5-*N*,*C*-DISUBSTITUTED CYCLOPENTADIENES FOR FACIALLY SELECTIVE DIELS-ALDER REACTIONS

by

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Abstract

This thesis describes research on the Diels-Alder facial selectivities of 5-*N*,*C*-disubstituted cyclopentadienes. Two novel chiral cyclopentadienes were created, both display facial selectivity in Diels-Alder reactions. Moreover, the two cyclopentadienes display opposing facial selectivities, and thus allow tunable control of faciality. The results obtained in the course of these studies have important implications for ongoing synthetic efforts in our laboratory.

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Abbreviations

^{o}	degree (of angle or temperature)
θ	degree (of angle)
α	the position once removed from a reference point (i.e. a carbonyl)
Ac	acetyl
APT	attached proton test
aq.	aqueous
Ar	aryl group
atm	atmosphere (s)
β	the position twice removed from a reference point
B	generic base
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BPG	big protecting group
br	broad (as in a spectral feature)
Bu	butyl
^{o}C	degree Celsius
^{13}C	carbon-13
ca	about (Latin circa)
CBZ	carboxybenzylcarbamate
cf	compare (Latin confer)
cm^{-1}	wavenumbers

Cp	cyclopentadiene
CPBA	chloroperoxybenzoic acid
δ	chemical shift in ppm
d	doublets or day (s)
D, *d*	^{2}H, deuterium, deuteron
DBU	1,8-diazabicycloundec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
eq.	molar equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EWG	electron withdrawing group
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate
FT	Fourier-transform
g	gram (s)
hex	hexane (s)
HMDS	hexamethyldisilizane
hr	hour (s)

HR	high resolution
hν	irradiation
Hz	hertz
IBX	2-iodoxybenzoic acid
Im	imidazole
IR	infrared
J	coupling constant
K	degree Kelvin
LDA	lithium diisopropylamine
LG	leaving group
LR	low resolution
M^+	parent molecular ion
m	meta
m	multiplet
Me	methyl
mg	milligram (s)
mL	millilitre (s)
mmol	millimole (s)
mol	mole
MOM	methoxymethyl
Ms	methanesulfonyl
MS	mass spectrum / mass spectrometry
m/z	mass-to-change ratio

n	normal
(N)	nitrogenous group or a moiety which may be converted easily to nitrogen
NaCl	sodium chloride
NaH	sodium hydride
NBS	*N*-bromosuccinamide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o	ortho
p	para
PBB	*p*-bromobenzyl
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
q	quartet
R	hydrocarbyl group, unless otherwise defined
RT	room temperature
s	singlet, strong
sat.	saturated
SiR_3	generic silicon protecting group

t	tertiary
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyl dimethyl silyl
TES	triethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonic
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Tol	toluene
Ts	4-toluene sulfonyl
ν	stretching frequency
x	carbamate protecting group
xs	excess

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"*No battle plan survives first contact with the enemy.*"

-Helmuth von Moltke

1. INTRODUCTION

The research about to be discussed was motivated by a desire to explore synthetic avenues to palau'amine and related substances. These marine alkaloids display notable anti-cancer, antibiotic, antifungal, and immunomodulatory activity.[1,2] In addition, they exhibit a chemically intriguing structure that lends itself nicely to the development of new synthetic methodology. Thus, on both chemical and medicinal grounds, an enantioselective total synthesis of palau'amine represents a highly worthwhile pursuit. Indeed, considerable activity has been registered in this domain during the past few years.[3-31] These efforts culminated in 2009 with the first total synthesis of palu'amine by Baran and collaborators.[32-34]

The Baran synthesis served also to ascertain the relative configuration of the natural product, which had remained in doubt for some time. Specifically, the structure of the molecule was initially assigned as **1.1**.[1,2] However, the spectroscopic properties of synthetic compounds possessing a structure very similar to **1.1** were in disaccord with those of authentic material.[24] This prompted a structural revision to **1.2**.[35-38] A noteworthy feature of **1.2** is a *trans*-fused 3-azabicyclo[3.3.0]octane subunit, which is quite strained. Not surprisingly, such a proposal met with some skepticism, but synthetic **1.2** ultimately proved to be identical to natural palau'amine.

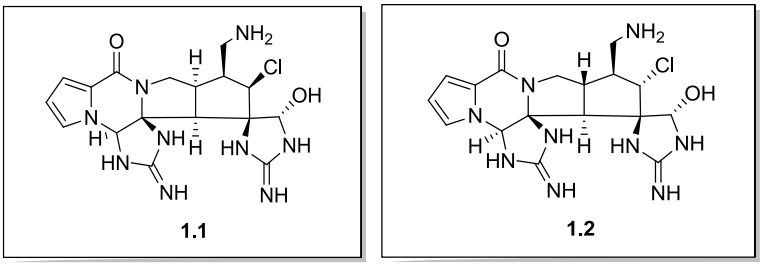
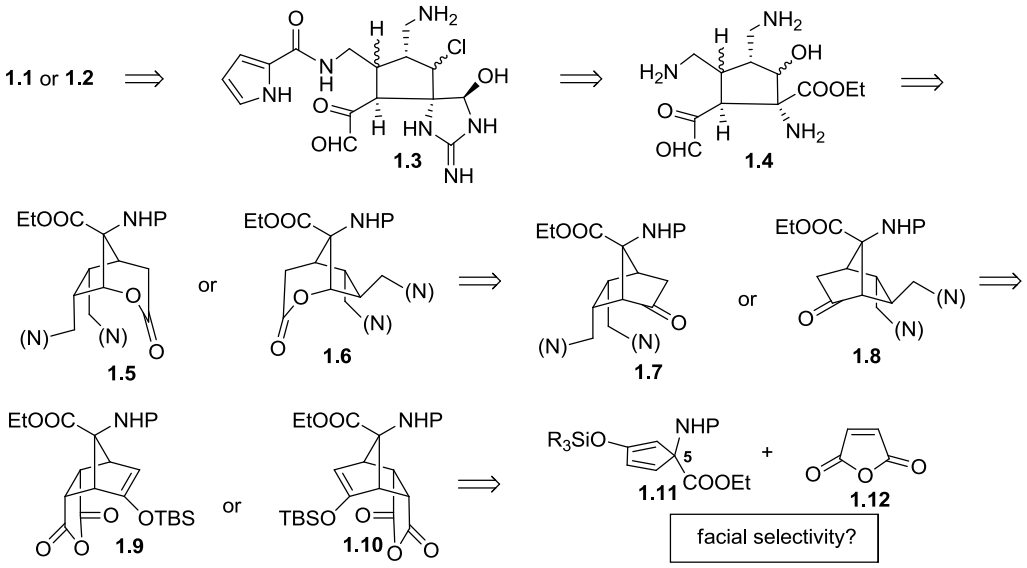


Figure 1.1. Putative and reassigned structures of palau'amine.

At the onset of our research, the relative configuration of the molecule was still uncertain; i.e., palau'amine could have been **1.1**, or **1.2**, or any other diastereomer of like constitution. Accordingly, we became interested in exploring a strategy that would permit access to stereochemical variants of structure **1.4** (Scheme 1.1). An opportunity was identified in the form of a facially selective Diels-Alder reaction of a chiral 2-siloxycyclopentadiene that incorporated both a nitrogenous functionality and a carbon substituent at position 5; e.g., **1.11**. Provided that the Diels-Alder reaction of such a diene were indeed facially selective, the resulting adducts **1.9** or **1.10** seemed to be amenable to elaboration into any one of the diastereomeric forms of **1.4**, as outlined in Scheme 1.1.



Scheme 1.1: Envisioned Diels-Alder sequence.

1.1 Previously Known 5-Substituted Cyclopentadienes

Dienes of the type **1.11** were unknown at the beginning of our investigations; so, no knowledge was available concerning their facial preference during Diels-Alder reactions. On the other hand, a variety of 5-substituted cyclopentadienes had been previously studied by other research groups.[27,39-53] Figure 1.2 illustrates a number of such dienes, most of which carry a single substituent at position 5. The paucity of species carrying a nitrogen substituent at C-5 is apparent, as is that of chiral cyclopentadienes. Equally apparent is the fact that many of the below molecules are 5-monosubstituted cyclopentadienes. As a consequence of the well known

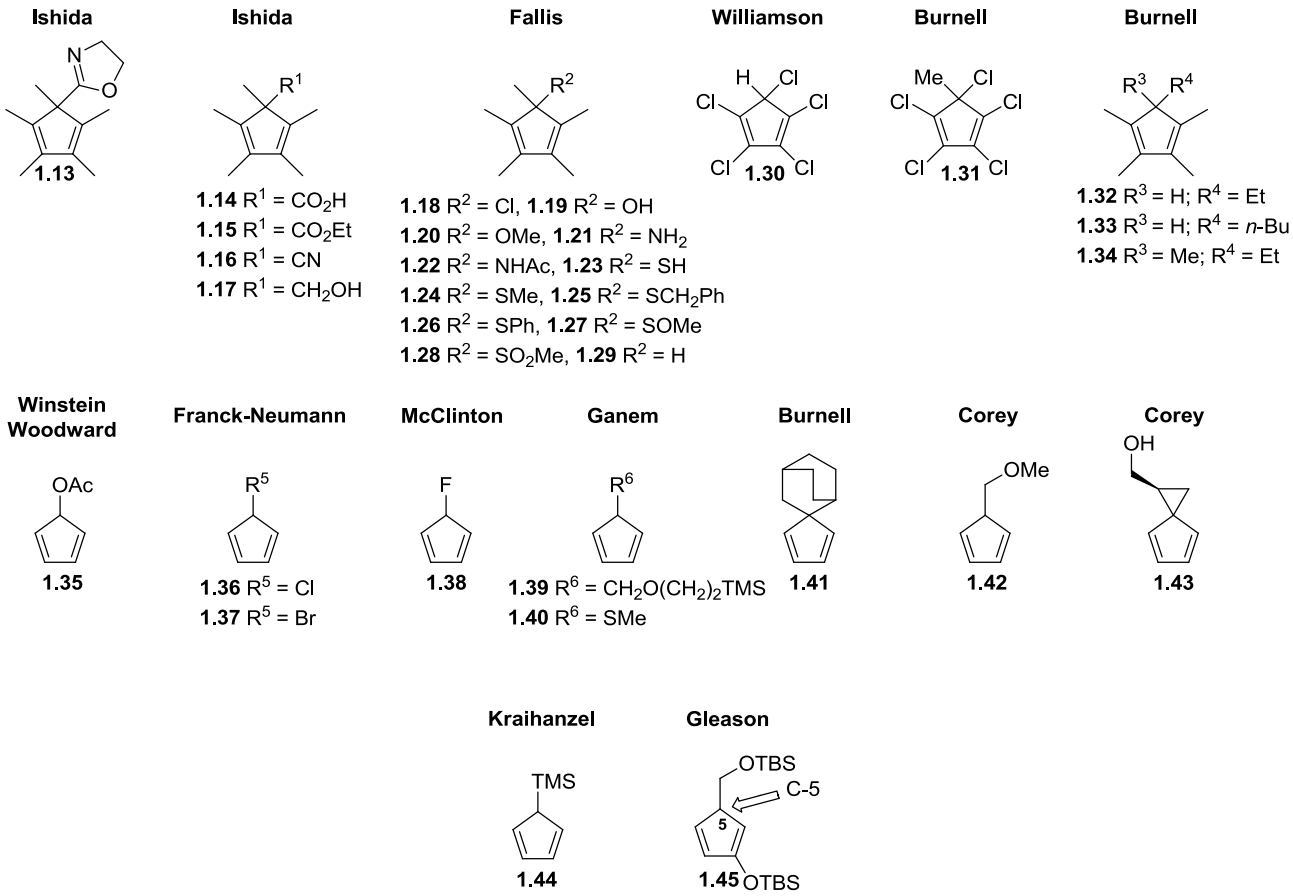
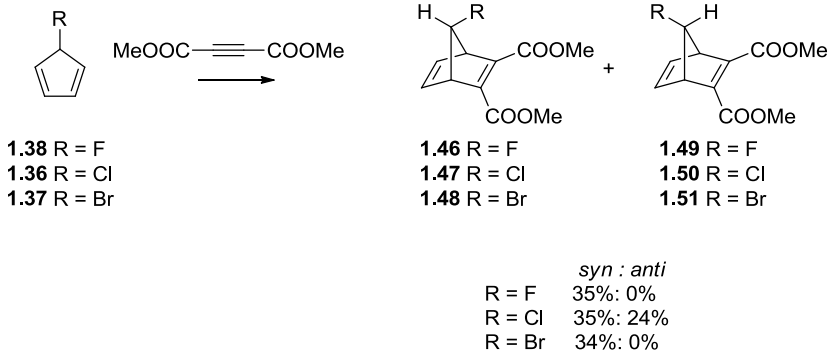


Figure 1.2: Previously studied 5-substituted cyclopentadienes.

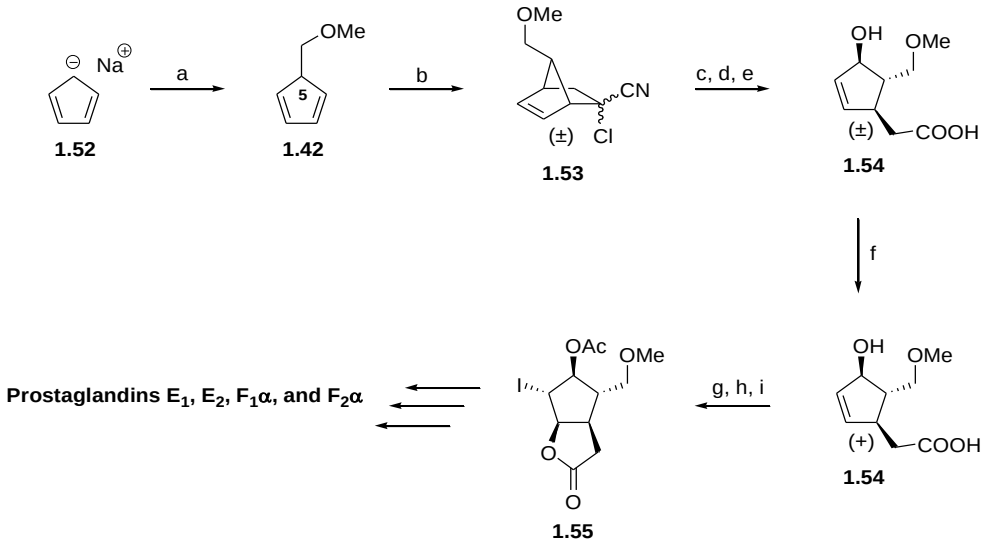
propensity of these species to undergo facile, but generally undesirable,[27,39-54] [1,5]-hydride shifts at room temperature, their Diels-Alder reactions must often be carried out at low temperatures (–78°C to 0°C). Nonetheless, they constitute an important class of Diels-Alder synthons, which have been extensively used to probe the factors that determine facial selectivity. Such studies have revealed that subtle structural differences could cause radically different selectivity patterns. For instance, Franck-Neumann[46] found that **1.37** reacts with *syn* facial selectivity, and McClinton[47] likewise found that **1.38** reacts with exclusive *syn* facial selectivity. However, Franck-Neumann[46] reported that compound **1.36** reacts with poor *syn* faciality. The poor selectivity of **1.36** was not predicted, and was not fully explained in the seminal publication. Thus *a-priori* predictions regarding the facial selectivity of a novel cyclopentadiene are imprudent.



Scheme 1.2: Facial selectivities for 5-halo-cyclopentadienes.

Some of the foregoing dienes have found application in a number of landmark syntheses, the most important of which is arguably Corey's total synthesis of prostaglandins E_1, E_2, $F_{1\alpha}$, and

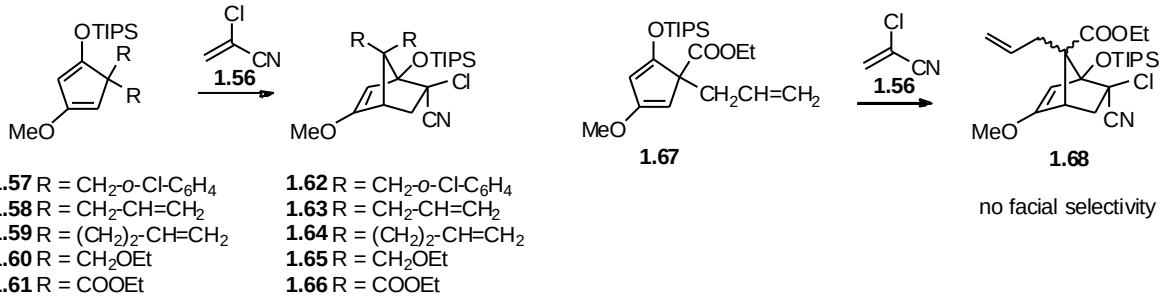
$F_{2\alpha}$.[51,55,56] As shown in Scheme 1.3, the opening moves of this effort entailed the facially *anti*-selective reaction of **1.42** with 2-chloroacrylonitrile, a reactive ketene equivalent,[57] to generate **1.53**. The substituted norbornene **1.53** was then converted into the ketonic analogue upon treatment with potassium hydroxide. Baeyer-Villiger reaction and hydrolysis of the lactone with sodium hydroxide yielded racemic **1.54**, which was then resolved. The correct enantiomer, (+)-**1.54**, was made to undergo iodolactonization and acetylation to garner **1.55**. The highly substituted cyclopentane **1.55** was then advanced to prostaglandins E_1, E_2, $F_{1\alpha}$, and $F_{2\alpha}$. A remarkable aspect of this work is the rapid elaboration of a simple material such as **1.42** into complex intermediate **1.55** in a short order, using technology that was already mature 40 years ago.



Reagents and conditions: a) MOM-Cl, THF –55°C; b) 2-chloroacrylonitrile, $Cu(BF_4)_2$, 0°C; 70% over two steps; c) KOH, H_2O/DMSO, 80%; d) $ArCO_3H$, $NaHCO_3$, CH_2Cl_2, 95%; e) NaOH, H_2O; f) resolution with (+)-ephedrine; g) $NaHCO_3$, H_2O; h) KI_3, H_2O, 80%; i) Ac_2O, pyr, 97%.

Scheme 1.3: Cyclopentadiene as a synthon for prostaglandins E_1, E_2, $F_{1\alpha}$, and $F_{2\alpha}$.

Synthetic applications of 5,5-disubstituted cyclopentadienes are considerably less common. A recent example has been detailed by the Ciufolini group,[58,59] and is illustrated in Scheme 1.4. Thus, achiral cyclopentadienes **1.57**-**1.61** furnished Diels-Alder adducts that were rapidly elaborated to structurally complex analogues of the antifungal natural product, sordarin, for SAR studies. In the course of these investigations, the Diels-Alder behavior of chiral cyclopentadiene **1.67** was examined. No facial selectivity was observed in the reaction of **1.67** with 2-chloroacrylonitrile. Evidently, steric and stereoelectronic effects are insufficiently pronounced to induce appreciable facial bias in this system.

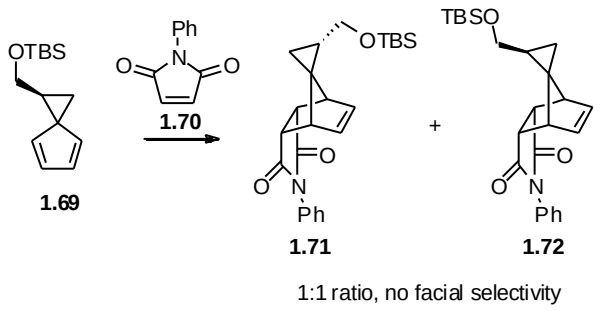


1.57 R = CH_2-*o*-Cl-C_6H_4
1.58 R = CH_2-CH=CH_2
1.59 R = $(CH_2)_2$-CH=CH_2
1.60 R = CH_2OEt
1.61 R = COOEt

1.62 R = CH_2-*o*-Cl-C_6H_4
1.63 R = CH_2-CH=CH_2
1.64 R = $(CH_2)_2$-CH=CH_2
1.65 R = CH_2OEt
1.66 R = COOEt

Scheme 1.4: 5-Disubstituted cyclopentadienes used for sordarin analogue synthesis.

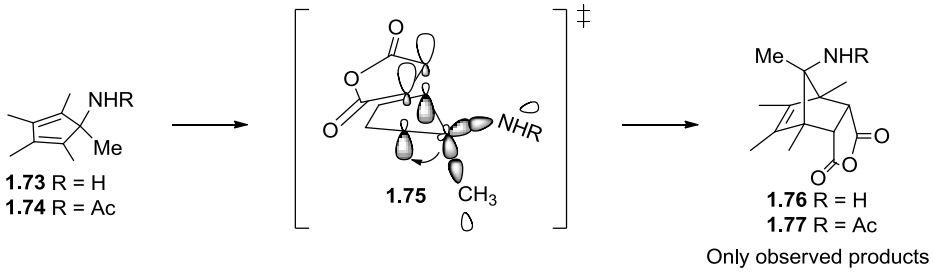
In a like fashion, Scheme 1.5 shows that Carreira's variant of a Corey diene,[52,60] **1.69**, suffered from insufficient bias to effect facial selectivity. Despite the unselective Diels-Alder reaction, Carriera found that heating in chlorobenzene could isomerize **1.71** to **1.72**. However, this example serves to illustrate that the dearth of 5-substituted cyclopentadiene systems which display facial selectivity and incorporate sufficient functional group handles.



Scheme 1.5: Corey-Carreira cyclopentadiene for the palau'amine core.

1.2 Proposed 5-*N*,*C*-Disubstituted Cyclopentadienes

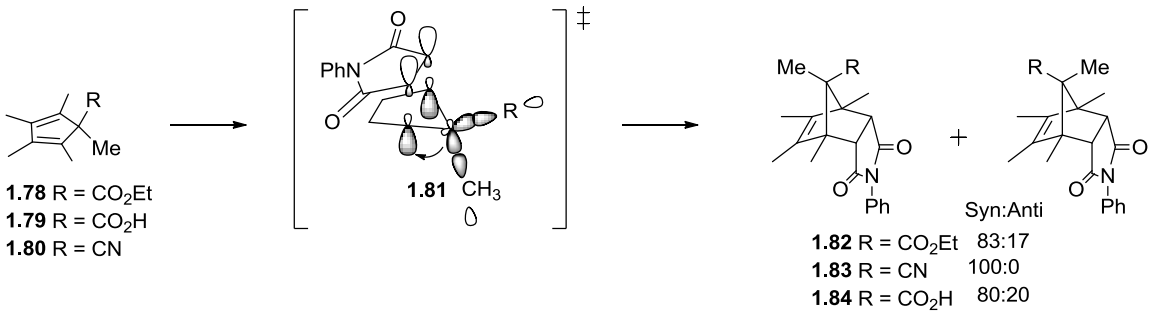
A cyclopentadiene of the type **1.11** (*cf.* Scheme 1.1) incorporates both a nitrogen functionality and an ester group (or other hydroxymethyl equivalent) at the C-5 position. In a sense, compound **1.11** is a hybrid of a Fallis[41] and an Ishida[40] cyclopentadienes. The Fallis system (**1.73** and **1.74**) reacts with maleic anhydride with complete *N-syn* facial selectivity (Scheme 1.6).[41] Because the steric effect of the two substituents must be very similar (Me and NH_2 have comparable A-values,[61] i.e. similar steric demands), the observed selectivity must be rooted in a stereoelectric effect. A Cieplak-type rationale[62] may be formulated in the sense that hyperconjugative delocalization of C-5 $\sigma_{C\text{-}N}$ electron density into the developing σ* orbitals of incipient bonds is significantly less efficient than C-5 $\sigma_{C\text{-}C}$ donation. Ergo, the dienophile reacts in an *N-syn* manner to maximize C-5 $\sigma_{C\text{-}C}$ stabilization of the transition state **1.75**. We also note,



Scheme 1.6: Facial selectivity of the Fallis 5-*N*-cyclopentadienes with maleic anhydride.

that despite the successful predictions that arise from a Cieplak analysis, a survey of the literature shows a continued dialectic on the relative merit of a diversity of effects in regard to facial selectivity.[40,41,62-72]

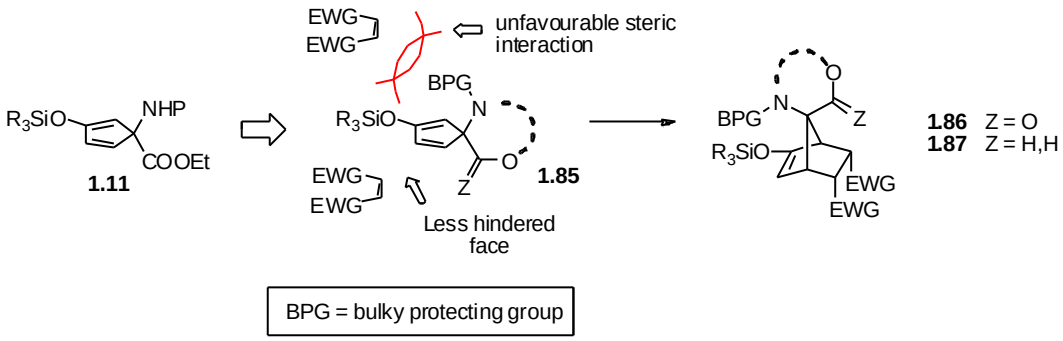
On the other hand, the Ishida cyclopentadienes (compounds **1.78-1.80**), wherein a carbonyl or nitrile group is present at the C-5 position, largely react with carbonyl-, or nitrile-, *syn* selectivity.[40] The outcome can also be rationalized in a Cieplak mode. Due to the polarization induced by an electron withdrawing group, C-5 carbonyl/nitrile $\sigma_{C\text{-}C}$ donation into the σ* of incipient bonds is significantly lower than C-5 methyl $\sigma_{C\text{-}C}$ donation. Ergo, the dienophile reacts *syn* to carbonyl/nitrile groups to maximize C-5 $\sigma_{C\text{-}C}$ stabilization of the transition state **1.81**.



Scheme 1.7: Facial selectivity of the Ishida 5-carbonyl-cyclopentadienes with *N*-Ph maleimide.

In summary, both a nitrogen functionality and a carbonyl group are *syn*-facially directing. The simultaneous presence of such groups at C-5 of a cyclopentadiene makes it entirely unclear whether significant facial selectivity would result (*cf.* Scheme 1.1). An attractive feature of a

cyclopentadiene such as **1.11** is that a hypothetical lack of facial selectivity, or selectivity in an *N-syn* sense, might have been circumvented as detailed in Scheme 1.8. A variant of **1.11,** wherein a bulky protecting group is affixed to the nitrogen atom may possess significant steric bias as to favor Diels-Alder faciality *anti* to the nitrogenous functionality. Such a steric effect could be further amplified by tethering N and C substituents, so as to force the *N*-protecting group to reside upon the *N-syn* face of the diene. In either case, experimental verification was required. Moreover, Diels-Alder products **1.86** or **1.87** would be of significant interest to other ongoing projects in our laboratory.



