Thesis for the degree
of Candidatus Scientiarum

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Synthesis of α,α'- Di substituted Spiro[5, 5]-undecanes

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To my family in Iraq, thank you for your patience and support. I hope that everything is OK with you.

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Saad Aziz Said Al Baldawi
Oslo, may 2003

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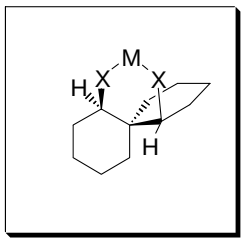
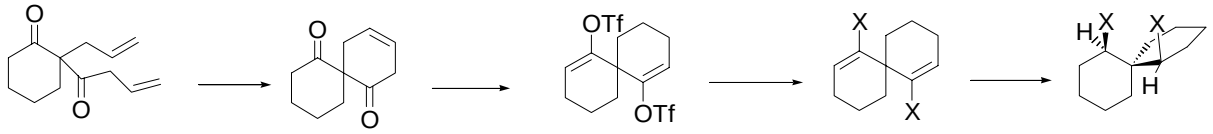
Introduction and goals for the project

A spirane is an orthogonal structure where two rings share one common atom. The spirane framework is rigid, and as a consequence spiranes are potentially useful as rigid frameworks for attachment of coordination functions for metal complexation.



A rigid spiro[5.5]undecane as framework in a metal complex

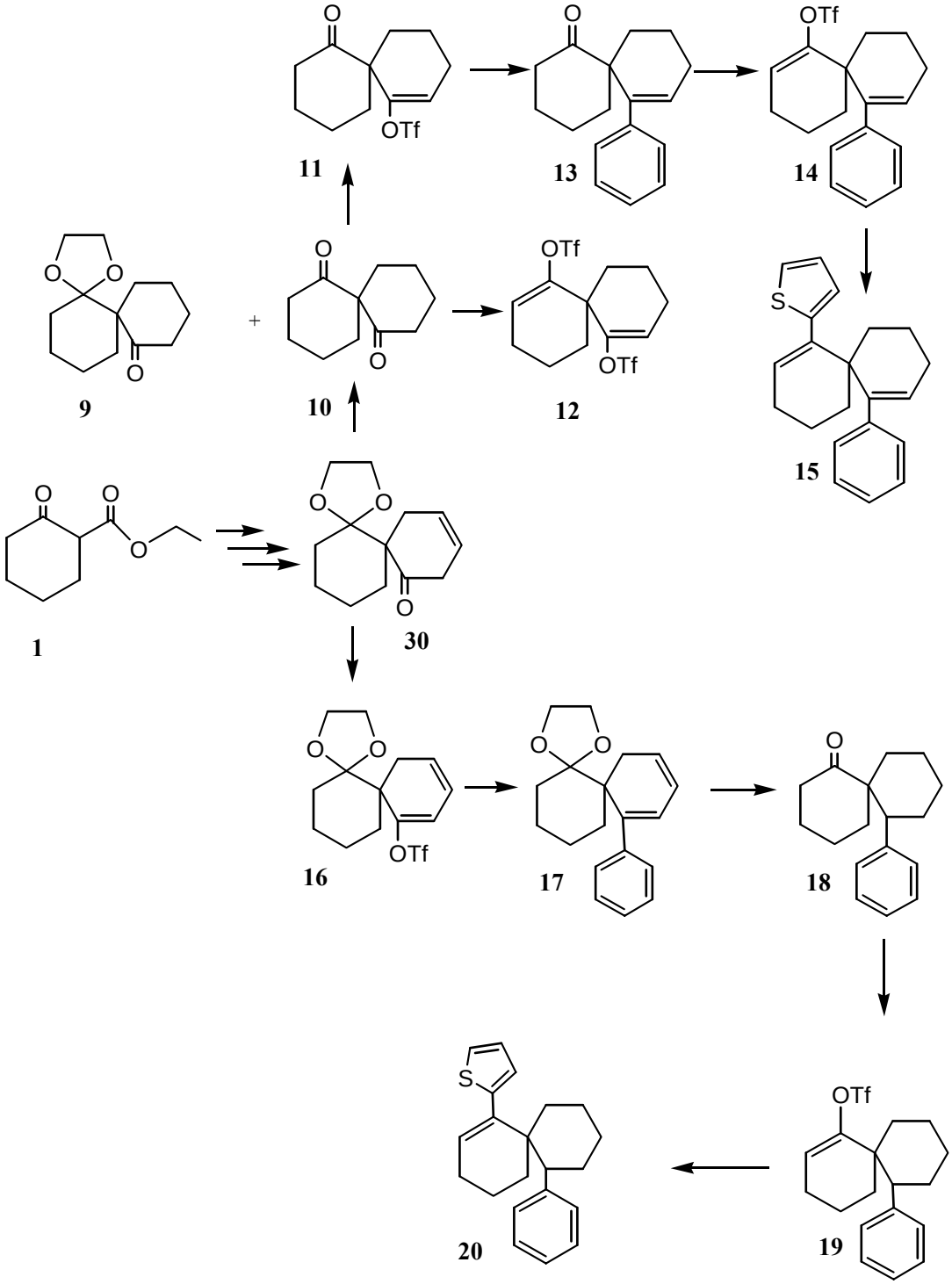
The goal for the project was 1) to synthesise I the dioxospiorne using ring closing methathesis (RCM), 2) for se if this reaction could provide I as a pure enantiomer, 3) to be triflated and substituents introduced via palladium- mediated coupling reactions. Stereoselective reduction was planned to furnish the *cis*,*cis* substituted functionalised spiranes II.



I **II**

A graphical summary of the project

An illustration of the project is presented where the different synthesised molecules have been drawn in order to make it easier for the reader to understand the scheme of the work.



Abbreviations

[α]	specific rotation
Ac	acetyl
9-BBN	9-borobicyclononane
Boc	*tert*-butoxycarbonyl
^{t}Bu, *t*-Bu	*tert*-butyl
*n*Buli	normal butyllithum
CI	chemical ionisation(in mass spectrometry)
conc.	concentrated
COSY	correlation spectroscopy (NMR)
cy	cyclohexyl
δ	chemical shift (NMR)
d	doublet
dba	dibenzylidineacetone
DDC	dicyclohexylcarbodiimide
DMAP	4-dimethyaminopyridine
DME	1,2-dimethoxyethane
ee	enatiomeric excess
eq.	equivalent
GC	gas chromatography
HRMS	high-resolution mass spectrum
IR	infrared
L	ligand
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
$LiBH(Et)_3$	super hydride
LiHMDS	lithium hexamethyl disilazane
m	multiplet
m/z	mass/charge
Me	methyl
MS	mass spectroscopy
MVK	methyl lvinyl ketone
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PCC	pyridinium-chlorochromate
Ph	phenyl
PPI	plane-polarised light
PTSA	toluene-4-sulfonic acid
RCM	ring-closing metathesis
rfx	reflux
Ri	from latin rectus(clockwise)
Si	from latin sinister(anticlockwise)
s	singlet
t	triplet
TFA	trifluoroacetic acid
Tf_2O	triflic anhydride
THF	tetrahydrofurane
TLC	thin layer chromatography

Chapter 1

Ru(II)-catalysed ring-closing metathesis in the synthesis of α-oxospiranes

1.1 Introduction

In spiranes there is no rotation around the quaternary spirocenter. As a consequence, spiranes are rather rigid structures and potentially useful as rigid frameworks for attachment of functional groups, pharmacophoric groups or coordination functions for metal complexation. The goal of the work described in this chapter has been to synthesize α-oxospiranes (figure 1.1). We have demonstrated that Ru(II)-catalysed RCM-reactions provide an efficient method for the preparation of functionalised spirane. Six– membered rings formed in the spiroannulation reaction will be intermediates in our further synthesis.

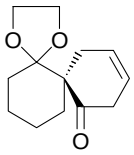


Figure 1.1 Target molecule

1.2 Strategy

Ring- closing metathesis (RCM) is a versatile technique for the formation of five- to seven-membered carbocycles and heterocycles.[1, 2, 3, 4, 5] The Grubbs Ru(II)-catalyst systems have become a very important tool in organic synthesis. A retro synthetic analysis shows that the functionalized spirane I can be prepared by Ru(II)-catalysed ring-closing metathesis reaction using a cycloalkane with a set of gem-dialkene groups as substrates, (figure 1.2).

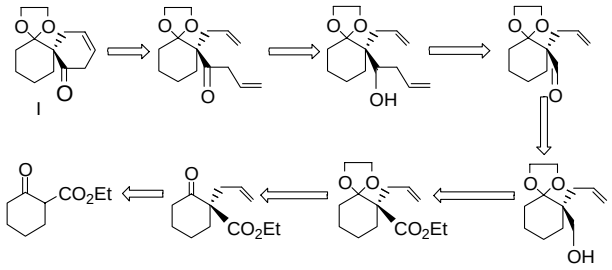
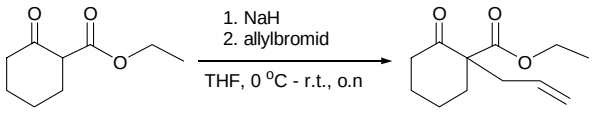


Figure 1.2 Strategy for synthesis of α- oxospirane.

1.3 Synthesis of ethyl 1-allyl-2-oxocyclohexane-1-carboxylate (2)[6]

Ethyl 2-oxocyclohexane-1-carboxylate (**1**) was added to sodium hydride in THF at 0 ^{0}C, followed by addition of allyl bromide in THF at same temperature. The reaction mixture was stirred overnight, allowed to reach room temperature overnight. The product **2** was purified by flash chromatography, and isolated as a colourless oil in 82% yield (figure 1.3).



1 **2**

Figure 1.3 Allylation of 1

1.4 Synthesis of ethyl 1-allyl-2,2-ethylenecyclohexane-1-carboxylate (3)[6]

A mixture of the cyclohexanone **2**, ethylene glycol, toluene-4-sulfonic acid monohydrate and benzene was heated to reflux overnight with removal of water with a Dean-Stark trap. The reaction mixture was cooled, washed with aqueous 10% ammonia and then with water. The product **3** was purified by flash chromatography and isolated as a colourless oil in 85%.

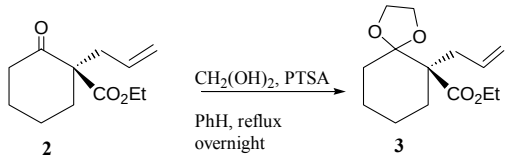


Figure1.4 Protection of the oxo group in 2

1.5 Synthesis of 1-allyl-2,2-ethylenedioxycyclohexane-1-methanol (4)[6]

A solution of ethyl 1-allyl-2,2-ethylenecyclohexane-1-carboxylate (**3**) in dry THF was cooled to 0 ^{o}C under argon, and then LAH in dry THF was added dropwise. After the addition was, the reaction mixture was stirred at room temperature overnight. Excess LAH was completed destroyed with saturated NH_4Cl solution and mixture extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and the crude product was purified by flash chromatography to yield (93%) of a colourless oil (**4**).

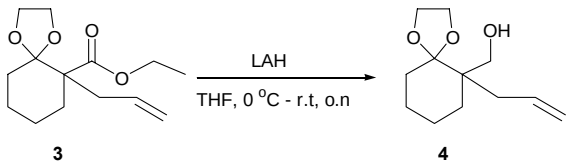


Figure 1.5 Reduction of ester 3

1.6 Synthesis of 1-allyl-2,2-ethylenedioxycyclohexane-1-carbaldehyde (5)[6]

The hydroxy group in1-allyl-2,2-ethylenedioxycyclohexane-1-methanol (**4**) was oxidised to aldehyde by using PCC in CH_2Cl_2. The reaction mixture was stirred at room temperature for 6 h. Anhydrous ether was added, and the ether solution filtered through florisil. The product **5** was purified by flash chromatography and isolated in 80% yield (figure 1.6).

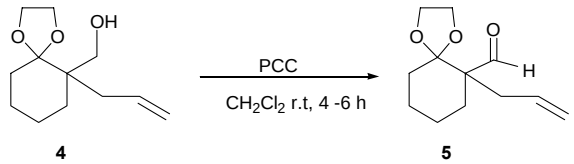


Figure 1.6 Oxidation of alkohol 4

1.7 Synthesis of 1-(allyl-2,2-ethylenedioxycyclohexan-1-yl)-3-buten-1-ol (6a and 6b)[6]

The hydroxy derivatives (**6a, 6b**) were obtained by treatment of the carbaldehyde **5** with a Grignared reagent (allylmagnesium chloride) in THF under argon at 0 ^oC. The reaction was stopped after 2 h. The diastereomers **6a** and **6b** were purified by flash chromatography, and isolated together as a colourless oil (1:4 mixture) in 80% total yield (figure 1.7).

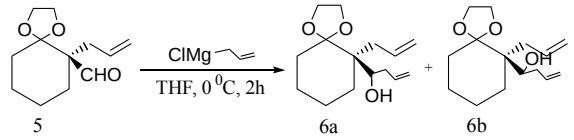


Figure 1.7 Synthesis of hydroxy intermediates 6a and 6b

1.8 Synthesis of (allyl-2,2-ethylenedioxycyclohexan-1-yl)-3-buten-1-one (7)[6]

The oxidation was carried out on the epimeric mixture of alcohols **6a:6b** (1:4) using pyrdinium chlorochromate in dichloromethane for 6 h. The product was purified by flash chromatography. The ketone (**7**) was isolated as a colourless oil (71%) (figure 1.8).

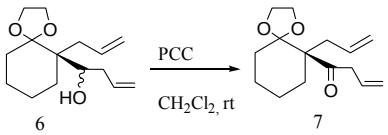


Figure 1.8 Oxidation of the hydroxy group in 6

1.9 Synthesis of 7,7-ethylenedioxyspiro[5.5]undecan-3-en-one (8)[6]

The RCM reaction of the ketone **7** is shown in figure 1.8. Toluene was used as solvent with 5 mol% Ru(II)-catalyst. The mixture was heated for 3 h, and the product purified by flash chromatography. The product was isolated as a colourless oil in 92%.

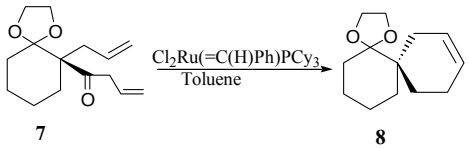


Figure 1.9 RCM reaction of oxo-diene

1.10 Ring-Closing Metathesis (RCM)

1.10.1 The catalyst

Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride[7] (**9**) (figure 1.9) is commercially available and was used as catalyst in the RCM reaction of the diene **7**.

