CHAPTER 1: 
INTRODUCTION TO 7-AZABICYCLO [2.2.1] HEPTANE SKELETON AND APPROACHES TOWARDS TOTAL SYNTHESIS OF PANCRATISTATIN
Section A
1A.1 : An introduction to 7-azabicyclo[2.2.1]heptane skeleton ; synthetic routes and importance

Three different types of structures are possible for 7-azabicyclo[2.2.1]heptane skeleton (1); the fully saturated (1a), partially unsaturated (1b) and fully unsaturated (1c). A large number of synthetic sequences are known in literature towards the construction of these skeletons. For sometimes, the interest in the synthesis of these systems were only a matter of academic interest since no naturally occurring compound was known at that time which contained these ring systems. From 1990 onwards the scenario started changing after the isolation of large number of naturally occurring alkaloids from amphibian toad skin by Daly et al. The most notable and celebrated among the hundreds of isolated alkaloids was epibatidine (2). (-)-Epibatidine (2), a new alkaloid isolated from Ecuadorian poison frog, *Epipedobates tricolor*, featuring the 7-azabicyclo[2.2.1]heptane ring system with an exo oriented 5-(2-chloropyridyl) moiety (Figure 1) displayed strong analgesic property though it was not a member of *opioid class*. Due to the novel biological activity associated with 2 and its paucity in nature (1 mg isolated from 750 frogs), the total synthesis of 2 had aroused huge interest amongst organic chemists around the world.

![Figure 1.](image)

The extraordinary pharmacology of 2 had indicated its potential for nicotinic acetylcholine receptor (nAChR) ligands for serving as a new therapeutic class of host of CNS disorders. Many of such ligands are natural products, or analogues thereof, which represent a significant challenge to the synthetic chemist.

The chance of 2 ever being used as a medicinal agent became quite low because of its high toxicity, however, in order to cope up with toxicity, several analogues of 2 have been deliberated and synthesized by altering the side chain as well as bicyclic skeleton. One of the interesting analogue is epiboxidine (3), a hybrid of epibatidine...
and ABT-418 (4) which is an isosteric analogue of nicotine, where chloropyridine ring has been replaced by methylisoxazole (Figure 2). Although not as potent as epibatidine, epiboxidine (3) has higher affinity than nicotine and has been found 20 fold less toxic than 2.

![Epiboxidine](image1.png)

![ABT-418](image2.png)

Figure 2.

Another class of the epibatidine analogues such as homoepibatidine (5), bis homoeipibatidine (6) and diazabicyclopyrazine DBO-83 (7) (Figure 3) in which the azabicycloheptane ring is altered has been synthesized and tested. However, none of these could be developed as a drug so far.

![Homoepibatidine](image3.png)

![Bis-homoepibatidine](image4.png)

![DBO-83](image5.png)

Figure 3.

In search of better selectivity, conformationally restricted analogue 8 as well as fused analogue 9 has also been synthesized and screened (Figure 4). Although, these analogues show low affinity and do not encompass the ideal conformation for the high affinity, they surely provide valuable information concerning the pharmacophore studies.

![Conformationally restricted analogue](image6.png)

![Fused analogue](image7.png)

Figure 4.
Despite significant progress in the research dealing with the chemistry of 7-azabicyclo[2.2.1]heptane ring system, most of these important structures have been used in the synthesis of epibatidine and its analogues. We got interested in this particular ring system by visualizing its immense potential for the synthesis of various important structural motifs as shown in Fig. 5.

Our previous experiences with 7-azabicyclo[2.2.1]heptane structural frameworks\textsuperscript{[9]} led us to understand well that C4-N7 cleavage of this skeleton will generate a cyclohexene skeleton from which depending on the nature and stereochemistry of R, various aminocyclitols, diaminocyclitols and *Amaryllidaceae* alkaloids could possibly be synthesized. Similarly, stereoselective C5-C6 functionalization followed by C4-N7 cleavage would in principle generate a fully substituted cyclohexene moiety; which can easily be manipulated to many all carbon substituted aminocyclitols. Synthesis of these aminocyclitols otherwise have proved to be difficult. Another important class of structures could be generated by first dihydroxylation of C5-C6 olefinic bond followed by cleavage leading to all substituted pyrrolidines skeleton; an essential requirement for the synthesis of Preussin and Hyacinthin class of compounds. Lastly another potential disconnection could be thought of between C2-C3 which could
generate cis- and trans- 2,5-dialkylated pyrrolidines; an ubiquitous structural features in many important naturally occurring alkaloids. Because of immense importance of 7-azabicyclic frame work, various groups have developed different approaches for its construction. Therefore, before dwelling upon our contribution in this field, it would be appropriate to describe some of the selected examples for the construction of 7-azabicyclo[2.2.1]heptane frame work from literature.

1A.2. Various approaches for the construction of 7-azabicyclic system

1A.2a trans-Annular cyclization
Trost et al.[10] reported the first asymmetric synthesis of (-)-epibatidine (2) using Pd-catalyzed desymmetrization of meso-10 to produce 11 which was later converted into a key precursor 12. The intermediate 12 was subjected to trans-annular cyclization to construct 7-azabicyclic system producing (-)-2 with 81% yield and >95% ee as depicted in Scheme 1.

Scheme 1.
Lee et al.[11] developed a short and concise procedure for gram-scale synthesis of 2 by intramolecular cyclization of 14 followed by the radical dehalogenation to provide 15 as a sole product which was further epimerized to (-)-2 as shown in Scheme 2.
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Scheme 2.
Sanchez and co-workers reported\cite{12} the NaH/DMF-promoted heterocyclization reaction of \( N\)-(3-cis,4-trans-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (16) to afford 7-azabicyclo [2.2.1] heptane derivative 17 in good yield (81%) which on basic hydrolysis followed by acetylation gave 18 in 72% yield (Scheme 3).

Scheme 3.
Another excellent example of transannular cyclization could be found in literature by Savoia et al.\cite{13} where synthesis of optically pure endo-7-azabicyclo[2.2.1]heptane 20 is reported by cyclization of 19 using Mitsunobu protocol. Subsequent removal of benzylic substituents by reductive hydrogenation in the presence of palladium hydroxide in methanol containing 2.5 eq. HCl/MeOH produced endo-7-azabicyclo[2.2.1]heptan-2-amine (21) as a single isomer in 97% yield (Scheme 4).

Scheme 4.
1A.2b Intramolecular cyclization

Albertini et al.[14] have reported conceptually attractive strategy for the enantioselective construction of 7-azabicyclo[2.2.1]heptanes skeleton 24 in high yield (92%), employing a facial and regio-selective intramolecular nucleophilic ring opening of a chiral cyclic sulfate 23 derived from D-(-)-quinic acid 22 as shown in Scheme 5. Intermediate salt 24 was further transformed to 7-azabicyclic ketone 26 for the synthesis of (+)-2.

Scheme 5.

Synthesis of 7-azabicyclic ring system 28 is reported[15] in excellent yield (96%) involving β-elimination of silyl ether of 27 followed by cyclization to afford 28. Intermediate 28 was further converted into 2-substituted 7-azabicyclo[2.2.1]heptane glutamic acid analogue 29 employing simple transformations (Scheme 6).

Scheme 6.

Asymmetric hetero Diels-Alder reaction as a key step have been utilized[16] for the synthesis of (-)-epibatidine involving 32, obtained in high yield and selectivity from
an asymmetric Diels-Alder cycloadduct 30. The precursor 31 was further converted to (-)-2 by intramolecular cyclization as shown in Scheme 7.

Scheme 7.

Elena and co-workers\(^{[17]}\) developed a protocol for the synthesis of 7-azabicyclic system 42 by intramolecular cyclization of a mixture of 40 and 41 which in turn was obtained by the cyclization of 35. The key intermediate 35 was obtained by Diels-Alder reaction of (Z)-2-phenyl-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5-oxazolone 33 and Danishefsky’s diene 34 (Scheme 8).

Scheme 8.

1A.2c Intramolecular iminium cyclization
Rapoport et al.\(^{[18]}\) have introduced a novel “Chiron” concept of decarbonylation/intramolecular iminium-ion cyclization of 43, for the construction of
enantiopure trans-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes (-)-44 and (+)-44 in 1:3 ratio, those were further converted in to (+)-26 and (-)-26 respectively, via single chemical manipulation as shown in Scheme 9.

Scheme 9.
Karsten et al.\cite{19} developed a method for the construction of enantiopure 7-azabicyclo[2.2.1]heptanes skeleton 46 in 75% yield by intramolecular N-acyliminium ion cyclization of the N, O-acetal 45 and ozonalysis of 46 to produce a key precursor (-)-26 for (+)-epibatidine (Scheme 10) synthesis.

Scheme 10.

1A.2d Asymmetric elimination
Simpkins et al.\cite{20} have reported an unique approach for the total synthesis of (-)-epibatidine (2), utilizing asymmetric elimination of a sulfone group from a vicinal bis-sulfone having the 7-azabicyclo[2.2.1]heptanes skeleton 47 by the sodium alkoxide derivative of (IR,2S)-ephedrine (50). Key precursor 49 was further converted in to (-)-2 by simple chemical transformation (Scheme 11).
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1A.2e Asymmetric Diels-Alder cycloaddition

A very interesting approach has been adopted by Node and co-workers\textsuperscript{[21]} for the construction of enantiopure 7-azabicyclo[2.2.1]heptanes system \textit{53} (86\%) as a sole product utilizing asymmetric Diels-Alder reaction of di-L-(2)-menthyl allene-1,3-dicarboxylate (\textit{R})-51 with \textit{N}-Boc-pyrrole 52 in the presence of \textit{AlCl}\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} at -78 °C. Compound \textit{53} was subsequently converted into a synthetic precursor \textit{26} for the synthesis of (-)-epibatidine (Scheme 12).

Scheme 12.

1A.3 Our lab contribution

Owing to its intriguing pharmacological activity, interesting structural features and scarcity in nature, our group also got attracted for synthesis of 2 and its analogues. The first racemic synthesis was reported by us using cycloaddition of non stabilized azomethine ylide, generated by the sequential double desilylation of \textit{N}-alkyl-\textit{α,α'}-di(trimethylsilyl) cyclic amines using Ag(I)F as one electron oxidant, with a variety of dipolarophiles (Scheme 13).\textsuperscript{[22]}
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Scheme 13.
Our group had also reported less toxic racemic epiboxide (±)-3 synthesis using a similar Diels-Alder cycloaddition approach (Scheme 14).\cite{23}

\[
\text{Scheme 13.}
\]

\[
\begin{align*}
\text{TMS} & \quad \text{TMS} \\
\text{TMS} & \quad \text{Bn}
\end{align*}
\]

\[
\text{EWG}\ a = -\text{CO}_2\text{Et} \\
b = -\text{CH}_3\text{CHO} \\
c = -\text{CN} \\
d = -\text{NO}_2
\]

\[
\begin{align*}
\text{Scheme 14.}
\end{align*}
\]

A short enantioselective synthesis of 2 was also reported by us employing a chiral auxiliary guided [3+2] cycloaddition of non stabilized azomethine ylide\cite{24}(Scheme 15).
Scheme 15.
Although several different synthetic approaches have been described for the construction of 7-azabicyclic systems, the efficacy of desymmetrization of meso-7-azanorbornene for the synthesis of these kinds of frameworks remained unexplored for so many years. Visualizing the importance of 7-azabicyclo[2.2.1]heptanes system, our continuing efforts directed towards the development of novel methodologies for the construction of enantiopure 7-azanorbornene frameworks. Our group has developed a conceptually new and efficient route via asymmetric desymmetrization of meso-64 using chiral diolate of 65 to produce optically pure 7-azabicyclic frame 66 with excellent diastereoselectivity and yield (99% de, 82% yield)\(^\text{(9)}\) as outlined in Scheme 16. The enantiopure ketone 67 was exploited for the total synthesis of various conduramines and substituted cyclohexane derivatives.

Scheme 16.
Mechanistically, the formation of product requires nucleophilic attack of alcoholate anion onto the vinylic carbon atom of 64. The least encumbered trajectory is the one where phenyl group point upwards and alkyl to the side. The elimination of phenyl sulfinate anion generates vinylic sulfone moiety which is again being attacked by the second alcoholate anion to generate carbanion and finally protonation occurs according to exo-rule to give endo sulfone. However, this product seems to be a kinetic product as under basic condition it undergoes epimerization to give exclusively exo sulfone as a single diastereomer (Figure 5).