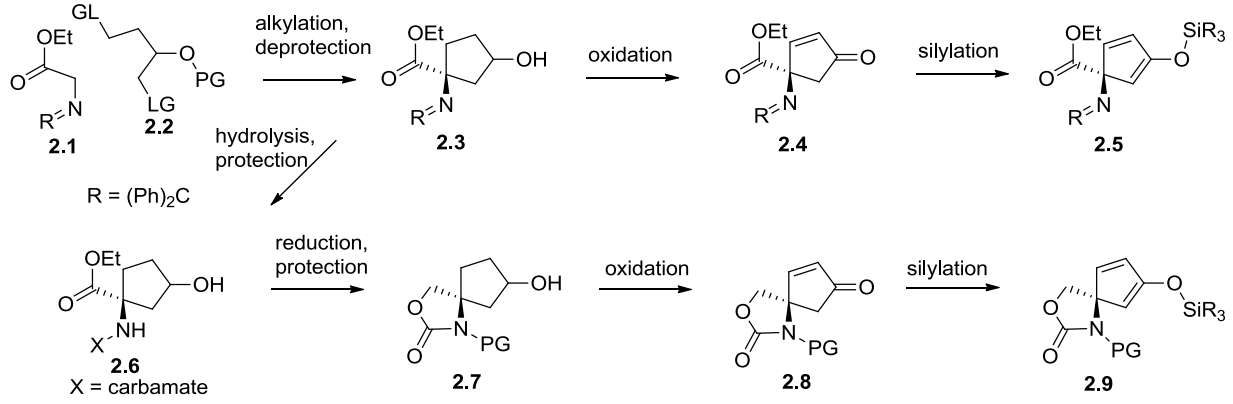
Scheme 1.8: Envisioned sterically controlled Diels-Alder.

2. RESULTS AND DISCUSSION

2.1 Objectives and Approach

Enantioselective routes to enone precursors of cyclopentadienes of the type **2.4** are known.[73,74] However, it will be recalled that the question of facial selectivity was our primary concern. Accordingly, the work described in this thesis was carried out with racemic compounds. The issue of enantiopurity of the diene was to be left for future studies.

As shown in Scheme 2.1, our plan for the synthesis of racemic **2.5** built upon work previously reported by Howarth.[75] We would thus synthesize the cyclopentane ring by bis-alkylation of **2.1** with **2.2**. This would be followed by deprotection and redox operations, culminating with formation of the silyl enol derivative **2.5** of enone **2.4**. We also envisioned a route to facially biased diene **2.9** from intermediate **2.3**, which would first be converted into protected oxazolidone **2.7**, and then advanced to diene **2.8**. Details of our efforts are described in the following section.

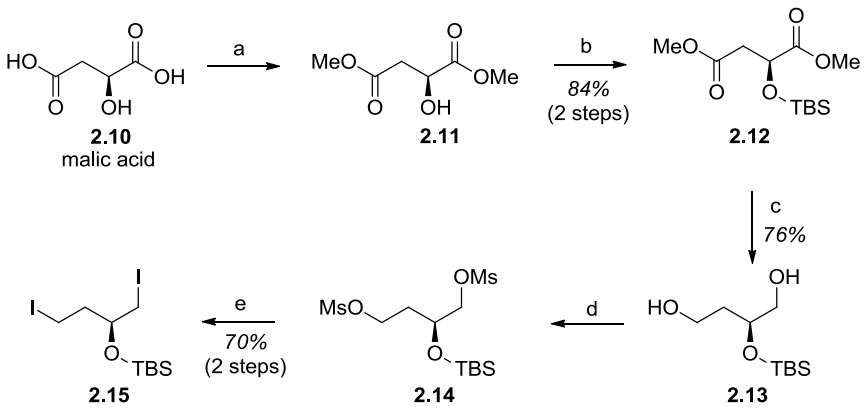


Scheme 2.1: Planned route to cyclopentadienes **2.5** and **2.9**.

2.2 Bis-Alkylation/Bis-Oxidation Route

Initially, we focused on the construction of electrophilic agent **2.15**. A very similar compound has been described in the literature.[76] Accordingly, we patterned our synthesis after the known route.

Commercially available malic acid was subjected to Fischer esterification to generate diester **2.11**. Subsequent TBS protection of the free alcohol provided **2.12** in an overall yield of 84% over two steps. Then, **2.12** was reduced to diol **2.13** with DIBAL-H in 76% yield. This diol was mesylated (MsCl and TEA) and the resultant **2.14** was reacted with NaI under Finkelstein conditions,[77] garnering diiodo compound **2.15** in 70% yield over two steps.

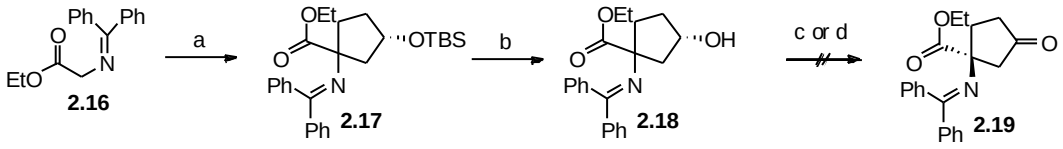


Reagents and conditions: a) $SOCl_2$, MeOH; b) TBS-Cl, Im, DMAP, CH_2Cl_2; c) DIBAL-H, THF, 0°C; d) MsCl, TEA, CH_2Cl_2; e) NaI, acetone, reflux.

Scheme 2.2: Synthesis of bis-iodo electrophile.

The union of **2.15** with commercially available **2.16** was achieved with some difficulty according to the route of Scheme 2.3. The bis-alkylation reaction proceeded in low yield (30-40% conversion by ^{1}H-NMR) and the purification of cyclopentane **2.17** was problematic.

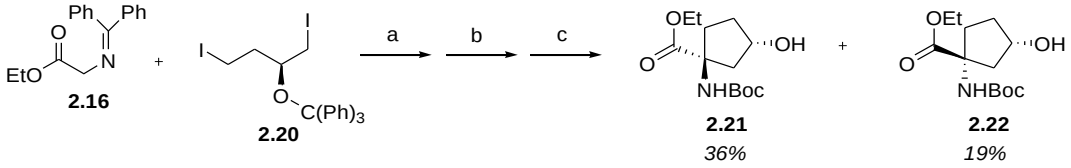
Specifically, clean chromatographic separation of **2.17** from numerous aromatic side products was not achieved. Therefore, **2.17** was purified to the extent found possible and further reacted as is discussed below.



Reagents and conditions: a) LiHMDS, **2.15**, THF, -78°C to RT; b) TBAF, THF; c) PCC, CH_2Cl_2; d) DMP, CH_2Cl_2.

Scheme 2.3: Bis-alkylation.

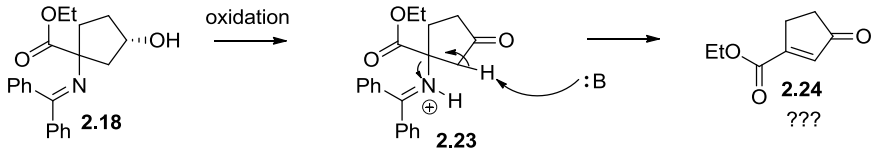
Furthermore, and in contrast to the Howarth case[75] (Scheme 2.4), no significant level of diastereoselectivity was observed in the bis-alkylation reaction. This stereochemical outcome can be rationalized based on the larger steric demand of the trityl group with respect to the TBS group. Fortunately, this was inconsequential, in that either diastereomer of **2.17** would converge to the desired (racemic) ketone **2.19** after desilylation and oxidation.



Reagents and conditions: a) LiHMDS, THF, −78°C; b) 2 M (aq.) HCl; c) $(Boc)_2O$, Na_2CO_3, $CHCl_3$:H_2O, reflux.

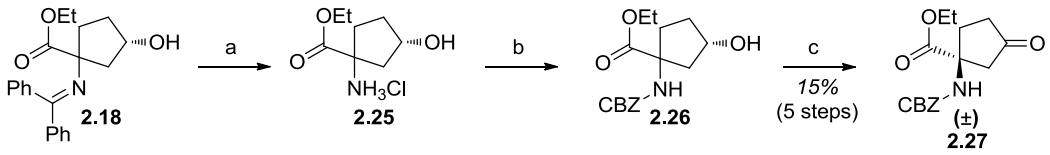
Scheme 2.4: Howarth's bis-alkylation diastereoselectivity.

A more serious complication materialized when partially purified **2.17** (silica gel chromatography) was desilylated and the resulting free alcohol was oxidized. The action of either PCC or DMP on **2.18** furnished a product, identified as **2.24** and not fully characterized, which had lost the amino moiety, presumably *via* a β-elimination pathway.



Scheme 2.5: Problematic oxidation.

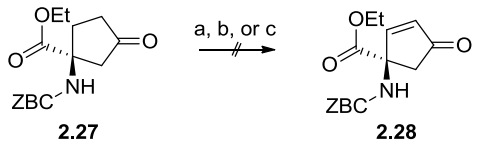
As shown in Scheme 2.6, such problematic issues were bypassed by converting **2.18** into **2.25** *via* acidic hydrolysis with 3N HCl and reprotection of the amino group with CBZ-Cl. The subsequent oxidation of the alcohol yielded cyclopentanone **2.27** in a modest 15% isolated yield over 5 steps from **2.16** (*ca.* 69% yield per step). The alkylation step was by far the poorest-yielding one of the sequence, but any optimization of that reaction was postponed until the facial preference of a cyclopentadiene derived from **2.27** had been determined.



Reagents and conditions: a) 3N HCl, diethyl ether; b) CBZ-Cl, TEA, acetone/H_2O; c) DMP, CH_2Cl_2.

Scheme 2.6: Ketone synthesis by imine hydrolysis.

Such an objective required first the introduction of a double bond within **2.27**; i.e, the formation of enone **2.28**. Efforts toward that end met with failure. A Nicoloau-type oxidation[78] with IBX and base produced only trace amounts of **2.28**, detectable by ^{1}H-NMR only after three days of heating. Better results were obtained upon conversion of **2.27** into a silyl enol ether,

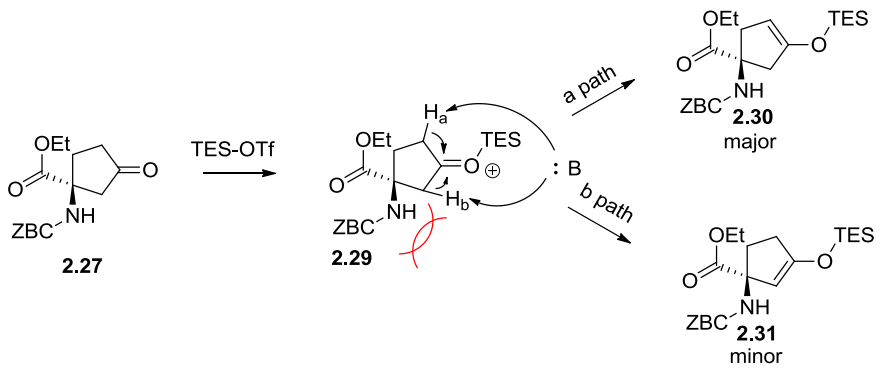


2.27 **2.28**

Reagents and conditions: a) IBX, PPTS, DMSO, tol, 70°C, 72 hr; b) TMS-OTf, TEA, CH_2Cl_2: –78°C to RT; c) i) TES-OTf, TEA, CH_2Cl_2; –78°C to RT; ii) NBS, $NaHCO_3$, CH_2Cl_2, –78°C to 0°C iii) Li_2CO_3, tol, reflux.

Scheme 2.7: Problematic generation of desired cyclopentenone.

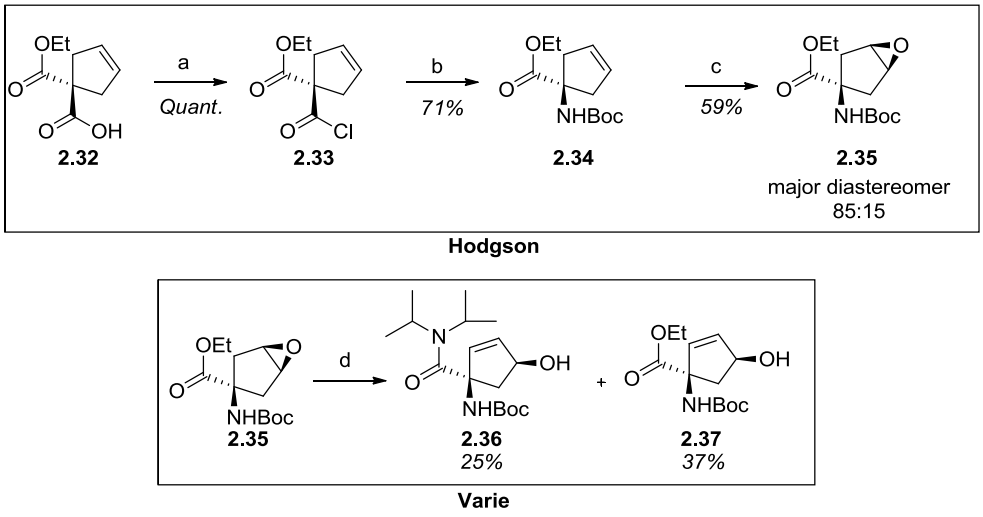
an event that would prepare the molecule for oxidative conversion into **2.28**. Notably, the formation of the TES silyl enol ethers derivative of **2.27** (TES-OTf, Et_3N) occurred regioselectively (4:1 ratio) in favor of the desired isomer **2.30**. We presume that this is due to steric effects, as illustrated in Scheme 2.8, the H_b deprotonation is slowed due to its position. In contrast, the TMS silyl enol ether was found to be too sensitive, immediately desilylating back to **2.27** upon aqueous workup. Unfortunately, attempts to install a bromine atom and eliminate to **2.28** were also unsuccessful, leading to a complex, intractable mixture of products. This series of setbacks, coupled with low yields and a lengthy synthetic pathway, induced us to abandon the present route and focus on another approach.



Scheme 2.8: Silylation selectivity.

2.3 Alternative Route to 5-*N,C*-cyclopentenones

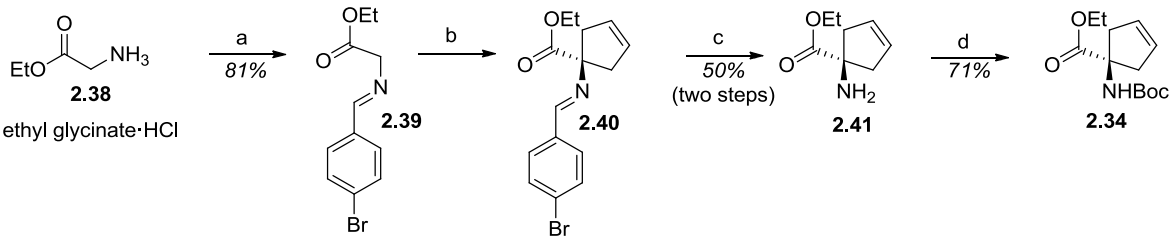
An alternative avenue to the requisite **2.28** (or a variant thereof) was charted based on the work of Hodgson[73] and Varie[74], who developed a strategy for the generation of similar cyclopentenones (Varie oxidized the ^{t}butyl-ester analogue of **2.37** to the corresponding cyclopentenone). In accord



Reagents and conditions: a) $SOCl_2$, CH_2Cl_2; b) i) NaN_3, acetone/H_2O; ii) ^{t}BuOH, $SnCl_4$ (cat.), Tol.; c) *m*CPBA, $NaHCO_3$, CH_2Cl_2; d) LDA, THF, 0°C.

Scheme 2.9: Hodgson's and Varie's route to cyclopentenols.

with this logic, we utilized the Kurth[79,80] route to converge onto common intermediate **2.34**. First, the hydrochloride salt of ethyl glycinate was condensed with *p*-bromobenzaldehyde to form imine **2.39** in 81% yield. The alkylation of **2.39** with *cis*-dichlorobut-2-ene occurred uneventfully under the influence of NaH in THF. The imine was now hydrolyzed with aqueous 1N HCl. This step occurred with concomitant hydrolysis of a portion of the ethyl ester. The crude product was therefore subjected to Fisher esterification to effect complete conversion into **2.41**. This material emerged in a moderate 50% yield over two steps. Reprotection of the hindered amine with Boc_2O generated the known compound **2.34** in 71% yield.

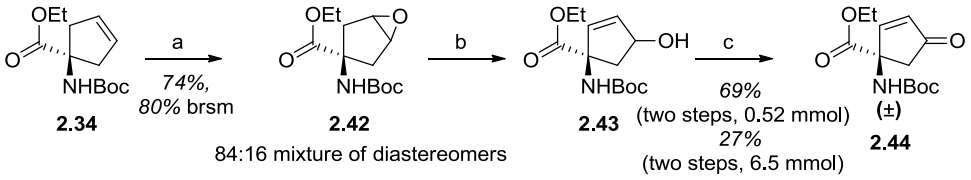


Reagents and conditions: a) PPB, TEA, Na_2SO_4, CH_2Cl_2; b) NaH, *cis*-dichlorobut-2-ene, THF; c) i) 1N HCl/Et_2O; ii) $SOCl_2$, EtOH; d) Boc_2O, $NaHCO_3$, CH_2Cl_2/H_2O.

Scheme 2.10: Cyclopentene synthesis.

Compound **2.34** was now reacted with *m*CPBA to afford a 84:16 (by ^{1}H-NMR) mixture of diastereomeric epoxides. Whereas the major isomer was obtained in pure form upon chromatography, no stereochemical characterization has been carried out at this time. On the other hand, the observations of Hodgson suggest that our major product is likely to have the *syn* relationship between oxiranyl and nitrogen functions. Regardless, **2.42** rearranged smoothly to

the allylic alcohol upon reaction with LDA, and the resulting **2.43** was oxidized with DMP to furnish **2.44** in 69% yield over two steps, on a scale of 0.52 mmol.

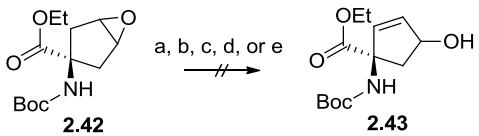


Reagents and conditions: a) *m*CPBA, $NaHCO_3$, CH_2Cl_2; b) LDA, THF, 0°C; c) DMP, CH_2Cl_2.

Scheme 2.11: Successful synthesis of enone.

Unfortunately, it was found that the rearrangement step did not scale well. When the reaction was repeated with 6.5 mmol of epoxide, the yields dropped to below 30%. This outcome is in accordance with the result Varie has reported with a 37% isolated yield of **2.37** (*cf.* Scheme 2.9), largely due to competing LDA attack upon the ester to furnish **2.36**.

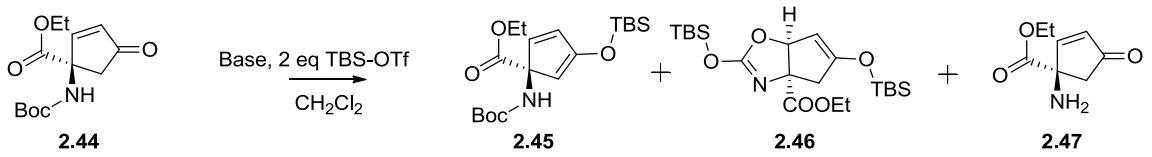
Our attempts to improve the yields by the use of other known epoxide-rearranging agents were unfruitful (Scheme 2.12). Reagents such as KO^{t}Bu, LDA/KO^{t}Bu,[81] $ClAlEt_2$/TMP,[82] had no effect upon **2.42**. Clean reduction back to **2.34** occurred upon reaction with **(**$Zn/Ti(Cp)_2Cl_2$),[83] while complex mixtures of products were obtained with TES-OTf and TEA, followed by DBU.[84] Again, in the interest of addressing the key issue of this research, the facial selectivity of dienes such as **1.11**, the optimization of the rearrangement step was left for a more opportune time.



Reagents and conditions: a) KO^{t}Bu, THF, RT; b) KO^{t}Bu, LDA, THF, –78°C to RT; c) Zn, $Ti(Cp)_2Cl_2$, THF; d) $ClAlEt_2$/TMP, tol, 0°C to RT; e) i) TES-OTf, TEA, CH_2Cl_2; ii) DBU.

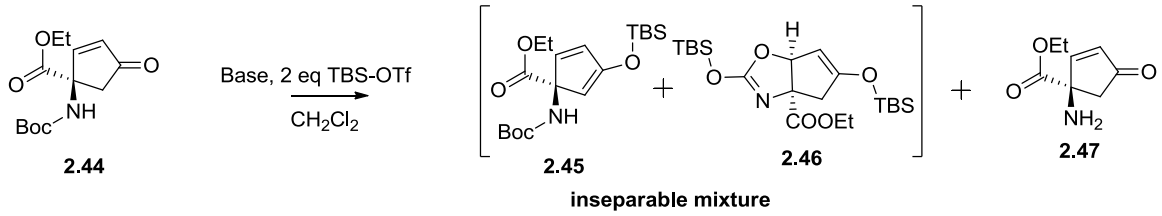
Scheme 2.12. Screening of epoxide rearrangement agents.

The conversion of enone **2.44** into the corresponding silyl enol ether was problematic on accounts of two competing reactions (Scheme 2.13): a Michael-type addition of the carbamate to the enone occurring concomitantly with exchange of the *tert*-butyl group with a silyl residue (*cf.* **2.46**), and the release of the BOC protecting group (*cf.* **2.47**).



Scheme 2.13. General product distribution of silylation attempts.

The product distribution depended on experimental conditions. As shown in Table 2.1, reaction of **2.44** with 2 equivalents of TBS-OTf and 2,6-lutidine generated only amine **2.47**, while in the presence of Hunig's base the Michael addition product **2.46** was the sole product. Other bases tested yielded mixtures of **2.45** and **2.46**. The use of 1.5 equivalents or less of TBS-OTf resulted in formation of a statistical mixture of **2.44**, **2.45**, and **2.46**. The best that could be done at this juncture was to employ 2 equivalents of silyl triflate in the presence of *N*-dimethylbenzylamine or triethylamine, whereupon a 5:4 mixture of products **2.45** and **2.46** was obtained in 81% combined yield (with triethylamine). These substances were found to be extremely acid-sensitive, a fact which necessitated the use of neutral alumina for chromatographic purification. The use of base washed silica did not significantly improve the survivability of **2.45** during chromatography.



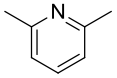
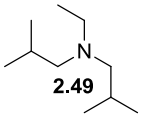
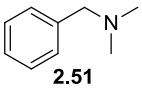
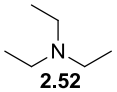
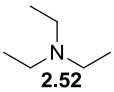
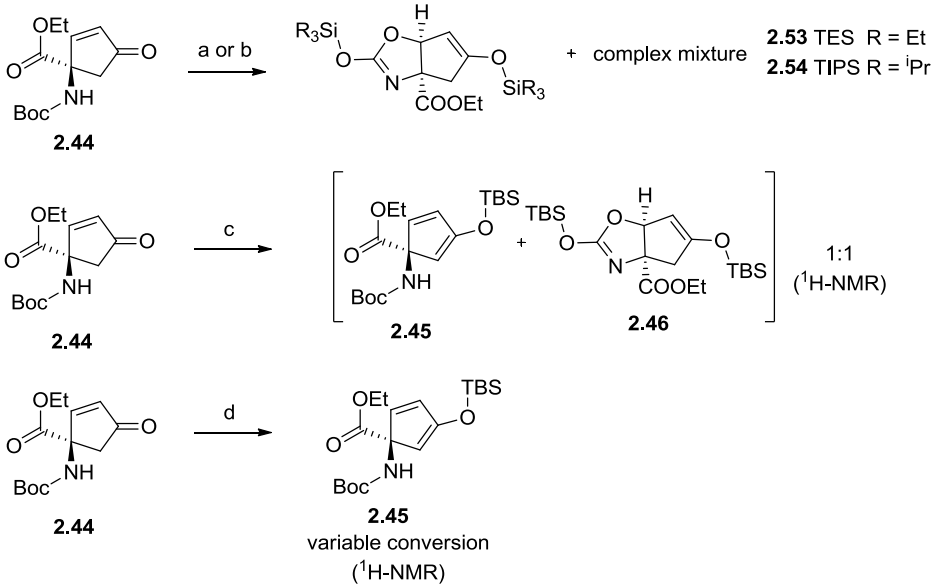
entry	base	ratios (crude ^{1}H-NMR)	temperature
a	 **2.48**	0 : 0 : 1	-78 °C to RT
b	 **2.49**	0 : 1 : 0	-78 °C to RT
c	 **2.50**	1 : 2 : 0	-78 °C to RT
d	 **2.51**	5 : 4 : 0	-78 °C to RT
e	 **2.52**	5 : 4 : 0	-78 °C to RT
f	 **2.52**	0 : 1 : 0	-78 °C

Table 2.1: Screening of bases for diene formation.

On a final note, our choice of a TBS enol ether was motivated by results obtained during investigations on the sordarin problem (Scheme 1.4).[58,59] This effort had revealed that a TBS enol ether provides an ideal balance between good chemical stability and moderate steric demand during Diels-Alder reactions. Besides, the action of TES and TIPS triflates on **2.44** generated even more complex mixtures of products containing Michael adducts (^{1}H-NMR spectroscopy), but no significant amounts of the desired dienes (Scheme 2.14). Attempts to generate these by silylation of a preformed enolate (LDA) were disappointing. Again a statistical

mixture of **2.45** and **2.46** was found when TBS-OTf was employed as the silylating agent. The use of TBS-Cl as the silyl source cleanly afforded **2.45** as the only product detectable by ^{1}H-NMR, albeit in small and variable yields (less than 10%). The balance of starting **2.44** was recovered unchanged. It is probable that the key to an efficient generation of **2.45** is a future optimization of this route.



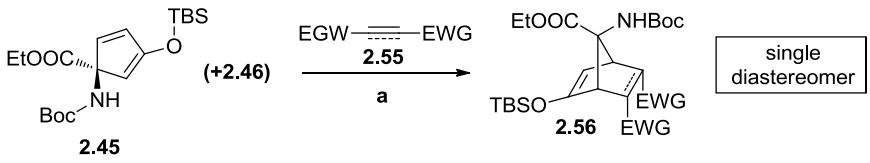
Reagents and conditions: a) TES-OTf, TEA, CH_2Cl_2, –78°C to RT; b) TIPS-OTf, TEA, CH_2Cl_2, –78°C to RT; c) LDA, TBS-OTf, –78°C to RT, THF; d) LDA, TBS-Cl, –78°C to RT, THF.

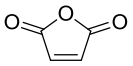
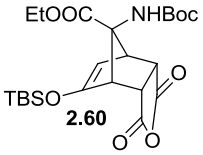
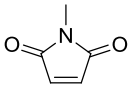
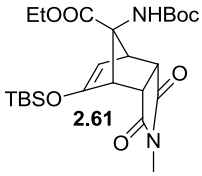
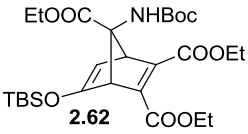
Scheme 2.14: Screening for diene formation.

