's procedure[8], substrate **245** was prepared *via* the addition of lithiated dihydropyran to the commercially available 2-methylpropenal in THF, which gave the alcohol **244** in 83% yield. Further oxidation in DCM yielded dienone **245** in 49% yield. Achiral nucleophiles were selected in this preliminary study based on their efficiency of performing Michael addition. 1,4-Diaza-bicyclo(2,2,2)-octane (DABCO), anchonidine (Anc) and *tri*butyl-phosphine are well-known in the literature to accomplish this task[18] (*Scheme 2.5*).



Solvent (mL)	**Nucleophile** (eq)	**Time** (h)	**Temperature** (°C)	**Yield** (%)
DMF/H_2O (3/0.3)	^{b}DABCO (1.1)	12-12	23-150	**246** (60)
DMF/H_2O (3/0.3)	^{c}Anc (1.1)	12-29	23-150	**246** (60)
DMF (3)	$(Bu)_3P$ (1.1)	17	153	**246** (55)
DMF (3)	/	29	153	**246** (71)

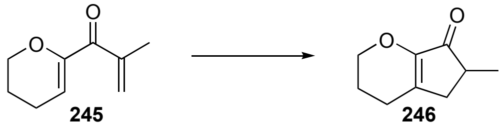
[a] dienone **245** (20 mmol) [b] DABCO: 1,4 diazabicyclo(2,2,2)octane [c] Anc: anchonidine

Scheme 2.5: Preliminary Results of Substrate **245** Cyclization *via* Michael Addition

When dienone **245** was stirred in DMF/H_2O media in the presence of DABCO for 12h at room temperature and 12h reflux, we were pleased to isolate cleanly the cyclic product **246** in 60% yield. The use of equimolar quantities of anchonidine and *tri*butyl-phosphine as nucleophiles led to similar yields. None of the Michael product (**241**, *Scheme 2.2*) could be detected by H^1 NMR spectroscopy. When a control reaction was performed without any nucleophile, the product **246** could be formed after 29h reflux in slightly increased yield (71%). Clearly, the nucleophile species in these conditions do not play any role in the cyclization process. Instead, the heat provided to the system was sufficient to induce the 4π electrocyclization following a conrotatory pathway in the case of substrate **245**. To the best of our knowledge, this represents the first recorded example of a neutral thermal Nazarov cyclization in the absence of external acid promoters.

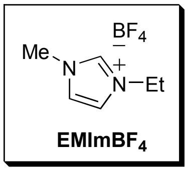
II-2-Optimization of the Neutral Nazarov Cyclization Conditions

We were concerned about the extended refluxed time (29h) required for the neutral thermal Nazarov ring closure of dienone **245** to reach completion. Microwave technology appeared as an ideal alternative[19]. Since the first reports of microwave-assisted synthesis[20] in 1986, the technique has been accepted as a method for reducing reaction times often by an order of magnitude and for increasing yields of product compared to conventional methods. In addition, it provides the ability to control the temperature, pressure and reaction time, which give the opportunity to optimize reactions in a very short time. A brief survey of reaction solvent indicated that polar aprotic solvents such as DMA or DMF worked well in the microwave, solvents such as DCM, MeOH and acetonitrile were poor solvent in the reaction, producing none of the desired cyclopentenone. Taking advantage of the microwave heating effect, we opted for the high dielectic constant organic solvent DMA, which gave 9% increased yield, compared to the conventional oil bath method, after 30 min reaction time at 180°C (*Scheme 2.6*).



245 **246**

Solvent (mL)	**conditions**	**Yield** (%)
DMF (3)	^{a}oil bath, 29h, 153 ^{o}C	**246** (71)
DMA (0.5)	^{b}microwave, 300W, 30 min, 180 ^{o}C	**246** (80)
^{d}**EMImBF$_4$** (0.5)	^{c}microwave, 100W, 2 min, 250 ^{o}C	**246** (82)



EMImBF$_4$

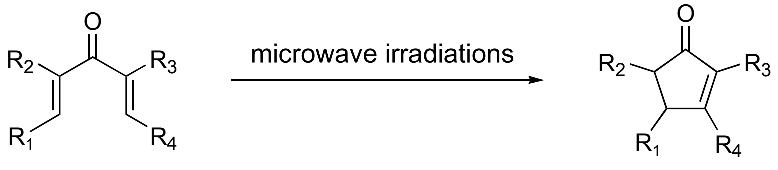
^{a} dienone **245** (20 mmol). ^{b} dienone **245** (0.4-0.83 mmol), pressure=300 PSI, ramp time=5 min, hold time=30 min, stirring=on. ^{c} dienone **245** (0.4-0.83 mmol), pressure=100 PSI, ramp time=1 min, hold time=2 min, stirring=on. ^{d} EMImBF$_4$= 1-ethyl-3-methylimidazolium tetrafluoroborate.

Scheme 2.6: Conventional method *vs* Microwave Procedure

Although the high boiling point polar DMA solvent is an excellent medium to perform the reaction, the subsequent work-up procedure is slightly more complicated by the need to remove the solvent at the end of the reaction. One significant alternative to this traditional organic solvent is the room temperature ionic liquids (RTILs), which exhibit specific chemical and physical properties. RTILs are salts composed of organic cations and bulky fluoro-anions such as 1-ethyl-3-methylimidazolium tetrafluoroborate (**EMImBF$_4$**). The latter is liquid at room temperature, stable toward air and moisture, and displays very good dissolution properties for most organic and inorganic compounds. The most important feature that makes RTILs remarkable under microwave irradiation is their high stability at elevated temperature[21]. Indeed, when **EMImBF$_4$** was used as reaction solvent, a reaction temperature of 250°C could be reached under microwave irradiation, which allowed the completion of the reaction within 1 min and gave 82% yield of the desired product **246**. With these two optimized microwaves procedures in hand, the scope of this methodology could be further extended to alternative substrates.

II-3-Scope and Limitation of the Neutral Nazarov Cyclization Methodology

Dienones **247a-c** were synthesized by respective literature methods[12,22,23] and subjected to thermal Nazarov cyclization in EMImBF$_4$ and DMA (*Scheme 2.7*).



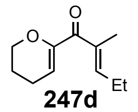
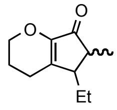
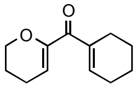
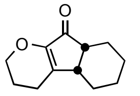
247a-c **248a-c**

247, R$_1$, R$_2$	**247**, R$_3$, R$_4$	**solvent**	**Time** (min)	**Temperature** (°C)	**Yield** (%)
Ph, Me	Me, Ph	EMImBF$_4$	2	250	[a]**248a** (98)
H, Me	Me, Ph	EMImBF$_4$	2	250	**248b** (85)
H, OEt	Me, Et	DMA	30	180	**248c** (68)

[a] **248a** *trans/cis* 5:1

Scheme 2.7: α,α'-Dialkyl and α,α'-OxyAlkyl Dienones **247a-c** Thermal Nazarov Cyclization

We were pleased to observe the expected cyclopentenones **248a-c** produced in good to excellent yields[24] for a range of α,α'-dialkyl and α,α'-oxyalkyl dienones **247a-c**. Although α,α'-dialkyl dienones **247a** and **247b** were stable under the ionic liquid procedure, α,α'-oxyalkyl dienones **247c** underwent slight decomposition at 250°C resulting to a lower yield than with the use of DMA as solvent. We observed a similar trend with monocyclic and bicyclic α,α'-oxyalkyl dienones **247d** and **247e**, which provided better yields with DMA procedure compared to EMImBF$_4$ conditions (*Scheme 2.8*).

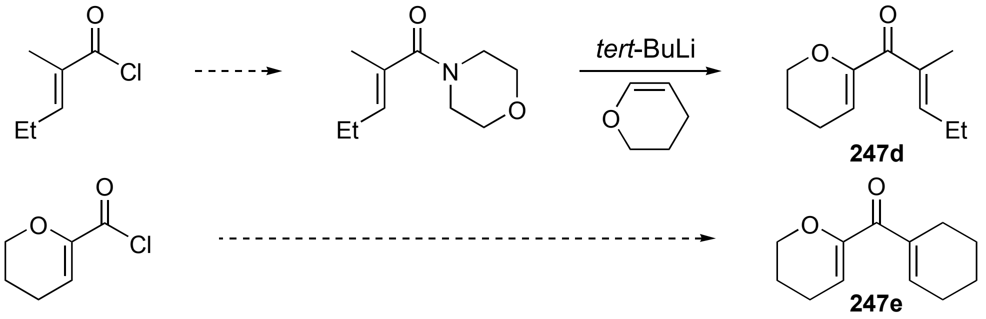
procedure	**dienone**	**Time** (min)	**product**	**Yield** (%)
DMA	 **247d**	30		[a]**248d** (61)
DMA	 **247e**	30		**248e** (71)

[a]**248d** 9:1 unassigned

Scheme 2.8: Monocyclic and Bicyclic α,α'-OxyAlkyl Dienones **247d** and **247e** Thermal Nazarov Cyclization

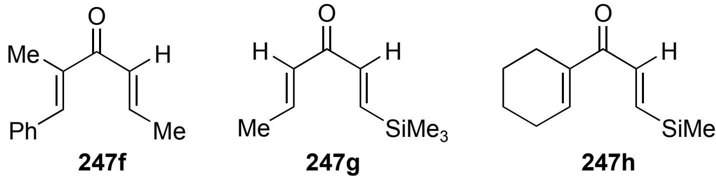
Bicyclic and tricyclic cyclopentanoid products **248d** and **248e** were produced in satisfactory yields. In all cases, the cyclopentenone regioisomer having the most substituted double bond was the only isolated product of the reaction.

The novel dienone **247d** was synthesized through the addition of 2-lithiodihydropyran to the appropriate morpholine amide using the same procedure[12] as the known dienone **247e**. (*Scheme 2.9*).



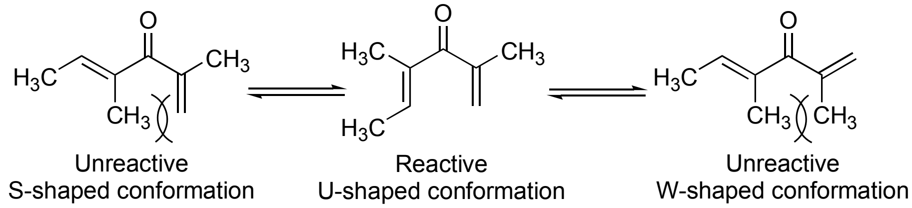
Scheme 2.9: Synthesis of Dienones **247d** and **247e**

When mono α-substituted and α,α'-unsubstituted dienones **247f-h** were synthesized by respective literature methods[23,25] respectively and subjected to thermal Nazarov cyclization in $EMImBF_4$ and DMA, none of the desired Nazarov products could be detected (*Scheme 2.10*).



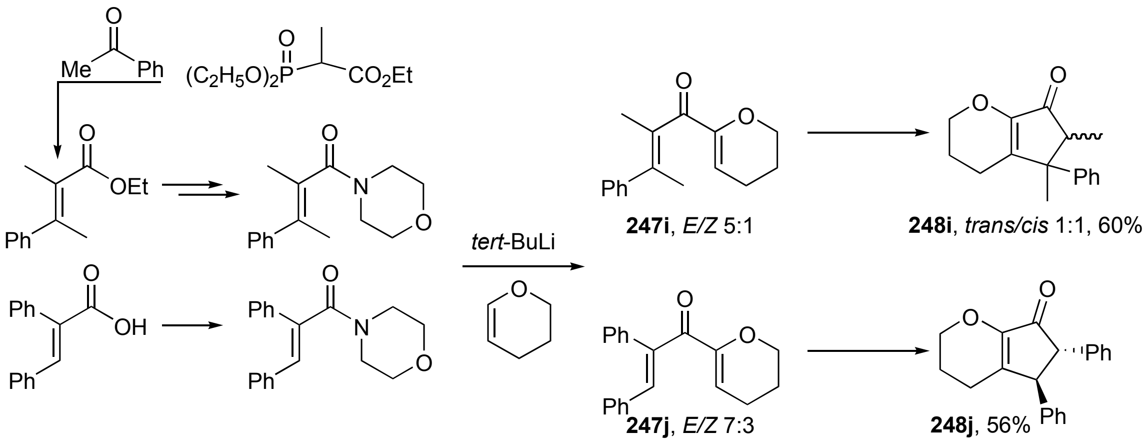
Scheme 2.10: Mono α-Substituted and α,α'-Unsubstituted Dienones **247f-h**

Instead, almost quantitative recovery of the starting substrate was isolated after reaction. Therefore, it seems that substitution α- to the ketone group is a necessary criterion for successful reaction. This substitution pattern is common in Nazarov substrates[9] and is thought to promote the population of the U-shaped conformation necessary for cyclization by raising the energy of the unreactive S and W-shaped conformers (*Scheme 2.11*).



Scheme 2.11: Conformational Equilibrium Illustrated for α,α'-Alkyldienone

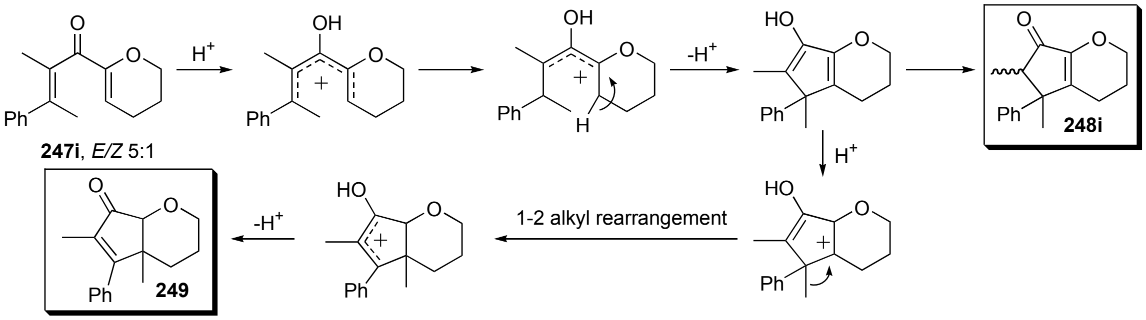
Substitution at the β-position by contrast is not as important (substrates **247b** and **247c**, *Scheme 2.7*). Wadsworth-Emmons reaction between the alkoxy phosphine oxide and acetophenone produced the appropriate tetrasubstituted-α,β-unsaturated ester, which after hydrolysis, morpholine enamide formation[12] and treatment with lithiodihydropyran produced substrate **247i** with *E/Z* ratio of 5:1 (*Scheme 2.12*).



Scheme 2.12: Synthesis of dienones **247i** and **247j** and their Nazarov Cyclizations

Substrate **247j** with a *E/Z* ratio of 7:3 was readily synthesized using α-phenyl-cinnamic acid, which followed the same synthetic route as **247i**. When the neutral DMA Nazarov cyclization method was applied to both substrates, **248i** was formed smoothly in 60%

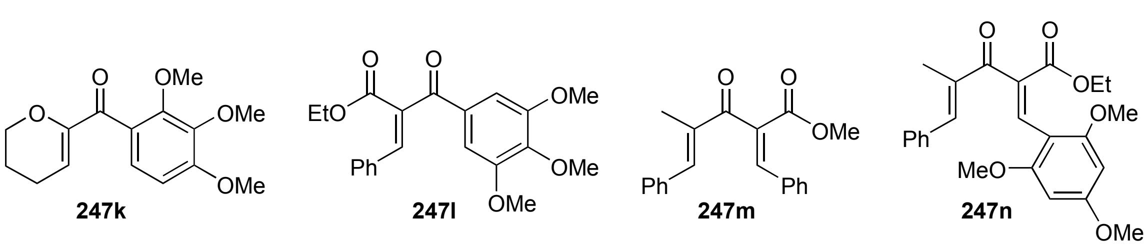
yield with a trans/cis ratio of 1:1 and **248j** was selectively produced in 56% yield. We believe that both moderate yields are likely due to a failure of the minor *Z* isomer in the starting dienones to undergo the desired ring closure. The requisite U-shaped conformation that the dienones must adopt for cyclization is subject to severe steric hindrance (*Scheme 2.11*). Substrate **247i** was also synthesized with a view to examine possible alkyl shifts in the reaction[26] (*Scheme 2.13*).



Scheme 2.13: Possible Alkyl Shifts of β,β-Disubstituted Dienone **247i** Producing Rearranged Cyclopentenone **249**

β,β-Disubstituted dienones such as **247i** are especially vulnerable to produce rearranged products under the acidic conditions of the classical Nazarov. 1-2 Alkyl shift rearrangements resulting in products such as **249** can be readily observed when the activated cationic cyclic intermediate is formed by protonation of one of the double bond produced after the pericyclic ring closure step. Under the neutral conditions employed, no such rearrangement products could be detected and the expected cyclopentenone **248i** was produced smoothly in 60% yield.

The reaction conditions could not be extended to all substrates (*Scheme 2.14*).



Scheme 2.14: Unreactive and Decomposed Substrates **247k-n**

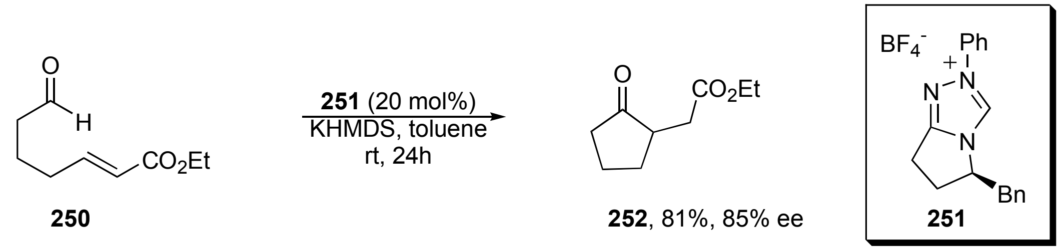
When substrates **247k** and **247l** were synthesized by literature methods[3,12] and subjected to thermal Nazarov cyclization in $EMImBF_4$ and DMA, none of the desired cyclopentenones could be detected. Instead, starting dienones were resistant to all attemps at achieving an aromatic Nazarov cyclization; starting materials were recovered from the microwave vessel after prolonged irradiation. β-Keto esters such as **247m** and **247n** were synthesized by literature methods[13] and were also poor substrates, undergoing extensive decomposition under the microwave conditions.

A final experiment has been carried out to investigate whether or not traces of Brønsted acid were present in the reaction solvent or in the microwave vessel, which would have catalyzed the Nazarov cyclization. Dienone **247e** was irradiated in freshly distilled DMA, in the presence of one equivalent of proton sponge, using a base-washed microwave vessel. A slightly attenuated 60% yield was recorded, indicating that in DMA, genuine thermal cyclization can occur in the absence of any catalysis. The success of the reaction in ionic liquids, by contrast, may in part be due to their weakly Lewis acidic character reinforcing their qualities as superb microwave solvents[27,28].

III-Conclusion and Future Work

We have discovered a new reagent-free protocol for Nazarov cyclization that produces highly substituted cyclopentenones in good to excellent yields. In addition to the economic and environmental benefits of conducting reagent-free carbon-carbon bond formation, the neutral reaction conditions may enable the extension of Nazarov methodology to acid-sensitive substrates that have been previously inaccessible.

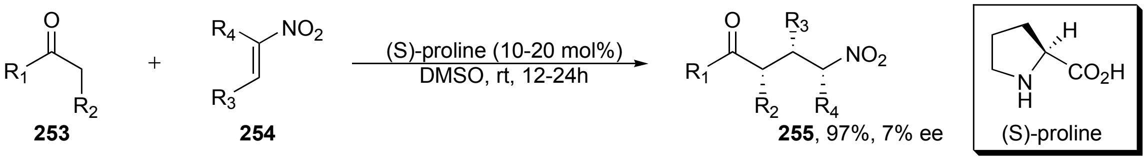
Although efforts directed toward the nucleophilic catalysis of substrate **245** (*Scheme 2.5*), which rely on concerted Michael addition and 5-*endo* cyclization reaction did not occur when nucleophilic species such as DABCO, anchonidine and *tri*butyl-phosphine were used, considerable progress accomplished in the domain of organocatalysis[15,17,29] drive us back to this original proposal. For instance, Rovis et *al.* reported in 2002, the asymmetric intramolecular Stetter reaction[30] of aliphatic substrate **250**, which employs carbene nucleophile **251** (*Scheme 2.15*).



Scheme 2.15: Asymmetric Intramolecular Stetter Reaction Catalyzed by **251**

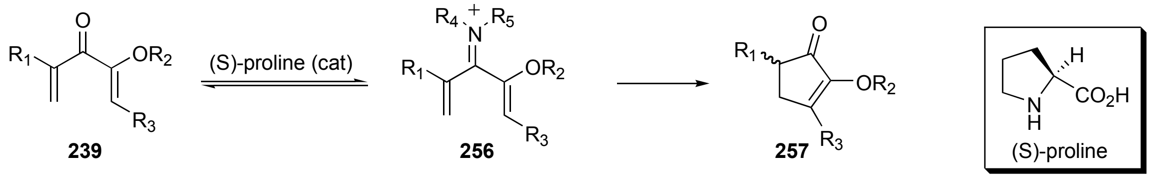
Although nucleophile **251** reacts with the aldehyde of **250** rather than with Michael acceptor here, the good stereoselectivity and efficient catalytic turnover of this 5-*exo* ring closure demonstrate the high reactivity of carbene nucleophiles and its potential in organic synthesis as organocatalytic species. In addition, recent progress[31] in carbene chemistry allows derivatives of species **251** to be readily available and stable at room temperature, which point that carbene nucleophiles may be an interesting candidate for our methodology.

List et *al.* reported in 2001 the first direct asymmetric proline-catalyzed Michael reaction[32] of ketones **253** and nitro olefins **254**, which produced species **255** in high yields and poor enantioselectivities (*Scheme 2.16*).



Scheme 2.16: First Direct Asymmetric proline-Catalyzed Michael Reaction

Although enantioselectivity of the reaction needs to be optimized, this demonstrates that asymmetric enamine catalytic Michael reaction is viable under proline catalysis. In addition, Kellogg described this year the remarkable insight into the behavior of enantiomerically enriched proline under heterogeneous conditions[33], which may involves immediate implications for asymmetric catalysis. Therefore, proline catalysis seems to be an attractive alternative toward our methodology (*Scheme 2.17*).



Scheme 2.17: Michael Acceptor Activation *Via* Iminium-Ion Formation

Proline catalyst may activate Michael receptor **239** *via* an iminium-ion intermediate **256**, which may initiate the 5-*endo* ring closure to give product **257**.

IV-Experimental

NMR spectra were recorded on a Brüker AC250 (250MHz) instrument. The H^1 NMR data are presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet,) and the coupling constant (J, in hertz). The C^{13} NMR data are reported as the ppm on the δ scale followed by the interpretation. IR spectra were recorded on a JASCO FT/IR-460 plus instrument using 4mm sodium chloride disks. The wavelengths of the maximum absorbance (ν_{max}) are quoted in cm^{-1}. Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea. Accurate mass measurements were obtained on a Finnigan MAT 900 XLT double focusing mass spectrometer. The data are recorded as the ionisation method followed by the calculated and measured masses.

TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light and/or anisaldehyde or potassium permanganate stains. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. The eluent is quoted as a percentage.

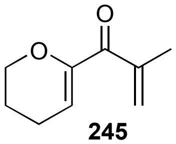
All solvents were dried before use unless otherwise stated. THF was dried over sodium with benzophenone as an indicator. DCM was distilled over calcium hydride. Diisopropylamine and pyridine were dried and stored over potassium hydroxide. N, N-dimethylacetamide (DMA) was distilled at 42°C, 0.8 mBar from CaH_2, and stored over molecular sieves under nitrogen.

All other chemicals were purchased from a chemical supplier and used as received.

IV-1-Synthesis of starting dienones

Dienones **245**[8], **247a**[22], **247b,f**[23], **247c**,e[12]**, 247l**[3], **247m**,**n**[13] and **256g**,**h**[25] were prepared according to literature procedures.

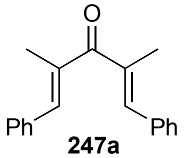
1-(5,6-Dihydro-4H-pyran-2-yl)-2-methylpropenone, **245**[8]



245

Colorless oil; H^1 NMR (CDCl$_3$, 250 MHz) δ 5.84 (m, 1H), 5.66 (m, 1H), 5.64 (m, 1H), 4.11 (t, 2H, J = 5.0Hz), 2.22 (m, 2H), 1.93 (d, 3H, J = 1.0Hz) and 1.87 (2H, m).

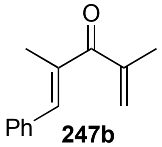
2,4-Dimethyl-1,5-diphenylpenta-1,4-dien-3-one, **247a**[22]



247a

White solid; H^1 NMR (CDCl$_3$, 250 MHz) δ 7.45-7.25 (m, 10H), 7.25-7.15 (m, 2H) and 2.20 (s, 6H).

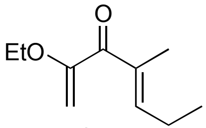
2,4-Dimethyl-1-phenylpenta-1,4-dien-3-one, **247b**[23]



247b

Colorless oil; H^1 NMR (CDCl$_3$, 250 MHz) δ 7.43-7.27 (m, 6H), 5.69 (dq, 1H, J = 1.5, 1.5Hz), 5.58 (dq, 1H, J = 1.5, 1.0Hz), 2.13 (d, 3H, J = 1.5Hz) and 2.03 (dd, 3H, J = 1.5, 1.0Hz).

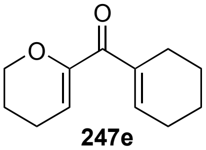
2-Ethoxy-4-methylhepta-1,4-dien-3-one, **247c**[12]



247c

Pale yellow oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 6.55 (m, 1H), 4.67 (d, 1H, J = 2.5Hz), 4.50 (d, 1H, J = 2.5Hz), 3.82 (q, 2H, J = 7.0Hz), 2.26-2.18 (m, 2H), 1.81 (s, 3H), 1.35 (t, 3H, J = 7.0Hz) and 1.04 (m, 3H).

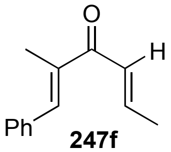
Cyclohex-1-enyl-(5,6-dihydro-4H-pyran-2-yl)-methanone, **247e**[12]



247e

Colorless oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 6.66 (m, 1H), 5.64 (t, 1H, J = 4.0Hz), 4.06 (t, 2H, J = 5.0Hz), 2.19 (m, 6H), 1.83 (m, 2H) and 1.59 (m, 4H).

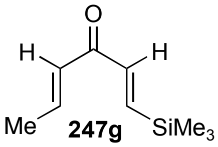
2,5-Dimethyl-1-phenylpenta-1,4-dien-3-one, **247f**[23]



247f

H^1 NMR ($CDCl_3$, 250 MHz) δ 7.46 (m, 1H), 7.43-7.34 (m, 5H), 6.80 (m, 1H), 6.72 (m, 1H), 2.11 (m, 3H) and 1.96 (m, 3H).

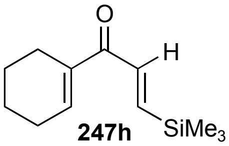
1-Trimethylsilanyl-1,4-hexadien-3-one, **247g**[25]



247g

Yellow oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 7.12 (d, 1H, J = 19Hz), 6.93 (dq, 1H, J = 15.0, 7.0Hz), 6.72 (d, 1H, J = 19Hz), 6.43 (m, 1H), 2.03 (dd, 3H, J = 7.0, 1,5Hz) and 0.33 (s, 9H).

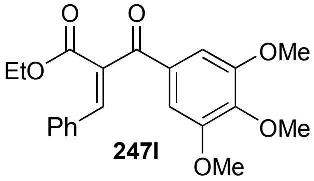
1-Cyclohex-1-enyl-3-trimethylsilanyl-propenone, **247h**[25]



247h

Yellow oil; H[1] NMR ($CDCl_3$, 250 MHz) δ 7.08 (d, 1H, J = 19.0Hz), 6.96 (m, 1H), 5.61 (m, 1H), 2.32-2.25 (m, 4H), 1.71-1.60 (m, 4H), and 0.15 (s, 9H).

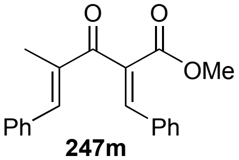
3-Phenyl-2-(3,4,5-trimethoxy-benzoyl)-acrylic acid ethyl ester, **247l**[3]



247l

Yellow solid; M.p. 69-70°C. This material was identified as being the (E)-isomer. H[1] NMR ($CDCl_3$, 250 MHz) δ 7.99 (s, 1H), 7.40-7.25 (m, 5H), 7.19 (s, 2H), 4.36 (q, 2H, J = 7.0Hz), 3.90 (s, 3H), 3.82 (s, 6H), and 1.26 (t, 3H, J = 7.0Hz).

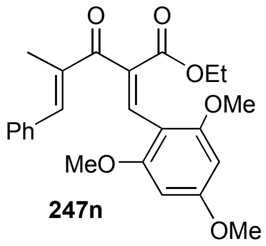
2-Benzylidene-4-methyl-3-oxo-5-phenyl-pent-4-enoic acid methyl ester, **247m**[13]



247m

Yellow oil; H[1] NMR ($CDCl_3$, 250 MHz) δ 7.90 (m, 1H), 7.48-7.28 (m, 11H), 3.42 (s, 3H) and 2.20 (d, 3H, J = 1.5Hz).

4-Methyl-3-oxo-5-phenyl-2-(2,4,6-trimethoxy-benzylidene)-pent-4-enoic acid ethyl ester, **247n**[13]

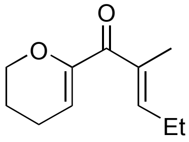


247n

Yellow solid; H^1 NMR ($CDCl_3$, 250 MHz) δ 8.02 (s, 1H), 7.35-7.27 (m, 6H), 5.98 (s, 2H), 4.21 (q, 2H, J = 7.0Hz), 3.75 (s, 3H), 3.66 (s, 6H), 2.08 (s, 3H) and 1.22 (t, 3H, J = 7.0Hz).

The remaining dienones were synthesized through the addition of 2-lithiodihydropyran to the appropriate morpholine amide using the following procedure[12]: To 2,4 dihydropyran (1mL, 11.0 mmol) in THF (0.45 mL) at -78°C was added *tert*-butyllithium (6.5 mL, 1.7 M in pentane, 11.0 mmol) and the reaction mixture was allowed to warm to -5°C over 1h. The reaction mixture was then cooled to -78°C and the morpholine amide (8.6 mmol) in THF (10 mL) was added via canula and the reaction mixture was stirred for 1h at -78°C. The reaction mixture was quenched with brine/Et_2O (75 / 20 mL), extracted with Et_2O (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane:Et_2O = 9:1) to afford the dienone in 27-56% yield.

1-(5,6-Dihydro-4*H*-pyran-2-yl)-2-methyl-pent-2-en-1-one, **247d**

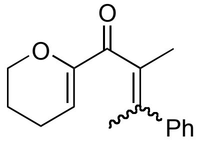


247d

Yellow oil; IR(thin film/cm^{-1}): ν_{max} 2933, 1651, 1286, 1064, 917; H^1 NMR ($CDCl_3$, 250 MHz) δ 6.36 (m, 1H), 5.65 (m, 1H), 4.11 (t, 2H, J = 5.0Hz), 2.17-2.26 (m, 4H), 1.83–1.87 (m, 2H), 1.83 (s, 3H) and 1.05 (t, 3H, J = 7.5Hz); C^{13} NMR ($CDCl_3$, 63 MHz) δ

193.20, 151.09, 144.25, 134.38, 111.96, 66.10, 21.87, 21.39, 20.56, 12.87 and 12.40; HRMS (ES$^+$): calcd for $C_{11}H_{16}O_2$ $[M+H]^+$:181.1223, found: 181.1223.

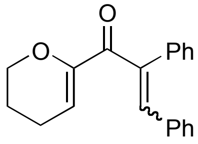
1-(5,6-Dihydro-4*H*-pyran-2-yl)-2-methyl-3-phenyl-but-2-en-1-one, **247i**



247i, *E/Z* 5:1

Colourless oil; 5:1 mixture of *E* and *Z* isomers. IR(thin film/cm^{-1}): ν_{max} 2933, 2873, 1667, 993. H^1 NMR ($CDCl_3$, 250 MHz) (major *E* isomer only) δ 7.37-7.19 (m, 5H), 6.14 (m, 1H), 4.17 (t, 2H, J = 5.5, Hz), 2.30 (m, 2H), 2.08-1.87 (m, 2H), 1.85 (m, 3H) and 1.77 (m, 3H); C^{13} NMR ($CDCl_3$, 63 MHz) (major *E* isomer only) δ 196.52, 150.75, 141.79, 136.40, 131.08, 128.11, 127.73, 126.85, 116.15, 66.33, 22.15, 21.07, 20.40 and 18.05; HRMS (ES$^+$): calcd for $C_{16}H_{18}O_2$ $[M+H]^+$:243.1380, found: 243.1380.

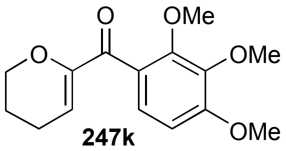
1-(5,6-Dihydro-4*H*-pyran-2-yl)-2,3-diphenyl-propenone, **247j**



247j, *E/Z* 7:3

Yellow solid; 7:3 mixture of *E* and *Z*-isomers; IR (thin film/cm^{-1}): ν_{max} 2932, 2359, 1624, 1070, 931, 765; H^1 NMR ($CDCl_3$, 250 MHz) (major *E* isomer only) δ 6.91-8.09 (m, 11H), 5.77 (m, 1H), 3.94-3.79 (m, 2H), 2.06-1.99 (m, 2H) and 1.71–1.61 (m, 2H); C^{13} NMR ($CDCl_3$, 63 MHz) (major *E* isomer only) δ 192.06, 151.53, 139.83, 136.85, 136.28, 134.82, 130.04, 129.26, 128.70, 128.49, 128.04, 127.68, 114.71, 66.17, 21.35 and 20.89; HRMS (EI$^+$): calcd for $C_{20}H_{18}O_2$ $[M^+]$: 290.13068, found: 290.13038.

(5,6-Dihydro-4H-pyran-2-yl)-(3,4,5-trimethoxy-phenyl)-methanone, **247k**



247k

White solid; M.p. = 59°C; IR(thin film/cm^{-1}): ν_{max} 2938, 1582, 1329, 1126, 1002, 731; H^1 NMR ($CDCl_3$, 250 MHz) δ 7.07 (s, 2H), 5.85 (t, 1H, J = 4.0Hz), 4.20 (t, 2H, J = 5.1Hz), 3.90 (s, 9H), 2.47-2.31 (m, 2H) and 2.16-2.07 (m, 2H); C^{13} NMR ($CDCl_3$, 63 MHz) δ 189.65, 152.42, 151.17, 141.53, 131.93, 114.46, 106.89, 66.22, 60.65, 56.03, 21.26 and 20.73; HRMS (ES$^+$): calcd for $C_{15}H_{18}O_5$ [M+H]$^+$:279.1227, found: 279.1228.

IV-2-General Procedure for Microwave-Assisted Nazarov Cyclization

All microwave irradiations were carried out in a CEM Discover microwave equipped with an Explorer module controlled by an external computer. A solution of the dienone (0.4 – 0.83mmol) in DMA or $EMImBF_4$ (0.5mL) was made up in a microwave vessel equipped with a stirrer bar. The mixture was stirred and irradiated under the following conditions:

$EMImBF_4$: µpower = 100W, pressure = 100psi, ramp time = 1min, hold time = 2min, temperature = 250°C.

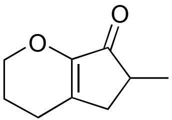
DMA: µpower = 300W, pressure = 300psi, ramp time = 5min, hold time = 30min, temperature = 180°C.

Reaction times are listed separately for each compound. The reaction mixture was quenched with Et_2O (20 mL), filtered through celite and absorbed onto silica gel (1.0 g). Flash column chromatography using hexane/Et_2O mixtures gave the pure cyclopentenone in 56-98% yield.

Cyclopentenones **246**[8], **248a**[34], **248b**[35] and **248e**[8] have been previously described in the literature.

