DEVELOPMENT OF THE METHODOLOGY FOR THE SYNTHESIS OF BIS-AMINOINOSITOLS

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Cyclitols are cyclic compounds having hydroxyl groups which attached to different carbons on the ring. Cyclitols have attracted a great deal of attention for having diverse biological activities. Cyclic alcohols play an important role in biological processes such as inhibition of glycosidase, cellular recognition, and signal transduction. In addition to this, these compounds are very important molecules due to being capable of using while synthesizing natural products or pharmaceuticals. In this study, development of new methodology for the synthesis of bis-aminoinositol derivatives was aimed. The starting material, cis-diester, was synthesized from the Diels-Alder reaction of furan and maleic anhydride followed by reaction with MeOH. As a second key compound, trans-diester was obtained from the Diels-Alder reaction of furan and fumaryl chloride followed by esterification. The diester functionality in these two compounds was planned to be converted into the hydrazide upon treatment with hydrazine monohydrate. Before this reaction, double bond was protected via stereo selective oxidation reaction with m-CPBA due to preventing retro Diels-Alder reaction. Then, hydrazide functionality was converted into acyl azide through β-nitroso hydrazide intermediate. Subsequent Curtius rearrangement
reaction resulted in the formation of the isocyanate which was converted to the corresponding bis-urethane by treatment with MeOH. Attempt to cleave the oxabridge in urethane with sulfamic acid provided the unexpected tricyclic product 148. Furthermore, hydrolysis of isocyanate with aqueous HCl formed the diamine 156. However, O-bridge could not be opened with any reagents used for that of urethane derivative as described above. Then, the cis-diol 157 was synthesized to prevent the neighboring group participation during the epoxide-opening reaction. Further ring-opening reactions are under investigation.

**Keywords**: Aminocyclitols, aminoinositols, retro Diels-Alder, Curtius rearrangement, ring-opening of oxa-bridge.
ÖZ

BİS-AMİNOİNOSİTOL SENTEZİ İÇİN YENİ METOTLARIN GELİŞTİRILMESİ

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Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2011, 87 sayfa


**Anahtar kelimeler:** Aminosiklitol, amininositol, retro Diels-Alder, Curtius düzenlenmesi, oksa köprüsünün açılması.

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To my family and lover...
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<tr>
<td>m-CPBA</td>
<td><em>meta</em>-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMP</td>
<td>2,2-Dimethoxypropane</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-(n)-butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TPP</td>
<td>Tetraphenylnporphyrin</td>
</tr>
<tr>
<td>PTSA</td>
<td>(p)-Toluenesulfonic acid</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>IR</td>
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<td>milligram</td>
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<td>mmol</td>
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CHAPTER 1

INTRODUCTION

1.1 Cyclitols

Glycosidase inhibitors and glycomimics have drawn attention in recent years. They are used in treatment for some diseases such as diabetes, cancer, AIDS, etc. Carbohydrates which like monosaccharides in shape and size have been devised and activities of these compounds were analyzed. It was determined that they show various biological activities [1].

Cyclitols are cyclic compounds having hydroxyl groups which attached to different carbons on the ring. Cyclitols are carbasugars in which \textit{endo}-oxygen is replaced with a carbon atom. They are very important compounds due to having biological activities. Cyclitols play important role in some biological processes such as inhibition of glycosidase, cellular recognition and signal transduction. Furthermore, cyclitols are used for the synthesis of various natural products showing similar activities [1]. Conduritols (1), quercitols (2), and inositols (3) are the most general types of cyclitols (Figure 1).

![Cyclitol derivatives](image)

\textbf{Figure 1} Cyclitol derivatives
1.2 Conduritols

Conduritols (1) are cyclohex-5-ene-1,2,3,4-tetrols. There are six stereoisomers (Figure 2) among which two are meso-compounds; conduritol-A (4) and conduritol-D (7), and four are enantiomeric pairs; conduritol-B (5), conduritol-C (6), conduritol-E (8), and conduritol-F (9). Conduritol-A (4) and conduritol-F (9) are naturally occurring compounds.

Conduritols and their derivatives are very important compounds due to they have biological activities; for instance, they can be used as inhibitors of glycosidase. Conduritol-A (4) analogues are used for releasing of insulin from isolated pancreatic islets when glucose concentration is changing. Furthermore, conduritol derivatives are involved in some antibiotics. They show antileukemic growth-regulating activities. Besides, conduritol derivatives are used as key compounds for the synthesis of inositols, quercitols, deoxyinositols, aminoconduritols, conduritol epoxides etc. [2].

![Figure 2 Conduritol diastereomers](image-url)
Conduritol-A (4) was discovered in 1908. Conduritol-A (4) was the first compound known as cyclohexenetetrol. Kübler isolated it from the bark of the vine *Mursdenia Condurango* [3]. Moreover, Balcı et al. developed a new and concise synthetic method for conduritol-A (4) [4]. For the synthesis of conduritol-A (4), the key compound 10 was submitted to photooxygenation reaction to give compound 11. To cleave peroxide linkage, thiourea was used for selective reduction to provide compound 12. After hydrolysis of ketal functionality, conduritol-A (4) was obtained (Scheme 1).

![Scheme 1 Synthesis of conduritol-A](image)

Also Balcı et al. successfully synthesized conduritol-B (5) and conduritol-F (9) through the acid-catalyzed epoxide ring-opening reaction in acetic anhydride by using oxepine-benzenoxide system (13) as starting agent (Scheme 2) [5]. The formation of conduritol-B (5) has an explanation on the basis of involving of the neighboring acetoxy group in the process of the epoxide ring-opening.

For the synthesis of conduritol-E (8), compound 17 was reacted with *m*-CPBA to give epoxy compound 18. It is well known that epoxide ring-opening reaction is trans and forms a single product. In the case of ring-opening of compound 18, due to the unsymmetrical structure, two ring-opening products are expected. However,
treatment of compound 18 with water in presence of acid provided compound 19 as the sole product, which is precursor of conduritol-E (8). By using DMP and Zn/DMSO, di-O-isopropylidene derivative 20 was obtained. After addition acid, ketal functionality was removed and conduritol-E (8) was produced (Scheme 2) [6].

Scheme 2 Synthesis of conduritol-F, conduritol-B and conduritol-E
1.3 Quercitols

Quercitols are cyclic compounds which have six carbon atoms. Except one carbon atom, each has one hydroxyl group. So, they are considered as cyclohexanepentols. There are sixteen stereo isomeric forms of quercitols and four of them are symmetric (Figure 3). Other 12 forms are grouped as 6 pairs of enantiomers. Only three of them, which are optically active namely (+)-proto-quercitol, (-)-proto-quercitol, and (-)-vibo-quercitol are found in plants [7]. There are many ways for the synthesis of quercitols such as reduction (hydrogenation) of inososes and inosos oximes or deoxyinososes, hydrogenation of bromoquercitols, reduction of anhydroinositols and transformation of conduritols.

![Quercitol stereoisomers](image)

Figure 3 Quercitol stereoisomers
Synthesis of ten stereoisomers among sixteen molecules was accomplished with different ways. Natural products or commercially available compounds can be used as starting materials to synthesize quercitol stereoisomers in many steps [8].

(+)-proto-quercitol (21) was discovered in 1849 by Braconnot who isolated it from the acorns of an oak tree (genus *Quercus*) as a colorless, crystalline compound, $C_6H_{12}O_5$ [9]. Its cyclohexapentol structure was detected in 1885, and its configuration in 1932. However, there had been no synthesis which was pronounced until the 1960s. In 1961, Plouvier discovered (-)-proto-quercitol in leaves of the tree Eucalyptus populnea F. Muell. The other quercitol derivative, which is a natural compound, (-)-vibo-quercitol (23) was found in many plants such as *gymnema sylvestre*, *stephania hernandifolia menispennum canadanse* and *viburnum tinus* [8].

Proto-quercitol (21) was synthesized by removal of the hydroxyl group at the position C-2 of (-)-chiro-inositol (Scheme 3) [9].

Scheme 3 Synthesis of proto-quercitol

McCasland and Horswill started with naturally occurring *myo*-inositol (34) to synthesize *vibo*-quercitol (23). In this pathway, firstly acetyl bromide was added and then the resulting molecule 35 was treated with HCl for hydrolysis. After hydrogenation of compound 36, *vibo*-quercitol (23) was obtained (Scheme 4) [10].
Balcı et al. synthesized vibo-, proto- and gala-quercitols from 1,4- cyclohexadiene (37) in three steps. In addition to this, the synthesis of vibo- (23), proto- (21) and gala- (29) quercitols by using singlet oxygen ene reaction combined with the singlet oxygen [2+4] cycloaddition was the first reported by Balcı and his coworkers (Scheme 5) [11].

Scheme 4 Synthesis of vibo-quercitol

Scheme 5 Synthesis of proto- (4) and gala- (12) quercitols
Inositols are cyclic compounds which have hydroxyl groups. They are cyclohexanols and resemble sugar as a basis of skeleton. The difference between inositol and sugar is that one oxygen in cyclohexane skeleton of sugar is replaced with a carbon atom. So, they are also called as carbasugars. In nature, there are nine stereoisomers (Figure 4) [12]. All of these isomers are known and three of them are commercially available. The most important and naturally occurring one is myo-inositol (34). This was the first cyclohexanehexol discovered by Schere in 1850 [13]. Schere isolated myo-inositol (34) from meat. Then, all cyclohexanehexols were started to be called as inositol. Myo-inositol (34) plays an important role in some cellular processes. Scyllo- (49), chiro- (31 and 48), muco- (46) and neo- (47) inositol are other naturally occurring stereoisomers of inositols. Besides, these isomers are considered to be formed from myo-inositol by inversion of configuration [12]. The others are cis- (43), epi- (44), allo- (45) are unnatural synthetic isomers [14].