2.4 Facial Selectivity in the Diels-Alder Reactions of Diene 2.45

The mixture of **2.45** and **2.46** obtained as described in Table 2.1 was purified by chromatography on neutral alumina, as silica would not allow the recovery of either compound in appreciable yield. On the other hand, we were unable to separate **2.45** from **2.46** without incurring unacceptable losses. The study detailed in this section was therefore carried out with an

essentially 1:1 mixture of **2.45** and **2.46**. Clearly, only the former can participate in a Diels-Alder reaction.



entry	dienophile	product	chromatographed yield
1	 2.57		*26%* (two steps) *62%* from diene*
2	 2.58		*41%* (two steps) *92%* from diene*
3	EtOOC—≡—COOEt 2.59		*39%* (two steps) *86%* from diene*

Reagents and conditions: a) 3 eq. dienophile, CH_2Cl_2.
*estimated yields from **2.45**, based on ^{1}H-NMR ratios of purified **2.45**:**2.46** ratios**.**

Table 2.2: Facially selective Diels-Alder

Gratifyingly, diene **2.45** smoothly underwent facially selective Diels-Alder reaction with maleic anhydride at room temperature to yield the expected product **2.60** as a single diastereomer within the limits of ^{1}H-NMR spectroscopy. The yield of chromatographically purified **2.60** was a modest 26% (62% based on the mixture of **2.45**:**2.46**). This was disappointing in light of spectral evidence suggesting that near complete conversion of **2.45** to **2.60** had occurred. Indeed, we

subsequently determined that contact with silica gel is deleterious to the survival of **2.60**, while chromatography on milder supports, such as alumina or florisil, afforded unacceptable levels of purification. Future experiments will have to identify isolation methods that bypass chromatography, such as multiple recrystallizations. Moreover, the sensitive nature of Michael adduct **2.46** resulted in a low recovery from silica chromatography, inconsistent with mass balance.

The structure of **2.60** was assigned on the basis of multiple NMR experiments (^{1}H, ^{13}C, COSY, NOESY). Both the *endo*- and *syn*- nature of the product was deduced from the 2D-NOESY spectrum. Specifically, the presence of strong dipolar coupling between the Boc group and the equatorial hydrogens indicate both *endo*- and *syn*- product. In addition, the *syn* relationship was further confirmed by coupling of the ester and TBS groups.

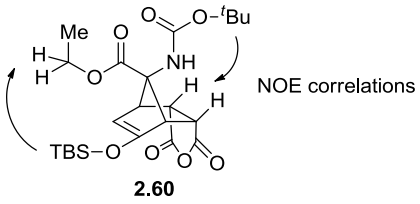
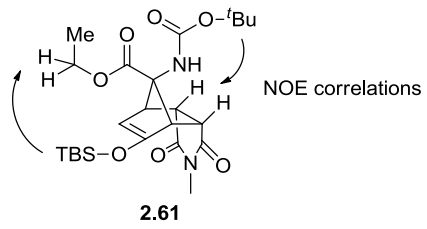


Figure 2.1: NOESY correlations for Diels-Alder adduct **2.60**

The Diels-Alder adducts arising from reaction of **2.45** with N-methylmaleimide and diethyl acetylenedicarboxylate, **2.61** and **2.62**, also formed as single diastereomers within the limits ^{1}H-NMR spectroscopy. These products were more stable than **2.60**, and were isolated in 41% and 39% yield, respectively, after silica gel chromatography. Moreover, the calculated yield

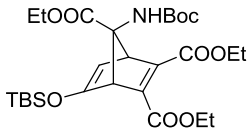
from **2.45**:**2.46** mixtures was 92% and 86% respectively. The structure of **2.61** was again assigned on the basis of 2D-NOESY NMR spectral properties (Figure 2.2), which confirmed the *N-syn* facial selectivity of the cycloaddition step.



2.61

Figure 2.2: NOESY correlations for Diels-Alder adduct **2.61**

In contrast to **2.60** and **2.61**, an unequivocal structural elucidation of **2.62** could not be carried out because the ^{1}H-NMR chemical shifts of the three ethyl esters are too close to allow meaningful correlations. Regardless, the compound was clearly a single diastereomer. It seems unlikely that the acetylenedicarboxylate dienophile should have reacted with a faciality opposite

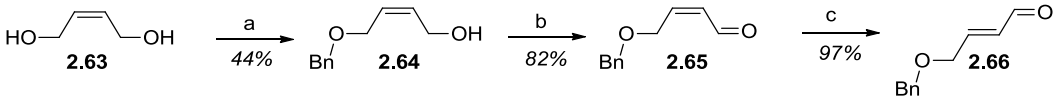


2.62

Figure 2.3: Presumed structure of Diels-Alder adduct **2.62.**

that of maleic anhydride and N-methylmaleimide. Therefore, we presume that **2.62** also resulted from an *N-syn* facially selective cycloaddition, even though experimental confirmation of this surmise is yet unavailable.

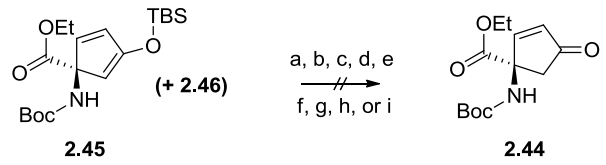
In the interest of testing a trans-dienophile, known compound **2.66** was generated in three steps in accord with literature procedures.[85,86] Thus, (*Z*)-but-2-ene-1,4-diol was benzyl protected to **2.64** with NaH and Bn-Br in a modest 44% yield. Mono-benzyl protected **2.64** was oxidized to **2.65** with IBX in a good 82% yield. Finally, aldehyde **2.66** was isomerized with catalytic quantities of PPTS in an excellent 97% yield. The short synthetic pathway and low cost of starting materials engender no desire to optimize yields at this stage.[87]



Reagents and conditions: a) NaH, Bn-Br, DMF, 0°C to RT; b) IBX, DMSO; c) PPTS (cat.), CH_2Cl_2.

Scheme 2.15: Synthesis of dienophile **2.66**.

Sadly, dienophile **2.66** failed to combine with cyclopentadiene **2.45**, either under the previously established conditions (*cf.* Table 2.2) or upon admixture with **2.45** in neat form. Instead, a slow desilylation of **2.45** back to **2.44** was observed after a period of several days. The more reactive dimethyl fumarate also failed to undergo Diels-Alder reaction with **2.45**, even under the influence of Lewis acid activators such as $(Et)_2AlCl$, $Yb(OTf)_3$, and $Eu(fod)_3$, as did 2-chloroacrylonitrile (Scheme 2.16).

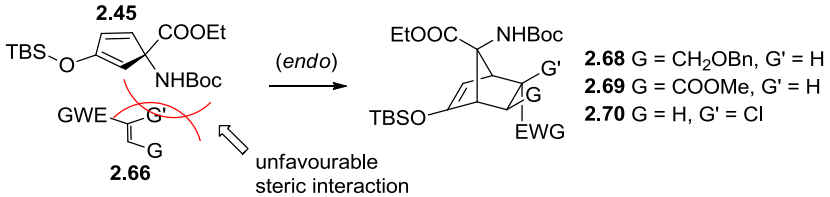


Reagents and conditions: a) **2.66**, CH_2Cl_2; b) **2.66** (neat); c) **2.66**, $Eu(fod)_3$, CH_2Cl_2; d) 2-chloroacrylonitrile, CH_2Cl_2; e) 2-chloroacrylonitrile (neat); f) dimethylfumarate, CH_2Cl_2; g) dimethylfumarate, $(Et)_2AlCl$, CH_2Cl_2, –78°C to RT; h) $Yb(OTf)_3$, dimethylfumarate, CH_2Cl_2; i) $Eu(fod)_3$, dimethylfumarate, CH_2Cl_2.

Scheme 2.16: Disappointing scope limitations of **2.45**.

As delineated in Scheme 2.17, the foregoing failures could be due to unfavorable steric compression between groups G and G' of the dienophile and the NHBOC substituent, at or near the transition state for the reaction. This being the case, the Diels-Alder pathway would be seriously retarded, leaving the diene sufficient time to degrade back to **2.44**. This unfortunate decomposition is a well known fate of unreactive siloxydienes, and it has been hypothesized to be due to catalytic amounts of acid generated by adventitious water and Lewis acidic contaminants.[88] Hopefully, appropriate refinements of reaction conditions will ultimately enable the conduct of the aforementioned Diels-Alder reactions.

In summary, diene **2.45** has been shown to react in Diels-Alder reactions with high *N-syn* facial selectivity. Thus, the hypothesis that *N-syn* selectivity would result due to Cieplak-type

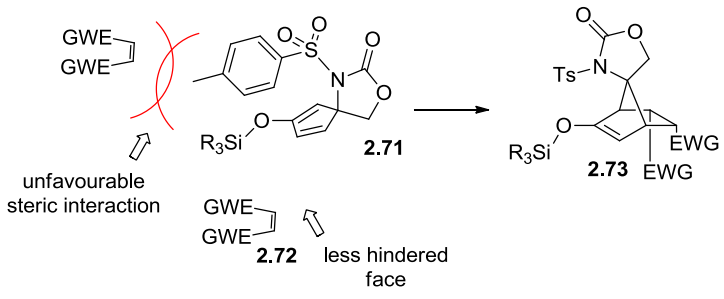


Scheme 2.17: Unfavorable steric interactions during the reaction of **2.45** with **2.66**, **1.56**, and dimethylfumarate.

stereoelectronic effects has been upheld for this system. Three Diels-Alder adducts were synthesized, of which **2.60** is of special interest to ongoing projects in our laboratory. Unfortunately, *trans*-disubstituted dienophiles and 2-chloroacrylonitrile failed to react with **2.45**, leading almost exclusively to silyl release.

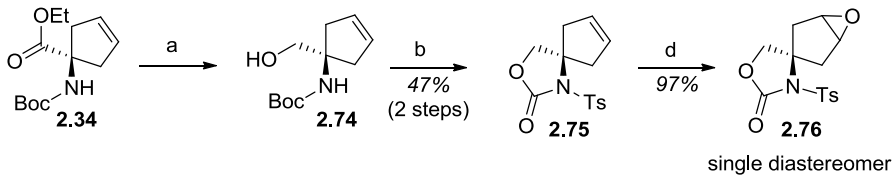
2.5 Forcing *N-Anti* Facial Selectivity

Having attained the goal of the elucidating the Diels-Alder facial selectivity of **2.45**, we refocused our efforts on reversing such a preference through a sagacious juxtaposition of moieties that would promote *N-anti* facial selectivity. A way to override stereoelectronic effects inherent to **2.45** was to decrease the steric demand of the ester group and increase that of the nitrogen functionality. Compound **2.71** (Scheme 2.17) is an *N*-arylsulfonyl oxazolidinone analog of diene **2.45** that fulfills such requirements. The bulky sulfonyl moiety bars the dienophile from approaching the *N-syn* face of **2.71**, while the *N-anti* face of the molecule is fairly readily accessible. This diene should thus react with *N-anti* facial selectivity.



Scheme 2.18: Envisioned Diels-Alder facial selectivity.

The preparation of **2.71** commenced with $LiBH_4$ reduction of previously synthesized intermediate **2.34**. Treatment of the resulting alcohol **2.74** with NaH induced cyclization, which underwent N-tosylation *in situ* upon the addition of Ts-Cl. Compound **2.75** thus emerged in a moderate 47% isolated yield over two steps. Notably, executing the cyclization and tosyl protection in one pot generated **2.75** in a higher yield than a two-step sequence (47% *vs*. 25%). Epoxidation of **2.75** with *m*CPBA yielded epoxide **2.76** as a single diastereomer in an excellent 97% yield. The diastereoselectivity of the epoxidation reaction is inconsequential, so the relative configuration of **2.76** was not ascertained. However, we assumed, on steric grounds, that the epoxide formed *anti* to the nitrogen functionality.

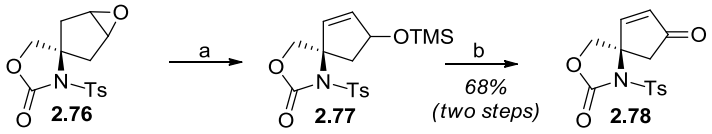


Reagents and conditions: a) $LiBH_4$, THF, 0°C to RT; b) i) NaH, THF, 0°C to RT; b) ii) Ts-Cl, THF, 0°C to RT; d) *m*CPBA, $NaHCO_3$, CH_2Cl_2.

Scheme 2.19: Oxazolidinone and epoxide installation.

As seen previously in Scheme 2.39, epoxide **2.76** was destined to undergo rearrangement to an allylic alcohol. Attempts to effect this transformation using the basic conditions of Scheme 2.39 (LDA) yielded only an intractable polymeric brown mass, but unlike the case of **2.42**, the Noyori method of epoxide rearrangement[84] performed extremely well with **2.76**. Thus, conversion into **2.77** occurred in high yield upon treatment with TMS-OTf/TEA followed by

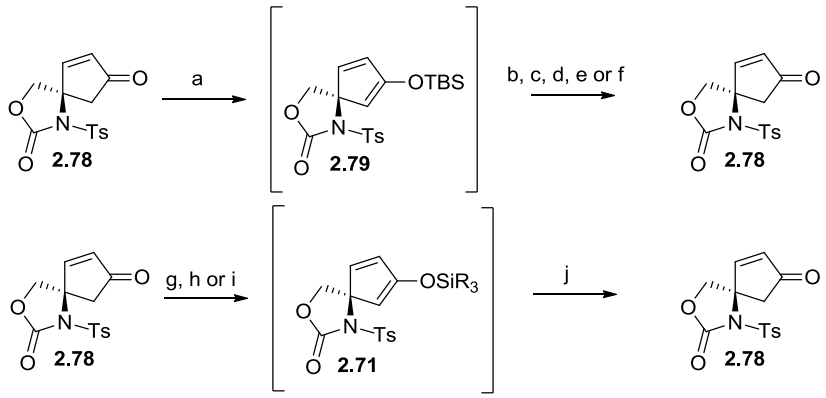
addition of DBU. Furthermore, formation of **2.78** followed smoothly upon exposure of **2.77** to the action of PCC. The overall yield of **2.78** was 68% over two steps. Evidently, the acidic nature



Reagents and conditions: a) i) TMS-OTF, TEA, CH_2Cl_2; ii) DBU; b) PCC, CH_2Cl_2.

Scheme 2.20: Noyori epoxide rearrangement.

of PCC induced both cleavage of the TMS ether and oxidation of the liberated alcohol. It is worthy of note that enone **2.78** is only slightly soluble in common organic solvents such as CH_2Cl_2, THF, hexanes, ethyl acetate, and ether. This complicated subsequent transformations, including the formation of the corresponding silyl enol ether. Specifically, the formation of the



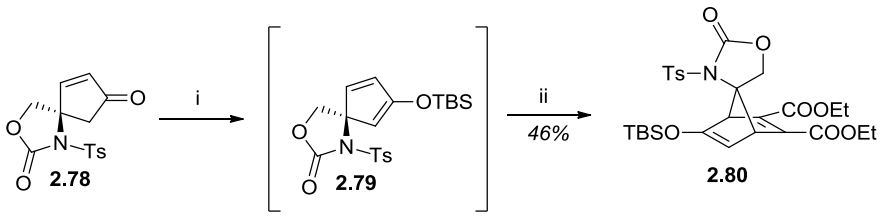
Reagents and conditions: a) TBS-OTF, TEA, CH_2Cl_2, –78°C to RT; b) maleic anhydride, CH_2Cl_2; c) maleic anhydride, K_2CO_3, CH_2Cl_2; d) maleic anhydride, CH_2Cl_2, $AlClMe_2$, –78°C; e) maleic anhydride, benzene; f) maleic anhydride, benzene, 60°C; g) TIPS-OTf, TEA, CH_2Cl_2, –78°C to RT; h) TES-OTf, TEA, CH_2Cl_2, –78°C to RT; i) TMS-OTf, TEA, CH_2Cl_2, –78°C to RT; j) maleic anhydride, CH_2Cl_2.

Scheme 2.21: Problematic Diels-Alder sequences.

silyl enol ether required high dilution (*cf.* 0.02M), even at which point some of **2.78** did not fully dissolve despite sonication.

Diene **2.79** was found to be a sensitive material that was rather unreactive in Diels-Alder reactions. For instance, no cycloadduct was formed upon reaction with freshly sublimed maleic anhydride: only silyl group release occurred during several such attempts. The undesired reactivity persisted regardless temperature (RT or 60°C), solvent (CH_2Cl_2 or Benzene), or nature of the silyl ether (TMS, TES, TIPS - compound(s) **2.71**), and of whether a Lewis acid such as $AlClMe_2$ was utilized to promote the Diels-Alder reaction or a mild base such as K_2CO_3 was introduced to preserve the diene (destruction of adventitious acid).

Fortunately, **2.79** underwent Diels-Alder reaction with neat diethyl acetylenedicarboxylate at 60°C. Compound **2.80** was thus obtained as a single diastereomer (within the limits of ^{1}H-NMR spectroscopy) in a 46% isolated yield. No significant reaction



Reagents and conditions: i) TBS-OTF, TEA, CH_2Cl_2, –78°C to RT; ii) diethyl but-2-ynedioate (neat), 60°C.

Scheme 2.22: Diels-Alder reaction of **2.79** with diethyl acetylenedicarboxylate.

occurred (^{1}H-NMR) at room temperature. Unlike the *N-syn* facially selective diene **2.45**, **2.79** could be directly reacted with diethyl but-2-ynedioate, precluding the need for alumina chromatography. As illustrated in Figure 2.4, NOESY-NMR experiments confirmed that **2.80** had formed through an *N-anti* facially selective Diels-Alder reaction.

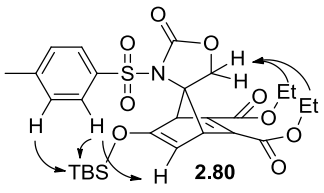
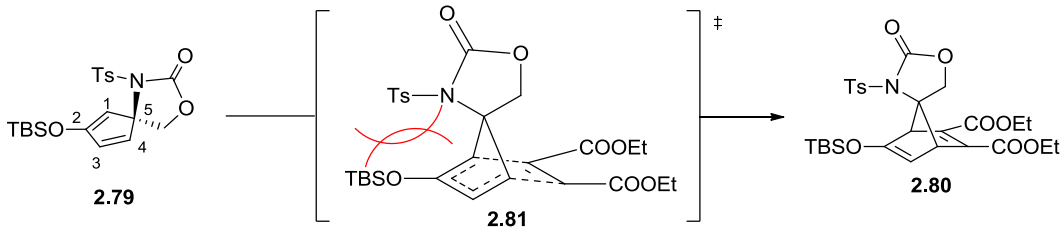


Figure 2.4: NOE correlations for **2.80**.

The sluggish Diels-Alder reaction of **2.79** with diethyl but-2-ynedioate, and its lack of reactivity toward maleic anhydride, stand in stark contrast to the faster reactions of **2.45** (*cf.* 6 hr vs 90 min). It is apparent that **2.79** is much less reactive than **2.45**. This can be attributed to two factors. First, Cieplak-type stereoelectronic effects (*cf.* Scheme 1.6) favor bond formation from the *N-syn* face, while strongly disfavoring reactivity from the *N-anti* face. This second mode of cycloaddition is therefore kinetically slower. Moreover, as the C-1 and C-4 carbon atoms of the cyclopentadiene pyramidalize during the reaction, a decrease in the dihedral angle θ between N-C5-C1-C2 and N-C3-C4-C5 results in compression of the Ts group against the remainder of the cyclopentadiene ring.



Scheme 2.23: Steric effects decreasing rate.

In summary, diene **2.79** has been shown to react in Diels-Alder reactions with the predicted *N-anti* facial selectivity. Thus, our notion of overriding inherent stereoelectronic preferences through steric effects has been validated. However, the price for *N-anti* selectivity was a significantly diminished reactivity due to both decreased stereoelectronic stabilization and increased steric forces in the transition state. The sluggish Diels-Alder reactivity of **2.79** is currently a major drawback, but future work may well produce a cure for such ills.

3. CONCLUSION

In summation, the research described in this thesis has culminated in the synthesis of two novel chiral cyclopentadienes which display virtually complete facial selectivity in Diels-Alder reactions. The results obtained in the course of these studies are essential to the progress of various synthetic efforts ongoing in our laboratory.

REFERENCES

(1) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J., *J. Am. Chem. Soc.* **1993,** *115*, 3376-3377.

(2) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J., *J. Org. Chem.* **1998,** *63*, 3281-3286.

(3) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C., *J. Am. Chem. Soc.* **1997,** *119*, 7159-7160.

(4) Dilley, A. S.; Romo, D., *Org. Lett.* **2001,** *3*, 1535-1538.

(5) Lovely, C. J.; Du, H.; Dias, H. V. R., *Org. Lett.* **2001,** *3*, 1319-1322.

(6) Bèlanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C., *J. Org. Chem.* **2002,** *67*, 7880-7883.

(7) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T., *Tetrahedron Lett.* **2002,** *43*, 3699-3702.

(8) Poullennec, K. G.; Kelly, A. T.; Romo, D., *Org. Lett.* **2002,** *4*, 2645-2648.

(9) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J., *Org. Lett.* **2003,** *5*, 3623-3626.

(10) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C.; Austin, D. J., *Org. Lett.* **2003,** *5*, 2203-2206.

(11) Poullennec, K. G.; Romo, D., *J. Am. Chem. Soc.* **2003,** *125*, 6344-6345.

(12) Katz, J. D.; Overman, L. E., *Tetrahedron* **2004,** *60*, 9559-9568.

(13) Lovely, C. J.; Du, H.; He, Y.; Rasika Dias, H. V., *Org. Lett.* **2004,** *6*, 735-738.

(14) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D., *Org. Lett.* **2005,** *7*, 1679-1682.

(15) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G., *Angew. Chem., Int. Ed.* **2005,** *44*, 765-769.

(16) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D., *Tetrahedron* **2006,** *62*, 5223-5247.

(17) Gergely, J.; Morgan, J. B.; Overman, L. E., *J. Org. Chem.* **2006,** *71*, 9144-9152.

(18) Nakadai, M.; Harran, P. G., *Tetrahedron Lett.* **2006,** *47*, 3933-3935.

(19) Schroif-Gregoire, C.; Travert, N.; Zaparucha, A.; Al-Mourabit, A., *Org. Lett.* **2006,** *8*, 2961-2964.

(20) Tan, X.; Chen, C., *Angew. Chem., Int. Ed.* **2006,** *45*, 4345-4348.

(21) Wang, S.; Dilley, A. S.; Poullennec, K. G.; Romo, D., *Tetrahedron* **2006,** *62*, 7155-7161.

(22) Lanman, B. A.; Overman, L. E., *Heterocycles* **2006,** *70*, 557-570.

(23) Cernak, T. A.; Gleason, J. L., *J. Org. Chem.* **2007,** *73*, 102-110.

(24) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S., *J. Am. Chem. Soc.* **2007,** *129*, 12896-12900.

(25) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J., *Org. Lett.* **2007,** *9*, 3861-3864.

(26) Bultman, M.; Ma, J.; Gin, D., *Angew. Chem., Int. Ed.* **2008,** *47*, 6821-6824.

(27) Hudon, J.; Cernak, T.; Ashenhurst, J.; Gleason, J., *Angew. Chem., Int. Ed.* **2008,** *47*, 8885-8888.

(28) Zancanella, M. A.; Romo, D., *Org. Lett.* **2008,** *10*, 3685-3688.

(29) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G., *J. Org. Chem.* **2009,** *74*, 5909-5919.

(30) Mukherjee, S.; Dias, H. V. R.; Lovely, C. J., *Org. Biomol. Chem.* **2009,** *7*, 3215-3218.

(31) Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R.; Nishizawa, M., *Chem. Eur. J.* **2009,** *15*, 6560-6563.

(32) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S., *J. Am. Chem. Soc.* **2008,** *130*, 16490-16491.

(33) Yamaguchi, J.; Seiple, I.; Young, I.; O'Malley, D.; Maue, M.; Baran, P., *Angew. Chem.* **2008,** *120*, 3634-3636.

(34) Seiple, I.; Su, S.; Young, I.; Lewis, C.; Yamaguchi, J.; Baran, P., *Angew. Chem.* **2009,** *122*, 1113-1116.

(35) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J., *J. Org. Chem.* **2007,** *72*, 2309-2317.

(36) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J., *Tetrahedron Lett.* **2007,** *48*, 4573-4574.

(37) Grube, A.; Köck, M., *Angew. Chem., Int. Ed.* **2007,** *46*, 2320-2324.

(38) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S., *Tetrahedron Lett.* **2007,** *48*, 2127-2129.

(39) Ishida, M.; Hirasawa, S.; Inagaki, S., *Tetrahedron Lett.* **2003,** *44*, 2187-2190.

(40) Ishida, M.; Tomohiro, S.; Shimizu, M.; Inagaki, S., *Chem. Lett.* **1995,** *24*, 739-740.

(41) Macaulay, J. B.; Fallis, A. G., *J. Am. Chem. Soc.* **1990,** *112*, 1136-1144.

(42) Williamson, K. L.; Hsu, Y.-F. L., *J. Am. Chem. Soc.* **1970,** *92*, 7385-7389.

(43) Williamson, K. L.; Hsu, Y.-F. L.; Lacko, R.; Youn, C. H., *J. Am. Chem. Soc.* **1969,** *91*, 6129-6138.

(44) Letourneau, J. E.; Wellman, M. A.; Burnell, D. J., *J. Org. Chem.* **1997,** *62*, 7272-7277.

(45) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B., *J. Am. Chem. Soc.* **1955,** *77*, 4183-4184.

(46) Franck-Neumann, M.; Sedrati, M., *Tetrahedron Lett.* **1983,** *24*, 1391-1394.

(47) McClinton, M. A.; Sik, V., *J. Chem. Soc. Perkin Trans.* **1992**, 1891-1895.

(48) Goering, B. K.; Ganem, B., *Tetrahedron Lett.* **1994,** *35*, 6997-7000.

(49) King, S. B.; Ganem, B., *J. Am. Chem. Soc.* **1994,** *116*, 562-570.

(50) Burnell, D. J.; Goodbrand, H. B.; Kaiser, S. M.; Valenta, Z., *Can. J. Chem.* **1984,** ***62***, 2398–2400.

(51) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W., *J. Am. Chem. Soc.* **1969,** *91*, 5675-5677.

(52) Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R., *Tetrahedron Lett.* **1975,** *16*, 1161-1164.

(53) Kraihanzel, C. S.; Losee, M. L., *J. Am. Chem. Soc.* **1968,** *90*, 4701-4705.

(54) Wellman, M. A.; Burry, L. C.; Letourneau, J. E.; Bridson, J. N.; Miller, D. O.; Burnell, D. J., *J. Org. Chem.* **1997,** *62*, 939-946.

(55) Corey, E. J.; Noyori, R.; Schaaf, T. K., *J. Am. Chem. Soc.* **1970,** *92*, 2586-2587.

(56) Corey, E.; Schaaf, T.; Huber, W.; Koelliker, U.; Weinshenker, N., *J. Am. Chem. Soc.* **1970,** *92*, 397-398.

(57) Aggarwal, V. K.; Ali, A.; Coogan, M. P., *Tetrahedron* **1999,** *55*, 293-312.

(58) Liang, H.; Schulè, A.; Vors, J.-P.; Ciufolini, M. A., *Org. Lett.* **2007,** *9*, 4119-4122.

(59) Schulè, A.; Liang, H.; Vors, J.-P.; Ciufolini, M. A., *J. Org. Chem.* **2009,** *74*, 1587-1597.