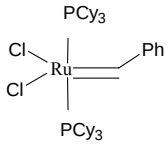


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Figure 1.10

1.10.2 Mechanism of the RCM reaction

The RCM reaction has been studied in detail [8]. The generally accepted mechanism for the RCM reaction is shown in figure 1.11.

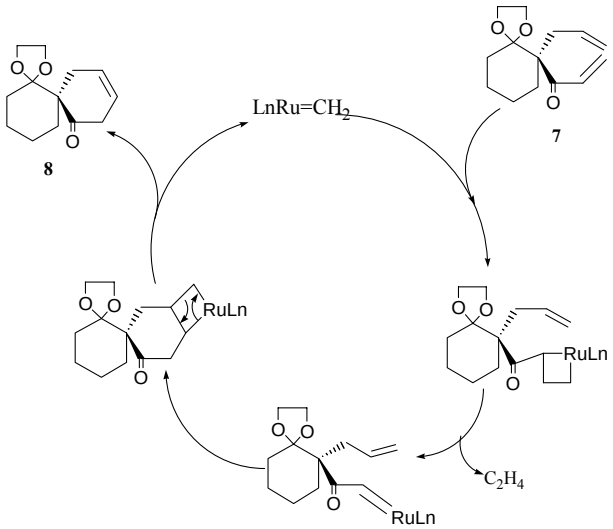


Figure 1.11 Mechanism of RCM reaction

Chapter 2

Ru(II)-catalysed ring-closing metathesis for the construction of optically pure spirane αά- diones.

2.1 Introduction

2.1.1 Aim of the study

The aim was aimed to prepare optically pure spirane αα′- diones by copper(II)-catalyzed and Michael addition which allows the construction of quaternary carbon centre with *ee* values in excess of 95%. Optically active spirane α,ά- dione was to be an intermediate in our work.

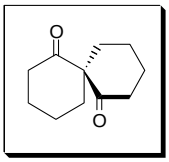


Figure 2.1 Target molecule

2.1.2 Background theory

The Michael addition is a common and valuable C-C bond forming reaction[22] that has been known for over 100 years[23] and is commonly catalyzed by a strong Brønstedt base.[22] In order to avoid the disadvantages of basic reaction conditions, a number of transition metal-catalyzed procedures have been published in recent years. This has resulted in improved chemoselectivtiy due to the milder conditions[24]. Moreover, chiral auxiliaries can be utilized here to achieve asymmetric catalysis of the Michael reaction. Recent examples were reported by Enders et al[25], d' Angelo et al.,[26] and Koge et al.[27] Pioneering work on the symmetric catalysis of the Michael reaction has been performed by Wynberg et al.,[28] who applied

cinchona alkaloids as chiral Brønstedt-basic catalysts. Brunner and Hammer,[29] Desimoni et al.,[30] Ito et al., [31] and Pfaltz et al.[32] have investigated chiral metal complexes in the asymmetric catalysis of the Michael reaction. In 1996, Shibasaki *et al*. introduced heterobimetallic catalysts.[33]

2.1.3 Mechanistic proposal for the copper-catalysed [$Cu(OAc)_2 \cdot H_2O$] asymmetric Michael reaction of enaminoester.

In the classic base-catalysed Michael reaction, the *β*-dicarbonyl donor **1,** as show in the retrosynthetic analysis (figure 2.3), is deprotonated prior to the reaction with electrophile to give a planar intermediate dionato anion. The negative charge is delocalized over the nucleophilic carbon center and the two carbonyl oxygen atoms. At least for Ni-, Co-, Cu-, and Fe-catalyst processes, the intermediate dionato anion coordinates to the metal center as a chelating ligand.[34] Dionato metal complexes of this sort are not nucleophilic enough to be alkylated at the acceptor. For example, methyl vinyl ketone **36** needs further activation by coordination of the carbonyl moiety to a Lewis acid. The metal center of the dionato complex can act as this Lewis acid to form a metal template that maintains the donor and acceptor in close proximity and activates both by coordination.

It is proposed a template reaction of such a kind for the copper-catalysed conversion of enamino ester **22** with MVK **36**. The acetate counterion of the Cu(II) cation deprotonates the acidified enamino proton to give an aza-diketonate which coordinates to the copper center as chelating ligand. The choice of counterion seems to be crucial for the enantioselctivity of the reaction. $Cu(OTf)_2$, $CuCl_2$, or $CuCl_2 \cdot 2H_2O$, which do not have sufficient Brønstedt basicity, all give lower ee values than $Cu(OAc)_2 \cdot H_2O$.

After coordination of aza- diketonates to the copper center, the additional donor function D, being a carboxylic amide, leads to diastereofacial differentiation of the *Si* and *Re* faces of the Michael donor. Another chelate ring is formed which makes the enaminoester anion a tridentate ligand bond on one face of the octahedral coordination polyhedron. Coordination of D from the upper *Si* face (figure 2.2)[60] results in a pseudoequatorial arrangement of the alkyl residue on the amino acid in the five- membered chelate ring. Coordination from the lower *Re* face would place the alkyl group into pseudoaxial conformation, which is eventually

disfavoured due to diaxial strain with one of the other ligands (L, which is presumably water or solvent). Interestingly, this strain seems to be distinct with alkyl residues that contain α-branching, namely *i*Pr, *s*Bu, and *t*Bu. This hypothesis is strongly supported by the fact that selectivities >90 ee are observed with auxiliaries derived from L-valine, L-isoleucine, and L-*tert*-leucine only. Without activation by lewis acid, the conversion of MVK **36** with enamines **22** is very slow at ambient temperature.[35] Consequently, the acceptor needs to be activated by coordination to the lewis-acid copper center. With additional donor function D coordinating from the *Si* face of aza-dionate, the MVK **36** must coordinate at the opposite *Re* face. After activation, **36** react from this *Re* face with the aza-dionateto result exclusively in product **23** with R configuration. After the conjugate addition, π-electron density cannot be delocalized over the quaternary carbon center. Therefore, a copper-chelate complex no longer exhibits particular thermodynamic stability. The enolate moiety of the former MVK **36** deprotonates the next equivalent of the enaminoester **22**. The primary product is an imine, which is hydrolyzed to the product **23** upon aqueous protic workup (figure 2.2).

In addition to the correct choice of the central metal, the counterion, and the stereogenic alkyl group in the auxiliary (α-branching is required), the additional function D is an important parameter. Only carboxylic amides results in high selectivities. The use of thioether or tertiary amines has not been successful.

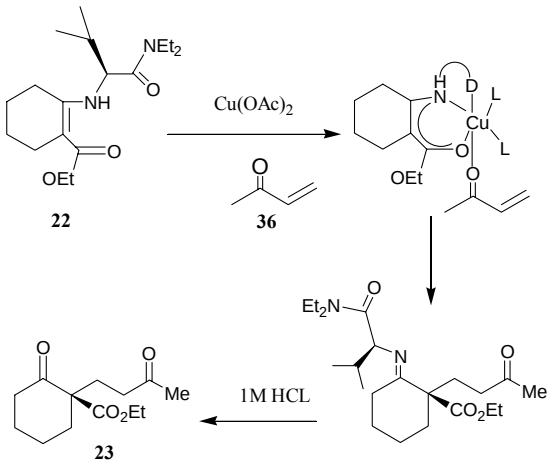


Figure 2.2

2.2 Strategy

Our retrosynthetic analysis is shown in figure 2.3. The starting material is a cycloketo ester which is to be converted into a chiral enamine by reaction with L-valine dimethylamide as auxiliary to give an imine or enamine and subjected to a Michael addition with methyl vinyl ketone.

As the most important result, selectivities >95% ee were obtained by using $Cu(OAc)_2 \cdot H_2O$ as the metal catalyst.[36]

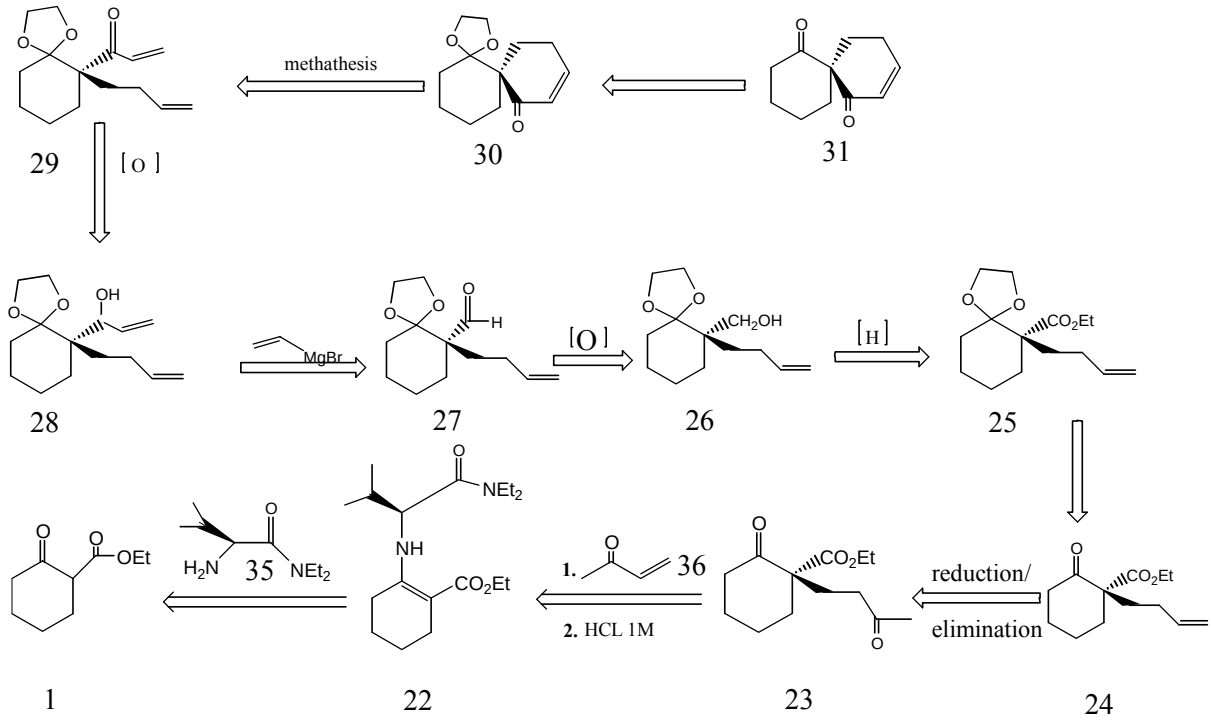


Figure 2.3

2.3 Synthesis of (S)-2-tert-butoxycarbonylamino-3-methylbutyric acid

There are different protocols for *N*-Boc protections of amino acids in the literature. We tried two for synthesis of (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid (**33**). Method (**2**) was our favoured procedure to protect 2-amino-3-methyl-butyric acid (*L*-valin) (**32**).

2.3.1 Method 1[60]

2-Amino-3-methylbutyric acid (*L*-valin) (**32**) was converted to the 2-*tert*-butoxycarbonylamino-3-methylbutyric acid (**33**) with one equivalent of Boc_2O and one equivalent of Na_2CO_3 in MeOH/H_2O (1:1) overnight at ambient temperature. After removal of the solvent and acidification with citric acid, the mixture was extracted with CH_2Cl_2 to furnish the protected amino acid (**33**). Residual *tert*- butyl alcohol was removed under high vacuum (7 h). The product **33** was purified by flash chromatography and isolated in 85% (figure 2.4A).

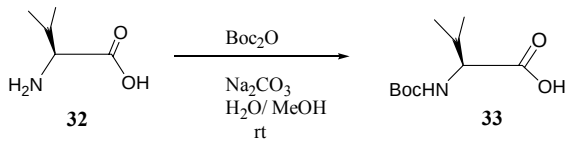


Figure 2.4A

2.3.2 Method 2 [66]

A solution of *L*-valine **32**, one equivalent of Boc_2O and one equivalent of NaOH in *tert*-BuOH/H_2O (1:1) was stirred at room temperature overnight. After removal of the solvent and acidification with $KHSO_4$ (pH 2), the mixture was extracted with diethyl ether. The product was purified by flash chromatography and isolated in 95% (figure 2.4B).

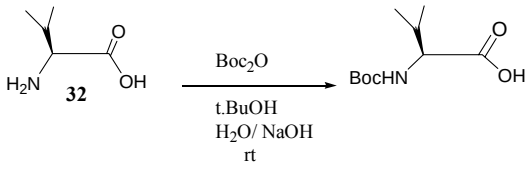


Figure 2.4B

2.4 Synthesis of (S)-2-Amino-N,N-diethyl-3-methylbutyramide 35.

we also tried two different methods for the synthesis of (*S*)-2-amino-*N*,*N*-diethyl-3-methyl-butyramide.

2.4.1 Method 1:[60]

$HNEt_2$ was added to a solution of compound **33** and DCC (1.1 eq.) in CH_2Cl_2 at 0 ^oC, and the resulting solution was stirred at room temperature over night. After work up and purification by flash chromatography, the product **34** was isolated in 75% yield (figure 2.5).

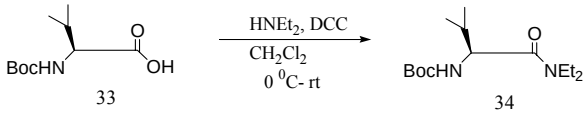
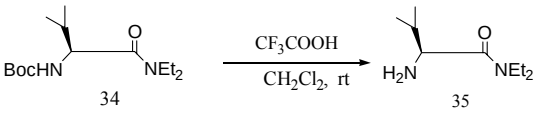


Figure 2.5

The compound **34** was dissolved in CH_2Cl_2 and conc. TFA was added to the reaction mixture. The reaction was stirred at ambient temperature overnight and monitored on TLC and GC. The solution was evaporated almost to dryness at reduced pressure, and the residue partitioned between water and diethyl ether was added. The phases were separated, the aqueous layer brought to pH 12 by the addition of 1 M NaOH. The aqueous mixture was extracted with diethyl ether. The compound **35** was obtained by Kugelrohr distillation in 60% yield (figure 2.6).