**Figure 4** Inositol stereoisomers
In the literature, there are many ways for the synthesis of the inositols and their derivatives. They have been evaluated for their biological properties [13]. Chung et al. synthesized six inositol stereoisomers from conduritol intermediates (Scheme 6) [15].

Scheme 6 Synthesis of six inositol stereoisomers from conduritol intermediates

D- (+) - and L- (-)-chiro-inositol are the most abundant in nature. They exist in plants as the methyl esters of D- (+)-pinitol (53) and L- (-)-quebrachitol (54) (Figure 5) [16]. L-quebrachitol is an inositol which is used as an intermediate for the synthesis of polyhydroxylated natural products.

Figure 5 D- (+)-pinitol and L- (-)-quebrachitol
Scyllo-inositol exists in animals and plants and it was isolated. It was explored that some insects and mammalian urines has scyllo-inositol [17].

1.4.1 Bis-Homoinositol

Bis-homoinositol are hydroxymethylated inositol. There is a methylene group attached to hydroxyl group in the structure (Figure 6).

![Figure 6 Bishomoinositols](image)

In 2003, Balcı and Kara developed a new and short synthetic method for the synthesis of bis-homoinositol 61 starting from cyclooctatetraene (57) (Scheme 7) [13].

![Scheme 7 Synthesis and characterization of a new inositol analogue, bishomoinositol from commercially available cyclooctatetraene](image)
In 2008, Balcı and Baran established a new synthetic method for the synthesis of bis-homoinositol derivatives. 1,3,3a,7a-tetrahydro-2-benzofuran (62) was used as starting compound. In this methodology, photooxygenation, epoxidation and cis-hydroxylation was applied to compound 62 in order to synthesize various bis-homoinositol derivatives (63-66) (Scheme 8) [12].

![Scheme 8 Synthesis of bishomo-inositol derivatives (63-66)](image)

**Scheme 8** Synthesis of bishomo-inositol derivatives (63-66)

### 1.5 Aminocyclitol

Aminocyclitols, N-linked inositols, are types of inositols in which one or more hydroxyl groups are substituted by amine functionality [18].
Amino substituted molecules have drawn attention for they are promising in drug discovery such as compound 67 and 68, especially voglibose (69) (Figure 7) which employs as 2 type diabetes therapy [19].

![Figure 7 Aminocyclitol derivatives](image)

Because aminocyclitols have important biological properties, synthesis of its mimics which have different ring sizes such as seven, eight and nine-membered ring system has attracted attention [18].

Recently, Mehta et al. reported the synthesis of nine-membered ring aminocyclitol (78) starting from commercially available bicyclo[4.3.1]deca-2,4-dien-10-one. The detailed reaction steps for this conversion are given in Scheme 9 [19].
Research into aminoglycoside antibiotics has attracted attention. Recently, synthesis of compounds derived from inositols has been widely studied. A great number of inositols has become interesting compounds for this field of research.

In 2007, Amadeu L’ebaria et al. worked on synthesis of aminocyclitols as glycolipid mimetic which are used for glucocerebrosidase enzyme inhibitors. In the light of this, starting from p-benzoquinone, enantiomerically pure 1-amino-1-deoxy-myoinositol (85) was synthesized (Scheme 10) [20].
Aminocyclitols play an important role in biological events. They constitute a comprehensive group of natural products. Aminocyclitols are found extensively in nature in different areas. They are used for inhibition of some enzymes such as glycosidases. Recently, carbohydrate mimetics, like compound 86 and 87 have drawn attention (Figure 8). Lately, seven- and eight-membered ring systems and decane derivatives which contain polyhydroxy and amino groups have risen to notice in the domain of science [18].

Figure 8 Carbohydrates mimetic
Significantly, attention has been directed towards compounds containing amino-cyclic unit due to their biological activities.

In 2006, Balcı et al. reported a synthetic pathway for the synthesis of new aminocyclitol derivative 91 starting from cyclooctatetraene (57) (Scheme 11) [18].

![Scheme 11 Synthesis of new aminocyclitol derived from cyclooctatetraene](image)

Aminocyclitols are very important compounds for being capable of using as amines/bases in some catalytic reactions.

Rudolf K. Alleman et al. worked on the effect of 6-aminocyclitols (92) on Pd/C catalyzed hydrogenolysis reaction (Scheme 12). Cyclitol amines are used as amines and bases. They are poisonous to Pd/C catalysts and reactivity of them can be changed against O-benzyl protecting group [21].
Aminocyclitol antibiotics are used in some pharmaceuticals which are capable of using for treatment of some diseases such as cancer. This encourages scientists to search into aminosugar chemistry. KA-3093 antibiotic, 5-\textit{O}-methyl-\textit{myo}-inosamine (94), has \textit{myo}-inositol configuration and this unit is the first pointed cyclitol moiety regarding with hygronycin A which exists an inosamine unit (95) in the structure (Figure 9) [22].
1.6 Aim of the study

Cyclitols and especially aminocyclitols have recently attracted the scientists. It was proven that those compounds and their derivatives have shown a various biological activities in many biologically important processes. Therefore, our aim was to develop a new methodology for the synthesis of bis-aminoinositols. Starting with cis- and trans-diester of bicyclic systems 98 and 102, our purpose was to convert diester groups to amino groups and cleave $O$-bridge to obtain cyclohexane skeleton. We planned to transform diester groups to $\text{-NH}_2$ through Curtius rearrangement and then cleave $O$-bridge whereby way of acidic epoxide ring-opening reaction to obtain bis-aminoinositols (Scheme 13).

Scheme 13 Synthetic plan for the synthesis of bis-aminoinositols
CHAPTER 2

RESULTS AND DISCUSSION

To synthesize aminocyclitol derivatives; furan, maleic anhydride and fumaryl chloride were used as starting materials. The reason why we used these compounds as starting materials is that they are commercially available and cheap. Our aim was to synthesize cis- and trans-diesters of bicyclic system \( 98 \) and \( 102 \) as key compounds through Diels-Alder reaction (Scheme 14, Scheme 15).

Scheme 14 Reaction pathway for formation of \( 98 \)
2.1 Synthesis of key compound 98

2.1.1 Synthesis of exo-adduct 108

First, we started with the synthesis of oxanorbornane skeleton 108. In 2008, Chola et al. obtained this compound from the Diels-Alder reaction of furan and maleic anhydride. According to the literature, a mixture of furan and maleic anhydride was stirred at room temperature for 16 h and exo-adduct was obtained in 98% yield [23].

To carry out this reaction, maleic anhydride was dissolved in furan and the resulting mixture was stirred for 3 h at room temperature. This reaction gave thermodynamically more stable exo-adduct 108 in a yield of 95% (Scheme 16).
Exclusive formation of *exo*-adduct 108 was observed at the end of the reaction. The stereochemistry of *exo*-adduct 108 was determined by $^1$H NMR spectrum. The olefinic protons resonate at 6.58 ppm as triplet. Double bond and bridgehead protons resonate as quasi-triplet (AA'BB'). On the other hand, the protons adjacent to carbonyl groups resonate as singlet due to the dihedral angle between the relevant protons. We know from Karplus equation that when dihedral angle between two protons approaches to 90°, coupling constant decreases. We assume dihedral angle between those protons is close to 90°, which clearly indicates the formation of *exo*-product. According to the literature, for *endo*-adduct of reaction of furan and N-phenyl-maleimide, dihedral angle is approximately 30° and coupling constant between two protons is $J = 5.2$ Hz [24]. Actually, *endo*-isomer is initially formed in reaction media two times faster than *exo*-isomer but it goes back to its reactants because rate of reverse reaction is greater than that of forward reaction. Then, *exo*-adduct 108 is formed. At this time, reaction does not reverse due to thermodynamical stability of this product [25].

In $^1$H NMR spectrum, olefinic protons resonate at 6.58 ppm as quasi-triplet. Bridgehead protons and other two protons on the ring resonate as triplet and singlet at 5.46 and 3.18 ppm.

In $^{13}$C NMR spectrum, there are four signals at 169.9, 137.0, 82.3, 48.7 ppm.

IR spectrum also confirmed the formation of the product with carbonyl signal at 1789 cm$^{-1}$.

**2.1.2 Synthesis of half ester of bicyclic system 109**

According to the literature, when *exo*-adduct 108 was dissolved in MeOH at room temperature, half ester of this bicyclic system 109 was obtained in 87% yield [23].

![Scheme 17 Synthesis of compound 109](image)
This reaction was carried out for 2 d and the desired compound 109 was obtained in 97% yield (Scheme 17).

The structure of the compound 109 was proven by $^1$H and $^{13}$C NMR spectra. In $^1$H NMR spectrum, olefinic protons resonate as an AB system between 6.43-6.39 ppm with coupling constants of $J = 5.7$ Hz (AB coupling) and $J = 1.6$ Hz (coupling with bridgehead protons). Bridgehead protons couple with only olefinic protons. They do not give any coupling with other protons which attached to carbons neighboring carboxylic acid and ester group on account of dihedral angle does not permit to eventuate any coupling. They resonate at 5.25 and 5.21 ppm. The other protons on the bicyclic ring resonate at 2.81 and 2.78 ppm as an AB system. The coupling constant between those protons is $J = 9.0$ Hz. In $^{13}$C NMR spectrum, there are nine signals which are compatible with the structure. They appear at 177.0, 171.7, 136.8, 136.5, 80.6, 80.3, 52.3, 47.3, 46.8 ppm.