(60) Starr, J. T.; Koch, G.; Carreira, E. M., *J. Am. Chem. Soc.* **2000,** *122*, 8793-8794.

(61) Hoffman, R. V., *Organic Chemistry: an Intermediate Text*. 1 ed.; John Wiley and Sons: Hoboken, 2004.

(62) Cieplak, A. S., *Chem. Rev.* **1999,** *99*, 1265-1336.

(63) Anh, N. T., *Tetrahedron* **1973,** *29*, 3227-3232.

(64) Coxon, J. M.; McDonald, D. Q., *Tetrahedron Lett.* **1992,** *33*, 651-654.

(65) Inagaki, S.; Fujimoto, H.; Fukui, K., *J. Am. Chem. Soc.* **1976,** *98*, 4054-4061.

(66) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S., *Bull. Chem. Soc. Jpn.* **1993,** *66*, 3430-3439.

(67) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S., *J. Am. Chem. Soc.* **1990,** *112*, 8980-8982.

(68) Kiri, S.; Odo, Y.; Omar, H. I.; Shimo, T.; Somekawa, K., *Bull. Chem. Soc. Jpn.* **2004,** *77*, 1499-1504.

(69) Kolakowski, R. V.; Williams, L. J., *Nat Chem 2*, 303-307.

(70) Poirier, R. A.; Pye, C. C.; Xidos, J. D.; Burnell, D. J., *J. Org. Chem.* **1995,** *60*, 2328-2329.

(71) Pye, C. C.; Xidos, J. D.; Burnell, D. J.; Poirier, R. A., *Can. J. Chem.* **2003,** *81*, 14-30.

(72) Xidos, J. D.; Poirier, R. A.; Pye, C. C.; Burnell, D. J., *J. Org. Chem.* **1998,** *63*, 105-112.

(73) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J., *Tetrahedron* **1999,** *55*, 10815-10834.

(74) Varie, D. L.; Beck, C.; Borders, S. K.; Brady, M. D.; Cronin, J. S.; Ditsworth, T. K.; Hay, D. A.; Hoard, D. W.; Hoying, R. C.; Linder, R. J.; Miller, R. D.; Moher, E. D.; Remacle, J. R.; Rieck, J. A.; Anderson, D. D.; Dodson, P. N.; Forst, M. B.; Pierson, D. A.; Turpin, J. A., *Org. Process Res. Dev.* **2007,** *11*, 546-559.

(75) Howarth, N. M.; Wakelin, L. P. G.; Walker, D. M., *Tetrahedron Lett.* **2003,** *44*, 695-698.

(76) Bertus, P.; Zhang, J.-H.; Sir, G.; Weibel, J.-M.; Pale, P., *Tetrahedron Lett.* **2003,** *44*, 3391-3395.

(77) Finkelstein, H., *Chem. Ber.* **1910,** *43*, 1528-1532.

(78) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S., *J. Am. Chem. Soc.* **2000,** *122*, 7596-7597.

(79) Park, K.-H.; Olmstead, M. M.; Kurth, M. J., *J. Org. Chem.* **1998,** *63*, 113-117.

(80) Park, K.-H.; Olmstead, M. M.; Kurth, M. J., *J. Org. Chem.* **1998,** *63*, 6579-6585.

(81) Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M., *Tetrahedron* **1990,** *46*, 2401-2410.

(82) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H., *J. Am. Chem. Soc.* **1974,** *96*, 6513-6514.

(83) Bermejo, F.; Sandoval, C., *J. Org. Chem.* **2004,** *69*, 5275-5280.

(84) Murata, S.; Suzuki, M.; Noyori, R., *J. Am. Chem. Soc.* **1979,** *101*, 2738-2739.

(85) Vialettes, A. Efforts Towards the Total Synthesis of Mitomycins. M.Sc Thesis, UBC, Vancouver, BC, 2009.

(86) Fournier, J. F.; Mathieu, S.; Charette, A. B., *J. Am. Chem. Soc.* **2005,** *127*, 13140-13141.

(87) 500g of **2.58** costs $58.40 from Aldrich (September, 2010).

(88) Hudon, J. Methodologies in Organic Chemistry and their Applications to the Synthesis of Bio-active Small Molecules. Ph.D. Dissertation. McGill, Montreal, Quebec, 2009.

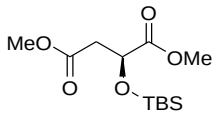
APPENDIX

A1.1 Experimental Protocols

Unless otherwise stated, all IR were run neat sandwiched between 2 NaCl plates, and the spectrum recorded on a Thermo Nicolet Model 4700 Model FT-IR spectrometer. NMR spectra were recorded at room temperature on a Bruker AV-300 spectrometer (300MHz for ^{1}H and 75.5 MHz for ^{13}C) using deuteriochloroform ($CDCl_3$) as a solvent. All coupling constants are reported in hertz (Hz), all chemical shifts are reported in parts per million (ppm). ^{13}C NMR spectra are referenced to the natural-abundance carbon signal of the solvent employed, ^{1}H NMR spectra are referenced to the residual protio isotopomer present in a particular solvent. Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "quin" (quintet) "dd" (doublet of doublets), "td" (triplet of doublets), "m" (multiplet), or "br" (broad). Low-resolution mass spectrometry were obtained in the electrospray (ESI) mode on a Waters Micromass ZQ mass spectrometer. High-resolution mass spectra (m/z) were recorded in the ESI mode of a Micromass LCT mass spectrometer by the UBC Mass Spectrometry laboratory. Elemental analyses were performed on a Carlo Erba EA model 1108 elemental analyzer by the UBC Microanalysis laboratory.

All reagents and solvents were commercially available products, and used without further modification, except CH_2Cl_2 (distilled from CaH_2 under argon) and THF (distilled from Na/benzophenone under argon). Commercial *n*-BuLi was titrated against diphenyl acetic acid. Analytical TLC was carried out with Merck silica gel 60 plates with a fluorescent indicator. All flash chromatography were run with 40-63 μm (230-400 mesh) silica on columns of appropriate size. All reactions were performed under dry argon in oven-dried flasks equipped with Teflon™

stirbars. All flasks were equipped with rubber septa for introducing solvents, substrates, and reagents via syringe.



A1.2 Preparation of (*S*)-dimethyl 2-(*tert*-butyldimethylsilyloxy)succinate (2.12)

To a stirring solution of malic acid (5.120g, 38.18mmol) in MeOH (30mL) was added $SOCl_2$ (5.0mL, 69mmol) dropwise. The reaction was then stirred at RT for 22 hr and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20mL), followed by addition of TBS-Cl (6.240g, 41.40mmol), imidazole (8.0g, 120mmol), and DMAP (0.202g, 1.65mmol). The yellow reaction mixture was stirred at RT for 24 hr, and then poured into sat. aq. $NaHCO_3$ (100mL), and then extracted with CH_2Cl_2 (3x50mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The yellow oily residue was flash chromatographed (1:9 to 1:1, EtOAc:hex) revealing **2.12** (8.897g, 84% yield) as a clear oil.

^{1}H:	4.63 (dd, 1H, J = 8.00, 4.70), 3.73 (s, 3H), 3.68 (s, 3H), 2.74 - 2.65 (AB_m, 2H) , 0.86 (9H, s), 0.09 (3H, s), 0.05 (3H, s)	
^{13}C:	172.9, 170.9, 69.26, 52.3, 51.9, 40.2, 25.7, 18.3, -4.8, -5.5	
IR (cm^{-1}):	2954, 2858, 1743, 1438, 1258, 1168, 1137, 836, 780	
MS:	299.4 $[M+23]^+$	
HRMS:	calcd for $C_{12}H_{24}O_5Si$:	299.1291 $[M+Na]^+$
	found:	299.1298 $[M+Na]^+$

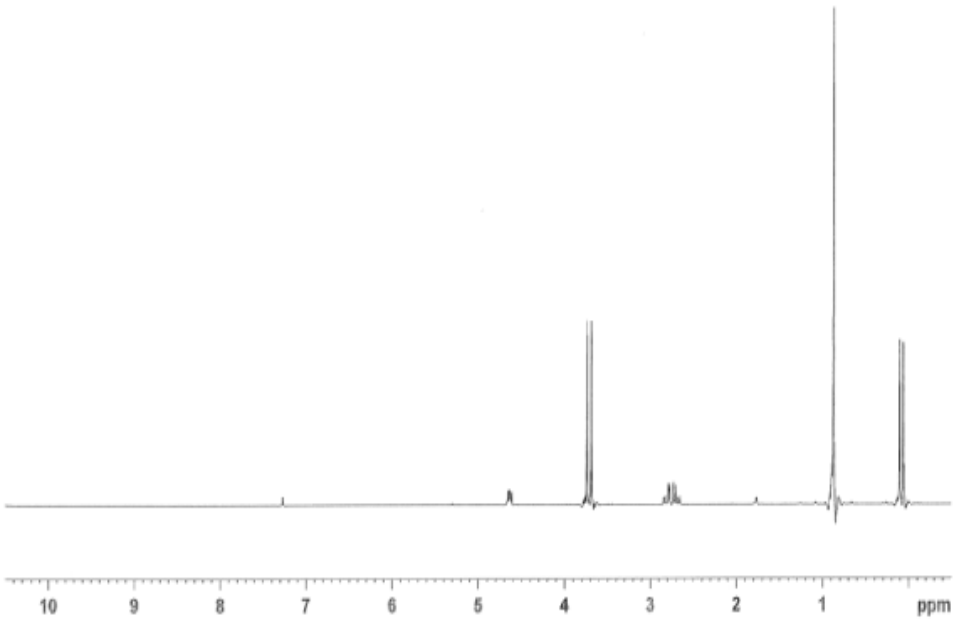


Figure A1: ^{1}H-NMR spectrum of **2.12**

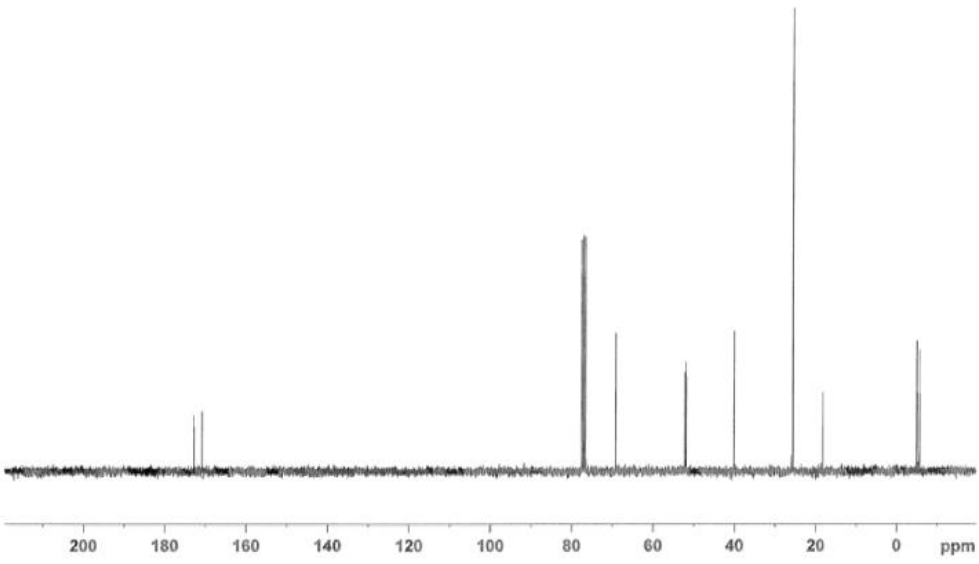


Figure A2: ^{13}C-NMR spectrum of **2.12**

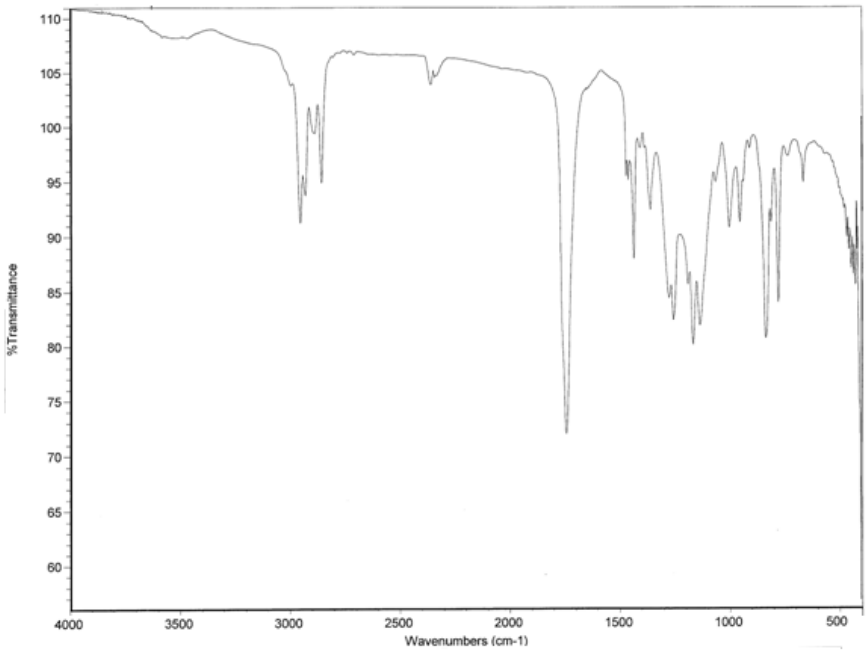
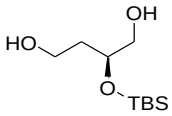


Figure A3: IR spectrum of **2.12**



A1.3 Preparation of (*S*)-2-(*tert*-butyldimethylsilyloxy)butane-1,4-diol (2.13)

A stirring solution of **2.12** (0.6462g, 2.338mmol) in THF (11mL) was cooled to 0°C in an ice bath. Dibal-H (1M in hexanes, 10mL, 10mmol) was added dropwise. The reaction was left stirring for 5 hr at 0°C, then quenched with MeOH (5mL), and the resulting gelatinous slurry was warmed to RT. The slurry was added to sat. aq. Rochelle's Salt (50mL) and EtOAc (50mL). The resultant biphasic solution was stirred at RT for 1 hr. The phases were separated, followed by extraction of the aqueous phase with EtOAc (2x50mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* yielding **2.13** (0.3920g, 76% yield) as a clear oil.

^{1}H:	3.93 (quin, 1H, *J* = 5.1), 3.79-3.64 (m, 2H), 3.61-3.50 (m, 2H), 2.96 (br s,1H), 2.81 (br s,1H), 1.79 (q, 2H, *J* = 5.6), 0.88 (s, 9H), 0.08 (s, 6H)	
^{13}C:	71.0, 66.3, 59.0, 36.9, 25.9, 18.1, -4.5, -4.7	
IR (cm^{-1}):	3334, 2930, 2858, 1472, 1464, 1256, 1049, 939, 837, 776, 668	
MS:	243.4 $[M+Na]^+$	
HRMS:	calcd for $C_{10}H_{24}O_3Si$:	243.1392 $[M+Na]^+$
	found:	243.1390 $[M+Na]^+$

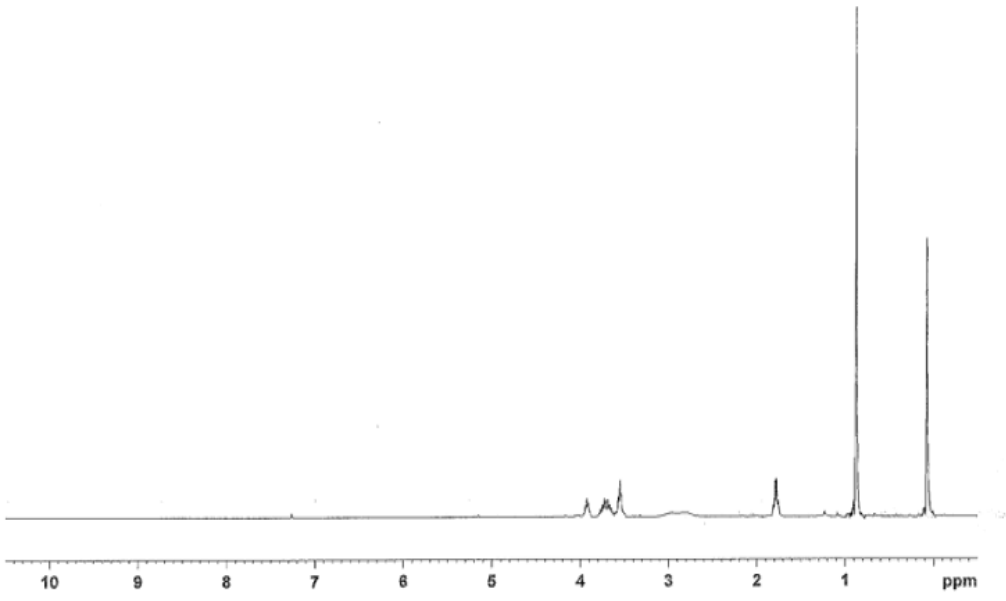


Figure A4: ^{1}H-NMR spectrum of **2.13**

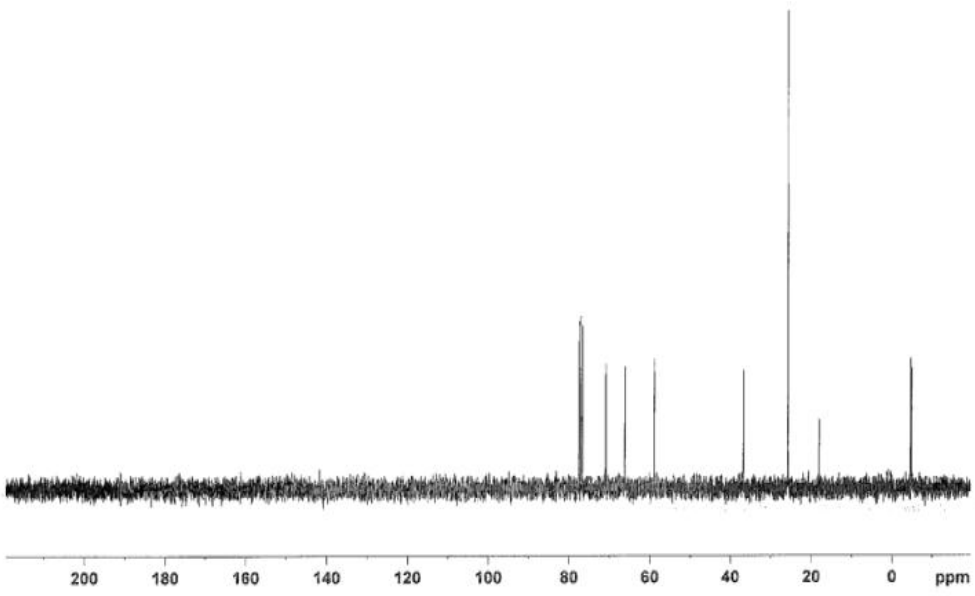


Figure A5: ^{13}C-NMR spectrum of **2.13**

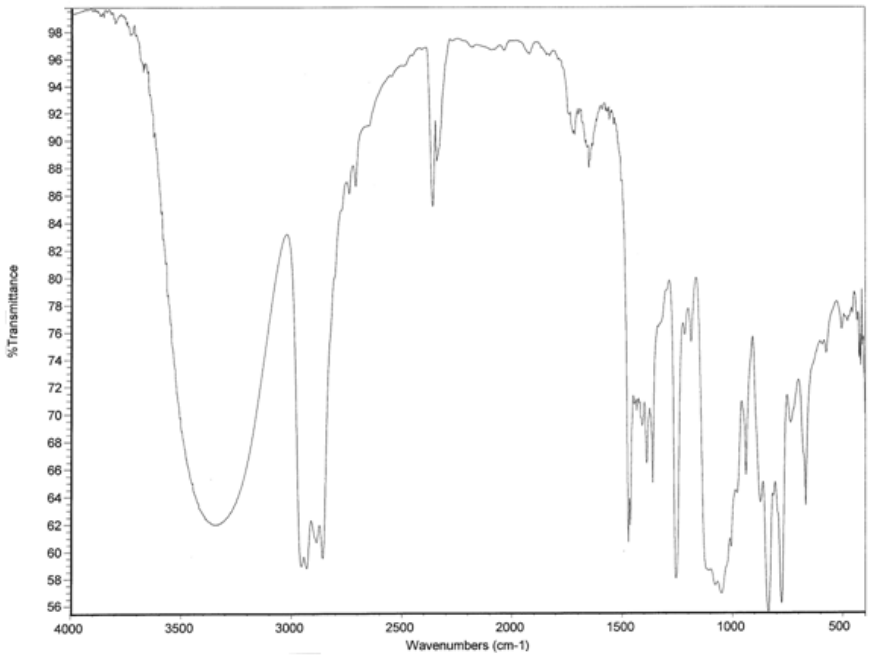
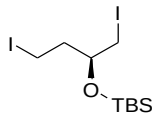


Figure A6: IR-NMR spectrum of **2.13**



A1.4 Preparation of (*S*)-*tert*-butyl(1,4-diiodobutan-2-yloxy)dimethylsilane (2.15)

A solution of **2.13** (3.010g, 13.66mmol) in CH_2Cl_2 (25mL) was cooled to 0°C in an ice bath. TEA (12mL, 87mmol) was then added as a single portion, followed by dropwise addition of Ms-Cl (3.4mL, 44mmol). The reaction was warmed to RT and stirred for 1 hr, and then diluted with CH_2Cl_2 (30mL). The solution was washed with H_2O (75mL), 0.1N HCl (75mL), H_2O (3x75mL), and brine (50mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The orange oily residue was dissolved in acetone (21mL), and then NaI (11g, 73mmol) was added as a single portion. The mixture was refluxed for 15 hr and then concentrated *in vacuo*. The residue was dissolved in ether (50mL), and washed with H_2O (50mL). The layers were separated, and the aqueous layer was further extracted with ether (2x50mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* revealing **2.15** (4.156g, 70% yield) as an orange oil.

^{1}H:	3.58 - 3.67 (m, 1 H), 3.12 - 3.30 (m, 4 H), 3.45 - 3.74 (m, 1 H), 0.91 (s, 9 H), 0.13 (s, 6H)	
^{13}C:	70.7, 40.9, 25.9, 18.1, 13.1, 2.4, -4.2, -4.3	
IR (cm^{-1}):	2954, 2928, 2856, 1255, 1078, 1052, 886, 804, 777	
MS:	313.3 $[M-I]^+$	
HRMS:	calcd for $C_{10}H_{22}I_2OSi$:	313.0485 $[M-I]^+$
	found:	313.0488 $[M-I]^+$

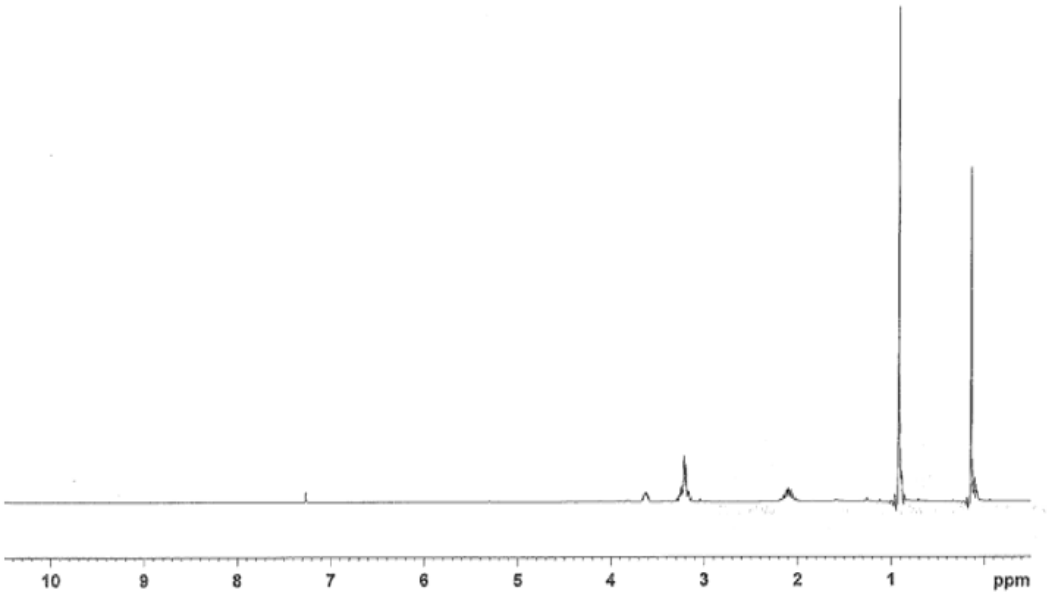


Figure A7: ^{1}H-NMR spectrum of **2.15**

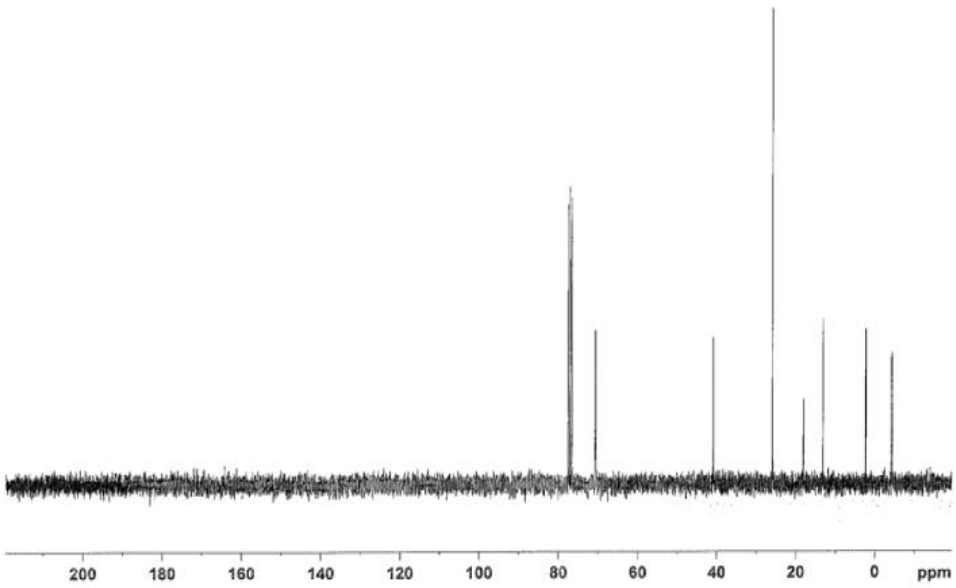


Figure A8: ^{13}C-NMR spectrum of **2.15**

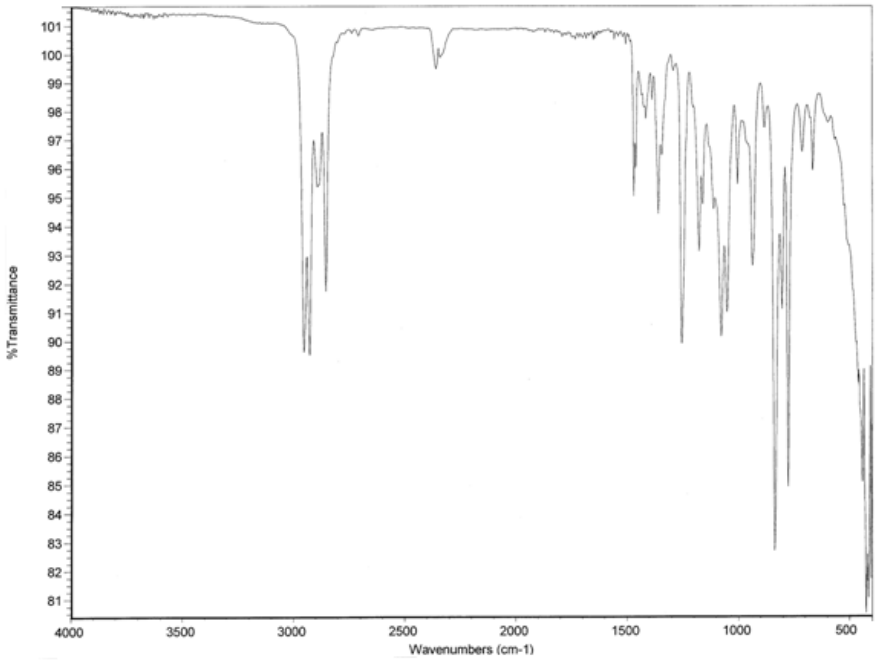
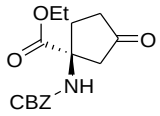


Figure A9: IR spectrum of **2.15**



A1.5 Preparation of (*R*)-ethyl 1-(benzyloxycarbonylamino)-3-oxocyclopentanecarboxylate (2.27)

To a -78°C stirring solution of HMDS (7.7mL, 36mmol) in THF (60mL) was added BuLi (1.2M in hexanes, 30mL, 36mmol). The reaction mixture was stirred at -78°C for 0.5 hr, and then **2.16** (4.34 g, 18.2mmol) in THF (60mL) was added dropwise at -78°C. Then, **2.15 (**4.0g, 9.1mmol) in THF (36mL) was added dropwise at -78°C. The reaction solution was stirred at -78°C for 1.5 hr, then allowed to warm to RT. The black reaction mixture was stirred at RT for 4 hr, and then poured into H_2O (400mL). The solution was extracted with EtOAc (3x200mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The brown oil residue was flash chromatographed (1:99 to 3:97, EtOAc:hex) yielding an orange oil whose spectral (^1H, MS) properties correspond to semipure **2.17**. The orange oil was dissolved in TBAF (1M in THF, 15mL, 15mmol) and the resulting mixture was stirred for 3 hr at RT. The reaction mixture was then diluted with EtOAc (180mL), washed with H_2O (2x120mL), and brine (120mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The brown residue was dissolved in ether (24mL) and an aq. solution of HCl (2N, 24mL). The reaction mixture was then stirred at RT for 19 hr, followed by phase separation. The aqueous phase was further washed with ether (2x24mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The clear film residue was dissolved in acetone (7mL) and H_2O (7mL). To the reaction mixture was added K_2CO_3 (0.3288g, 2.379mmol) and CBZ-Cl (0.33mL, 2.4mmol) as single portions. The reaction mixture was then stirred at RT for 2 hr, and then extracted with EtOAc (3x40mL). The combined organic extracts were dried ($MgSO_4$) and

concentrated *in vacuo*. The residual orange oil was filtered on a plug of silica and then dissolved in CH_2Cl_2 (10mL) (note: "wet" CH_2Cl_2 was used). A single portion of DMP (0.400g, 0.943mmol) was added, and then the orange reaction mixture was stirred at RT for 2 hr. The reaction mixture was washed with a 1:1 solution of sat. aq. $NaHCO_3$ (15mL) and sat. aq. NaS_2O_3 (15mL). The aqueous phase was further extracted with CH_2Cl_2 (2x20mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The residual white oil was flash chromatographed (1:2 EtOAc:hex) revealing **2.27** as a clear oil (0.4274g, 15%).