IV-3-Nazarov Products

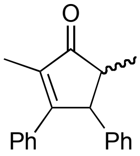
6-Methyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one, **246**[8], ($EMImBF_4$, 2min)



246

Colourless oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 4.10 (m, 2H), 2.69 (m, 1H), 2.38 (m, 1H), 2.32 (t, 2H, J = 6.0Hz), 2.03 (m, 1H), 1.95 (m, 2H), and 1.18 (d, 3H, J = 7.5Hz).

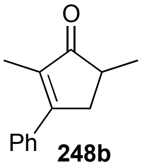
2,5-Dimethyl-3,4-diphenyl-cyclopent-2-enone, **248a**[34], ($EMImBF_4$, 3min)



248a *trans/cis* 5:1

Colorless oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 7.34-7.06 (m, 10H), 3.97 (m, 1H), 2.39 (m, 1H), 1.99 (d, 3H, J = 2.0Hz) and 1.32 (d, 3H, J = 7.5Hz).

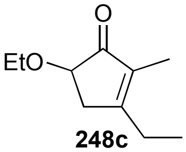
2,5-Dimethyl-3-phenyl-cyclopent-2-enone, **248b**[35], ($EMImBF_4$, 2min)



248b

Colorless oil; H^1 NMR($CDCl_3$, 250 MHz) δ 7.38 (m, 5H), 3.14 (ddq, 1H, J = 18.0, 7.5 and 2.0Hz), 2.55 (m, 1H), 2.30 (m, 1H), 1.91 (m, 3H) and 1.22 (d, 3H, J = 7.0Hz).

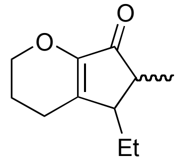
5-Ethoxy-3-ethyl-2-methyl-cyclopent-2-enone, **248c**, (DMA, 45 min)



248c

Pale yellow oil; IR(thin film/cm^{-1}): ν_{max} 2933, 1708, 1644, 1347. H^1 NMR ($CDCl_3$, 250 MHz) δ 3.91–3.77 (m, 2H), 3.57-3.41 (m, 2H), 2.77 (dd, 1H, J = 17.5, 7.0Hz), 2.45-2.26 (m, 2H), 1.62 (s, 3H), 1.17 (t, 3H, J = 7.0Hz), and 1.05 (t, 3H, J = 7.5Hz); C^{13} NMR ($CDCl_3$, 63 MHz) δ 206.8, 171.6, 133.7, 77.1, 65.6, 36.0, 24.0, 15.1, 11.1 and 7.5; HRMS (ES^+): calcd for $C_{10}H_{20}NO_2$ $[M+NH_4]^+$:186.1489, found: 186.1488.

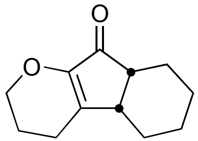
5-Ethyl-6-methyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **248d**, (DMA, 30 min)



248d 9:1 unassigned

Colourless oil; 9:1 mixture of diastereoisomers (unassigned). IR(thin film/cm^{-1}): ν_{max} 2929, 1706, 1647, 1456, 1296; H^1 NMR ($CDCl_3$, 250 MHz) (major diastereoisomer) δ 4.40-4.20 (m, 2H), 2.30 (m, 1H), 2.17-2.05 (m, 2H), 1.90-1.82 (m, 3H), 1.68 (m, 1H), 1.22 (m, 1H), 1.09 (d, 3H, J = 7.5Hz) and 0.84 (t, 3H, J = 7.5Hz); C^{13} NMR ($CDCl_3$, 63 MHz) (major diastereoisomer) δ 202.66, 149.47, 146.54, 66.38, 47.48, 43.81, 24.94, 22.60, 22.08, 15.90 and 11.02; HRMS (ES$^+$): calcd for $C_{11}H_{20}NO_2$ $[M+NH_4]^+$:198.1489, found: 198.1487.

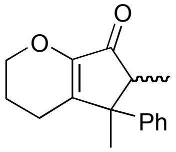
3,4,4b,5,6,7,8,8a-Octahydro-2H-1-oxa-fluoren-9-one, **248e**[8], (DMA, 15min)



248e

Colourless oil; H^1 NMR ($CDCl_3$, 250 MHz) δ 4.07-3.99 (m, 2H), 2.67 (m, 1H), 2.40-2.11 (m, 3H), 1.93-1.60 (5H, m) and 2.49-1.07 (m, 5H).

5,6-Dimethyl-5-phenyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **248i**, (DMA, 15 min)

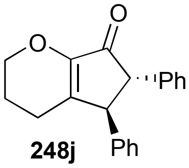


248i, *trans/cis* 1:1

Colourless oil; 1:1 mixture of diastereoisomers (unassigned). IR(thin film/cm^{-1}): ν_{max} 2932, 1713, 1649, 1444, 1267; H^1 NMR ($CDCl_3$, 250 MHz) δ 7.69-6.99 (m, 10H), 4.33-

4.17 (m, 4H), 2.51-1.99 (m, 10H), 1.73 (s, 3H), 1.53 (s, 3H), 1.18 (d, 3H, J = 7.5Hz), and 0.68 (d, 3H, J = 7.5Hz); C^{13} NMR (CDCl$_3$, 63 MHz) δ 202.17, 202.09, 150.40, 150.19, 149.85, 148.58, 145.03, 141.87, 128.57, 128.12, 126.87, 126.48, 126.36, 125.79, 66.75, 66.69, 54.07, 52.27, 48.25, 47.47, 23.79, 21.48, 20.21, 19.64, 11.18 and 9.57; HRMS (ES$^+$): calcd for $C_{16}H_{22}NO_2$ $[M+NH_4]^+$:260.1645, found: 260.1643.

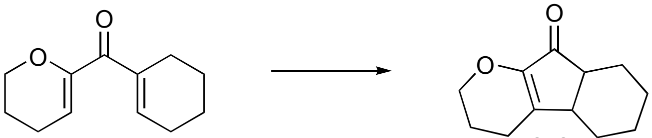
trans-5,6-Diphenyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[b]pyran-7-one, **248j**, (DMA, 45 min)



248j

White solid; M.p. = 136.2°C; IR(thin film/cm^{-1}): ν_{max} 3027, 1713, 1649, 1121, 1068; H^1 NMR (CDCl$_3$, 250 MHz) δ 7.82-7.42 (m, 8H), 7.29-6.95 (m, 2H), 4.71-4.32 (m, 2H), 3.96 (d, 1H, J = 2.0Hz), 3.59 (d, 1H, J = 2.0Hz), 2.32-2.25 (m, 4H); C^{13} NMR (CDCl$_3$, 63 MHz) δ 199.61, 150.83, 146.16, 140.54, 138.40, 128.93, 128.68, 127.80, 127.20, 127.00, 66.92, 60.23, 54.29, 22.08 and 21.39; HRMS (EI$^+$): calcd for $C_{16}H_{18}O_2$ $[M]^+$: 290.13068, found: 290.13059.

IV-4-Nazarov cyclisation of dienone **247e** in the presence of proton sponge



247e **248e**

A base-washed (KOH/EtOH) microwave vessel was charged with a solution of the dienone **256e** (50 mg, 0.26 mmol) and 1-8-Bis(dimethylamino)-naphthalene (proton sponge) (56 mg, 0.26 mmol) in freshly distilled, dry DMA (0.5 mL). The reaction mixture was stirred and heated under microwave irradiation for 30 min. at 180 °C, then diluted with Et$_2$O (20 mL) and quenched with aqueous HCl solution (1M, 20 mL). The organic phase was separated, filtered and concentrated on silica gel (1.0 g). The product was purified by column chromatography (hexane:Et_2O = 6:4) to afford 30 mg (60%) of *cis*-3,4,4b,5,6,7,8,8a-octahydro-2*H*-1-oxa-fluoren-9-one[8], **248e** as a colorless oil. H^1 NMR ($CDCl_3$, 250 MHz) δ 4.07-3.99 (m, 2H), 2.67 (m, 1H), 2.40-2.11 (m, 3H), 1.93-1.60 (5H, m) and 2.49-1.07 (m, 5H).

V-References

(1) Habermas, K. L.; Denmark, S.; Jones, T. K. *in Organic Reactions*, Ed. Paquette, L. A. John Wiley & Sons: New York, **1994**, *45*, 238.

(2) Browder, C. C.; Marmsater, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375.

(3) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380.

(4) Fernandez-Mateos, A.; Rentzsch, M.; Sanchez, L. R.; Gonzalez, R. R. *Tetrahedron* **2001**, *57*, 4873.

(5) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328.

(6) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1941**, 211.

(7) Liang, G. X.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544.

(8) Liang, G. X.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931.

(9) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.

(10) Forest, J.; Bee, C.; Cordaro, F.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4069.

(11) Tokeshi, B. K.; Tius, M. A. *Synthesis* **2004**, 786.

(12) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927.

(13) Aggarwal, V. K.; Belfield, A. G. *Org. Lett.* **2003**, *5*, 5075.

(14) Groger, H.; Wilken, J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 529.

(15) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

(16) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(17) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.

(18) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(19) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.

(20) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

(21) Mele, A.; Tran, C. D.; Lacerda, S. H. D. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4364.

(22) Yates, P.; Yoda, N.; Brown, W.; Mann, B. *J. Am. Chem. Soc.* **1958**, *80*, 202.

(23) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747.

(24) Douelle, F.; Tal, L.; Greaney, M. F. *Chem. Commun.* **2005**, 660.

(25) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377.

(26) Motoyoshiya, J.; Yazaki, T.; Hayashi, S. *J. Org. Chem.* **1991**, *56*, 735.

(27) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.

(28) Hoffmann, J.; Nüchter, M.; Ondruschka, B.; Wasserscheid, P. *Green Chem.* **2003**, *5*, 296.

(29) List, B. *Acc. Chem. Res.* **2004**, *37*, 548.

(30) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934.

(31) Igau, A.; Gruetzmacher, H.; Baceiredo, H.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.

(32) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

(33) Kellogg, R. M. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 494.

(34) Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1026.

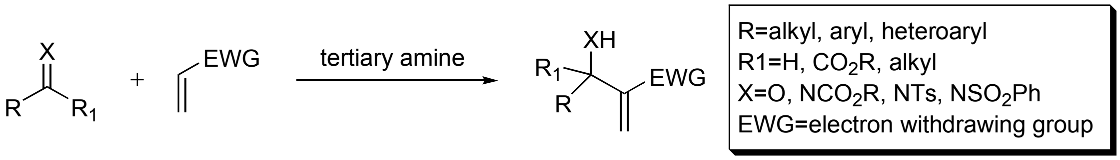
(35) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* **1978**, *43*, 1481.

Chapter 3

Highly Diastereoselective Synthesis of *vicinal* Quaternary and Tertiary Stereocentres Using the Iodo-Aldol Cyclization

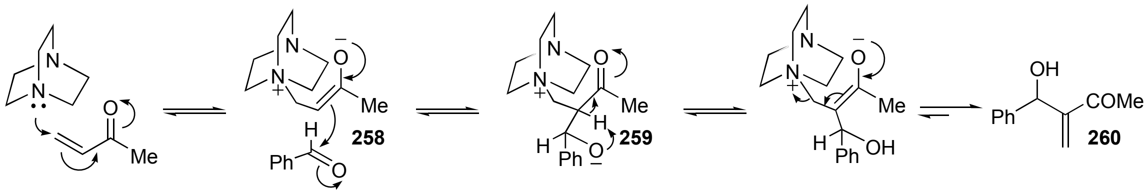
I-Iodo-Aldol Reactions as part of the Morita-Baylis-Hillman Family

The Morita-Baylis-Hillman (MBH) reaction was first reported by Morita in 1968[1], and followed by a German patent filed by Baylis and Hillman in 1972[2]. The three-component reaction is described by the coupling of the α-position of the activated alkenes with carbon electrophiles under the catalytic influence of a tertiary amine providing a simple and convenient methodology for synthesis of densely functionalized compounds[3] (*Scheme 3.1*).



Scheme 3.1: The MBH Reaction

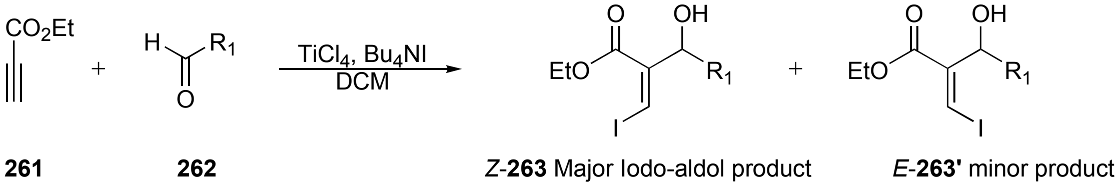
Mechanism of the reaction is believed to proceed through the Michael-initiated addition-elimination sequence. The most generally accepted mechanism[4] of the amine-catalyzed reaction is illustrated with methyl vinyl ketone (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO (*Scheme 3.2*).



Scheme 3.2: Mechanism of the MBH Reaction

The first step involves the Michael nucleophilic addition to produce the zwitterionic enolate **258**, which induces a nucleophilic attack onto the aldehyde in an aldol fashion to generate zwitterions ion **259**. Subsequent proton migration and release of the Lewis base provide the desired MBH product **260**.

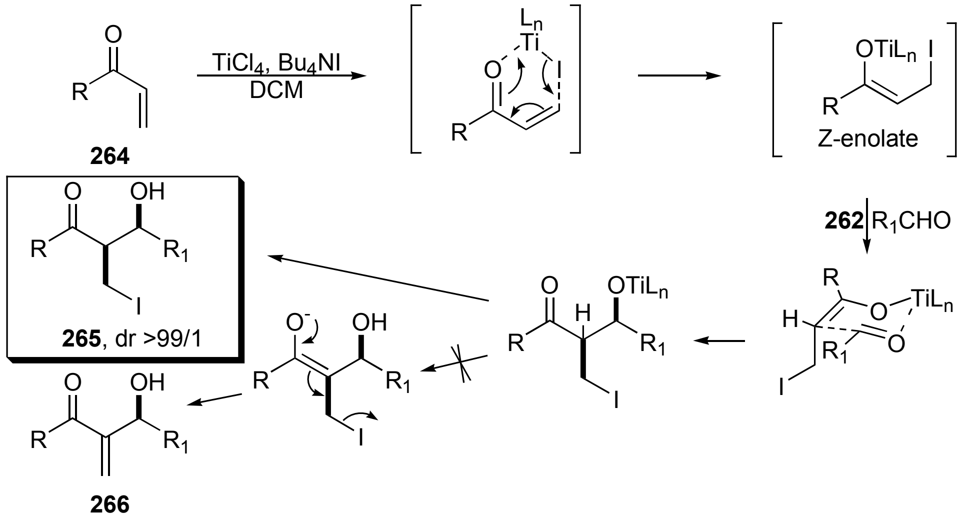
In 1986, Tanagushi et *al.* first reported[5] the reaction between α,β-acetylenic esters **261** and aldehydes **262** in the presence of a Lewis acid ($TiCl_4$) and a nucleophile (Bu_4NI) (*Scheme 3.3*).



Scheme 3.3: Intermolecular Iodo-Aldol Reaction of Acetylenic Ester **261** with Aldehyde **260**

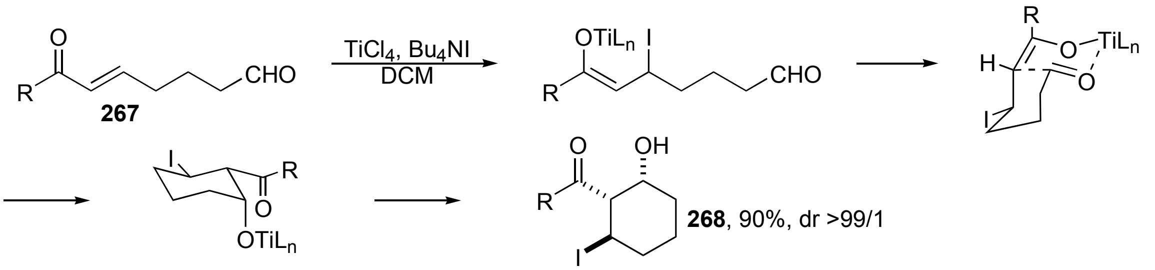
It was shown that sp Michael acceptor **261** underwent conjugate addition with iodide followed by intermolecular aldol reaction with aldehyde **262** to give β-Iodo-aldol adducts **263** essentially. Since then iodo-aldol reactions has been recognized as part of the Morita-Baylis-Hillman (MBH) family of tandem conjugate addition/aldol processes, which is becoming an increasingly well-developed strategy for C-C bond formation[6-11].

For instance, Oshima et *al.* showed in 2001 that intermolecular iodo-aldol reaction with the combination of $TiCl_4$ and Bu_4NX (X=halogens) could be applied to α,β-unsaturated ketones and aldehydes[9] (*Scheme 3.2*).



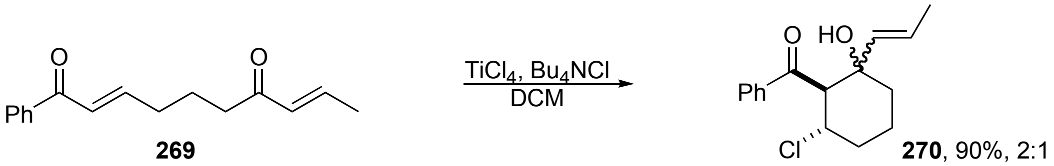
Scheme 3.4: Intermolecular Iodo-Aldol Reaction of α,β-Unsaturated Ketones **264** with Aldehyde **262**

When sp^2 Michael acceptors **264** were employed, β-iodo carbonyl products **265** were essentially produced rather than the eliminated MBH products **266**. As with the reductive aldol reaction, the nucleophile is thus incorporated into products **265** and a chiral centre is installed adjacent to the carbonyl group. Stereoselectively of the reaction was demonstrated with the conjugate addition of activated “$^{-}$ITiCl$_4$-*n*Bu$_4$N^{+}” species toward vinyl ketones **264** of s-*cis* conformation, which provides *Z*-enolates. The subsequent aldol reaction of *Z*-titanium enolate with aldehydes **262** proceeds through a rigid six-membered transition state to afford *syn* adducts. A year later, Oshima et *al.* successfully applied the iodo-aldol methodology to α,β-enones **267** substrates^{11}, which demonstrates the intramolecular viability of this method (*Scheme 3.5*).



Scheme 3.5: Intramolecular Iodo-Aldol Reaction of α,β-Enones **267**

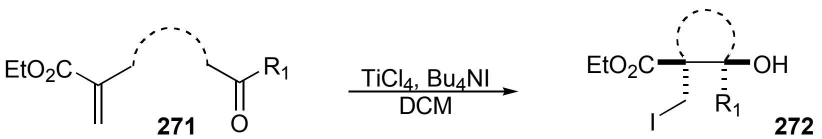
Similarly, iodo titanium enolate was furnished by titanium iodide species to the α,β-enones **267**, which undergoes the intramolecular aldol reaction *via* a chelated six-membered transition state and provides hydroxy ketone **268** with the axial hydroxy group. The use of Bu_4NCl as nucleophile instead allowed the cyclization of enone **269**, which affords product **270** bearing a quaternary centre *vicinal* to the ketone functionality (*Scheme 3.6*).



Scheme 3.6: Cyclization to Product **270** bearing a Quaternary Centre

The iodo aldol features several strengths inherent to all MBH-type reactions: Excellent atom economy and complexity generation, providing 1, 2 or 3 chiral centres from often simple starting materials in a single step[12-16]. It also enables enolate chemistry without the requirement of strong base and it is amenable to (asymmetric) catalysis[17-22].

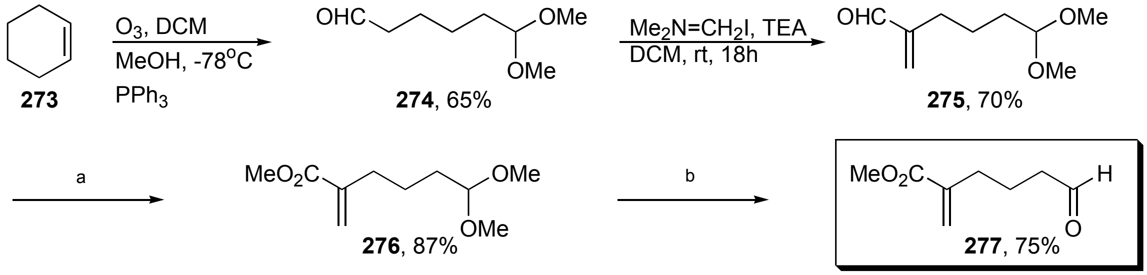
A current limitation of the iodo-aldol reaction and tandem aldol processes in general, is their relative lack of application to the construction of quaternary centres[17,23-29]. Given the value and challenge associated with quaternary centre generation in complex molecule synthesis, we were interested in examining the scope of the iodo-aldol process for the synthesis of hindered γ-iodoalcohols. The vast majority of tandem aldol procedures in the literature use mono or 1,2-substituted Michael acceptor as substrates, whereas quaternary centre construction will require a α-substituted Michael acceptor such as **271** (*Scheme 3.7*).



Scheme 3.7: The Intramolecular Iodo-Aldol Reaction for Quaternary Centre Construction

II-Results and Discussion

We decided to study the intramolecular iodo-aldol reaction as our method for quaternary centre generation as this potentially powerful variant has been the subject of only one previous report[11]. Enoate aldehyde **277** was chosen as carbocyclization substrate, which was synthesized from readily available cyclohexene **273** (*Scheme 3.8*).



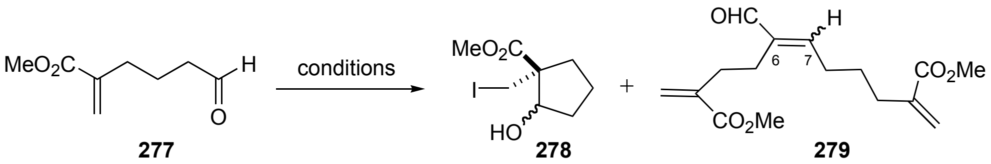
[a] 1. *t*-BuOH, aq $NaClO_2$, 2-methyl butene, NaH_2PO_4, rt, 2.5h; 2. acetone, K_2CO_3, $(Me)_2SO_4$, rt, on.
[b] acetic acid/aq HCl (1N) 3:1, 0 to 5°C, 2h.

Scheme 3.8: Synthesis of Substrate **277**

Ozonolysis[30] of cyclohexene **273** in methanol, which was treated with PPh_3 to decompose the ozonide intermediate, afforded the acetal-aldehyde **274** in 65% yield. This type of compound, which holds acetal functionality was not stable under neither EI nor FAB mass spectroscopy. Therefore, Accurate mass characterization of every acetal derivatives was not available. Methylation *via* Eschenmoser's salt using TEA as base installed the enal functionality **275** in 70% yield, which could be oxidized and deprotected[31] to give **277**.

II-1-Optimization of the Iodo-Aldol Cyclization with Enoate Aldehyde **277**

With substrate **277** in hand, iodo-aldol reaction was attempted and optimized (*Schemes 3.9, 3.10 and 3.12*). The initial iodo-aldol ring closure method (*entry 1*) was carried out under N_2 atmosphere and a solution of $TiCl_4$ (1.0 M in DCM, 1.2 eq) was added dropwise to a solution of *n*-Bu_4NI (1.2 eq) in DCM (5 mL) at 0°C. The resulting dark-red solution was stirred for 10 min and neat enoate aldehyde **277** (0.32 mmol) was added dropwise to the reaction mixture at 0°C. The reaction was stirred for 12h at room temperature and worked up[32].

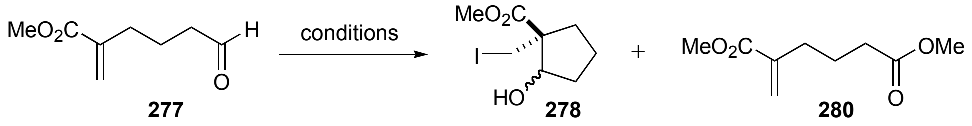


entry	**$TiCl_4$** (eq)	**Bu_4NI** (eq)	**solvent** (mL)	**Temperature** (°C)	**Time** (h)	**Yield** (%)
1	1.2	1.2	DCM (5)	0 to rt	12	**278** (12) + **277** (major)
2	1.2	1.2	DCM (5)	0 to reflux	24	**279** (32)
3	2.4	2.4	DCM (3)	0 to rt	8	**278** (39) + **277** (major)
4	4.8	4.8	DCM (3)	0 to rt	7	**278** (33) + **277** (major)

Scheme 3.9: Optimization of Iodo-Aldol Cyclization Method Using Substrate **277**

After purification by column chromatography, carbocyclized product **278** was isolated in 12% yield along with the recovered starting substrate **277**. When the reaction was refluxed for a day, after addition of the enoate aldehyde **277**, H^1 NMR spectroscopy after column chromatography showed the dimerized product **279** (*entry 2*). The latter seems to be formed by successive aldol and dehydration reaction between two aldehyde functionalities of substrate **277**. Product **279** was clearly showed the C-H unsaturated proton at C-7, the aldehyde proton at C-6 and the correct proton integration for the remaining molecule. The increase of the Lewis acid and nucleophile quantities by a factor of two and four (*entries 3 and 4*), as well as more concentrated media gave slightly enhanced yields of 39% and 33% respectively.

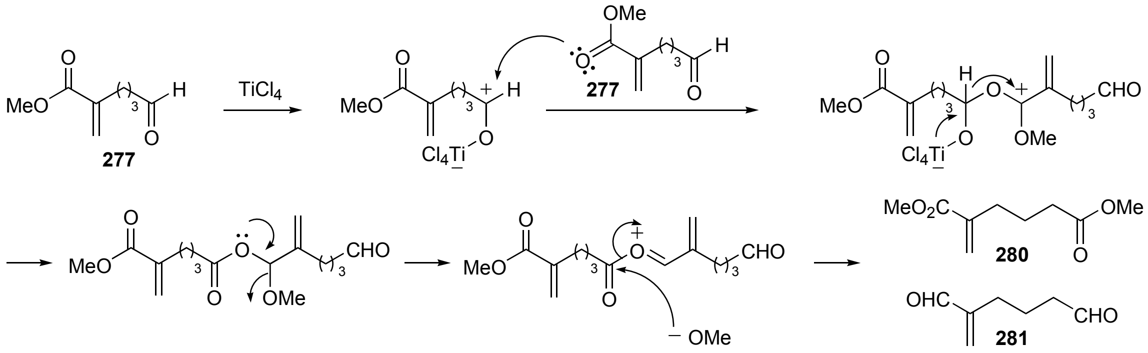
In an effort of leading the reaction until completion, substrate **277** was dissolved in DCM or $CHCl_3$ (1 mL) and added dropwise to the reaction mixture at a temperature varying between -78 °C to 0 °C (*Scheme 3.10*). When the enoate addition was carried out at -10 °C and the reaction mixture was stirred at room temperature for 15 h (*entry 6*), the best yield of desired product **278** was isolated (50%). Unfortunately, a significant quantity of the crossed Tishchenko product **280** (14%) was also produced [33] during the course of the reaction.



entry	**$TiCl_4$** (eq)	**Bu_4NI** (eq)	**solvent** (mL)	**Temperature** (°C)	**Time** (h)	**Yield** (%)
5	2.4	2.4	$CHCl_3$ (1+1)	-78 to tr	15	**278** (46) + **280** (18)
6	2.4	2.4	$CHCl_3$ (1+1)	-10 to rt	15	**278** (50) + **280** (14)
7	2.4	2.4	DCM (1+1)	0 to rt	15	**278** (46) + **280** (20)
8	2.4	2.4	DCM (2+2)	0 to rt	15	**278** (64) + **280** (8)

Scheme 3.10: Optimization of Iodo-Aldol Cyclization Method Using Substrate **277**

A plausible mechanism was postulated, which describes the oxido-reduction reaction between two moieties of substrate **277** giving products **280** and **281** (*Scheme 3.11*).

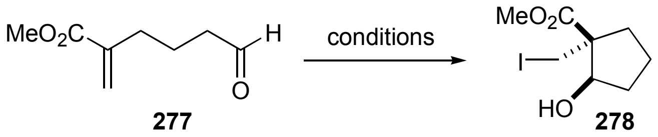


Scheme 3.11: Plausible Mechanism of the Formation of Tishchenko Product **280** and **281**

Although compound **281** was not detected at the end of the reaction, it is thought that the latter was first formed and decomposed, due to its high reactivity in solution.

Lower and higher temperatures of the enoate addition gave similar yields (*entries 5 and 7*), which demonstrate that reaction temperature does not appear to be a critical parameter that fluctuates the reaction yield here. When enoate was twice more diluted and added dropwise to the reaction mixture at 0°C (*entry 8*), crossed Tishchenko product **280** was still formed (8%) along with product **278**, which was obtained in 64% yield. It is worth noting that the enoate dilution prior to addition seemed to reduce the formation of species **280** and enhances the yield of compound **278**.

To amplify the dilution effect, the enoate aldehyde **277** was diluted four more times and a syringe pump was utilized to extend the enoate addition time to one hour at room temperature (*Scheme 3.12*).



entry	**TiCl$_4$** (eq)	**Bu$_4$NI** (eq)	**solvent** (mL)	**Temperature** (°C)	**Time** (h)	**Yield** (%)
9	2.4	2.4	DCM (2+4)	rt	^{b}1	**278** (79)
10	1.2	1.2	DCM (2+4)	rt	^{b}1	^{a}**278** (81)

^{a} **278**, dr 88:12; ^{b} use of syringe pump to add **277** over 1h.

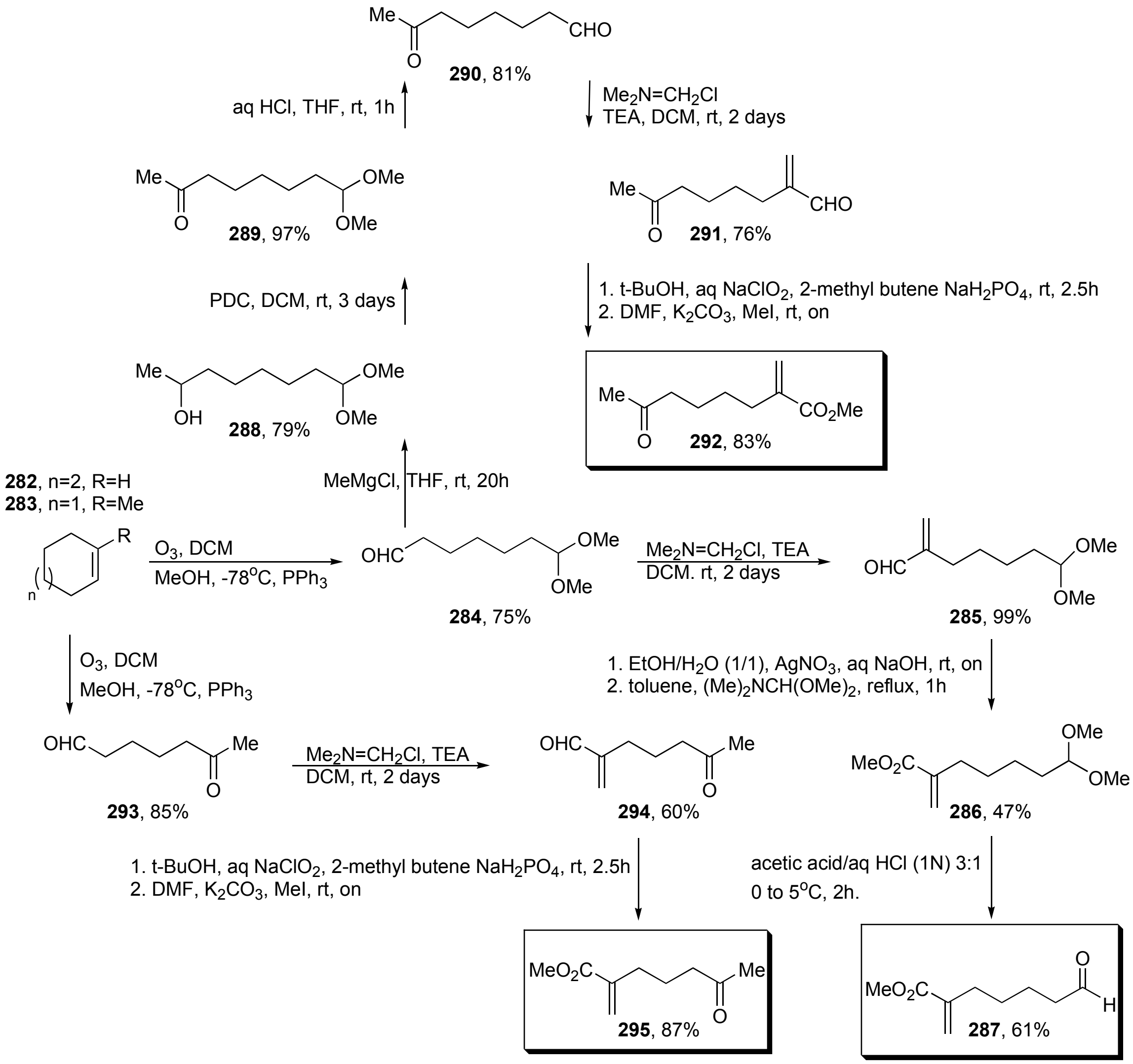
Scheme 3.12: Optimization of Iodo-Aldol Cyclization Method Using Substrate **277**

The reaction mixture was worked up and purified immediately after the addition of the enoate aldehyde **277**, which gave 79% yield of the desired product when 2.4 equivalents of TiCl$_4$/Bu$_4$NI was used (*entry 9*). When a slight excess of the Lewis acid-nucleophile combination (1.2 eq) was utilized, we were pleased to observe that the best conversion of **276** was obtained in 81% yield after column chromatography separation of the minor diastereoisomer (dr 9:1) (*entry 10*). The latter reaction conditions were selected as the general procedure for the scope and limitation of this study.

II-2-Stochiometric Iodo-Aldol Carbocyclization

With the procedure of iodo-aldol cyclization optimized in hand, on the basis of enoate aldehyde **277** carbocyclization (*Scheme 3.12*), the scope and limitation of this methodology was explored. It was of interest to prepare the enoate aldehyde **287** and enoate ketone **292** and **295** using a similar synthetic sequence (*Scheme 3.13*).

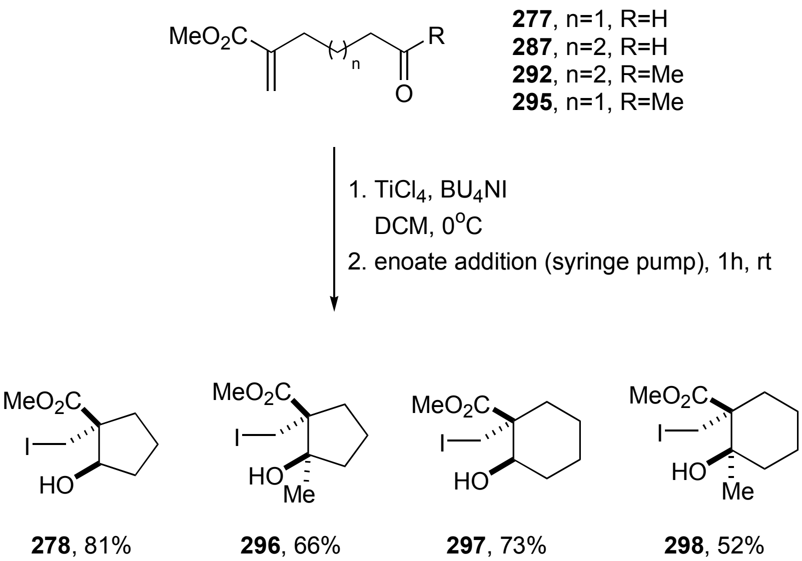
Ozonolysis[34] of cycloheptene **283** in methanol afforded the acetal aldehyde **284** in 75% yield. Methylation *via* Böhme's salt using TEA as base installed the enal functionality **285** in 99% yield, which could be oxidized and deprotected to give enoate aldehyde **287** in 54% yield.



Scheme 3.13: Synthesis of Substrates **287**, **292** and **295**

Ketone functionality of enoate ketone **292** could be readily accessed from the Grignard reaction of acetal aldehyde **284** followed by PDC oxidation[35] and deprotection[36] of the acetal, giving ketone **290** in very good yield. Subsequent methylation using Böhme's salt and oxidation of the aldehyde to the ester functionality produced enoate ketone **292** in good yield. The shorter synthetic route of enoate ketone **295** started with the ozonolysis[37] of 1-methylcyclohexene, followed by methylation and oxidation.