In IR spectrum, peaks at 3023, 1736 cm$^{-1}$ indicate existence of carboxylic acid.

2.1.3 Synthesis of cis-diester 98

To synthesize cis-diester 98, carboxylic acid functionality must be converted to ester group. For this reason, SOCl$_2$ was added to a solution of 109 in MeOH gently [26]. The mixture was stirred at reflux temperature for 3.5 h. Compound 98 was obtained at the end of the reaction in 70% yield (Scheme 18).

$^1$H and $^{13}$C NMR are compatible with the structure. In $^1$H NMR spectrum, double bond protons resonate as quasi-triplet with coupling constant of $J = 0.9$ Hz. Bridgehead protons give also quasi-triplet at 5.20 ppm and protons attached to
carbon adjacent ester group resonate as singlet at 2.76 ppm. In $^{13}$C NMR spectrum, there are five signals resonating at 171.9, 136.6, 80.4, 52.3, 46.9 ppm. In IR spectrum, disappearance of carboxylic acid peak proves the conversion to ester.

After synthesizing the key compound 98, our plan was to convert ester functionalities into hydrazides. In 2009, Balcı et al. succeeded this conversion by treatment of furan diester 112 with hydrazine monohydrate in MeOH (Scheme 19) [27].

![Scheme 19 Reaction of furan diester 112 with hydrazine monohydrate](image)

To apply this reaction to our system, hydrazine monohydrate was added to a solution of compound 98 in MeOH at room temperature. However, after completion of the reaction, NMR spectral studies did not reveal the formation of the expected product 114, instead a retro Diels-Alder reaction occurred.

![Scheme 20 Reaction of compound 98 with hydrazine monohydrate](image)
2.1.3.1 Retro Diels-Alder reaction

Diels-Alder reaction may be reversible reaction. If diene or dienophile or both are much more stable molecules than cycloaddition product, then reverse reaction can take place.

High temperature is necessary for retro Diels-Alder reaction to overcome activation barrier. However, in some cases, retro Diels-Alder reaction is observed even at very low temperatures. In following example, when an oxide anion is attached to position 1 or 2 in cyclohexadiene ring (115) (Scheme 21), the rate of retro Diels-Alder reaction increases.

![Scheme 21](image)

**Scheme 21** Retro Diels-Alder reaction of 115

There is an example which expresses the role of oxide anion for retro Diels-Alder reaction at low temperature. Cyclo compound 118 gives Diels-Alder reaction with dimethyl but-2-ynedioate. Compound 119 has oxide anion at position 2, it gives retro Diels-Alder reaction by treatment with TBAF at 20 °C (Scheme 22) [28].

![Scheme 22](image)

**Scheme 22** Function of an oxide anion in retro Diels-Alder reaction

Therefore, we assume that the presence of oxygen-bridge plays in this case an important role and decreases the energy barrier for retro Diels-Alder reaction.
2.2 Synthesis of cis-epoxide 122

To prevent retro Diels-Alder reaction, double bond protection was required. To do this, double bond was thought to be epoxidized. In our system, to a stirred solution of cis-diester 98 in CH₂Cl₂, m-CPBA was added at 0 °C and the resulting mixture was stirred at room temperature for 24 h [29]. After completion of reaction, epoxidation of double bond was successfully achieved and compound 122 was obtained in a yield of 98% (Scheme 23).

![Scheme 23 Epoxidation of compound 98](image)

1H and 13C NMR supported the formation of epoxide. In 1H NMR spectrum, singlets at 4.78 and 3.63 ppm were assigned to bridgehead and ester methyl protons. Epoxide protons resonate at 3.31 ppm as singlet and protons attached to carbon next to ester group also give singlet at 2.92 ppm. In 13C NMR spectrum, disappearance of olefinic carbon resonances proved the formation of product; there are five signals at 170.3, 76.4, 52.4, 49.2, and 49.1 showing the presence of symmetrical structure.

The NMR spectral studies confirmed that the epoxidation reaction was stereo-selective and only exo-epoxide-isomer 122 was formed.

The exclusive formation of the exo-isomer can be explained by the pyramidalization of the double bond as well as the directing effect of bridge oxygen atom.

2.2.1 Double bond pyramidilization

Double bond pyramidilization means that there is a deviation of angle between double bond and olefinic protons. Electrophile approaches from one face of bicyclic system. For our molecule 98, m-CPBA would attack from exo face of the double bond (Figure 10).
Balcı et al. reported that the bromination of 6,7,8,9-tetrahydro-5H-5,9-ethenobenzo[a][7]annulene (123) occurs exclusively from endo face of double bond due to double bond pyramidilization (Scheme 24) [30].

**Scheme 24** Bromination of 6,7,8,9-tetrahydro-5H-5,9-ethenobenzo[a][7]annulene reaction

2.3 Reaction of epoxide 122 with hydrazine monohydrate

After protection of the double bond in 98, the formed bicyclic epoxide 122 was treated with hydrazine monohydrate at room temperature in presence of MeOH (Scheme 25). NMR spectral studies of the reaction mixture indicated the presence of three products.
The major product 126 was isolated by dissolving of the resulting mixture in chloroform at 60 °C. Amino-imide 126 was soluble in chloroform.

For the formation of 126, we propose the following mechanism. We assume one of the ester groups in 122 reacts first with one mole of hydrazine to give monohydrazide 127, which undergoes cyclization reaction to give 126 (Scheme 26).

The structure 126 is consistent with ¹H and ¹³C NMR spectral data. In ¹H NMR spectrum, epoxide protons resonate at 3.12 ppm as singlet. Bridgehead protons and other two protons on the ring also resonate as singlets at 4.63 and 3.68 ppm. -NH₂ protons appear also as singlet at 5.05 ppm. In ¹³C NMR spectrum, there are four
carbon resonances. Carbonyl carbon resonates at 173.7 ppm and other saturated carbon atoms on the ring give signals at 75.7, 49.1, 45.8 ppm.

With the formation of cyclization product 126, the expected cis-dihydrazide 99 was also observed in the reaction media. *Cis*-dihydrazide 99 may be formed by two different routes. By the first route, one of the carbonyl group in 126 can be attacked by hydrazine (Scheme 27). The ring-opening reaction of amino-imide can form *cis*-dihydrazide 99 as shown in Scheme 27. Due to solubility problem, all attempted purification methods failed, therefore, we could not isolate *cis*-dihydrazide.

By the second route, the initially formed 127 can undergo further substitution reaction with an additional mole hydrazine to give 99 (Scheme 27).

![Scheme 27 Formation of cis-dihydrazide 99](image)

In order to distinguish these two different ways, the time of the reaction was increased from 1 d to 2 d. The spectral analysis of the reaction mixture after 2 d showed that there was an increase in the proportion of *cis*-dihydrazide 99 (Scheme 28). Then, it was considered that there was a conversion of cyclization product 126 to bicyclic *cis*-dihydrazide 99.
In $^1$H NMR spectrum of 99, $-\text{NH}$ and $-\text{NH}_2$ protons resonate at 8.40 and 4.10 ppm as singlet. Bridgehead and epoxide protons give also singlets at 4.52 and 3.40 ppm and other protons attached to carbon neighbouring hydrazide functionality resonate at 2.80 ppm as singlet.

To prove the formation of cis-dihydrazide, an additional reaction was performed. To a solution of cyclization product 126 in MeOH, $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ was added to see whether there was a conversion or not. One day after, 20% conversion to bicyclic cis-dihydrazide 99 was observed (Scheme 29).

**Scheme 28** Reaction of compound 122 with hydrazine monohydrate for 2 d

**Scheme 29** Equilibrium between 126 and 99
Prolonged reaction time did not change the ratio. Therefore, we assume that equilibrium between 126 and 99 was established at the reaction temperature. 

*trans*-dihydrazide 103 was also formed as the third product.

The ratio of this product was not affected by prolonged reaction time as much as the ratio of 99. There was an inversion of configuration. How this epimeric form could be formed is that there was an enolate formation after *cis*-dihydrazide (99) was formed.

We carried out an additional reaction lasting for three days and observed that the ratio of 103 was increased from 32% up to 44% at the expense of *cis*-hydrazide 99 (Scheme 30).

![Scheme 30 Reaction of compound 122 with hydrazine monohydrate for 3 d](image)

Furthermore, we treated *trans*-dihydrazide in MeOH with hydrazine monohydrate under the same reaction conditions to see whether 103 would undergo a configurational isomerization or not. We noticed that the *trans*-dihydrazide 103 was stable.
Enol form of compound 99 was formed and then converted into *trans*-product through C-α epimerization. Because *trans*-product is thermodynamically more stable form, reaction did not reverse (Scheme 31).

![Scheme 31](image)

**Scheme 31** Formation of 103 from *cis*-dihydrazide 99

It is established that during esterification of compound 129, there occurs a C-α epimerization when treatment of compound 129 with DCC/DMAP.HCl (Scheme 32) [31].

![Scheme 32](image)

**Scheme 32** C-α epimerization

The isomerized product 103 is formed by isomerization of the *cis*-dihydrazide 99. However, the starting material, diester 122 can also undergo partly configurational isomerization followed by substitution of the ester groups with hydrazine monohydrate.

As a conclusion, following scheme can be shown for the summary of this reaction pathway (Scheme 33).
We assume that these two ways are responsible for configurational isomerization. After getting all these results, all attention was directed towards use of trans-diester 122 of the bicyclic system 102 as a key compound.