^{1}H:	7.34 (s, 5 H), 5.59 (s, 1H), 5.09 (s, 2H), 4.20 (d, 2H, *J* = 5.34), 2.99 - 2.73 (m, 2H), 2.51 - 2.33 (m, 4H), 1.22 (t, 3H, *J* = 7.20)	
^{13}C:	214.1, 172.9, 155.5, 136.0, 128.7, 128.4, 128.3, 67.1, 62.5, 62.4, 47.8, 36.2, 32.7, 14.1	
IR (cm^{-1}):	3340, 2981, 1732, 1520, 1455, 1257, 1158, 1097, 1051, 742, 699	
MS:	328.4 $[M+23]^+$	
HRMS:	calcd for $C_{16}H_{19}NO_5$:	328.1161 $[M+23]^+$
	found:	328.1168 $[M+23]^+$

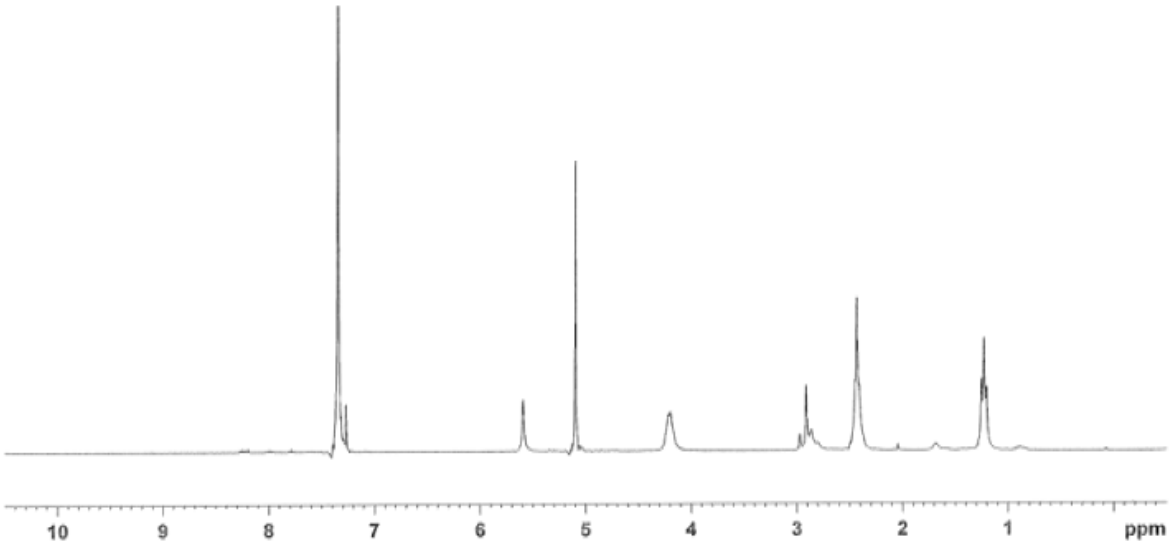


Figure A10: ^{1}H-NMR spectrum of **2.27**

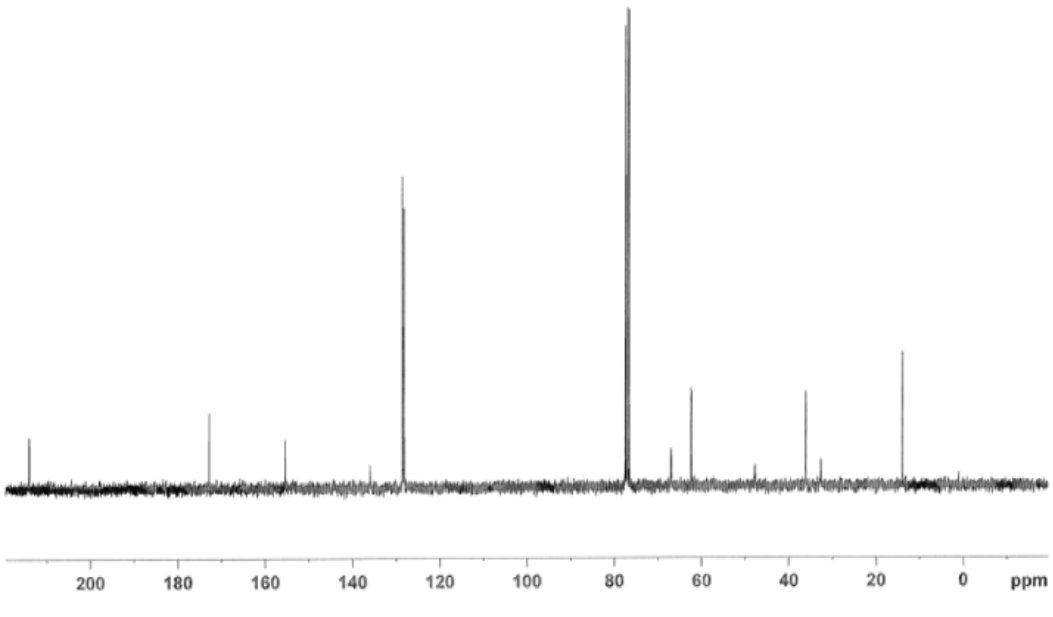


Figure A11: ^{13}C-NMR spectrum of **2.27**

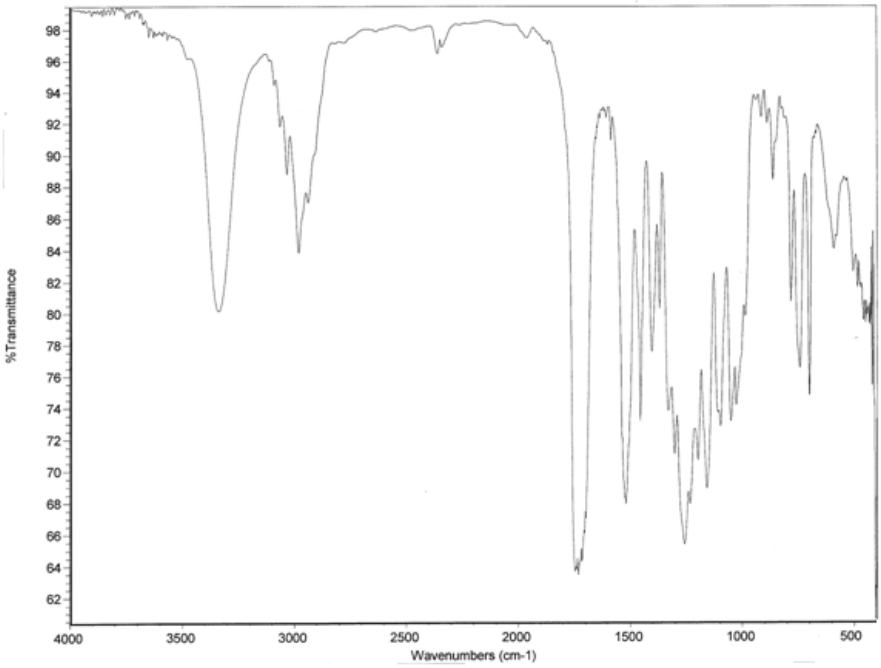
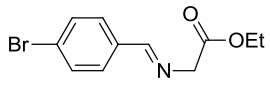


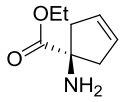
Figure A12: IR spectrum of **2.27**



A1.6 Preparation of (*E*)-ethyl 2-(4-bromobenzylideneamino)acetate (2.39)

A mixture of ethyl 2-aminoacetate hydrochloride (10.282g, 73.664mmol), 4-bromobenzaldehyde (13.0g, 70.3mmol), Na_2SO_4 (10g) was dissolved in CH_2Cl_2 (120mL). The reaction mixture was stirred at RT and TEA (20mL, 140mmol) was added as a single portion. The reaction was stirred at RT for 20 hr, and then filtered. The filtrate was reduced *in vacuo*, and the residue dissolved in diethyl ether (250mL). The solution was washed with H_2O (100mL), dried ($MgSO_4$) and concentrated *in vacuo* revealing the title compound (15.45g, 81%) as a yellow oil.

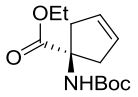
2.39 is a known compound, spectral data (^1H, ^{13}C, MS) is in agreement with literature values (Park, K. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998,** *63*, 113-117).



A1.7 Preparation of ethyl 1-(*tert*-butoxycarbonylamino)cyclopent-3-enecarboxylate (2.41)

A solution of **2.39** (28.5g, 106mmol) in THF (120mL) was added dropwise to a stirring solution of NaH (8.4g, 60% dispersion in mineral oil, 210mmol) in an ice bath. Then cis-1,4-dichlorobut-2-ene (10.4mL, 10.8mmol) was added as a single portion. The reaction was stirred at 0°C for 20 min, and then warmed to RT and further stirred for 1 hr. The reaction was concentrated *in vacuo* and then dissolved in ether (300mL). A solution of aq. HCl (1N, 200mL) was added, and the mixture was stirred at RT for 15 min. The phases were then separated, and the aqueous phase was made alkaline (pH 8) with aq. NaOH (2N) and extracted with EtOAc (3x200mL). The aqueous phase was concentrated *in vacuo* and then dissolved in EtOH (125mL). The mixture was stirred as $SOCl_2$ (10mL) was added dropwise, and left stirring at RT for 14 hr. The reaction mixture was then concentrated *in vacuo* and dissolved in H_2O (100mL). The aqueous solution was made alkaline (pH 8) with aq. NaOH (2N), and extracted with CH_2Cl_2 (3x100mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo,* revealing **2.41** (8.221g, 50%) as a red oil, which was used without further purification.

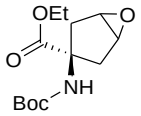
2.41 is a known compound, spectral data (^1H, ^{13}C, MS) is in agreement with literature values (Park, K. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998,** *63,* 113-117).



A1.8 Preparation of ethyl 1-(*tert*-butoxycarbonylamino)cyclopent-3-enecarboxylate (2.34)

A solution of Boc_2O (3.097g, 14.19mmol) in CH_2Cl_2 (12mL) was added dropwise to a stirring solution of **2.41** (2.154g, 13.87mmol) in CH_2Cl_2 (12mL). Then, an aqueous solution of $NaHCO_3$ (3.0g, 36mmol) in H_2O (20mL) was added as a single portion. The reaction was stirred at RT for 3 hr, then extracted with CH_2Cl_2 (3x30mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The brown solid residue was left standing overnight, then washed with hexanes to reveal **2.34** (2.510g, 71%) as a white solid.

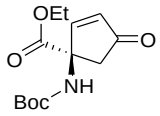
2.34 is a known compound, spectral data (^1H, ^{13}C, MS) is in agreement with literature values (Park, K. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579–6585.).



A1.9 Preparation of ethyl 3-(*tert*-butoxycarbonylamino)-6-oxabicyclo[3.1.0]hexane-3-carboxylate (2.42)

To a stirring solution of **2.34** (0.560g, 2.19mmol) and $NaHCO_3$ (0.336g, 4.00mmol) in CH_2Cl_2 (20mL) was added *m*CPBA (70%, 0.560g, 2.2mmol). After 16 hr of stirring at RT, the reaction was diluted with CH_2Cl_2 (40mL) and washed with sat. aq. Na_2SO_3 (50mL). The aqueous layer was back-extracted with CH_2Cl_2 (2x30mL), followed by H_2O (2x50mL) washes of the combined organic layers. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The orange oily residue was flash chromatographed (1:19 to 1:5, EtOAc:hex) revealing **2.42** (0.4407g, 74% yield, 80% based on 0.043g recovered **2.34**) as a clear film with a 84:16 mixture of diastereomers (by ^{1}H-NMR).

2.42 is a known compound, spectral data (^{1}H, ^{13}C, MS) is in agreement with literature values (Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J.).



A1.10 Preparation of (*S*)-ethyl 1-(*tert*-butoxycarbonylamino)-4-oxocyclopent-2-enecarboxylate (2.44)

To a 0°C stirring solution of diisopropylamine (0.23mL, 1.7mmol) in THF (2.5mL) was added BuLi (1.6M in hexanes, 1.00mL, 1.66mmol). The reaction mixture was stirred at 0°C for 40 min, and then **2.42** (0.1406g, 0.5182mmol) in THF (2.5mL) was added dropwise. The reaction mixture was stirred at 0°C for 45 min, and then poured into sat. aq. NH_4Cl (12mL). The solution was extracted with EtOAc (3x15mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. To the orange oily residue was added DMP (0.404g, 0.953mmol), then the mixture was dissolved in CH_2Cl_2 (4.5mL) (note: "wet" CH_2Cl_2 was used). The orange reaction mixture was stirred at RT for 3 hr. The reaction mixture was washed with a 1:1 solution of sat. aq. $NaHCO_3$ (15mL) and sat. aq. NaS_2O_3 (15mL). The aqueous phase was further extracted with CH_2Cl_2 (2x20mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The residual white oil was flash chromatographed (1:4 EtOAc:hex) revealing **2.44** (0.0961g, 69%) as an off-white solid.

^{1}H:	7.44 (d, 1H, *J* = 5.14), 6.34 (d, 1H, *J* = 5.59), 5.68 (s, 1H), 4.21 (q, 2H, *J* = 7.15), 3.09 - 2.50 (AB, 2H), 1.41 (s, 9H), 1.24 (t, 3H, *J* = 7.13)
^{13}C:	205.3, 170.8, 159.7, 154.4, 135.8, 80.8, 65.1, 62.9, 46.0, 28.3, 14.0
IR (cm^{-1}):	3346, 2980, 1727, 1506, 1368, 1288, 1255, 1166, 1044, 817, 788
MP:	84-86°C
MS:	292.4 $[M+23]^+$

HRMS: calcd for $C_{13}H_{19}NO_5$: 292.1161 $[M+23]^+$

found: 292.1166 $[M+23]^+$

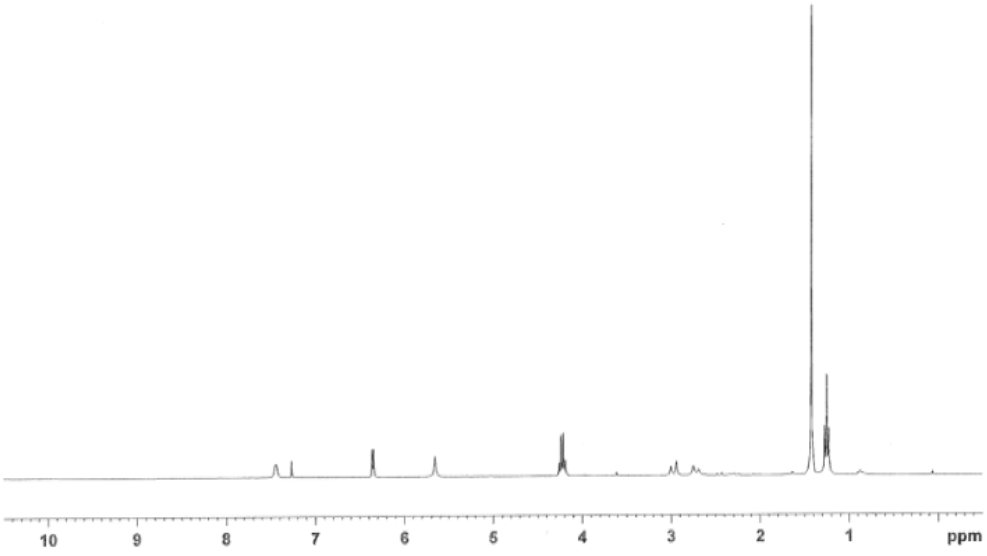


Figure A13: ^{1}H-NMR spectrum of **2.44**

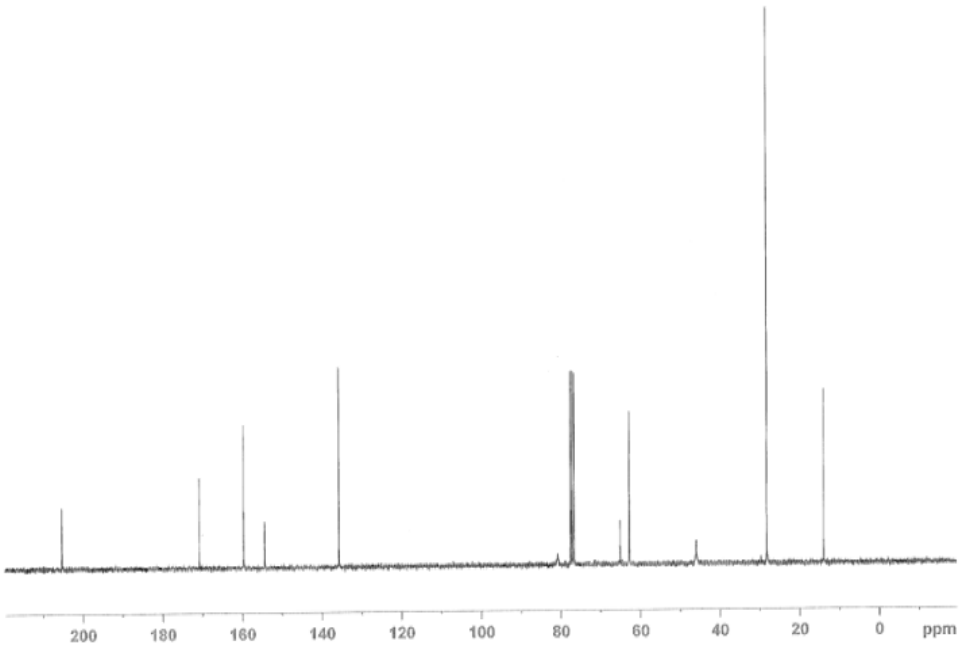


Figure A14: ^{13}C-NMR spectrum of **2.44**

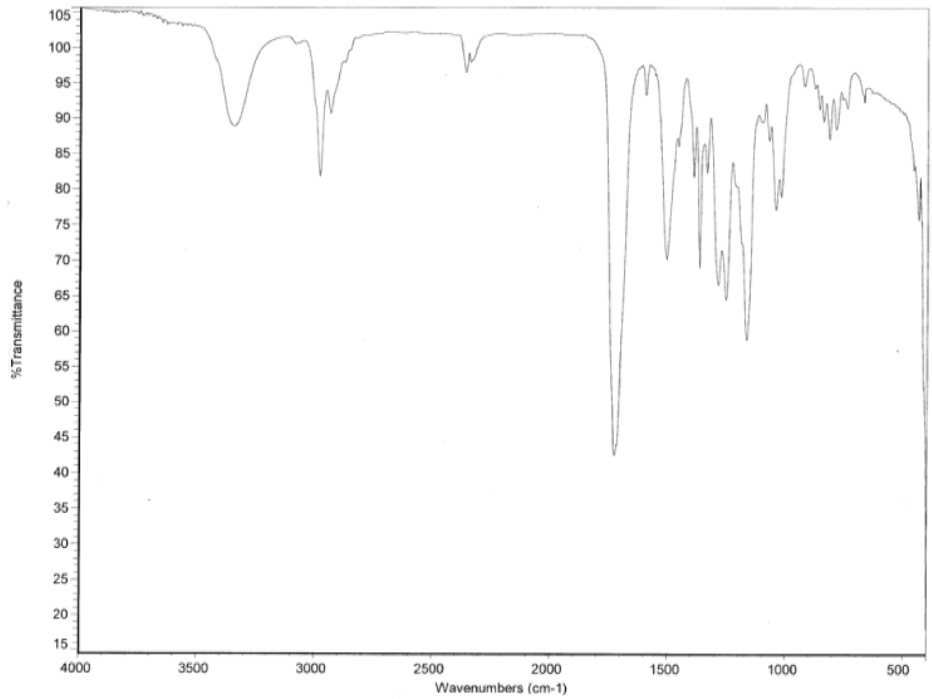
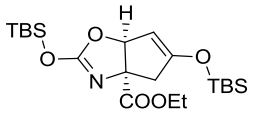


Figure A15: IR spectrum of **2.44**



A1.11 Preparation of (3a*R*,6a*S*)-ethyl 2,5-bis(*tert*-butyldimethylsilyloxy)-4,6a-dihydro-3a*H*-cyclopenta[d]oxazole-3a-carboxylate (2.46)

To a stirring solution of **2.44** (0.054g, 0.20mmol) in CH_2Cl_2 (1mL) was added Hunig's base (0.10mL, 0.57mmol), the mixture was then cool to -78°C by a dry ice/acetone bath. TBS-OTf (0.09mL, 0.4mmol) was added dropwise to the stirring reaction mixture, and then the solution was allowed to warm to RT. After 4 hr of stirring, the reaction was quenched by addition of H_2O (10mL). The aqueous layer was then extracted with CH_2Cl_2 (3x6mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Then, the oily residue was flash chromatographed (1:19 to 1:5, EtOAc:hex) on neutral alumina (Bockman grade I) revealing the title compound (0.0288g, 33%) as a pale yellow oil.