34 35

Figure 2.6

2.4.2 Method 2[67]

To a solution of *N*-Boc-protected amino acid **33** and 1.1 eq. *N*-hydroxysuccinimide in CH_2Cl_2 was added (1.1 eq.) dicyclohexylcarbodiimide (DCC) at 0 ^{0}C followed by addition of $NHEt_2$ (3 eq.). the reaction was stirred at ambient temperature overnight. The reaction mixture was filtered and the filtered, solution washed with 1 M K_2CO_3. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product **34** was hydrolysed without any further purification.

Crude product **34** and 5 eq. TFA in CH_2Cl_2 were refluxed for 2 h and stirred at room temperature over night. The reaction mixture was washed with aqueous saturated K_2CO_3 (pH 12). The product **35** was purified by flash chromatography and dried under high vacuum overnight, 70% yield (figure 2.7).

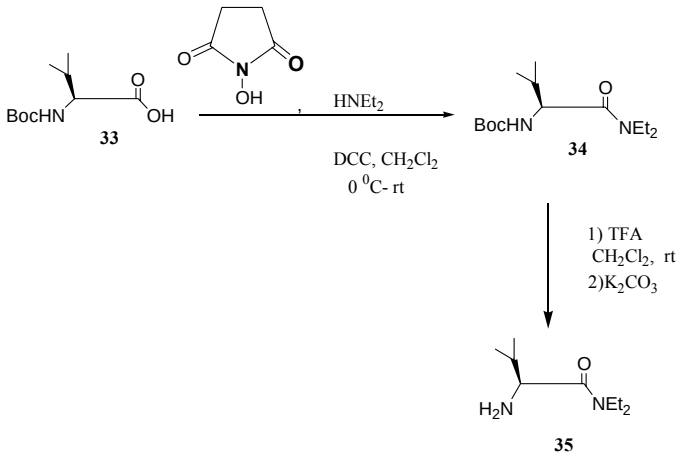


Figure 2.7

Mechanistic proposal for the formation of compound **34** from substitute **33**. The latter was activated with DCC and reacted with a secondary amine to give the amide **34** (figure 2.8).

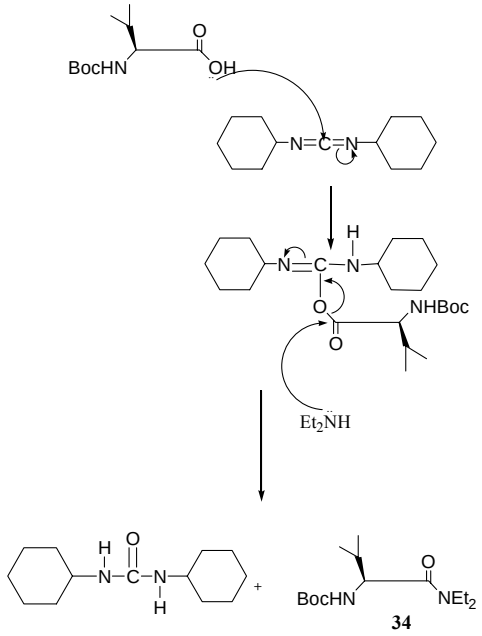


Figure 2.8

2.5 Synthesis of N-(2-ethoxycarbonyl-1-cyclohexenyl)-L-valine diethylamide 22 [60]

A mixture of oxo ester **1**, auxiliary **35**, and molecular sieves (4 Å) under nitrogen in toluene was treated with a catalytic amount of concentrated HCl (1 drop) and stirred overnight at 60-65 ^{0}C. The reaction mixture was filtered and the residue washed with CH_2Cl_2. All volatile materials were removed in vacuo and the residue was chromatographed on aluminium oxide 90 and compound **22** was isolated in 70% (figure 2.9).

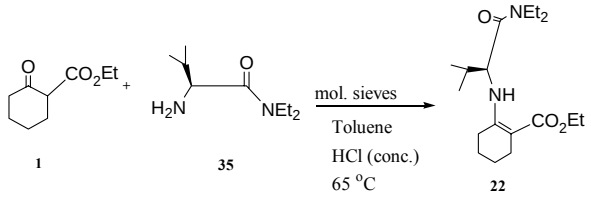


Figure 2.9

2.6 Synthesis of (R)-ethyl-2-oxo-1-(3-oxobutyl)cyclohexanecarboxylat (23). [60]

Enaminoester **22** and $Cu(OAc)_2 \cdot H_2O$ were stirred together in acetone (1 ml per 0.2-0.3 mmol **22**) at room temperature for 1 h. MVK (**36**) (2 eq.) was added, and the mixture was stirred for a further 12-14 h at room temperature.

All volatile materials were removed in vacuo and the residue was treated with 1 M HCl. The mixture was stirred vigorously for 3 h at 0 ^{0}C and subsecquently extracted with diethyl ether. After washing with 10% Na_2CO_3 and saturated aqueous K_2CO_3, the combined extracts were dried over $MgSO_4$. The solvent was evaporated, and the product was purified by flash chromatography on silca gel. In the literature procedure it was used strongly aqueous KOH to work up this reaction. May be the use of less alkaline carbonate might have helped to obtain the higher stereoselectivity (+96 *ee*, litterature value +95 *ee*).

The stereoselective synthesis had to furnish the (*R)*-configuration at the stereogenic center in compound **23**. The *ee*- value was determined by using plan-polarised light (ppl).

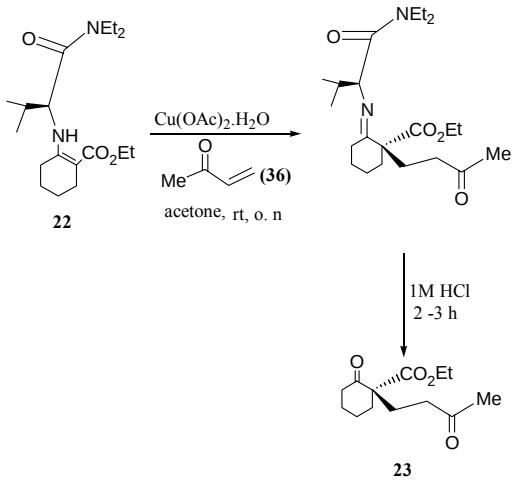


Figure 2.10

2.7 Attempts to synthesise 2-oxo-1-(3-trifluoromethanesulfonyloxy-but-3-enyl)cyclohexane carboxylic acid ethyl ester (41).

Attempts to triflate compound **23** were performed by two different methods. Firstly, by using LDA, secondly by using LiHMDS.
An excess of base is always present, and the ketone is deprotonated completely. The temperature is kept low. Under these conditions, the major product is the **kinetic enolate**. Kinetic enolates tend to be the less highly substituted ones.

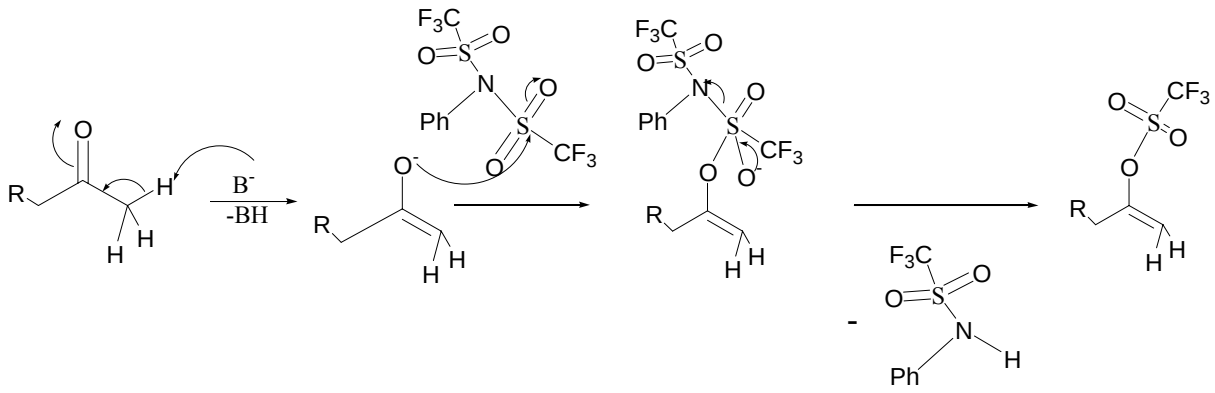


Figure 2.11 General mechanism for triflation of ketone with $PhNTf_2$

2.7.1 Method 1

Compound **23** was dissolved in THF and added to a solution of LDA (1 eq.) in THF at -78 ^{0}C. After 15 min, the triflating reagent was added. The mixture was stirred at the same temperature for 3-4 h (figure 2.12). The reaction was monitored by TLC, and a new spot could be seen.

The reaction was stirred overnight and allowed to slowly reach room temperature. But after work up and NMR analysis, the unwanted product **42** was isolated in 80%.
The reaction was repeated several times using more than one equivalent of LDA and triflating agent but without any success.

2.7.2 Method 2

The reaction conditions were the same as in method 1. But it was decided to use LiHMDS (1 eq.) instead of LDA. The same product **42** was isolated in same yield.

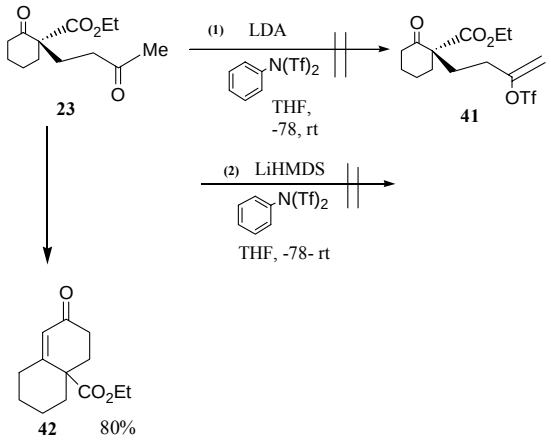


Figure 2.12

2.7.3 Conclusion

In these cases, the triflation reactions took an undesireable course. After initial enolization using LDA or LiHMDS at –78 ^{0}C, a rapid intramolecular aldol reaction occurred. In no case did we succeed to trap the enolate as the triflate **41.**

2.8 Synthesis of ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxlate as a racemate (40) [60]

The racemic product **40** was prepared using enamine **38** derived from cyclohexylamine **(37)** The method used to prepare **40** from **38** was the same as that of **23** (figure 2.10).

The reason for the preparation of racemate **40** was that the starting material used in this synthesis was cyclohexylamine which is commercially available and provides an easily available test substance. Therefore, compound **40** will be used in all next attempts to get the target molecule instead of using compound **23**.

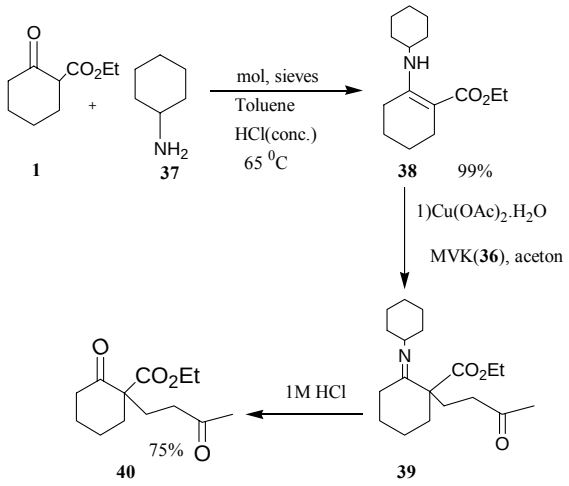


Figure 2.13

2.9 Attempts to synthesise 1-but-3-enyl-2-oxo-cyclohexane carboxlic acid ethyl ester 44.

2.9.1 By selective reduction.

Selective reduction of one out of two different carbonyl moieties is an important synthetic operation. The selectivity is commonly achievable by using modified hydride reagents formed by replacement of hydride with sterically bulky substituents or electron withdrawing groups

in order to discriminate the structural or electronic environment of the carbonyl group.The sterically less hindered or electronically more labile carbonyl moiety is more easily reduced.[37]

In this approach it was decided to change the acetyl moiety in **40** into an olefin **44**. This requires selective reduction of the methyl keto group in the presence of the cyclic keto group in structure **40.**

The bulky metal hydrides LiAlH(*t*-BuO)$_3$, LiBH(*s*-Bu)$_3$ and LiBH(Et)$_3$ in THF at -78 ^{0}C were tested. In most reactions a mixture of alcoholic products were obtained. This was also case when using 9-BBN and $NaBH_4$. When using H_2/ PtO_2 (bar), the starting material remained unchanged.

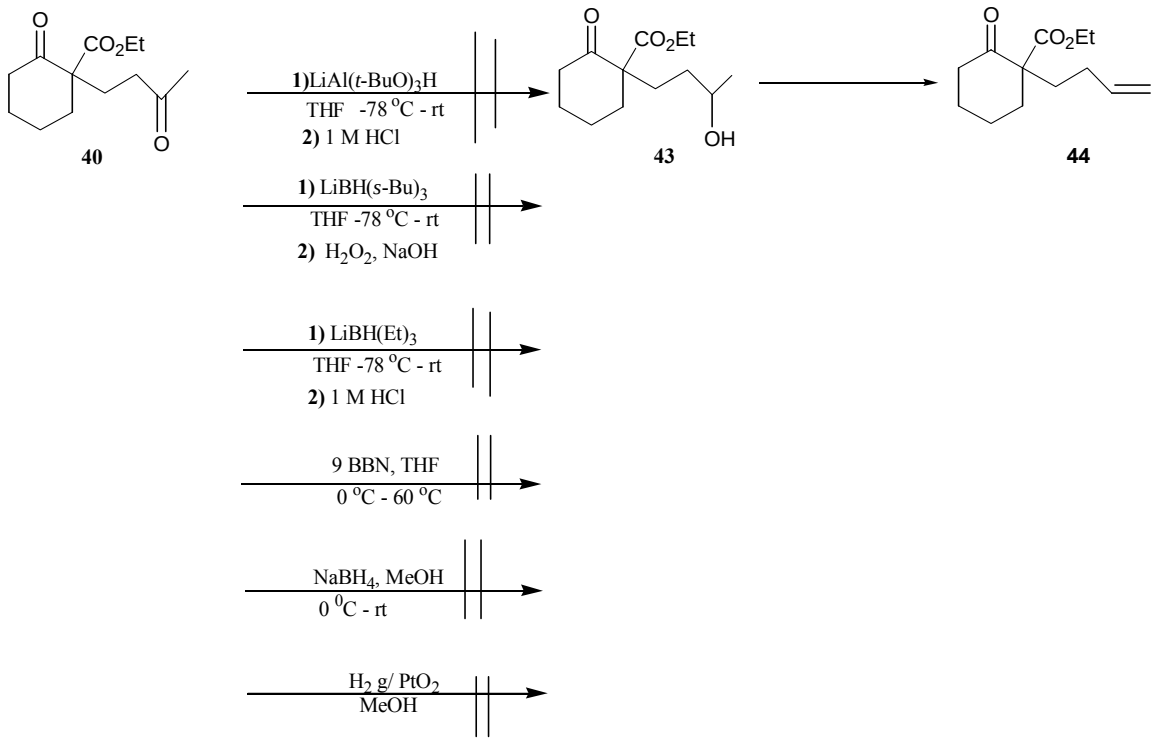


Figure 2.14

2.10 Attempt to cleave off the acetyl methyl group using the haloform reaction. [65]

We wanted to use the haloform reaction as a key step to reach the target compound **31** (figure 2.1).