2.4 Synthesis of key compound 102

To synthesize key compound 102, fumaryl chloride (110) was added to furan at 0°C. Then, at 10 °C, triethylamine was added in presence of MeOH to obtain trans-diester of the bicyclic system 102. At the end of the reaction, compound 102 was synthesized in a yield of 72% (Scheme 34).

\(^1\)H and \(^{13}\)C NMR spectra supported the formation of compound 102. In \(^1\)H NMR spectrum, olefinic protons resonate at 6.29 and 6.45 as doublet of doublets. Large coupling between these two olefinic protons is 5.7 Hz and small coupling caused by bridgehead protons is 1.7 Hz. The bridgehead protons give doublet at 5.18 ppm. The proton with cis-configuration to O-bridge resonates as triplet at 3.55 ppm with a coupling constant of \(J = 4.3\) Hz. The other proton attached to carbon neighboring ester group resonates at 2.78 ppm as doublet with coupling constant of \(J = 4.3\) Hz. Finally, methoxy methyl protons resonate at 3.60 and 3.69 ppm as singlets.
To avoid retro Diels-Alder reaction, oxidation of double bond was the further step before the dihydrazide formation reaction.

2.5 Synthesis of trans-epoxide 132

Our reaction pathway was followed by epoxidation of double bond for preventing retro Diels-Alder reaction. The bicyclic alkene 102 was dissolved in CH$_2$Cl$_2$ and cooled to 0 °C. To this solution, m-CPBA was added gently. The resulting solution was stirred at room temperature for 2 days. The compound 132 was obtained in 72% yield as a white solid (Scheme 35).

In $^1$H NMR spectrum, disappearance of double bond proton resonances proved formation of epoxide 132. One of the bridgehead protons resonates at 4.68 ppm and gives doublet with the coupling constant of $J = 5.3$ Hz.
The other bridgehead proton gives a singlet at 4.75 ppm. Epoxide ring protons resonate at 3.39 and 3.33 ppm as individually doublet and form AB system with chemical shift difference of 21.7 Hz and coupling constant is $J = 3.3$ Hz. On the other hand, one proton which is neighboring with ester group with cis-configuration to O-bridge resonates at 3.58 ppm and gives triplet with coupling constant of $J = 5.0$ Hz. -OCH$_3$ protons give characteristic singlets at 3.68 and 3.69 ppm respectively.

In $^{13}$C NMR spectrum, there are 10 signals. Carbonyl carbons resonate at 171.3 and 170.0 ppm, bridgehead carbons appear at 77.9 and 74.9 ppm and the other carbons resonate at 52.7, 52.5, 50.5, 49.1, 48.3, 48.1 ppm.

### 2.6 Synthesis of trans-dihydrazide 103

To a solution of compound 132 in MeOH, N$_2$H$_4$.H$_2$O was added at room temperature and stirred for 24 h. After completion of reaction, as expected, only one product 103 was observed in 91% yield (Scheme 36).

$^1$H and $^{13}$C NMR are consistent with the structure. In $^1$H NMR spectrum, there are two signals at 9.08 and 9.19 ppm arising from –NH protons. –NH$_2$ protons are split into doublet separately at 4.18 and 4.20 ppm with coupling constant of $J = 3.9$ Hz.
One of the epoxide protons gives doublet at 3.42 ppm with a coupling of $J = 3.5$ Hz whereas the other epoxide proton resonance is overlapped by –OCH$_3$ signal. One of bridgehead protons is not coupled with neighboring protons due to the dihedral angle of approximately 90°. Other bridgehead proton gives doublet with a coupling constant of $J = 5.1$ Hz. One of the protons which is near hydrazide group and has trans-configuration with O-bridge resonates at 2.90 ppm and split into doublet, whereas the other proton resonance is again overlapped by methyl proton resonance. In $^{13}$C NMR spectrum, there are eight resonances. There are two characteristic carbonyl carbon peaks at 170.4 and 167.8 ppm. Bridgehead carbons resonate at 78.5 and 74.7 ppm. Epoxide carbons and other two carbons on bicyclic ring give signals at 49.2, 48.9, 48.2, 45.7 ppm.

2.7 Synthesis of acyl azide 138

To convert compound 135 to corresponding acyl azide 137 through β-nitroso hydrazide intermediate 136, modified Sandmeyer reaction was used in 1986 by Kim et al [32]. During the reaction, firstly, NaNO$_2$ was protonated. After departure of water molecule, nitrosonium ion 134 was formed. Then, nonbonding electrons on nitrogen of -NH$_2$ part of hydrazide attack to positively charged nitrosonium ion to form β-nitroso hydrazide intermediate 136. After removal of water molecule, corresponding acyl azide 137 is formed as depicted in Scheme 37.

\[
\begin{align*}
\text{NaNO}_2 + \text{HCl} & \quad \rightarrow \quad \text{HONO} + \text{Na}^+ + \text{Cl}^- \\
\text{H}^+ + \text{HONO} & \quad \rightarrow \quad \text{\ddot{O}H}_2\text{NO} \\
\text{R'NH-NH}_2 \quad + \quad \ddot{\text{N=O}} & \quad \rightarrow \quad \left[ \text{R'NH-NH-N=O} \right] \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{R'N}_3
\end{align*}
\]

Scheme 37 Modified Sandmeyer reaction: Acyl azide through β-nitroso Hydrazide intermediate
According to our synthetic plan, hydrazide 103 should be converted into acyl azide 138 to follow the reaction pathway. For this reason, to a solution of compound 103 in 1 N HCl, NaNO₂ was added gently at 0 °C and reaction mixture was stirred for 0.5 h (Scheme 38).

The resulting product 138 was confirmed by IR spectrum. IR spectrum gave a sharp characteristics signal at 2165 cm⁻¹ which indicates azide moiety. In addition to this, ¹H and ¹³C NMR spectra supported the formation of corresponding acyl azide. In ¹H NMR spectrum, epoxide protons resonate at 3.42 ppm as an AB system. Because two doublet peaks are close to each other, it is seen as quartet and coupling constant is 3.2 Hz. Chemical shift difference is 6.1 Hz and Δδ/J is equal to 1.8. Due to this reason, roof effect is dominant and it is split into doublets of doublet via AB system. One of the bridgehead protons resonates at 4.69 ppm and is split into doublet due to the coupling with proton attached to adjacent carbon of azide functionality with a coupling constant of J = 5.2 Hz. Other bridgehead proton gives singlet at 4.75 ppm. In ¹³C NMR spectrum, there are eight resonances at 177.5, 176.4, 78.1, 75.2, 52.6, 50.0, 48.9, 48.2 ppm.

2.8 Synthesis of trans-urethane 131 through Curtius Rearrangement

Generally, acyl azides 137 can be converted into corresponding isocyanate 139 through Curtius rearrangement. This reaction was discovered by Theodor Curtius in 1894 (Scheme 39) [33].
During this reaction, after departure of N₂ gas, nitrene 140 is formed as intermediate. Nitrene has six valence electrons. It has empty π orbital. To fill out it, while electrons on nitrogen atom makes double bond, -R group migrates. This is called Curtius rearrangement.

In our system, bicyclic acyl azide 138 was heated in dry benzene at reflux temperature for 1 hour. Before adding MeOH to form corresponding urethane 143, it was cooled to 40 °C and treated with MeOH. After completion of reaction, final product 143 was obtained in 98% yield (Scheme 40).

\(^1\)H and \(^{13}\)C NMR spectra are compatible with the structure. In \(^1\)H NMR spectrum, broad –NH protons and methoxy protons confirmed the formation of bis-urethane 143. –NH protons resonate at 5.25 and 5.15 ppm as broad singlets. Epoxide protons again give doublets individually at 3.51 and 3.38 ppm with coupling constant of 3.2 Hz. One of the bridgehead protons gives sharp and highly intense singlet at 4.25 ppm. On the other hand, other bridgehead proton gives broad singlet at 4.73 ppm. Actually, it must appear as doublet because; it should have coupled with the proton which is adjacent urethane functionality. However, this bridgehead proton has cis-configuration with urethane group, and nitrogen decreases the relaxation time of
bridgehead proton and causes broad singlet. Therefore, any coupling could not be seen. Protons which are attached to carbon next to urethane group resonate at 3.69 and 3.54 ppm. -OCH₃ protons give individually singlets at 3.62 and 3.63 ppm. Mechanism of this reaction is shown following in Scheme 41.

**Scheme 41** Mechanism of formation of bicyclic urethane

2.9 Ring-opening reaction of 143

To generate cyclohexane skeleton, further step was the epoxide ring-opening reaction as well as the cleavage O-bridge. Recently, Balcı et al. successfully achieved to open epoxide ring and tetrahydrofuran ring of compound 145 through acid-catalyzed ring-opening reaction and synthesized compound 146 with 89% yield (Scheme 42) [12].
This ring-opening procedure was applied to our system. To a solution of compound 143 in Ac₂O/AcOH, catalytic amount of sulfamic acid was added and reaction mixture was stirred for 24 hour at reflux temperature. Our expectation was that epoxide ring would be opened through stereoselective S₅² reaction. Since the structure 147 looks like a tetrahydofuran ring, we would also expect cleavage of O-bridge. But at the end of the reaction, ¹H and ¹³C NMR measurements indicated that the compound 147 was not formed (Scheme 43).

Exact structure could not be determined by ¹H and ¹³C NMR as well as 2D-NMR (DEPT-90, DEPT-135, COSY, HMQC and HMBC) experiments. Single crystal X-ray analysis proved the formation of tricyclic compound 148 (Figure 11).
For the formation of **148**, we suggest the following mechanism. After protonation of epoxide oxygen atom, oxygen atom of carbonyl group of *endo*-configurated urethane moiety attacks the epoxide carbon in **149** through S_N2 reaction and epoxide ring-opening and cyclization take place. Acetylation of hydroxyl group is carried out through attack of oxygen of hydroxyl group to acetic anhydride in presence of acetic
acid. After that, water has nucleophilic character and attacks the carbon atom in 150. Removal of CH$_3$OH forms cyclic amide 152. Further acetylation of –NH group results in the formation of final product 148 (Scheme 44).