Figure 6. Mechanistic insight for desymmetrization.
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1A.4. References.

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SECTION B: Synthetic studies towards pancratistatin and related natural products

1B. 1a Introduction.

Over the years, plants of the Amaryllidaceae family have long been known for their medicinal and toxic properties. These alkaloids have attracted considerable attention from the synthetic community because of their interesting structures and potent biological activities. Extremely low natural abundance, as well as practical complications in the separation of the desired compound from plant constituents had diminished the probability of reasonable supply by means of isolation. Therefore, significant efforts have been made in developing viable synthetic routes towards these important alkaloids (68-71).

Figure 7: Structure’s of isocarbostyril alkaloids.

The task has been addressed by various research groups in two different dimensions over two decades, one of the two has been dealing with the quest for short, high yielding synthesis of the naturally occurring isocarbostyril’s which promoted the screening and development of great number of existing and new methodologies for their capabilities. The other dimension is looking for the potential and more bio-available derivatives to substitute them in all respects. This particular search resulted in the syntheses of various truncated and unnatural derivatives through which the scientific community has been enlightened with the substantial amount of this information regarding essential and variable pharmacophores of these molecules.
This section constitutes an update of the major developments in *Amaryllidaceae* isocarboxyls. Since the detailed discussion of all the literature reported syntheses have already been reviewed by many others\(^{[47]}\) and also it would be beyond the scope of this dissertation, the foregoing discussion would mainly focus on few of the important methodologies involved in the literature reported syntheses of Pancratistatin and related compounds (68-71).

**1B.1b. Synthetic approaches toward Pancratistatin (68).**

a) Danishefsky’s approach

The first total synthesis\(^{[18]}\) of the racemic 68 was accomplished in 27 steps and in less than 1 % overall yield by employing iodolactonization on aryl cyclohexadiene 70 to obtain C\(_{1}\)-C\(_{10b}\) cis-relationship in 71. The Overman rearrangement of 72 gave required C\(_{4a}\) amino group stereochemistry. Finally, vicinal cis oxygenation of C\(_{3}\)-C\(_{4}\) double bond of 73 followed by lactamisation gave racemic 68 (Scheme-6).

![Scheme 17](image)

*Reagents and Conditions: i) a) AllylMgBr, Et\(_2\)O, -78 °C; b) MsCl, TEA, DBU, DCM; c) (E)-(2-nitrovinylsulfonyl) benzene, CHCl\(_3\), reflux; d) Bu\(_3\)SnH, AIBN, PhCH\(_3\),*
reflux; ii) a) TBAF, THF, 0 °C; b) (Bu$_3$Sn)$_2$O, PhCH$_3$, 2h, I$_2$; iii) a) Ag$_2$O, DMF, BnBr, rt; b) OsO$_4$, NMO, DCM, THF, rt; c) DBU, toluene, reflux, 1.5 h; d) 2-acetoxyisobutyric bromide, CH$_3$CN, 0 °C, 5 min; e) OsO$_4$, NMO, THF, rt; f) (Bu$_3$Sn)$_2$O, PMBBr, PhCH$_3$; Ag$_2$O, BnCl, DMF g) DDQ, DCM, H$_2$O; h) Zn, HOAc; iv) NaH, CCl$_3$CN, THF, 100 °C; v) OsO$_4$, NMO, THF, rt; vi) a) K$_2$CO$_3$, MeOH, DCM, reflux; b) H$_2$/Pd (OH)$_2$, 1 atm.

b) Hudlicky’s approach

A concise enantioselective total synthesis$^{[19,20]}$ of 68 was accomplished in 14 steps and in 2 % overall yield. This route involved the regioselective aziridine (derived form cyclohexadiene cis-diol 76) ring opening of 77 using higher order cyano cuprate 78 to afford 79. Finally, setreospecific opening of epoxide in 81 followed by lactamisation afforded 68 (Scheme-7).

Scheme 18
Reagents and Conditions: a) PhI=NTs, Cu (acac)$_2$, CH$_3$CN; b) BuSnH, AIBN, THF; ii) a) s-BuLi, TMEDA, THF, -90 °C; b) CuCN, -90 to -20 °C; c) Tosyl azide, -78 °C to rt; iii) a) s- BuLi, THF; b) (Boc)$_2$O; c) Na/anthractene DME, 78 °C; d) TBAF, THF; iv) a) SMEAH/Morpholine, -45 °C, THF; b) BnBr, K$_2$CO$_3$, DMF; c) NaClO$_2$, KH$_2$PO$_4$, 2-methyl-2-buten, t-BuOH, H$_2$O; d) CH$_2$N$_2$; e) HOAc, THF, H$_2$O, 60 °C; f) t-BuOOH, VO(acac)$_2$, PhH, 60 °C; v) a) H$_2$O, B$_2$ONa (cat), 100 °C; b) H$_2$, Pd(OH)$_2$/C, EtOAc.
c) Trost’s approach

An effective enantioselective total synthesis of 68 was developed\(^{[21]}\) in 19 steps and in 8 % overall yield by combining the palladium-catalyzed desymmetrization protocol\(^{[21b]}\) with a novel cyclization strategy (Scheme-8).

![Scheme 19](image)

**Scheme 19**

*Reagents and Conditions: i) 0.5 mol % (\(\mathbf{[C_3H_7PdCl]}\), a, 0.75 mol %, TMSN\(_3\), CH\(_3\)Cl, rt, (> 95% ee), 83 %; ii) 55, CuCN, THF, ether, 0 °C; iii) a) Cat, OsO\(_4\), NMO.H\(_2\)O, DCM, rt, 62 % (two steps); b) TESOTf, 2,6-Lutidine, CH\(_2\)Cl\(_2\), quant; c) NBS, DMF, 75 %; iv) a) (CH\(_3\))\(_3\)P, THF, H\(_2\)O; b) COCl\(_2\), THF, Et\(_3\)N; c) t-C\(_4\)H\(_9\)Li, ether, -78 °C, 62 % (three steps); v) a) TBAF, THF, -78 °C; b) SOCl\(_2\), Et\(_3\)N; c) cat. RuCl\(_3\).H\(_2\)O, NaIO\(_4\), CCl\(_4\), CH\(_3\)CN, H\(_2\)O, rt, 72 %; vi) PhCO\(_2\)Cs, DMF, THF, H\(_2\)O, cat. H\(_2\)SO\(_4\), 75 %; viii) a) CH\(_3\)OH, K\(_2\)CO\(_3\), rt; b) LiI, DMF, 80 °C, 85 %.


d) Magnus’s Approach.

An attractive synthesis of the antitumor alkaloid (+)-Pancreatistatin was reported utilizing the β-azidonation reaction via prochiral 4-arylcyclohexanone (91).\(^{[23]}\)
Scheme 20

Reagents and conditions: a) n-BuLi, THF, -78 °C; b) POCl₃, DBU, Py; c) H₂/Pd-C, EtOH; d) TsOH, MeOH; e) 48, LiCl, TIPSOTf, THF, -78 °C; f) (PhIO)ₙ, TMSN₃, DCM, -15 °C; g) LAH, Et₂O; h) MeOCOCl, Py; i) MCPBA; j) H₃O⁺; k) KOtBu, HMPA; l) TMSOTf, TEA; m) PhSeOCOCF₃ then H₂O₂; n) NaHCO₃, H₂O₂, MeOH; o) L-selectride, THF; p) PhCO₂Na, H₂O; q) Ac₂O, Py; r) Tf₂O, DMAP; s) BBr₃; t) NaOMe, MeOH.

e) Rigby’s Approach.
Authors reported a new synthetic Scheme using a hydrogen bond guided aryl enamide photocyclization strategy for the synthesis of (+)-pancratistatin and (+)-narciclasine, its natural congener. In this approach, chemoenzymatic resolution was employed for the synthesis of optically active syn-epoxy alcohol 100.
A new total synthesis of pancratistatin (68) was accomplished in 21 steps and 4 % overall yield by employing Claisen rearrangement of dihydropyranethylene 108 as a key step for the construction of A and C-ring in 110, followed by stereo- and regio-controlled functional group interchange affording the final molecule (Scheme-9).[25]
A concise approach towards (+)-pancratistatin (68) was developed in 13 steps and 9% overall yield starting from pinitol by employing an ultrasound assisted arylcerium induced ring opening of cyclic sulfate 114 as a key step (Scheme-10).[(26a)]

An organocatalytic approach for the synthesis of racemic as well as (+)-pancratistatin was reported using 2-methoxymethylpyrrolidine as a catalyst to control the enantioselective [3+3] annulation of β-(hetero)aryl-α-nitro-α,β-enals with commercial 2,2-dimethyl-1,3-dioxan-5-one, a procedure that rendered highly oxygenated nitrocyclohexanes with five new stereocenters.[(26b)]
Scheme 24
Reagents and conditions: (a)(R)-2-(methoxymethyl)-pyrrolidine (b) H$_4$NCOOH, Pd-C, MeOH (c) ClCO$_2$Me, DMAP, CH$_2$Cl$_2$ (d) Dowex 50WX, MeOH (e) NaBH(OAc)$_3$, DCE/THF (f) Ac$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$ (g) Tf$_2$O, DMAP, CH$_2$Cl$_2$, 0°C (h) HCl, Dioxane, rt (i) BBr$_3$, CH$_2$Cl$_2$, -78°C-0°C, 50% (j) NaOMe, MeOH/THF, 86%

1B. 1c. Approaches towards (+)-7-deoxypancratistatin (69).

a) Paulsen’s approach
The first chiral synthesis of (+)-7-deoxypancratistatin (69) was accomplished by conjugate addition of 121 to nitroolefin 122 (derived from D-glucose) followed by lactamization to afford the final molecule in total 9 steps and 6.5 % overall yield (Scheme-11).[3]

Scheme 25
Reagents and Conditions: i) THF, -78 °C; ii) HOAc; iii) K$_2$CO$_3$, MeOH; iv) Pd/H$_2$, EtOH; v) K$_2$CO$_3$, MeOH.
b) Keck’s approach

An efficient total synthesis of 69 was accomplished in 13 steps and 21 % overall yield by employing a radical cascade strategy involving 6-exo radical cyclization of phenyl radical 131 as the key step (Scheme-12).\textsuperscript{[7,8]}

![Scheme 26](image)

**Scheme 26**

*Reagents and Conditions:* i) a) NaH, Cl\textsubscript{3}CCN, 0 °C; b) TfOH, THF, 0 °C, 75 % (two steps); ii) a) L- Selectride, DCM, -78 °C; b) HCl.H\textsubscript{2}NOBn, Pyridine 96 %, (two steps); c) TBSTf, 2,6-lutidine, DCM, 0 °C; d) HF.Pyridine, THF; iii) a) TPAP, NMO, 4 A° MS; b) 1-amino-2-phenylaziridine, EtOH, 0 °C. 83 % (two steps); iv) a) Ph\textsubscript{3}SnH, AIBN, PhH, 78 %; v) SmI\textsubscript{2}, TFAA, 88 %; vi) a) PCC, 83 %; b) BF\textsubscript{3}.OEt\textsubscript{2}; b) K\textsubscript{2}CO\textsubscript{3}, MeOH, 88 % (two steps).

c) Plumet’s approach.

Total synthesis of 69 was accomplished in 21 steps with 3 % overall yield starting from readily available furan by following the sequence as shown in Scheme 13.\textsuperscript{[31]}
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Scheme 27

Reagents and Conditions: i) a) BuLi, THF/Tol, \(-78^\circ C\); ii) a) BuOOH, BuLi, THF, \(-78^\circ C\), 84%; b) Na-Hg, MeOH/THF, \(-23^\circ C\), 81%; c) TfO, pyr, CH2Cl2, 0°C; d) Bu4NN3, benzene, 82%; iii) a) NaIO4/RuCl3, CH3CN/CCl4/H2O; iv) a) H2, 40 psi, Pd(C) 10%, MeOH, 88%; b) CF3COOH, 0°C; c) K2CO3, MeOH, reflux, 82%.

d) Madsen’s Approaches

Approach-1

The utility of olefin metathesis was explored in the elaboration of C-ring of 7-deoxypancratistatin (69) by Madsen et al. in total 13 steps and 1.4% overall yield. (Scheme14). In their synthesis, the diene 142 was subjected to metathesis with Grubbs’ first-generation catalyst to afford cyclohexene 143 which was oxygenated to complete the synthesis of the natural product.\[^{32a}\]

Scheme 28
Approach-2

In this strategy, reaction between ribofuranoside 144 (derived from D-Xylose) and 140 in the presence of zinc followed by ring-closing metathesis yielded 145:146 in 2:1 ratio. Subsequent Overman rearrangement\textsuperscript{[32b]} of 145, dihydroxylation and deprotection afforded 69 in 23 steps with 4.3 % overall yield (Scheme-15).