^{1}H:	5.31 (t, 1H, *J* = 1.79), 4.82 (q, 1H, *J* = 1.80), 4.29 (q, 2H, *J* = 7.12), 3.36 (dd, 1H, *J* = 16.85, 1.84), 2.57 (dt, 1H, *J* = 16.86, 1.84), 1.00 (s, 9H), 0.95 (s, 9), 0.40 (s, 3H), 0.22 - 0.29 (overlapping s, 6H), 0.13 (s, 3H)	
^{13}C:	173.1, 161.7, 159.7, 100.9, 88.0, 70.5, 63.3, 45.7, 28.0, 26.0, 19.6, 18.8, 14.5, -4.2, -4.4, -4.5, -4.7.	
IR (cm^{-1}):	2932, 2859, 1749, 1646, 1338, 1354, 1201, 1056, 1022, 953, 839, 785	
MS:	464.4 $[M+Na]^+$	
HRMS:	calcd for $C_{21}H_{40}NO_5Si$:	464.2445 $[M+Na]^+$
	Found:	464.2304 $[M+Na]^+$

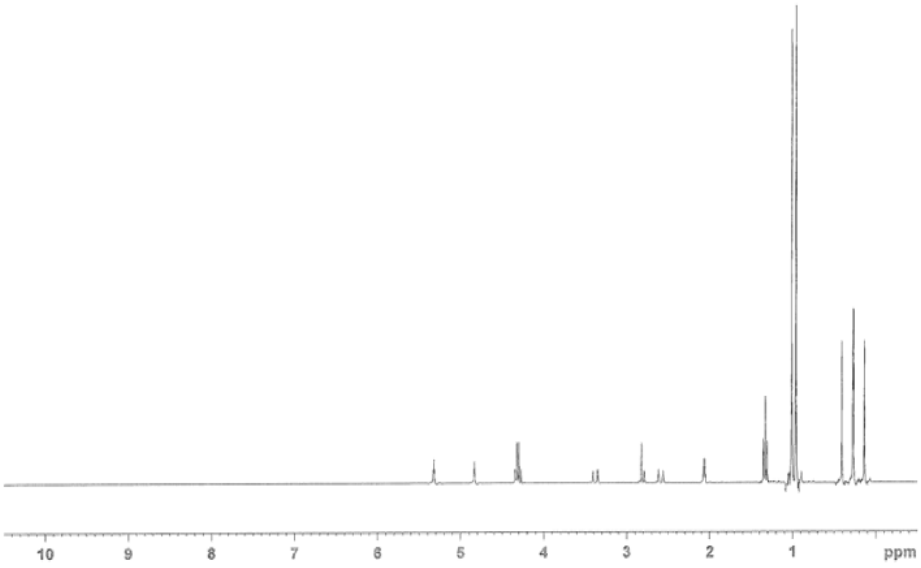


Figure A16: ^{1}H-NMR spectrum of **2.46**

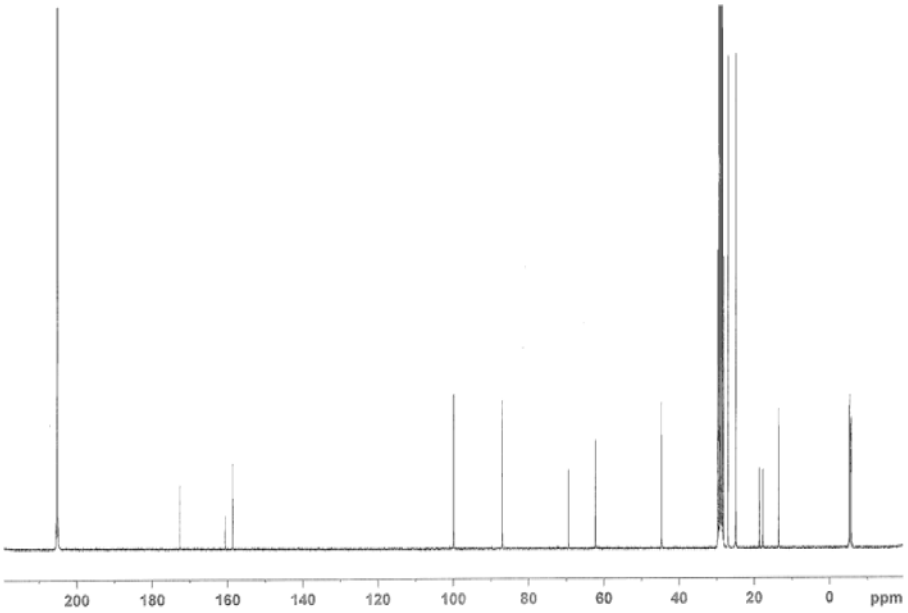


Figure A17: ^{13}C-spectrum NMR of **2.46**

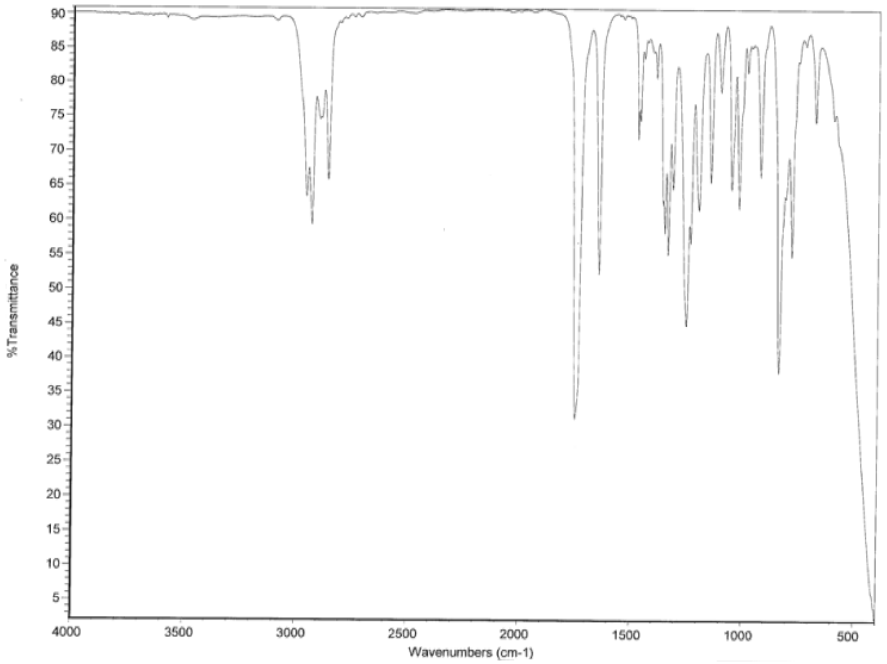
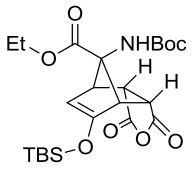


Figure A18: IR spectrum of **2.46**



A1.12 Preparation of tricycle (2.60)

To a stirring solution of **2.44** (0.0550g, 0.204mmol) in CH_2Cl_2 (1mL) was added TEA (0.10mL, 0.72mmol), the mixture was then cool to -78°C by a dry ice/acetone bath. TBS-OTf (0.10mL, 0.44mmol) was added dropwise to the stirring reaction mixture, and the solution was warmed to RT. After 15 min of stirring, the reaction was adsorbed directly unto neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) revealing **2.45** and **2.46** (0.0701g, 42% **2.45**, 42% **2.46**) as a clear oily 1:1 inseparable mixture.

Maleic anhydride (0.025g, 0.25mmol) was added to the clear oil, and the mixture was dissolved in CH_2Cl_2 (1mL). The reaction mixture was stirred at RT for 1.5 hr, and then the solvent was removed *in vacuo*. The oily residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) yielding **2.60** (0.0252g, 62% from **2.45**:**2.46**, 26% over two steps) as a white solid.

^{1}H ($(CD_3)_2CO$): 6.86 (br s, 1H), 4.87 (d, 1H, *J* = 2.0), 4.12 (q, 2H, *J* = 7.1), 4.02 (dd, 1H, *J* = 7.8, 4.6), 3.86 (dd, 1H, *J* = 7.7, 4.7), 3.70 (br s, 1H), 3.59 (br s, 1H), 1.40 (s, 9H), 1.22 (t, 3H, 7.1), 0.92 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H)

^{13}C($(CD_3)_2CO$): 171.7, 170.8, 169.1, 158.8, 154.1, 97.6, 79.3, 78.8, 60.6, 54.0, 48.8, 48.4, 44.7, 27.4, 24.7, 17.5, 13.5, -6.0, -6.2

IR (cm^{-1}): 1781, 1735

MP: 159-162°C

MS: 480.2 $[M-1]^-$

HRMS: calcd for $C_{23}H_{34}NO_8Si$: 480.2054 $[M-1]^-$

found: 480.2050 $[M-1]^-$

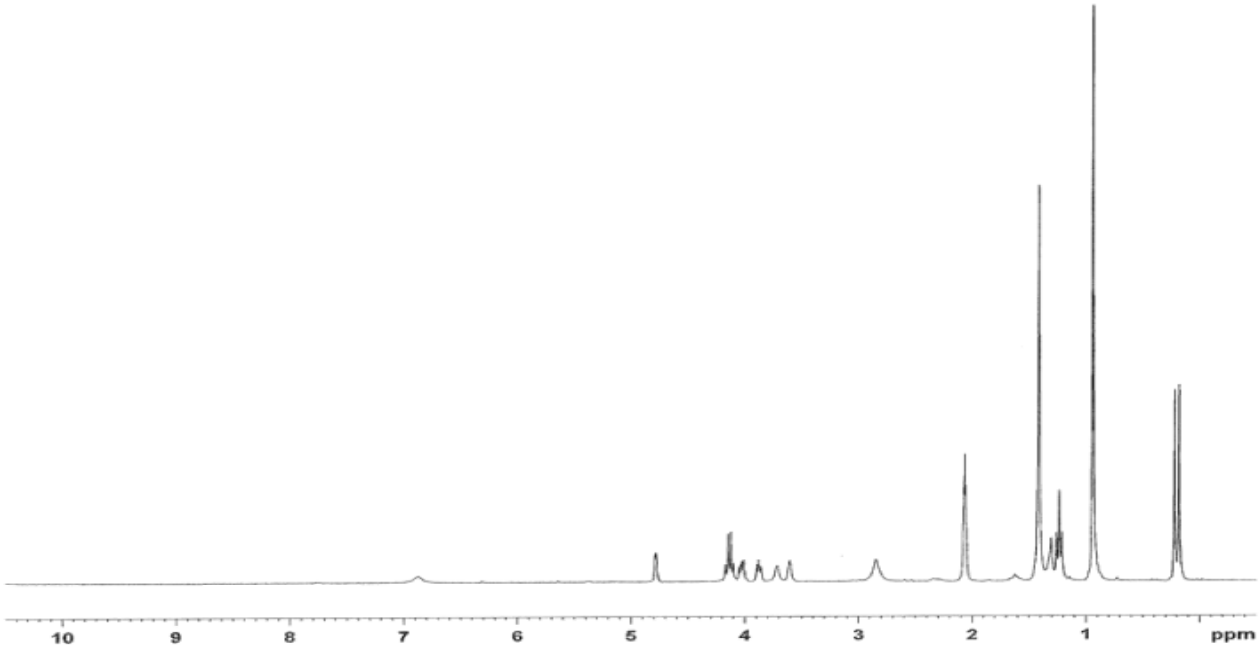


Figure A19: ^{1}H-NMR spectrum of **2.60**

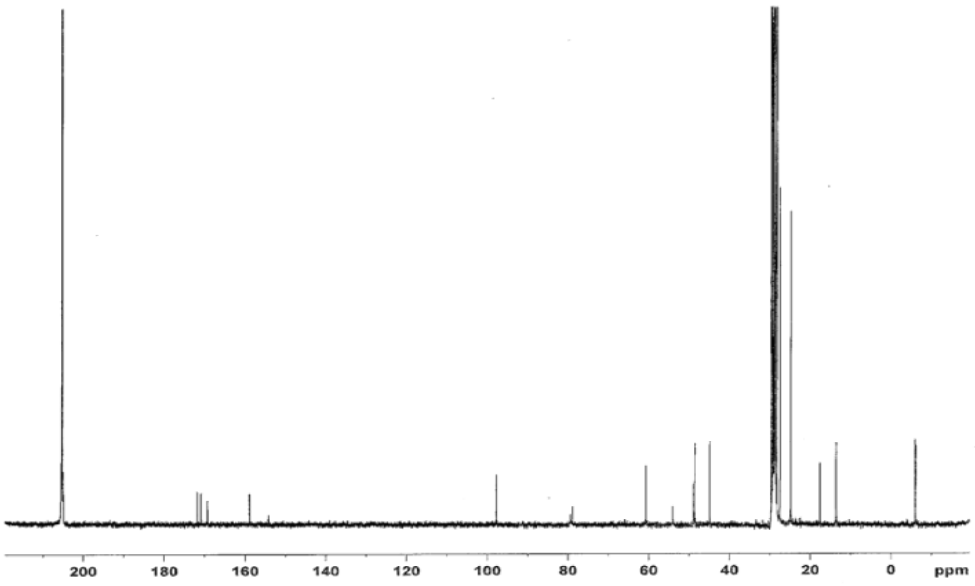


Figure A20: ^{13}C-NMR spectrum of **2.60**

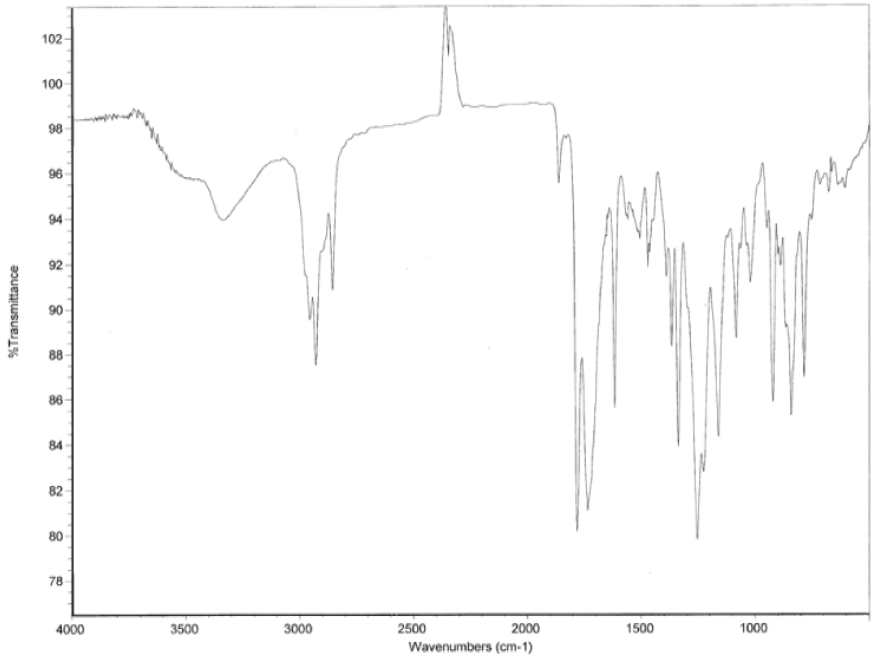


Figure A21: IR spectrum of **2.60**

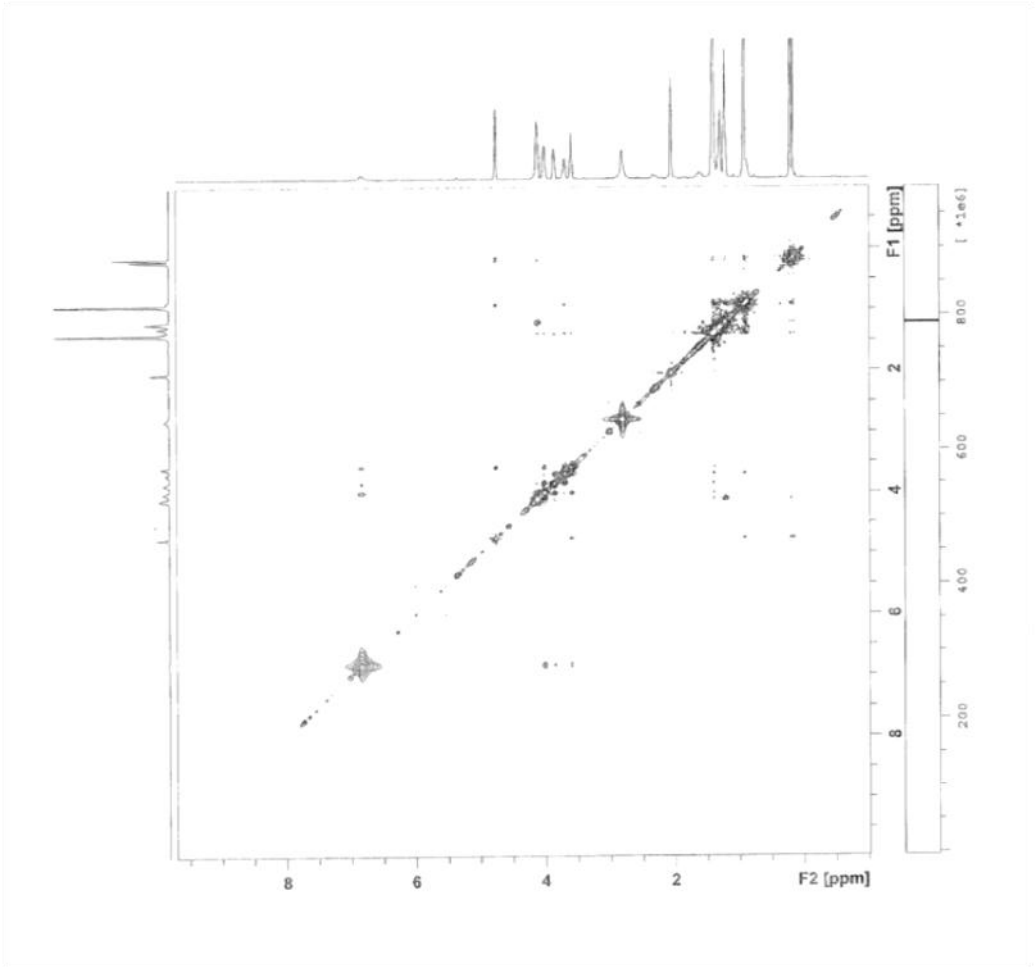


Figure A22: NOESY-NMR spectrum of **2.60**

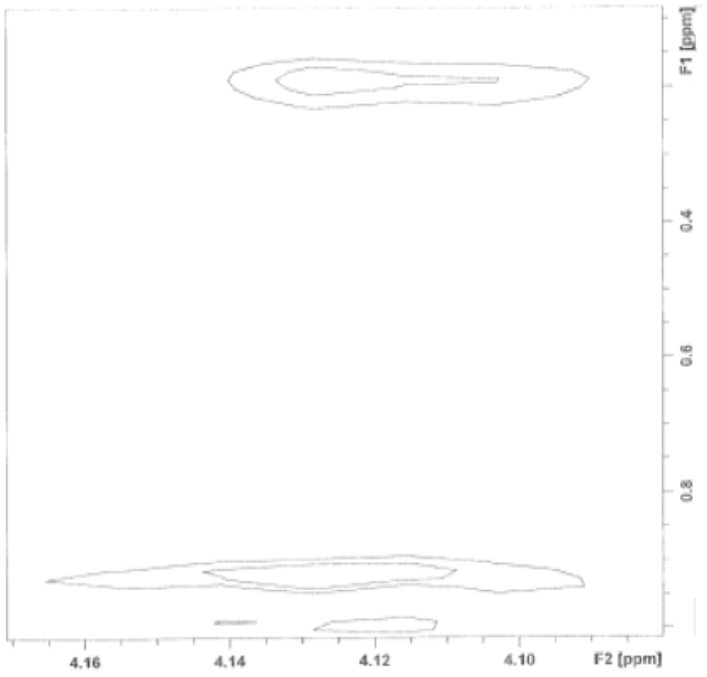


Figure A23: Selected signals of **2.60** NOESY-NMR spectrum

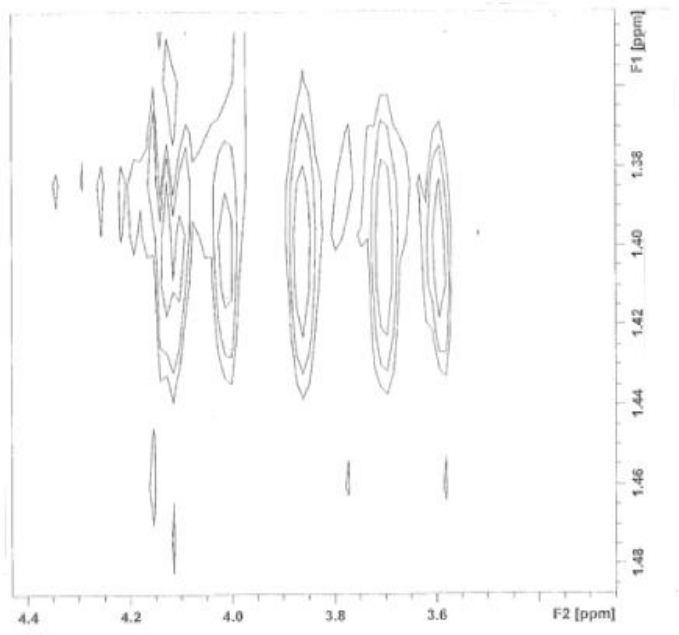
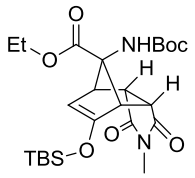


Figure A24: Selected signals of **2.60** NOESY-NMR spectrum



A1.13 Preparation of tricycle (2.61)

To a stirring solution of **2.44** (0.0501g, 0.186mmol) in CH_2Cl_2 (1mL) was added TEA (0.085mL, 0.61mmol), the mixture was then cool to -78°C by a dry ice/acetone bath. TBS-OTf (0.085mL, 0.37mmol) was added dropwise to the stirring reaction mixture, and the solution was warmed to RT. After 15 min of stirring, the reaction was adsorbed directly unto neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) unveiling **2.45** and **2.46** (0.0622g, 44% **2.45**, 37% **2.46**) as a clear oily 1.2:1 inseparable mixture

N-methylmaleimide (0.028g, 0.25mmol) was added to the clear oil, and the mixture was dissolved in CH_2Cl_2 (1mL). The yellow reaction mixture was stirred at RT for 2 hr, and then the solvent was removed *in vacuo*. The oily residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) yielding **2.61** (0.0377g, 92% from **2.45**:**2.46** mixture, 41% over two steps) as a white powder.

^{1}H(C_6D_6):	4.44 (dd, 1H, *J* = 3.50, 1.39), 3.84 - 4.01 (m, 2H), 3.79 (br s, 1H), 3.39 (br s, 1H), 2.98 - 2.91 (m, 1H), 2.88, (br s, 1H), 2.71 (s, 3H), 1.37 (s, 9H), 0.96 (t, 3H, *J* = 7.10), 0.06 (s, 3H), -0.01 (s, 3H)
^{13}C(C_6D_6):	176.5, 175.4, 170.2, 158.7, 154.4, 97.52, 78.76, 61.1, 53.9, 48.6, 47.1, 43.5,30.2, 28.3, 25.5, 24.5, 18.1, 14.2, -5.1 (2 overlapping peaks)
IR (cm^{-1}):	3337, 2931, 1705, 1618, 1367, 1339, 1252, 1165, 1090, 1058, 1010, 842, 830
MP:	161-165°C

MS:	517.3 $[M+Na]^+$	
HRMS:	calcd for $C_{24}H_{38}N_2O_7Si$:	517.2346 $[M+Na]^+$
	found:	517.2344 $[M+Na]^+$
EA:	calcd:	N 5.66%, C 58.27%, H 7.74%
	found:	N 5.51%, C 58.57%, H 7.80%