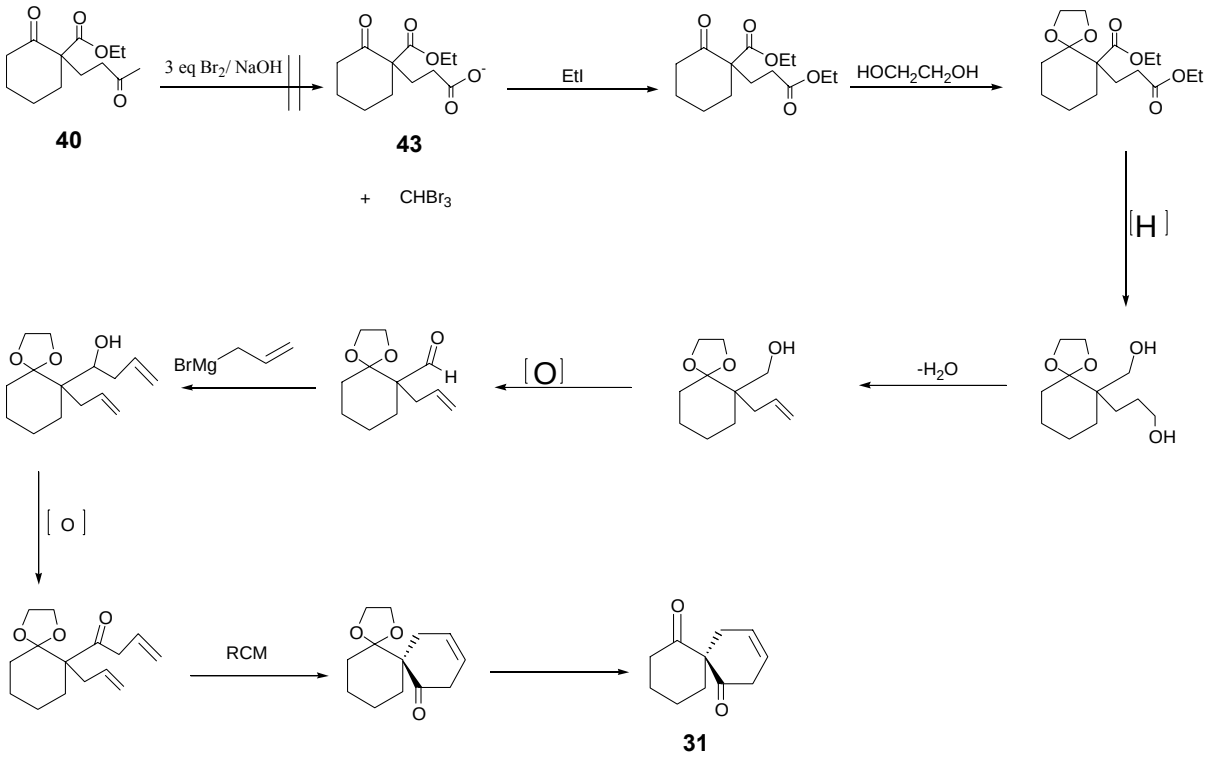
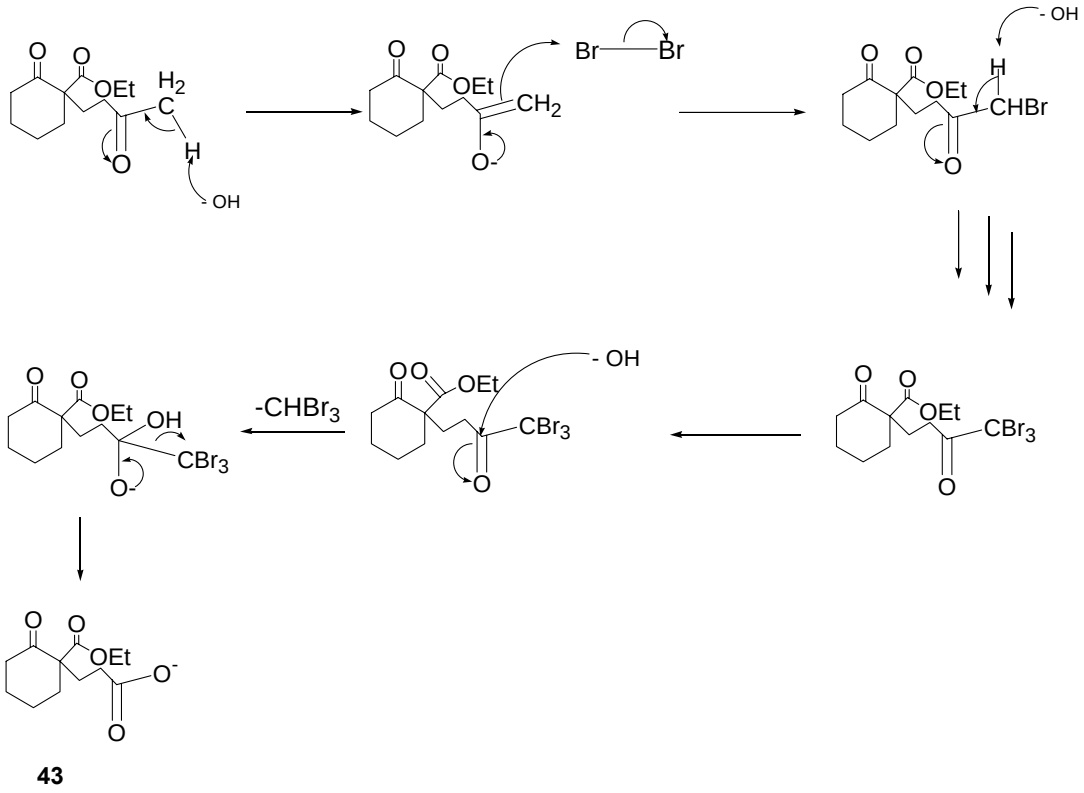


Figure 2.15

2.10.1 The mechanism for the haloform reaction.

The reaction is known as the haloform reaction because one of the products is haloform (figure 2.16). Once one of the α- hydrogen atoms is replaced by halogen. The geminal protons become more acidic. Enolization takes place a second and then a third time on the same side. Attack at the carbonyl group by base leads to the loss of the trihalocarbanion, a relatively stable species.



2.10.2 Attempt to synthesise 3-(1-ethoxycarbonyl-2-oxo-cyclohexyl)-propionic acid anion(43)[65]

Compound **40** was dissolved in dioxane and water at 0 ^{o}C. And a solution of a cold solution of freshly prepared hypobromate (literature) was added. The reaction mixture was stirred at 0 ^{o}C for 3 h before quenching it with a solution of sodium sulfite. The mixture was allowed to warm to 25 ^{o}C and then was acidified with conc. HCl and extracted with diethyl ether. The

product was purified using flash chromatography and many fractions were collected. Disappointingly none of the fractions isolated was the expected compound (figure 2.15).

2.11 Conclusion

It was very painful that the target molecules in this project could not be achieved. Several method were tried in the reduction and triflation processes without any succeed.

The important point in this chapter is that a very good *ee* value was achieved in preparation of **23**.

Chapter 3

Palladium-mediated carbosubstitution in oxospiranes

3.1 Introduction

Spirane skeletons are embedded in a variety of natural products. Syntheses of this class of natural products have yielded highly functionalized intermediate spiranes.[38] Stereochemical and chiroptical properties of substituted simple spirane systems have also been the focus for studies, particularly dienes with resemblances to allenes. In this context, successful chiral resolutions have been reported. [39]

As mentioned in the previous chapter, the framework of the spiranes is rigid. Use of the stiff scaffold of spiranes for stereocontrol of pharmacophoric groups in bioorganic molecules, or the use of appropriately substituted spiranes as chiral auxiliaries in dissymmetric catalytic operation, have received little attention. The enantiomers of *cis,cis*-spiro[4,4]nonane-1,6-diols, however, have been investigated for ability to induce stereoselsctivity in metal hydride reductions of phenyl alkyl ketones, [40] and in hydroformylation of styrene.[41]

Recent syntheses of spirane included palladium promoted intramolecular Heck reactions in spironannulations to carbo- or heterocyclic structures,[42]cascade reactions,[43,44] radical promoted spiroannulations,[45] spiroannulation of ketal,[46] rearrangement reactions,[47] Nickel mediated spiroannulations with acetylenes,[48] the formation of carbon- carbon bonds by asymmetric Heck reactions has also been used by Overman *et al.*[49] to make spirooxindoles.

Rhodium-catalysed hydroacylations,[50] copper or samarium mediated spiroannolations,[51, 52] acid or base catalysed aldol condensation as well as alkylations. [53, 54] Our group has reported on spiroannulations in the prepration of substituted spiro[4.4]nonanes by rhodium carbenoid insertion into C-H bonds.[55] Spiroannulation has also been effected by palladium catalysis.[56] A series of ruthenium(II)-catalysed spiroannalations of dihydropyrazines have given heterocyclic spiranes as intermediates in the stereoselective prepration of cyclic α-amino acids.[57]

Reactions involving carbonium intermediates at the α-carbon are likely to end up in skeletal rearrangements, and S_N2 reactions are excluded for steric reason. Addition of a metal hydride or organometallics to an α,α′ -dioxospirane gives diols which are sensitive to ring opening reactions, especially when the carbon substituent is an arene or the system is an annelated arene derivative.[9,10]

In this work we have chosen an alternative approach which avoids the intermediacy of 1,3-diols. Palladium-catalyzed cross-coupling carbylation reactions of enolate derived substrates are reported. The initial substrate in the reaction sequences were to be the corresponding triflates. The intermediate compound **8** that was prepared in previous chapter (**chapter 1**) was to be substrates for carbylation reactions.

3.2. Palladium as catalyst

Until about 1970, palladium had been mainly used to reduce and oxidize organic compounds, Pd-catalysed hydrogenation and Wacker oxidation being representative examples.[11] Over the last few decades, however, palladium has emerged as one of most useful metals in organic synthesis, especially for the formation of carbon-carbon bonds.[12] The ready accessibility of two oxidation states, *i.e.*, 0 and 2, and the readily reversible interconversion between the two oxidation states as well as the ready availability of Pd-containing species simultaneously one or more empty and filled non bonding orbitals are a few of the important factors that are responsible for the versatility and usefulness of Pd complexes as catalysts.

Specifically, palladium readily participates in oxidative addition, carbometalation, migratory insertion, nucleophilic substitution, and reductive elimination leading to carbon-carbon bond formation. Reductive elimination is thought to be the critical step in the Pd-catalysed cross-coupling reaction developed the mid-1970s[13] while carbopalladation undoubtedly is the key step in the Heck reaction.[13] The Tsuji-Trost reaction is an example of carbon-carbon formation involving nucleophilic attack on organic ligands of palladium complexes.[14]

In this work the active Pd(0) catalyst was generated *in situ* from $Pd(dba)_2$, $Pd(dba)_3L$ (L=CHCl3) and $Pd(PPh_3)_4$. The catalytically active Pd species requires two vacant

coordination sites for the initial oxidative addition (i) → (ii) to occur (figure 3.1) and (figure 3.3). Thus when generating Pd (0) *in situ* it is usually advantageous to use 1:2 molar ratio of Pd (II) to phosphine.[15] $Pd(0)L_4$ is coordinatively saturated and catalytically inactive.

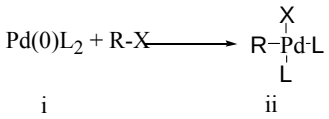


Figure 3.1

3.2.1 Preparation of palladium(0) complexes

The most extensively developed oxidative addition / transmetallation chemistry involves palladium(0)-catalysis and transmetallation with Li, Mg, Zn, Zr, B, Al, Sn, Si, Ge, Ti, Cu and Ni. There is a large literature on the subject, A very wide range of palladium catalysts or catalyst precursors have been used (figure 3.2).
These catalysts include preformed, stabile palladium (0) complexes such as $Pd(PhPh_3)_4$, ("tetrakis") $Pd(dba)_2/Pd(dba)_3.CHCl_3$ plus phosphine.[62]

In situ palladium(0) phosphine complexes, was prepared by reducing palladium(II) complexes in the presence of phosphines. Naked or ligandless palladium(0) species, including, in some cases, palladium on carbon. It should be noted that palladium(II) is very readily reduced to palladium(0) by alcohols, amines, CO, olefins, phosphines, and main group organometallics.[63]

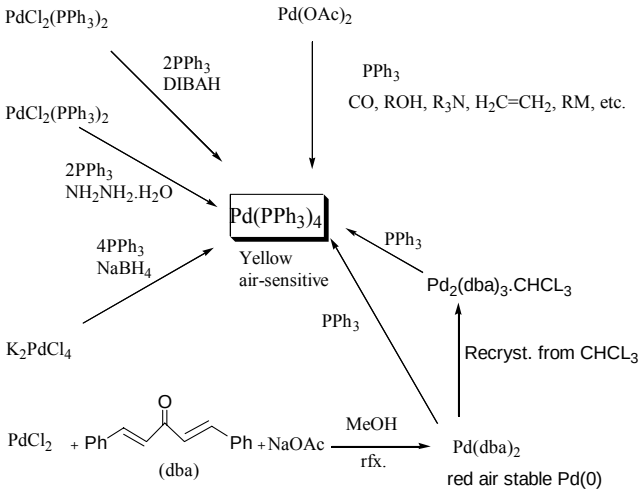


Figure 3.2

3.2.2 Mechanism of oxidative addition /transmetalletion

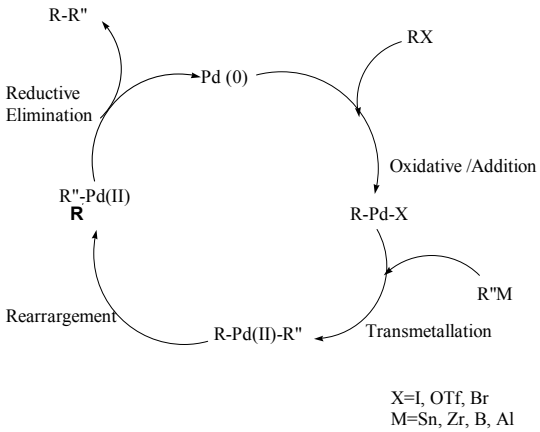


Figure 3.3 oxidative addition /transmetallation

3.3 Synthesis of 1,4-dioxa-dispiro[4.0.5.4]pentadecan-7-one (9)[16]

The synthesis of 1,4-dioxadispiro[4.0.5.4]pentadecan-7-one (**9**) has not been reported. The saturation of the double bond in the compound **8** was done by addition of hydrogen gas (1 bar) to the mixture of substrate **8** and 10% palladium on charcoal as a catalyst in ethanol. The mixture was stirred at room temperature 2 days. Compound **9** was isolated in 93% yield (figure 3.4).