![Chemical structure](image)

Scheme 29

Reagents and Conditions: i) a) Zn, THF, H₂O, 40 °C, ultrasound, then H⁺-resin, MeOH, 50 °C, b) Grubbs I⁺ generation catalyst, CH₂Cl₂, 40 °C; ii) CCl₃CN, DBU, CH₂Cl₂, -45 °C to -20 °C, then 1 mmHg, neat, 120 °C; iii) OsO₄, NMO, THF; iv) a) K₂CO₃, MeOH, 65 °C, b) H₂, Pd (OH)₃/C, EtOAc.

e) Padwa’s approach.

A racemic synthesis was reported by Padwa et al. in 23 steps and 3 % overall yield. Key features of the synthetic strategy included 1) one-pot Stille/intramolecular Diels-Alder cycloaddition cascade to construct the core skeleton 2) conversion of the initially formed Diels-Alder adduct into an aldehyde intermediate 153 which undergoes a stereospecific decarbonylation reaction mediated by Wilkinson’s catalyst to set the trans-B-C ring junction of 69.\textsuperscript{[33]}
Scheme 30

Reagents and Conditions: i) Pd (0), 150, 82 %; ii) a) NaH, PhCH₂Br, b) LiOH, THF; c) (COCl)₂, ZnBH₄; c) TPAP, NMO, 70 %; iii) a) RhCl(PPh₃)₃, heat, 63 %, b) H₂, Pd (OH)₂, c) NaH, CS₂, MeI, heat, 85 %; iv) a) OsO₄/NMO, 68 %, b) SOCl₂, c) NaIO₄/RuCl₃, 82 %, d) PhCO₂Cs, e) H⁺, 75 %, f) LiOH, g) H₂, Pd (OH)₂, 80 %.

1B.1d. Background and our group contribution:

In the last decade our group was actively involved in the synthesis of different kinds of amaryllidaceae classes of alkaloids. Among many of these important alkaloids, synthesis of pancratistatin and its natural congeners were also targeted through various synthetic designs. We had developed an attractive approach\(^{48}\) for generation of arene radical cation through photoinduced electron transfer processes and its intramolecular cyclization with tethered silyl enol ether as a nucleophile for benzannulation reaction. The reaction was initiated through single electron transfer processes from excited state of electron rich arenes to the ground state of electron deficient 1, 4-dicyanonaphthalene (DCN) as represented in the Fig-8.
Figure 8: Mechanistic insight for benzannulation.

This methodology was applied for a successful synthesis of model compound (+)-160, 7-dideoxypancratistatin in a very concise manner as depicted in Scheme 31.

Scheme 31

Excited over this result, we evaluated the possibility of total synthesis of pancratistatin as shown in Scheme 32. However, unfortunately the optimized reaction condition failed to produce any cyclized product.
Another interesting approach was also reported\[^{50}\] by us in recent past involving aza–Michael reaction for the crucial cyclization, unfortunately, the resultant BC-ring junction was observed to be ‘cis’ instead of desired ‘trans’ (Scheme-33).

Reagents and conditions: (i) nBuLi, HMPA, THF, -78°C, TBSCI, 88% (ii) hv, DCN, CH$_3$CN, H$_2$O, 6h

**Scheme 33**

Reagents and conditions: (i) Pd(PPh$_3$)$_4$, 5 mol%, 84% (ii) nBuLi, HMPA, THF, 83%

**1B.1e. Intention of present study**

The ideal and/dream cancer drug is a molecule which would selectively eliminate the cancerous cell without affecting normal human cells. Such a magic drug, though very much desirable, is still anonymous. A recent study\[^{51,52}\] involving pancratistatin and some related compounds invoked a rare sense of hope among scientists in this regard,
where it was shown that pancratistatin causes preferential apoptosis of tumor cells without affecting much to the healthy cells. Such a discovery is indeed very encouraging but biological studies involving pancratistatin and its derivatives suffer from a number of road blocks. One primary issue is the availability of sufficient amount for such studies where as the other concern is poor water solubility. That’s why a number of creative new approaches\textsuperscript{[53,54]} to the syntheses of Amaryllidaceae constituents (68-71) continue to appear despite the fact that almost thirty years elapsed since the first synthesis of pancratistatin (68). Several groups around the globe are still in search of an ideal/ near ideal synthetic sequence which will solve at least its availability concern. Our group is also involved in this area for over a decade. Our present intention is to find out a synthetically viable route which will provide good amount of compound for preclinical studies. The following section will elaborate our success as well as failures and disappointments.

1B.2. Retrosynthetic analysis:

We viewed our synthetic approach for 68 and 69 through retrosynthetic path as outlined in the Scheme-34. The key step envisaged in our approach was the conjugate addition of aryl Grignard reagent to the fully functionalized 167 in presence of Cu(I) salt. We imagined the addition would undergo in a trans fashion to the protected β-amino group. The amino and aromatic group cyclization could be attained in later stage by employing Bischler-Napieralski reaction\textsuperscript{[55]}. The requisite 167, crucial for this transformation could be obtained from 168 through Seagussa-Ito oxidation protocol.\textsuperscript{[56]} The 168 in turn could be synthesized from the acetonide protected 169 by simple oxidation which could arise from selective acetonide protection of 170 generated by regioselective opening of the epoxide 171. The required syn-epoxide 171 could possibly be assembled from trans-aminocyclohexenol 172 via chelation controlled stereoselective epoxidation of the double bond. The trans-aminocyclohexenol synthesis has been achieved earlier in our laboratory starting with enantiomerically pure 7-azabicyclo[2.2.1]hept-2-one (67) via intermediacy of 174 through an anionic rearrangement involving C4-N7 bond rupture.
Scheme 34. Retrosynthesis of pancratistatin
1B.3. Results and discussions:

In order to test the feasibility of our hypothesis as depicted in above retrosynthetic analysis, we needed 172 in good amount. Therefore, we proceeded towards this molecule from 67 as described below:

1B.3a. Synthesis of 172:

After having required 67 in hand by following previously reported\(^{57}\) procedure by our group, we proceeded to reduce the carbonyl moiety in stereoselective manner. Interesting results were obtained when reduction with lithium borohydride was attempted at variable temperature. The results showed preference of \textit{exo}-175 at higher temperature and \textit{endo}-174 at lower temperature. Fortunately, both diastereomers were easily separable by silica gel column chromatography. The results are summarized in Table 1.

Scheme 35. Reaction of 67

![Scheme 35](image)

The relative configurations of both the alcohols were unambiguously deduced from their \(^1\)H NMR spectrum. For illustration, the H-2 proton in 174, appeared as a doublet of doublet (\(J = 9.3, 4.4\) Hz) coupling with bridgehead H-1 and H-3 whereas H-3 appeared as ddd (\(J = 9.6, 9.3, 4.6\) Hz) coupling with H-2, bridgehead H-4 and O-H proton. The coupling with O-H (d, \(J = 9.6\) Hz) was confirmed by D\(_2\)O exchange which simplified the coupling to dd (\(J = 9.3, 4.6\) Hz). Similarly, in the case of 175, the H-2 showed doublet (\(J = 6.5\) Hz) coupling only with H-3 whereas H-3 appeared as dd (\(J = 9.7, 6.5\) Hz) coupling with H-2 as well as O-H indicating the \textit{endo}-orientation of proton. This result is in complete agreement with the observation reported previously by our group\(^{57}\) and others\(^{58}\) where no coupling occurs between bridgehead and the \textit{endo}-hydrogen in 7-azabicyclo[2.2.1]heptane system.
Table 1. Yields and ratio of 174 and 175 during reduction of ketone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Ratio (174/175)</th>
<th>Time</th>
<th>Yield(%) (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>7:3</td>
<td>30 min.</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>-90</td>
<td>7.5:2.5</td>
<td>45 min.</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>1:9</td>
<td>12 h</td>
<td>78</td>
</tr>
</tbody>
</table>

1B.3b. Anionic fragmentation

The ring opening of 175 by the addition of excess of methyl magnesium bromide\textsuperscript{[57]} in a THF solution at room temperature produced 176 in 80% yield as a crystalline solid \([\alpha]_{D}^{25} -69.0 (c 1.00, \text{CHCl}_3), m.p. 131 ^\circ \text{C}\) (Scheme 36).

In the \(^1\text{H}\) NMR of 176, the proton signal appearing at \(\delta 7.19\) (dd, \(J = 4.9, 2.5 \text{ Hz}, 1H\)) was assigned to olefinic proton. The mass spectrum of 176 showed molecular ion peak at 354 (M\(^+\)+H).

![Scheme 36. Synthesis of 173](image)

Reagents and Conditions: (i) MeMgBr (6equiv.), THF, rt, 3 h, 80% (ii) KHMDS, THF, -78 °C, 4 h to rt, 70% (iii) MeMgBr (10 equiv.), THF, 0 °C- rt, 10 h, 88%
However, a similar reaction of 174 with methyl magnesium bromide failed to give any product (Scheme 36). A close look at the structure of 174 indicated that in this molecule, the orientation of sulfone moiety is *endo* which possibly do not allow the fragmentation due to lack of antiperiplanarity between the bonds to be cleaved. Fortunately, the sulfone group of 174 could be successfully epimerized using KHMDS to 174a (70 %) which on subjecting to ring opening reaction under identical experimental protocol as described above for 175, yielded 173 (Scheme 23) in 70% yield as a crystalline solid { mp 125 °C [α]_D^{25} +14.6 (c 0.40, CHCl₃) }

In the ¹H NMR of 173, the signal appearing at δ 7.19 (dd, J = 4.9, 2.5 Hz, 1H) was assigned to olefinic proton. The mass spectrum of 173 showed molecular ion peak at 354 (M⁺+H). Since we were interested to increase net yield of 173, reaction of 174 with 10 equivalent of MeMgBr at 0°C followed by stirring for additional 6-8 h at rt produced 173 in excellent yield (85 %). The sulfone moiety was removed selectively using 6% sodium amalgam in presence of NaHPO₄ as buffer in methanol to obtain 172 in over 83% isolated yield (Scheme 37).

![Scheme 37. Synthesis of 172](image)

**1B.3c. Synthesis of 167:**
The 167, central molecule in our synthetic planning, was achieved in multigram quantity by following the sequences as shown in Scheme-38
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approches towards....

Scheme 38. Synthesis of 167

Compound 172 upon epoxidation using m-CPBA in dichloromethane produced 171 in 79 % yield as a single diastereomer. The 1H NMR spectrum of 171 displayed two multiplets at δ 3.37 and δ 3.34-3.31, integrating for one proton each, which were assigned to two protons attached to epoxide ring. The coupling constant for the proton at δ 3.37 (dd, J = 2.0, 4.0 Hz, 1 H) indicated it to be a syn epoxide. The proton attached to the free hydroxyl group was assigned at δ 3.75 (dd, J = 2.3, 8.5 Hz, 1 H) and the proton attached to NHBoc group discerned at δ 3.59 (dd, J = 0.8, 8.8 Hz, 1 H). The N-H proton appeared at δ 4.53. The 9 proton of the tert- butyl carbamate group appeared at δ 1.46 as a singlet. The remaining four protons accounting for two methylene groups appeared at δ 2.02 - 1.96 (m, 2 H), 1.76 - 1.69 (m, 1 H), 1.36 - 1.28 (m, 1 H), respectively.

The 13C NMR spectrum of 171 displayed nine carbon signals at δ 156.7, 80.1, 73.2, 56.7, 54.6, 50.7, 28.3, 26.9 and 22.0. DEPT experiment revealed the presence of two quaternary carbon signals at δ 156.7 and 80.1 which could be assigned to the carbonyl group of carbamate and quaternary carbon of tert butyl group, respectively. The molecular ion peak was found at 252 (M^+ + Na^+) in the mass spectrum of 171.