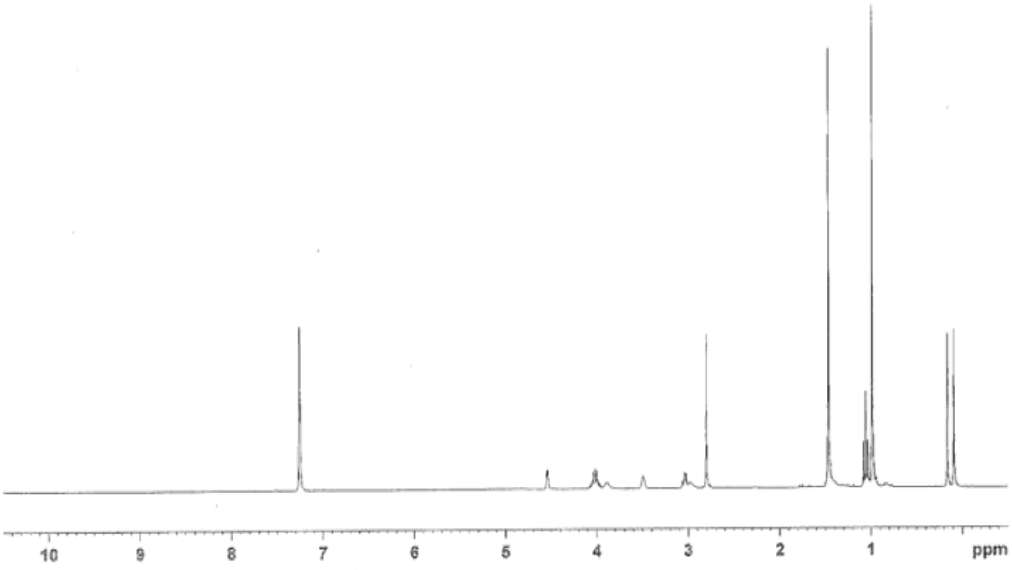


Figure A25: ^{1}H-NMR spectrum of **2.61**

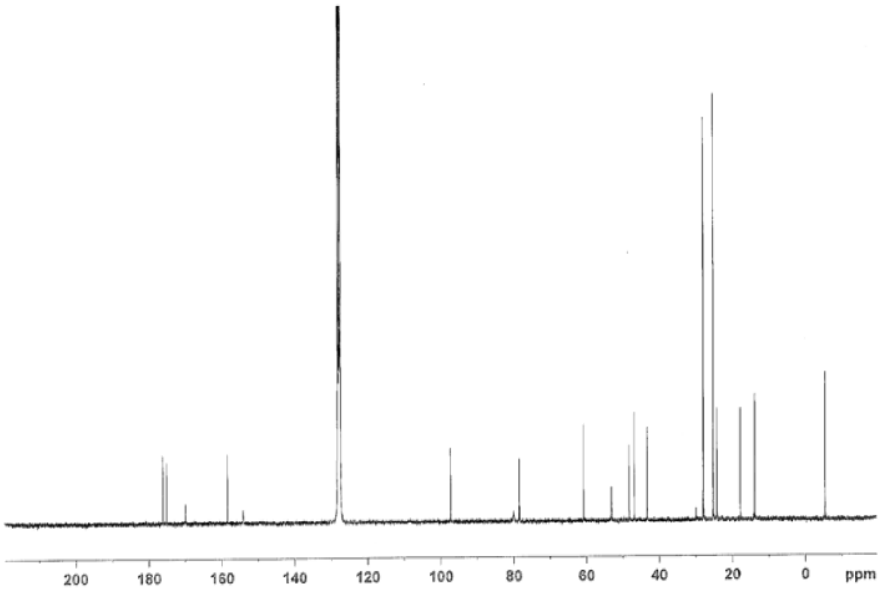


Figure A26: ^{13}C-NMR spectrum of **2.61**

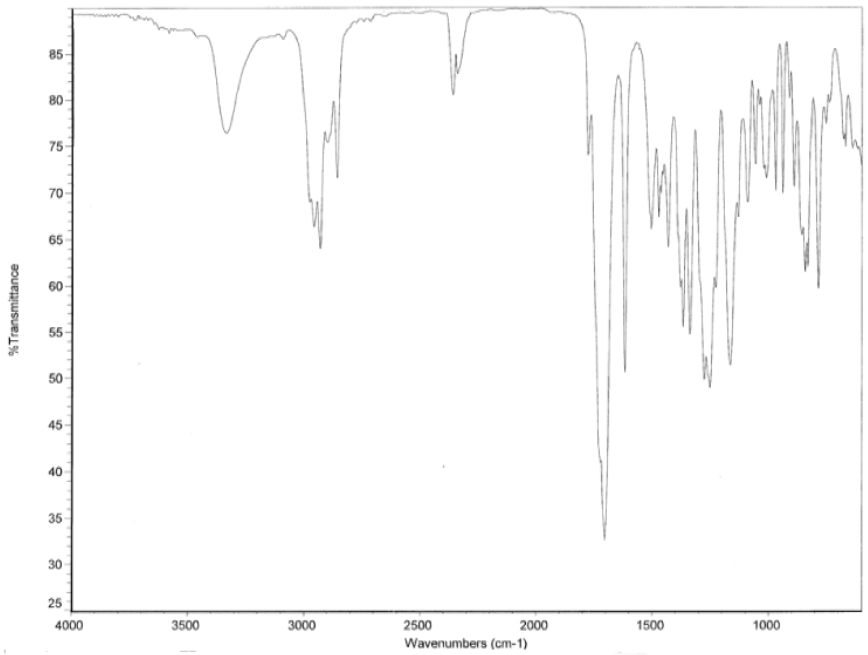


Figure A27: IR spectrum of **2.61**

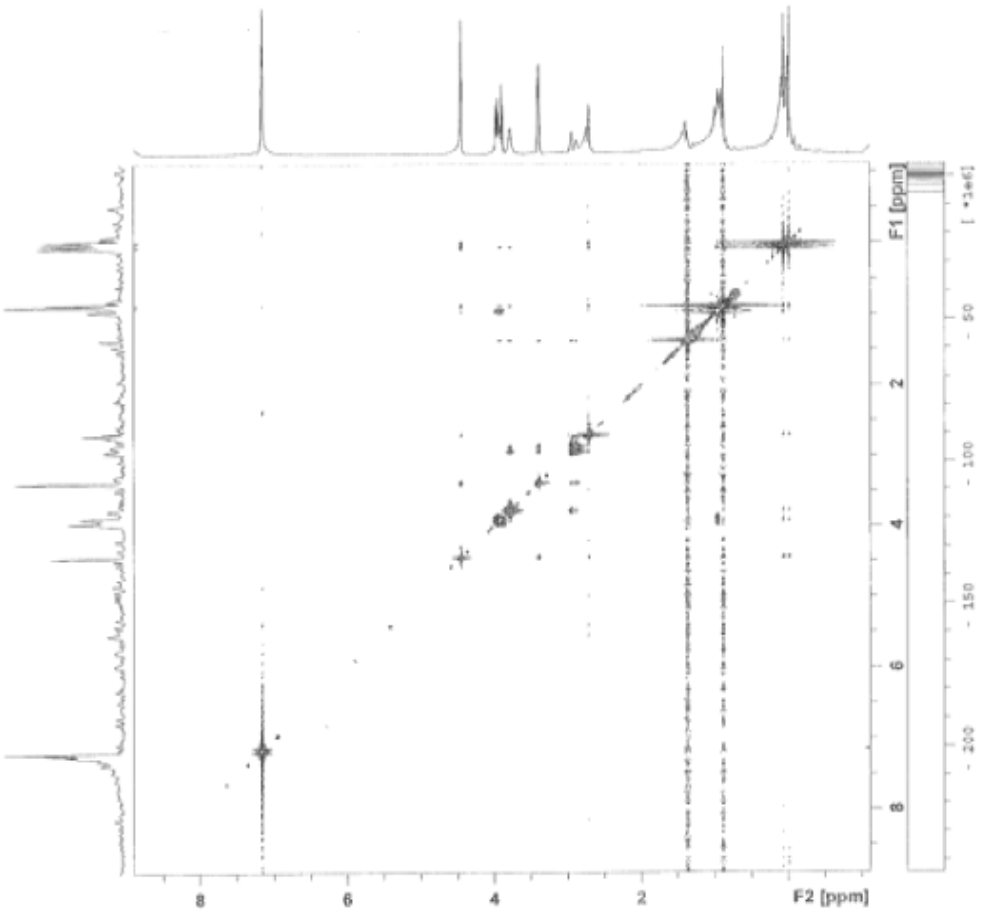


Figure A28: NOESY-NMR spectrum of **2.61**

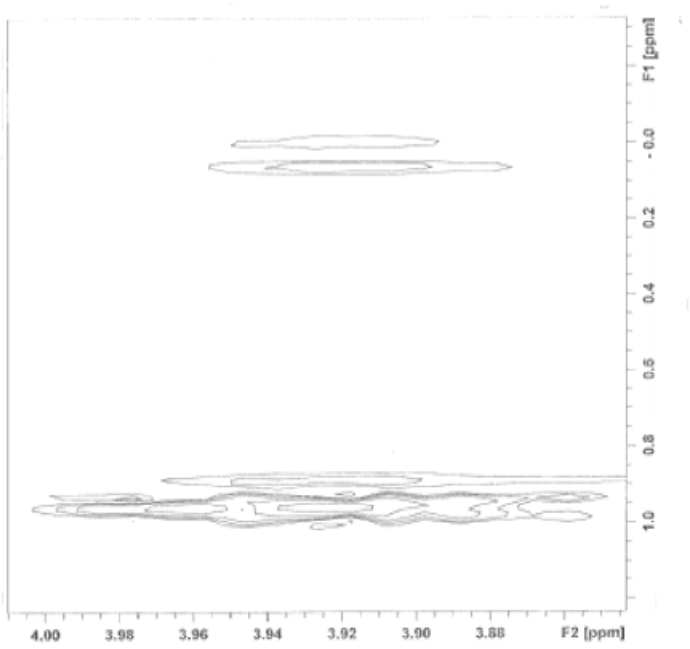


Figure A29: Selected signals of **2.61** NOESY-NMR spectrum

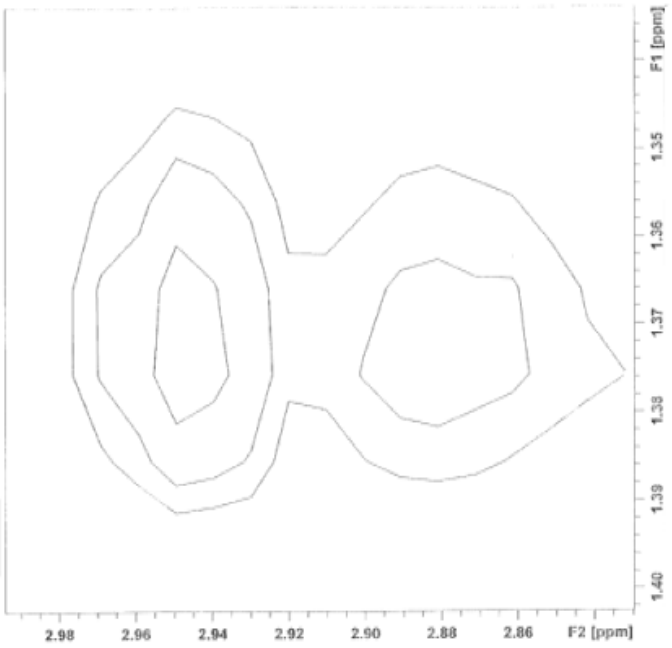
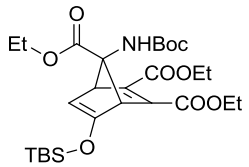


Figure A30: Selected signals of **2.61** NOESY-NMR spectrum



A1.14 Preparation of (1*R*,4*S*,7*S*)-triethyl 7-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldimethylsilyloxy)bicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate (2.62)

To a stirring solution of **2.44** (0.0420g, 0.156mmol) in CH_2Cl_2 (0.75mL) was added TEA (0.07mL, 0.5mmol), the mixture was then cool to -78°C by a dry ice/acetone bath. TBS-OTf (0.07mL, 0.3mmol) was added dropwise to the stirring reaction mixture, and the solution was warmed to RT. After 15 min of stirring, the reaction was adsorbed directly unto neutral alumina (Bockman grade I) and flash chromatographed (0:1 to 1:19, EtOAc:hex) to give **2.45** and **2.46** (0.058g, 45% **2.45**, 45% **2.46**) as a clear oily 1:1 inseparable mixture

The clear oil was dissolved in CH_2Cl_2 (1mL) and stirred as diethyl but-2-ynedioate (0.04mL, 0.2mmol) was added dropwise, and the reaction mixture was stirred at RT for 15 hr. Then, the solvent was removed *in vacuo*. The remaining orange oily residue was flash chromatographed (0:1 to 1:9, EtOAc:hex) yielding **2.62** (0.0333g, 86% from **2.45**:**2.46** mixture, 39% over two steps) as a pale yellow oil.

^{1}H (C_6D_6):	5.33 (s, 1H), 5.13 (dd, 1H, *J* = 3.7, 1.36), 4.50 (br s, 1H), 4.33 (br s, 1H), 4.23 - 3.70 (m, 6H), 1.34 (s, 9H), 0.94 - 1.05 (m, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H)
^{13}C (C_6D_6):	169.9, 169.8, 164.8, 164.3, 154.4, 151.2, 146.6, 103.9, 91.7, 79.9, 62.3, 61.0 (3 overlapping peaks), 56.9, 30.2, 28.2, 25.7, 18.3, 14.1(2 overlapping peaks), -4.8 (2 overlapping peaks)
IR (cm^{-1}):	3350, 2931, 1716, 1618, 1367, 1297, 1254, 1200, 1165, 1050, 842, 785

MS:	576.5$[M+23]^+$	
HRMS:	calcd for $C_{27}H_{43}NO_9Si$:	576.2608$[M+23]^+$
	found:	576.2605$[M+23]^+$
EA:	calcd:	N 2.67%, C 58.86%, H 7.91%
	found:	N 2.53%, C 58.57%, H 7.83%

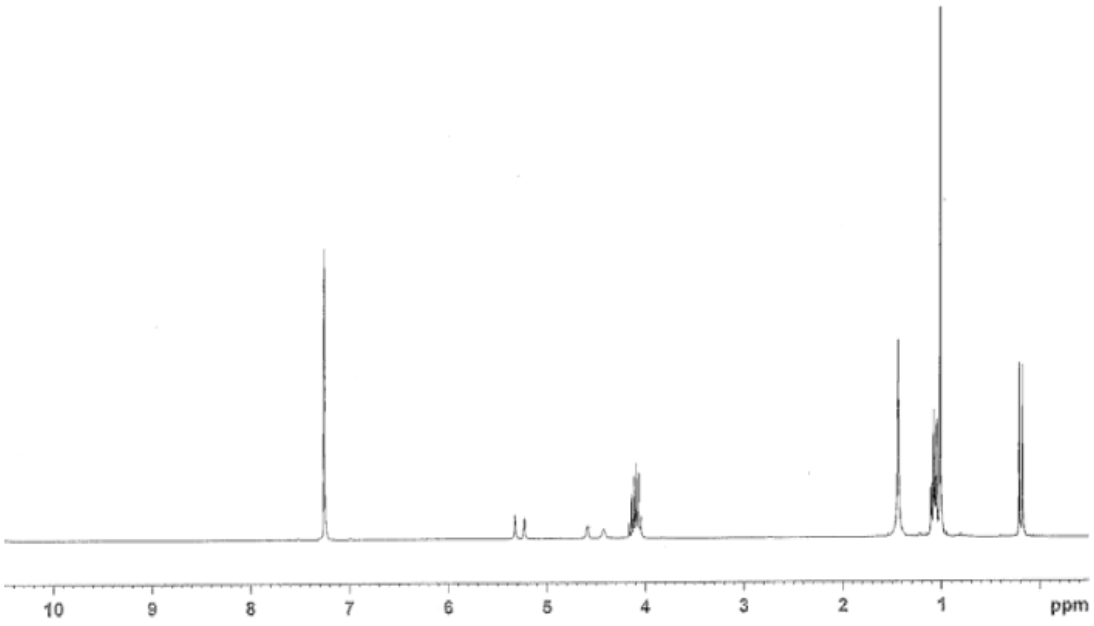


Figure A31: ^{1}H-NMR spectrum of **2.62**

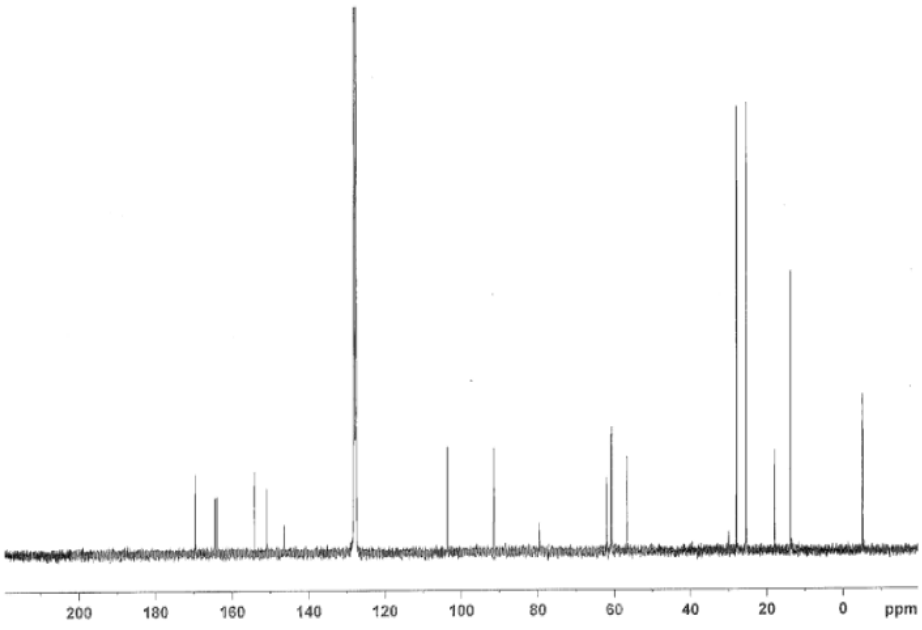


Figure A32: ^{13}C-NMR spectrum of **2.62**

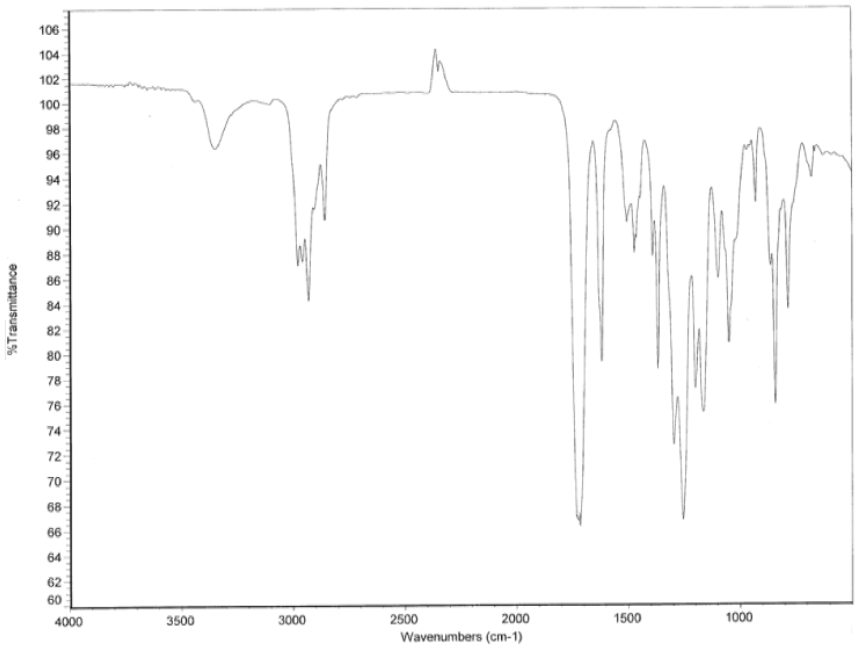
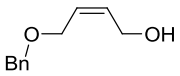


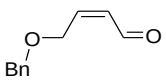
Figure A33: IR spectrum of **2.62**



A1.15 Preparation of (*Z*)-4-(benzyloxy)but-2-en-1-ol (2.64)

NaH (60%, 1.0g, 25mmol) was suspended in DMF (16mL), and then the mixture was cooled in an ice bath. A solution of (*Z*)-but-2-ene-1,4-diol (4.00mL, 48.7mmol) in DMF (8mL) was added dropwise to the stirring reaction mixture. The pink reaction mixture was stirred at 0°C for 1hr, followed by dropwise addition of BnBr (3.0mL, 24mmol). The solution was stirred at 0°C for 1 hr, and then was warmed to RT and stirred for an additional 4 hr. The reaction mixture was then quenched with sat. aq. NH_4Cl (20mL), and extracted with EtOAc (40mL). The organic phase was washed with H_2O (3x32mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was flash chromatographed (2:8 to 1:0, EtOAc:hex) revealing the title compound (3.845g, 44%) as a pale yellow oil.

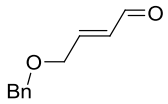
2.64 is a known compound, spectral data (^1H, MS) is in agreement with literature values (Vialettes, A. Efforts Towards the Total Synthesis of Mitomycins. M.Sc. Thesis, UBC, Vancouver, BC, 2009).



A1.16 Preparation of (*Z*)-4-(benzyloxy)but-2-enal (2.65)

A mixture of IBX (2.00g, 7.14mmol) and **2.64** (1.10g, 6.17mmol) was dissolved in DMSO (20mL). The pale yellow reaction mixture was stirred at RT for 1 hr, and then directly flash chromatographed (2:8 EtOAc:hex) revealing **2.65** (0.90g, 82%) as a pale yellow oil.

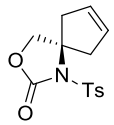
2.65 is a known compound, spectral data (^{1}H, MS) is in agreement with literature values (Fournier, J. F.; Mathieu, S.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141).



A1.17 Preparation of (*E*)-4-(benzyloxy)but-2-enal (2.66)

TsOH (0.015g, 0.087mmol) was added to a stirring solution of **2.65** (0.90g, 5.1mmol) in CH_2Cl_2 (25mL). The reaction mixture was stirred at RT for 30 min, and then filtered over a plug of silica with 1:1 EtOAc:hexanes unveiling **2.66** (0.8625g, 97%) as a yellow oil.

2.66 is a known compound, spectral data (^{1}H, MS) is in agreement with literature values (Fournier, J. F.; Mathieu, S.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141).



A1.18 Preparation of 3'-tosyl-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazolidin]-2'-one (2.75)

To a stirring solution of **2.34** (5.19g, 20.3mmol) in THF (200mL) at 0°C, was added $LiBH_4$ (2M in THF, 16.1mL, 32.2mmol). The reaction mixture was stirred at 0°C for 15 min, then warmed to RT and stirred for an additional 24 hr. The reaction mixture was then cooled to 0°C and quenched with sat. aq. NH_4Cl (100mL) and H_2O (100mL). The solution was extracted with CH_2Cl_2 (1x200mL, 2x150mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (100mL) and cooled to 0°C. NaH (60%, 2.5g, 63mmol) was then added portionwise to the stirring solution. The reaction mixture was warmed to RT and stirred for 19 hr. Then, the reaction mixture was cooled to 0°C and Ts-Cl (9.0g, 47mmol) was added as a single portion to the brown solution. The reaction mixture was warmed to RT and stirred for 15 hr, and then cooled to 0°C. The reaction was poured into sat. aq. NH_4Cl (100mL), and then extracted with EtOAc (3x100mL). The brown residue was flash chromatographed (2:8 to 1:1, EtOAc:hex) giving the title compound (2.822g, 47%) as a white solid.

^{1}H:	7.96 (d, 2H, *J* = 8.36), 7.34 (d, 2H, *J* = 8.36), 5.73 (s, 2H), 4.19 (s, 2 H), 3.49 (d, 2H, *J* = 15.31), 2.52 (d, 2H, *J* = 14.96), 2.44 (s, 3H)
^{13}C:	152.8, 145.6, 135.8, 129.7, 128.9, 128.3, 79.1, 70.7, 43.9, 21.8
IR (cm^{-1}):	2925, 1785, 1596, 1363, 1285, 1188, 1133, 1061, 814, 761, 703, 578, 547
MP:	131-134°C
MS:	294.3 $[M+H]^+$

HRMS: calcd for $C_{14}H_{15}NO_4S$: 294.0800 $[M+H]^+$

found: 294.0793 $[M+H]^+$

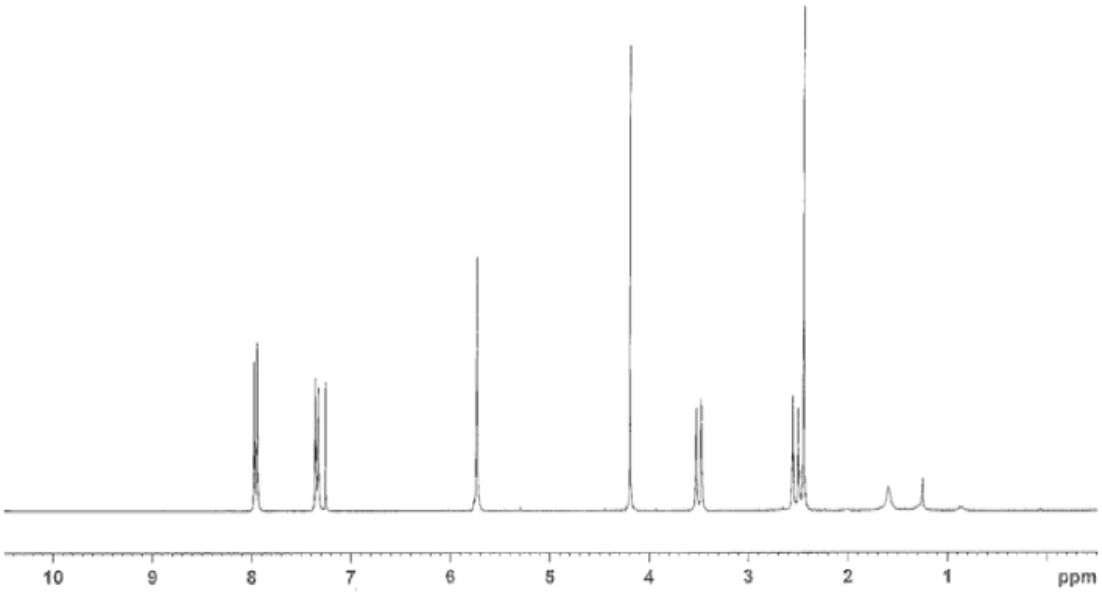


Figure A34: ^{1}H-NMR spectrum of **2.75**

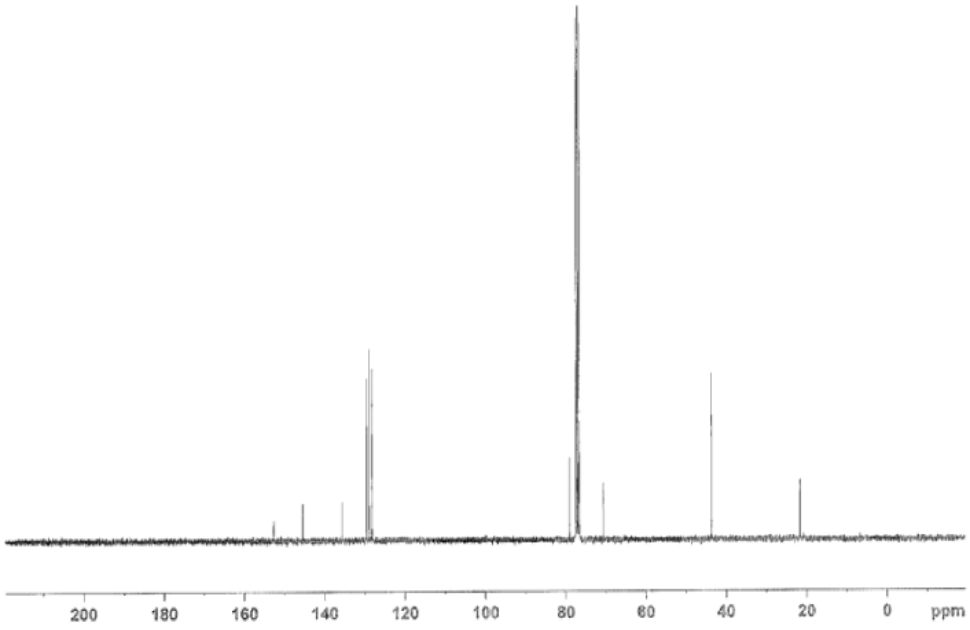


Figure A35: ^{13}C-NMR spectrum of **2.75**

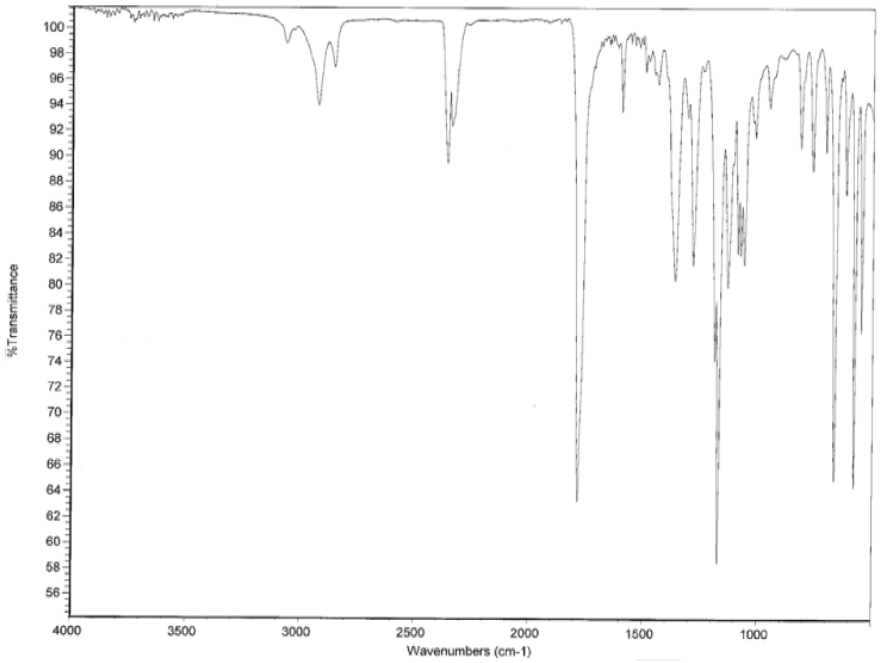
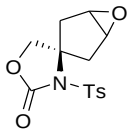


Figure A36: IR spectrum of **2.75**



A1.19 Preparation of 3'-tosyl-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazolidin]-2'-one (2.76)

A combination of **2.75** (0.770g, 2.62mmol), $NaHCO_3$ (0.534g, 6.36mmol), and *m*CPBA (70%, 0.830g, 3.36mmol) was suspended in CH_2Cl_2 (12mL). The reaction mixture was stirred at RT for 24 hr, then diluted with CH_2Cl_2 (18mL) and washed with sat. aq. $NaSO_3$ (100mL). The aqueous phase was further extracted with CH_2Cl_2 (2x30mL). The combined organic phases were washed with H_2O (2x30mL), then dried ($MgSO_4$). Concentration *in vacuo* revealed the title compound (0.7844g, 97%) as a white solid.