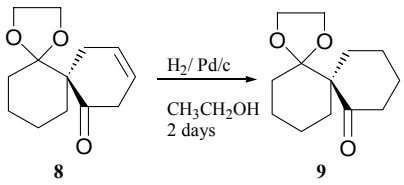


Figure 3.4 Hydrogenation of the double bond in 8

3.4 Synthesis of spiro[5.5]undecane-1,7-dion (10) [16]

3.4.1 Method 1

The methodology for the preparation of the compound **10** was the same as that described in 3.3. However, the reaction time was longer in order to remove the protecting group as well as to reduce the double bond. After 7 days, the catalyst was filtered off and compound **10** was isolated in 60% yield as a white crystalline solid. In addition, compound **9** was produced in 30% (figure 3.5).

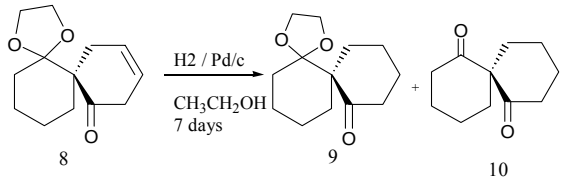


Figure 3.5

3.4.2 Method 2: hydrolysis of compound 9 in the preparation of synthesise 10[17]

Hydrolysis of the monoprotected spirane **9** was performed by dilute aqueous HCl (5 M) in CH_2Cl_2. The reaction was stirred at ambient temperature overnight. Compound **10** was isolated in 95% yield (figure 3.6).

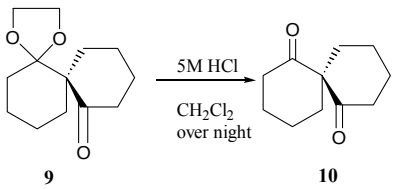


Figure 3.6

3.5 Synthesis of trifluoromethanesulfonic acid 7-oxospiro[5.5]undec-1-ylester (11) [59]

Triflation of the 1,7-diketone **10** was effected by $PhNTf_2$ (phenyl-bis-trifluoromethyl-amine) using LiHMDS (lithium hexamethyl disilazane) as base in THF at -78 ^{0}C over night. The monotriflated product **11** was isolated in 60% yield (figure 3.7).

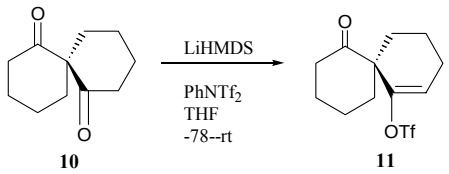


Figure 3.7 Triflation of diketone 10

3.6 Synthesis of triflоromethanesulfonic acid-8-methylene-7 triflоromethansulfonyloxyspiro[5.5]undec-1-yl ester (12) [18]

Triflation of 1,7-diketone **10** was effected by Tf_2O (triflic anhydride) using pyridine as a base in dichloromethane, at -78 ^{0}C . After **7** days at ambient temperature the ditriflated product **12** was isolated in (5%) yield. The most of substrate was converted to monotriflated **11** isolated in 50% yield. (figure 3.8).

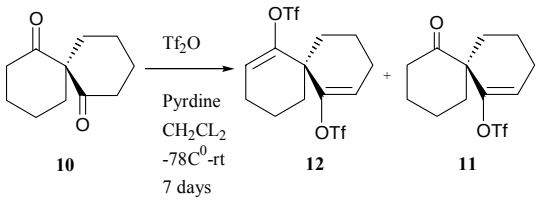


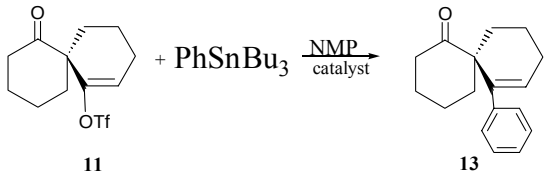
Figure 3.8

3.7 Synthesis of 7-phenyspiro[5.5]undec-7-en-1-one (13)

The phenyl derivative 13 was formed by using two different Pd-catalyst.

3.7.1 Method 1[18]

To a solution of compound 11, Pd(dba_2) in *N*-methyl-2-pyrrolidinone (NMP) as the week coordinating donor, phenyltributylstannane ($PhSnBu_3$) was added under argon. The solution mixture was stirred at ambient temperature for 4 h but there was no sign of product. The solution was heated gradually while monitoring the reaction on TLC, GC until a temperature of 50 ^{0}C was achieved. After 6 h, there was one new spot on the TLC. The temperature was elevated to 80 ^{0}C and the solution mixture was stirred over night. The product was purified by using flash chromatography. The product **13** was isolated in 50% (figure 3.9).



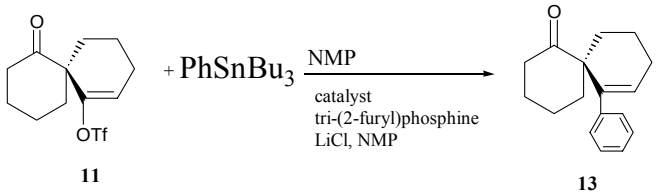
11 **13**

Figure 3.9

3.7.2 Method 2 [58]

The attempt to increase the yield by using more active, less strongly coordinated Pd-catalyst, generated from Pd($dba)_3$·$CHCl_3$.

A NMP solution containing compound **11**, $Pd_2(dba_2)_3$·$CHCl_3$, tri-(2-furyl)phosphine as ligand for palladium in the presence of lithium chloride and phenyltributylstannane were heated to 80 ^{0}C over night. The product **13** was isolated in 60% (figure 3.10).



11 **13**

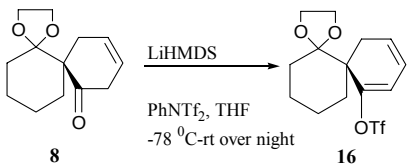
Figure 3.10

Catalyst	***Temperature***	***Yield***
$Pd(dba)_2$	Rt	0%
	50 ^{0}C	23%
	80 ^{0}C	50%
$Pd_2(dba)_3 \cdot CHCl_3$	80 ^{0}C	60%

3.8 Synthesis of trifluoromethanesulfonic acid 1,4-dioxa-dispiro[4.0.5.4]pentadeca-7,9-yl ester (16) [59]

The method for triflation of 7,7-ethylenedioxyspiro[5.5]undecan-3-en-one **(8)** was the same as that of the 1,7-diketone **10** (see 3.5)[59] (figure 3.7).

In this case, the product **16** was isolated in the high yield, between (80%-90%). The reason for high yield is probably that the α-proton in compound **8** is further activated by the β-δ double bond (figure 3.11).



8 **16**

Figure 3.11

3.9 Synthesis of 7-phenyl-1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-diene (17) [18]

The coupling between the monotriflate **16** and phenyltributylstannanes was effected with (dibenzylideneacetone)palladium by warming a solution in NMP containing lithium chloride. The product **17** was isolated in good yield (figure 3.12).

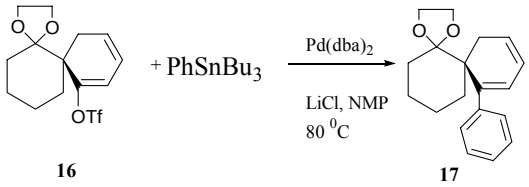


Figure 3.12

3.10 Synthesis of 7-phenylspiro[5.5]undecan-1-one (18) [16]

The saturation of double bounds in the compound **17** and removal of the protecting group at the same time was done by addition of hydrogen gas (1 bar) to the mixture of substrate **17** and 10% palladium on charcoal as a catalyst in ethanol. The mixture was stirred at room temperature for 3 days. Compound **18** was isolated in good yield 75% (figure3.13).

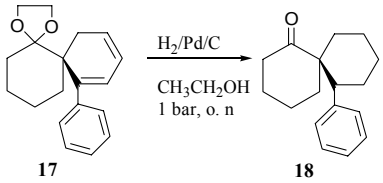


Figure 3.13

3.11 Synthesis of trifluoro-methansulfonic acid 7-phenyl-spiro[5.5]undec-1en-1-yl ester (19) [18]

Triflation of monosubstituted ketone **18** was effected using triflic anhydride. The solution was stirred at ambient temperature for 2 days. The reaction was examined by TLC and GC which showed that the starting material was reacted. The compound **19** was isolated in 88%. See figure 3.14.

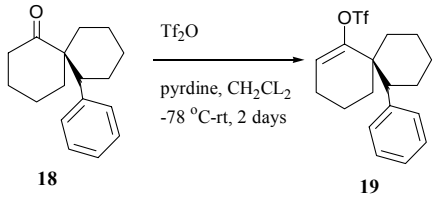


Figure 3.14

3.12 Synthesis of 2-(7-phenyl-spiro[5.5]undec-1-en-1-yl-thiophene (20)

The reactions were performed with different Pd- catalysts, different solvents and under different temperatures.

3.12.1 Attempts to prepare compound 20 using $Pd(Ph_3P)_4$ as catalyst.

Trifluoromethansulfonic acid 7-phenyl-spiro[5.5]undec-1-en-1-yl ester (**19**), tributyl-thiophen-2-yl-stannane (2 eq) and $Pd(Ph_3P)_4$ (10%) were dissolved in dry dioxane under argon. The reaction was warmed and stirred at (50 ^{0}C - 70 ^{0}C) overnight. The reaction was monitored on both TLC and GC. After 18 h, TLC showed that there was only unreacted starting material **19**.

In this case, there are many reasons why this reaction could not be effected. Firstly, the oxidative addition did not occur because $Pd(Ph_3P)_4$ is coordinatively saturated and catalytically inactive. If the oxidation addition had taken place, probably the transmetallation

with unreactive tinreagent would not take place because the sterice hindrance is very large on this side (figure 3.15).

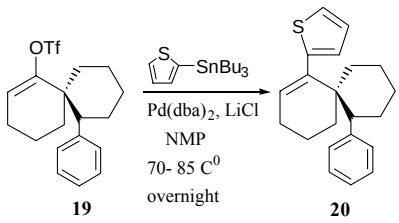


Figure 3.15

3.12.2 Method(I) to synthesis 20 using $Pd(dba)_2$ as catalyst.[18, 58]

In this attempt it was decided to try a more active, less strongly coordinated Pd-catalyst, generated from $Pd(dba)_2$ in the presence of LiCl, NMP (N-methyl-2-pyrrolidene) was used as the coordinating donor instead of dioxane. It was found that NMP allowed coupling to proceed at an appreciable rate.

Compound **19**, $Pd(dba)_2$ and LiCl weredissolved in NMP. After 10 min, tributylthiophen-2-ylstannane was added. The reaction was heated to 70 ^{0}C – 80 ^{0}C overnight under argon and monitored on both TLC and GC. After purification by flash chromatography, the desired product was isolated in only 10% yield (figure3.16).

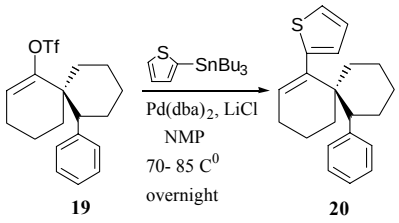


Figure 3.16

3.12.3 Method(II) to synthesise 20 using $Pd_2dba_3 \cdot CHCl_3$ as catalyst. [58]

This methodology was the same as that described in method (I) (figure 3.12) exept that a Pd-catalyst with weaker ligands, such as $Pd_2dba_3 \cdot CHCl_3$ in stead of $Pd(dba)_2$, were used.

Tri-(2-furyl)phosphine is a ligand that is a better σ-donor which can substitute with dibenzylidene acetone (dba = PhCH=CO-CH=Ph) a week coordinator palladium to generate a more active Pd-catalyst.[64] In this case, compound **20** was isolated in 40% yield (figure 3.17).

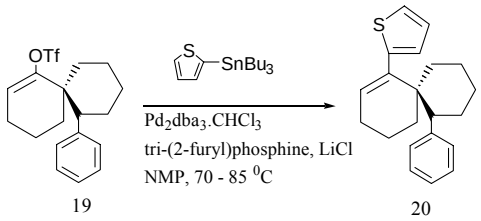


Figure 3.17

3.12.4 Results and Discussion

Steric hindrance might have been one of the key reasons for the low yields. But during the three experiments in 3.12 we found that when the activity of the Pd-catalyst was increased and the yield was increased, in addition, under these conditions, the catalyst decomposed during the reaction, resulting in lower conversions. However, with the $Pd_2dba_3 \cdot CHCl_3$ catalyst in NMP (figure 3.13), a fast reaction was obtained. NMP was less reactive towards these catalysts.

Lithium chloride is essential for the success of the reaction. In absences of LiCl decomposition of the catalyst took place.

3.13 Synthesis of 2-(7-phenyl-spiro[5.5]undeca-1,7,9-trien-1-yl)-thiophene (15)[20]

Transmetallic of allyl or aryl groups from organoboranes is difficult to effect. Addition of anionic base to neutral organoboranes dramatically increases the nucleophilicity of the organic groups and transmetallation from boron to palladium can be achieved. This is the basis of the Suzuki reaction. [19]

Compound **14** and 2-thiopheneboronic acid were heated at 100 ^{o}C overnight in DME to which had been added 2 M Na_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$. EtOAc and water were added to the cold reaction mixture and the layers separated. The aqueous phase was extracted, and the combined organic extracts washed with dilute aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a blue oil. The product **15**[20] was isolated by flash chromatography to give 70% of a colourless oil (figure 3.18).