We attempted epoxide ring opening using different Lewis acid and alcohols but all efforts remained unsuccessful. When 171 was treated with aq. HCl, the resultant reaction mixture turned out to be an inseparable mixture of diastereomers. Finally, we
succeeded in opening the epoxide ring by treating with 1M sulphuric acid solution in tetrahydrofuran at rt, which produced 170 in almost quantitative yield and in analytically pure form.

The $^1$H NMR spectrum of 170 in deuterium oxide displayed multiplets between $\delta$ 3.83- 3.60, integrating for four protons, assignable to the protons attached to three OH groups and one NHBoc group. The nine proton of Boc group appeared as a singlet at $\delta$ 1.37 and the remaining four protons appeared in between $\delta$ 1.84 - $\delta$ 1.45 as two sets of multiplets. The $^{13}$C NMR spectrum of 170 displayed nine carbon signals at $\delta$ 157.9, 81.0, 72.5, 71.1, 69.3, 50.4, 27.6, 25.9, 24.3. The molecular ion peak was found at 270 (M$^+$+Na$^+$) in the mass spectrum of 170.

The two syn hydroxyl group of 170 were preferentially protected as acetonide to get 169 (95% yield) by following literature procedure.$^{[59]}$ The $^1$H NMR spectrum of 169 displayed four multiplets integrating for five protons in low field region between $\delta$ 4.77 - 3.80 which were assigned to four protons of the cyclohexane ring and the N-H proton. The two methyl groups, characteristics of acetonide, appeared separately at $\delta$ 1.51 (s, 3 H) and $\delta$ 1.36 (s, 3 H). The $^{13}$C NMR spectrum of 169 displayed twelve carbon signals at $\delta$ 155.3, 108.9, 79.6, 78.8, 77.34, 69.3, 49.8, 28.3, 28.0, 26.4, 26.1, 24.0. In DEPT spectrum three quaternary carbon signals were visible at $\delta$ 155.3, 108.9, 79.6 which corresponded to carbonyl group of Boc, quaternary carbon attached to acetonide and that of tert- butyl group of Boc. The four signals at $\delta$ 78.8, 77.34, 69.3, 49.8 were assigned to the cyclohexyl methine carbons attached to hetero atoms. The C5 and C6 methylenic carbon signals were observed at $\delta$ 26.1 and 24.0. The three tert butyl carbamate methyl group carbons appeared together at $\delta$ 28.0. The molecular ion peak was found at 310 (M$^+$+Na$^+$) in the mass spectrum of 169.

Compound 169 was oxidized to 168 (60%) with IBX (2-iodoxybenzoic acid) initially by refluxing in ethyl acetate. However, yield was improved to 94% by stirring in DMSO at rt. The two hydrogens attached to the ‘O’ atoms of acetonide group appeared together as multiplets at $\delta$ 4.51 - 4.38 (m, 2 H). The proton attached to NHBoc was visible at $\delta$ 4.01 - 3.88 (m, 1 H). The two protons $\alpha$-to carbonyl moiety appeared at $\delta$ 2.56 - 2.42 (m, 2 H) as multiplets. Remaining two cyclohexyl protons appeared separately at $\delta$ 2.34 - 2.12 (m, 1 H) and 2.03 - 1.89 (m, 1 H) as multiplets.
Twelve protons appeared between $\delta$ 1.50 - 1.41 which was assigned to three methyl groups of Boc group and a methyl group of acetonide. The other methyl group protons of acetonide were visible at $\delta$ 1.38 (s, 3 H) as a singlet. The $^{13}$C NMR spectrum of 168 displayed twelve carbon signals at $\delta$ 207.2, 155.4, 110.5, 80.3, 79.5, 77.9, 49.1, 34.8, 28.3, 27.0, 25.7, 25.3. In DEPT spectrum four quaternary carbon signals were easily detected at $\delta$ 207.2, 155.4, 110.5, 80.3 corresponding to carbonyl group attached to cyclohexane ring and Boc, quaternary carbon attached to acetonide and that of tert-butyl group of Boc. The molecular ion peak was found at 308 (M$^+$+Na$^+$) in the mass spectrum of 168.

The conversion of 168 to 167 proved to be troublesome initially. Direct method from ketone to enone as described$^{[60]}$ by Nicolaou et al. proved unsuccessful as very miniscule amount of 167 was detected on TLC with no recovery of even starting material. Later, we explored the possibility of employing a two step protocol by first attaching the SePh group $\alpha$ to the ketone followed by oxidation using H$_2$O$_2$. Though this method led to successful isolation of crucial enone167 but it suffered from low isolation yield (only 20%). Disappointed by this, we attempted to perform Seagussa-Ito oxidation protocol$^{[56]}$ of enol ethers. For this purpose, we first converted 168 to corresponding silyl enolether by reaction with LiHMDS and trimethylsilyl chloride at 0°C- rt. Usual work up followed by stirring of the crude with Pd(OAc)$_2$ in anhydrous DMSO in the presence of oxygen for 24 h gave 167 up to 55% yield. Later it was found out that use of $p$-benzoquinone as an additive in this reaction improved the yield up to 67%.

The characteristic olefinic protons were easily characterised at $\delta$ 6.80 (tdd, $J = 0.6, 4.2, 10.2$ Hz, 1 H), 6.24 - 6.10 (m, 1 H) which are in good agreement with the characteristics of $\alpha,\beta$-unsaturated carbonyl compound. The three methyl group protons of Boc appeared at $\delta$ 1.46 (s, 9 H) as a singlet and the two methyl groups of acetonide appeared separately at $\delta$ 1.41 (s, 3 H) and $\delta$ 1.40 (s, 3H) as two singlets. The $^{13}$C NMR of 167 revealed twelve signals at $\delta$ 194.4, 154.9, 146.0, 128.9, 110.1, 80.7, 77.7, 74.4, 48.4, 28.3, 27.4, 25.9. From DEPT studies the presence of four quaternary carbons was confirmed. The signal at $\delta$ 194.4 was assigned to the carbonyl of enone moiety. The signal at $\delta$ 154.9 was assigned to carbonyl carbon of carbamate group and the signal at $\delta$ 110.1 was assigned to quaternary carbon of acetonide. The
quaternary carbon of tert- butyl group of Boc was traced to 80.7. The mass spectrum of 167 showed 306 (M^+Na^+) as molecular ion peak.

![Chemical structures and reactions](image)

Reagents and conditions: (a) Mg, CuBr.SMe₂, THF, -15°C, 2h, 76%
(b) NaBH₄, MeOH, 0°C, 1h, 97%.

Scheme 39. Conjugate addition
1B.3d. Conjugate addition.

With the required 167 in hand, we next explored the possibility of performing conjugate addition with Grignard reagent derived from 166 in the presence of copper (I) catalysts such as CuCl, CuCN which ultimately proved futile. When we tried conjugate addition with freshly prepared Grignard reagent along with CuBr.SMe₂ the reaction proceeded smoothly at -15°C giving rise to only one diastereomer.
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards.

The IR spectrum of 177 showed strong absorption band at 1716 cm\(^{-1}\) and 1695 cm\(^{-1}\), the characteristic bands of a cyclohexanone carbonyl and carbamate, respectively. In the \(^1\)H NMR spectra, aromatic protons were easily detected appearing at δ 6.82 - 6.65 (m, 3 H). The two protons of methylene dioxy group appeared as a doublet at δ 5.96, 5.95. The benzylic proton (β proton with respect to the carbonyl group) was assigned to a multiplet at δ 2.86. Three cyclohexane ring protons which are attached to hetero atoms appeared at δ 3.62, 4.28, 4.56, respectively. Six protons of two methyl groups of acetonide moiety appeared as two singlets at δ 1.50 and δ 1.43. Nine protons of Boc group appeared relatively upfield at δ 1.25 as compared to the starting enone. This shift can be explained considering the proximity of aromatic group deshielding the protons due to ring current. The observed splitting pattern in the \(^1\)H NMR and \(^13\)C NMR, due to restricted rotation about NCO bond (rotamers), did not allow to establish relative stereochemistry beyond doubt at this stage.

After succeeding in carrying out conjugate addition, we decided to convert 177 to trans-dihydro lycoricidine (179) via 178, a known congener of pancratistatin. Dihydro congeners of pancratistatin are known to possess equally rich biological activities.\(^1\) Therefore, we needed to construct the crucial B ring with the hope that stereochemical assignments could also be established precisely. In this direction, first 177 was reduced by NaBH\(_4\) to obtain 180. The proton spectra of 180 surprisingly got simplified after simple chromatographic purification. After scrutinizing carefully the 2D NMR (COSY, NOESY, HETCOR), relative stereochemistry of H-10b, H-4a in 180 as syn was unravelled. This unfortunate outcome was disappointing and thus forced us to abandon the pursuit of pancratistatin and its congeners through this route.

The syn relationship between H-10b, H-4a in 180 implied that conjugate addition of ArMgX (166) actually proceeded from the same face of the NHBoc group, which was contrary to general perception.\(^6\) We could offer two imprecise/tentative explanations for this apparent anomaly. First, we reasoned that the alpha face of 167 is sterically congested due to the presence of acetonide group which completely covered it like an umbrella, which results a preferred beta face for the incoming nucleophile.
Figure 9.
Second alternative might be due to an internal delivery of the aryl group by virtue of a co-ordinating bond between NBoc and CuAr reagent as in 167a (Fig.). The actual cause might be any one of these two factors or a combination of both. Opportunity to unravel the complete ambiguity does exist and active research is being performed in our laboratory in that direction. As it was apparent that the stereochemical outcome of conjugate addition will largely depend on the nature of the enone, syntheses of variety of enones (181-184) were targeted. The work is in progress in our laboratory.

Figure 10.

Since \textit{trans} B C ring fusion is a must for bio-activity of these molecules\cite{53,54}, it was decided to address this issue at the premature stage of the synthetic sequence. Furthermore, it was envisioned that only one double bond in the cyclohexane ring could be required to manipulate rest of the remaining four carbons with hydroxyl groups for the functionalization of C-ring of 68, 69 and related compounds. Based on these thoughts, we planned an imaginary basic skeleton as shown in Scheme 1.

As soon as we finalized the identification of basic unit 185 as an advanced precursor, we searched for an amicable method to construct the complete molecular skeleton. Towards this end, it was thought that 185 might simply be synthesized from \(\alpha,\beta\)-unsaturated sulfone (186, 187) via desulfonylation reaction. Now these structural frameworks (186, 187), are well known to us barring the aromatic ring, where in place of aromatic group hydroxyl group was placed (173), a fact which prompted us to think a bicyclic structural framework (188, 189) as precursors.
Scheme 40. Our planned sequence towards 185

To obtain the correct *trans* geometry in (186, 187), the aromatic group should be *endo* in (188, 189). Therefore, it was envisioned that construction of this moiety could be achieved through simple hydrogenation of the olefinic bond between $\text{SO}_2\text{Ph}$ and $\text{Ar}$ group of 190, 191. Since, the bicyclic ring in 188, 189 is locked in a boat like conformation, it was expected that the hydrogen atoms would come selectively from *exo* face resulting into the aromatic as well as sulfone group to the *endo* position.

Synthesis of 190, 191 were proposed to be obtained from the *meso*-disulfone via aromatic Grignard reagent addition.

1B.5. Results and discussion:

1B.5a. Synthesis of 190

The synthesis of 190 began by a simple addition of aryl Grignard reagent to vinyl disulfone 192 which approached preferentially from beta position of the sulfone group. The resultant carbanion pushed out the other sulfone group forming 190 in 92% yields.
The characterization of 190 was done with the help of $^1$H NMR spectrum in which three protons of electron rich aromatic group appeared at $\delta$ 6.78 - $\delta$ 7.11 as a multiplet along with methylenedioxy protons at $\delta$ 5.99 (s, 2H). The bridge head protons of 190 were found shifted upfield at $\delta$ 4.88 (brs, 1 H) and $\delta$ 4.95 - 4.93 (d, 1 H), respectively.