The general iodo-aldol cyclization procedure of enoate ketone **295** was carried out using $TiCl_4$ (1.2 eq) and Bu_4NI (1.2 eq) in DCM at 0°C, with slow addition of the substrate (*Scheme 3.14*).

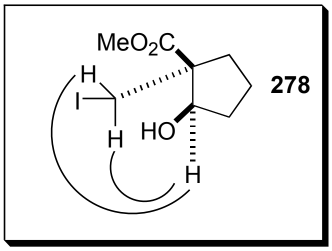


Scheme 3.14: Iodo-Aldol Carbocyclization

We were pleased to observe smooth cyclization in 1h of single diastereoisomer **296** featuring *vicinal* tertiary and quaternary carbon centres, in a slightly attenuated yield 66% yield compared to 1,1-disubstituted cyclopentane **278**. Enoate aldehyde **287** and ketone **292** were likewise competent substrates for diastereoselective 6-*exo* iodo-aldol cyclization, forming the neopentyl iodides **297** (73%) and **298** (52%) as single diastereoisomers. As previously observed for the cyclopentannulation of **295**, some erosion of yield was observed for the construction of the hindered *vicinal* tertiary and quaternary carbon centres in the diastereomerically pure product **298**.

II-3-Stereochemical Features of Iodo-Aldol Products

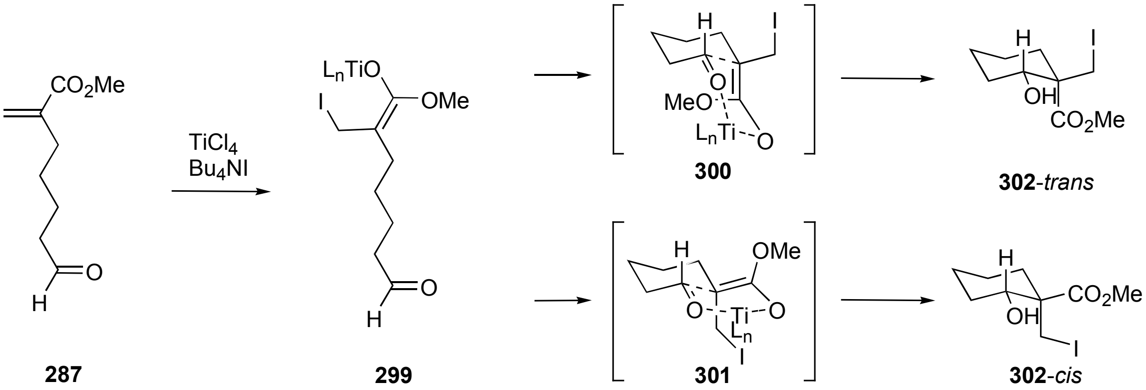
The stereochemistry of 1,1-disubstituted cyclopentane **278** was assigned as *trans* on the basis of NOESY data showing enhancements between the proton and the iodomethyl group, indicating that both groups were on the same face of the cyclopentane ring (*Scheme 3.15*).



Scheme 3.15: Observed NOESY Enhancements in Compound **278**

By analogy with **278**, and in light of subsequent X-ray data (*vide infra*)[38] stereochemistry was assigned as *trans* in all cases.

The observed stereoselectivity can be explained using the model shown for substrate **287**, based upon the twin requirements of initial conjugate addition of iodide giving the *Z*-enolate **299** (*Scheme 3.16*).

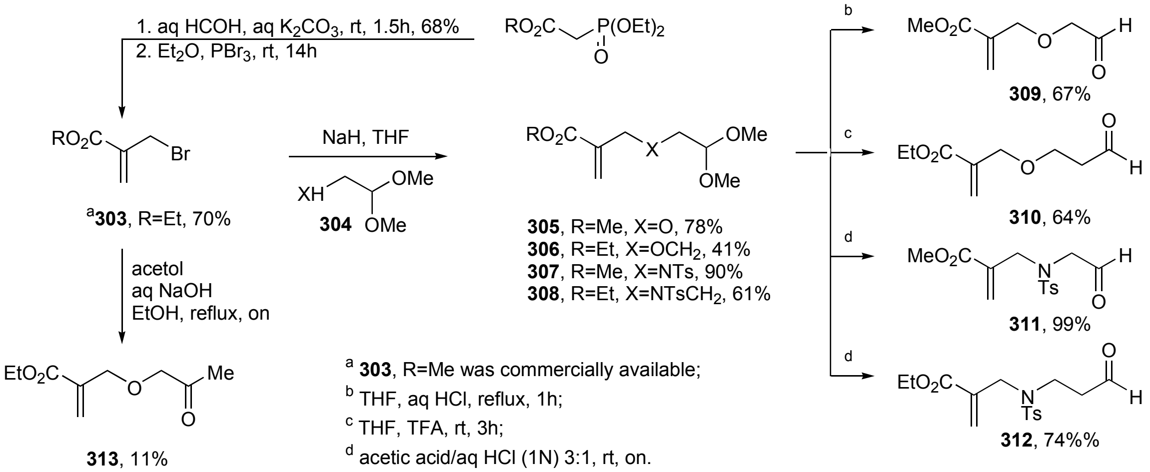


Scheme 3.16: Stereochemical Model for Iodo-Aldol Cyclization

Subsequent aldol reaction takes place *via* a six-membered chelated chair transition state that have been observed in previous iodo-aldol studies[7-11]. Two chair-chair transition states **300** and **301** are consistent with the chelated *Z*-enolate, with the observed stereoselectivity arising from the *cis*-decalin type structure **300**. Discrimination between **300** and **301** is likely due to the orientation of the bulky CH_2I group, which is placed in the least hindered equatorial position in **300**, with the small H (or Me) group occupying the axial position. The *trans*-decalin **301**, by contrast, has the CH_2I group occupying the more-hindered axial position, accounting for the lack of cis-**302** product observed in the iodo-aldol cyclization.

II-4-Stochiometric Iodo-Aldol cyclization of Hetero Substrates

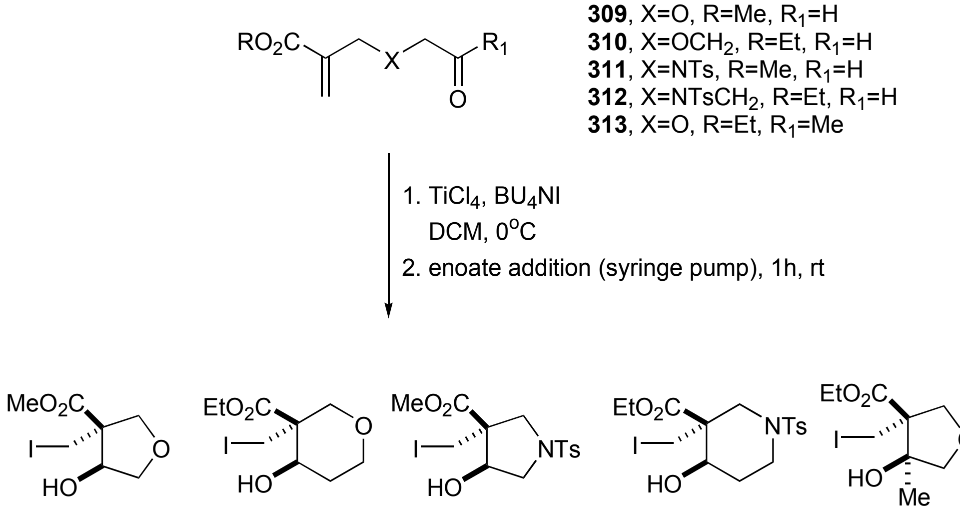
We next looked to extend the cyclization to heterocycle synthesis, an area that has received little attention in previous iodo-aldol studies[11]. Ethyl bromomethylacrylate starting material **303** was synthesized by double Horner-Wadsworth-Emmons reaction[39] of triethylphosphonoacetate and aqueous formaldehyde (37%) followed by bromination in 69% yield (*Scheme 3.17*).



[a] **303**, R=Me was commercially available;
[b] THF, aq HCl, reflux, 1h;
[c] THF, TFA, rt, 3h;
[d] acetic acid/aq HCl (1N) 3:1, rt, on.

Scheme 3.17: Synthesis Route of Hetero Substrates **309-313**

Oxygen and tosylated amine[40] linked enoate acetals **305-308** could be prepared in THF using NaH as a base by alkylation of Bromomethylacrylate **303** with the suitable acetal **304** in moderate to good yields. Deprotection of the aldehyde functionality using different acidic conditions furnished enoate hexanals **309** and **311** and the heptanals **310** and **312** in good to excellent yields. The methyl ketone **313** was prepared in one step by reaction of ethyl bromoacrylate **303** with acetol in 11% yield. Effort of improving the reaction yield was attempted by using different bases (NaH, KOH or K_2CO_3), enhancing the reaction time and using larger excess of acetol. However, the extreme acetol reactivity, which tends to decompose in solution, did not allow higher conversion rate. Iodo-Aldol cyclization was again successful with good isolated yields of the furan **314**, pyran **315**, pyrrolidine **316** and piperidine **317** being recorded (*Scheme 3.18*).



309, X=O, R=Me, R_1=H
310, X=OCH_2, R=Et, R_1=H
311, X=NTs, R=Me, R_1=H
312, X=$NTsCH_2$, R=Et, R_1=H
313, X=O, R=Et, R_1=Me

314, 74% **315**, 64% **316**, 72% **317**, 74% **318**, 47%

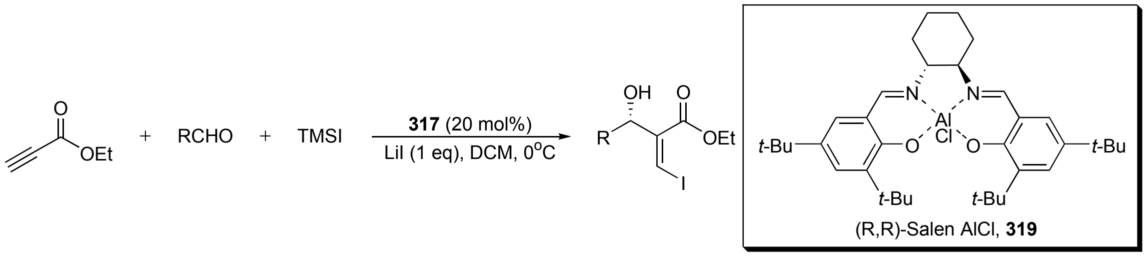
Scheme 3.18: Iodo-Aldol Cyclization of Hetero Substrates

As previously, the reaction displayed high levels of stereoselectivity for each substrate, with H^1 NMR spectroscopy showing a single diastereoisomer being formed in each case. A single crystal structure of the 3,5-dinitrobenzoate derivatives of the five and six-membered ring structures **316** and **317** could be grown and the X-ray data supported the *trans*-stereochemistry originally assigned on the basis of NOESY data (*Scheme 3.15*).

The reaction could be successfully extended to the enoate ketone **313**, but as with the analogous carbocyclization, the yield of the furan **318** (47%) was attenuated somewhat in the construction of the extremely hindered tertiary centre.

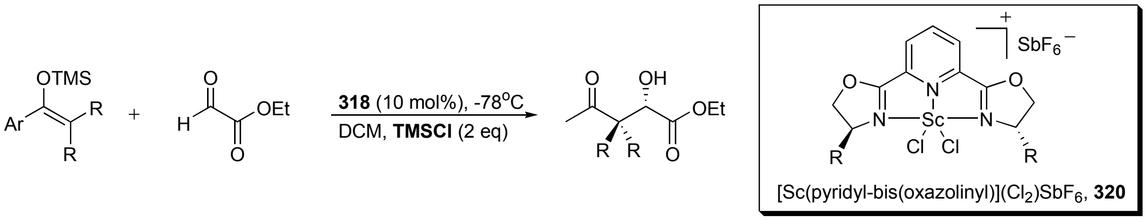
II-5-Catalytic Iodo-Aldol cyclization to Furan **318** and Pyran **315**

Inspired by Li et *al.*, which recently reported the first iodo-aldol reactions[19] that employ catalytic amounts of Lewis acid **319** for the intermolecular allenoate iodo-aldol reaction (*Scheme 3.18*), we were interested in exploring the possibility of lowering the amounts of $TiCl_4$ utilized in our system .



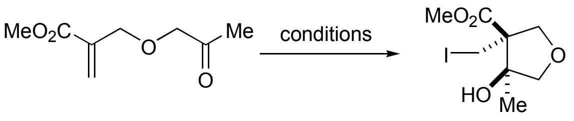
Scheme 3.18: Asymmetric Catalytic Halo Reaction of β-Iodo Allenoate with Aldehyde Using Chiral Salen Catalyst **319**

Although Li's methodology provides moderate enantioselectivity and yields when (R,R)-Salen AlCl **319** was used for a variety of aromatic aldehydes, these results seem encouraging for our future developments in asymmetric catalysis. In addition, Evans et *al.* described that Mukaiyama aldol systems[41], which carried out with an additional silylating agent can facilitate turnover of Lewis acid (*Scheme 3.18*). In this respect, we incorporated TMS-based nucleophile in our catalytic methodology.



Scheme 3.19: Mukaiyama Aldol Systems Catalyzed by **320** in the Presence of TMSCl

Preliminary experiments were carried out with enoate ketone **313** (0.32 mmol), which was added over 1h to the reaction mixture composed of a catalytic amount of Lewis acid (0.2 eq) and a nucleophile such as Bu_4NI or TMSI. The reaction temperature along with the nature of the Lewis acid were also evaluated (*Scheme 3.20*).



313 **318**

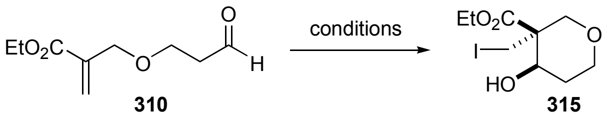
[a]*entry*	**Bu_4NI** (eq)	**TMSI** (eq)	**$TiCl_4$** (eq)	**$AlEt_2Cl$** (eq)	**Salen-AlCl, 317** (eq)	**T°C** (°C)	**Yield** (%)
1	1.2	/	0.2	/	/	0	**313** (major)
2	/	1.2	0.2	/	/	0	**318** (25)
3	/	1.2	0.2	/	/	-20	**318** (26)
4	/	2.4	0.2	/	/	-78	**318** (53)
5	/	2.4	/	0.2	/	-78	**318** (8)
6	/	2.4	/	/	0.2	-78	**318** (10)

[a] **313** (0.32 mmol), addition time: 1h.

Scheme 3.20: Survey of Catalytic Iodo-Aldol Cyclization Method Using Substrate **313**

When 1.2 equivalent of Bu_4NI nucleophile was combined with $TiCl_4$, product **318** was not detected; instead enoate substrate **313** was the only species in solution (*entry 1*). 1.2 Equivalent of TMSI promoted desired product **318** in 25% yield (*entry 2*), and when the enoate addition was achieved at -20 °C, a similar yield of cyclic product **314** was isolated (*entry 3*). We were delighted to observe that 2.4 equivalent of TMSI allowed **318** conversion to 53% at -78 °C (*entry 4*). When $AlEt_2Cl$ and Salen-AlCl **319** replaced $TiCl_4$, diminished **314** yields of 8% and 10% were isolated (*entries 5 and 6*).

We decided to extend the catalytic iodo-aldol survey with the case of O linked enoate heptanal **310** (*Scheme 3.21*).



[a]*entry*	**Bu$_4$NI** (eq)	**TMSI** (eq)	**TMSCl** (eq)	**TiCl$_4$** (eq)	**Salen-AlCl, 317** (eq)	**T°C** (°C)	**Yield** (%)
1	/	/	2.4	0.2	/	0	**310** (major)
2	1.2	/	2.4	0.2	/	-20	**315** (35)
3	/	1.2	/	0.2	/	-78	**315** (38)
4	/	1.2	/	0.2	/	0	**315** (49)
5	/	1.2	/	/	0.2	-78	**315** (0)

[a] **310** (0.32 mmol), addition time: 1h.

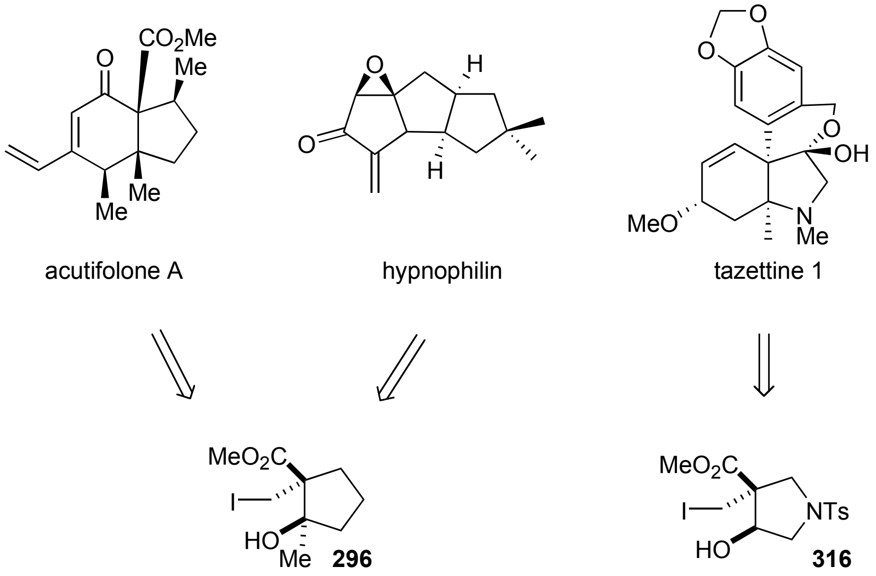
Scheme 3.21: Survey of Catalytic Iodo-Aldol Cyclization Method Using Substrate **310**

TMSCl combined with TiCl$_4$ did not induce any reaction product (*entry 1*). Conversely, Bu$_4$NI showed some activity and produced pyran **315** in 35% yield at -20 °C (*entry 2*). However, TMSI provided the best conversion of product **315** with 49% yield (*entry 4*). We were surprised to observe that the same conditions carried out at -78 °C gave **315** in the attenuated yield of 38% (*entry 3*). At last, Li catalyst **319** was not a suitable Lewis acid showing no activity under these conditions (*entry 5*).

Preliminary experiments on O-linked compound **313** and O-linked enoate heptanal **310** indicate that catalytic iodo-aldol strategy is effective for our system. Furan **318** was obtained in slightly higher yield (53%) compared to the stoichiometric method (47%). A similar protocol furnished the pyran **315** in the slightly attenuated yield of 49%.

III-Conclusion and Future Work

We have developed the intramolecular iodo-aldol cyclization of enoate aldehydes and ketones to afford quaternary centre containing hetero and carbocycles. The reaction transforms simple, pro-chiral starting materials into cyclic alcohols, containing *vicinal* quaternary and secondary/tertiary stereocentres, in good yields with excellent stereoselectivity. In addition, the products display a collection of orthogonal functional groups that may be further elaborated in the synthesis of complex natural product targets, which will be the focus of our future work in the area. Among a myriad of natural occurring compounds, which hold *vicinal* quaternary and secondary/tertiary stereocentres with considerable biological activities, acutifolone A[42], part of sesquiterpenes possessing the bicyclo-[4,3,0]nonane may be regarded as a plausible direction for the application of our 5-*enolexo* ring closure (*Scheme 3.22*).



Scheme 3.22: Some Natural Products Containing *Vicinal* Quaternary and Secondary/Tertiary Stereogenic Centres

After the synthetic degree of conciseness, with which hypnophilin was recently described in the litterature[43], the total synthesis of this sesquiterpene may be referred as an ambitious task in which our carbocyclization may play a key role. Finally, tazettine 1, known as alkaloid of the *Amaryllidaceae* family[44], which showcases hundreds of interesting biological natural bases may satisfy the architectural requisite dictated by our methodology performed for the synthesis of pyrrolidine **316**.

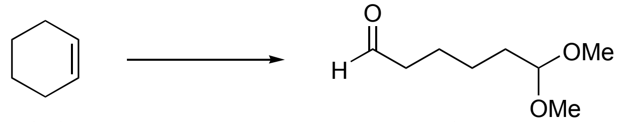
IV-Experimental

H^1 NMR and C^{13} NMR spectra were recorded on a Bruker dpx 250 (250 MHz) instrument. Electron Ionisation (EI) high resolution mass spectroscopy was performed by the EPSRC National Mass Spectrometry Service Centre Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer as well as the University of Edinburgh School of Chemistry mass spectrometry service using Kratos MS50 instrument. FAB HRMS was carried out by the University of Edinburgh School of Chemistry mass spectrometry service using Kratos MS50 instrument. The data are recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. Triethylamine was distilled over CaH_2 prior to use. DCM, DMF, THF and MeOH were used from a solvent purification system (Innovative Technology Inc.). All other chemicals were purchased from a chemical supplier and used as received.

IV-1-Synthesis of iodo-aldol substrates

*Synthesis of 2-methylene-6-oxo-hexanoic acid methyl ester **277***

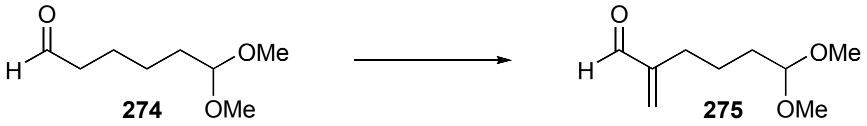
6,6-Dimethoxy hexanal **274**[30]



273 **274**

A solution of cyclohexene **273** (6.16 g, 75.0 mmol) in DCM (250 mL) and MeOH (50 mL) was stirred at -78 °C where O_3 was bubbled through the solution as it was stirred. O_3 addition was stopped when the solution turned blue. N_2 was passed through the solution until the blue colour was discharged, the cold bath was removed and PTSA (1.215 g, 10% w/w) was added. The reaction mixture was stirred at rt for 90 min under N_2. Anhydrous $NaHCO_3$ (25.2 g, 300 mmol) was added to the flask, the reaction mixture was stirred for 15 min and dimethyl sulfide (12 mL, 150 mmol) was added. After being stirred for 12 h, the heterogeneous mixture was concentrated to approximately 50 mL by rotary evaporation. DCM (100 mL) was added and the mixture was washed with H_2O (75 mL). The aqueous layer was extracted with DCM (2 × 100 mL) and the combined organic layers were washed with H_2O (100 mL). After extracting the aqueous layer with DCM (100 mL), the combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/Et_2O 1:1) providing 6,6-dimethoxyhexanal (7.81 g, 65 %) as a pale yellow oil. H^1 NMR (250MHz, $CDCl_3$): δ 9.70 (t, 1H, J = 2.5Hz), 4.30 (t, 1H, J = 5.5Hz), 3.30 (s, 6H), 2.40-2.45 (m, 2H) and 1.70-1.40 (m, 6H).

6,6-Dimethoxy-2-methylene hexanal **275**

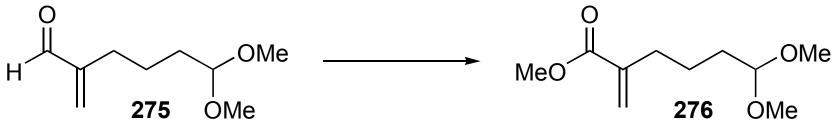


274 **275**

To a solution of 6,6-dimethoxy hexanal **274** (727 mg, 4.5 mmol) in DCM (340 mL) and TEA (3.13 mL, 22.5 mmol, 5 equiv) was added Eschenmoser's salt (4.16 g, 22.5 mmol, 5 equiv). After stirring for 18 h, the reaction mixture was quenched with saturated

$NaHCO_3$ aqueous solution (100 mL), the layers were separated and the aqueous layer was extracted with DCM (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing 6,6-dimethoxy-2-methylene-hexanal (362 mg, 70 %) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2949, 1689, 1127, 1070. H^1 NMR (250MHz, $CDCl_3$): δ 9.53 (s, 1H), 6.26 (d, 1H, J = 0.5Hz), 6.00 (d, 1H, J = 0.5Hz), 4.35 (t, 1H, J = 9.5Hz), 3.30 (s, 6H), 2.28-2.00 (m, 2H) and 1.63-1.50 (m, 4H). C^{13} NMR (63MHz, $CDCl_3$): δ 194.79, 150.05, 134.26, 104.44, 52.96, 32.26, 27.62 and 22.83.

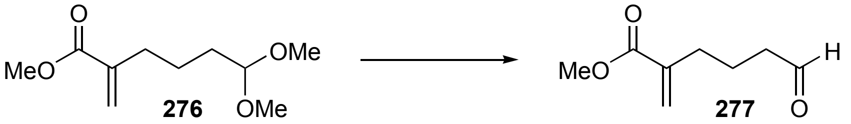
6,6-Dimethoxy-2-methylene hexanoic acid methyl ether **276**



To a solution of 6,6-dimethoxy-2-methylene hexanal **275** (2.96 g, 17.19 mmol) and 2-methyl-2-butene (3.62 g, 51.64 mmol, 3 equiv) in *t*-butyl alcohol (60 mL) was added a solution of sodium chlorite (3.58 g, 39.61 mmol, 2.3 equiv) and sodium dihydrogenphosphate (5.36 g, 34.38 mmol, 2 equiv) in H_2O (25 mL) dropwise over 10 min. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue dissolved in H_2O (30 mL) and extracted with hexane (100 mL). The aqueous layer was acidified to pH = 3 with HCl solution (2N) and extracted with Et_2O (2 × 50 mL). The combined organic layers was washed with H_2O (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield 2-methylene-6-oxo heptanoic acid (2.80 g, 83%) as yellow oil. No further purification was required.

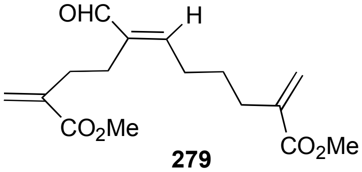
To a solution of 6,6-dimethoxy-2-methylene hexanoic acid (2.12 g, 11.27 mmol) in acetone (60 mL) was added a solution of K_2CO_3 (6.22 g, 45.09 mmol, 4 equiv). The resulting mixture was vigorously stirred for 5 min. To the mixture was added $(Me)_2SO_4$ (1.56 g, 12.40 mmol, 1.1 equiv) via syringe. The corresponding mixture was vigorously stirred at rt overnight. H_2O/EtOAc (100 mL, 1:1) were added and the aqueous layer acidified to pH = 3 by addition of HCl solution (1N). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 50 mL), saturated $NaHCO_3$ aqueous solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1) providing 6,6-dimethoxy-2-methylene hexanoic acid methyl ether (2.07 g, 91%) as yellow oil. IR (thin film/cm^{-1}): ν_{max} 2936, 2359, 1995, 1716. H^1 NMR (250MHz, $CDCl_3$): δ 6.13 (d, 1H, J = 0.5Hz), 5.53 (d, 1H, J = 0.5Hz), 4.34 (t, 1H, J = 5.5Hz), 3.73 (s, 3H), 3.30 (s, 6H), 2.34-2.27 (m, 2H) and 1.66-1.54 (m, 4H). C^{13} NMR (63MHz, $CDCl_3$): δ 167.82, 140.39, 125.06, 104.49, 52.89, 51.93, 32.16, 31.71 and 23.49.

2-Methylene-6-oxo hexanoic acid methyl ester **277**[31]



6,6-Dimethoxy-2-methylene hexanoic acid methyl ether **276** (1.43 g, 7.07 mmol) was dissolved in acetic acid (7.0 mL) and the solution was cooled to 0-5°C in an ice bath. As soon as the solution started to freeze, HCl solution (1N, 2.3 mL) was added in one portion and the solution stirred for 2 h. The mixture was diluted with DCM (30 mL), washed successively with water (4 mL), saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), water (4 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 2-methylene-6-oxo hexanoic acid ethyl ester (1.10 g, 100%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2982, 2723, 1717, 1186. H^1 NMR (250MHz, $CDCl_3$): δ 9.77 (t, 1H, J = 1.5Hz), 6.17 (d, 1H, J = 2.5Hz), 5.54 (d, 1H, J = 2.5Hz), 3.72 (s, 3H), 2.50-2.30 (m, 4H) and 1.92-1.71 (m, 2H). C^{13} NMR (63MHz, $CDCl_3$): δ 202.72, 167.54, 140.51, 125.86, 51.96, 43.74, 31.78 and 21.46. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_8H_{12}O_3$, 156.0786 found 156.0786.

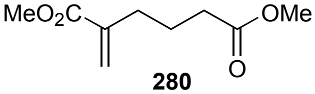
5-Formyl-2,10-dimethylene-undec-5-enedioic acid dimethyl ester **279**



279

H^1 NMR (250MHz, $CDCl_3$): δ 9.37 (s, 1H), 6.44 (m, 1H), 6.15 (d, 2H, J = 2.5Hz), 5.53 (d, 2H, J = 2.5Hz), 3.74 (s, 6H) and 2.55-2.28 (m, 10H).

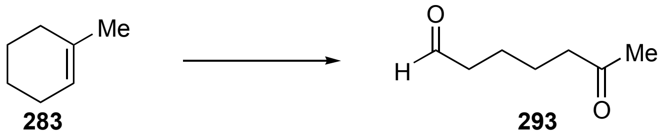
2-Methylene hexanedioic acid dimethyl ester **280**[45]


280

H^1 NMR (250MHz, $CDCl_3$): δ 6.15 (d, 1H, J = 1.0Hz), 5.54 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.32 (t, 4H, J = 7.5Hz) and 1.80-1.87 (m, 2H).

*Synthesis of 2-methylene-6-oxo-heptanoic acid methyl ester **295***

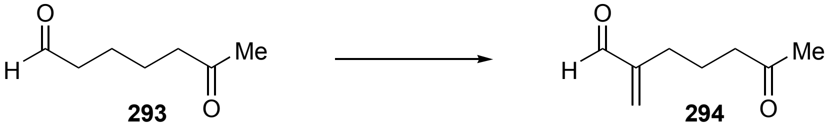
6-Oxo heptanal **293**[37]



283 **293**

A stream of O_3 was bubbled through a solution of 1-methylcyclohexene **283** (8.10 g, 84.2 mmol) in DCM (1000 mL) at -78°C until the solution turned pale blue in colour. Triphenylphosphine (26.5 g, 101 mmol, 1.2 equiv) was added slowly into the solution, which was allowed to warm up to rt over 10 h and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane//EtOAc, 7:3) providing 6-oxo heptanal (9.20 g, 85%) as a colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 9.74 (t, 1H, J = 1.5Hz), 2.45-2.43 (m, 4H), 2.12 (s, 3H) and 1.61-1.58 (m, 4H).

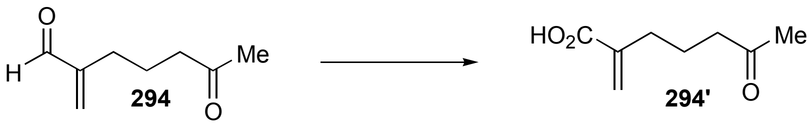
2-Methylene-6-oxo heptanal **294**



293 **294**

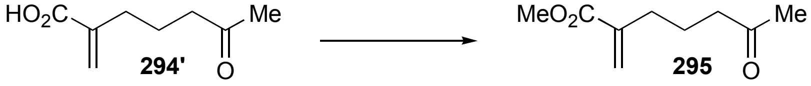
To a solution of 6-oxo heptanal **293** (100 mg, 0.78 mmol) in DCM (35 mL) and TEA (540 µL, 3.9 mmol, 5 equiv) was added Böhme's salt (570 mg, 3.9 mmol, 5 equiv). After stirring for 2 days the reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) providing 2-methylene-6-oxo-heptanal (65 mg, 60%) as a yellow oil. H^1 NMR (250MHz, $CDCl_3$): δ 9.49 (s, 1H), 6.26 (s, 1H), 6.00 (s, 1H), 2.42 (t, 2H, J = 7.5Hz), 2.20 (t, 2H, J = 7.5Hz), 2.10 (s, 3H) and 1.78-1.63 (m, 2H)

2-Methylene-6-oxo heptanoic acid **294’**



To a solution of 2-methylene-6-oxo heptanal **294** (2.41 g, 17.19 mmol) and 2-methyl-2-butene (3.62 g, 51.64 mmol, 3 equiv) in *t*-butyl alcohol (60 mL) was added a solution of sodium chlorite (3.58 g, 39.61 mmol, 2.3 equiv) and sodium dihydrogenphosphate (5.36 g, 34.38 mmol, 2 equiv) in H_2O (25 mL) dropwise over 10 min. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue dissolved in H_2O (30 mL) and extracted with hexane (100 mL). The aqueous layer was acidified to pH = 3 with HCl solution (2N) and extracted with Et_2O (2 × 50 mL). The combined organic layers was washed with H_2O (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield 2-methylene-6-oxo heptanoic acid (2.22 g, 83%) as a yellow oil. No further purification was required. IR (thin film/cm^{-1}): ν_{max} 2944, 1712, 1628, 1369, 1172. H^1 NMR (250MHz, $CDCl_3$): δ 6.31 (s, 1H), 5.66 (s, 1H), 2.46 (t, 2H, J = 8.0Hz), 2.30 (t, 2H, J = 8.0Hz), 2.14 (s, 3H) and 1.85-1.70 (m, 2H). C^{13} NMR (63MHz, $CDCl_3$): δ 208.86, 172.36, 139.47, 127.80, 42.95, 30.85, 30.06 and 22.49. MS FAB (+ve) *m/z* [M+H]$^+$ calculated for $C_8H_{13}O_3$, 157.0865 found 157.0863.

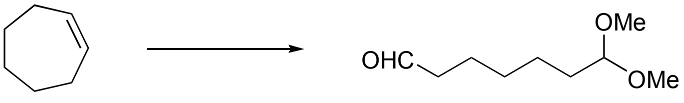
2-Methylene-6-oxo heptanoic acid methyl ester **295**



To a solution of 2-methylene-6-oxo heptanoic acid **294’** (1.76 g, 11.27 mmol) in DMF (44 mL) was added a solution of K_2CO_3 (1.71 g, 12.40 mmol, 1.1 equiv) in H_2O (9 mL). The resulting mixture was vigorously stirred for 5 min. To the mixture was added MeI (763 µL, 12.40 mmol, 1.1 equiv) via syringe. The corresponding mixture was vigorously stirred at rt overnight. H_2O/EtOAc (100 mL, 1:1) were added and the aqueous layer acidified to pH = 3 by addition of HCl solution (1N). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers was washed with H_2O (3 × 50 mL), saturated $NaHCO_3$ aqueous solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1) providing 2-methylene-6-oxo heptanoic acid methyl ester (1.74 g, 91%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 3432, 1716, 1632, 1167. H^1 NMR (250MHz, $CDCl_3$): δ 6.15 (s, 1H), 5.55 (s, 1H), 3.74 (s, 3H), 2.44 (t, 2H, J = 7.5Hz), 2.29 (t, 2H, J = 7.5Hz), 2.13 (s, 3H) and 1.82-1.64 (m, 2H). C^{13} NMR (63MHz, $CDCl_3$): δ 208.66, 167.66, 140.01, 125.43, 51.97, 42.98, 31.28, 30.04 and 22.50. MS FAB (+ve) *m/z* $[M+H]^+$ calculated for $C_9H_{15}O_3$, 171.1021 found 171.1019.