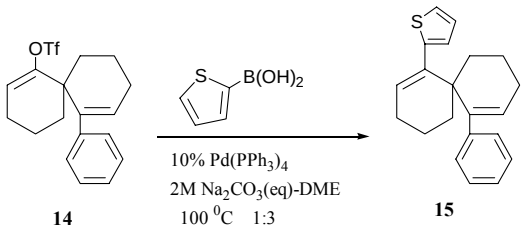
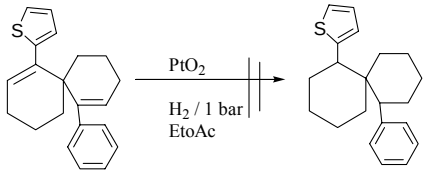


Figure 3.18

3.14 Attempts to synthesise 2-(7-phenyl-spiro[5.5]undec-1-yl)-thiophene (21)[21]

A mixture of compound **15** and 20% of PtO_2 in ethyl acetate under H_2 (1 bar) was stirred at ambient temperature. The reaction was monitored on both TLC and GC. After 6 h TLC showed that a new product has been formed. GC showed that only a small part of the starting material has reacted. The reaction was left to continue for 4 days. The reaction was stopped and the crude product was purified by flash chromatography. Three fractions were collected.

^{1}HNMR, ^{13}CNMR and MS showed that none of these fractions was the expected compound (figure3.19).



15 21

Figure 3.19

3.13 Conclusion

Carbosubstitutions in spirene triflates can be effected by Pd-catalysed coupling with stannylated or boronated arenes. Differential carbosubstitution resulted from stepwise triflation and coupling in spiro[5.5]undecane-1,7-dione (**10**).

In our group, satisfactory monotriflation using $PhNTf_2$ (benzyl-bis-trifluoromethylamine) with LiHMDS as a base in THF, initially at -78 ^{0}C has been achieved. Ditriflation was more difficult and ditriflated material was only formed the low yield.

A different Pd catalysts was used because Pd complexes have different reactivities. Some of the reasons for not obtaining the target molecules, could be either steric effects or because a right reaction condition was not obtained. In Jiro Tsuji s book,[61] it has been stated that the generation of Pd(0) *in situ* is not an easy process and in some cases the catalytic process will not work. Sometimes $Pd(PPh)_3$ is less active as catalyst because it has too many ligands to allow the coordination of some reactions.

Also when the coupling was done in the presence of tri-(2-furyl)phosphine and LiCl, a better result was obtained. The reason for the lower yield using
$Pd_2dba_3{\cdot}CHCl_3$, is probably due to steric reasons.

Chapter 4

Experimental

General

All glassware was oven-dried at 120 ^{o}C overnight before use. Most of the experiments were run in an argon or nitrogen atmosphere. Nitrogen was dried with concentrated H_2SO_4. Dry THF, benzene and toluene were distilled from sodium and benzophenone. Benzene and toluene were degassed by bubbling argon through the solvents. Dry hexane and dichloromethane were dried using molecular sieve. Dry NMP was used under an argon atmosphere. Silica gel for flash chromatography was MERCK Kiselgel 60 (F_{254}).

NMR Spectroscopy

^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz, 300 MHz, or 500 MHz using Bruker DPX 200, DPX 300, or DPX 500. ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz, and 125 MHz using the instruments mentioned above respectively. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm), and $CDCl_3$ (77.0 ppm) as references. In addition, other NMR techniques such as DEPT, COSY, HETCOR, COLOC and proton-proton decoupling were used to assign the peaks.

Mass Spectroscopy

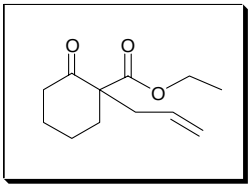
Mass spectra were recorded using a VG Prospec instrument under electron impact conditions at 70 eV (EI). NH_3 was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.).

IR Spectroscopy

IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet Magna FT-IR 550 spectrometer (ATR spectra).

4.1 Experimental for Chapter 1

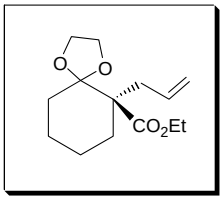
Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate (2)[60]



A solution of ethyl 2-oxocyclohexane-1-carboxylate (6.7 g, 39.41 mmol) in THF (60 ml) was added dropwise to a solution of sodium hydride (1.01 g, 43.27 mmol, 55-65% moistened with oil) in THF (60 ml). The mixture was stirred at ambient temperature for 1 h before a solution of allyl bromide (5.2 g 43.35 mmol) in THF (60 ml) was added dropwise over 30 min.
The mixture was left at ambient temperature overnight, the solvent distilled off, the residual material redissolved in ethy acetate (250 ml) and the solution washed with brine (2 x 50), dried ($MgSO_4$) and the product isolated after flash chromatography using hexane –EtOAc 10:1, R_f 0.30. The product was a colourless oil (5.5 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.19 (3H, t, *J* 6.9 Hz, CH_3CH_2O), 1.39-1.93 (6H, m, 3 x CH_2), 2.21-2.29 (1H, dd, *J* 14.8 Hz, $CH_2CH=CH_2$), 2.34-2.38 (3H, m, 1H from CH_2,CH_2), 2.42-2.56 (1H, dd, *J* 14.7 Hz, $CH_2CH=CH_2$), 4.07-4.14 (2H, q, *J* 7 Hz, CH_3CH_2O), 4.92-4.98 (2H, m, $CH_2CH=CH_2$), 5.59-5.71 (1H, m, $CH_2CH=CH_2$).

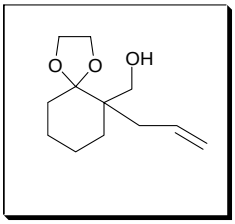
Ethyl 1-allyl-2,2-ethylenedioxycyclohexane-1-carboxylate (3)[60]



A solution of the cyclohexanone **2** (5.8 g, 28.0 mmol), ethylene glycol (5.7 ml), and *p*-toluenesulfonic acid (0.3 g) in benzene (200 ml) then distilled off, the residual material poured into 10% NH_3 (50 ml) and the mixture extracted with diethyl ether (3 x 50 ml). The combined etheral extracts were dried ($MgSO_4$), the ether distilled off and the residual material subjected to flash chromatography using hexane-EtOAc 8:1, R_f 0.29. The product (4.9 g, 85%) was a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.22 (3H, t, CH_3CH_2O), 1.35-1.94 (8H, m, 4 x CH_2), 2.21-2.32 (1H, dd, *J* 14.8 Hz, $CH_2CH{=}CH_2$), 2.68-2.80 (1H, dd, *J* 14, 6.5 Hz $CH_2CH{=}CH_2$), 3.80-3.89(4H, m, OCH_2CH_2O), 4.02-4.13(2H, q, *J* 7 Hz, CH_3CH_2O), 4.90-5.02(2H, m, $CH_2CH{=}CH_2$), 5.48-5.70 (1H,m,$CH_2CH{=}CH_2$).

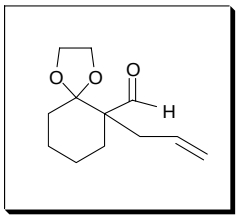
1- Allyl- 2,2-ethylenedioxycyclohexane-1-methanol (4)[60]



LAH (1.36 g, 0.036 mml) was added in five portions to a solution of the carboxylic ester **2** (5.28 g, 21 mml) in dry THF (80 ml) at 0 ^{0}C and the mixture stirred at this temperature for 1 h and at ambient temperature overnight. Excess LAH was destroyed with saturated NH_4Cl, the mixture extracted with ethyl acetate (3 x 50 ml), the combined organic extracts dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography using hexane-EtOAc 5:1, Rf o.15. The product (1.3 g, 93%) was a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.56 (8H, m, 4 x CH_2), 2.07-2.14 (1H, dd, *J* 14.2, 8.2 Hz, *CH_2*CH=CH_2), 2.29-2.36 (1H, dd, *J* 14.2, 8.2 Hz, *CH_2*CH=CH_2), 2.80-2.84 (1H, dd, *J* 7, 4 Hz, CH_2OH), 3.27-3.43 (1H, dd, J 12.7 Hz, CH_2OH), 3.66-3.71 (1H, dd, *J* 12.3 Hz, CH_2OH), 3.71-3.90 (4H, m, OCH_2CH_2O), 4.94-5.02 (2H, m, CH_2CH=*CH_2*), 5.70-5.79 (1H, m, CH_2*CH*=CH_2).

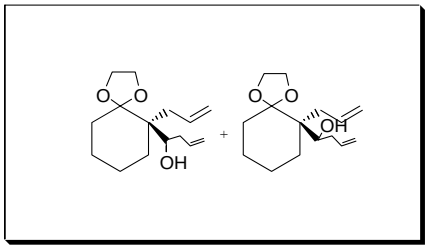
1-Allyl-2,2-ethylenedioxycyclohexane-1-carbaldehyde (5)[60]



A solution of **4** (1.26 g, 6.3 mmol)in dichloromethane (6 ml) was added rapidly to a suspension of pyridinium chlorochromate (2.04 g, 9.5 mmol) in dichloromethane (10 ml) at ambient temperature. The reaction mixture became a clear solution before precipitate appeared. TLC monitoring showed that the reaction had gone to completion after 6 h. The black reaction mixture was dilute with 5 volume of anhydrous diethyl ether the solvent decanted, the black solid washed twice with ether, the combined ether solution filtered through Florisil, the filtrate evaporated and the residual material subjected to flash chromatography using hexane- EtOAc 7:1. The product colourless oil (1.0 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35-1.50 (6H, m, 3 x CH_2), 1.59-1.87 (2H, m, CH_2), 2.20-2.28 (1H, dd, *J* 14.6 Hz, *CH_2*CH=CH_2), 2.57-2.64 (1H, dd, *J* 14.8 Hz, *CH_2*CH=CH_2), 3.82-3.93 (4H, m, O*CH_2CH_2*O), 4.92-4.98 (2H, m, CH_2CH=*CH_2*), 5.42-5.48 (1H, m, CH_2*CH*=CH_2), 9.62 (1H, s, CH=O).

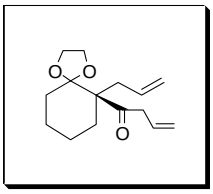
1-(Allyl-2,2-ethylenedioxycyclohexan-1-yl)-3-buten-1-ol (6a) and (6b)[60]



Allylmagnesium chloride (3.54 ml, 6.02 mmol, 1.7 M in THF) was added dropwise to a solution of the carbaldehyde **5** (0.84 g,4.3 mmol) in THF (10 ml) under argon at 0 ^{o}C. The reaction was stopped after 2 h by addition of saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml), the combined organic layers dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography using hexane:EtOAc 7:1 as eluent. The product as colourless oil (*6a:6b* 1:4 mixture) (0.7 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18-1.70 (8H, m, 4 x CH_2), 2.14-2.50 (4H, m, 2H from *CH_2*CH=CH_2, 2H from OH*CH_2*CH=CH_2), 3.58-3.63 (1H, s, CHOH(*6a*), m, CHOH(*6b*)), 3.86-3.98 (5H, m, 1H, CHOH, 4H, OCH_2CH_2O), 4.90-5.03 (4H, m, CH_2CH=*CH_2*, $CH(OH)CH_2CH$=*CH_2*), 5.81-5.93 (2H, m, CH_2*CH*=CH_2, $CH(OH)CH_2$*CH*=CH_2).

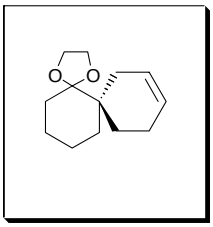
1-(Allyl-2,2-ethylenedioxylcyclohexan-1-yl)-3-buten-1-one (7)[60]



The mixture of the alcohol **6a** and **6b** (0.448 g,2 mmol) in dichloromethane (3 ml) was added rapidly to a suspension of pyridinium chlorochromate (0.648 g, 3 mmol) in dichloromethane (5 ml) at ambient temperature. The reaction mixture became briefly homogeneous before a black precipitate was formed. TLC monitoring showed that the reaction had gone to completion after 6 h. The black reaction mixture was diluted with diethyl ether, the combined ether solutions filtered through Florisil, the filtrate evaporated and the residual material subjected to flash chromatography using hexane- EtOAc 10: 1. The product was a colourless oil (0.32 g, 71 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40-2.10 (8H, m, 4 x CH_2), 2.27-2.37 (1H, dd, J14.5, 8.0 Hz, $CH_2CH{=}CH_2$), 2.72-2.82 (1H, dd, *J* 15.7 Hz, $CH_2CH{=}CH_2$), 3.21-3.44 (2H, m, $COCH_2CH{=}CH_2$), 3.79-3.94 (4H, m, OCH_2CH_2O), 4.90-5.05 (4H, m, 2 x $=CH_2$), 5.32-5.53 (1H, m, $CH_2CH{=}CH_2$), 5.78-5.99 (1H, m, $COCH_2CH{=}CH_2$).

7,7-Ethylenedioxyspiro[5.5]undecan-3-en-one (8)[60]

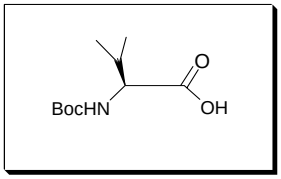


Bis(tricyclohexylphospine)benzylidene ruthenium dichloride (13 mg, 0.016 mmol) in dry toluene (3 ml), was added to a solution of the ketone **7** (0.150 g, 0.67 mmol) in dry toluene (20 ml) under argon. The mixture was stirred and heated at 60-70 ^{0}C for 1 h when another portion of bis(tricyclohexylphospine)benzylidene ruthenium dichloride (13 mg, 0.016 mmol) in dry toluene (3 ml) was added. The heating under argon was continued at 60-70 ^{0}C for 2 h. The cold reaction mixture was filtered, the filtrate evaporated the residual material to subjected flash chromatography using CH_2Cl_2:EtOAC 8:1 the product was a colourless oil (0.012 g, 92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04-1.09 (1H, m, from CH_2), 1.38-1.63 (5H, m, 2 x CH_2, 1H from CH_2), 2.01-2.11 (1H from CH_2), 1.38-1.63 (5H, m, 2 x CH_2, 1H from CH_2), 2.01-2.11 (1H, m, from CH_2), 2.15-2.28 (2H, m, CH_2), 2.52-2.60 (1H, m, CH_2), 2.70-2.95 (2H, m, CH_2), 3.75-4.00 (4H, m, OCH_2CH_2O), 5.52-5.58 (1H, m, CH=), 5.64-5.68 (1H, m, CH=).