Suggested mechanism of this reaction is shown in Scheme 45;

Scheme 45 Suggested mechanism of formation of tricyclic compound 148
The $^{13}$C spectrum of $^{148}$ showed the presence of 13 carbon resonances. Four of them appear in the sp$^2$-region at 172.9, 169.7, 155.8 and 147.2. We assigned these signals to carbonyl carbon resonances.

![Diagram of compound 148](image)

**Figure 12** DEPT-135 of compound 148

DEPT-135 spectrum showed nine distinct signals arising from –CH and –CH$_3$ groups (Figure 12). The fact that there was no negative signal clearly indicated the absence of any –CH$_2$ group.

DEPT-90 exhibits only –CH carbons. So, –CH and CH$_3$ carbons could be easily assigned. In this spectrum, C$_4$, C$_{4a}$, C$_8$, C$_6$, C$_7$, C$_{7a}$ carbons were observed.
The presence of only six carbon resonances in the DEPT-90 spectrum showed the presence of three CH$_3$ resonances. From the chemical shift of –CH$_3$ resonances, it was easy to distinguish between –OCH$_3$ and acetyl group (Figure 13).

In COSY spectra (Figure 14), all couplings between protons can be observed in one spectrum. Therefore, we could determine the neighboring protons. From COSY spectra, H$_8$ was assigned through coupling with –NH proton with coupling constant of $J = 6.4$ Hz and it resonates as doublet at 3.80 ppm in $^1$H NMR and at 57.7 ppm in $^{13}$C NMR. H$_{4a}$ appears as triplet at 4.76 ppm in $^1$H NMR due to the endo-configuration of the neighboring substituents H$_4$ and H$_{7a}$. The C$_{4a}$ carbon atom resonates at 67.4 ppm in $^{13}$C NMR.
In HMBC spectrum (Figure 15), correlation through 2 or 3 bonds between $^1$H and $^{13}$C peaks are seen. The determined correlations are in agreement with the determined structure.
For example, acetyl carbonyl carbon (C<sub>11</sub>) attached to nitrogen resonates at 172.9 ppm and correlates with –CH<sub>3</sub> proton resonance at 2.45 ppm. Acetate carbonyl carbon (C<sub>13</sub>) shows a correlation through 2 bonds with -CH<sub>3</sub> peak at 2.07 ppm and this methyl carbon resonates at 20.1 ppm.

C<sub>2</sub> can be determined only from HMBC spectrum. Because, there is no adjacent proton which gives direct correlation. C<sub>2</sub> correlates with H<sub>7a</sub> and H<sub>4</sub> through 3 bonds and it resonates at 147.2 ppm. Other carbonyl carbon involved in urethane group can be localized by using the information of correlation with methoxy proton. This carbonyl group resonates at 155.8 ppm. However, from <sup>1</sup>H NMR spectrum, it can be easily assigned due to there is an only one methoxy methyl proton and it gives singlet at 3.54 ppm in <sup>1</sup>H NMR spectrum and 51.3 ppm in <sup>13</sup>C NMR spectrum.

Carbonyl carbon C<sub>13</sub> signal intersects two cross peaks. One of them is methyl protons adjacent to C<sub>13</sub> which was defined before and other one is H<sub>7</sub>. On the basis of these correlations, H<sub>7</sub> resonance (5.12 ppm) as well as C<sub>7</sub> resonance (76.9 ppm) were assigned correctly.

C<sub>7a</sub> correlates with protons H<sub>7</sub>, H<sub>6</sub> and H<sub>4</sub> resonating at 5.12, 4.20 and 4.50 ppm. Resonance signal of C<sub>6</sub> and C<sub>4</sub> appear at 85.5 and 57.6 ppm. So, H<sub>7a</sub> could be easily defined and it gives doublet at 4.65 ppm in <sup>1</sup>H NMR and the corresponding C<sub>7a</sub> atom resonates at 81.7 ppm in <sup>13</sup>C NMR spectrum.

The location of C<sub>4</sub> was proven on the basis of the correlation between C<sub>2</sub> and, H<sub>7a</sub> and H<sub>4</sub>.

After determination of the correct structure of compound 148, it was easily realized that a carbonyl group having endo-configuration in 143 will always involve in the ring-opening process of the epoxide ring. At this stage, we decided to change our strategy and continue our synthetic process with a compound without epoxide ring or
without carbonyl group having \textit{endo}-configuration. Therefore, compound 138 should be converted into corresponding amine or the double bond in 98 should be protected as diol.

\textbf{2.10 Synthesis of corresponding amine 156}

We again turned our attention to isocyanate of bicyclic system. Isocyanate functionalities were decided to be converted into amine. In 2010, Balcı \textit{et al.} synthesized \textit{methyl 2-(aminomethyl)furan-3-carboxylate} (154) through hydrolysis reaction of isocyanate 153 (Scheme 46) \cite{34}.

![Scheme 46 Amine formation through hydrolysis of isocyanate](image)

We aimed to perform this reaction in 2 parts. First part was formation of ammonium salt of this system. To apply this reaction in our system, acyl azide 138 was converted into isocyanate 142 in dry benzene. Then, to this solution, 8M HCl was added and this mixture was stirred at room temperature for 1 h. After completion of reaction, compound 155 was obtained in 95 % yield (Scheme 47).

![Scheme 47 Formation of diammonium salt 155 from compound 142](image)
$^1$H and $^{13}$C NMR confirmed the formation of the product. In $^1$H NMR, one of the bridgehead protons resonates as singlet at 4.65 ppm and other one is split into doublet with $J = 4.6$ Hz and gives signal at 4.71 ppm. Epoxide protons resonate as AX system because chemical shift difference is much larger than coupling constant. Coupling between epoxide protons is $J = 3.2$ Hz and they resonate at 3.63 and 3.74 ppm. One of the protons neighboring $-^{14}$NH$_3$ resonates at 3.55 ppm as doublet. Other proton could not be seen due to the overlapping with solvent peak. $-^{14}$NH$_3$ protons resonate at 8.82 and 8.65 ppm.

In $^{13}$C NMR spectrum, epoxide carbons, carbons neighboring ammonium salt functional group and bridgehead carbons resonate at 47.2, 47.7, 54.6, 56.8, 74.1, 77.9 ppm.

The second part of the reaction was conversion of isocyanate functionality into amine. To do this, ammonium salt was dissolved in water and it was cooled to 0 °C (ice-bath). 0.5 M NaOH solution was added to adjust pH of the aqueous phase to 9 at 0 °C. Then, ethyl acetate was added and the mixture was stirred at the same temperature for 1 h. After completion of reaction, amine 156 was obtained as yellow oil (Scheme 48).

![Scheme 48 Diamine 156 formation](image)

$^1$H and $^{13}$C NMR are consistent with the structure. Epoxide protons resonate at 3.62 and 3.34 ppm as doublets with the coupling constant of $J = 3.4$ Hz. One of the bridgehead protons appear at singlet at 4.07 ppm and other one gives doublet with a coupling constant of $J = 4.7$ Hz at 4.25 ppm. Proton which is adjacent to amino group and has trans-configuration to O-bridge resonates at 2.55 ppm as doublet with
the coupling constant of $J = 2.7$ Hz. Other proton adjacent to amino group resonates as doublet of doublets at 3.14 ppm. In $^{13}$C NMR spectrum, there are six resonances at 87.3, 77.1, 75.4, 68.4, 67.3, 57.1 ppm. IR spectrum gave characteristics signal of amine functionality at 3446 cm$^{-1}$.

2.11 Synthesis of compound 157 through cis-dihydroxylation of compound 98

Van Rheenen et al. successfully achieved cis-dihydroxylation of double bond with OsO$_4$ (cat) in presence of NMO [35]. To apply this reaction to our starting material, cis-diester of bicyclic alkene 98, firstly OsO$_4$ solution was prepared in acetone/H$_2$O (1:1). To a solution of cis-diester in this solution, NMO was added at 0 °C under nitrogen atmosphere and reaction mixture was stirred at room temperature for 24 h then, bicyclic cis-diol 157 was obtained in 78% yield (Scheme 49).

\[
\text{Scheme 49 Cis-dihydroxylation of compound 98}
\]

$^1$H and $^{13}$C NMR results are compatible with the structure. Similarity was observed between NMR spectra of 157 and 122. A remarkable difference was observed between the resonances of $H_1$ and $H_2$ in 157 and 122 (Figure 16).

\[
\text{Figure 16 } H_1 \text{ and } H_2 \text{ in } 157 \text{ and } 122
\]
While $\text{H}_2$ protons resonate at 3.31 ppm, $\text{H}_1$ protons give singlet at 3.85 ppm. Epoxide proton resonances were shifted to higher field compared to the resonances of alkoxy protons in 157.

IR spectrum also proved the formation of diol 157 with the signal of hydroxyl group at 3357 cm$^{-1}$.

In $^{13}$C NMR spectrum, there are five lines which give signal at 171.0, 83.3, 72.1, 51.5, 46.3 ppm.

Ring-opening reactions with diol 157 as well as with amino-epoxide 156 will continue in the future.
3.1 General

Nuclear magnetic resonance ($^{1}$H-NMR and $^{13}$C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$d_6$ and CDCl$_3$ with TMS as internal reference. Chemical shifts ($\delta$) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quasi-triplet (quasi t) and multiplet (m) and coupling constants ($J$) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters ($\text{cm}^{-1}$).

Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ACD/NMR.

Solvents were purified as reported in the literature [36].
3.2 Synthesis of rel-(3aR,4R,7R,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxy-2-benzo furan-1,3-dione (108)

Maleic anhydride 107 (13.43 g, 136.9 mmol) was dissolved in 50 ml furane 106 at room temperature. This reaction was stirred at the same temperature for 3 h. A pure sample of exo-isomer 108 was obtained as a white solid after evaporating excess furane (21.6 g, 95%) (m.p. 112-113°C).

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{)} \delta: 6.58 (\text{q, } J = 0.9 \text{ Hz}), 5.46 (\text{q}, J = 0.9 \text{ Hz}), 3.18 (\text{s, } 2\text{H}) \]

\[ \text{13C-NMR (100.6 MHz, CDCl}_3\text{)} \delta: 169.9, 137.0, 82.3, 48.7 \]

IR (ATR) 1789, 1282, 1230, 1087, 1021, 904, 881

3.3 Synthesis of rel-(1R,2S,3R,4R)-3-(methoxycarbonyl)-7-oxabicyclo[2.2.1] hept-5-ene-2-carboxylic acid (109)

Methanol (203 μL) was added to exo-adduct 108 (3.25 g, 16 mmol) at room temperature. The reaction mixture was stirred until the anhydride was consumed (TLC). The solvent was evaporated in vacuo and the residue was dissolved in ethylacetate. After evaporating ethylacetate, white solid hemiester 109 was obtained (3.07 g, 97%) (m.p. = 106-107°C).

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{)} \delta: 9.77 (\text{br s, } \text{OH, } 1\text{H}), 6.40 (\text{dd}, J_{5,6} = 5.7 \text{ Hz}, J_{5,4} = 1.6 \text{ Hz}, 1\text{H, H-5}), 6.41 (\text{dd}, J_{6,5} = 5.7 \text{ Hz}, J_{6,1} = 1.6 \text{ Hz}, 1\text{H, H-6}) \]

\[ J_{B,A} = 9.0 \text{ Hz, } 1\text{H, H-2}, 2.78 \text{ (d, } J_{3,2} = J_{A,B} = 9.0 \text{ Hz, } 1\text{H, H-3}) \]

\[ \text{13C-NMR (100.6 MHz, CDCl}_3\text{)} \delta: 177.0, 171.7, 136.8, 136.3, 80.6, 80.3, 52.3, 47.3, 46.9 \]

IR (ATR) 3023, 2955, 1736, 1437, 1354, 1244, 1197, 909, 819
3.4 Synthesis of rel-(1R,2R,3S,4R)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (98)

Hemiester 109 (3.76 g, 19 mmol) was dissolved in MeOH (40 ml). To this solution was added thionyl chloride (2.73 ml) and the mixture was heated at reflux for 4 h. After completion of reaction, solvent and excess thionyl chloride was evaporated. rel-(1R,2S,3R,4S)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (98) was crystallized in ethyl acetate (25 ml). Then the crystals were removed by filtration (2.82 g, 70%) (m.p. = 117–118°C).

\[ \text{\textsuperscript{1}H-NMR (400 MHz, CDCl}_3) \delta \text{ ppm 6.39 (quasi t, } J = 0.9 \text{ Hz), 5.20 (quasi t, } J = 0.9 \text{ Hz), 3.64 (s, 3H, -OCH}_3), \]
\[ 2.76 \text{ (s, 2H, H-2, H-3)} \]

\[ \text{\textsuperscript{13}C-NMR (100.6 MHz, CDCl}_3) \delta \text{ ppm 171.9, 136.6, 80.4, 52.2, 46.9} \]

IR (ATR) 2988, 2948, 1746, 1733, 1434, 1344, 1196, 1008, 905

3.5 Synthesis of rel-(1S,2R,4S,5S,6S,7R)-dimethyl-3,8-dioxatricyclo[3.2.1.0\textsuperscript{2,4}]octane-6,7-dicarboxylate (122)

Diester 98 (1.0 g, 4.7 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (45 ml) and cooled to 0 °C. To this solution was added \textit{m}-CPBA (1.76 g, 9.4 mmol) and the reaction mixture was stirred for 1 day. Excess \textit{m}-CPBA was removed by filtration and to the filtrate was added saturated sodiumthiosulfate solution (100 ml) and the mixture was stirred for 10 min. After the organic layer was extracted, it was cooled to 0 °C. 0.5 M NaOH (100 ml) was added to cooled organic phase and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2x50 ml), dried over MgSO\textsubscript{4}. After evaporation of solvent, epoxide 122 was obtained as a white solid. (1.05 g, 98%) (m.p. = 143-144°C)

\[ \text{\textsuperscript{1}H-NMR (400 MHz, CDCl}_3) \delta \text{ ppm 4.78 (s, 2H, H-1, H-5), 3.63 (s, 6H, -OCH}_3), 3.31 (s, 2H, H-2, H-4), 2.92 \text{ (s, 2H, H-6, H-7)} \]

\[ \text{\textsuperscript{13}C-NMR (100.6 MHz, CDCl}_3) \delta \text{ ppm 170.3, 76.4, 52.4, 49.2, 49.1} \]

IR (ATR) 2953, 2253, 1740, 1437, 1280, 1215, 1168, 904, 725
3.6 Synthesis of compound 99, 103 and 126

To a solution of epoxide 122 (2.71 g, 11.8 mmol) in MeOH (50 ml) at 25 °C hydrazine monohydrate (4.04 ml, 83 mmol) was added and the resulting mixture was stirred at room temperature. After 24 h, solvent was evaporated in vacuo and excess hydrazine monohydrate was removed by washing cold MeOH (15 ml) to give compound 99 (1%), compound 103 (32%), compound 126 (67%). This mixture in chloroform was heated to 60 °C and stirred for 1 day. After filtration, filtrate was evaporated in vacuo and compound 126 (67%) (m.p. = 239-240 °C) was obtained as a white solid. When this reaction mixture was stirred under the same conditions for 2 d, compound 99, compound 103, compound 126 was obtained in the yield of 10%, 32%, 58%. When the reaction was carried out for 3 d under the same conditions, compound 99, compound 103 compound 126 was observed in reaction media in the yield of 12%, 44%, 44%.

3.6.1 rel-(1S,2R,4S,5S,6S,7R)-3,8-dioxatricyclo[3.2.1.0^2,4]octane-6,7-dicarbohydr azide (99)

\[\text{1H-NMR (400 MHz, DMSO-}d_6\text{) }\delta \text{ ppm 8.40 (s, 2H, -NH), 4.10 (s, 4H, NH}_2\text{), 4.52 (s, 2H, H-1, H-5), 3.40 (s, 2H, H-2, H-4), 2.80 (s, 2H, H-6, H-7)}\]

3.6.2 rel-(1aR,2S,2aR,5aS,6S,6aS)-4-aminopentahydro-1aH-2,6-epoxyxireno[f] isoindole-3,5-dione (126)

\[\text{1H-NMR (400 MHz, DMSO-}d_6\text{) }\delta \text{ ppm 5.05 (s, 2H, -NH}_2\text{), 4.63 (s, 2H, H-2, H-6), 3.68 (s, 2H, H-2a, H-5a), 3.12 (s, 2H, H-1a, H-6a)}\]

\[\text{13C-NMR (100.6 MHz, DMSO-}d_6\text{) }\delta \text{ ppm 173.7, 75.7, 49.1, 45.8}\]

IR (ATR) 3331, 3246, 1693, 1592, 1186, 1170, 1018, 854, 704

3.7 **Synthesis of rel-(1S,2S,4R,5S,6S,7S)-3,8-dioxytricyclo[3.2.1.0\(^{2,4}\)]octane-6,7-dicarbohydrazide** (103)

To a solution of **trans**-epoxide 132 (2.71 g, 11.8 mmol) in MeOH (50 ml) at 25 °C was added hydrazine monohydrate (4.04 ml, 83 mmol) and stirred for 1 d. After completion of reaction, the solvent was evaporated in vacuo and excess hydrazine monohydrate was removed by washing with MeOH (10 ml) to give dicarbohydrazide 103 as a white solid. (2.44 g, 91%) (m.p. > 300 °C)

\[ \begin{array}{c}
\text{CONNH}_2 \\
\text{CONNH}_2 \\
6 \quad 5 \\
7 \quad 2 \\
8 \quad 3
\end{array} \]

**\(^1H\)-NMR** (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 9.19 (s, 1H, -NH), 9.08 (s, 1H, -NH), 4.52 (d, \(J = 5.1\) Hz, 1H, H-5), 4.43 (s, 1H, H-1), 4.20 (d, \(J = 3.9\) Hz, 2H, -NH\(_2\)), 3.42 (d, \(J_{4,2} = J_{2,4} = 3.5\) Hz, 1H, H-4), 2.90 (d, \(J = 5.1\) Hz, 1H, H-7)

**\(^{13}C\)-NMR** (100.6 MHz, DMSO-\(d_6\)) \(\delta\) ppm 170.4, 167.8, 78.5, 74.7, 49.2, 48.8, 48.2, 45.7

**IR** (ATR) 3390, 3372, 3304, 1664, 1637, 1599, 1510, 1356, 1247, 1039, 928

**Anal. Calcd. for** C\(_8\)H\(_{12}\)N\(_4\)O\(_4\) (228,21): C 42.10, H 5.30, N 24.55, O 28.04; **Found:** C 43.61, H 5.258, N 24.07