Synthesis of 2-methylene-7-oxo-heptanoic acid methyl ester ***287***

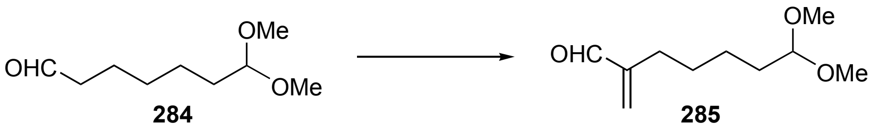
7,7-Dimethoxy heptanal **284**[34]



282 **284**

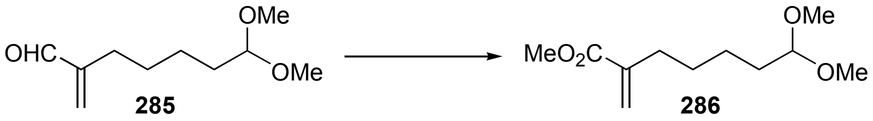
Ozone was bubbled through a stirred solution of cycloheptene **282** (5.00 g, 52.0 mmol) in DCM (250 mL) and MeOH (50 mL) at -78°C. Ozone addition was stopped when the solution turned blue. Nitrogen was passed through the solution until the blue colour was discharged, after which time the cold bath was removed. The drying tube and O_3 inlet were replaced with a stopper and rubber septum and *p*-toluenesulfonic acid (989 mg, 0.1 equiv) was added. The reaction mixture was stirred at rt over 90 min under N_2. Anhydrous $NaHCO_3$ (17.5 g, 4 equiv) was added to the flask, the mixture stirred for 15 min and then PPh_3 (27.28 g, 104 mmol, 2 equiv) was added. After being stirred for 12 h, the heterogeneous mixture was concentrated to 50 mL by rotary evaporation. DCM (100 mL) was added and the reaction mixture was washed with H_2O (75 mL). The aqueous layer was extracted with DCM (2 × 100 mL) and the combined organic layers were washed with H_2O (100 mL). After extracting the aqueous layer with DCM (100 mL), the organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 85:15) providing 7,7-dimethoxy heptanal (6.8 g, 75%) as a pale yellow oil. H^1 NMR (250MHz, $CDCl_3$): δ 9.72 (t, 1H, J = 2.0Hz), 4.32 (t, 1H, J = 6.0Hz), 3.26 (s, 6H), 2.38 (dt, 2H, J = 2.0, 7.0Hz), 1.62-1.50 (m, 4H) and 1.37-1.25 (m, 4H).

7,7-Dimethoxy-2-methylene heptanal **285**



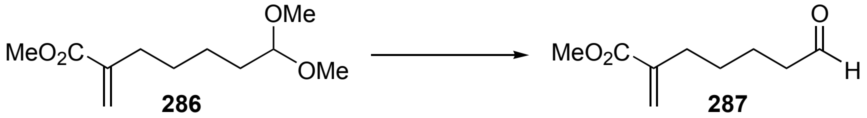
To a solution of 7,7-dimethoxy heptanal **284** (794 mg, 4.6 mmol) and TEA (3.17 mL, 22.8 mmol, 5 equiv) in DCM (200 mL) was added Böhme's salt (3.33 g, 22.8 mmol, 5 equiv) at rt. After stirring for 2 days, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (DCM) providing 7,7-dimethoxy-2-methylene heptanal (840 mg, 99%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2946, 2360, 1693, 1127. H^1 NMR (250MHz, $CDCl_3$): δ 9.52 (s, 1H), 6.24 (m, 1H), 5.98 (m, 1H), 4.34 (t, 1H, J = 6.0Hz), 3.29 (s, 6H), 2.27-2.16 (m, 2H) and 1.64-1.34 (m, 6H). C^{13} NMR (63MHz, $CDCl_3$): δ 194.77 150.24, 104.53, 104.44, 52.80, 32.37, 27.87, 27.71 and 24.36. MS ES (-ve) *m/z* $[M-H]^+$ calculated for $C_{10}H_{17}O_3$, 185.1172 found 185.1163.

7,7-Dimethoxy-2-methylene heptanoic acid methyl ester **286**



To a mixture of $AgNO_3$ (1.15 g, 6.8 mmol, 1.5 equiv) and 7,7-dimethoxy-2-methylene heptanal **285** (840 mg, 4.5 mmol) in $EtOH/H_2O$ (1:1, 10 mL) was added a solution of NaOH (1.08 g, 27.1 mmol, 6 equiv) in H_2O (15 mL) dropwise at 40 °C over 90 min. The reaction mixture was stirred for 1 h at 40 °C, then stirred overnight at rt. The reaction mixture was filtered, acidified with HCl solution (1N) to pH = 3 and extracted with Et_2O (3 × 50 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 7,7-dimethoxy-2-methylene heptanoic acid (721 mg, 80%) as a colourless oil. This crude product was taken into toluene (10 mL) and *N*,*N*-dimethylformamide dimethylacetal (720 μL, 5.4 mmol, 1.5 equiv) added. After refluxing for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) providing 7,7-dimethoxy-2-methylene heptanoic acid methyl ester (363 mg, 47%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2946, 2360, 1750, 1127. H^1 NMR (250MHz, $CDCl_3$): δ 6.13 (m, 1H), 5.51 (m, 1H), 4.34 (t, 1H, J = 6.0Hz), 3.74 (s, 3H), 3.30 (s, 6H), 2.33-2.26 (m, 2H) and 1.66-1.35 (m, 6H). C^{13} NMR (63MHz, $CDCl_3$): δ 167.89, 140.68, 124.85, 104.61, 52.80, 51.91, 32.43, 31.98, 28.37 and 24.32.

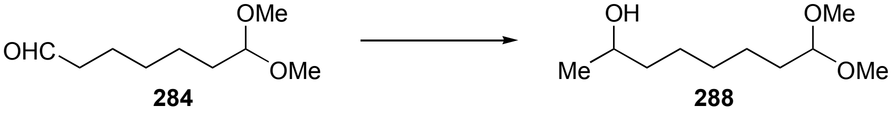
2-Methylene-7-oxo heptanoic acid methyl ester **287**



7,7-Dimethoxy-2-methylene heptanoic acid methyl ester **286** (363 mg, 1.68 mmol) was dissolved in acetic acid (2.0 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1M, 550 μL) was added and the solution was stirred for 2 h. The reaction mixture was diluted with DCM (30 mL), washed with water (4 mL), saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), water (4 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Hexane/EtOAc, 4:1) providing 2-methylene-7-oxo-heptanoic acid methyl ester (174 mg, 61%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 2950, 1721, 1439, 1144. H^1 NMR (250MHz, $CDCl_3$): δ 9.75 (t, 1H, J = 1.5Hz), 6.13 (m, 1H), 5.53 (m, 1H), 3.74 (s, 3H), 2.45-2.28 (m, 4H) and 1.66-1.50 (m, 4H). C^{13} NMR (63MHz, $CDCl_3$): δ 202.55, 167.73, 140.18, 125.16, 51.94, 43.75, 31.75, 28.00 and 21.68.

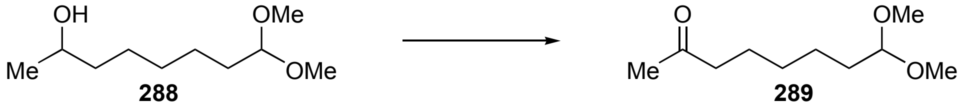
*Synthesis of 2-methylene-7-oxo-octanoic acid methyl ester **292***

8,8-Dimethoxy octan-2-ol **288**



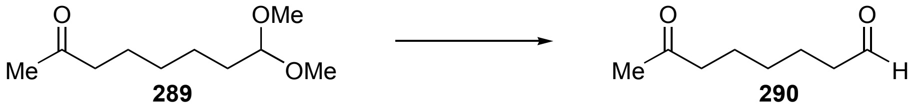
A solution of 7,7-dimethoxy heptanal **284** (2.48 g, 14.2 mmol) in THF (3 mL) was added over 3.5 h to a solution of MeMgCl (3 M in THF, 4.75 mL, 14.2 mmol, 1 equiv) at -10 °C. The reaction mixture was stirred to rt for 20 h and quenched with H_2O (10 mL). The aqueous layer was extracted with Et_2O (5 × 10 mL), the combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 85:15,) providing 8,8-dimethoxy octan-2-ol (2.13 g, 79%) as a colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 4.34 (t, 1H, J = 6.0Hz), 3.78 (m, 1H), 3.30 (s, 6H), 1.64-1.52 (m, 2H), 1.25-1.48 (m, 8H) and 1.18 (d, 3H, 6.0Hz).

8,8-Dimethoxy octan-2-one **289**[35]



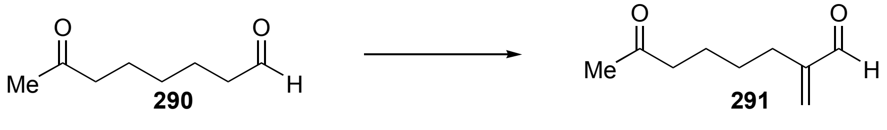
To a solution of 8,8-dimethoxy octan-2-ol **288** (1.88 g, 9.88 mmol) in DCM (60 mL) was added PDC (7.45 g, 19.8 mmol, 2 equiv) and the reaction mixture was stirred at rt for 3 days. Et_2O (70 mL) was added to the reaction mixture, the organic layer was filtered through celite and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 95:5) providing 8,8-dimethoxy octan-2-one (1.80 g, 97%) as a colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 4.32 (t, 1H, J = 5.0Hz), 3.31 (s, 6H), 2.43 (t, 2H, J = 8.0Hz), 2.13 (s, 3H) and 1.80-1.10 (m, 8H).

7-Oxo-octanal **290**[36]



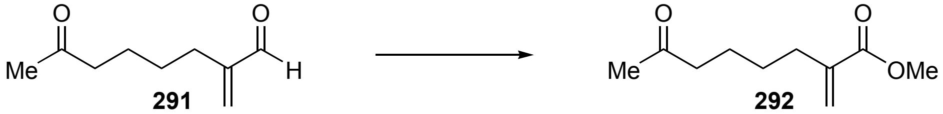
A solution of 8,8-dimethoxy octan-2-one **289** (2.01 g, 10.6 mmol) in THF (40 mL) and HCl solution (1M, 40 mL) was stirred at rt for 1 h. The reaction mixture was diluted with DCM (100 mL), washed with saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic) and H_2O. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing 7-oxo-octanal (1.22 g, 81%) as a colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 9.75 (t, 1H, J = 2.0Hz), 2.43 (m, 4H), 2.13 (s, 3H), and 1.67-1.21 (m, 6H).

2-Methylene-7-oxo-octanal **291**



To a solution of 7-oxo-octanal **290** (1.00 g, 7.03 mmol) and TEA (4.87 mL, 35.2 mmol, 5 equiv) in DCM (300 mL) was added Böhme's salt (5.14 g, 35.2 mmol, 5 equiv). After stirring for 2 days the reaction was quenched with saturated NH_4Cl aqueous solution and extracted with DCM. The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing 2-methylene-7-oxo-octanal (820 mg, 76%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 2939, 2341, 1687, 1359. H^1 NMR (250MHz, $CDCl_3$): δ 9.52 (s, 1H), 6.26 (d, 1H, J = 1.0Hz), 6.00 (d, 1H, J = 1.0Hz), 2.44 (t, 2H, J = 7.0Hz), 2.24 (t, 2H, J = 7.0Hz), 2.12 (s, 3H) and 1.58-1.40 (m, 4H). C^{13} NMR (63MHz, $CDCl_3$): δ 208.95, 194.80, 149.95, 134.43, 43.42, 30.06, 27.70, 27.32 and 23.39. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_9H_{14}O_2$, 154.0994 found 154.0994.

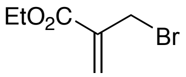
2-Methylene-7-oxo-octanoic acid methyl ester **292**



To a solution of the 2-methylene-7-oxo-octanal **291** (660 mg, 4.28 mmol) in *t*-butyl alcohol (15 mL) and 2-methyl-2-butene (903 mg, 12.88 mmol, 3 equiv) was added a solution of sodium chlorite (893 mg, 9.88 mmol, 2.3 equiv) and sodium dihydrogenphosphate (1.34 g, 8.59 mmol, 2 equiv) in H_2O (6 mL) dropwise over 10 min. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue dissolved in H_2O (10 mL) and extracted with hexane (25 mL). The aqueous layer was acidified to pH = 3 with HCl solution (2N) and extracted with Et_2O (2 × 15 mL). The combined organic layers was washed with H_2O (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield 2-methylene-7-oxo-octanoic acid (721 mg, 99%) as a yellow oil. Without further purification, the acid was taken into DMF (17 mL) and K_2CO_3 solution (651 mg, 4.71 mmol, 1.1 equiv) in H_2O (3 mL) added. After stirring the mixture vigorously for 5 min, MeI was added (263 μL, 4.71 mmol, 1.1 equiv) via syringe. The corresponding mixture was vigorously stirred at rt overnight. H_2O/EtOAc (40 mL, 1:1) was added and the aqueous phase acidified to pH = 3 by addition of HCl solution (1N). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers was washed with H_2O (3 × 50 mL), saturated $NaHCO_3$ aqueous solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1) providing 2-methylene-7-oxo-octanoic acid methyl ester (534 mg, 68%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 3420, 2950, 1716, 1439, 1166. H^1 NMR (250MHz, $CDCl_3$): δ 6.12 (d, 1H, J = 1.0Hz), 5.52 (d, 1H, J = 1.0Hz), 3.73 (s, 3H), 2.43 (t, 2H, J = 7.0Hz), 2.29 (t, 2H, J = 7.0Hz), 2.12 (s, 3H) and 1.75-1.40 (m, 4H). C^{13} NMR (63MHz, $CDCl_3$): δ 208.99, 167.74, 140.32, 125.02, 51.90, 43.51, 31.78, 30.01, 27.98 and 21.14. MS FAB (+ve) *m/z* $[M+H]^+$ calculated for $C_{10}H_{17}O_3$ 185.1178 found 185.1177.

Synthesis of 2-(3-oxo-propoxy)-acrylic acid methyl ester ***309***

Ethyl α-bromomethyl acrylate **303**[39]

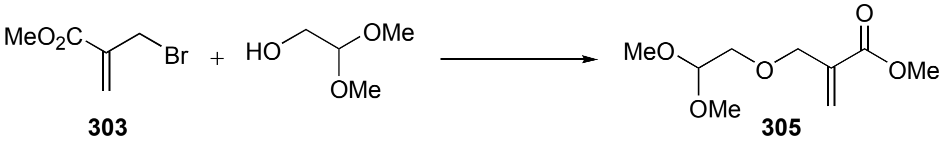


303

To a solution of triethyl-phosphonoacetate (63.96 g, 285 mmol) and aqueous solution of formaldehyde (37%, 150 mL, 2.0 mol) vigorously stirred, was added a saturated solution of K_2CO_3 (69.00 g, 500 mmol in 110 mL of H_2O) over 20 min. The reaction mixture was stirred for 1 h, quenched with 50% saturated aqueous NH_4Cl solution (150 mL) and extracted with Et_2O (3 X 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by distillation (0.55 mmHg, bp 61 °C) providing ethyl α-hydroxymethyl acrylate (25.21 g, 68%) as colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 6.25 (d, 1H, J = 1.0Hz), 5.82 (d, 1H, J = 1.0Hz), 4.32 (s, 2H), 4.24 (q, 2H, J = 7.0Hz), 2.36 (s, 1H) and 1.31 (t, 3H, J = 7.0Hz).

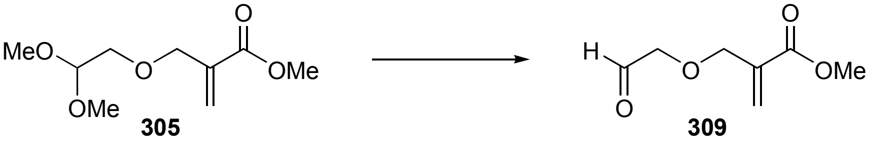
To a solution of ethyl α-hydroxymethyl acrylate (25.21 g, 194 mmol, 1.4 eq) in Et_2O (100 mL) at 0 °C under N_2 was added PBr_3 (13.6 mL, 143 mmol) dropwise *via* syringe. The solution was allowed to warm with stirring over 14 h, cooled to 0 °C and H_2O (30 mL) was slowly added *via* syringe. The reaction mixture was extracted with hexane (4 X 100 mL) at rt, the combined organic layers were washed with 50% saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was yielded ethyl α-bromomethyl acrylate (26.65 g, 70%) as yellow oil without any further purification. H^1 NMR (250MHz, $CDCl_3$): δ 6.34 (d, 1H, J = 0.5Hz), 5.95 (d, 1H, J = 0.5Hz), 4.28 (q, 2H, J = 7.0Hz), 4.19 (s, 2H) and 1.34 (t, 3H, J = 7.0Hz).

2-(2,2-Dimethoxy-ethoxymethyl)-acrylic acid methyl ester **305**



NaH (60%, 20 mg, 0.51 mmol, 1.1 eq) was added portionwise to a solution of glycolaldehyde dimethyl acetal (50 mg, 0.47 mmol) in THF (2 mL) and the mixture was stirred at rt for 1h under N_2. $INBu_4$ (4 mg, 0.01 mmol) and methyl α-bromomethyl acrylate **303**[46] (108 mg, 0.56 mmol, 1.2 eq) was added at 0°C and the reaction mixture was stirred overnight at rt, quenched with H_2O and concentrated *in vacuo*. The residue was diluted with H_2O, extracted with DCM, the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and again concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (9 : 1, Hexane : EtOAc) providing 2-(2,2-dimethoxy-ethoxymethyl)-acrylic acid methyl ester (74 mg, 78%) as colourless oil. IR(thin film/cm^{-1}): ν_{max} 2953, 1721, 1637, 1439, 1114, 956, 818. H^1 NMR (250MHz, $CDCl_3$): δ 6.28 (d, 1H, J = 1.5Hz), 5.87 (d, 1H, J = 1.5Hz), 4.50 (t, 1H, J = 5.0Hz), 4.23 (s, 2H), 3.74 (s, 3H), 3.51 (d, 2H, J = 5.0Hz) and 3.37 (s, 6H). C^{13} NMR (63MHz, $CDCl_3$): δ 166.33, 136.92, 126.22, 102.83, 70.59, 69.68, 54.09 and 51.90.

2-(3-Oxo-propoxy)-acrylic acid methyl ester **309**

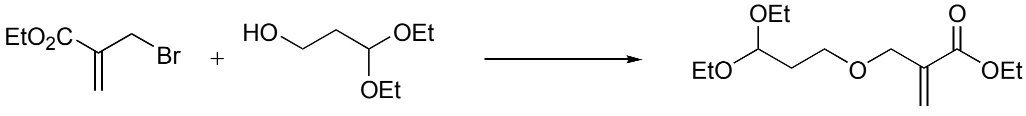


A solution of the 2-(2,2-dimethoxy-ethoxymethyl)-acrylic acid methyl ester **305** (580 mg, 2.84 mmol) in THF (8 mL) and HCl solution (0.5 M, 13 mL) was refluxed for 1 h. The reaction mixture was cooled to rt, diluted with H_2O (10 mL) and extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Hexane/EtOAc, 3:1) providing 2-(3-oxo-propoxy)-acrylic acid methyl ester (302 mg, 67%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 3448, 2954, 1720, 1439, 1120. H^1 NMR (250MHz, $CDCl_3$): δ 9.80 (s, 1H), 6.42 (d, 1H, J = 1.5Hz), 5.99 (d, 1H, J

= 1.5Hz), 4.37 (s, 2H), 4.22 (s, 2H) and 3.84 (s, 3H). C^{13} NMR (63MHz, $CDCl_3$): δ 200.36, 166.14, 136.55, 127.16, 76.14, 70.08 and 52.10. MS FAB (+ve) *m/z* $[M+H]^+$ calculated for $C_7H_{11}O_4$ 159.0657 found 159.0653.

*Synthesis of 2-(3-Oxo-propoxymethyl)-acrylic acid ethyl ester **310***

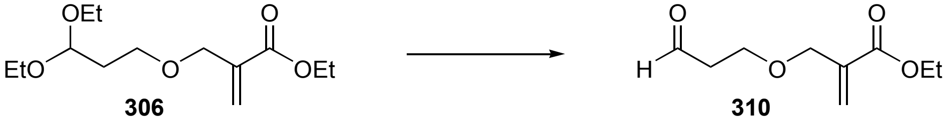
2-(3,3-Diethoxy-propoxymethyl)-acrylic acid ethyl ester **306**



303 **306**

To a solution of 3-hydroxypropanal diethyl acetal (4.26 g, 28.7 mmol) in THF (120 mL) was added NaH (60%, 1.26 g, 31.6 mmol, 1.1 equiv) portionwise and the reaction mixture was stirred at rt for 1 h. Ethyl *α*-bromomethyl acrylate **303** (6.66 g, 34.5 mmol, 1.2 equiv) was added at 0 °C, the reaction mixture was stirred at rt overnight, quenched with H_2O and concentrated *in vacuo*. The residue was quenched with H_2O, extracted with DCM, the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1) providing 2-(3,3-diethoxy-propoxymethyl)-acrylic acid ethyl ester (3.05 g, 41%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2982, 1721, 1107. H^1 NMR (250MHz, $CDCl_3$): δ 6.27 (d, 1H, J = 1.5Hz), 5.87 (d, 1H, J = 1.5Hz), 4.66 (t, 1H, J = 4.5Hz), 4.17 (m, 4H), 3.70-3.42 (m, 6H), 1.89 (q, 2H, 6.0Hz) and 1.33-1.16 (m, 9H). ^{13}C NMR (63MHz, $CDCl_3$): δ 166.02, 137.65, 125.41, 100.68, 69.16, 67.11, 61.64, 60.79, 34.31, 31.72, 22.78, 15.47 and 14.31.

2-(3-Oxo-propoxymethyl)-acrylic acid ethyl ester **310**

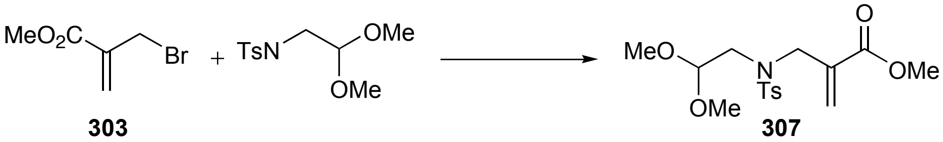


306 **310**

To a solution of 2-(3,3-diethoxy-propoxymethyl)-acrylic acid ethyl ester **306** (1.26 g, 4.84 mmol) in THF (50 mL) was added TFA (3.6 mL, 48.4 mmol, 10 equiv) dropwise at rt. The reaction mixture was stirred at rt for 3 h, diluted with H_2O (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing 2-(3-oxo-propoxymethyl)-acrylic acid ethyl ester (600 mg, 67%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2982, 1750, 1721, 1107. H^1 NMR (250MHz, $CDCl_3$): δ 9.80 (t, 1H, J = 2.0Hz), 6.29 (d, 1H, J = 1.5Hz), 5.83 (d, 1H, J = 1.5Hz), 4.27-4.17 (m, 4H), 3.84 (t, 2H, J = 7.5Hz), 2.70 (m, 2H) and 1.30 (t, 3H, J = 7.5Hz). ^{13}C NMR (63MHz, $CDCl_3$): δ 201.04, 165.85, 137.15, 125.87, 69.42, 64.56, 60.85, 43.86 and 14.26. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_9H_{14}O_4$, 186.0886 found 186.0889.

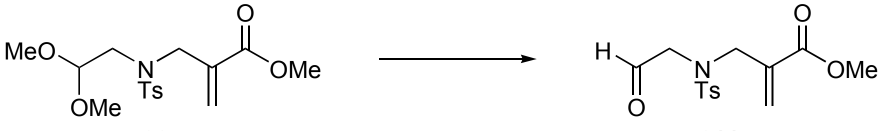
Synthesis of 2-{[(2-oxo-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid methyl ester ***311***

2-{[(2,2-Dimethoxy-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid methyl ester **307**



To a solution of N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide[40] (602 mg, 2.32 mmol) in DMF (10 mL) was added NaH (60%, 126 mg, 3.02 mmol, 1.3 equiv) at 0 ºC, the suspension was stirred for 30 min at rt and methyl 2-(bromomethyl) acrylate **303** (900 mg, 5.00 mmol, 2.15 equiv) was added dropwise. The solution was stirred overnight at rt, quenched with H_2O, and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ EtOAc, 3:1) providing 2-{[(2,2-dimethoxy-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid methyl ester (746 mg, 90%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2951, 1718, 1342, 1160. H^1 NMR (250MHz, $CDCl_3$): δ 7.68 (d, 2H, J = 8.5Hz), 7.31 (d, 2H, J = 8.5Hz), 6.31 (d, 1H, J = 1.0Hz), 5.80 (d, 1H, J = 1.0Hz), 4.41 (t, 1H, J = 5.5Hz), 4.13 (s, 2H), 3.69 (s, 3H), 3.31 (s, 6H), 3.25 (d, 2H, J = 5.5Hz) and 2.42 (s, 3H). C^{13} NMR (63MHz, $CDCl_3$): δ 166.45, 143.60, 137.03, 135.65, 129.80, 127.35, 104.01, 76.65, 54.77, 52.00, 50.40, 49.87 and 21.63. MS ES (+ve) *m/z* $[M+NH_4]^+$ calculated for $C_{16}H_{27}N_2O_6S$ 375.1584 found 375.1587.

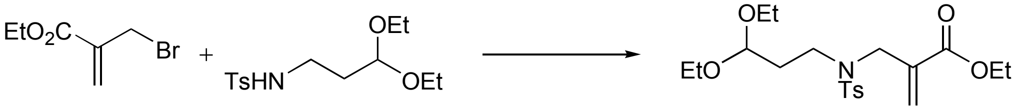
2-{[(2-Oxo-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}acrylic acid methyl ester **311**


307 **311**

2-{[(2,2-Dimethoxy-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid methyl ester **307** (743 mg, 2.08 mmol) was dissolved in acetic acid (2.4 mL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1M, 672 μL) was added and the solution was stirred overnight. The reaction mixture was diluted with DCM (30 mL), washed successively with water (4 mL), saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), water (4 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 2-{[(2-oxo-ethyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid methyl ester (640 mg, 99 %) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2954.4, 1724.0, 1336.4, 1158.0. H^1 NMR (250MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.68 (d, 2H, J = 8.5Hz), 7.31 (d, 2H, J = 8.5Hz), 6.36 (d, 1H, J = 1.0Hz), 5.91 (d, 1H, J = 1.0Hz), 4.06 (s, 2H), 3.90 (s, 2H), 3.71 (s, 3H) and 2.43 (s, 3H). C^{13} NMR (63MHz, $CDCl_3$): δ 197.76, 166.31, 144.26, 135.66, 135.27, 130.01, 129.07, 127.57, 57.72, 52.28, 50.10 and 21.68.

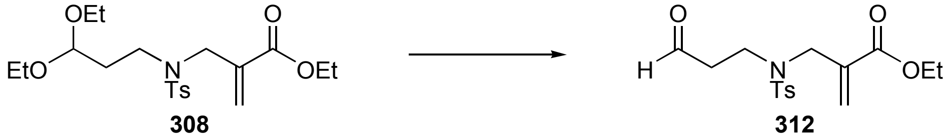
*Synthesis of 2-{[(3,3-oxo-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester **312***

2-{[(3,3-Diethoxy-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester **308**


303 **308**

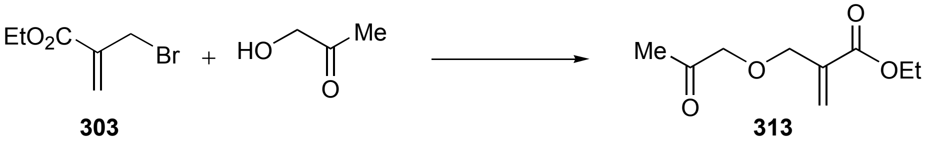
To a solution of N-(3,3-diethyl-propyl)-4-methyl-benzenesulfonamide[47] (1.69 g, 5.6 mmol) in DMF (20 mL) was added NaH (60%, 224 mg, 1.3 equiv) at 0 ºC. The suspension was stirred at rt for 1 h and ethyl α-bromomethyl acrylate **303** (5.00 g, 25.9 mmol, 2.15 equiv) was added dropwise at 0 ºC. The solution was stirred at rt for 2 days, quenched with H_2O, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (3 × 30 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 100:0 – 90:10) providing 2-{[(3,3-diethoxy-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester (1.42 g, 61%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2976, 2359, 1714, 1160. H^1 NMR (250MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 8.5Hz), 7.29 (d, 2H, J = 8.5Hz), 6.35 (d, 1H, J = 1.0Hz), 5.91 (d, 1H, J = 1.0Hz), 4.44 (t, 1H, J = 5.5Hz), 4.18 (q, 2H, J = 7.0Hz), 4.00 (s, 2H), 3.59-3.42 (m, 4H), 3.28-3.11 (m, 2H), 2.42 (s, 3H), 1.78-1.65 (m, 2H), 1.29 (3H, t, J = 7.0Hz) and 1.16 (t, 6H, J = 7.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 166.04, 143.50, 136.76, 136.23, 129.86, 127.47, 127.27, 100.89, 61.68, 61.09, 48.90, 45.41, 32.88, 21.64, 15.45 and 14.30.

2-{[(3,3-Oxo-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester **312**



2-{[(3,3-Diethoxy-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester **308** (100 mg, 0.24 mmol) was dissolved in acetic acid (277 µL) and the solution was cooled to 0-5 °C in an ice bath. As soon as the solution started to freeze, HCl solution (1M, 77 µL) was added and the solution was stirred for 1 h in the same bath. The mixture was diluted with DCM (10 mL) and the solution washed successively with water (4 mL), saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), water (4 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing 2-{[(3,3-Oxo-propyl)-(toluene-4-sulfonyl)-amino]-methyl}-acrylic acid ethyl ester (60 mg, 74%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2360, 1717, 1159. H^1 NMR (250MHz, $CDCl_3$): δ 9.70 (t, 1H, J = 1.0Hz), 7.68 (d, 2H, J = 9.5Hz), 7.31 (d, 2H, J = 9.5Hz), 6.33 (d, 1H, J = 1.0Hz), 5.84 (d, 1H, J = 1.0Hz), 4.18 (q, 2H, J = 7.0Hz), 4.00 (s, 2H), 3.45 (t, 2H, J = 7.0Hz), 2.75 (dt, 2H, J = 7.0 and 1.0Hz), 2.42 (s, 3H) and 1.28 (t, 3H, J = 7.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 199.98, 165.94, 143.86, 136.22, 136.10, 129.98, 127.67, 127.36, 61.22, 49.43, 43.54, 42.86, 21.56 and 14.26. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_{16}H_{21}NO_5S$ 339.1135 found 339.1139.

2-(2-Oxo-propoxymethyl)-acrylic acid ethyl ester **313**



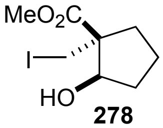
To a solution of acetol (3.80 g, 51.3 mmol) and ethyl α-bromomethyl acrylate (9.90 g, 51.3 mmol) **303** in EtOH (60 mL) was added an aqueous solution of NaOH (2.10 g in H_2O (50 mL)) dropwise. The reaction mixture was refluxed overnight and extracted with Et_2O (3 × 100 mL). The combined organic layers was washed with saturated NH_4Cl aqueous solution (100 mL), H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 85:15) providing 2-(2-oxo-propoxymethyl)-acrylic acid ethyl ester (995 mg, 11 %) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 2982, 2360, 1718, 1124. H^1 NMR (250MHz, $CDCl_3$): δ 6.31 (d, 1H, J = 1.5Hz), 5.87 (d, 1H, J = 1.5Hz), 4.25-4.12 (m, 4H), 4.09 (s, 2H), 2.15 (s, 3H) and 1.28 (t, 3H, J = 7.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 206.70, 165.78, 136.81, 126.39, 76.21, 69.78, 60.92, 26.44 and 14.25. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_9H_{14}O_4$, 186.0887 found 186.0884.

IV-2-Iodo-Aldol Procedures

Iodo Aldol cyclisations - Stoichiometric

Under an N_2 atmosphere, a solution of $TiCl_4$ (1.0 M in DCM, 1.2 equiv) was added dropwise to a solution of *n*-Bu_4NI (1.2 equiv) in DCM (2 mL) at 0 °C, and the resulting dark-red solution was stirred for 10 min. To the reaction mixture was added a solution of the enoate (0.32 mmol) in DCM (4 mL) at rt over 1 h *via* syringe pump. Following addition, the reaction was quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with DCM (3 X 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. H^1 NMR analysis of the crude reaction mixtures indicated that each iodo-aldol product was formed as essentially a single diastereoisomer with the exception of iodo-aldol **278**, where the dr was 88:12. Purification by flash column chromatography provided the pure compounds.

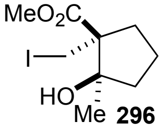
(±)-(1*R*, 2*R*)-2-Hydroxy-1-iodomethyl-cyclopentanecarboxylic acid methyl ester **278**



278

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) providing the title compound (74 mg, 81%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 3465, 2962, 1721, 1183. H^1 NMR (250MHz, CDCl$_3$): δ 4.16 (m, 1H) 3.74 (s, 3H), 3.42 (d, 1H, J = 10.0Hz) 3.20 (d, 1H, J = 10.0Hz), 2.94 (d, 1H, J = 2.0Hz) and 2.44-1.54 (m, 6H). C^{13} NMR (63MHz, CDCl$_3$): δ 174.0, 79.22, 59.58, 52.51, 33.21, 33.00, 20.55 and 10.91. MS ES (+ve) *m/z* [M]$^+$ calculated for C$_8$H$_{13}$IO$_3$, 283.9904 found 283.9903.

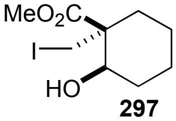
(±)-(1*R*, 2*R*)-2-Hydroxy-1-iodomethyl-2-methyl-cyclopentanecarboxylic acid methyl ester **296**



296

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing the title compound (63 mg, 66%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 3487, 2951, 1726, 1160. H^1 NMR (250MHz, CDCl$_3$): δ 3.75 (s, 3H), 3.69 (d, 1H, J = 9.5Hz), 3.02 (d, 1H, J = 9.5Hz), 2.60 (m, 1H), 2.13-1.62 (m, 6H) and 1.40 (s, 3H). C^{13} NMR (63MHz, CDCl$_3$): δ 173.56, 82.53, 62.42, 52.43, 40.30, 34.26, 23.06, 19.63 and 11.61. MS FAB (+ve) *m/z* [M+H]$^+$ calculated for, C$_9$H$_{16}$IO$_3$, 299.0144 found 299.0149.

(±)-(1*R*, 2*R*)-2-Hydroxy-1-iodomethyl-cyclohexanecarboxylic acid methyl ester **297**

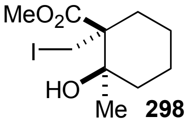


297

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1) providing the title compound (73 mg, 76%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 3485, 2938, 1727, 1222. H^1 NMR (250MHz, CDCl$_3$): δ 3.77 (s, 3H), 3.65 (m, 1H) 3.58

(d, 1H, J = 10.0Hz), 3.47 (d, 1H, J = 10.0Hz) and 2.30-1.34 (m, 8H). C^{13} NMR (63MHz, $CDCl_3$): δ 174.16, 74.05, 52.42, 51.88, 32.97, 32.01, 23.62, 22.56 and 12.97. MS EI (+ve) *m/z* $[M+NH_4]^+$ calculated for $C_9H_{19}INO_3$, 316.0404 found 316.0406.

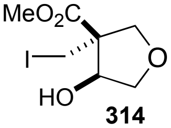
(±)-(1*R*, 2*R*)-2-Hydroxy-1-iodomethyl-2-methyl-cyclohexanecarboxylic acid methyl ester **298**



298

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 95:5) providing the title compound (52 mg, 52%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 3476, 2935, 2359, 1722. H^1 NMR (250MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.76 (d, 1H, J = 10.0Hz), 3.49 (s, 1H), 3.31 (d, 1H, J = 10.0Hz), 2.48-2.05 (m, 2H), 1.64-1.32 (m, 6H) and 1.26 (s, 3H). C^{13} NMR (63MHz, $CDCl_3$): δ 175.06, 73.20, 54.67, 52.35, 38.20, 31.14, 24.47, 22.04, 21.13 and 10.22. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_{10}H_{17}IO_3$, 312.0222, found 312.0223.

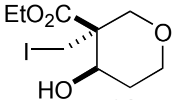
(±)-(3*R*, 4*S*)-4-Hydroxy-3-iodomethyl-tetrahydro-furan-3-carboxylic acid methyl ester **314**



314

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 6:4) providing the title compound (67 mg, 74%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 3428, 1735, 1438, 1199. H^1 NMR (250MHz, $CDCl_3$): δ 4.31 (m, 1H), 4.25 (dd, 1H, J = 10.0 and 1.5Hz), 4.11 (dd, 1H, J = 10.0 and 5.0Hz), 3.86 (d, 1H, J = 10.0Hz), 3.78 (s, 3H), 3.75 (dd, 1H, J = 10.0 and 5.0Hz), 3.50 (dd, 1H, J = 10.0 and 1.5Hz) and 3.24 (d, 2H, J = 10.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 171.28, 77.60, 74, 61, 72.84, 61.26, 52.80 and 7.26. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_7H_{11}IO_4$, 285.9702 found 285.9702.