Scheme 41. Synthesis of 188

The crucial hydrogenation reaction of 190 using 10% Pd-C catalyst in methanol at room temperature produced analytically pure 188 in 99% yield, which was characterized by the chemical shift values of bridge head protons H$_1$, H$_4$ as well as H$_2$ and H$_3$. For illustration, the bridge head proton H$_1$ appeared at $\delta$ 4.27 (br. s., 1 H) and H$_4$ at $\delta$ 4.38 (t, $J$=4.28 Hz, 1 H) whereas H$_3$ appeared at $\delta$ 3.64 (dd, $J$=11.46, 3.65 Hz, 1 H) and H$_2$ at $\delta$ 3.94 (d, $J$=9.82 Hz, 1 H), respectively.
Figure 12.
In COSY spectrum, correlation between H\textsuperscript{1}-H\textsuperscript{2}-H\textsuperscript{3} was visible indicating H-2 to be in an exo proton. Similarly, the other sets of correlation between H\textsuperscript{ex}-H\textsuperscript{1}-H\textsuperscript{2}, H\textsuperscript{ex}-H\textsuperscript{4}-H\textsuperscript{3}, H\textsuperscript{4}-H\textsuperscript{3}-H\textsuperscript{2}, suggested H-2 and H-3 to be exo i.e the aromatic ring and phenyl sulfonyl groups both to be in endo orientation. These observations were in complete agreement with the literature reports where couplings are seen between bridge head proton and exo proton\textsuperscript{[57,58]} The endo proton never coupled with the bridge head protons. This fact is further supported by NOESY where H\textsuperscript{en} showed correlation with H\textsuperscript{ar1}.

Figure 13.
With 188 in hand, we attempted anionic rearrangement utilizing strong base such as nBuLi, LiHMDS, KO\textsuperscript{t}Bu , however, desired product could not be obtained. Finally,
reaction with excess of methylmagnesiumbromide produced \( \text{186} \) (87\%) as a white crystalline solid (m.p.135\°C).

Scheme 42. Synthesis of 186
The presence of beta proton of vinyl sulfone at \( \delta \) 7.46 - 7.40 (m, 1 H) along with five proton of phenyl sulfonyl group at \( \delta \) 7.57 - 7.47 (m, 3 H), 7.37 (t, \( J = 7.7 \) Hz, 2 H), respectively, in \(^1\text{HNMR}\) spectrum confirmed the formation of 186. Further confirmation to the structure of 186 was indicated by observing molecular ion peak at 480 (\( \text{M}^+\text{Na}^-\)). Since 186 was crystalline solid, relative stereochemistry between H-10b and H-4a was determined by X-ray analysis which was found to be trans.

Figure 14: Crystal structure of 186.
Initially our attempt of desulfonylation of 186 using either sodium amalgam or Birch reduction condition unfortunately, produced mixture of 185 (41\%) and 185a (47\%). After a number of trials, fortunately reaction with sodium dithionite in a mixture of dimethyl formamide and water produced 185 in 78\% yields.
Scheme 43. Synthesis of 185

Presence of two characteristics olefinic protons appearing at δ 5.89 - 5.82 (m, 1 H), 5.59 (d, \( J = 7.6 \) Hz, 1 H) confirmed the transformation.

1B.5b. Functionalization of Proposed C-ring:

Figure 15:

Successful synthesis of 185 having a) correct proposed trans-BC ring junction stereochemistry b) an olefinic bond between C1-C2 set the stage to initiate the C-ring functionalization for crucial installation of four hydroxyl groups along the periphery of C-ring (C1, C2, C3 and C4) stereoselectively. Towards achieving this goal, first epoxidation of 185 was carried out using mCPBA in dichloromethane which resulted mixture of two diastereomeric epoxides 193 (49% ) and 194 (13% ), respectively. The ratios of these two epoxides (193/194) were found to be temperature dependent, e.g. at 0°C = 4:1, 41°C =5:2 and at -10°C it was 10:1 as measured by \(^1\)H NMR.
Scheme 44. Synthesis of 193
Since it was known in the literature\cite{25} that direct transformation of 194 to 197 via 195 through epoxidation would be futile and would require longer reaction sequence involving dihydroxylation and subsequent opening of cyclic sulfate, an alternative pathway for the synthesis of 204 involving \textit{anti} epoxide 193 was envisioned.

Scheme 45. Our planned sequence towards 204
We envisaged that 193 after opening with PhSeLi and subsequent selenoxide elimination would provide 199, from which the C-2 stereochemistry of C-ring could be easily fixed by chelation controlled epoxidation using either mCPBA or VO(acac)$_2$. The C-1 hydroxy stereochemistry could be re-tuned to \textit{syn} with respect to aromatic group via an oxidation reduction sequence involving 201. Subsequent opening of epoxide 202 using PhSeLi followed by selenoxide elimination would
provide 204. Since it was known\textsuperscript{[12,13]} that a similar structure as 201\textsuperscript{a} having ketone moiety at C-1 undergoes epimerization on standing due to presence of trans –BC ring junction, it was decided to proceed further along the proposed synthetic steps with 201 itself.

Therefore, reaction of 193 with PhSeLi gave 198 in 90% isolated yield. The presence of two sets of aromatic protons at $\delta$ 7.61 (dd, $J = 1.3, 8.1$ Hz, 2 H), 7.41 - 7.25 (m, 3 H) confirmed the presence of SePh group in the product. Oxidation elimination of PhSe moiety

Scheme 46. Our planned sequence towards 204

by treating with NaIO$_4$ in the presence of DIPEA produced 199 (88 %). The characteristic olefinic protons at $\delta$ 5.77 (brs, 2 H) in the $^1$H NMR confirmed its formation.

Scheme 47. Synthesis of 199
Chelation controlled epoxidation of 199 with mCPBA gave 200 (70% yield) which was characterized by the presence of two multiplets at $\delta$ 3.47 - 3.44 (m, 1 H), 3.35 ($J = 4.8$ Hz, 1 H) in the $^1$H NMR spectrum.

Scheme 48. Synthesis of 201
The crucial oxidation of 200 using Dess-Martin reagent$^{[62]}$ produced 201 in 90% yields. Compound 201 was found stable at room temperature for several days! Reduction of 201 by NaBH$_4$ at 0°C produced mixture of two epoxy alcohol 200 and 202 (7:3). Although, it was possible to enrich 202 from 200 by the oxidation/reduction sequence, the efficacy of the synthetic route would have been compromised. Since the carbonyl moiety of epoxy ketones can selectively be reduced$^{[63]}$ with NaBH$_4$/CeCl$_3$.7H$_2$O or with ZnBH$_4$$^{[64]}$, 201 was reduced by NaBH$_4$/CeCl$_3$.7H$_2$O to obtain selectively only 202 (85%). In the $^1$HNMR spectrum, H-10b which is now cis to H-1 and trans to H-4a appeared at $\delta$ 2.58 (td, $J = 5.2, 15.4$ Hz, 1 H) indicating a cis-trans relationship with adjoining protons H-1 and H-4a.

Scheme 49. Synthesis of 200
Reaction of 202 with PhSeLi by following identical reaction condition as described earlier for 198 produced 203 in 90% yields. The presence of five aromatic protons of PhSe group at $\delta$ 7.62 (d, $J = 5.8$ Hz, 2 H), 7.38 - 7.19 (m, 3 H) and H-2 at $\delta$ 4.26 (m, 1 H) in $^1$H NMR spectrum confirmed the transformation. Oxidation of 203 with
aqueous H$_2$O$_2$ produced 204 in over 81% yield. The two characteristics olefinic protons H-3 and H-4 of this molecule were found merged with the two methylenedioxy protons at $\delta$ 6.00 – 5.84 (m, 4 H) in the $^1$H NMR spectrum.

Scheme 50. Synthesis of 204

1B.5c. The end game.

Towards completing the synthesis of pancratistatin, remaining two hydroxyl groups at C-4 and C-3 were needed to be installed stereoselectively. Our previous experiences in the area of aminocyclitol synthesis$^{[57]}$, led us to proceed with dihydroxylation step from 204 directly to install hydroxyl moieties at C-4 and C-3 stereoselectively, though, it was contrary to literature report$^{[12,13,25]}$ where protection of hydroxyl group at C-1 and/C-2 was required. Dihydroxylation of 204 under standard reaction conditions produced 205 in 91% yield. The structure of 205 was suggested based on the observation of six multiplets appearing at $\delta$ 4.27 (t, $J$ = 11.2 Hz, 1 H), 4.05 - 4.03 (t, $J$ = 3.1 Hz, 1 H), 4.01 (br. s., 1 H), 3.76 (br. s., 1 H), 3.76 - 3.73 (dd, $J$ = 3.1, 10.6 Hz, 1 H), and at 3.11 (dd, $J$ = 1.6, 12.1 Hz, 1 H) in $^1$H NMR spectrum recorded in CD$_3$OD.

Successful synthesis of 205 having correct stereochemical dispositions of hydroxyl groups, set the stage for crucial B ring construction by modified$^{[65]}$ Bischler-Napieralski reaction. Towards this end, all four hydroxyl groups were protected as O-acetate (206 in 85% yields),

Scheme 51.
before being treated with freshly distilled trifluoromethane sulfonic anhydride (Tf₂O) and 2-chloropyridine in anhydrous dichloromethane at -84°C. The reaction occurred smoothly to deliver 207 in high yield (63%) which was characterized by NMR spectral data and compared with reported values\textsuperscript{[20]}. The details are presented in Table-2.

Scheme 52. Synthesis of 7-deoxypancratistatin

Figure 16.
Table 2.

<table>
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<th>Observed value</th>
<th>Literature reported value</th>
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<td>5.23 (t, $J = 2.7$ Hz, 1H)</td>
</tr>
<tr>
<td>H2</td>
<td>5.48 (t, $J = 2.8$ Hz, 1 H)</td>
<td>5.47 (t, $J = 2.9$ Hz, 1H)</td>
</tr>
<tr>
<td>H3</td>
<td>5.60 (t, $J = 2.6$ Hz, 1 H)</td>
<td>5.58 (m, 1H)</td>
</tr>
<tr>
<td>H4</td>
<td>5.19 (dd, $J = 3.4$, 10.9 Hz, 1 H)</td>
<td>5.20 (dd, $J = 3.5$, 10.8 Hz, 1H)</td>
</tr>
<tr>
<td>H4a</td>
<td>4.31 (dd, $J = 10.9$, 12.9 Hz, 1 H)</td>
<td>4.30 (dd, $J = 12.8$, 11.0 Hz, 1H)</td>
</tr>
<tr>
<td>H5(N–H)</td>
<td>5.83 (s, 1 H)</td>
<td>6.56 (s, 1H)</td>
</tr>
<tr>
<td>H7</td>
<td>7.61 (s, 1 H)</td>
<td>7.56 (s, 1H),</td>
</tr>
<tr>
<td>H10</td>
<td>6.58 (s, 1 H)</td>
<td>6.59 (s, 1H)</td>
</tr>
<tr>
<td>H10b</td>
<td>3.47 (dd, $J = 2.7$, 12.9 Hz, 1 H)</td>
<td>3.46 (dd, $J = 13.0$, 2.7 Hz, 1H)</td>
</tr>
<tr>
<td>H11</td>
<td>6.04 (dd, $J = 1.3$, 7.3 Hz, 2 H)</td>
<td>6.03 (m, 2H)</td>
</tr>
<tr>
<td>Me1, Me2, Me3, Me4</td>
<td>2.18 (s, 3 H), 2.10 (s, 3 H), 2.09(s, 3 H)</td>
<td>2.16 (s,3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H)</td>
</tr>
</tbody>
</table>

Lastly, four acetyl groups of 207 were deprotected by reacting with NaOMe in methanol[20] which produced 69 in 72% isolated yield. The total synthesis of 7-deoxypancratistatin (69) was achieved with only a single protecting group manipulation.

1B.6. Conclusion and outlook:

Two new approaches to pancratistatins utilizing racemic as well as enantiomerically pure 7-azabicyclo[2.2.1]heptenes derived from Diels-Alder reaction of pyrrole was discussed. The first generation approach was plagued with an unfortunate problem of undesired stereochemical outcome in crucial conjugate addition stage. Unfortunately, this step dismantled the need toward any further transformations. Active work is being pursued towards right direction in our group to solve this hurdle. Taking cue
from the first approach, we have put effort to tune the BC ring junction stereochemistry in the beginning of the planned sequence, which resulted in a successful 15 steps synthesis of racemic 7-deoxy-pancratistatin. The simplicity of the planning and operational ease in carrying out the transformations makes our strategy attractive. Minimal involvement of protecting group increases its efficacy. Still there are unfinished tasks ahead to project it as an alternative to existing protocols. Foremost is the synthesis in enantiomerically pure form, a challenge is being pursued in our laboratory actively and hopefully will find light in near future. But none the less the 15-step approach to 7-deoxypancratistatin (overall yield 6%) described in this chapter represent a solid basis for solving the supply problem for pancratistatin and its congeners upon further optimization.
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards...