3.8 **Synthesis of rel-(1R,2S,3S,4R)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate** (102)

Fumaryl chloride 110 (1.5 ml, 13 mmol) was added to furan 106 (1 ml, 13 mmol) which was pre-cooled to 0 °C (ice-salt bath). The reaction mixture was stirred for 0.5 h without removing the ice bath. After completion of reaction, light green solid was obtained. Anhydrous methanol (5 ml, 0.1 mol) and triethylamine (4.2 ml, 30 mmol) were added to ether (50 ml) at 10 °C. Then, light green solid was added with small portions to this solution at 10 °C and reaction mixture was stirred for 0.5 h. After that, cold water (40 ml) was added to solution. Then the mixture was extracted with ether (2 x 20 ml). The combined organic extracts were washed with water (40 ml) and brine (20 ml), dried over MgSO\(_4\) and the solvent was evaporated to give pale yellow solid 102. (1.98 g, 72%) (m.p. = 78–79 °C). The product was crystallized in ether.
**1H-NMR** (400 MHz, CDCl₃) δ ppm 6.45 (dd, J₅,₆ = 5.74, J₅,₄ = 1.7 Hz, 1H, H-5), 6.29 (dd, J₆,₅ = 5.79, J₆,₁ = 1.50 Hz, 1H, H-6), 5.19-5.16 (m, 2H, H-4, H-1), 3.69 (s, 3H, -OCH₃), 3.60 (s, 3H, -OCH₃), 3.55 (t, J₃,₁ = J₃,₂ = 4.3 Hz, 1H, H-3), 2.78 (d, J₂,₃ = 3.9 Hz, 1H, H-2)

**13C-NMR** (100.6 MHz, CDCl₃) δ ppm 171.3, 170.0, 77.9, 74.9, 52.7, 52.5, 50.5, 49.1, 48.3, 48.1

**IR (ATR)** 2955, 1727, 1434, 1377, 1196, 1178, 1163, 1023, 915, 870

### 3.9 Synthesis of rel-(1S,2R,4S,5S,6S,7S)-dimethyl-3,8-dioxatricyclo[3.2.1.0²⁴]octane-6,7-dicarboxylate (132)

Diester 102 (1.0 g, 4.7 mmol) was dissolved in CH₂Cl₂ (45 ml) and cooled to 0 °C. To this solution was added m-CPBA (1.76 g, 9.4 mmol) and the reaction mixture was stirred for 2 days. Excess m-CPBA was removed by filtration and to the filtrate was added saturated sodiumthiosulfate solution (100 ml) and the mixture was stirred for 10 min. After the organic layer was extracted, it was cooled to 0 °C. 0.5 M NaOH (100 ml) was added to cooled organic phase and extracted with CH₂Cl₂ (2x50 ml), dried over MgSO₄. After evaporation of solvent, epoxide 132 was obtained as a white solid. (0.7 g, 72%) (m.p. = 108-109 °C)

**1H-NMR** (400 MHz, CDCl₃) δ ppm 4.68 (d, J₁,₇ = 5.3 Hz, 1H, H-1), 3.69 (s, 3H, -OCH₃), 3.58 (t, J₇,₁ = J₇,₆ = 5.0 Hz, 1H, H-7), 3.39 (d, J₂,₄ = J₄,₅ = 3.3 Hz, 1H, H-2), 3.33 (d, J₄,₂ = J₂,₄ = 3.3 Hz, 1H, H-4), 3.01 (d, J₆,₇ = 4.9 Hz, 1H, H-6)

**13C-NMR** (100.6 MHz, CDCl₃) δ ppm 171.4, 170, 78.0, 74.9, 52.7, 52.5, 50.5, 49.1, 48.4, 48.1

**IR (ATR)** 2959, 1720, 1434, 1372, 1344, 1307, 1250, 1215, 998, 970, 887, 857
3.10 Synthesis of rel-(1S,2R,4S,5S,6S,7S)-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane-6,7-dicarbonyl azide (138)

The dihydrazide 103 (2.46 g, 10.8 mmol) was dissolved in aq. HCl (35 ml, 1M) at 0 °C. To a stirred solution, sodium nitrite (0.78 g, 11.38 mmol) in water (9 ml) was added dropwise and reaction mixture was stirred at 0-5 °C for 0.5 h. (2x60 ml) EtOAc was used for extraction. After organic phases were combined, aq Na$_2$CO$_3$ solution (40 ml) was used to wash organic phase. Then, it was washed with brine (30 ml), dried over MgSO$_4$. After evaporation of solvent, acyl azide 138 was obtained as a white solid. (1.3 g, 63%)

$^1$H-NMR (400 MHz, CDCl$_3$) δ ppm 4.75 (s, 1H, H-5) 4.69 (d, J$_{1,7}$ = 5.1 Hz, 1H, H-1), 3.42 (d, J$_{2,4}$ = J$_{A,B}$ = J$_{4,2}$ = J$_{B,A}$ = 3.2 Hz, 2H, H-2, H-4), 3.59 (t, J$_{7,1}$ = J$_{7,6}$ = 5.0 Hz, 1H, H-7), 3.00 (d, J$_{6,7}$ = 4.9 Hz, 1H, H-6)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$) δ ppm 177.5, 176.4, 78.1, 75.2, 52.6, 50.0, 48.9, 48.2

IR (ATR) 2165, 1696, 1324, 1285, 1209, 1176, 985, 860

3.11 Synthesis of rel-(1S,2R,4S,5S,6S,7S)-dimethyl-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane-6,7-diyldicarbamate (143)

(0.89 g, 4.6 mmol) Acyl azide 138 is added to dry benzene (40 ml) and is heated to reflux temperature. The solution is stirred at this temperature for 1 h. At this stage, acyl azide 138 is converted into isocyanate 142. Then, this solution of isocyanate 142 is cooled to 40 °C and distilled methanol (1.2 ml, 29.4 mmol) was added to this solution. It is allowed to stir at reflux temperature for 1 h. After completion of reaction, solvent was evaporated in vacuo to give urethane 143 as a white solid. (1.16 g. 98%) (m.p. = 191-192 °C)

$^1$H-NMR (400 MHz, CDCl$_3$) δ ppm 5.25 (br s, 1H, -NH) 5.15 (s, 1H, -NH) 4.73 (br s, 1H, H-1), 4.25 (s, 1H, H-5), 3.69 (m, 1H, H-7), 3.63 (s, 3H, -OCH$_3$), 3.62 (s, 3H, -OCH$_3$) 3.54 (m, 1H H-4) 3.51 (d, J$_{2,4}$ = 3.2 Hz, 1H, H-2), 3.38 (d, J$_{4,2}$ = 3.2 Hz, 1H, H-4)
**13C-NMR** (100.6 MHz, CDCl₃) δ ppm 156.34, 156.3, 79.1, 73.1, 61.1, 61.0, 56.9, 51.5, 51.3, 47.7

**IR** (ATR) 1682, 1541, 1311, 1281, 1238, 1196, 1022, 890, 820

**Anal. Calcd. for** C₁⁰H₁₄N₂O₆ (258,23): C 46.51, H 5.46, N 10.85, O 37.18; Found: C 48.07, H 5.23, N 10.88

**3.12 Synthesis of rel-(4aS,4R,6S,7aR,7R,8S)-3-acetyl-2-oxohexahydro-2H-4,6-methanofuro[2,3-e][1,3]oxazin-7-yl acetate-8-yl carbamate (148)**

Sulfamic acid (0.08 g, 0.82 mmol) was added to a stirred solution of urethane 143 (0.85 g, 3.29 mmol) in AcOH/AC₂O (15 ml 1:1). The mixture was stirred at reflux temperature for 24 h. 50 ml water was poured into this mixture and 2-3 drop of HCl was added to acidify the solution. For extraction of organic phase, dichloromethane was used. (2x50 ml) Water and (2x25 ml) NaHCO₃ were used for washing organic phase which was then dried over MgSO₄. After evaporation, white solid 148 which was then crystallized in CHCl₃ over hexane atmosphere was obtained. (27 %, 0.29 g) (m.p. = 201-202 °C)

**1H-NMR** (400 MHz, DMSO-d₆) δ ppm 7.63 (d, 1H, -NH), 5.12 (s, 1H, H-7), 4.76 (t, J₄₄₇₇ = J₄₄₄₅ = 5.4 Hz, 1H, H-4a) 4.65 (d, J₇₇₄₄ = 5.3 Hz, 1H, H-7a), 4.50 (d, J₄₄₇₇ = 5.3 Hz, 1H, H-4), 4.20 (s, 1H, H-6), 3.81 (d, J₈₈₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋˓→

**13C-NMR** (100.6 MHz, DMSO-d₆) δ ppm 172.9, 169.7, 155.8, 147.2, 85.5, 81.7, 76.9, 67.4, 57.7, 57.6, 51.3, 26.8, 20.6

**IR** (ATR) 1682, 1541, 1311, 1281, 1238, 1196, 1022, 890, 820

**Anal. Calcd. for** C₁₃H₁₈N₂O₈ (328,27): C 47.56, H 4.91, N 8.53, O 38.99; Found: C 47.17, H 4.98, N 8.39

56
3.13 Synthesis of rel-(1S,2R,4S,5S,6S,7S)-3,8-dioxatricyclo[3.2.1.0\(^2\),4]\(\)octane-6,7-diaminiumchloride (155)