4.2 Experimental for Chapter 2

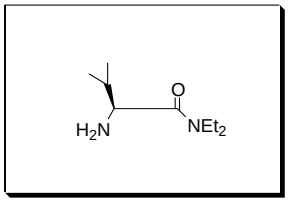
(S)-2-*tert*-Butoxycarbonylamino-3-methylbutyric acid (33) (method 2).[60]



A solution of *L*-valine **32** (1.2 g, 10 mmol), Boc_2O (2.2g, 10 mmol) and NaOH (0.44 g, 10 mmol) in *tert*-BuOH/H_2O (1:1) was stirred at room temperature overnight. The mixture was extracted with pentane to remove *tert*-BuOH and the aqueous phase was acidified with 20% $KHSO_4$ (pH 2) and then extracted with diethyl ether. The combined ether extracts were dried ($MgSO_4$), the ether distilled off and the residual material subjected to flash chromatography using diethyl ether: hexane 1:2. Yield 2.1 g, 95% of white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88-0.85 (3H, d, *J* 9 Hz, 3 x CH_3), 0.94-0.91 (3H, d, *J* 9 Hz, 3 x CH_3), 1.4 (9H, s, 3 x CH_3), 4.2-4.1 (1H, m, 1 x CH), 5.12-5.09 (1H, d, *J* 9 Hz, 1 x CH).

(S)-2-Amino-*N*,*N*-diethyl-3-methylbutyramide (35) (method 2)[67]

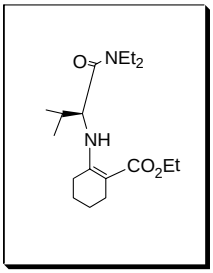


A solution of *N*-Boc-protected amino acid **33** (2 g, 9.2 mmol), and anhydride amide (1.5 g, 10 mmol) in CH_2Cl_2 was added dicyclohexylcarbodiimid (DCC) (2.1 g, 10 mmol) at 0 ^oC followed by addition of $NHEt_2$ (2.0 g, 28 mmol). The reaction was stirred at ambient temperature overnight. The reaction mixture was filtrered and the filtrered solution washed with 1M K_2CO_3. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product **34** was hydrolysed without any purification.

Crude product **34** and 5 eq TFA in CH_2Cl_2 was refluxed for 2 h and stirred at room temperature overnight. The reaction mixture was washed with saturated K_2CO_3 (pH 12). The product **35** was purified by flash chromatography and dried under high vacuum overnight (1.4 g, 70% yield) .

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87-0.85 (3H, d, *J* 6Hz, 3 x CH_3), 1.01-0.99 (3H, d, *J* 6 Hz, 3 x CH_3), 1.3-1.2 (3H, m, 1 x CH_3), 1.7-1.6 (3H, m, 1 x CH_3), 1.8-1.7 (2H, m, 1 x CH_2), 2.2-2.0 (2H, m, 1 x CH_2), 3.9-3.8 (2H, m, 2 x CH), 5.8 (1H, s, 1 x NH).

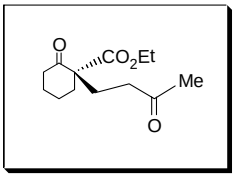
N-(2-Ethoxycarbonyl-1-cyclohexenyl)-*L*-valine diethylamide (22)[60]



A mixture of oxo ester compound **1** (1.7 g, 9.6 mmol), auxiliary **35** (1.4 g, 8 mmol) and molecular sieves (5 g) (4 Å) under nitrogen in toluene was treated with a catalytic amount of concentrated HCl (1 drop) and the mixture stirred at 60-65 ^{o}C overnight. The reaction mixture was filtered and the residue washed with CH_2Cl_2. All volatile materials were removed in vacuum and the residue was chromatographed on Al_2O_3 90 using diethyl ether :hexane (2:3). Compound **22** was isolated in (1.2 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, *J* 6.8 Hz, 3H), 1.02 (d, *J* 6.8 Hz, 3H), 1.24 (t, *J* 7.1 Hz, 3H), 1,45-1.66 (m, 4H), 1.98-2.10 (m, 2H), 2.18-2.31 (m, 3H), 2.96 (s, 3H), 3.07 (s, 3H), 4.07-4.18 (m, 3H), 9.27 (d, *J* 9.0 Hz, 1H).

Ethyl(*R*)- 2-oxo-1-(3-oxobutyl)cyclohexanecarboxlate (23).[60]



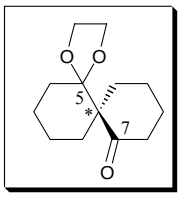
$Cu(OAc)_2 \cdot H_2O$ (16.55 mg, 0.08 mmol) was added to solution of enamine **22** (479 mg, 1.47 mmol) in acetone (15 ml). The mixture was stirred at ambient temperature until all solid had been dissolved (1 h). Methyl vinyl keton **36** (231 mg, 3.3 mmol) was added and the mixture was stirred for overnight at ambient temperature. The solvent was distilled off and the residue was treated with 1 M HCl.

The mixture was stirred vigorously for 3 h at 0 ^{0}C and subsequently extracted with diethyl ether, the mixture washed with 10% Na_2CO_3, saturated aqueous K_2CO_3 and dried over $MgSO_4$. The solvent was evaporated and the product was purified by flash chromatography on SiO_2 using hexane: diethyl ether (2:1). The product **23** was isolated as a colorless oil in (0.38 g, 80% yield). [α]= +96 (c= 0.1732 g in 10 ml CH_2Cl_2 96% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22-1.20 (3H, t, *J* 6.0 Hz,1 x CH_3), 1.97-1.25 (8H, m,4x CH_2 from cyclohexanone), 2.00 (3H, s, 1 x CH_3), 2.43-2.22 (4H, m, 2 x CH_2), 4.08-4.02 (2H, q, J 3.0 Hz, 1 x CH_3).

4.3 Experimental for Chapter 3

1,4-Dioxadisipro[4.0.5.4]pentadecan-7-one (9)



1,4-dioxadispiro[4.0.5.4]pentadec-9 en-7-one (**8**) (500 mg, 2.25 mmol) in ethanol (30 ml) was hydrogenated over 10% palladium on charcoal (500 mg, 0,5 mmol) at 1 bar at ambient temperature for 2 d. The catalyst was filtered off and the solvent evaporated. The crude product was purified by flash chromatography with hexane:EtOAc 20:1. (Yield 0.47 g, 93%) of yellow oil (**9**).

^{1}H NMR (300 MHZ, $CDCl_3$): δ 1.20-1.74 (12H, m, 6 x CH_2), 2.35 (4H, m, 2 x CH_2) 3.79-3.96 (4H, m, OCH_2-CH_2O).

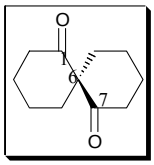
^{13}C NMR (75MHz, $CDCl_3$): δ 20.57 (CH_2) 21,1 (CH_2), 23.2 (CH_2), 27.2 (CH_2), 31.8 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 40.4 (CH_2), 56.0 (6C*), 64.1-64.0 (CH_2-CH_2), 110.9 (5C), 213.2 (7C).

MS(EI): 224 (M+, 26%), 179 (52), 99 (100), 86 (38).

HRMS: Calc for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1409

IR(film)νcm^{-1}: 2938 (C-H), 1702 (C=O)

Spiro[5.5]undecane-1,7-dione (10)



Method 1

1,4-Dioxadispiro[4.0.5.4]pentadec-9-en-7-one **8** (500 mg, 2.25 mmol) in ethanol (30 ml) was hydrogenated over 10% palladium on charcoal (500 mg, 0.5 mmol) at 1 bar at ambient temperature for 7 d. The catalyst was filtered off and the solvent evaporated. The crude product was purified by flash chromatography using hexane:EtOAc 20:1. (0.3 g, 60%) of a white crystalline solid. Some of product **10** (1,4-dioxa-dispiro[4.0.5.4]pentadecan-7-one) was also recovered in (0.15 g, 30%).

Method 2

A solution of the 1,4-dioxadisipro[4.0.5.4]pentadecan-7-one **9** (500 mg, 2.2 mmol) in CH_2Cl_2 (10 ml) and 5 M HCl (8 ml) was stirred overnight at ambient temperature. The mixture was extracted with diethyl ether (2 x 15 ml), washed with water, with saturated $NaHCO_3$ solution and brine. The solvent was evaporated, the crude product was purified by flash chromatography using hexan:EtOAc 6:1. The product **10** was isolated in 95% as a white crystalline solid.

MP: 49-50 ^{0}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-1.75 (12H, m, 6 x CH_2), 3.38-2.45 (4H, m, 2 x CH_2)

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (2 x CH_2), 21.6 (2 x CH_2), 27.7 (2 x CH_2), 36.2 (2 x CH_2), 40.8 (2 x CH_2), 64.5 (C), 210.9 (2 x C=O).

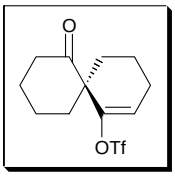
MS (EI): 180 (M+, 41%), 152 (57), 124 (70), 111 (61), 67 (63), 55 (95), 41 (100).

HRMS: Calc. for $C_{11}H_{16}O_2$: 180.1150. Found: 180.1146

Elemental Analysis: Calc. for $C_{11}H_{16}O_2$: C 73.09, H 9.04. Found C 73.30, H 8.95

IR(film)νcm^{-1}: 2900 (C-H), 1686 (C=O)

Trifluoromethanesulfonic acid 7-oxospiro[5.5]undec-1-en-1-yl ester (11)



LiHMDS (2.4 mmol) in THF (10 ml) was added dropwis to a solution of spiro[5.5]undecane-1,7-dion **10** (370 mg, 2.05 mmol) and $PhNTf_2$ (900 mg, 2.46 mmol) in THF (15 ml) under argon at – 78 ^{0}C. The mixture was allowed to reach ambient temperature overnight when GLC showed the reaction to be complete. Diethyl ether and water were added to the cold reaction mixture, the layers separated and the aqueous layer extracted with diethyl ether (2x). The combined ether solution was shaken with aqueous Na_2CO_3, dried over $MgSO_4$ and the solution evaporated to dryness. The product was isolated from the residual material after flash chromatography using hexane: EtOAc 10:1.The product **11** 222 mg (60%) was a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36-2.31 (12H, m, 6 x CH_2), 2.30-2.60 (2H, m, CH_2), 5.90 (1H, t, CH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH_2), 20.6 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 33.4 (CH_2), 34.8 (CH_2), 38.5 (CH_2), 54.5 (6-C), 86.7 (CF_3), 120.7 (CH), 149.8 (C-O), 209.6 (C=O).

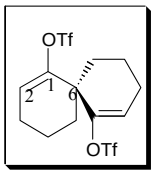
MS (EI): 313 (M^+,55%), 268 (30,8), 179 (138), 163 (100), 135 (62), 179(38).

HRMS: Calc for $C_{12}H_{15}O_4SF_3$: 313.0721. Found: 313.0713

Elemental Analysis: calc. for $C_{12}H_{15}O_4SF_3$ C 46.15%, H 4.84%. Found C 46.84%, H 4.76%

IR(film)νcm^{-1}: 2926, 2855 (C-H), 1710 (C=O)

Triflоromethanesulfonic acid8-methylene-7-triflоromethansulfonyloxy-spiro[5.5]undeca-1,7-dien-1-yl (12)



Triflic anhydride (0.9 ml, 5.6 mmol) was added neat with a syringe to a solution of spiro[5.5]undecane-1,7-dione **10** (0.5 mg, 2.8 mmol) and pyridine (442 mg, 5.6 mmol) in dry dichloromethane (40 ml) at – 78 ^{0}C under argon. The reaction mixture was allowed to reach ambient temperature and stirred at this temperature for 7d. The solvent was evaporated and the crude product was purified by flash chromatography eluting with hexane;EtOAc 5:1. (Yield o.o25 mg, 5%) of a colourless oil.

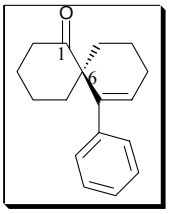
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56-1.91 (8H,m,4 x CH_2), 2.17-2.22 (4H, m, 2 x CH_2), 5.95-5.97 (2H, t, *J* $3H_Z$, 2 x CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 17.68 (2 x CH_2), 24.0 (2 x CH_2), 31.7 (2 x CH_2), 43.6 (C-6), 116.2 (q, 2 x CF_3), 120.3 (2 x CH), 148.6 (2 x C-O).

MS (CI): 444 (M+, 100%), 445(24), 446(16), 311 (9), 143 (20).

IR(film)νcm^{-1}: 1634 (C=C), 2880 (C-H).

7-Phenylspiro[5.5]undec-7-en-1-one (13)



Trifluoromethanesulfonic acid 7-oxospiro[5.5]undec-1-yl ester **11** (130 mg, 0,42 mmol), $Pd(dba)_3.CHCl_3$ (13 mg, 0.03 mmol), tri(2-furyl)phosphine (12 mg, 0.05 mmol) and LiCl (35.2 mg, 0.83 mmol) were dissolved in dry NMP (7 ml) phenyltributylstannane (1.6 ml, 0.5 mmol) was added with a syringe after 10 min. The solution was stirred at 80 ^{0}C for 16 h before treatment with 1 M aqueous KF solution (7 ml) for 30 min, diluted with ethyl acetate and filtered. The filtrate was washed with water (10 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with hexane:ETOAc 10:1; Yield (0.08 g, 60%) of a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23-1.66 (10H, m, 5 x CH_2), 1.80-1.87 (2H, m, CH_2), 2.20-2.61 (2H, m, CH_2), 5.93-5.96 (H, t, *J* 6 Hz CH=), 7.08-7.22 (5H, m, Ar).