1B.7. References:


Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approches towards...


Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards...


1B.8. EXPERIMENTAL:

Preparation of tert-butyl ((1S,2S)-2-hydroxycyclohex-3-en-1-yl)carbamate(172)

To a solution of tert-butyl ((1S,2R)-2-hydroxy-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate (1.0 g, 2.83 mmol, 1.0 equiv.) in methanol: tetrahydrofuran (1:1, 20.0 mL) in a round-bottomed flask equipped with a magnetic stir bar was added NaH$_2$PO$_4$•2H$_2$O (3.39 g, 28.29 mmol, 10 equiv.). The flask was cooled to 0 ºC and stirred for 10 min under argon atmosphere, after which Na-Hg (6.33 g, 28.29 mmol, 10 equiv.) was added in portions over 10 min. The reaction was allowed to stir for 60 min at 0 ºC and was quenched with saturated ammonium chloride (20.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (20% EtOAc in hexanes) to afford 172 (0.5 g, 83%) as a white crystalline solid (m.p. 112-114 ºC).

$[\alpha]^{27.2}$D : -4.97 (c 1.12, CHCl$_3$)

IR (neat) $\nu_{\text{max}}$ cm$^{-1}$ : 3405, 3301, 1708, 1682, 1150

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ :

- 5.81 - 5.72 (m, 1 H), 5.69 - 5.62 (m, 1 H), 4.65 (d, $J$ = 8.5 Hz, 1 H), 4.09 - 4.03 (m, 1 H), 3.67 (br. s., 1 H), 3.59 - 3.50 (m, 1 H), 2.22 - 2.10 (m, 2 H), 1.95 - 1.87 (m, 1 H), 1.62 - 1.53 (m, 1 H), 1.46 (s, 9 H)

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ : 157.0, 128.9, 128.1, 80.1, 72.5, 54.0, 28.3, 26.7, 24.3

Mass (ESI): $m/z$ : 214 (M$^+$+H), 236 (M$^+$+Na), 252 (M$^+$+K)
Preparation of tert-butyl ((1R,2R,3S,6S)-2-hydroxy-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (171)

To a solution of 172 (1.0 g, 4.69 mmol, 1.0 equiv.) in dichloromethane (30.0 mL) in a round-bottomed flask equipped with a magnetic stir bar, was added 3-chlorobenzoperoxoic acid (1.26 g, 5.63 mmol, 1.2 equiv.). The flask was cooled to 0 °C and stirred for 3 h under argon atmosphere and was quenched with saturated sodium hydrogen carbonate solution (20.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (40% EtOAc in hexanes) to afford 171 (0.85 g, 79%) as a white crystalline solid.

\[
\begin{align*}
&\text{[α]}^{31}\text{D} : \ -17.0 \ (c \ 1.0, \ \text{CHCl}_3) \\
&\text{IR (neat) } \nu_{\text{max}} \text{ cm}^{-1} : \ 3405, 3301, 1705, \ 1150 \\
&\text{^1H NMR (400 MHz, CDCl}_3\text{)} \ \delta : \ 4.53 \ (d, \ J = 7.5 \text{ Hz}, \ 1 \text{ H}), \ 3.75 \ (dd, \ J = 2.3, \ 8.5 \text{ Hz}, \ 1 \text{ H}), \ 3.59 \ (dd, \ J = 0.8, \ 8.8 \text{ Hz}, \ 1 \text{ H}), \ 3.37 \ (dd, \ J = 2.0, \ 4.0 \text{ Hz}, \ 1 \text{ H}), \ 3.34 - 3.31 \ (m, \ 1 \text{ H}), \ 2.02 - 1.96 \ (m, \ 2 \text{ H}), \ 1.76 - 1.69 \ (m, \ 1 \text{ H}), \ 1.47 - 1.42 \ (m, \ 9 \text{ H}), \ 1.36 - 1.28 \ (m, \ 1 \text{ H}) \\
&\text{^13C NMR (50 MHz, CDCl}_3\text{)} \ \delta : \ 156.7, \ 128.3, \ 80.1, \ 73.2, \ 56.7, \ 54.6, \ 50.7, \ 28.3, \ 26.9, \ 22.3 \\
&\text{Mass (ESI): } m/z : \ 230 (M^+ + \text{H}), \ 252 (M^+ + \text{Na})
\end{align*}
\]
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards....

Preparation of tert-butyl ((1S,2R,3S,4R)-2,3,4-trihydroxycyclohexyl)carbamate (170)

To a solution of 171 (0.7 g, 3.05 mmol, 1.0 equiv) in tetrahydrofuran: water (5:1, 30.0 mL) in a round-bottomed flask equipped with a magnetic stir bar was added 0.1 mL of conc. sulphuric acid. The flask was stirred for 0.5 h at ambient temperature and was quenched with saturated sodium hydrogen carbonate solution (20.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to afford 170 (0.75 g, 99%) as a white crystalline solid.

\[ \alpha \]_D $^3$ : -9.0 (c 1.2, MeOH)

IR (neat) $\nu_{\text{max}}$ cm$^{-1}$ : 3404, 3301, 1692

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ : 3.83 (dd, $J = 2.0$, 5.8 Hz, 1 H), 3.71 (d, $J = 6.0$ Hz, 2 H), 3.60 (dd, $J = 3.6$, 4.1 Hz, 1 H), 1.84 - 1.67 (m, 3 H), 1.57 - 1.45 (m, 2 H), 1.37 (s, 9 H)

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ : 157.9, 81.0, 72.5, 71.1, 69.3, 50.4, 27.6, 25.9, 24.3

Mass (ESI): m/z : 270 (M$^+$+Na)

Preparation of tert-butyl ((3aR,4S,7R,7aS)-7-hydroxy-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-yl)carbamate (169)

To a solution of 170 (1.0 g, 4.04 mmol, 1.0 equiv.) in anhydrous DMF (30.0 mL) in a round-bottomed flask equipped with a magnetic stir bar was added 2,2 dimethoxypropane (4.95 mL, 40.44 mmol, 10 equiv.) and pTSA (0.766 g, 4.45 mmol, 1.1 equiv). The flask was stirred at ambient temperature until TLC monitoring showed complete conversion of starting compound. The reaction was quenched with water (150.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30.0 mL). The combined
organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to 169 (1.1 g, 95%) as colorless liquid.

\[\alpha\]_{25}^{25.2} : 2.0 (c 1.2, CHCl₃)

IR (neat) \(\nu_{\text{max}}\) cm\(^{-1}\) : 3405, 2985, 1705, 1134

\(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) : 4.77 (br. s., 1 H), 4.03 (br. s., 2 H), 3.99 (br. s., 1 H), 3.80 (br. s., 1 H), 1.90 - 1.78 (m, 2 H), 1.57 (d, \(J = 17.1\) Hz, 2 H), 1.51 (s, 3 H), 1.44 (s, 9 H)

\(^{13}\)C NMR (50 MHz, CDCl₃) \(\delta\) : 155.3, 108.9, 79.6, 78.8, 69.1, 71.1, 69.3, 49.8, 28.3, 28.0, 26.4, 26.1, 24.0

Mass (ESI): \(m/z\) : 310 (M⁺+Na)

Preparation of tert-butyl ((3aR, 4S, 7aR)-2,2-dimethyl-7-oxohexahydrobenzo[d][1,3]dioxol-4-yl) carbamate (168)

To a solution of 169 (0.639 g, 2.22 mmol, 1.0 equiv.) in anhydrous toluene:DMSO (2:1) (36.0 mL) in a round-bottomed flask equipped with a magnetic stir bar was added IBX (0.934 g 3.34 mmol, 1.5 equiv.). The flask was heated at 55° C temperature until TLC monitoring showed complete conversion of starting compound (6 h). The reaction was quenched with water (100.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporator. The crude material after column chromatography (EtOAc:Hexanes 1:5) afforded 168 (0.6 g, 94.5%) as amorphous solid.

\[\alpha\]_{25.5}^{25.5} : -23.5 (c 1.5, CHCl₃)

IR (DCM) \(\nu_{\text{max}}\) cm\(^{-1}\) : 2988, 1710, 1683, 1147
Chapter I: 7-azabicyclo[2.2.1]heptane skeleton and approaches towards....

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 4.51 - 4.38 (m, 2 H), 4.01 - 3.88 (m, 1 H), 2.56 - 2.42 (m, 2 H), 2.34 - 2.12 (m, 1 H), 2.03 - 1.89 (m, 1 H), 1.50 - 1.41 (m, 12 H), 1.38 (s, 3 H)

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 207.2, 155.4, 110.5, 80.3, 79.5, 77.9, 49.1, 34.8, 28.3, 27.0, 25.7, 25.3

Mass (ESI): $m/z$: 286 (M$^+$+H), 308 (M$^+$+Na)

Preparation of tert-butyl ((3aR,4S,7aR)-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)carbamate(167)

To a solution of 168 (0.06 g, 0.21 mmol, 1 equiv.) in anhydrous THF (1 mL) in a round-bottom flask equipped with a magnetic stir bar was added LiHMDS (0.633 mL, 0.631 mmol, 3 equiv. 1M solution in THF) in 0°C. After 30 min TMSCl (0.032 mL, 0.252 mmol, 1.2 equiv.) was added drop wise. The flask was allowed to warm to room temperature and stirred at that temperature until TLC monitoring showed complete conversion of starting compound (3 h). The reaction was quenched with water (1.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to afford the enol ether as a yellow liquid, which was used as crude for the next reaction.

The crude enol ether was dissolved in anhydrous DMSO (1 mL) to which palladium (II)acetate (0.007 g, 0.033 mmol, 0.2 equiv.) was added while stirring at ambient temperature in oxygen atmosphere until TLC showed complete conversion of enol ether (16h). The reaction was quenched with water (5.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5.0 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated by rotary evaporation and chromatographed (EtOAc:Hexanes1:5) to afford 167 (0.032 g, 67%) as a white solid.

$[\alpha]^{23.5}_D$: 115 (c 1.1, CHCl$_3$)

IR (neat) $\nu_{\text{max}}$ cm$^{-1}$: 1696, 1682, 1151
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approach to...

\[ ^1H \text{ NMR (200 MHz, CDCl}_3 \] \( \delta \): 6.80 (tdd, \( J = 0.6, 4.2, 10.2 \text{ Hz}, 1 \text{ H} \)), 6.24 - 6.10 (m, 1 H), 4.91 (dd, \( J = 0.8, 8.6 \text{ Hz}, 1 \text{ H} \)), 4.58 - 4.39 (m, 3 H), 1.46 (s, 9 H), 1.41 (d, \( J = 2.9 \text{ Hz}, 6 \text{ H} \))

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \] \( \delta \): 194.4, 154.9, 146.0, 128.9, 110.1, 80.7, 77.7, 74.4, 48.4, 28.3, 27.4, 25.9

Mass (ESI): \( m/z \): 284 (M\(^+\)+H), 306 (M\(^+\)+Na)

tert-butyl ((3aR,4S,7aR)-2,2-dimethyl-7-oxo-3a,4,5,6,7,7a-hexahydro-[5,5'-bibenzo[d][1,3]dioxol]-4-yl)carbamate (177)

To a stirred and cooled (-15°C) suspension of CuBr.SMe\(_2\) (0.163 g, 0.794 mmol, 4.5 equiv.) in anhydrous THF (0.5 mL) was added freshly prepared ArMgBr (0.935 mL, 0.617 mmol, 3.5 equiv.) and stirred for 0.5 h after which 167 (0.05 g, 0.176 mmol, 1.0 equiv.) in THF (0.5 mL) was added very slowly. The reaction mixture was stirred at that temperature for 2 h and quenched with 10% aqueous ammonium chloride solution (2 mL) after which it was diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous sodium sulphate and was concentrated in vacuo. It was purified via flash silica gel column chromatography (EtOAc:hexanes 3:17) to get 177 (0.055 g, 76%) as light yellowish liquid.