(0.89 g, 4.6 mmol) Acyl azide 138 is dissolved in dry benzene (40 ml) and is heated to reflux temperature. The solution is stirred at this temperature for 1 h. At this stage, acyl azide 138 is converted into isocyanate 142. Then, to this solution, 8M HCl (10 ml) was added and this mixture was stirred at room temperature for 1 h. After completion of reaction, water phase which includes diaminium salt is separated from organic phase (dry benzene phase). Solvent was evaporated in vacuo and light brown salt 155 is obtained. (0.93 g, 95%)

\(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.82 (br s, 1H, H-9), 8.65 (br s, 1H, H-10), 4.71 (d, \(J_{1,7} = 4.6\) Hz, 1H, H-1), 4.65 (s, 1H, H-5), 3.74 (d, \(J_{2,4} = 3.2\) Hz, 1H, H-2), 3.63 (d, \(J_{4,2} = 3.2\) Hz), 3.55 (m, 2H, H-7, H-6)

\(^13\)C-NMR (100.6 MHz, DMSO-\(d_6\)) \(\delta\) ppm 77.9, 74.1, 56.8, 54.6, 47.7, 47.2

IR (ATR) 3174, 3089, 2983, 2895, 2809, 1599, 1506, 1479, 1231, 1087, 1071, 956, 927

HRMS Spectrum: Found: 143.08181; Calculated [M+H]^+: 144.0815

3.14 Synthesis of rel-(1S,2R,4S,5S,6S,7S)-3,8-dioxatricyclo[3.2.1.0\(^2\),4]\(\)octane-6,7-diamine (156)

After dissolving compound 155 (0.8 g, 3.7 mmol) in water (15 ml), ethyl acetate (15 ml) was added and this mixture was cooled 0 °C. The pH value of the aqueous phase was adjusted to 10 by the addition of 0.5 M NaOH solution at the same temperature. The mixture was extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO\(_4\) and the solvent was evaporated to give yellow oily amine 156 (0.11 g, 23%).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 4.25 (d, \(J_{1,7} = 4.7\) Hz, 1H, H-1), 4.07 (s, 1H, H-5), 3.62 (d, \(J_{2,4} = 3.4\) Hz, 1H, H-2), 3.34 (d, \(J_{4,2} = 3.4\) Hz, 1H, H-4), 3.14 (dd, \(J_{7,1} = 4.7\) Hz and \(J_{7,6} = 2.7\) Hz, 1H, H-7), 2.55 (d, \(J_{6,7} = 2.7\) Hz, 1H, H-6)
\[ ^{13}\text{C-NMR} \text{(100.6 MHz, CDCl)}_3 \delta \text{ppm 87.3, 77.1, 75.4, 68.4, 67.3, 57.1.} \]

\[ \text{IR (ATR) 3523.9, 3502.7, 3446.8, 1737.7, 1372.7, 1232.6, 1044.06} \]

\[ \text{HRMS Spectrum: Found: 143.07978; Calculated } [\text{M+H}]^+: 143.0815 \]

3.15 Synthesis of rel-(1S,2R,3S,4S,5R,6S)-dimethyl-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (157)

Cis-diester of bicyclic system 98 (0.4 g, 2 mmol) was dissolved in canned OsO\(_4\) solution which contains 12 mg (0.048 mmol) OsO\(_4\) in 10 ml of acetone/H\(_2\)O (1:1) and (0.5 g, 4.35 mmol) NMO was added to this solution at 0 °C. The resulting mixture was stirred at room temperature for 24 h. under nitrogen atmosphere. After evaporation of solvent under vacuo, pale yellow solid 157 was obtained. (0.35 g, 78 %) (m.p. = 200-201 °C)

\[ ^1\text{H-NMR} \text{(400 MHz, DMSO-}\text{d}_6) \delta \text{ppm 4.83 (d, } J_{1,6} = J_{4,5} = 4.4 \text{ Hz, 2H, H-1,H-4), 4.32 (s, 2H, -OH), 3.77 (d, } J_{6,1} = J_{5,4} = 4.4 \text{ Hz, 2H, H-6, H-5), 3.53 (s, 6H, -OCH}_3\text{), 3.03 (s, 2H, H-3, H-2)} \]

\[ ^{13}\text{C-NMR} \text{(100.6 MHz, DMSO-}\text{d}_6) 171.0, 83.3, 72.1, 51.5, 46.3 \]

\[ \text{IR (ATR) 3357, 2951, 1732, 1717, 1435, 1356, 1247, 1196, 1169, 1037, 983, 920} \]

\[ \text{HRMS Spectrum: Found: 245.07395; Calculated } [\text{M-H}]^-: 245.06668 \]
CHAPTER 4

CONCLUSION

Cylitols concerning a large group of natural products have attracted a great deal of attention from the synthetic community due to their glycosidase inhibition activities and their versatility as synthetic intermediates. Aminocylitols also play an important role in biological events. They compose of comprehensive group of natural products. Aminocylitols are found extensively in nature in different areas. They have a character of inhibition of some enzymes such as glycosidases. So, bis-aminoinositol synthesis is the interest of this study.

In this work, we tried to develop a new synthetic methodology for the synthesis of bis-aminoinositol derivatives, such as compound 100, 101, 105 and 104. For this synthesis, compound 98 and 102 were considered to be our key compounds. To convert the diester functionality in compound 98 and 102 into hydrazide group, hydrazine monohydrate was used. In this step, retro Diels-Alder reaction was observed. Then, double bond in bicyclic system was oxidized with m-CPBA to prevent reverse Diels-Alder reaction. For the reaction of cis-diester of epoxide 122 with hydrazine monohydrate, we observed three different products which are 99, 103 and 126. Formation of compound 103 was thought due to α-epimerization. Then, we turned our attention to only trans endo-diester of bicyclic epoxide 132. Treatment of compound 132 with hydrazine monohydrate gave only one product, compound 103 due to thermodynamic stability. Then compound 103 was converted into acyl azide through modified Sandmeyer. This acyl azide 138 was converted to isocyanate followed by methanol addition to give urethane 143. Further step was the cleavage of oxa-bridge with the help of acid-catalyzed ring-opening reaction. However, highly stable tricyclic product 148 was formed. Furthermore, Lewis acids such as BF₃·Et₂O
and BCl$_3$ and sulfuric acid as well were used to open oxa-bridge, but we could not achieve. After Curtius rearrangement reaction, hydrolysis of the isocyanate functionality in presence of HCl resulted in corresponding amine 156. Further step was to cleave oxa-bridge to get cyclic structure. However, O-bridge could not be opened with any reagents used for urethane derivative as described above. Then, we turned our attention to follow reaction pathway with diol of bicyclic system 157 due to preventing neighboring group participation like that in formation of compound 148. So, we submitted compound 98 to OsO$_4$ – NMO oxidation reaction and we obtained compound 157. We planned to apply hydrazine monohydrate addition reaction. Further reactions to complete this project are planned.

This developed methodology opens up a new entry to the synthesis of isomeric 1,2-aminoinositol derivatives.
REFERENCES


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Figure 17 $^1$H-NMR Spectrum of Compound 108
Figure 18 $^{13}$C-NMR Spectrum of Compound 108

Figure 19 IR Spectrum of Compound 108
Figure 20 $^1$H-NMR Spectrum of Compound 109

Figure 21 $^{13}$C-NMR Spectrum of Compound 109
Figure 22 IR Spectrum of Compound 109

Figure 23 $^1$H-NMR Spectrum of Compound 98
Figure 24 $^{13}$C-NMR Spectrum of Compound 98

Figure 25 IR Spectrum of Compound 98
Figure 26 $^1$H-NMR Spectrum of Compound 122

Figure 27 $^{13}$C-NMR Spectrum of Compound 122
Figure 28 IR Spectrum of Compound 122

Figure 29 $^1$H-NMR Spectrum of Compound 103
Figure 30 $^{13}\text{C}$-NMR Spectrum of Compound 103

Figure 31 IR Spectrum of Compound 103
Figure 32 $^1$H-NMR Spectrum of Compound 138

Figure 33 $^{13}$C-NMR Spectrum of Compound 138
Figure 34 IR Spectrum of Compound 138

Figure 35 $^1$H-NMR Spectrum of Compound 126
Figure 36 $^{13}$C-NMR Spectrum of Compound 126

Figure 37 IR Spectrum of Compound 126
Figure 38 $^1$H-NMR Spectrum of Compound 102

Figure 39 $^{13}$C-NMR Spectrum of Compound 102
**Figure 40** IR Spectrum of Compound 102

**Figure 41** $^1$H-NMR Spectrum of Compound 132
Figure 42 $^{13}$C-NMR Spectrum of Compound 132

Figure 43 IR Spectrum of Compound 132
Figure 44 $^1$H-NMR Spectrum of Compound 143

Figure 45 $^{13}$C-NMR Spectrum of Compound 143
Figure 46 IR Spectrum of Compound 143

Figure 47 $^1$H-NMR Spectrum of Compound 148
Figure 48 $^{13}$C-NMR Spectrum of Compound 148

Figure 49 IR Spectrum of Compound 148
Figure 50 DEPT 90 spectrum of compound 148

Figure 51 DEPT 135 of compound 148
Figure 52 COSY spectrum of compound 148

Figure 53 HMBC spectrum of compound 148
Figure 54 $^1$H-NMR Spectrum of Compound 155

Figure 55 $^{13}$C NMR Spectrum of Compound 155
Figure 56 IR Spectrum of Compound 155

Figure 57 $^1$H-NMR Spectrum of Compound 156
Figure 58 $^{13}$C-NMR Spectrum of Compound 156

Figure 59 IR Spectrum of Compound 156
Figure 60 $^1$H-NMR Spectrum of Compound 157

Figure 61 $^{13}$C-NMR Spectrum of Compound 157
**Figure 62** IR Spectrum of Compound 157