^{13}CNMR (75 MHz, CDCL3): δ 18.1 (CH_2), 20.5 (CH_2). 25,6 (CH_2), 26.1 (CH_2), 34.4 (CH_2), 37.6 (CH_2), 38.5 (CH_2), 54.1 (C-6), 126.2, 127.8, 128.5 (C-H Ar), 130.5 (CH=), 141.1 (C-Ar), 142.7 (CH=), 213.9 (C=O)

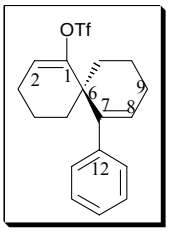
MS (EI): 240 (M^+, 100%) , 211 (77),169(31), 155(31), 141 (38), 91(27), 77 (15).

HRMS: calc. for $C_{17}H_{20}O$: 240,1514 Found: 240,1510

Elemental Analysis: calc. for $C_{17}H_{20}O$: C 79.98% H 8.50%. Found: C 80.82% H 7.85 %

IR(film)νcm^{-1}: 2938, 2862 (C-H), 3028 (C-H Ar), 1700 (C=O), 1600 (C=C)

Trifluoromethanesulfonic acid 7-phenyl-spiro[5,5]undeca-1,7-dien-1-yl ester (14)



Triflic anhydride (110.03 mg, 0.39 mmol) was added neat with a syringe to a solution of 7-phenyspiro[5.5]undec-7-en-1-one **13** (63 mg, 0.262 mmol) and pyridine (30.81 mg, 0.39 mmol) in dry CH_2Cl_2 (6 ml) at -78 ^{0}C under argon. The reaction mixture was allowed to heat slowly to ambient temperature over 24 h. The solvent was purified by flash chromatography eluting with hexane: EtOAc 10:1; yield (90%) of a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3-2.2 (12H, m, 6 CH_2), 5.80 (dd, 2.75, *J* 2.72 Hz, 1H, CH=), 5.86 (t, *J* 4.01 Hz,1H, CH=), 7.2-7.3 (5H, m, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9 (CH_2), 17.3 (CH_2), 23.4 (CH_2), 24.4 (CH_2), 31.5 (CH_2), 32.8 (CH_2), 42.0 (C-6), 117.1 (CH-2), 116.9 (q, CF_3), 125.7, 126.7, 128.1, 139.7 (Ar), 130.7 (CH-8), 140.9 (C-7), 151.9 (C-1).

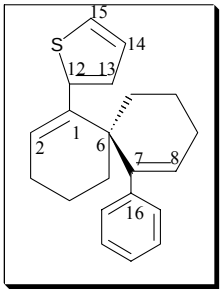
MS (EI): 372 (M+, 27%), 222 (29), 130 (100), 117 (39), 91(9).

HRMS*:* Calc. for $C_{18}H_{19}O_3F_3S$: 372.1007. Found: 372.0986

Elemental Analysis*:* calc. for $C_{18}H_{19}O_3F_3S$: C 57.36% H 5.87%. Found: 57.74% H 5.65%

IR(film)νcm^{-1}: 2910 (C-H), 3020 (C-H Ar), 1672 (C=C)

2-(7-Phenylspiro[5.5]undeca-1,7-dien-1-yl)thiophene (15).



Trifluoromethanesulfonic acid 7-phenylspiro[5,5]undeca-1,7-dien-1-yl ester **14** (300 mg, 0.81 mmol), and 2-thiophene boronic acid[20] (206.5 mg, 1.61 mmol), and $Pd(PPh_3)_4$ were dissolved in 2 M Na_2CO_3:DME (1:3). The reaction mixture was heated at 100 ^{0}C. After 4 h, TLC showed a new spot just over the starting material. The reaction mixture was stirred at same the temperature overnight. EtoOAc and water were added and the layers separated. The aqueous phase was extracted with EtOAc (3x30 ml) the combined organic extracts washed with dilute aqueous sodium bicarbonate, brine, and dried ($MgSO_4$) before the solvent was distilled off. Flash chromatography of the residual material using hexane:EtOAC 20:1 gave the product **15** as colourless oil; yield 70%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27-1.74 (8H, m, 4 x CH_2), 2.03-2.3 (4H, m, 2 x CH_2), 6.00-6.03 (1H, t, *J* 9.0 Hz, CH-8), 6.26-6.29 (1H, dd, *J* 3.0 Hz, *J* 3.0 Hz, CH-2), 6.87-6.90 (1H. dd. *J* 3.0 Hz, *J* 3.0 Hz, CH-14), 7.00-7.07 (1H, t, *J* 3.0 Hz, CH-13), 7.23 (1H, s, CH-15), 7.16-7.33 (5H, m, CH-Ar).

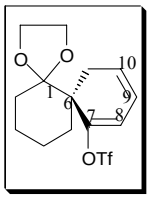
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 CH_2, 18.2 CH_2, 26.1 CH_2, 26.2 CH_2, 34.7 CH_2, 34.9 CH_2, 42.7 (C-6), 123.0 (C-14), 124.2 (C-13), 126.3 (C-15), 126.9 (C-Ar), 127.6 (2 x C-Ar), 128.8 (2 x C-Ar), 129.3 (C-8), 130.6 (C-2), 138.3 (C-16), 143.1 (C-7), 144.8 (C-1), 146.3 (C-12).

MS (EI): 306 (M^+, 24%), 302(16), 208 (100), 212 (29), 176 (12), 91 (38).

HRMS: calc. for $C_{21}H_{22}S$: 306.1442. Found: 306.1430

IR(film)νcm^{-1}*:* 1618 (C=C), 2824-2966 (C-H), 3072 (C-H Ar)

Trifluoromethanesulfonic acid 1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-dien-7-yl ester (16)



1 M LiHMDS (600 mg, 3,76 mmol) in THF (15 ml) was added dropwise to a solution of 1.4-dioxadispiro[4.0.5.4]pentadec-9-en-7-one **8** and $PhNTf_2$ (1360 mg, 3.8 mmol) in THF (10 ml) under argon at -78 ^{0}C. The mixture was allowed to reach ambient temperature overnight when GLC showed the reaction to be complete. Diethyl ether and water were added to the cold reaction mixture, the layers separated, the aqueous layer extracted with diethyl ether (2x), the combined ether solution shaken with aqueous Na_2CO_3, dried over $MgSO_4$ and the solution evaporated to dryness. The product was isolated from residual material after flash chromatography using hexane: EtOAc 10:1.The product **16** was a yellow oil, (yield 1.1 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51-1.71(6H, m, CH_2), 2.15 (2H, m, CH_2), 2.36 (2H, m, CH_2), 3.79-4.04 (4H, m, CH_2), 5.7 (H, t, *J*3.0 Hz CH=) 5.77 (1H, dd, *J* 3.0, 3.0 Hz CH=) 5.95 (H, d, *J*6 Hz CH=).

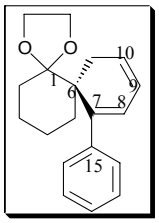
^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_2), 23.5 (CH_2), 30.5 (CH_2), 34.0 (CH_2), 35.2 (CH_2), 45.0 (C-6), 64.7 (CH_2), 65.9 (CH_2), 117.0 (q, CF_3), 118.5 (CH), 120.5 (CH), 127.8 (CH), 130.2 (C-1), 151.7 (C-7).

MS (EI): 354 (M^+, 31.57), 353 (100), 220 (27.88), 99 (46.22), 55(23).

HRMS: calc. for $C_{14}H_{17}O_5F_3S$: 354.0749. Found: 354.0731

IR(film)νcm^{-1}: 2950 (C-H), 1664 (C=C)

7-Phenyl-1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-diene (17)



Trifluoromethanesulfonic acid 1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-dien-7-yl ester **16** (860 mg, 2,43 mmol) and $Pd(dba)_2$ (130 mg, 0.12 mmol) were dissolved in dry NMP (20 ml) phenyltributyltin (0.95 ml, 2.90 mmol) was added with a syringe after 10 min. The solution was stirred at ambient temperature for 4 h before treatment with 1 M aqueous KF solution (9 ml) for 30 min, diluted with ethyl acetate and filtered. The filtrate was washed with water (2x), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with hexan:EtOAc 10:1; yield 0.64 g, 75% of a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19-1.68 (8H ,m, 4 x CH_2), 2.72-2.73 (2H, m, CH_2), 3.22-3.83 (4H, m, 2 x CH_2), 5.71-5.78 (2H, m, 2 x CH), 5.89-5.92 (1H, m, CH), 7.11-7.25 (5H, m, 5 x CH Ar).

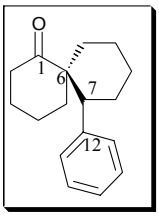
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7 (CH_2), 22.3 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 33.1 (CH_2), 44.1 (C-6), 62.3 (CH_2), 63.8 (CH_2), 112.6 (C-7), 123.2 (CH), 124.2 (CH), 124.7 (CH Ar)125.5 (2 x CH Ar), 126.4 (CH), 128.6 (2 x CH Ar), 143.1 (C-15), 143.8 (C-1).

MS (EI): 282 (M^+, 45%), 281 (44), 220 (83), 167 (79),165(55), 128(37), 99 (56), 73 (100).

HRMS: calc. for $C_{19}H_{22}O_2$: 282.1620. Found: 282.1623

IR(film)νcm^{-1}: 1653 (C=C), 2950 (C-H), 3451 (C-H Ar)

7-Phenylspiro[5,5]undecan-1-one (18)



7-Phenyl-1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-diene **17** (220 mg, 0.78 mmol) in ethanol (30 ml) was hydrogenated over 10% palladium on charcoal (440 mg) at 1 bar at ambient temperature for 3 d. The catalyst was filtered off and the solvent evaporated. The crude product was purified by flash chromatography with hexane:EtOAc 20:1. Yield 1.6 g, (75%) of white solid.

Mp 88 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.8 (12H, m, CH_2), 2.0 -2.4 (4H, m, CH_2), 2.6-2.7 (1H, m, CH), 7.1-7.3 (5H, m, Ar).

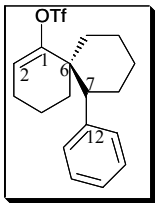
^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0 (CH_2), 21.1 (CH_2), 25.9 (CH_2), 26.4 (CH_2), 29.6 (CH_2), 36.8 (CH_2), 38.8 (CH_2), 40.1 (CH_2), 52.4 (C-6), 53,9 (CH) 125.9, 127.6, 130.4 (CH-Ar), 143.6 (C-Ar), 162.3 (C-7), 214.5 (C=O).

MS (EI): 242 (M^+,100%), 129 (51), 111 (65), 98(50), 91(60), 39 (52).

HRMS: calc . for $C_{17}H_{22}O$: 242.1670. Found: 242.1664

IR(film)νcm^{-1}: 1702 (C=O), 2900 (C-H), 3030 (C-H Ar).

Trifluoromethansulfonic acid 7-phenylspiro[5,5]undec-1en-1-yl ester (19)



Triflic anhydride (0,05 ml) was added neat with a syringe to a solution of 7-phenyl-spiro[5,5]undecan-1-one **18** (50 mg, 0,21 mmol) and pyridine (24,5 mg, 0,31 mmol) in dry CH_2Cl_2 (6 ml) at -78 ^{0}C under argon. The reaction mixture was allowed to slowly reach ambient temperature over 24 h . The solvent was purified by flash chromatography eluting with hexane: EtOAc 10:1; yield (0.04 g, 88%) of colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42-2.20 (14H, m, CH_2), 2.55 (1H, m, CH), 5.71 (1H , t, *J* 3.0 Hz, CH), 7.16-7.23 (5H, m, C-H Ar).

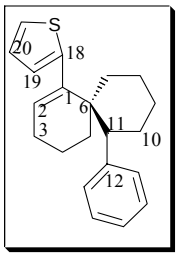
^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0 (CH_2), 22.5 (CH_2), 24.9 (CH_2), 26.1 (CH_2), 30.6 (CH_2), 39.2 (CH_2), 40.2 (CH_2), 42.1 (C-6), 54.5 (CH), 116.6 (q, CF_3), 117.4 (CH), 126.9, 128.5, 129.5 (CH Ar), 143.7 (C Ar), 155.6 (C-O).

MS (EI): 374(M^+, 37%), 224 (25), 132 (61), 91 (100),

HRMS: calc. for $C_{18}H_{21}O_3F_3S$: 374.1164. Found: 374.1185

IR(film)νcm^{-1}: 1664 (C=C), 2890 (C-H), 3029 (C-H Ar)

2-(7-Phenylspiro[5,5]undec-1-en-1-yl)thiophene (20)



Trifluoromethansulfonic acid 7-phenylspiro[5,5]undec-1-en-1-yl ester **19** (0.05 mg, 0.16 mmol) , $Pd(dba)_2$ (8,28 mg, 0.008 mmol) and LiCl (14 mg, 0.32 mmol) were dissolved in dry NMP (5 ml). Tributyl(thiophen-2-yl)stannane (71.76 mg, 0.19 mmol) was added with a syringe after 10 min. The solution was stirred at 70 ^{0}C overnight before treatment with 1 M aqueous KF solution (7 ml) for 30 min, diluted with ethyl acetate and filtered. The filtrate was washed with water (3x), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with hexane:EtOAc 5:1; yield (0.005 mg, 10%) of colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24-1.80 (10H, m, 5 x CH_2), 2.03-2.07 (2H, m, CH_2), 2.20-2.29 (2H, m, CH_2), 2.86-2.91 (1H, t, *J* 10.0 Hz, CH-11), 5.71-5.75 (1H, t, *J* 7.8 Hz, CH-2), 6.04-6.08 (1H, d, *J* 3.4 Hz, CH-19), 6.64-6.68 (1H, dd, *J* 3.57 Hz, *J* 3.61 Hz, CH-20), 6.94-6.97 (1H, d, *J* 5.12 Hz, CH), 7.11-7.32 (5H, m, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0 (CH_2), 21.6 (CH_2), 23.5 (CH_2), 25.6 (CH_2), 29.7 (CH_2), 36.4 (CH_2), 36.7 (CH_2), 41.2 (C-6), 50.5 (C-11), 123.7 (C-2), 125.7 (CH-phenyl), 128.6 (2 x CH-phenyl), 130.3(2 x CH-phenyl), 139.2 (C-12), 126.2 (2 x CH-thiophene), 134.2 (CH-thiophene), 147.1 (C-18 thiophene), 146.7 (C-1).

MS (EI): 308 (M^+, 100%), 309(23), 189 (43), 177(21), 175 (40), 164 (34), 91(24), 77 (5)

HRMS: calc. for $C_{21}H_{24}S$: 308.1599. Found: 308.1612

IR(film)νcm^{-1}: 1620 (C=C), 2920 (C-H), 3059 (C-H Ar)

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