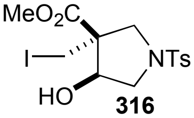
(±)-(3*R*, 4*S*)-4-Hydroxy-3-iodomethyl-tetrahydro-pyran-3-carboxylic acid ethyl ester **315**



315

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 75:25) providing the title compound (64 mg, 64%) as a colourless oil. IR(thin film/cm^{-1}): ν_{max} 3435, 2927, 2359, 1729. H^1 NMR (250MHz, CDCl$_3$): δ 4.35-4.02 (m, 4H), 3.83 (m, 1H), 3.64-3.45 (m, 4H), 3.29 (d, 1H, J = 7.0Hz), 1.92 (m, 1H), 1.71 (m, 1H) and 1.31 (t, 3H, J = 7.0Hz). C^{13} NMR (63MHz, CDCl$_3$): δ 172.30, 70.14, 69.96, 65.05, 61.85, 50.94, 30.82, 14.29 and 6.72. MS EI (+ve) *m/z* [M]$^+$ calculated for $C_9H_{15}IO_4$, 314.0009 found 314.0020.

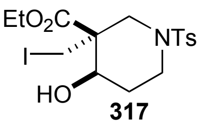
(±)-(3*R*, 4*S*)-4-Hydroxy-3-iodomethyl-1-(toluene-4-sulfonyl)-pyrrolidine-3-carboxylic acid methyl ester **316**



316

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 6:4) providing the title compound (102 mg, 72%) as a yellow oil. IR (thin film/cm^{-1}): ν_{max} 1737, 1341, 1160. H^1 NMR (250MHz, CDCl$_3$): δ 7.69 (d, 2H, J = 8.0Hz), 7.35 (d, 2H, J = 8.0Hz), 4.26 (m, 1H), 3.72 (s, 3H), 3.66 (d, 1H, J = 10.5Hz), 3.63 (d, 1H, J = 11.5Hz), 3.56 (d, 1H, J = 10.5Hz), 3.30 (d, 1H, J = 10.5Hz), 3.21 (d, 1H, J = 11.5Hz), 3.06 (d, 1H, J = 10.5Hz), 2.93 (d, 1H, J = 5.0Hz) and 2.44 (s, 3H). C^{13} NMR (63MHz, CDCl$_3$): δ 170.80, 144.10, 133.54, 130.01, 127.76, 75.56, 59.41, 53.80, 52.98, 52.48, 21.72 and 5.93. MS EI (+ve) *m/z* [M+H]$^+$ calculated for $C_{14}H_{19}INO_5S$, 440.0023 found 440.0020.

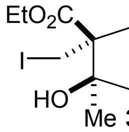
(±)-(3*R*, 4*S*)-4-Hydroxy-3-iodomethyl-1-(toluene-4-sulfonyl)-piperidine-3-carboxylic acid ethyl ester **317**



317

The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) the title compound (111 mg, 74%) as a colourless oil. IR(thin film/cm^{-1}): ν_{max} 3501, 2927, 1735, 1165. H^1 NMR (250MHz, CDCl$_3$): δ 7.64 (d, 2H, J = 8.0Hz), 7.32 (d, 2H, J = 8.0Hz), 4.24 (q, 2H, J = 7.0Hz), 4.02 (d, 1H, J = 3.0Hz), 3.54 (q, 2H, J = 11.0Hz), 3.48-2.78 (m, 5H), 2.43 (s, 3H), 2.07-1.58 (m, 2H) and 1.33 (t, 3H, J = 7.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 171.88, 143.97, 133.17, 129.97, 127.71, 69.06, 62.21, 51.03, 48.31, 42.33, 28.95, 21.67, 14.27, and 6.63. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_{16}H_{22}INO_5S$, 467.0258 found 467.0239.

(±)-(3*R*, 4*S*)-4-Hydroxy-3-iodomethyl-4-methyl-tetrahydro-furan-3-carboxylic acid ethyl ester **318**



318

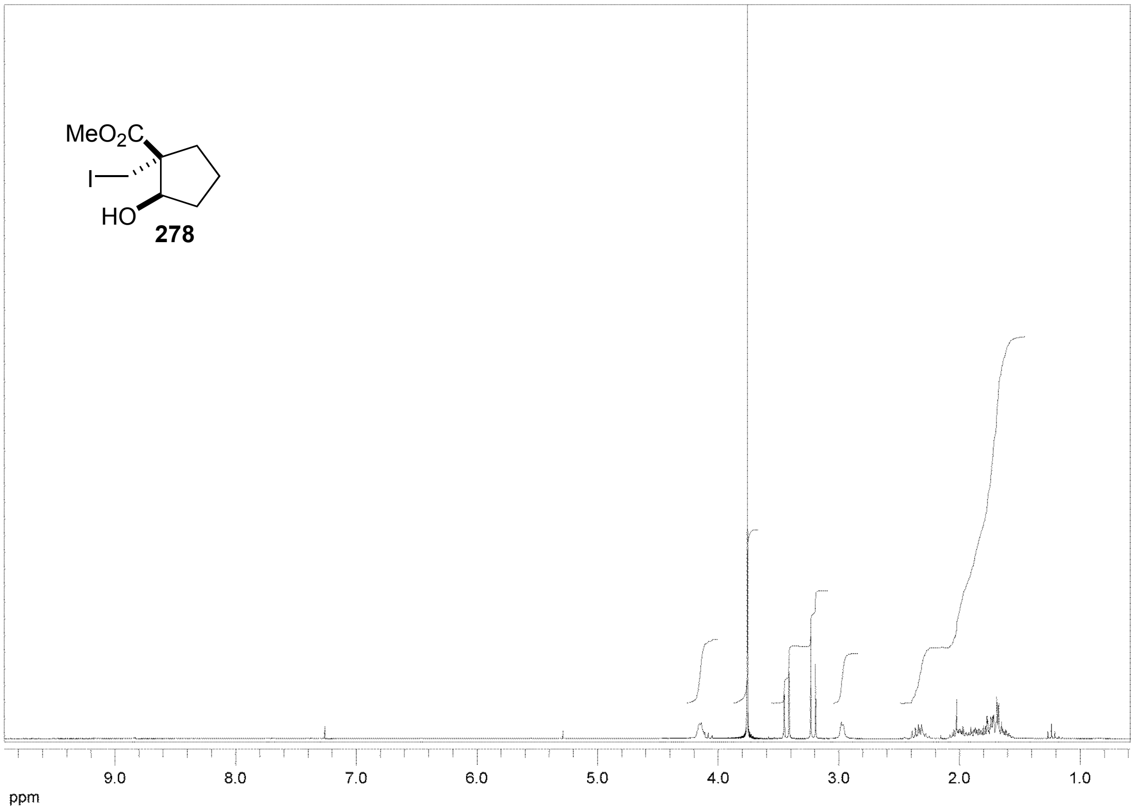
The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing the title compound (47 mg, 47%) as a colourless oil. IR (thin film/cm^{-1}): ν_{max} 3399, 2359, 1727. H^1 NMR (250MHz, $CDCl_3$): δ 4.62 (d, 1H, J = 9.5Hz), 4.31-4.21 (m, 2H), 3.86-3.63 (m, 4H), 3.10 (d, 1H, J = 9.5Hz), 2.65 (s, 1H), 1.41 (s, 3H) and 1.33 (t, 3H, J = 7.0Hz). C^{13} NMR (63MHz, $CDCl_3$): δ 170.48, 81.80, 79.15, 75.92, 62.53, 61.88, 18.46, 14.39 and 8.74. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_9H_{15}IO_4$, 314.0009 found 314.0001.

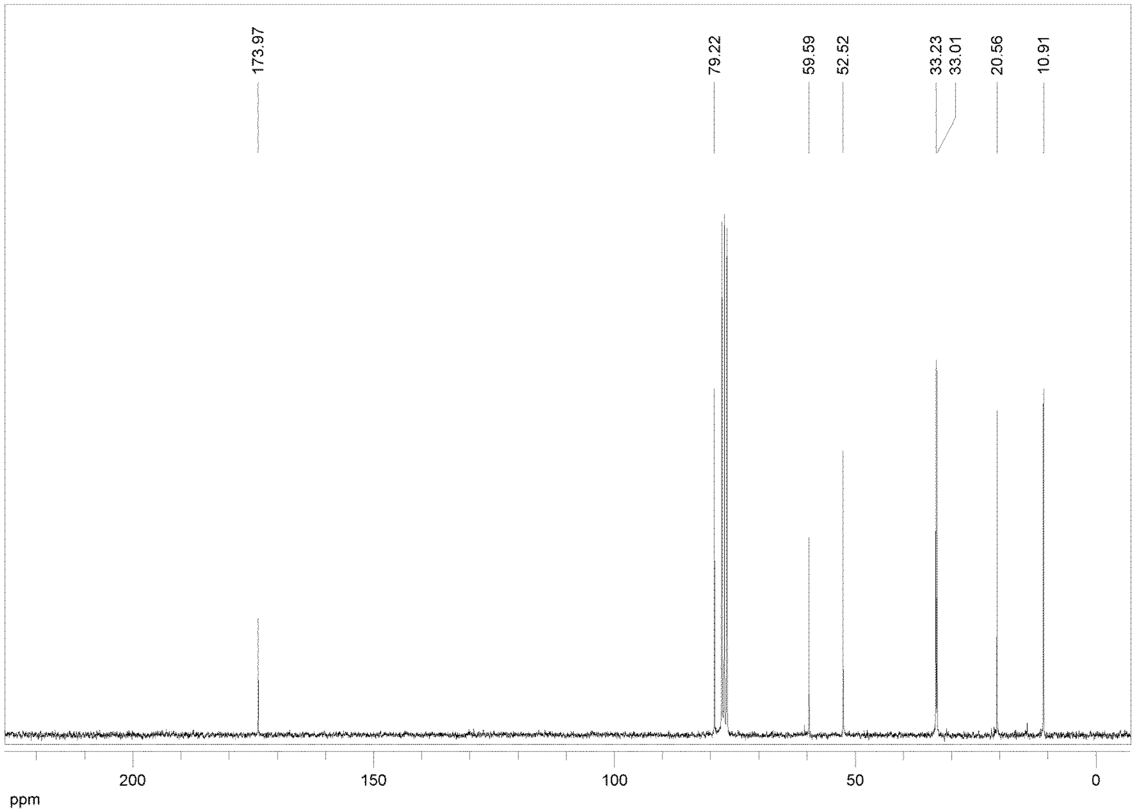
Iodo Aldol cyclisations: Catalytic

Under an N_2 atmosphere, a solution of $TiCl_4$ (1.0 M in DCM, 0.2 equiv) was added dropwise to a solution of TMSI (2.4 equiv) in DCM (2 mL) at 0 °C, and the resulting dark-red solution was stirred for 10 min. To the reaction mixture was added a solution of 2-(2-oxo-propoxymethyl)-acrylic acid ethyl ester, **313** (0.32 mmol) in DCM (4 mL) at -78 °C over 30 min. The reaction was quenched with aqueous $Na_2S_2O_3$ solution (10%, 5 mL) at -78 °C, warmed to rt then extracted with EtOAc (3 X 25 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) providing (±)-(3*R*, 4*S*)-4-hydroxy-3-iodomethyl-4-methyl-tetrahydro-furan-3-carboxylic acid ethyl ester **318** (53 mg, 53%) as a colourless oil.

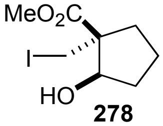
Under an N_2 atmosphere, a solution of $TiCl_4$ (1.0 M in DCM, 0.2 equiv) was added dropwise to a solution of TMSI (1.2 equiv) in DCM (2 mL) at 0 °C, and the resulting dark-red solution was stirred for 10 min. To the reaction mixture was added a solution of 2-(3-oxo-propoxymethyl)-acrylic acid ethyl ester **310**, (0.32 mmol) in DCM (4 mL) at rt over 2 h. The reaction was quenched with aqueous $Na_2S_2O_3$ solution (10%, 5 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 75:25) providing (±)-(3*R*, 4*S*)-4-hydroxy-3-iodomethyl-tetrahydro-pyran-3-carboxylic acid ethyl ester **315** (49 mg, 49%) as a colourless oil.

IV-3-Spectroscopic data

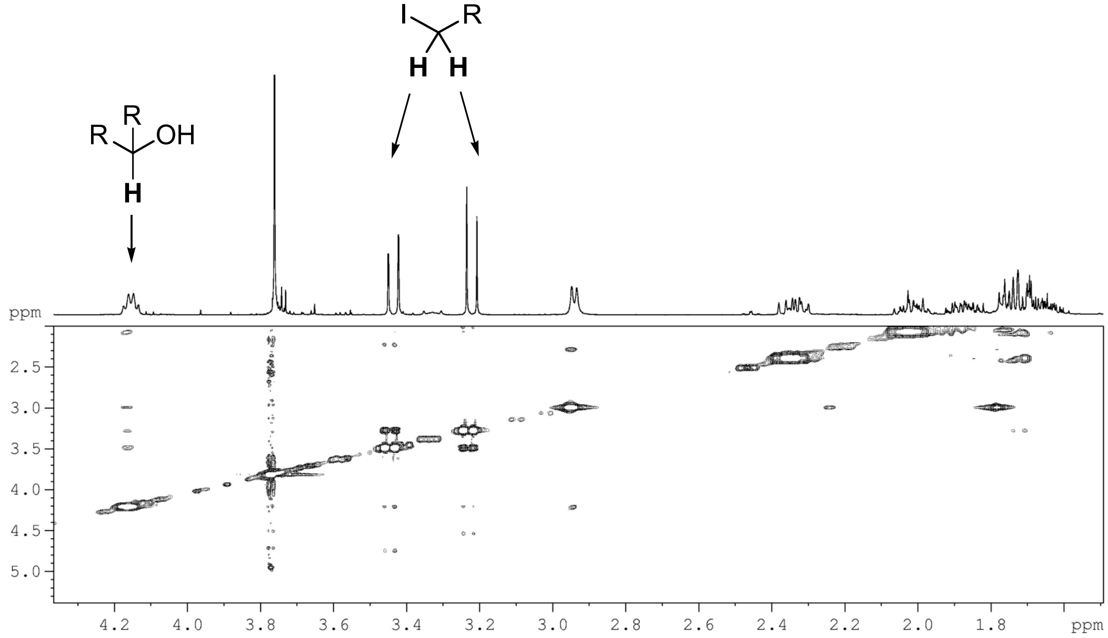


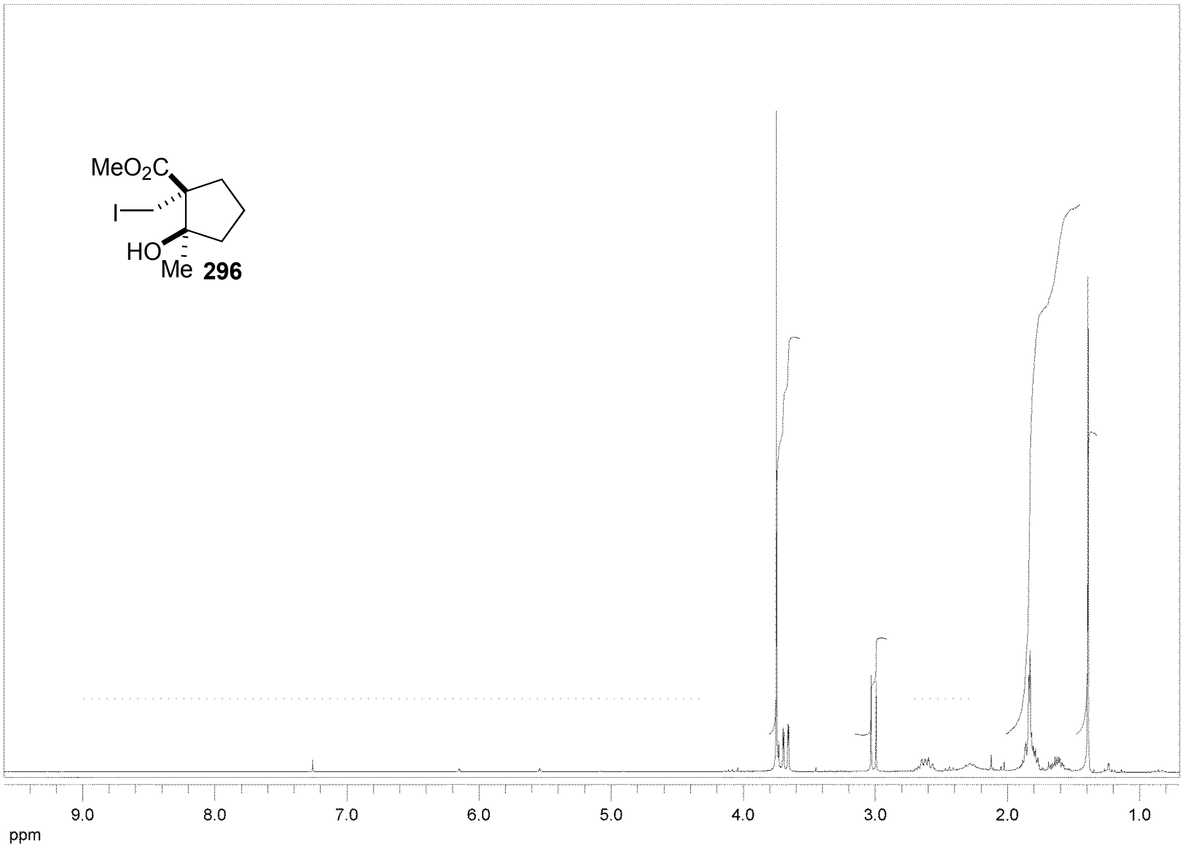


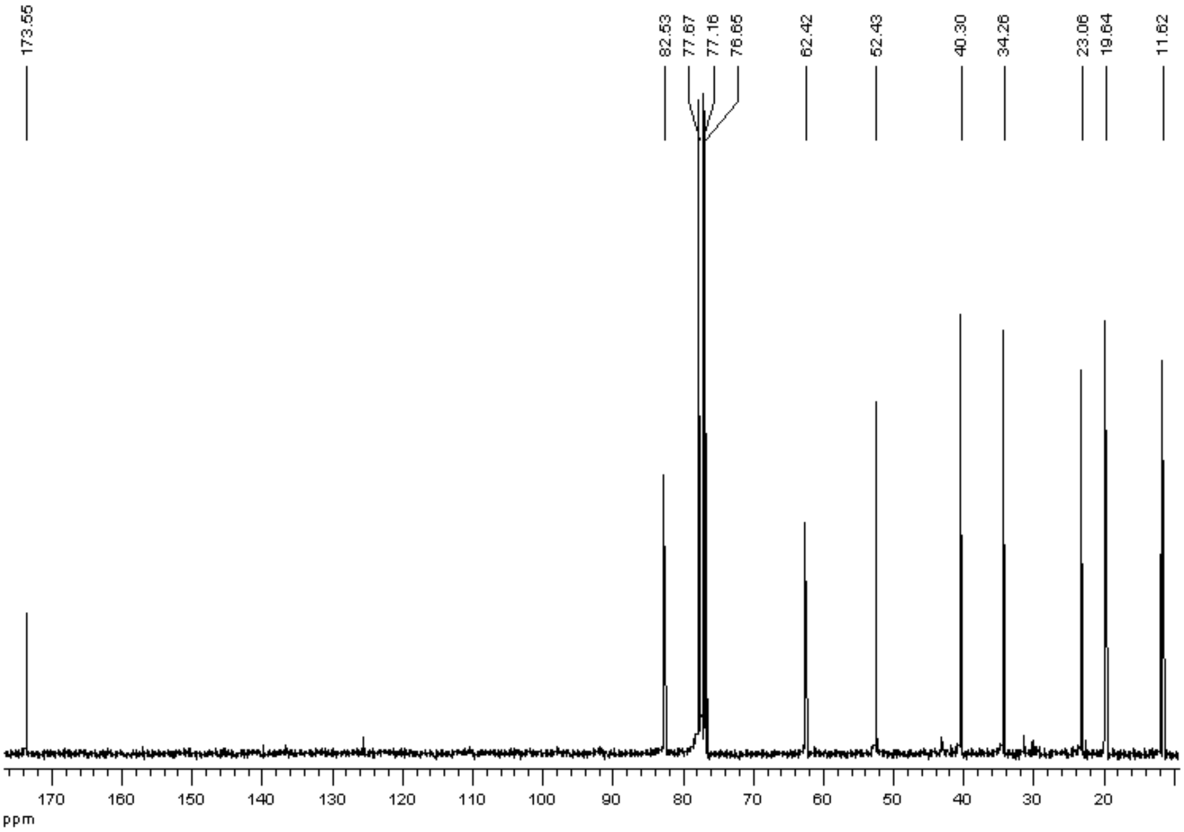
NOESY data for **278**

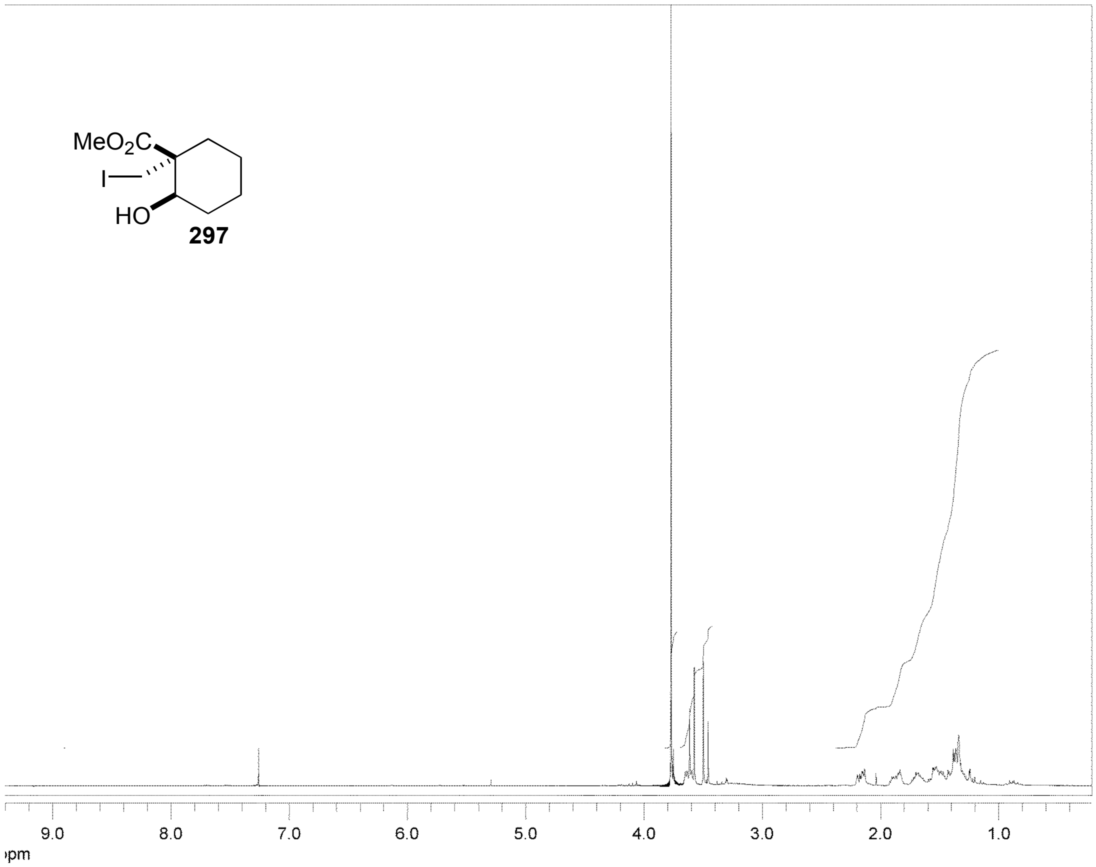


278

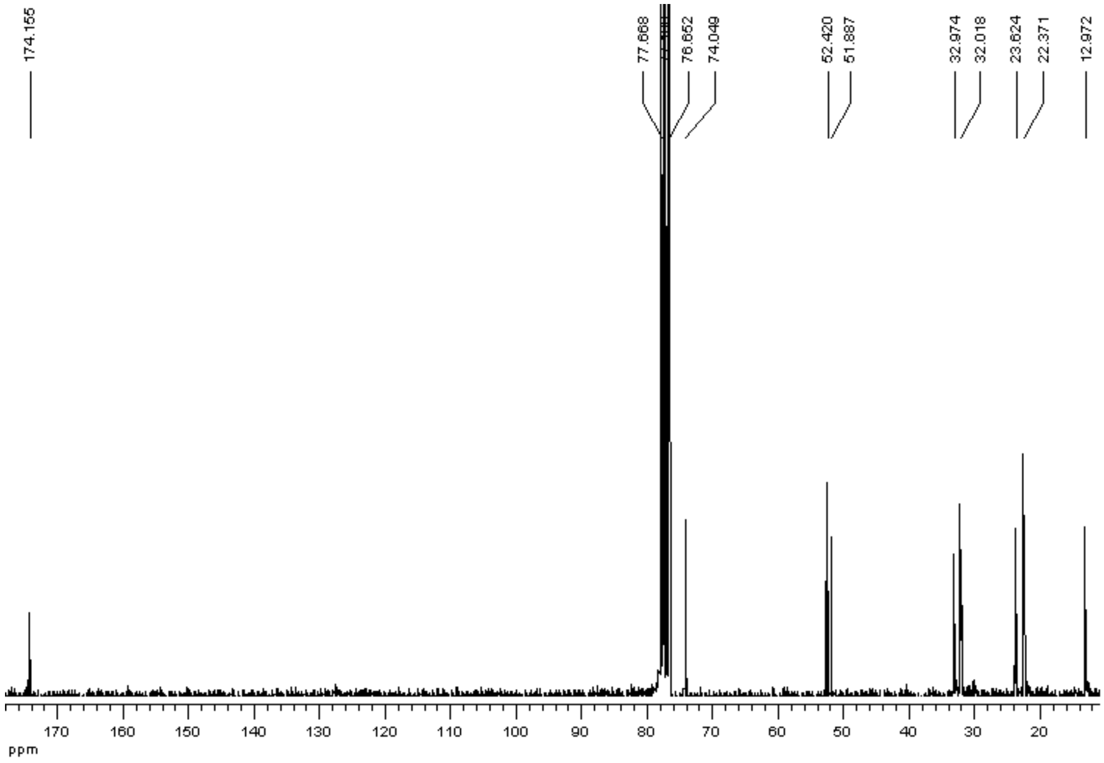


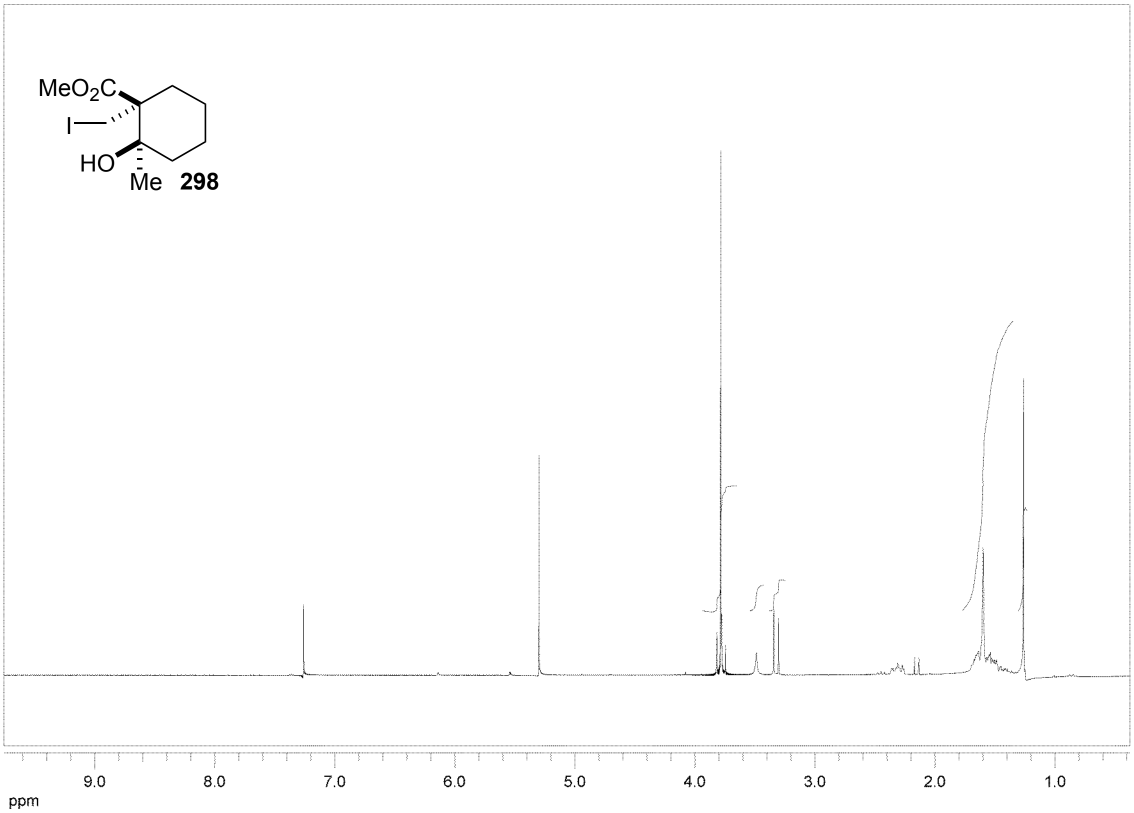

MeO2C
I
HO
Me
296
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

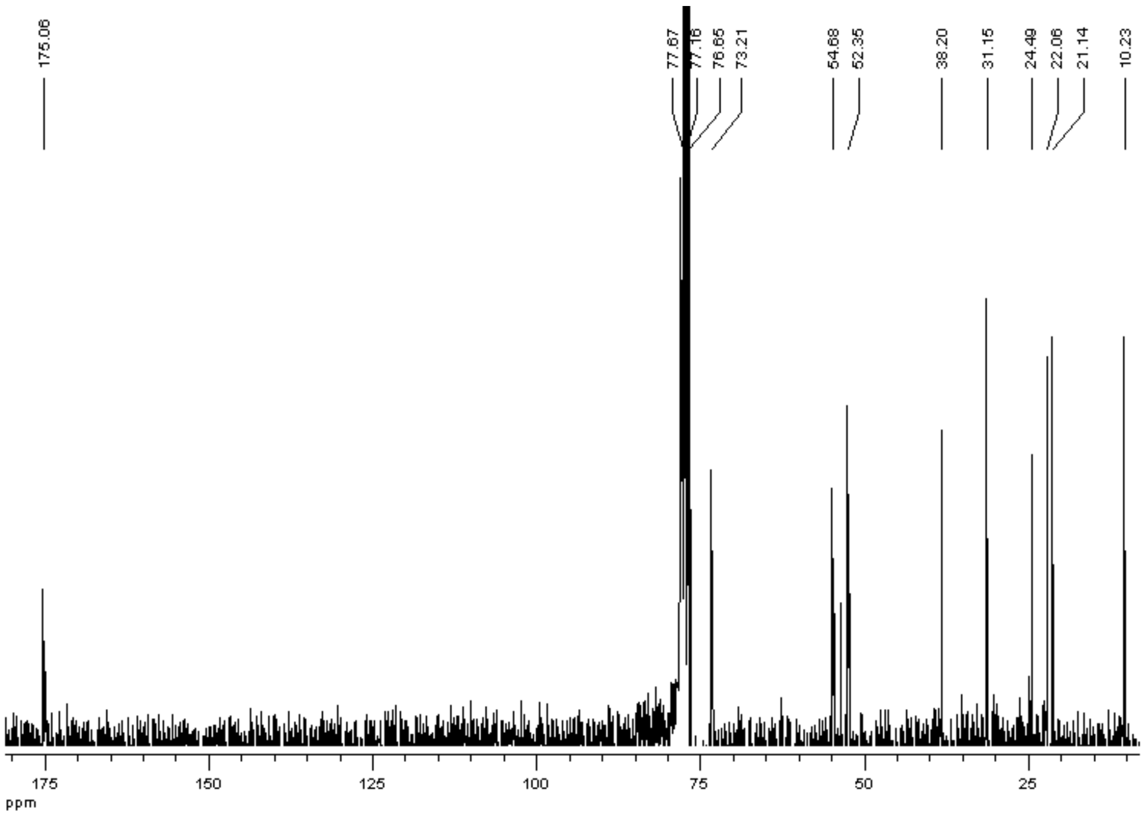

173.55
82.53
77.67
77.16
76.65
62.42
52.43
40.30
34.26
23.06
19.64
11.62
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