^{1}H:	7.90 (d, 2H, *J* = 8.26), 7.33 (d, 2H, *J* = 8.11), 4.03 (s, 2 H), 3.61 (s, 2 H), 3.03 (d, 2H, *J* = 14.15), 2.43 (s, 3H), 2.25 (d, 2H, *J* = 14.15)	
^{13}C:	152.2, 145.7, 129.7, 128.8, 79.5, 66.8, 54.6, 38.7, 21.8	
IR (cm^{-1}):	1758, 1457, 1364, 1311, 1173, 1140, 1087, 1067, 828, 762, 620, 664, 581	
MS:	332.3 $[M+Na]^+$	
HRMS:	calcd for $C_{14}H_{15}NO_5S$:	332.0569 $[M+Na]^+$
	found:	332.0577 $[M+Na]^+$

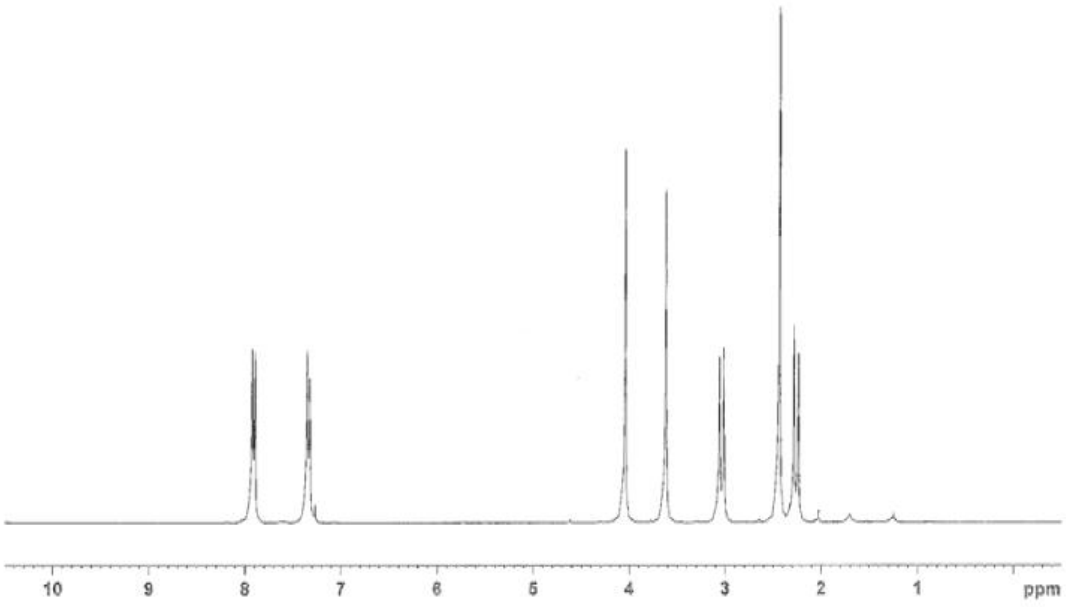


Figure A37: ^{1}H-NMR spectrum of **2.76**

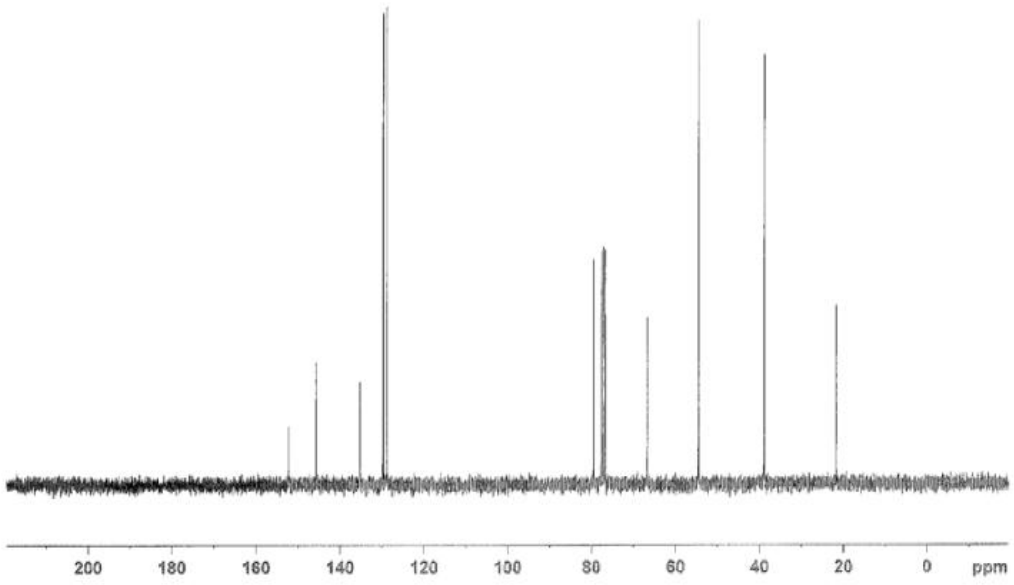


Figure A38: ^{13}C NMR spectrum of **2.76**

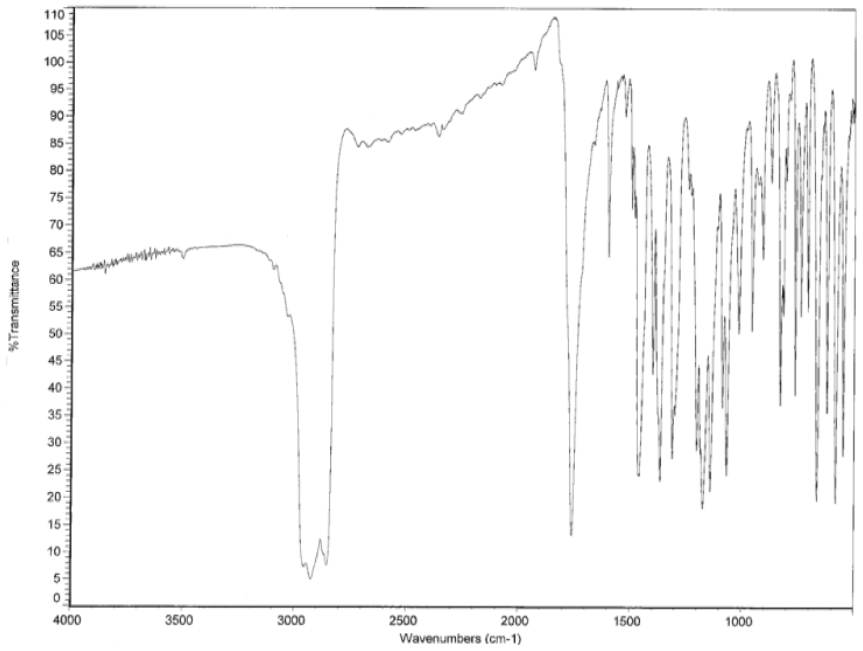
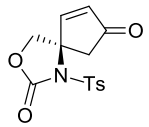


Figure A39: IR spectrum of **2.76**



A1.20 Preparation of (*R*)-1-tosyl-3-oxa-1-azaspiro[4.4]non-8-ene-2,7-dione (2.78)

TMS-OTf (1.09mL, 6.02mmol) was added dropwise to a stirring solution of **2.76** (1.240g, 4.01mmol) and TEA (2.2mL, 16mmol) in CH_2Cl_2 (12mL). The reaction mixture was stirred at RT for 1.5 hr, and then DBU (3mL, 20mmol) was added dropwise. The reaction mixture was stirred for an additional 6 hr, diluted with CH_2Cl_2 (30mL) then poured into sat. aq. NH_4Cl (30mL). The aqueous phase was extracted with CH_2Cl_2 (3x20mL). The combined organic phases were washed with H_2O (3x50mL), then dried ($MgSO_4$) and concentrated *in vacuo*, revealing a black oil residue. A mixture of the residue and PCC (2.50g, 11.6mmol) was dissolved in a CH_2Cl_2 (12mL), and the reaction mixture was stirred at RT for 4 hr. The reaction mixture was filtered over fluorocil and concentrated *in vacuo.* The residue was flash chromatographed (1:9 to 1:2 to 1:0 EtOAc:hex) yielding **2.78** (0.838g, 68%) as a white solid.

^{1}H (CD_2Cl_2): 7.91 (d, 2H, *J* = 8.36), 7.47 (d, 1H, *J* = 5.64), 7.42 (d, 2H, *J* = 8.21), 6.45 (d, 1H, *J* = 5.64), 5.35 (residual protioisomer), 4.33 (d, 2H, *J* = 8.46), 3.30 (d, 1H, *J* = 18.44), 2.64 (d, 1H, *J* = 18.44), 2.49 (s, 3 H)

^{13}C (CD_2Cl_2): 202.4, 157.6, 151.6, 146.5, 136.8, 134.8, 129.9, 128.9, 72.3, 69.3, 53.52 (CD_2Cl_2), 45.9, 21.6

IR (cm^{-1}): 1770, 1716, 1463, 1364, 1243, 1172, 1121 1087, 1067, 591

MP: 203-205°C

MS: 330.3 $[M+Na]^+$

HRMS: calcd for $C_{14}H_{13}NO_5$: 330.0412 $[M+Na]^+$

found: 330.0418 $[M+Na]^+$

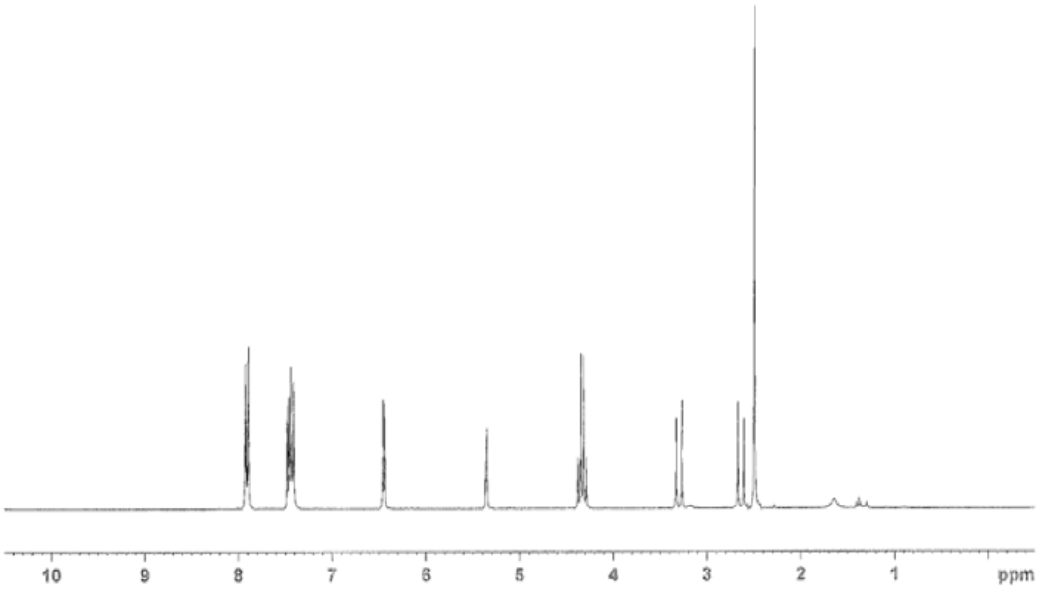


Figure A40: ^{1}H-NMR spectrum of **2.78**

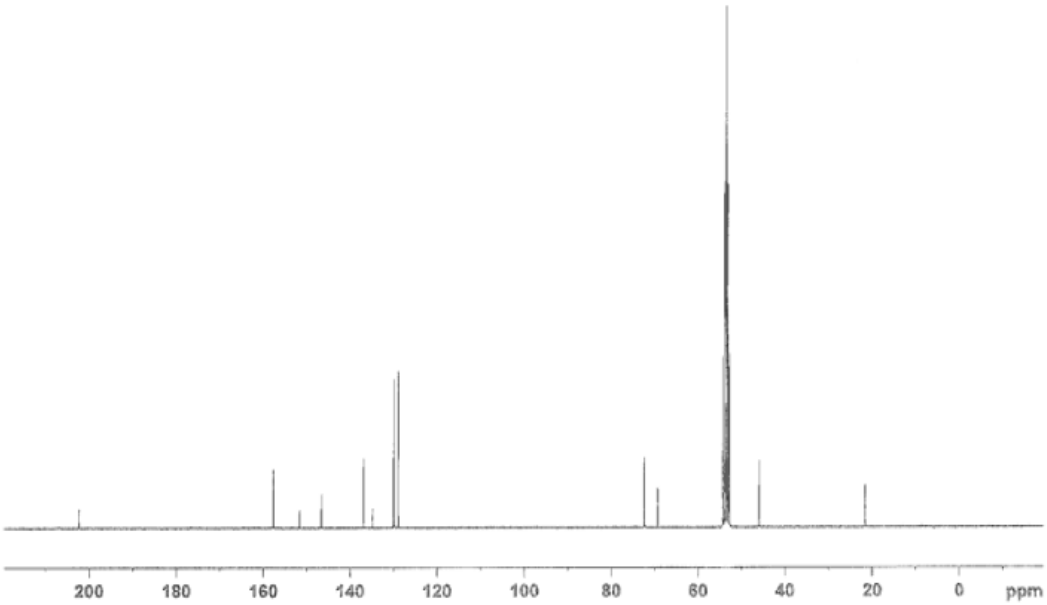


Figure A41: ^{13}C NMR spectrum of **2.78**

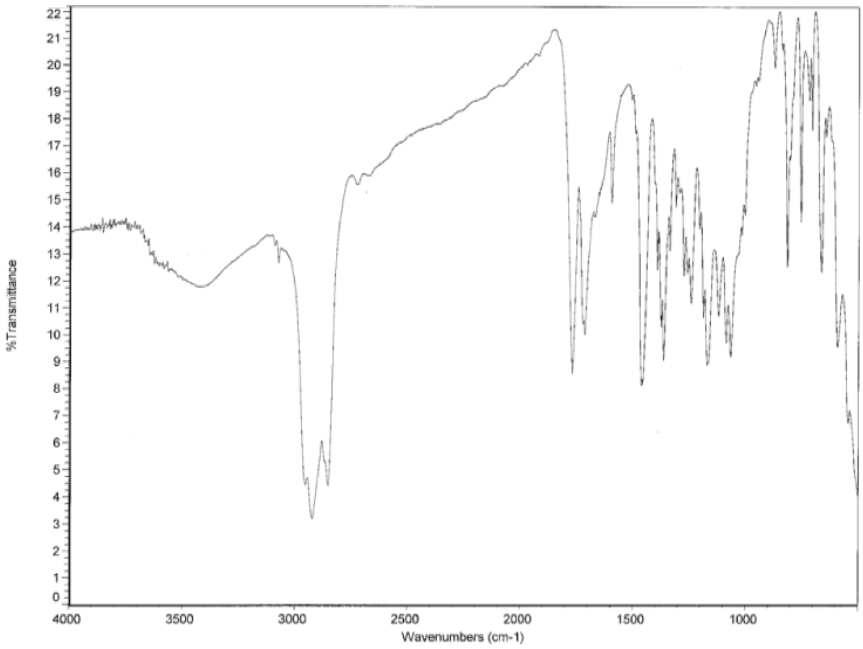
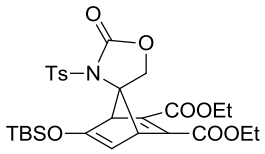


Figure A42: IR spectrum of **2.78**



A1.21 Preparation of (1*S*,4*R*,4'*S*)-diethyl 5-(*tert*-butyldimethylsilyloxy)-2'-oxo-3'-tosylspiro[bicyclo[2.2.1]hepta[2,5]diene-7,4'-oxazolidine]-2,3-dicarboxylate (2.80)

To a stirring solution of **2.78** (0.0801g, 0.261mmol) in CH_2Cl_2 (7mL) was added TEA (0.11mL, 0.79mmol), the mixture was then cool to -78°C by a dry ice/acetone bath. TBS-OTf (0.11mL, 0.48mmol) was added dropwise to the stirring reaction mixture, and the solution was warmed to RT. After 1.5 hr of stirring, MeOH (0.5mL) was added, and then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in diethyl but-2-ynedioate (1.5mL, 9.3mmol), and the reaction mixture was stirred at 60°C for 6 hr. Then, the remaining orange oily residue was flash chromatographed (1:9 to 2:8, EtOAc:hex) revealing the title compound (0.0714g, 46%) as a yellow oil.

^{1}H (CD_3)$_2$CO): 7.97 (d, 2H, *J* =8.36), 7.44 (d, 2H, *J* = 8.06), 4.90 (dd, 1H, *J* = 3.50, 0.98), 4.40 (d, 2H, *J* = 4.63), 4.18 - 4.27 (m, 4 H), 3.96 (t, 1H, *J* = 3.37), 3.85 (dd, 1H, *J* = 3.20, 1.08), 2.45 (s, 3 H), 1.27 (td, 6H, *J* = 7.13, 2.92), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.09 (s, 3 H)

^{13}C-APT (C_6D_6): 169.0, 164.3, 163.2, 154.5, 152.9, 144.5, 144.2, 138.2, 129.3, 128.4, 104.7, 97.8, 70.5, 61.4, 61.3, 59.6, 57.8, 25.7, 21.3, 18.3, 14.1, 14.0, -3.91, -4.88

IR (cm^{-1}): 2931, 2859, 1798, 1714, 1621, 1472, 1256, 1056, 929, 840, 786, 755, 664

MS: 614.4$[M+Na]^+$

HRMS: calcd for $C_{28}H_{37}NO_9SSi$: 614.1856$[M+Na]^+$

found: 614.1851$[M+Na]^+$

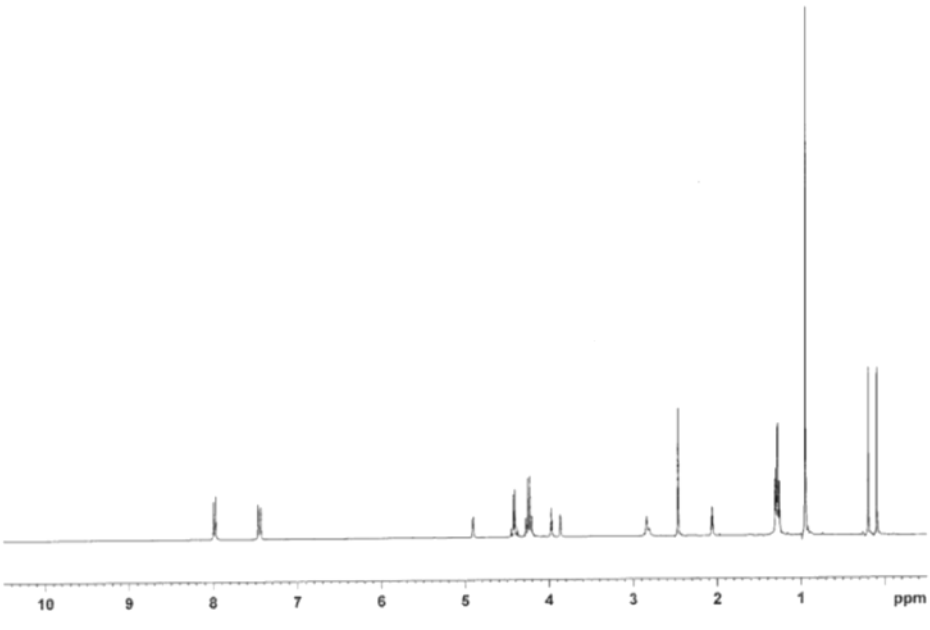


Figure A43: ^{1}H NMR spectrum of **2.80**

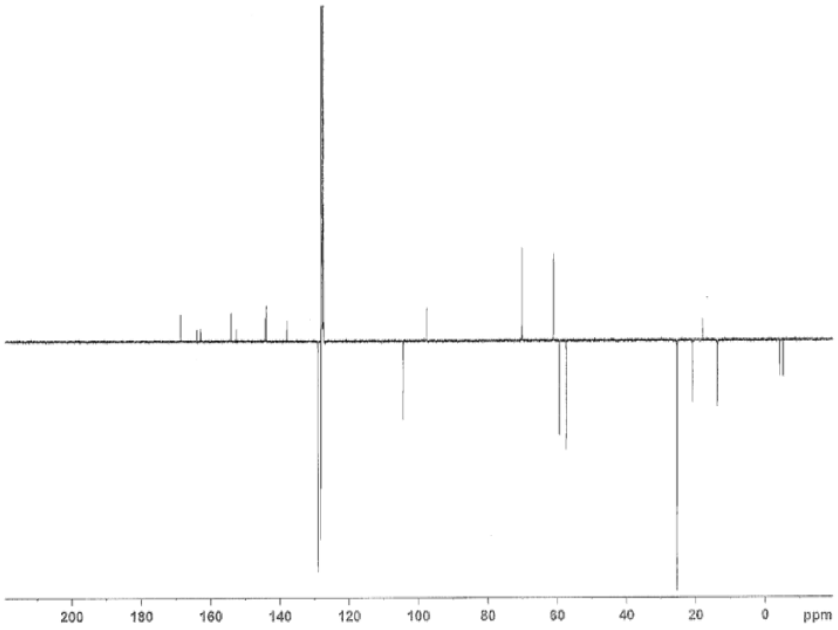


Figure A44: ^{13}C-APT NMR spectrum of **2.80**

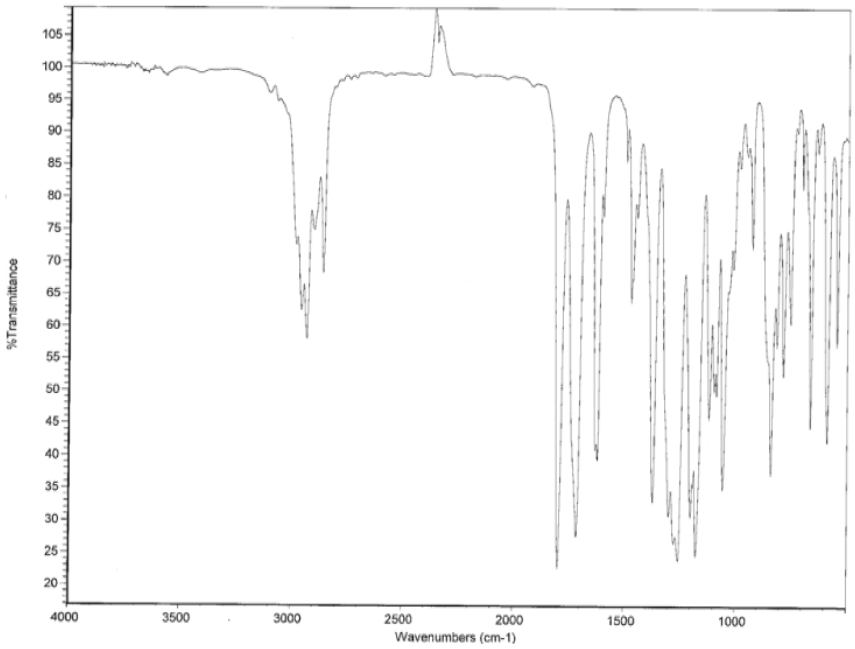


Figure A45: IR spectrum of **2.80**

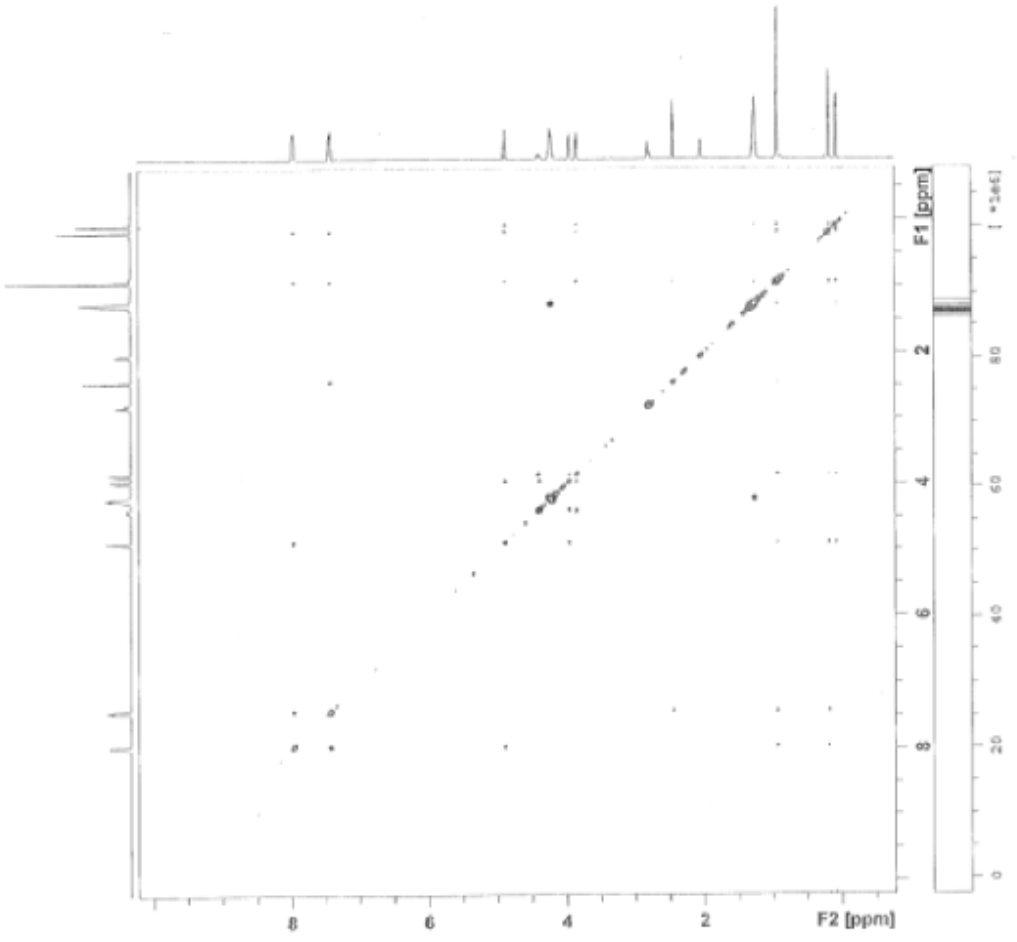


Figure A46: NOESY-NMR spectrum of **2.80**

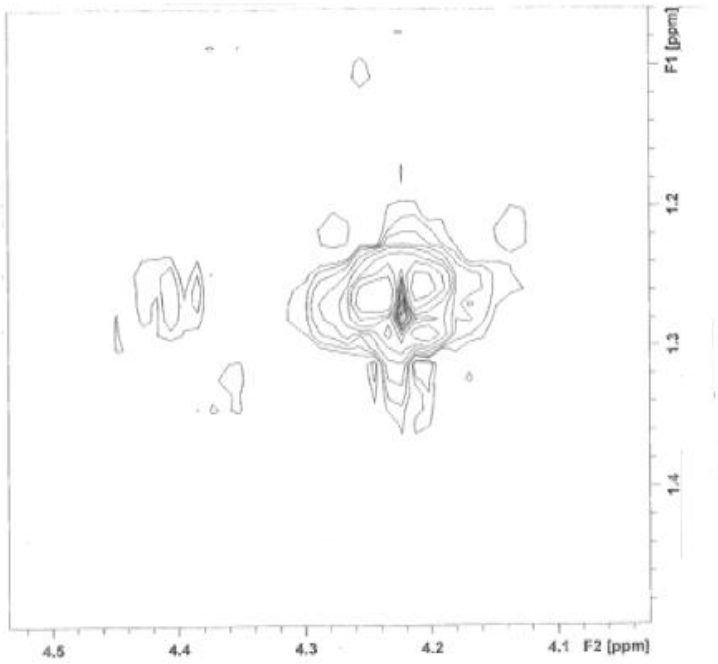


Figure A47: Selected signals of **2.80** NOESY-NMR spectrum

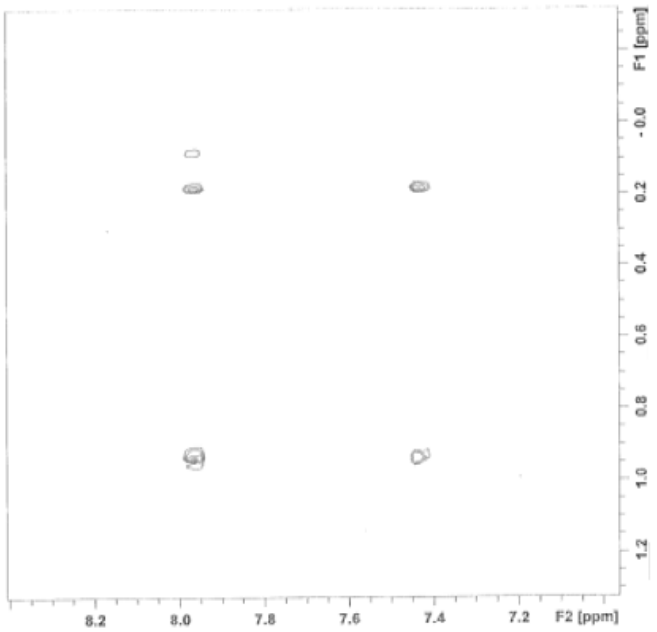


Figure A48: Selected signals of **2.80** NOESY-NMR spectrum