IR (neat) \( \nu_{\text{max}} \text{ cm}^{-1} \): 1716, 1695, 1145

\[ ^1H \text{ NMR (400MHz ,CDCl}_3 \] \( \delta \): 6.82 - 6.77 (m, 1 H), 6.75 - 6.70 (m, 1 H), 6.70 - 6.64 (m, 1 H), 5.95 (d, \( J = 4.8 \text{ Hz}, 2 \text{ H} \)), 4.62 - 4.46 (m, 2 H), 4.25 (br. s., 1 H), 3.58 (br. s., 1 H), 2.83 (br. s., 1 H), 2.61 (br. s., 1 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 1.33 - 1.16 (m, 9 H)

HRMS (ESI): \( m/z \) calcd. for C\(_{21}\)H\(_{27}\)NO\(_2\)Na ([M+Na]\(^+\]): 428.1680, found: 428.1683
**Chapter I: 7-azabicyclo[2.2.1]heptane skeleton and approaches towards...**

**tert-butyl ((3aR,4S,5R,7S,7aS)-7-hydroxy-2,2-dimethyl-3a,4,5,6,7,7a-hexahydro-5,5'-bibenzo[d][1,3]dioxol)-4-yl)carbamate (180)**

![Chemical structure of 180](image1.png)

To a stirred and ice cooled solution of 177 (0.05 g, 0.123 mmol, 1.0 equiv.) in distilled methanol (2 mL) was added NaBH₄ (0.009 g, 0.246 mmol, 2 equiv.) and stirred at that temperature for 1 h after which the reaction was quenched with brine (2 mL) and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was washed with EtOAc (3x5 mL) and the combined organic layer was dried over anhydrous sodium sulphate and was concentrated *in vacuo*. It was purified via flash silica gel column chromatography (EtOAc:hexanes 1:1) to get 180 (0.049 g, 97%) as white amorphous solid.

\[ \alpha \]²³.₅ : 65 (c 1.1, CHCl₃)

IR (neat) \( \nu_{\text{max}} \text{ cm}^{-1} \) : 3408, 1698, 1152

\(^1\)H NMR (400MHz ,CDCl₃) \( \delta \) : 6.76 (d, \( J = 8.0 \) Hz, 1 H), 6.70 - 6.55 (m, 2 H), 5.95 (d, \( J = 1.3 \) Hz, 2 H), 4.37 - 4.18 (m, 4 H), 4.18 - 4.09 (m, 1 H), 3.55 (br. s., 1 H), 2.31 - 2.18 (m, 1 H), 1.96 - 1.84 (m, 1 H), 1.59 (s, 3 H), 1.41 (s, 3 H), 1.37 (s, 9 H)

HRMS (ESI): \( m/z \) calcd. for C₂₁H₂₉NO₇Na ([M+Na]⁺): 430.1836, found: 430.1831.

**tert-butyl-2-(benzo[d][1,3]dioxol-5-yl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (190):**

![Chemical structure of 190](image2.png)
The Grignard reagent prepared from 1-bromo-3,4-(methyleneedioxy)benzene (6.66 g, 33.12 mmol, 1.05 equiv.) in anhydrous THF (30 mL) was transferred via cannula to a solution of 192 (15.0 g, 31.54 mmol, 1 equiv.) in dry THF (70 mL) maintained at 0°C. After transfer was complete, the solution was stirred at 25°C until the reaction was complete as shown by TLC (~2 h). The reaction mixture was again cooled to 0°C and quenched by addition of a saturated aqueous solution of ammonium chloride after which it was diluted with ethyl acetate and filtered. The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 X 50 mL) and the combined organic layer was dried over anhydrous sodium sulphate and was concentrated \textit{in vacuo}. It was purified via flash silica gel column chromatography (15:85 ethyl acetate:hexane) to give the compound 190 (12.9 g, 89%) as a white, amorphous solid.

$1^H$ NMR (400 MHz, CDCl$_3$) $\delta$: 7.84 (d, $J = 8.1$ Hz, 2 H), 7.58 (t, $J = 7.2$ Hz, 1 H), 7.48 (t, $J = 7.7$ Hz, 2 H), 7.13 - 7.07 (m, 2 H), 6.82 (d, $J = 8.3$ Hz, 1 H), 6.01 (s, 2 H), 4.97 (br. s., 1 H), 4.91 (br. s., 1 H), 2.15 - 2.07 (m, 2 H), 1.74 - 1.67 (m, 1 H), 1.40 (br. s., 1 H), 1.30 (br. s., 9 H)

$^{13}$C NMR (101 MHz, CHLOROFORM-d) $\delta$: 24.52, 27.97, 28.31, 64.23, 67.58, 80.86, 101.51, 108.10, 109.85, 123.76, 124.29, 127.58, 129.02, 133.38, 140.93, 147.49, 149.17, 155.10

Mass (ESI): $m/z$: 456 (M$^+$$+$H), 478 (M$^+$$+$Na)
Chapter I: 7-azabicyclo[2.2.1]heptane skeleton and approaches towards...

t-butyl-2-(benzo[d][1,3]dioxol-5-yl)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (188):

![Chemical Structure](image)  

Compound 190 (10.0 g, 21.95 mmol, 1.0 equiv.) was taken in methanol (100 mL) to which was added 10% Pd/C (1.04 g, 0.04 equiv.) and stirred rapidly at ambient temperature under hydrogen at atmospheric pressure. The reaction was monitored periodically for completion by TLC (~12 h). The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The crude compound was recrystallized (ethylacetate:hexane 1:9) to get 188 (10.0 g, 99%).

1H NMR (400 MHz, CDCl₃) δ: 1.43 (s, 9 H) 1.72 - 1.84 (m, 1 H) 1.84 - 1.95 (m, 1 H) 2.30 - 2.43 (m, 1 H) 2.92 (ddd, J=12.84, 8.81, 4.28 Hz, 1 H) 3.64 (dd, J=11.46, 3.65 Hz, 1 H) 3.94 (d, J=9.82 Hz, 1 H) 4.27 (br. s., 1 H) 4.38 (t, J=4.28 Hz, 1 H) 5.99 (d, J=5.54 Hz, 2 H) 6.74 (d, J=8.06 Hz, 1 H) 6.89 (d, J=7.55 Hz, 1 H) 7.09 (br. s., 1 H) 7.43 - 7.52 (m, 2 H) 7.55 - 7.70 (m, 3 H)

13C NMR (100 MHz, CDCl₃) δ: 154.4, 147.2, 146.8, 140.4, 133.3, 128.9, 127.6, 127.5, 124.4, 111.3, 107.6, 100.9, 80.5, 67.0, 63.5, 59.6, 49.6, 28.0, 23.7, 23.6

Mass (ESI): m/z : 480.1 (M⁺+Na)
7-azabicyclo [2.2.1] heptane skeleton and approaches towards...

tert-butyl (-2-(benzo[d][1,3]dioxol-5-yl)-3-(phenylsulfonyl)cyclohex-3-en-1-yl)carbamate(186):

To a well stirred and ice cooled solution of 188 (10.0 g, 21.86 mmol, 1 equiv.) in dry THF (30 mL) was added methylmagnesiumbromide solution (1.4 M solution in THF/toluene, 62.45 mL, 87.42 mmol, 4 equiv.) over a period of 30 min. The ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 6 h until TLC showed complete consumption of starting material. The reaction mixture was again cooled to 0°C and quenched by the careful addition of saturated aqueous ammonium chloride solution (100 mL). The reaction mixture was diluted with water (100 mL) and DCM (200 mL) to ensure that all the precipitate dissolves. The two layers were separated and the aqueous layer was washed with DCM (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified via silica gel chromatography (30:70 ethyl acetate:hexanes) to obtain 186 (8.7 g, 87%) as a white crystalline solid.

IR (chloroform) \( \nu_{\text{max}} \) cm\(^{-1} \) : 2976, 1699, 1640, 1503, 1445

\(^1\)H NMR (400MHz, CD\(_3\)OD) \( \delta \) : 7.57 - 7.47 (m, 3 H), 7.46 - 7.40 (m, 1 H), 7.37 (t, \( J = 7.7 \) Hz, 2 H), 6.66 (br. s., 1 H), 6.55 - 6.44 (m, 2 H), 6.36 (br. s., 1 H), 5.83 (d, \( J = 16.1 \) Hz, 2 H), 3.83 (br. s., 1 H), 3.66 (br. s., 1 H), 2.54 (br. s., 2 H), 1.77 (br. s., 2 H), 1.39 (s, 9 H)

\(^13\)C NMR (100MHz, CDCl\(_3\)) \( \delta \) : 155.0, 147.3, 146.3, 140.3, 140.1, 140.1, 139.8, 132.7, 128.5, 128.0, 122.0, 108.6, 107.9, 100.9, 79.6, 51.5, 45.1, 28.3, 21.7, 19.6

Mass (ESI): m/z : 480 (M\(^+\)+Na)
Chapter I: 7-azabicyclo[2.2.1]heptane skeleton and approaches towards...

tert-butyl (-2-(benzo[d][1,3]dioxol-5-yl)cyclohex-3-en-1-yl)carbamate(185):

![Chemical structure of 185]

To a well-stirred solution of 186 (2.0 g, 4.37 mmol, 1 equiv.) in DMF/H$_2$O (10 mL:10 mL) was added Na$_2$S$_2$O$_4$ (2.28 g, 13.11 mmol, 3 equiv.) and NaHCO$_3$ (1.39 g, 13.11 mmol, 3 equiv.). The round-bottom flask was fitted with a condenser and heated in an oil bath at 105°C for 3 h. The reaction mixture was cooled and diluted with ethyl acetate (30 mL) and washed 3 times with an equal volume of water. The organic layer was dried over anhydrous sodium sulphate and concentrated. The product was purified via silica gel column chromatography (10% ethyl acetate in hexane) to obtain 185 (1.08 g, 78%) as a white crystalline solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 6.79 - 6.66 (m, 13 H), 5.95 - 5.81 (m, 13 H), 5.59 (d, $J = 7.6$ Hz, 4 H), 4.67 (br. s., 4 H), 3.68 (br. s., 4 H), 3.21 (br. s., 4 H), 2.28 - 2.06 (m, 9 H), 1.95 - 1.82 (m, 5 H), 1.65 - 1.51 (m, 5 H), 1.38 (s, 39 H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 155.2, 147.5, 146.1, 136.7, 128.2, 127.8, 121.5, 108.7, 107.9, 100.7, 79.0, 52.4, 47.8, 28.3, 25.7, 23.1

HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{23}$NO$_4$Na ([M+Na]$^+$): 340.1519, found: 340.1519

tert-butyl (2-(benzo[d][1,3]dioxol-5-yl)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate(193):

![Chemical structure of 193]
To a stirred solution of 185 (0.5 g, 1.58 mmol, 1.0 equiv.) in dichloromethane was added mCPBA (0.882 g, 3.94 mmol, 2.5 equiv.) at 0°C. After stirring at that temperature for 7 h, the reaction was quenched by the addition of saturated aqueous solution of NaHCO₃. This was diluted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 5:1) to obtain major isomer 193 (0.35 g, 67%) as a white solid along with minor isomer 194 also as a white solid. Rf 0.5 (hexane/EtOAc 4:1).