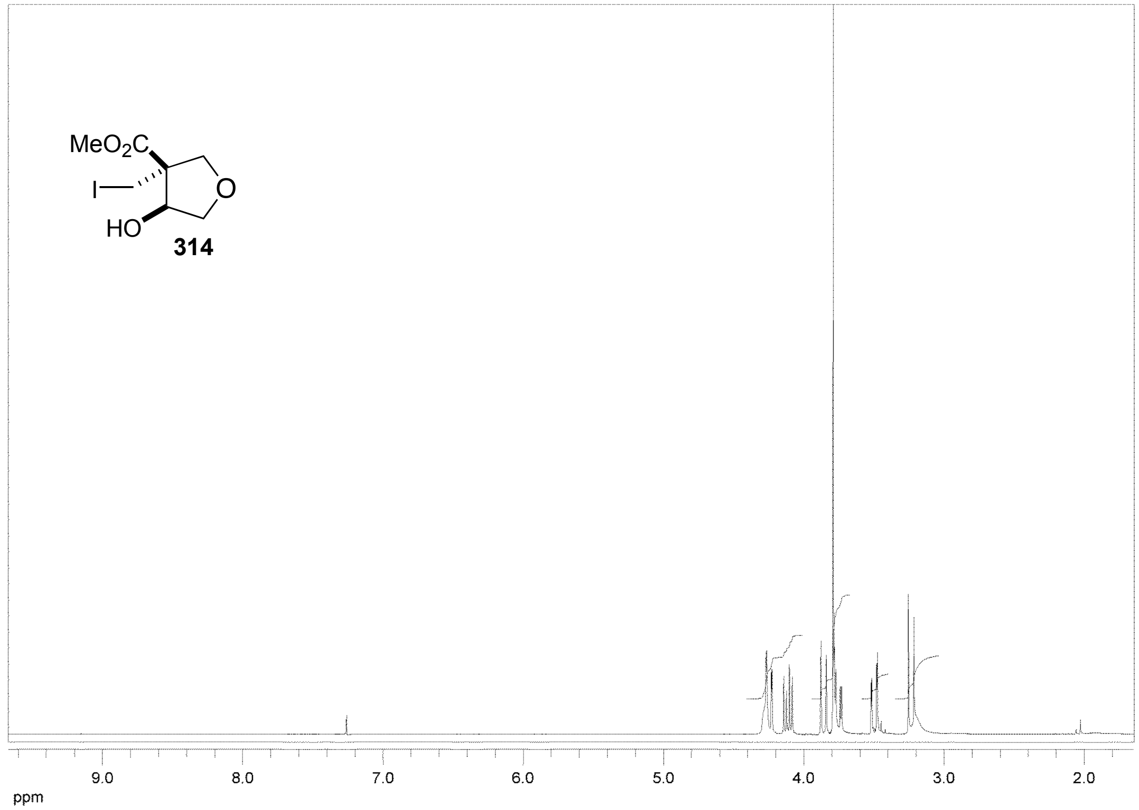

MeO2C
I
HO
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

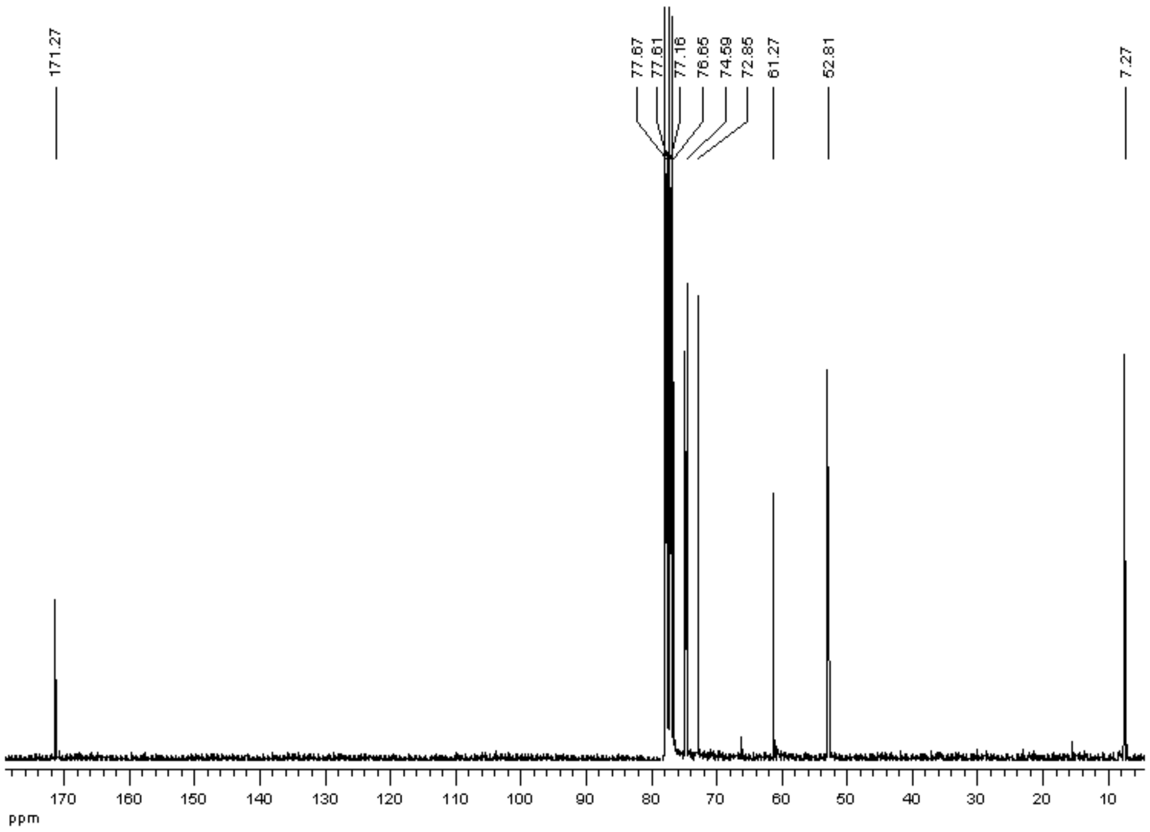
297

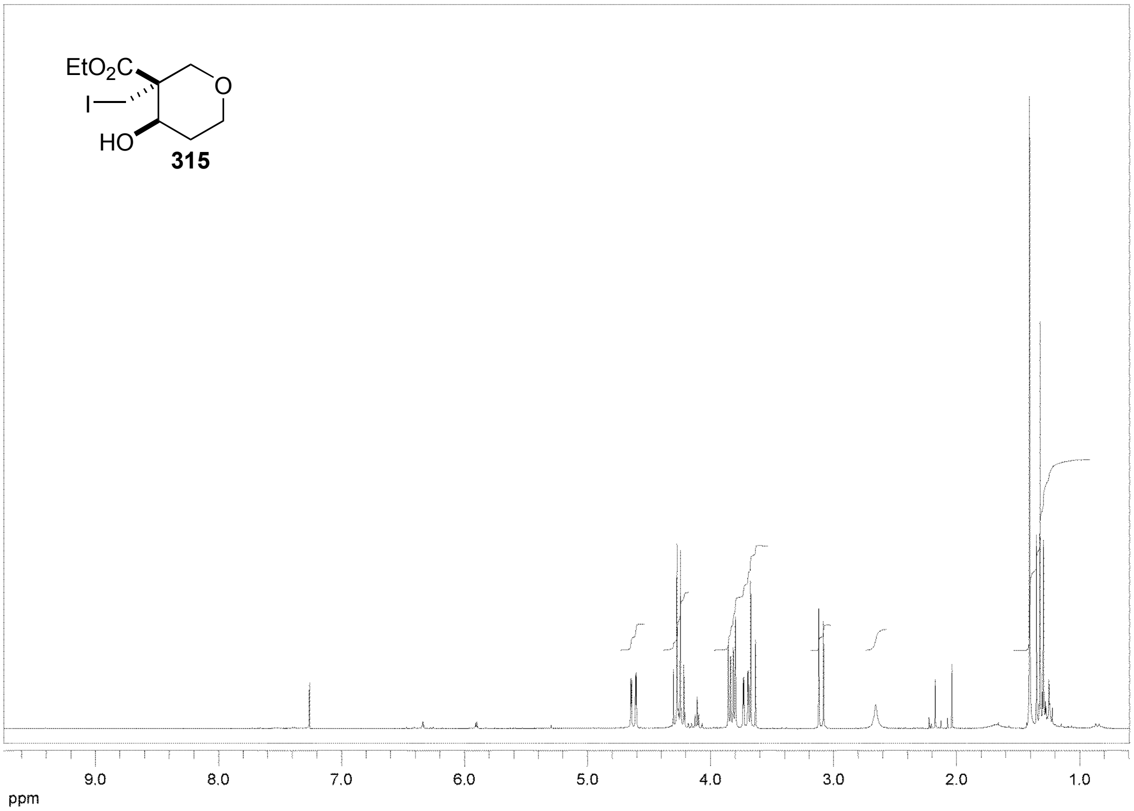

174.155
77.668
76.652
74.049
52.420
51.887
32.974
32.018
23.624
22.371
12.972
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


MeO$_2$C
I
HO
Me
298
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


175.06
77.67
77.16
76.65
73.21
54.68
52.35
38.20
31.15
24.49
22.06
21.14
10.23
175
150
125
100
75
50
25
ppm

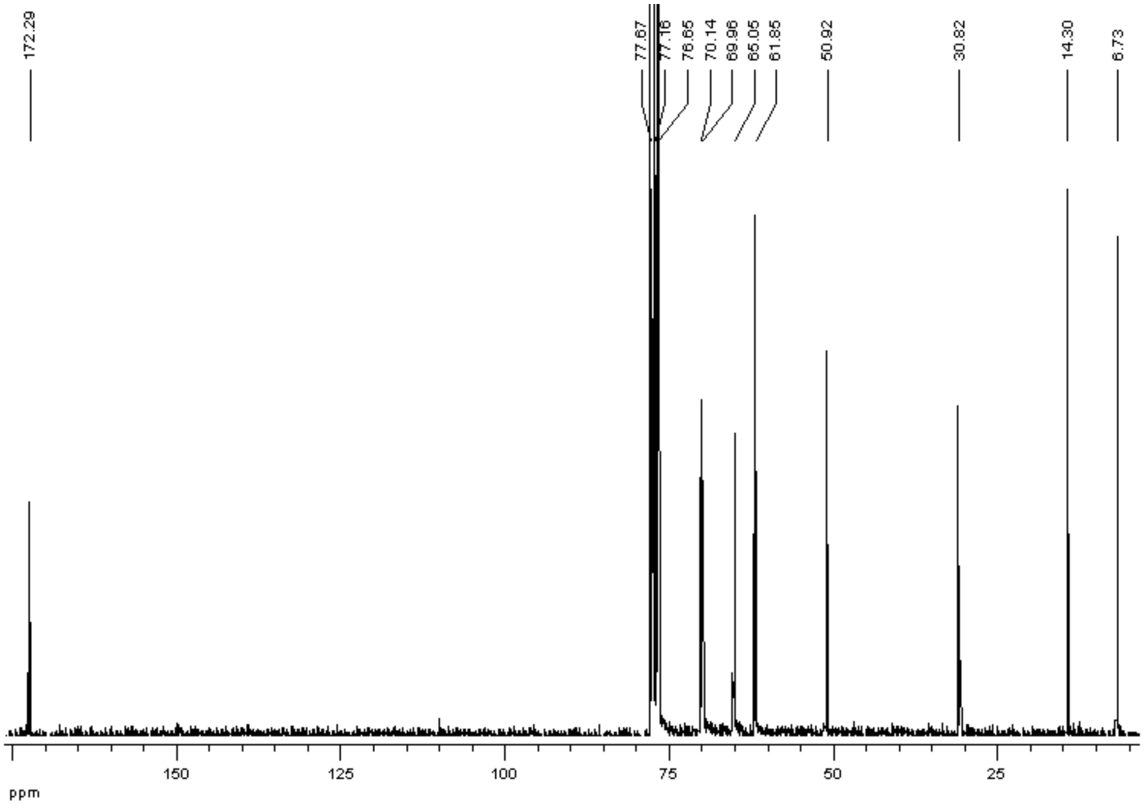

MeO$_2$C
I
O
HO
314
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm


171.27
77.67
77.61
77.16
76.65
74.59
72.85
61.27
52.81
7.27
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

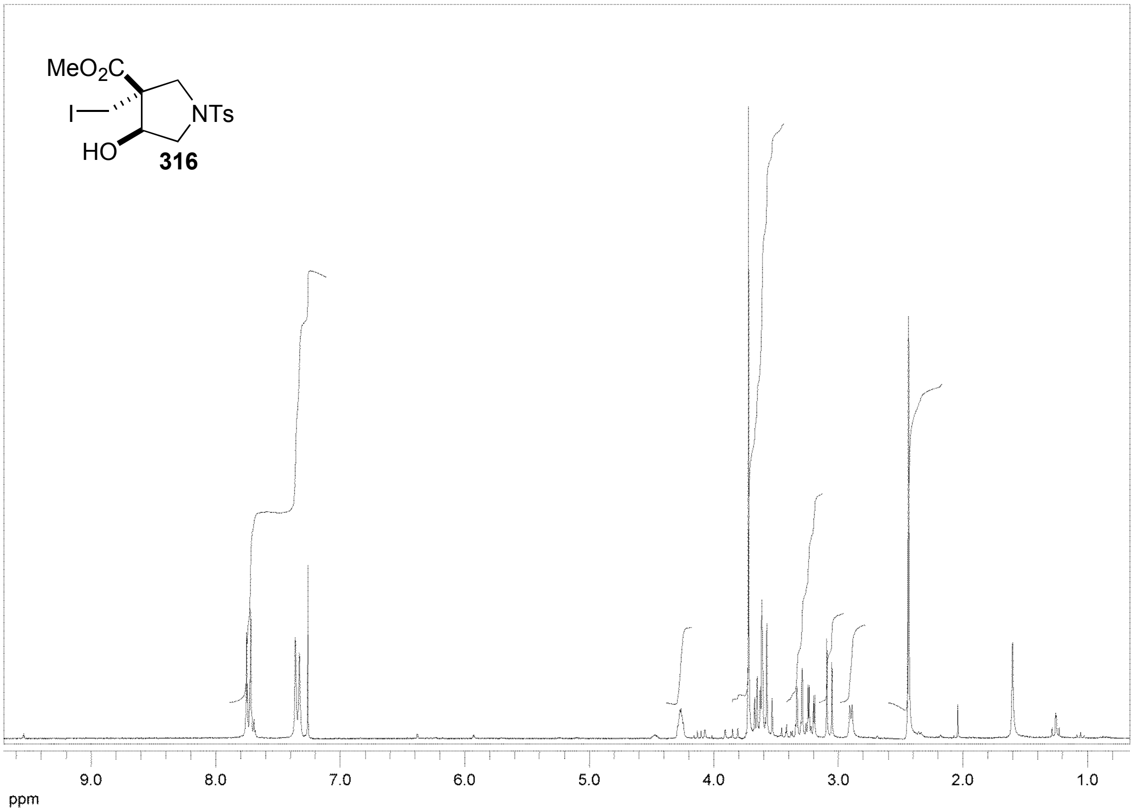


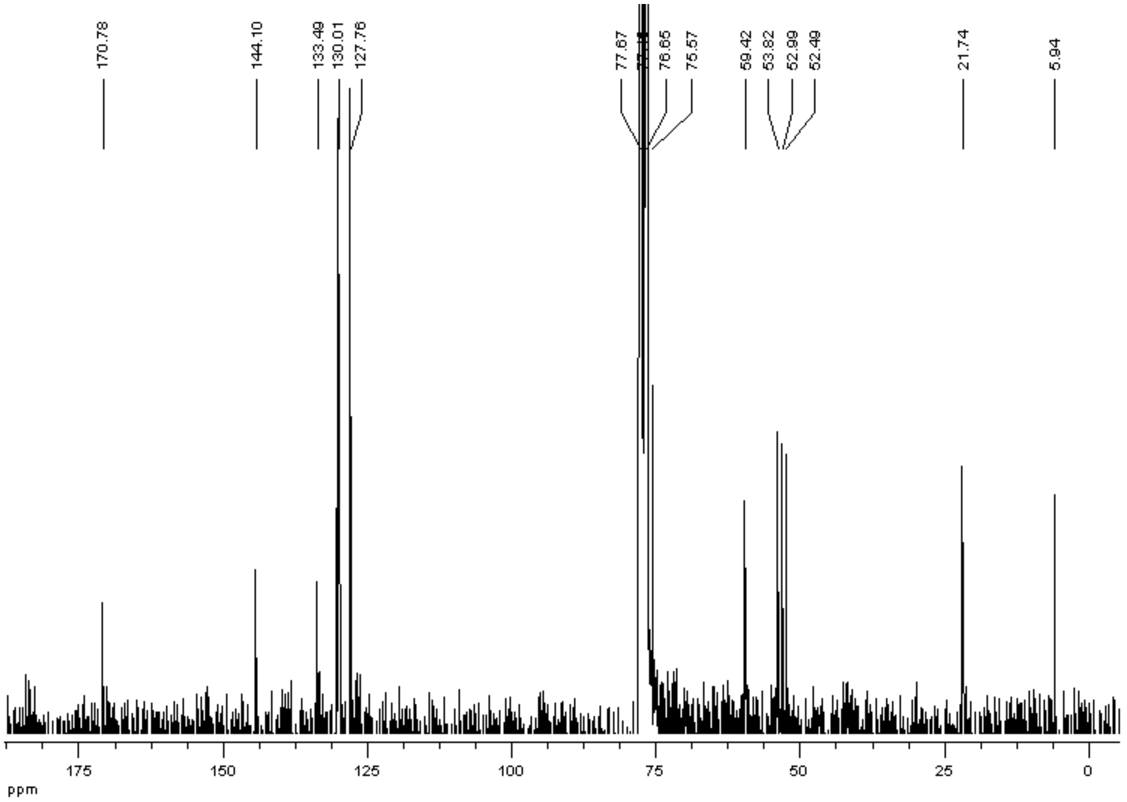
315

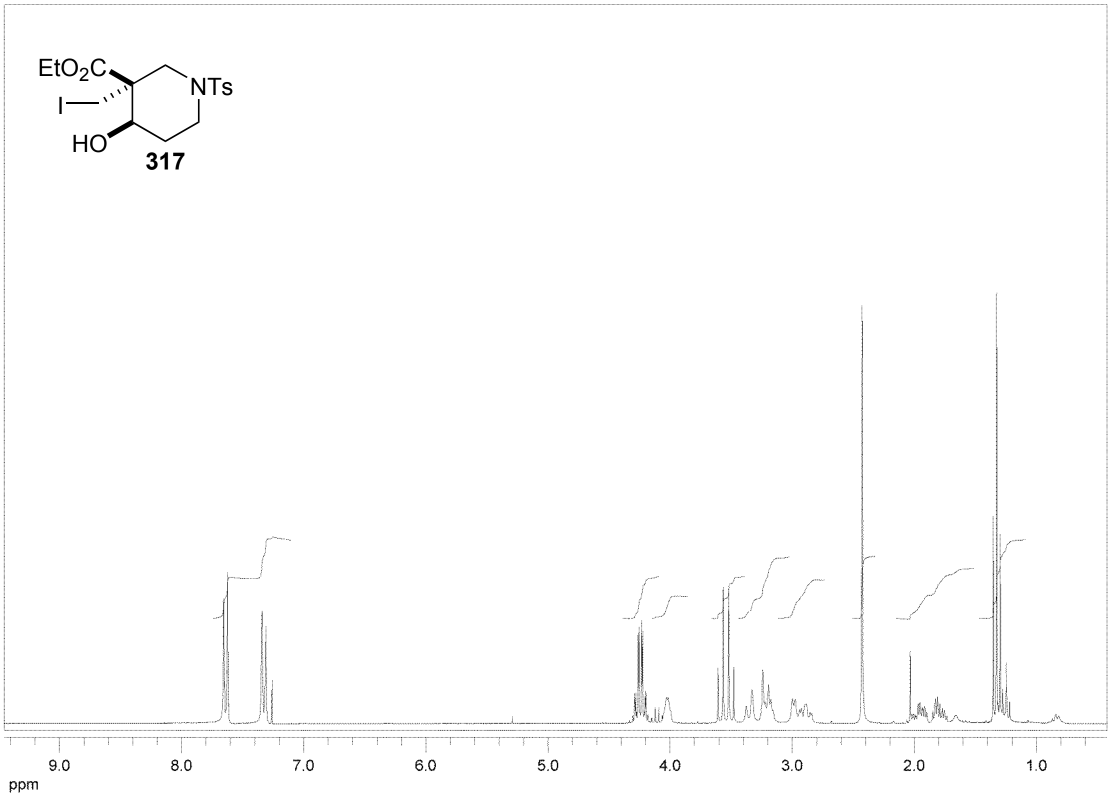
EtO2C
I
HO
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

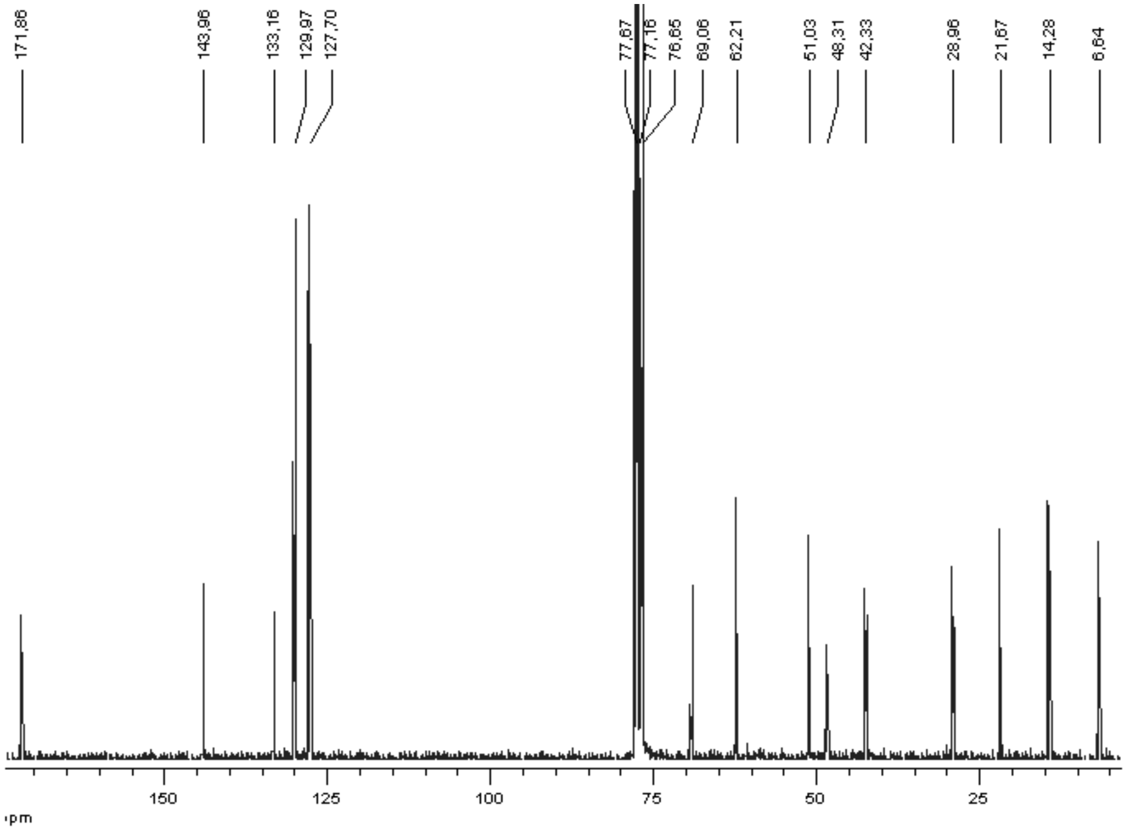


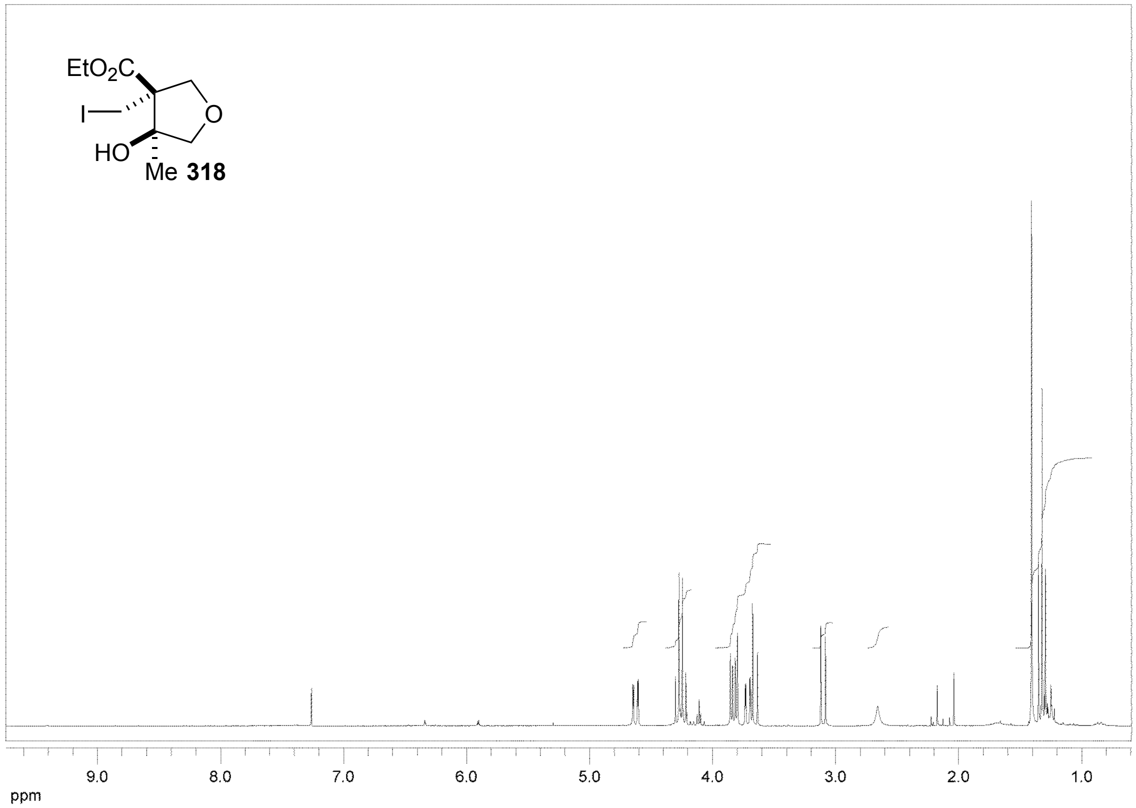
172.29
77.67
77.16
76.65
70.14
69.96
65.05
61.85
50.92
30.82
14.30
6.73
150
125
100
75
50
25
ppm


MeO2C
I
NTs
HO
316
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

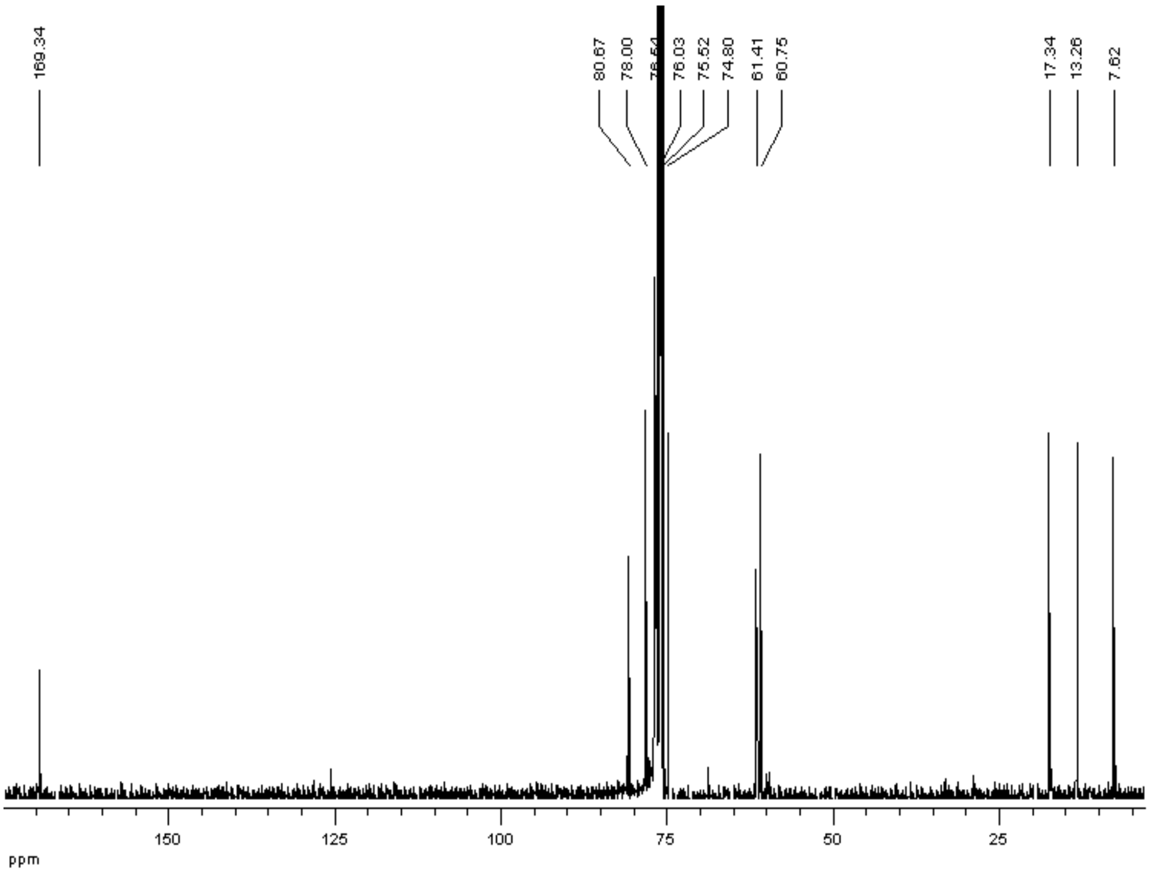

170.78
144.10
133.49
130.01
127.76
77.67
76.65
75.57
59.42
53.82
52.99
52.49
21.74
5.94
175
150
125
100
75
50
25
0
ppm


EtO2C
I
NTs
HO
317
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


171,86
143,96
133,16
129,97
127,70
77,67
77,16
76,65
69,06
62,21
51,03
48,31
42,33
28,96
21,67
14,28
6,64
150
125
100
75
50
25
ppm

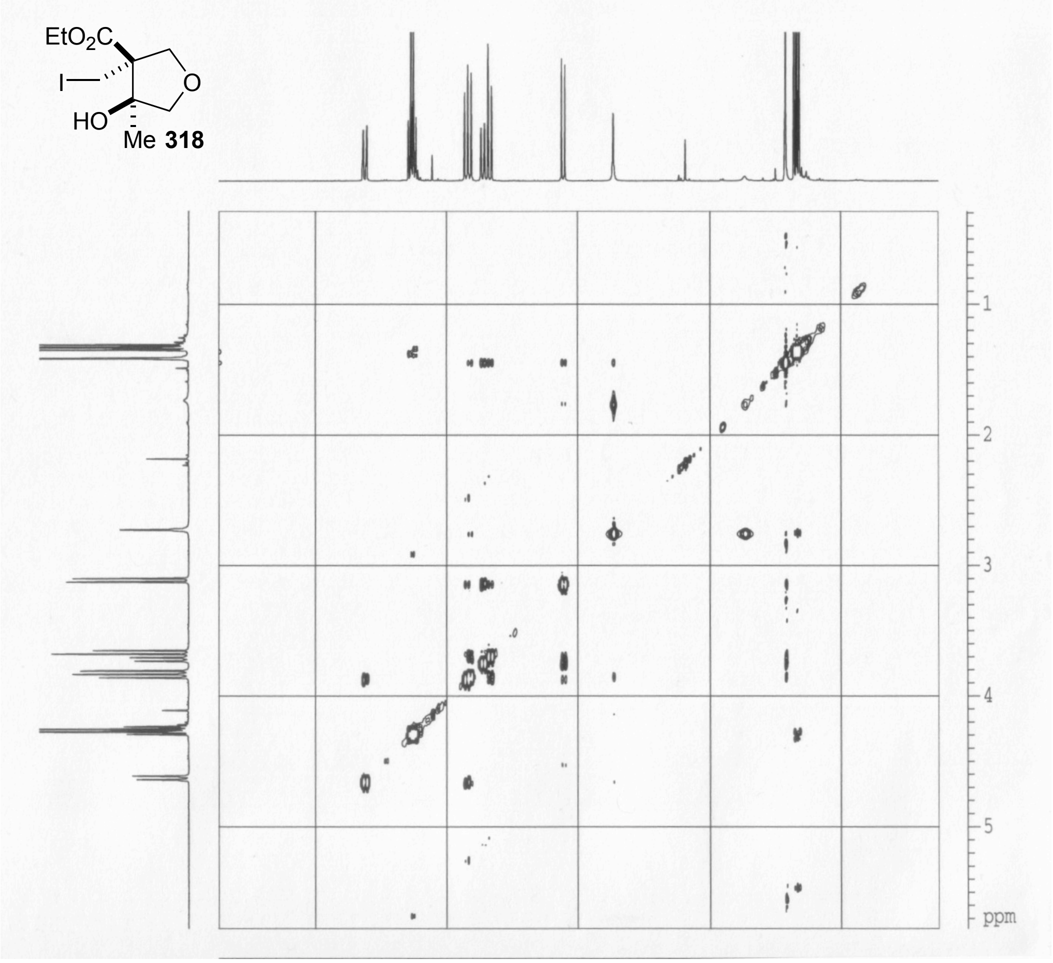


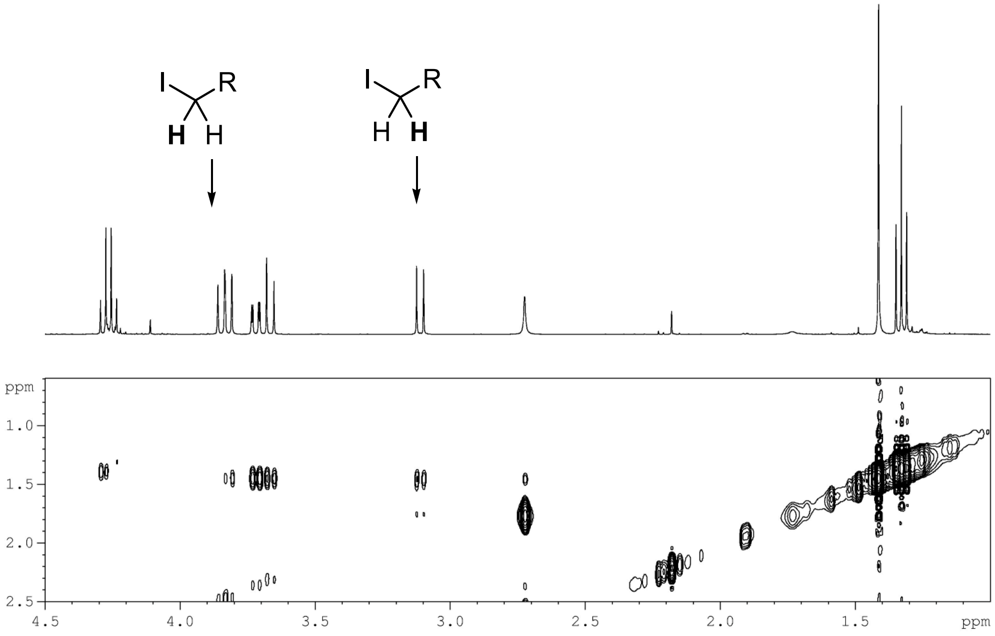
EtO$_2$C
I
O
HO
Me **318**
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm



169.34
80.67
78.00
76.03
75.52
74.80
61.41
60.75
17.34
13.26
7.62
150
125
100
75
50
25
ppm

NOESY data for **318**

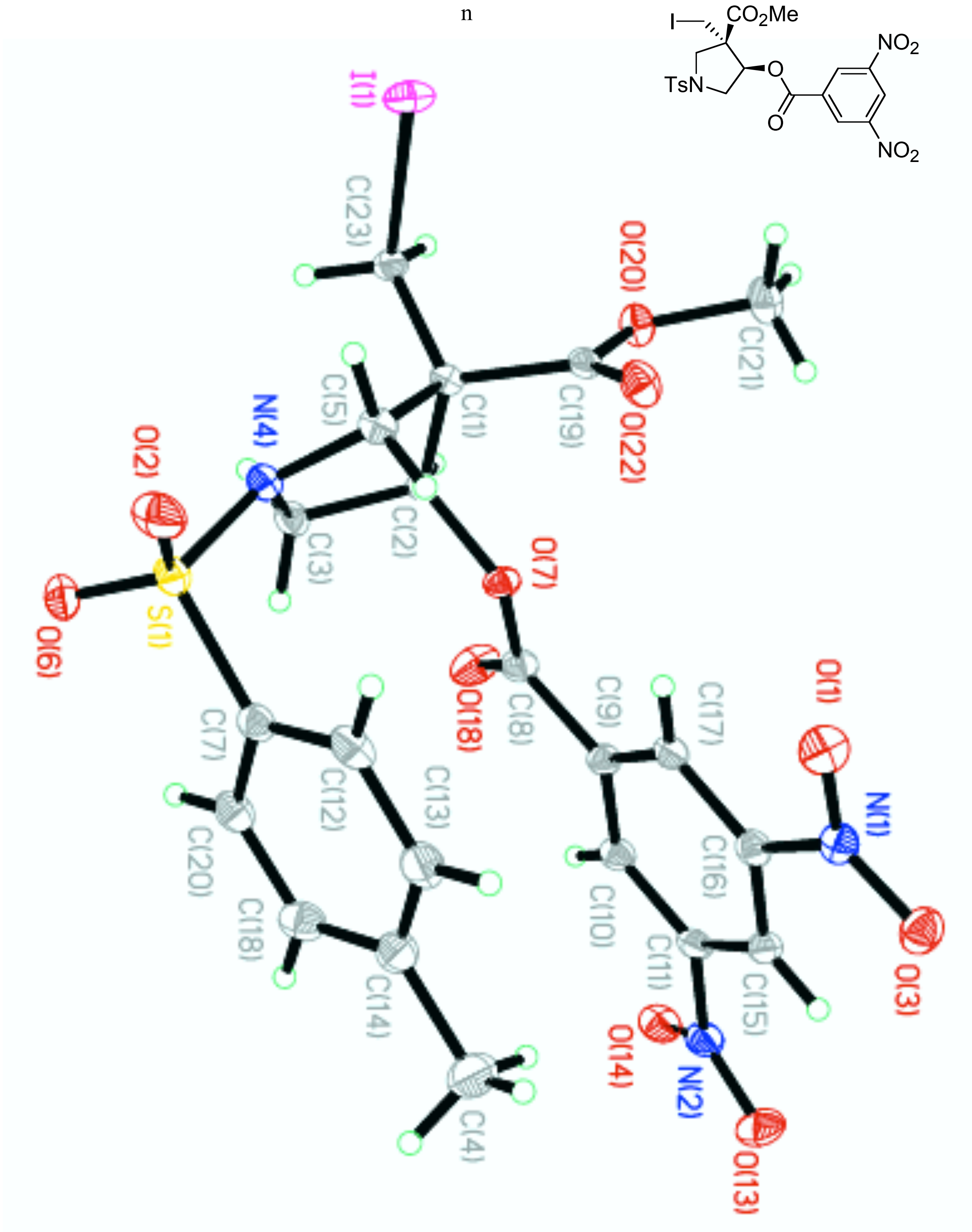




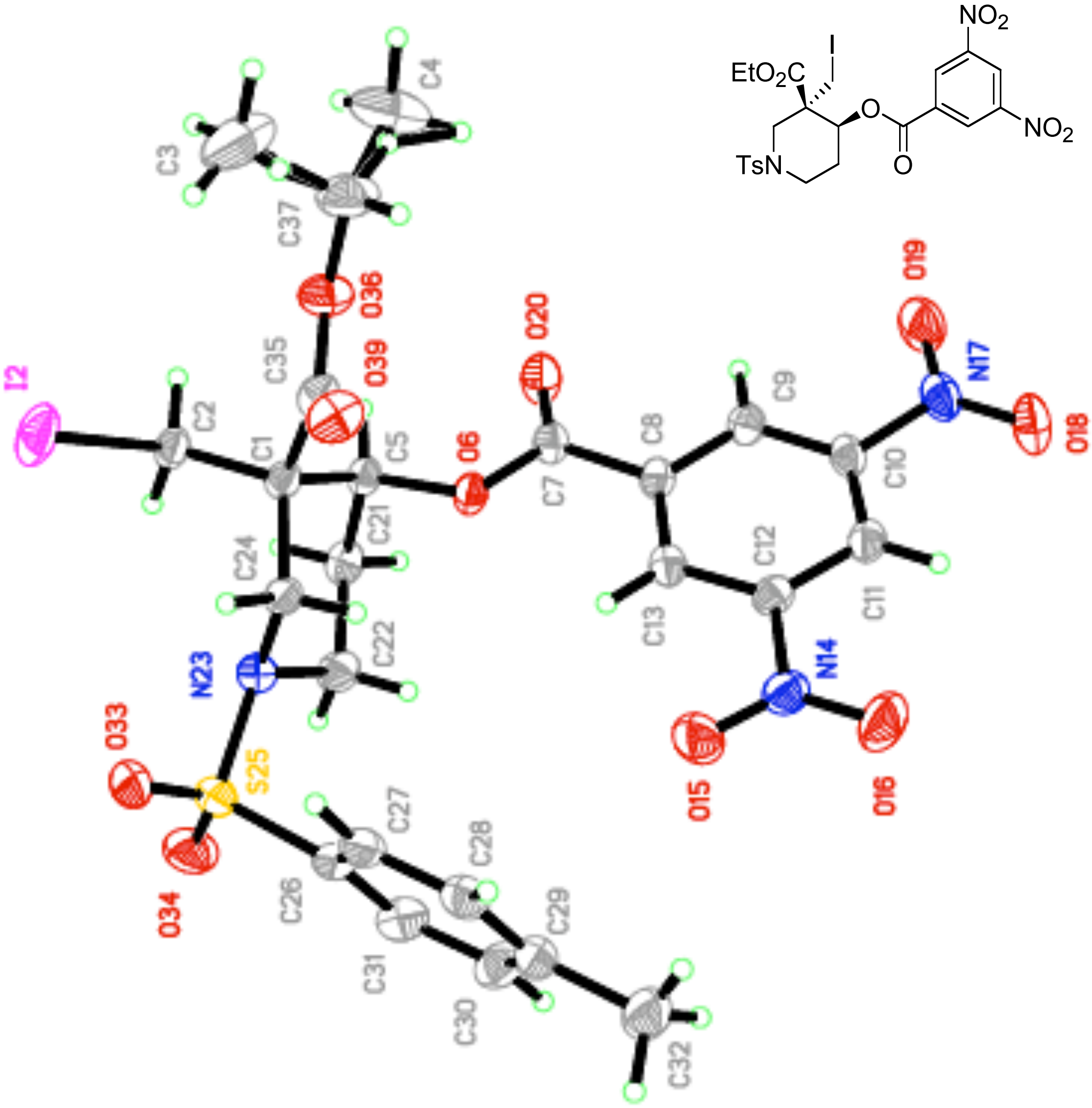
IV-4-X-Ray Structures

3,5-Dinitrobenzoate derivative of **314**

n



3,5-Dinitrobenzoate derivative of **315**



V-References

(1) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(2) Baylis, A. B.; Hillman, M. E. D. *German Patent 2155113* **1972**.

(3) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(4) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(5) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767.

(6) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274.

(7) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1384.

(8) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987.

(9) Han, Z. F.; Uehira, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7854.

(10) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 978.

(11) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111.

(12) Shi, M.; Jiang, J. K.; Feng, Y. S. *Org. Lett.* **2000**, *2*, 2397.

(13) Wei, H. X.; Hu, J. L.; Purkiss, D. W.; Pare, P. W. *Tetrahedron Lett.* **2003**, *44*, 949.

(14) Karur, S.; Hardin, J.; Headley, A.; Li, G. G. *Tetrahedron Lett.* **2003**, *44*, 2991.

(15) Li, G. G.; Wei, H. X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.

(16) Wei, H. X.; Kim, S. H.; Caputo, T. D.; Purkiss, D. W.; Li, G. G. *Tetrahedron* **2000**, *56*, 2397.

(17) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972.

(18) Timmons, C.; Kattuboina, A.; Banerjee, S.; Li, G. G. *Tetrahedron* **2006**, *62*, 7151.

(19) Chen, D. J.; Guo, L.; Kotti, S. R. S. S.; Li, G. G. *Tetrahedron Asymmetry* **2005**, *16*, 1757.

(20) Li, G. G.; Xu, X.; Chen, D. J.; Timmons, C.; Carducci, M. D.; Headley, A. D. *Org. Lett.* **2003**, *5*, 329.

(21) Li, G. G.; Wei, H. X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823.

(22) Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, S.; Kataoka, T. *Eur. J. Org. Chem.* **2003**, 4852.

(23) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353.

(24) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181.

(25) Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2005**, *46*, 5135.

(26) Lee, C. A.; Floreancig, P. E. *Tetrahedron Lett.* **2004**, *45*, 7193.

(27) Zhao, G. L.; Shi, Y. L.; Shi, M. *Org. Lett.* **2005**, *7*, 4527.

(28) Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4580.

(29) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.

(30) Nakamura, H.; Aoyagi, K.; Shim, J. G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372.

(31) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929.

(32) See Experimental part for more information.

(33) Tishchenko, W. *Chem. Zentr.* **1906**, *II*, 1309.

(34) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210.

(35) Cockerill, G. S.; Kociensky, P.; Treadgold, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2101.

(36) Keinan, E.; Sahai, M.; Shvily, R. *Synthesis* **1991**, 641.

(37) Erkkilae, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.

(38) See Experimental part for X-ray data.

(39) Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995.

(40) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

(41) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375.

(42) Clarke, P. A.; Black, R. J. G.; Blake, A. J. *Tetrahedron Lett.* **2006**, *47*, 1453.

(43) Paquette, L. A.; Geng, F. *J. Am. Chem. Soc.* **2002**, *124*, 9199.

(44) Watson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 1519.

(45) Charonnet, E.; Filippini, M. H.; Rodriguez, J. *Synthesis* **2001**, 788.

(46) Methyl α-bromomethyl acrylate was purchased from Aldrich chemicals supplier.

(47) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54.

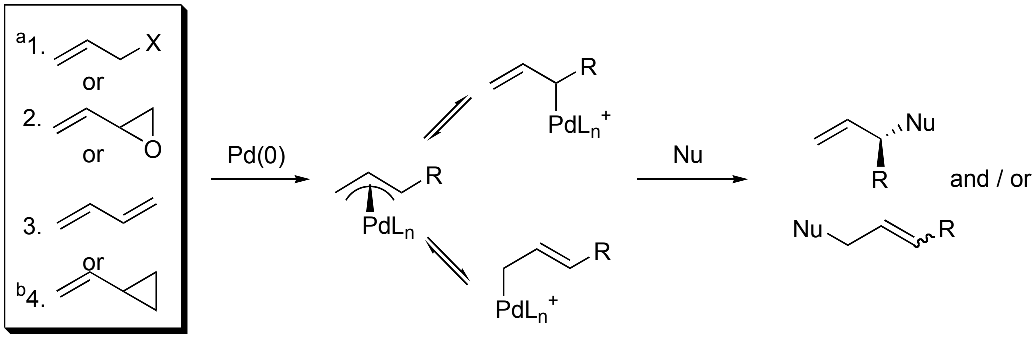
Chapter 4

Tetronic Acid Motif Synthesis *Via* π-Allyl-Palladium Mediated Cyclization

I-π-Allyl-Palladium Chemistry

I-1-Allyl Bond Formation

Allylic bond formation through intermediacy of π-allyl palladium complexes is an important synthetic transformation and remains an area of intense research[1]. Known as one of the most useful applications of palladium in organic chemistry[2], η^3 or π-allyl palladium species are readily formed by Pd(0) metallation of various organic substrates (*Scheme 4.1)*.



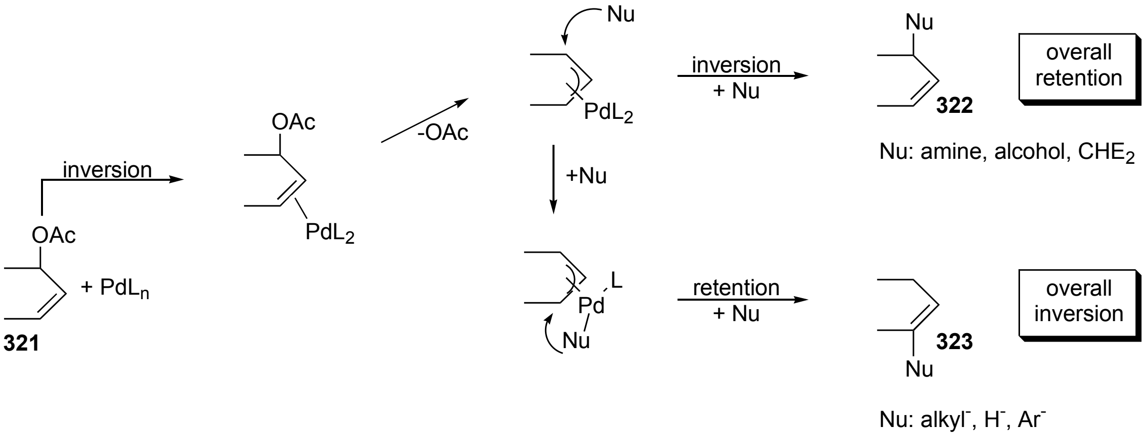
a X=Cl, OCOR, OCO_2R, OAr. b electron deficient cyclopropane

Scheme 4.1: π-Allyl-Pd System Formed From Various Precursors

The starting substrates have to contain at least one double bond and an allylic leaving group in the form of an allylic ester or ether (including cyclic ethers like epoxides and higher oxacyclic systems) or an electron-deficient cyclopropane ring. The π-allyl complex may be in equilibrium with its two isomeric σ-allyl complexes, which can be substituted by a number of carbon and hetero-atom nucleophiles. In the case of Pd(0)-catalyzed reactions of allylic substrates, the allylic leaving group is lost after the metallation step. In the overall reaction (oxidative addition-substitution-reductive elimination), the oxidation state of the palladium is described by a zero-sum redox cycle.

I-2-Stereospecificity of Pd-Catalyzed Sustitution Reaction

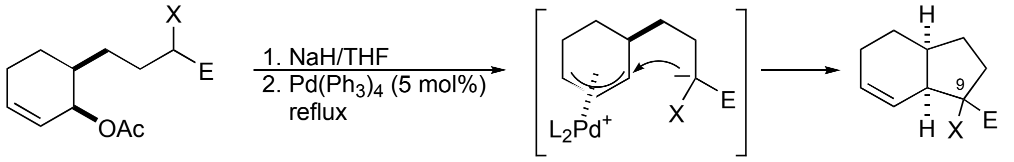
The π-allyl palladium chemistry's pioneers such as Trost[3-6] and Tsuji[7,8] reported in the seventies that the palladium catalyzed-substitution of allylic esters proceeds with high degree of stereospecificity (*Scheme 4.2*).



Scheme 4.2: Stereospecificity of Pd-Catalized Sustitution Reaction

In the first reaction step, metallation occurs, where the leaving group is replaced by the metal with inversion of configuration *via* coordination of palladium to the allylic double bond. The Pd-π-allyl complex intermediate next undergoes nucleophilic substitution, which is dependent on the nature of the nucleophile. Soft nucleophiles (stabilized carbanions and many heteroatom nucleophiles) react with a further inversion of the stereochemistry. As a result, the reaction of the allylic acetate **321** to substrates **322** (Nu: amine, ether or malonate type compound) is described with overall retention of configuration. If the incoming substituent is a hard nucleophile (such as hydride and nonstabilized carbon nucleophile), the attack at the carbon skeleton is preceded by coordination of the nucleophile to the palladium. The final substitution proceeds *via cis* migration, which results in an inversion of configuration from **321** to **323**.

In 1977, Trost et *al.* were the first to report[9] the intramolecular substitution of a palladium-π-allyl complex with soft carbon anions describing a favored 5-*exo-trig* ring closure (*Scheme 4.3*).



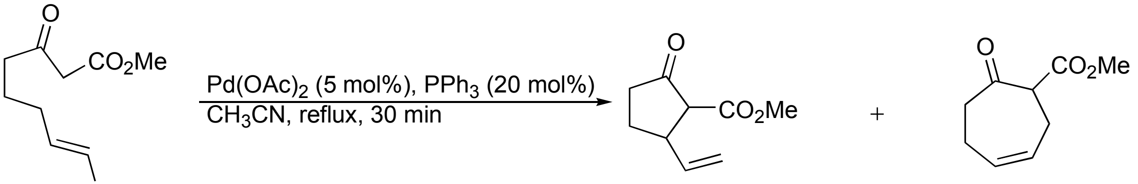
324, $E=CO_2Me$, $X=PhSO_2$ **325**, $L=Ph_3$ **326**, isomers at C_9 4:1 67-75%

Scheme 4.3: Intramolecular Substitution of a Palladium-π-Allyl Complex With Soft Carbon Anions

This methodology demonstrates the general features of palladium-catalyzed cyclopentannulation of allylic substrates, which describes an elegant manner for C-C bond formation. Under the now "classical" reaction conditions of strong base (NaH) followed by a Pd(0) catalyst in the presence of phosphine ligand, the transformation proceeds with high yields and high degree of selectivity. As mentioned before, the overall retention stereocontrol is characteristic of the soft malonate type nucleophile.

I-3-Reaction Stereospecificity Illustrated by 5-*Exo-Trig* and 7-*Endo-Trig* Ring Closure

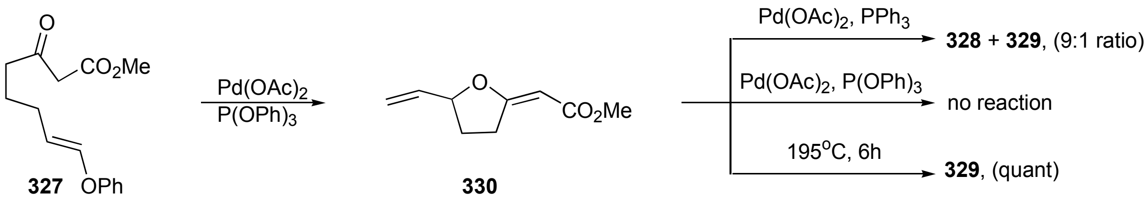
A few years later, Tsuji et *al.* described[10] the selective preparation of five-membered cyclic ketones. This palladium-catalyzed intramolecular reaction occurs from an active methylene with allylic ether moiety substrates without the use of base (*Scheme 4.4*).



327 **328**, 87% **329**, 13%

Scheme 4.4: Selective 5-Membered Cyclic Ketone Formation **328** *Via* Pd-Catalyzed Intramolecular Reaction

Although Trost et al. reported a year before in this context that the larger rings (7-*endo*-*trig*) are preferentially formed rather than the smaller ones (5-*exo*-*trig*)[11], the formation of the allylic isomer giving the favored 5-*exo*-*trig* product **328** was predominant (87%). The reaction was achieved by treatment of substrate **327** with $Pd(OAc)_2$ in the presence of phosphine ligand in acetonitrile under reflux for half an hour. The soft nucleophile chosen in this survey allows the unexpected inversion of configuration. It was found that the nature of phosphine ligands such as PPh_3, PBu_3 and bis(diphenylphosphino)ethane (DIPHOS) was not crucial on the yield of the reaction. In addition to **328** and **329**, formation of the *O*-alkylated product **330** from the enolate intermediate was detected, which was rearranged to **328** and **329** during the course of the reaction by the palladium catalyst (*Scheme 4.5*).

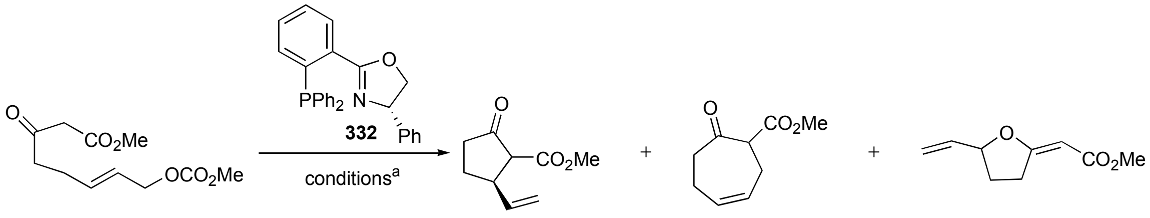


327 **330**

Scheme 4.5: Formation of Intermediate **330** During the Reaction

Interestingly, **330** was obtained selectively when triphenyl phosphite was used as a ligand. This means that the Pd-phosphite catalyst has no catalytic activity for the rearrangement of **330** to **328** and **329**. These results suggest that **328** and **329** were formed directly from **327**, and also *via* the formation of **330** and its rearrangement. Although *O*-alkylated product **330** was essentially observed as an intermediate under these conditions, the latter demonstrates that 5-*exo-trig* cyclization from the enolate substrate **327** can occur.

The enantioselective intramolecular substitution of the Pd-π-allyl complex with soft carbon anions of substrates similar to **327** was described[12] in 1996 by Pfaltz and Koch. β-Keto-ester substrate *E*-**331** with (phosphinooxazoline)Pd(0) catalyst and the presence of bases (*N*,*O*-*bis*(trimethylsilyl)trifluoroacetamide (BSTFA) and KOAc) led to the optically active cyclopentannulated product (+)-**328** in 60% yield and 87% ee (*Scheme 4.6*).



E-**331** (+)-**328**, 60%, 87%ee **329**, not detected **330**, not detected

[a] **331** (0.01M), [Pd(m-C_3H_5)Cl_2] (2.5 mol%), **332** (6.25 mol%), BSTFA (1.5 eq), KOAc (10 mol%), benzene, 48h, 5°C

Scheme 4.6: Enantioselective Pd-Catalyzed Cyclization of Allyl Carbonate *E*-**331**

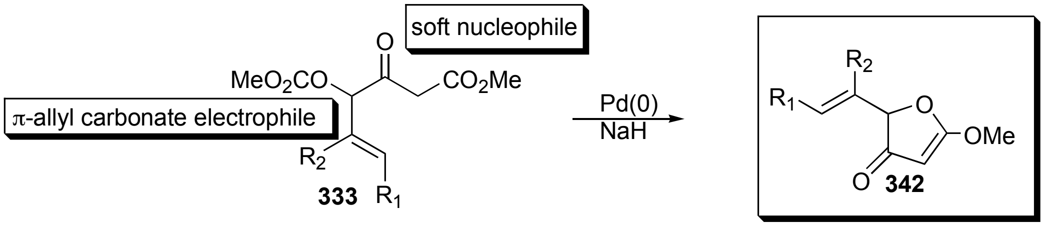
Again, the formation of the major 5-*exo-trig* cyclic product (+)-**326** was described by an unexpected overall inversion of the configuration. It was reported that ee's and yields were strongly dependent on the substrate **331** and ligand **332** structures along with the reaction conditions; careful optimization of the various reaction parameters was necessary. For instance, when the corresponding allyl acetate substrate replaced *E*-**331** allyl carbonate, the cyclopentannulation did not occur. Although none of the favored 7-*endo-trig* cyclic product **329** and the favored 5-*exo-trig* cyclic product **330** was detected under the present conditions, poor to moderate yields of both by-products were isolated at different stages of the optimization survey.

Intermolecular substitution of Pd-π-allyl complex with soft nucleophiles has proved to be a powerful synthetic transformation[13]. But in the context of the intramolecular reaction, stereospecificity of the reaction does not seem to be as general as the intermolecular version. Various factors have to be taken into consideration to understand it and then predict the reaction outcomes. The steric bulkness at the allylic termini[14], polarization of the functional groups adjacent to the complex[15,16], and electronic and steric ligand effects[17,18] are among them.

II-Results and Discussion

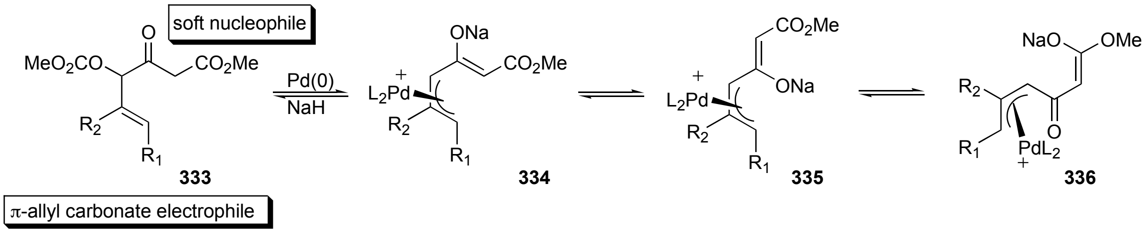
II-1-Design of Substrate **333** Favoring Tetronic Acid Formation

Inspired by Tsuji and Pfaltz's works[10,12] which showed the isolation of the *O*-alkylated cyclic side-product (**330**, *Scheme 4.5*) over the course of the intramolecular substitution of Pd-π-allyl complexes with soft nucleophiles, Pd-π-allyl chemistry along with the elaboration of suitable substrates **333** appeared to us as a solid medium for new methods of stereoselective synthesis of tetronic acid derivatives **342** (*Scheme 4.7*).



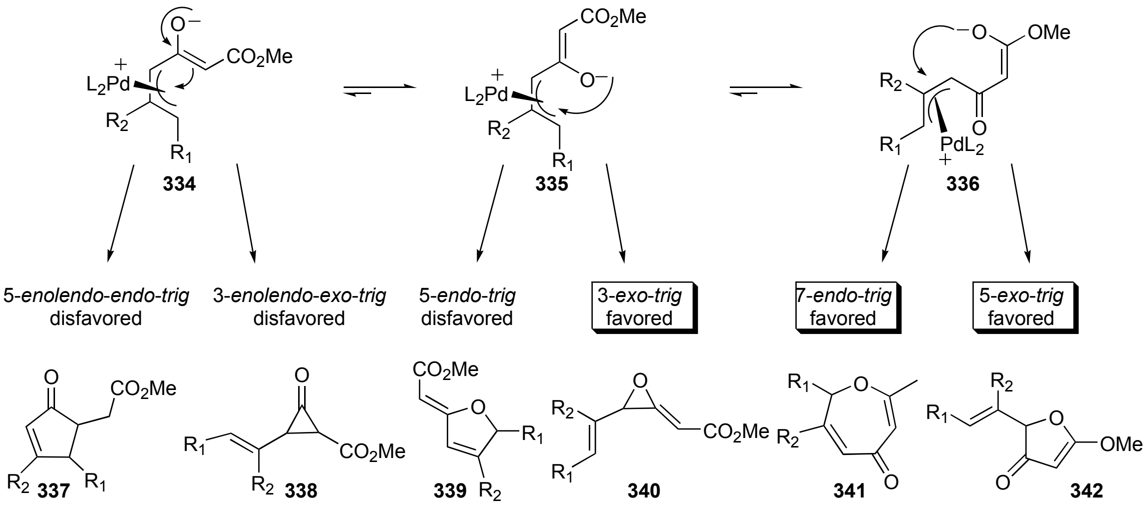
Scheme 4.7: Formation of Tetronic Acid Derivatives **342** *Via* Intramolecular Pd-π-allyl Chemistry

Hereby, the aim of this project is based on the synthesis of tetronic acid derivatives **342** *via* intramolecular Pd-π-allyl catalyzed reaction of substrate **333**, which may feasibly be upgraded by an asymmetric version as described previously (*Scheme 4.6*). The present methodology relies on the design of substrates **333**, which feature a β-dicarbonyl fragment soft nucleophile and a Pd-π-Allyl carbonate electrophile. The carbonate leaving group is located in α of the nucleophile and the π-system to favor the overall inversion of configuration, which may direct the desired cyclization toward the formation of the tetronic acid derivatives **342**. The latter key feature will be discussed later (*Scheme 4.10*). The deprotonation (NaH) and the oxidative addition of the Pd(0) source to substrates **333** may generate Pd-π-Allyl Complexes enolates **334-336** *in-situ* (*Scheme 4.8*).



Scheme 4.8: Deprotonated Pd-π-Allyl Complexes **334-336**

Taking into consideration the two isomeric σ-allyl complexes for each Pd-π-Allyl Complexes **334-336**, Baldwin empirical rules[19] were applied here to predict the pathways in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for cyclization (*Scheme 4.9*).

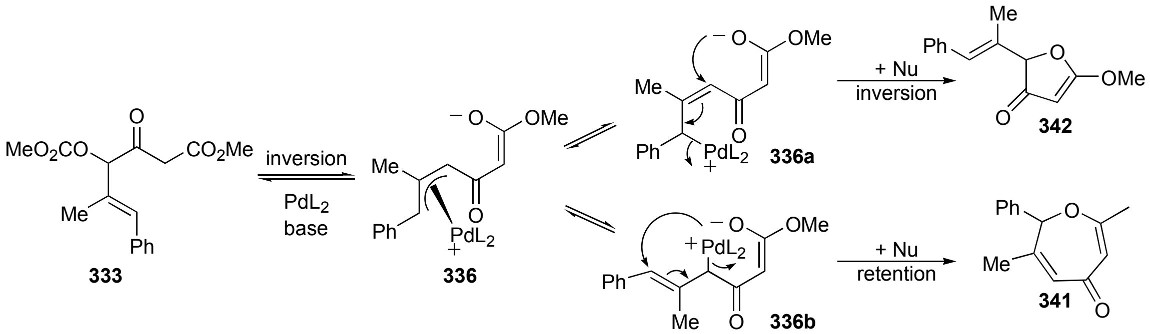


Scheme 4.9: Baldwin Rules applied to Pd-π-Allyl Complexes **334-336**

Although disfavoured cases require severe distorsion of bond angles and distances, a few cases in the literature are in disaccord with these[20]. However, Baldwin rules remain a reliable prediction toward the feasibility or not of five and six-membered rings formation especially. Three of the isomeric σ-allyl complexes are expected to cyclize, which give products **340-342**. It's worth mentioning that careful design of the substrate

333, which incorporates the Pd-π-Allyl and the nucleophile fragments into the ring prevents cyclization of intermediate **334** and the 5-membered product **339**. In addition, favored cyclic products **341** and **342** may drive the equilibrium of the Pd-π-Allyl complexes toward the formation of intermediate **336** as the major complex in solution.

Trost[6] and Tsuji[8] described the stereospecificity of the intermolecular palladium catalyzed-substitution of allylic esters (*Scheme 4.2*), which we utilized for our present intramolecular methodology developed with substrate **333** to predict the favored cyclization pathway (*Scheme 4.10*).

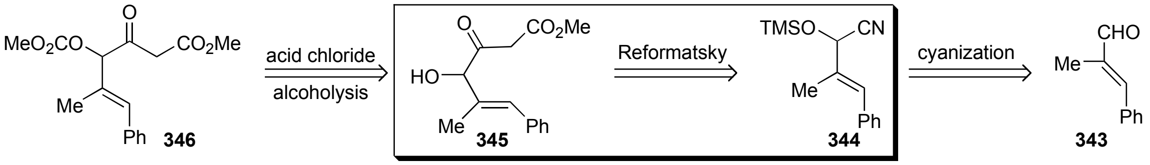


Scheme 4.10: Stereospecificity of the Intramolecular Substitution of the Pd-π-Allyl Complexes **336**

Assuming that electron-rich oxygen of the enolate species **336** acts as a soft nucleophile, it was demonstrated that a favored overall retention of configuration occurs over the formation of 5-*exo-trig* product **342**, while the formation of 7-*endo-trig* product **341** is unfavored (overall inversion of configuration).

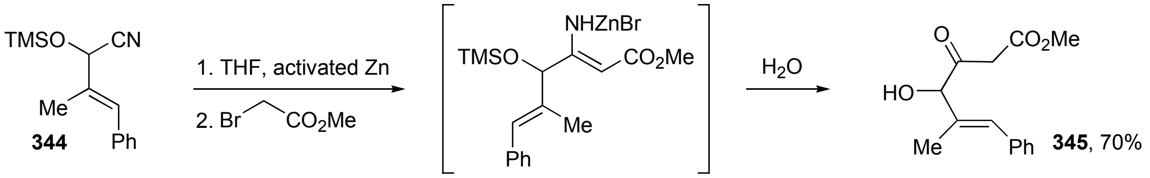
II-2-Synthesis of 5-Monosubstituted Tetronic Acid **342**

We decided to study the Pd-π-Allyl reaction with soft nucleophile as our method for tetronic acid derivatives synthesis. To the best of our knowledge, this potentially powerful variant has not been the subject of any reports in the literature. The retro-synthetic route of the selected substrate **346** is outlined below (*Scheme 4.11*).



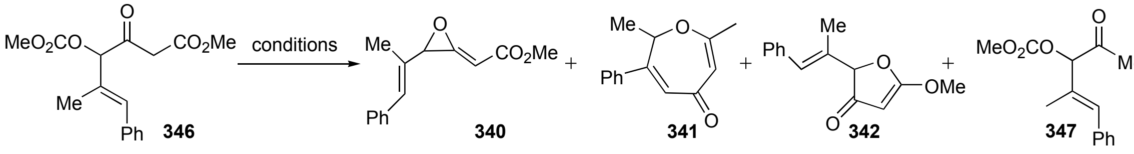
Scheme 4.11: Retro Synthetic Route of Substrate **344**

We elected the Reformatsky reaction as the method to install the β-oxo-ester fragment of **345**. The Reformatsky acceptor species **344** was readily synthesized by cyanization[21] of commercially available α-methyl cinnamaldehyde **343**. The reaction was carried out in DCM with the addition of trimethylsilyl cyanide (TMSCN) dropwise at 0 °C in the presence of catalytic amount of ZnI_2. After stirring the reaction mixture for 10 min and successive work-up, nitrile **344** was produced in quantitative yield without further purification. Acid chloride hydrolysis[22] of Reformatsky product **345** was performed in THF with a large excess of pyridine (10 eq) and catalytic amount of DMAP. Methyl chloroformate (10 eq) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature overnight. After specific work-up, substrate **346** was obtained as a white solid in good yield (62%) after column chromatography purification. Prior to Reformatsky reaction, the deactivating zinc oxide layer was removed from the metal zinc surface by chemical means[23]. Zinc activation procedure was based on successive washes with solution of HCl (3M), H_2O, acetone, Et_2O and dried under high vaccum pump. *O*-Silylated cyanohydrin **343** was added dropwise to a solution of activated *Zn* (2.8 eq) in THF[24] (*Scheme 4.12*).



Scheme 4.12: The Reformatsky reaction of **344**

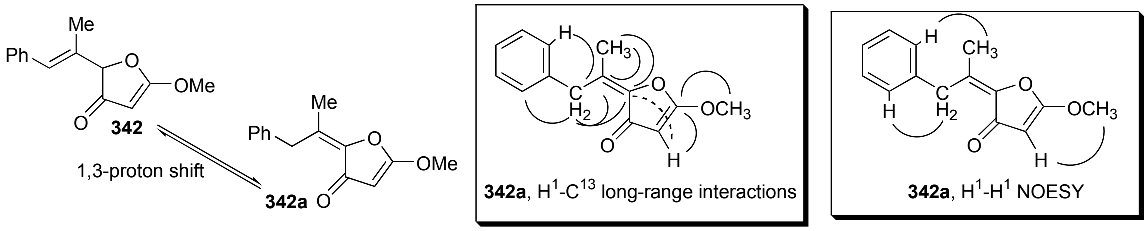
After addition of methyl bromo-acetate (3.0 eq), the reaction mixture was refluxed for 70 min. Zinc enamide intermediate was then produced, which after acidic hydrolysis and purification gave the desilylated β-oxo-ester **345** in 70% yield. Depending on the quality of the zinc metal activation accomplished, yields of this reaction fluctuated by ±15%. A more reliable procedure may be achieved by reduction of anhydrous zinc halides in the appropriate solvent[25]. With substrate **346** in hand, intramolecular catalytic Pd-π-Allyl reaction was attempted (*Schemes 4.13*).



entry	**334** (mmol)	**Pd source** (mol%)	**base** (eq)	**solvent** (mL)	**Temperature** (ºC)	**Time** (h)	**Yield** (%)
1	0.29	$Pd(PPh_3)_4$ (12)	/	THF (5)	rt to reflux	12-37	**347** (43)
2	0.29	$Pd(PPh_3)_4$ (20)	/	THF (5)	reflux	20	/
3	0.29	$Pd(PPh_3)_4$ (10)	/	DMF (3)	80 to reflux	9-9	/
4	0.07	Pd(dba) (10) and PPh_3 (20)	/	DMSO-d^6 (1.5)	rt-100-150	3-3-3	/
5	0.29	Pd(dba) (10) and PPh_3 (20)	NaH (1.5)	THF (5)	reflux	14	**342** (57)

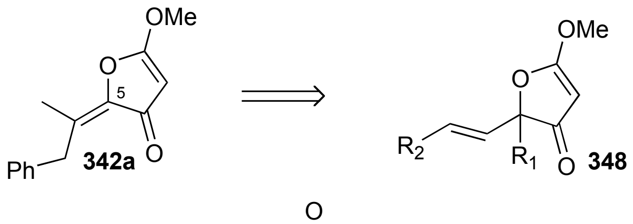
Scheme 4.13: Scope of the Intramolecular Catalytic Pd-π-Allyl reaction of Substrate **346**

The initial intramolecular catalytic Pd-π-Allyl reaction (*entry 1*) was carried out under N_2 atmosphere with **346** and $Pd(PPh_3)_4$ (12 mol%) as palladium(0) catalyst in THF (5 mL). After extended 37 h reflux time of the reaction mixture, the only detected species on H^1 NMR spectroscopy was the decarboxylate species **347** in 43% yield. An increase of Pd source loading (*entry 2*) or DMF as reaction solvent (*entry 3*) led to a complex reaction mixture after reflux for 20 and 9 hours respectively. Solution of **346** in DMSO-d^6 (0.046 M) was placed in a NMR tube in the presence of Pd(dba)-PPh_3, and the progress of the reaction was closely monitored by H^1 NMR spectroscopy every hour (*entry 4*). The disappearance of starting **346** could be observed along with an uninterpretable H^1 NMR spectrum after an hour at 150 °C. Clearly, Pd(0) catalyst in the absence of base did not induce any cyclization to depicted products **340**-**342**, and rather lead to significant decomposition pathways. However when 1.5 equivalent of sodium hydride was combined with Pd(dba)-PPH_3 catalyst in THF, we were pleased to observe that after 14 h reflux, the desired 5-*exo-trig* product **342** was furnished in moderate yield (57%). Prior work-up of the reaction mixture, tlc plate analysis showed that starting substrate **346** was totally consumed, which underlies that decomposition pathway still occurred. INEPT-ADEQUATE NMR experiments showed that the actual product of the reaction is **342a**, which arises from 1,3-proton shift of species **342** (*Scheme 4.14*).



Scheme 4.14: INEPT-ADEQUATE NMR experiments of Product **342a**

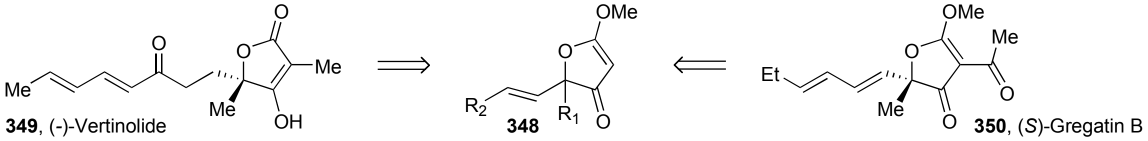
Intramolecular catalytic Pd-π-Allyl reaction to tetronic acid derivative **342a** remains to be optimized. The access of milder experimental conditions is required to overcome the significant decomposition of substrate **346** over the course of the reaction. Nevertheless Pd-π-allyl chemistry readily afforded the 5-monosubstituted tetronic acid motif **342a** as the major product of the catalytic reaction. With the present methodology in hand, we were intrigued by the synthesis of 5-disubstituted tetronic acid derivative **348**, which showcase a chiral centre at the C-5 position (*Scheme 4.15*).



Scheme 4.15: 5,5-Disubstituted Tetronic Acid Derivative **348**

II-3-Synthesis of 5-Disubstituted Tetronic Acid 348

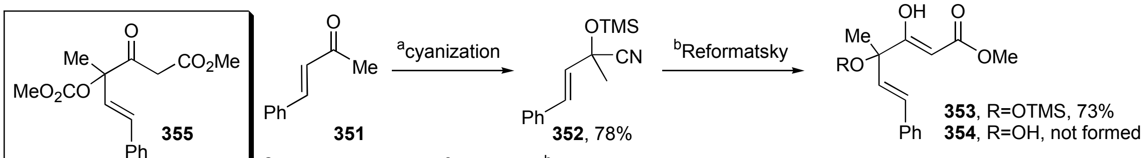
5,5-Dialkyl tetronic acid motif is heavily represented in natural occurring structures, which exhibit significant biological activity. For instance, architecture of (-)-Vertinolide **349** and (*S*)-Gregatin B **350**, which were respectively isolated from *Verticillium* *intertextum* in 1982 and *Cephalosporium gregatum* in 1975, feature a similar tetronic acid core relative to synthesized substrate **348** (*Scheme 4.16*).



Scheme 4.16: Naturally Occurring 5,5-Disubstituted Tetronic Acid Derivatives **349** and **350**

These two optically active natural products posed a challenging synthetic task to chemists, namely the control of chirality at C-5 position. Soon after their isolation, vertinolide **349** and (*S*)-gregatin B **350** have been the subject of many enantio-selective synthetic investigations[26]. However, to the best of our knowledge, there are currently no methods for the catalytic asymmetric synthesis of these structures. This lack will be the ultimate focus of this Pd-π-allyl chemistry methodology.

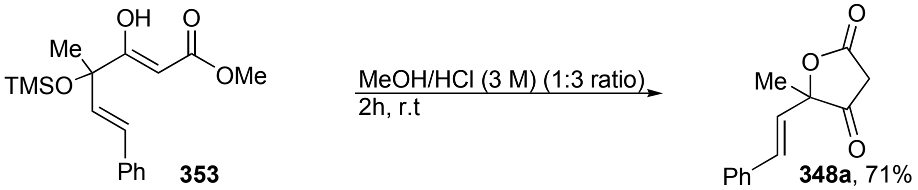
Preliminary studies on 5,5-Dialkyl tetronic acid derivatives synthesis were carried out with substrate **355** (*Scheme 4.17*), which is synthesized following the route described for the previous β-oxo-ester **346** (*Scheme 4.11*).



[a] DCM, TMSCN, I_2, 0°C, 20 min. [b] THF, activated Zn, $BrCH_2CO_2Me$, reflux, 70 min

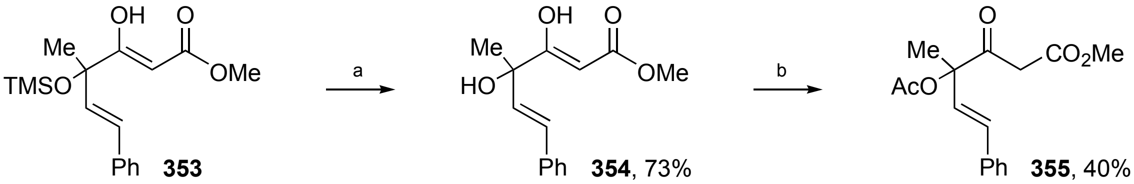
Scheme 4.17: Synthetic Route to Substrate **355**

Cyanization[27] of the less reactive benzalacetone **351** was carried out in DCM with TMSCN in the presence of I_2. After purification of the crude reaction by column chromatography, nitrile **352** was produced in 78% yield. When Reformatsky reaction[24] of *O*-silylated cyanohydrin **352** was carried out, none of the desired free alcohol **354** was detected. Instead, silylated β-oxo-ester **353** was isolated as the major product in good yield (73%). It seems that the acidity of the work-up was not strong enough to initiate the cleavage of the O-TMS bond. Silylated species **353** was stirred in a more acidic solution of MeOH and aqueous HCl (3 M) at room temperature (*Scheme 4.18*).



Scheme 4.18: 5-*Exo* Ring Closure of **353** Under Acidic Conditions

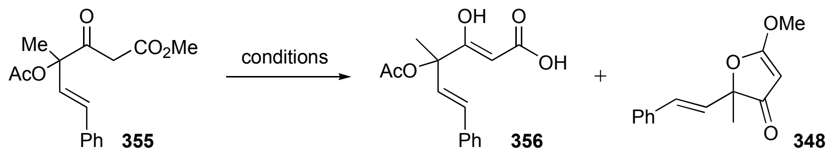
After two hours, tlc plate analysis showed the disappearance of the starting material and a clean new single spot, which was characterized as being tetronic acid derivative **348a**. This surprising result demonstrated that mild alcohol acidic media could readily give the desired 5-*exo-trig* tetronic acid **348a** in good yield (71%). Conversely, TBAF fluoride agent efficiently cleaved the Si-O bond in half an hour at room temperature, which furnished **354** in 73% yield (*Scheme 4.19*).



[a] THF/TBAF (1 M) (8:1 ratio), 30 min, r.t. [b] pyridine, Ac_2O, o.n, 80°C, recrystallization.

Scheme 4.19: Synthesis of substrate **355**

Acid chloride hydrolysis[22] was attempted on substrate **354** in pyridine, methyl chloroformate and with the presence of DMAP. After extended reaction time at room temperature, crude H^1 NMR spectrum revealed a complex mixture of products. When acetic anhydride was utilized in pyridine[28], substrate **354** solution was warmed to 80 °C overnight, which gave acetylated alcohol **355** as a white solid in 40% yield after a few recrystallizations from hexane. The depleted conversion rate of substrate **354** may be explained by the high degree of steric hindrance at the alcohol position. Intramolecular catalytic Pd-π-allyl conditions were attempted on substrate **355** (*Scheme 4.20*).



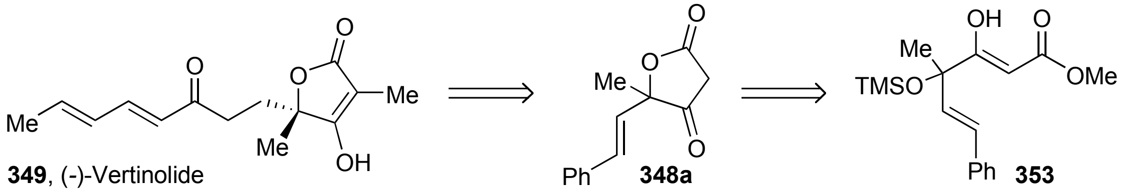
entry	**354** (mmol)	**Pd source** (mol%)	**base** (eq)	**solvent** (mL)	**Temperature** (°C)	**Time** (h)	**Yield** (%)
1	0.16	$Pd(OAc)_2$ (10) and PPh_3 (20)	/	THF (2)	r.t to reflux	o.n-3	**356** (65%)
2	0.16	$Pd(OAc)_2$ (10) and PPh_3 (20)	NaH (1.2)	THF (2)	r.t to reflux	o.n-3	**356** (not isolated)
3	0.16	/	NaH (1.2)	THF (2)	r.t to reflux	o.n-3	**356** (not isolated)

Scheme 4.20: Scope of the Intramolecular Catalytic Pd-π-Allyl Conditions Applied to Substrate **355**

When $Pd(OAc)_2$ and PPh_3 were introduced into a solution of **355** in THF at room temperature (*entry 1*), the progress of the reaction mixture was monitored by tlc plate analysis. After a few hours, the disappearance of the starting material was observed along with the appearance of a clean new spot. Reflux of the reaction mixture for 3 hours converted starting material **355** entirely. Purification by column chromatography gave the hydrolyzed product **356** in 65% yield. Whether a base was added to the Pd source (*entry 2*) or the base was used alone (*entry 3*), product **356** was the only species spotted on the tlc plate analysis after reflux conditions. This disappointing result demonstrates that Pd-π-allyl intermediate does not occur here, which prevented the formation of the desired product **348**. This may be explained by the high degree of steric hindrance located at C-5 of substrate **355**, which blocked the allyl bond formation.

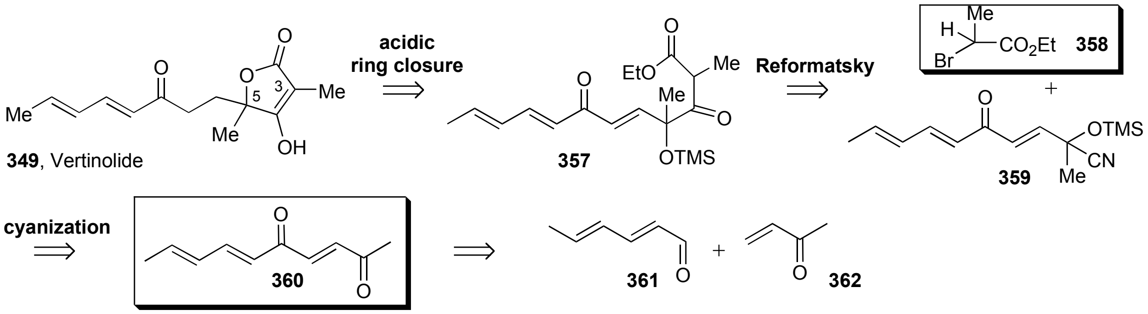
III-Conclusion and Future Work

Preliminary work achieved on Pd-π-allyl-mediated cyclization successfully produced 5-monosubstituted tetronic acid **342a** in moderate yield (*Scheme 4.13*). The procedure of the reaction remains to be optimized by the access of milder experimental conditions, which may limit the decomposition behavior of starting substrate **346**. However, this methodology already provides a simple, selective and expedite route (4 steps) to 5-monosubstituted tetronic acid derivatives. Unfortunately, this approach failed to undergo the cyclization of 5,5-disubstituted tetronic acid **348**, which is probably caused by the significant degree of steric hindrance located at C-5, position of the leaving group (*Scheme 4.20*). However, we found that silylated substrate **353** could readily give 5-*exo* tetronic acid **348a** in good yield (71%) under mild alcohol acidic media (*Scheme 4.18*). Although catalytic and asymmetric aspects of the reaction are not available, this fortunate result may be incorporated into a racemic synthesis of Vertinolide **349** (*Scheme 4.21*).



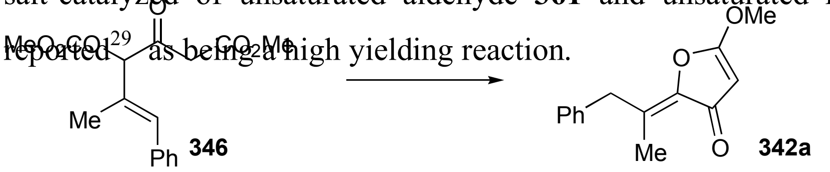
Scheme 4.21: Structural Similarities of Synthesised Tetronic Acid **348a** With (-)-Vertinolide **349**

Structural requirements imply a methyl substitution at C-3, which may be installed over the Reformatsky reaction, by using commercially available ethyl 2-bromopropionate **358** (*Scheme 4.22*).



Scheme 4.22: Racemic Synthesis of Vertinolide **349** *Via* Our Approach

And the synthesis of α,γ-diunsaturated ketone **360** may be envisaged by the thiazolium salt-catalyzed of unsaturated aldehyde **361** and unsaturated ketone **362**, which was reported[29] as being a high yielding reaction.

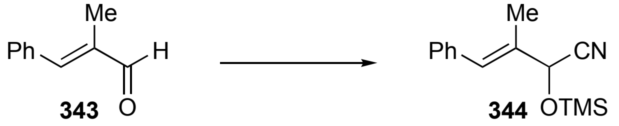


IV-Experimental

H^1 NMR and C^{13} NMR spectra were recorded on a Bruker dpx 250 (250 MHz) instrument. Electron Ionisation (EI) high resolution mass spectroscopy was performed by the EPSRC National Mass Spectrometry Service Centre Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer as well as the University of Edinburgh School of Chemistry mass spectrometry service using Kratos MS50 instrument. FAB HRMS was carried out by the University of Edinburgh School of Chemistry mass spectrometry service using Kratos MS50 instrument. The data are recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressureDCM, THF, DMPU and TMSCl were distilled from calcium hydride and stored over molecular sieves under N_2 atmosphere. Diisopropylamine and pyridine were dried over KOH. All other reagents were used as supplied.

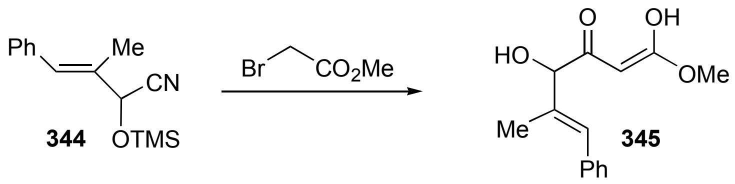
IV-1-Synthesis of 5-Mono Substituted Tetronic Acid **342a**

3-Methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile **344**[21]



To a stirred solution of α-methyl-cinnamaldehyde **343** (2.92 g, 20.0 mmol) and ZnI_2 (10 mg) was added TMSCN (2.00 g, 20.0 mmol) slowly and dropwise at 0 °C. The reaction mixture was stirred for 10 min at r.t, quenched with H_2O (100 mL) and extracted with DCM (3 X 100 mL). The combined organic layers were washed with sodium thiosulfate solution (15%, 100 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. 3-Methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile was formed quantitatively and was used without any further purification. H^1 NMR (250 MHz, $CDCl_3$) δ 7.21-7.07 (m, 5H), 6.34 (s, 1H), 4.82 (s, 1H), 1.71 (s, 3H), and 0.08 (s, 9H).

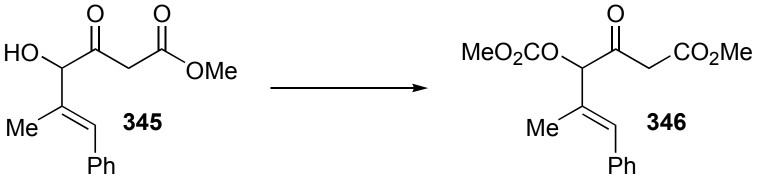
4-Hydroxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **345**[24]



Zinc powder was activated by successive washes with solution of HCl (3M), H_2O, acetone, Et_2O and dried under high vacuum pump. To a suspension of activated Zn (1.06 g, 16.22 mmol) in THF (15 mL) was added dropwise 3-methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile **344** (1.92 g, 5.76 mmol). After stirring the reaction mixture for 20 min, methyl bromo acetate (1.69 mL, 17.90 mmol) was added carefully over 50 min. The reaction mixture was refluxed for 70 min, cooled to r.t, quenched with H_2O / brine / HCl (3 M) (15 / 5 / 5) and extracted with EtOAc (5 X 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/diethyl ether, 1:1) to afford 940 mg (70%) of 4-hydroxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester as a yellow oil. IR(thin film/cm^{-1}): ν_{max} 3500, 3000, 1730, 1371. H^1 NMR

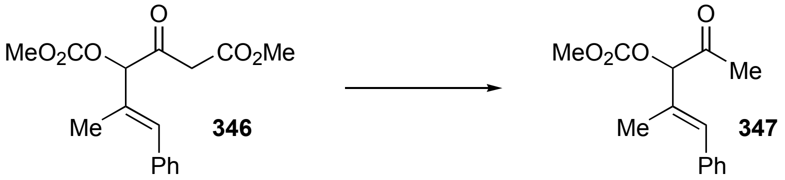
(250 MHz, $CDCl_3$) δ 7.32-7.12 (m, 5H), 6.75 (s, 1H), 4.85 (s, 1H), 3.79 (s, 1H), 3.74 (s, 3H), 3.63 (s, 2H) and 1.77 (3H, d, J = 1.5Hz). C^{13} NMR (63 MHz, $CDCl_3$) δ 203.17, 167.02, 136.55, 134.29, 132.52, 129.09, 128.49, 127.52, 84.13, 52.77, 44.11 and 12.87. MS EI (+ve) *m/z* $[M]^+$ calculated for $C_{14}H_{16}O_4$, 248.1049 found 248.1049.

4-Methoxycarbonyloxy-5-methyl-3-oxo-6-phenyl-hex-5-enc acid methyl ester **346**[22]



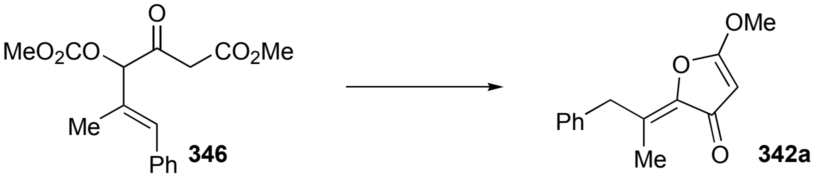
To a stirred solution of 4-hydroxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **345** (1.50 g, 6.0 mmol), pyridine (3.9 mL, 60.0 mmol) and DMAP (30 mg) in THF (7 mL) was added dropwise methyl chloroformate (4.5 mL, 60.0 mmol) over 1 h at 0 °C. The reaction mixture was stirred at r.t overnight, quenched with H_2O (35 mL), and the aqueous layer was extracted with Et_2O (3 X 15 mL). The combined organic layers were washed successively with HCl aqueous solution (10%, 3 X 10 mL), saturated $NaHCO_3$ solution (2 X 15mL), H_2O (3 X 15mL), saturated NaCl solution (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 6:4) providing 4-methoxycarbonyloxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester (1.14 g, 62%) as a white solid. M.p. = 64°C IR(thin film/cm^{-1}): ν_{max} 3000, 1730, 1440, 1371. H^1 NMR (250 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.79 (s, 1H), 5.61 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.63 (s, 2H), and 1.89 (d, 3H, J = 1.5Hz). C^{13} NMR (63 MHz, $CDCl_3$) δ 196.74, 166.15, 154.68, 136.07, 133.99, 129.80, 129.28, 128.59, 127.81, 86.90, 55.61, 52.81, 45.42 and 14.10. Accurate MS is not available for compound **346** such that it was not stable under MS EI and MS FAB conditions. However MS FAB of similar compound **355** is shown.

Carbonic acid 1-acetyl-2-methyl-3-phenyl-allyl ester methyl ester **347**



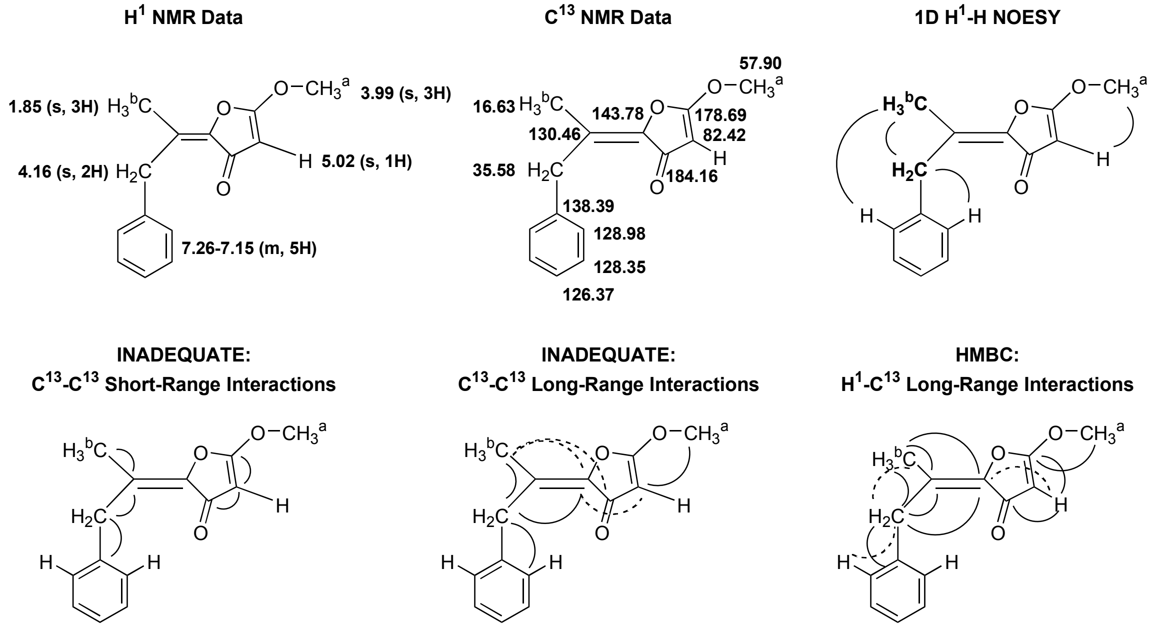
A stirred solution of 4-methoxycarbonyloxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **346** (93.5 mg, 0.30 mmol) and tetrakis(triphenylphosphine) palladium(0) (41 mg, 12 mol%) in THF (5 mL) was refluxed for 37 h. The reaction mixture was quenched with H_2O / Et_2O (5 / 5 mL), the aqueous layer was extracted with Et_2O (3 X 5mL), the combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 8:2) providing carbonic acid 1-acetyl-2-methyl-3-phenyl-allyl ester methyl ester (32 mg, 43%) as a white oil. IR(thin film/cm^{-1}): ν_{max} 3000, 1730, 1440, 1371. H^1 NMR (250 MHz, $CDCl_3$) δ 7.32-7.28 (m, 5H), 6.78 (s, 1H), 5.47 (s, 1H), 3.85 (s, 3H), 2.26 (s, 3H) and 1.88 (d, 3H, J = 1.5Hz). C^{13} NMR (63 MHz, $CDCl_3$) δ 202.19, 155.15, 136.24, 133.36, 130.38, 129.19, 128.55, 127.75, 87.52, 55.43, 26.11, and 14.04.

5-Methoxy-2-(1-methyl-2-phenyl-ethylidene)-furan-3-one **342a**



To a stirred solution of 4-methoxycarbonyloxy-5-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **346** (90 mg, 0.29 mmol) in THF (3 mL) was added NaH (13.9mg, 0.58 mmol) at 0°C for 10 min. The reaction mixture was stirred for 2 h at 0 °C, 2h at room temperature and a solution of tetrakis(triphenylphosphine) palladium (0) (34 mg, 10 mole%) in THF (2 mL) was added. The reaction mixture was stirred for 1 h, quenched with H_2O / saturated NaCl solution (5 / 5 mL), the aqueous layer was extracted with Et_2O (5 X 5mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Et_2O)

providing 5-methoxy-2-(1-methyl-2-phenyl-ethylidene)-furan-3-one (38 mg, 57%) as a white solid. IR(thin film/cm^{-1}): ν_{max} 3000, 1730, 1440, 1371. H^1 NMR (250 MHz, $CDCl_3$) δ 7.26-7.15 (m, 5H), 5.02 (s, 1H), 4.16 (s, 2H), 3.99 (s, 3H), and 1.85 (s, 3H). C^{13} NMR (63 MHz, $CDCl_3$) δ 184.16, 178.69, 143.78, 138.39, 130.46, 128.98, 128.35, 126.37, 82.42, 57.90, 35.58, and 16.63.



H^1 NMR Data

C^{13} NMR Data

1D H^1-H NOESY

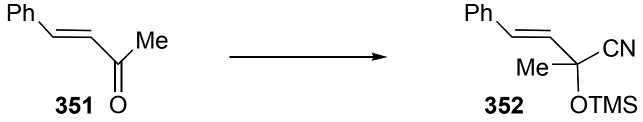
INADEQUATE: C^{13}-C^{13} Short-Range Interactions

INADEQUATE: C^{13}-C^{13} Long-Range Interactions

HMBC: H^1-C^{13} Long-Range Interactions

IV-2- Synthesis of 5-Disubstituted Tetronic Acid **348**

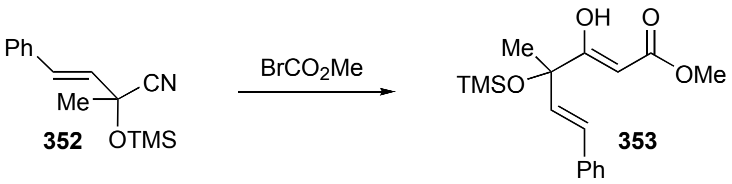
E-2-Methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile **352**[27]



To a stirred solution of the benzalacetone **351** (2.28 g, 15.6 mmol) and I_2 (47 mg, 5 mol%) in DCM (150 mL), was added slowly dropwise TMSCN (2.35 mL, 18.7 mmol, 1.2 eq) at 0 °C. The reaction mixture was stirred for 20 min at r.t, quenched with H_2O (100 mL) and extracted with DCM (3 X 100 mL). The combined organic layers were washed with sodium thiosulfate solution (15%, 100 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (9 : 1, Hexane : EtOAc) providing the *E*-2-methyl-4-

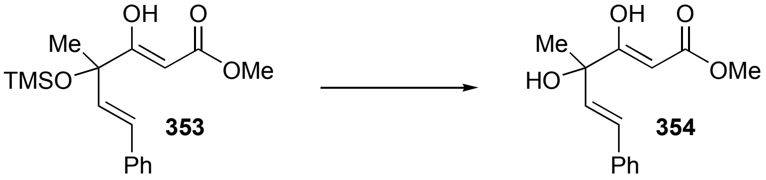
phenyl-2-trimethylsilanyloxy-but-3-enenitrile (3.00 g, 78%) as a colourless oil. H^1 NMR (250MHz, $CDCl_3$): δ 7.43-7.34 (m, 5H), 6.91 (d, 1H, J = 16.0Hz), 6.15 (d, 1H, J = 16.0Hz), 1.77 (s, 3H) and 0.26 (s, 9H).

E-4-Methyl-3-oxo-6-phenyl-4-trimethylsilanyloxy-hex-5-enoic acid methyl ester **353**[24]



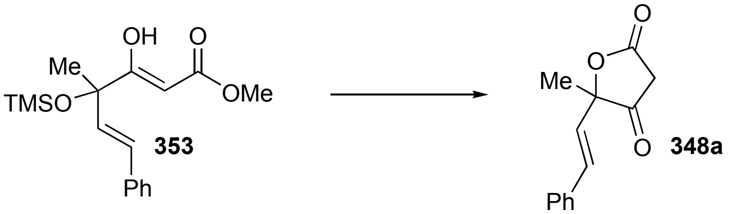
Zinc powder was activated by successive washes with HCl solution (3M), H_2O, acetone, diethyl ether and dried under high vacuum pump. To a suspension of activated Zn (750 mg, 11.4 mmol, 2.8 eq) in THF (20 mL) was added dropwise *E*-2-methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile **352** (1.00 g, 4.10 mmol). After stirring the reaction mixture for 20 min, methyl bromoacetate (1.20 mL, 12.7 mmol, 3.1 eq) was added carefully over 50 min. The reaction mixture was refluxed for 70 min and cooled to r.t, quenched with H_2O / brine / HCl (3 M) (15 / 5 / 5) and extracted with EtOAc (5 X 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (95 : 5, Hexane : EtOAc) providing (E)-4-methyl-3-oxo-6-phenyl-4-trimethylsilanyloxy-hex-5-enoic acid methyl ester (962 mg, 73%) as a yellow oil. IR(thin film/cm^{-1}): ν_{max} 3474, 2359, 1601, 1281. H^1 NMR (250 MHz, $CDCl_3$) δ 7.37-7.29 (5H, m), 6.61 (1H, d, J = 16.0Hz), 6.21 (1H, d, J = 16.0Hz), 4.55 (1H, s), 3.64 (3H, s), 1.66 (3H, s) and 0.17 (9H, s). C^{13} NMR (63MHz, $CDCl_3$) δ 171.15, 168.41, 136.36, 133.134, 131.17, 129.56, 128.86, 128.18, 126.87, 79.60, 50.35, 24.64 and 2.42. Accurate MS is not available for compound **353** such that it was not stable under MS EI and MS FAB conditions. However MS FAB of similar compound **354** is shown.

E-4-Hydroxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **354**



To a solution of (E)-4-methyl-3-oxo-6-phenyl-4-trimethylsilanyloxy-hex-5-enoic acid methyl ester **353** (400 mg, 1.25 mmol) in THF (8 mL) was added TBAF dropwise (1,25 mL 1 M solution in THF, 1 eq) at r.t. The reaction mixture was stirred for 30 min, quenched with H_2O (10 mL), stirred for 10 min and extracted with EtOAc (3 X 10 mL). The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (85 : 15, Hexane : EtOAc) providing (E)-4-Hydroxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester (200 mg, 65%) as a yellow oil. IR(thin film/cm^{-1}): ν_{max} 3474, 2359, 1601, 1281. H^1 NMR (250 MHz, $CDCl_3$) δ 7.36-7.26 (5H, m), 6.69 (1H, d, J = 16.0Hz), 6.29 (1H, d, J = 16.0Hz), 4.65 (1H, s), 3.65 (3H, s) and 1.64 (3H, s). C^{13} NMR (63MHz, $CDCl_3$) δ 171.00, 167.08, 136.12, 132.68, 129.60, 128.76, 128.22, 126.80, 80.33, 74.01, 50.41 and 28.31. MS FAB (+ve) *m/z* $[M]^+$ calculated for $C_{14}H_{16}O_4$, 248.1049 found 248.1048.

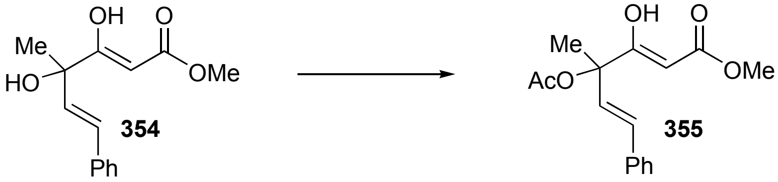
5-Methyl-5-(*E*-styryl)-furan-2,4-dione **348a**



To a solution of *E*-4-methyl-3-oxo-6-phenyl-4-trimethylsilanyloxy-hex-5-enoic acid methyl ester **353** (400 mg, 1.25 mmol) in MeOH (8 mL) was added dropwise HCl solution (3 M, 25 mL) at r.t. The reaction mixture was stirred for 2 h, diluted with DCM (30 mL), the organic layer was separated, washed with saturated $NaHCO_3$ aqueous solution (until the aqueous layer was basic), H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (85 : 15, Hexane : EtOAc) providing (E)-4-Hydroxy-4-methyl-3-oxo-6-phenyl-hex-5-

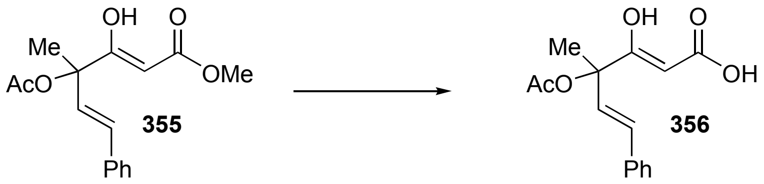
enoic acid methyl ester (192 mg, 71%) as white powder. M.p. = 89°C IR(thin film/cm^{-1}): ν_{max} 3399, 2360, 1710, 1611 H^1 NMR (250 MHz, CDCl$_3$) δ 7.37-7.30 (5H, m), 6.76 (1H, d, J = 16.0Hz), 6.19 (1H, d, J = 16.0Hz), 3.28 (2H, m) and 1.68 (3H, s). C^{13} NMR (63MHz, CDCl$_3$) δ 204.71, 169.01, 135.13, 131.66, 128.93, 127.00, 127.05, 124.89, 92.49, 36.32 and 23.00. MS FAB (+ve) *m/z* [M]$^+$ calculated for $C_{13}H_{12}O_3$, 216.0781 found 216.0779.

E-4-Acetoxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **355**[28]



To a stirred solution of *E*-4-Hydroxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **354** (800 mg, 3.22 mmol) in pyridine (16 mL) was added acetic anhydride (608 μL, 6.44 mmol, 2 eq) at r.t. The reaction mixture was warmed to 80 °C overnight, quenched with H_2O (20 mL) and extracted with EtOAc (5 X 20 mL). The combined organic layers were washed with H_2O (3 X 20 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (25 to 40% EtOAc, Hexane : EtOAc). Further recrystallizations in hexane was provided (E)-4-Acetoxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester (370 mg, 40%) as white powder. IR(thin film/cm^{-1}): ν_{max} 3447, 1743, 1616, 1237. H^1 NMR (CDCl$_3$, 250 MHz) δ 7.38-7.29 (5H, m), 6.73 (1H, d, J = 16.0Hz), 6.47 (1H, d, J = 16.0Hz), 4.80 (1H, s), 3.65 (3H, s), 2.10 (3H, s) and 1.84 (3H, s). C^{13} NMR (CDCl$_3$, 63 MHz) δ 170.83, 168.93, 164.02, 135.91, 131.84, 129.22, 128.80, 128.69, 126.95, 82.04, 81.72, 50.53, 24.35 and 22.02. MS FAB (+ve) *m/z* [M]$^+$ calculated for $C_{16}H_{18}O_5$, 290.1154 found 290.1144.

E-4-Acetoxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid **356**



To a stirred suspension of $Pd(OAc)_2$ (3.6 mg, 0.016 mmol, 10 mol%) and PPh_3 (8 mg, 0.032 mmol, 20 mol%) in THF (1 mL) for 30 min at r.t was added dropwise a solution of (E)-4-acetoxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid methyl ester **355** (46 mg, 0.16 mmol) in THF (1 mL). The reaction mixture was stirred overnight, refluxed for 3h and quenched with H_2O / saturated NaCl solution (5 / 5 mL). The aqueous layer was extracted with Et_2O (5 X 5mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Et_2O) providing *E*-4-Acetoxy-4-methyl-3-oxo-6-phenyl-hex-5-enoic acid (29 mg, 65 %) as a colourless oil. IR(thin film/cm^{-1}): ν_{max} 3283, 2359, 1717, 1531. H^1 NMR($CDCl_3$, 250 MHz) δ 8.63 (1H, s), 7.32-7.26 (5H, m), 6.72 (1H, d, J = 16.0Hz), 6.36 (1H, s), 6.47 (1H, d, J = 16.0Hz), 2.23 (3H, s) and 1.71 (3H, s). C^{13} NMR (63MHz, $CDCl_3$) δ 174.20, 169.63, 163.03, 135.24, 133.30, 128.90, 127.06, 126.83, 125.80, 97.40, 84.76, 24.21 and 23.08. Accurate MS is not available for compound **356** such that it was not stable under MS EI and MS FAB conditions. However MS FAB of similar compound **355** is shown.

V-References

(1) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(2) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 9509.

(3) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.

(4) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(5) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.

(6) Trost, B. M. *Pure Appl. Chem.* **1979**, *51*, 787.

(7) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 187.

(8) Tsuji, J. *Top. Curr. Chem.* **1980**, *91*, 29.

(9) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867.

(10) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475.

(11) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595.

(12) Pfaltz, A.; Koch, G. *Tetrahedron Asymmetry* **1996**, *7*, 2213.

(13) Godleski, S. A. *Comprehensive Organic Synthesis*; Pergamon: Oxford, **1991**, *4*, 67.

(14) Kienan, E.; Sahai, M. *J. Chem. Soc., Chem. Commun.* **1984**, 648.

(15) Tsuji, J.; Kobayashi, Y.; Kataoka, H. *Tetrahedron Lett.* **1981**, *22*, 2575.

(16) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3416.

(17) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

(18) Sjogren, M. P. T.; Hansson, S.; Akermark, B. *Organometallics* **1994**, *13*, 1963.

(19) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(20) Johnson, C. D. *Acc. Chem. Res.* **1997**, *26*, 476.

(21) Evans, D.; Carroll, G.; Truesdale, L. *J. Org. Chem.* **1974**, *39*, 914.

(22) Hayashi, M. *J. Am. Chem. Soc.* **1989**, *111*, 6307.

(23) Fürstner, A. *Synthesis* **1989**, 571.

(24) Gao, X.; Nakadai, M.; Snider, B. *Org. Lett.* **2003**, *5*, 451.

(25) Rathke, M. W. *Org. React.* **1975**, *22*, 423.

(26) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157.

(27) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703.

(28) Seki, M.; Hatsuda, M.; Mori, Y.; Yamada, S. *Tetrahedron Lett.* **2002**, *43*, 3269.

(29) Hermann, S.; Gerd, H.; Heinrich, K. *Chem. Ber.* **1979**, *112*, 84.