IR (chloroform) υmax cm⁻¹ : 2545, 1686, 1578, 1415

¹H NMR (400MHz ,CDCl₃) δ : 6.82 - 6.66 (m, 3 H), 5.94 (dd, J = 1.4, 3.4 Hz, 2H), 4.73 (br. s., 1 H), 3.55 (br. s., 1 H), 3.32 (br. s., 1 H), 3.21 - 3.06 (m, 1 H), 2.92-2.94 (d, J = 8.5 Hz, H), 2.30 - 2.11 (m, 1H), 2.11 - 1.94 (m, 1H), 1.74 - 1.59 (m, 1H), 1.50 - 1.40 (m, 1 H), 1.35 (br. s., 9H)

¹³C NMR (100MHz, CDCl₃) δ : 155.0, 147.8, 146.5, 134.5, 121.4, 108.6, 108.3, 101.0, 79.2, 56.1, 52.4, 51.5, 47.2, 29.7, 28.3, 22.7

HRMS (ESI): m/z calcd. for C₁₈H₂₃NO₅Na ([M+Na]⁺): 356.1468, found: 356.1470

tert-butyl (-2-(benzo[d][1,3]dioxol-5-yl)-3-hydroxy-4-(phenylselanyl)cyclohexyl) carbamate(198):

To a stirred solution of DPDS (0.56 g, 1.79 mmol, 2.6 equiv.) in tetrahydrofuran (10 mL) at ambient temperature was added n-butyllithium (0.985mL solution in hexane, 1.86 mmol, 2.7 equiv.) slowly. The yellow colour of the solution became colourless. After 10 min 193 (0.23 g, 0.69 mmol, 1 equiv.) in 20 mL tetrahydrofuran was added slowly. The reaction mixture was stirred at that temperature for 14 h and quenched by addition of 5 mL of saturated aqueous ammonium chloride solution. After extraction
with ethyl acetate, the crude mass was chromatographed (hexane/ethylacetate 7:3) which produced 198 (0.31 g, 91.6%) as a white crystalline solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ : 7.61 (dd, J = 1.3, 8.1 Hz, 2 H), 7.41 - 7.25 (m, 3 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.74 - 6.62 (m, 2 H), 5.99 - 5.90 (m, 2 H), 4.28 - 4.15 (m, 1 H), 3.55 (d, J = 10.1 Hz, 1 H), 3.46 (t, J = 9.9 Hz, 1 H), 3.08 - 2.97 (m, 1 H), 2.40 (t, J = 10.4 Hz, 1 H), 2.25 - 2.07 (m, 2 H), 1.69 - 1.54 (m, 1 H), 1.45 - 1.35 (m, 1 H), 1.28 (s, 9 H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ : 155.5, 148.2, 147.1, 136.8, 133.4, 129.9, 129.5, 128.8, 126.6, 122.3, 108.7, 101.3, 79.6, 75.8, 57.8, 52.9, 50.7, 34.3, 30.7, 28.6

HRMS (ESI): m/z calcd. for C$_{24}$H$_{29}$NO$_5$SeNa ([M+Na]$^+$): 514.1103, found: 514.1107

tert-butyl (-6-(benzo[d][1,3]dioxol-5-yl)-5-hydroxycyclohex-3-en-1-yl)carbamate(199)

To a stirred and cooled (0 °C) solution of 198 (0.5 g, 1.02 mmol, 1.0 equiv.) in dichloromethane (20 mL) was added 30 % aqueous hydrogen peroxide (1.05 mL, 10.2 mmol, 10 equiv.) and diisopropylethylamine (0.74 mL, 3.06 mmol, 3 equiv.). After 1 h, the reaction mixture was concentrated under vacuo and toluene (25 mL) was added, and the mixture was heated again at 111 °C for 1 h. The mixture was cooled to room temperature, evaporated in vacuo, and the residue was subjected to column chromatographic purification, using hexanes-ethyl acetate mixtures (2:3) to obtain 199 as a yellowish solid (0.3 g, 88%).

$^1$H NMR (400 MHz, CDCl$_3$) δ : 6.82 - 6.64 (m, 3 H), 5.93 (d, J = 5.5 Hz, 2 H), 5.77 (s, 2 H), 4.48 - 4.29 (m, 2 H), 3.97 (br. s., 1 H), 2.68 - 2.47 (m, 2 H), 2.15 - 1.98 (m, 1 H), 1.31 (br. s., 9 H)
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approches towards....

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 155.7, 148.4, 147.2, 133.3, 130.1, 127.2, 122.6, 108.7, 101.4, 79.7, 73.4, 55.6, 49.5, 33.6, 28.6
HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{24}$NO$_5$ ([M+H]$^+$): 334.1649, found: 334.1651

$^{1}$H NMR (800 MHz, CDCl$_3$) $\delta$: 6.77 (d, $J = 8.0$ Hz, 1 H), 6.72 (br. s., 1 H), 6.67 (d, $J = 8.0$ Hz, 1 H), 5.94 (d, $J = 13.6$ Hz, 2 H), 4.20 - 4.14 (m, 1 H), 4.14 - 4.09 (d, $J = 11.8$ Hz, 1 H), 3.77 (br. s., 1 H), 3.47 - 3.44 (m, 1 H), 3.35 (t, $J = 4.8$ Hz, 1 H), 2.61 (dd, $J = 9.8$, 11.8 Hz, 1 H), 2.56 - 2.50 (m, 1 H), 1.86 - 1.76 (m, 2 H), 1.28 (br. s., 9 H)

$^{13}$C NMR (200 MHz, CDCl$_3$) $\delta$: 155.1, 148.1, 147.1, 131.1, 122.5, 108.5, 101.1, 79.7, 73.2, 55.6, 52.0, 50.5, 48.6, 31.4, 28.2
HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{23}$NO$_6$Na ([M+Na]$^+$): 372.1418, found: 372.1418

*tert*-butyl(-4-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (200):

To a stirred and cooled (0°C) solution of 199 (0.5 g, 1.5 mmol, 1.0 equiv.) in dichloromethane (50 mL) was added mCPBA (1.18 g, 77%, 5.25 mmol, 3.5 equiv.). The reaction mixture was stirred at that temperature for 12 h. The reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution. The colour turned pink which after 2 h of stirring became colourless. The reaction mixture was extracted with DCM and the crude mass was purified with column chromatography using hexane:ethylacetate (1:1) mixture to obtain 200 (0.387 g, 73%) as a white solid.
Chapter I: 7-azabicyclo[2.2.1]heptane skeleton and approaches towards...

** tert-butyl (-4-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate 202):**

Dess-Martin periodinane (0.328 g, 0.773 mmol, 3 equiv.) was added to a solution of 200 (0.09 g) in dry DCM (6 mL) and the resulting heterogeneous reaction mixture was stirred under Ar atmosphere at ambient temperature for 1 h. The reaction mixture was diluted with 10 mL DCM and treated with 5 mL saturated aqueous solution of NaHCO₃ and 5 mL 5% aqueous solution of sodium thiosulfate. The reaction mixture was stirred for 15 min, by which time both layers became clear. It was extracted with DCM and concentrated to get crude 201 (0.089 g) which was as such re-dissolved in 10 mL of distilled methanol and cooled to 0°C. CeCl₃.7H₂O (0.105 g, 0.281 mmol, 1.1 equiv.) was added followed by NaBH₄ (0.01 g, 0.269 mmol, 1.05 equiv.). The reaction mixture was stirred at 0°C for 1 h and diluted with EtOAc (10 mL), quenched with brine (2 mL) and stirred for 4 h. The crude mixture was extracted with EtOAc and collective organic layers were concentrated under vacuo. The residue was subjected to column chromatographic purification using hexane: ethylacetate (3:2) to obtain 202 (0.076 g, 84%) as a white crystalline solid.

**¹H NMR (400 MHz, CDCl₃) δ:** 6.85 - 6.74 (m, 2 H), 6.69 (d, J = 7.8 Hz, 1 H), 5.94 (d, J = 3.3 Hz, 2 H), 4.27 (br. s., 1 H), 4.20 (br. s., 2 H), 3.32 (br. s., 1 H), 3.31 - 3.25 (m, 1 H), 2.89 (d, J = 8.3 Hz, 1 H), 2.58 (td, J = 5.2, 15.4 Hz, 1 H), 1.92 (d, J = 2.5 Hz, 1 H), 1.79 (dd, J = 8.3, 15.1 Hz, 1 H), 1.35 (br. s., 9 H)

**¹³C NMR (100 MHz, CDCl₃) δ:** 155.3, 148.0, 146.8, 131.8, 122.2, 109.5, 108.5, 101.0, 79.4, 69.9, 54.8, 52.1, 47.2, 42.6, 31.4, 28.3

**HRMS (ESI):** m/z calcd. for C₁₈H₂₃NO₆Na ([M+Na]+): 372.1418, found: 372.1422
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards…

tert-butyl(-2-(benzo[d][1,3]dioxol-5-yl)-3,4-dihydroxy-5-phenylselanyl)cyclohexyl)
carbamate (203):

A solution of n-butyllithium in hexane (0.69 mL, 1.89 M, 1.3 mmol, 4.55 equiv) was
added slowly to a stirred solution of diphenyl diselenide (0.402 g, 1.29 mmol, 4.5
equiv.) in anhydrous THF (6 mL) under inert atmosphere till the yellow colour of the
solution turned colourless. After 10 min, a solution of 202 (0.1 g, 0.287 mmol) in
THF (12 mL) was added drop wise and stirring continued for 12 h at room
temperature. The reaction was quenched by the addition of saturated aqueous solution
of NH₄Cl. The organic phase was worked up as usual. The crude product was
subjected to column chromatographic purification, using hexanes-ethyl acetate
mixtures (7:3) to obtain 203 as a floppy solid (0.131 g, 90% yield).

¹H NMR (400MHz, CDCl₃) δ : 7.62 (d, J = 5.8 Hz, 2 H), 7.38 - 7.19 (m, 3 H), 6.82
(s, 1 H), 6.75 - 6.56 (m, 2 H), 5.92 (s, 2 H), 4.56 - 4.34 (m, 2 H), 4.26 (br. s., 1 H),
3.93 (d, J = 3.5 Hz, 1 H), 3.43 (br. s., 1 H), 3.17 (br. s., 1 H), 2.90 (br. s., 1 H), 2.43
(br. s., 1 H), 2.29 - 2.15 (m, 2 H), 1.38 (br. s., 9 H)

¹³C NMR (101MHz, CDCl₃) δ : 155.3, 147.7, 146.4, 134.7, 132.5, 129.1, 127.8,
122.1, 109.7, 108.2, 100.9, 79.4, 75.2, 71.7, 49.0, 46.2, 43.8, 33.9, 28.3
HRMS (ESI): m/z calcd. for C₂₄H₂₉NO₆SeNa ([M+Na]⁺): 530.1052, found: 530.1060
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards...

tert-butyl (-6-(benzo[d][1,3]dioxol-5-yl)-4,5-dihydroxycyclohex-2-en-1-yl)carbamate (204):

To a stirred and cooled (0 °C) solution of 203 (0.110 g, 0.217 mmol, 1equiv.) in dichloromethane (6 mL) was added 30% aqueous hydrogen peroxide (0.2 mL, 2.17 mmol, 10 equiv.) and diisopropylethylamine (0.1 mL, 0.65 mmol, 3 equiv.). After 1h, the reaction mixture was concentrated under vacuo and toluene (5 mL) was added, and the mixture was heated again at 111 °C for 3 h. The mixture was cooled to room temperature, evaporated in vacuo, and the residue was subjected to column chromatographic purification, using hexanes-ethyl acetate mixtures (2:3) to obtain 204 as a yellowish solid (0.062 g, 81% yield).

IR (chloroform) $\nu_{\text{max}}$ cm$^{-1}$: 3436, 2919, 2850, 1680, 1038

$^1$H NMR (400MHz, CDCl$_3$) $\delta$: 6.86 (s, 1 H), 6.78 (s, 2 H), 6.00 - 5.84 (m, 4 H), 4.67 - 4.44 (m, 2 H), 4.02 (d, $J = 3.3$ Hz, 1 H), 3.91 - 3.85 (m, $J = 3.8$ Hz, 1 H), 3.16 (br. s., 1 H), 1.39 (s, 9 H)

$^{13}$C NMR (100MHz, CDCl$_3$) $\delta$: 155.3, 147.8, 146.6, 132.7, 132.2, 128.3, 121.9, 109.1, 108.3, 100.9, 79.7, 74.1, 68.7, 48.9, 47.1, 28.3

HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{23}$NO$_6$Na ([M+Na]$^+$): 372.1418, found: 372.1418
Chapter I: 7-azabicyclo [2.2.1] heptane skeleton and approaches towards...

tert-butyl (-2-(benzo[d][1,3]dioxol-5-yl)-3,4,5,6-tetrahydrocyclohexy)carbamate (205):

To a solution of 204 (0.01 g, 0.028 mmol, 1.0 equiv) in THF (0.8 mL) in a round bottomed flask equipped with a magnetic stir bar were added a 0.5 M solution of NMO in H₂O (0.171 mL, 85.5 μmol, 3 equiv) and a solution of OsO₄ in tBuOH (0.116 mL, 0.005 mmol, 0.2 equiv.). The reaction mixture was stirred in dark at room temperature under an atmosphere of Ar for 15 h. The reaction mixture was quenched with saturated aqueous sodium thiosulfate (5.0 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (5 x 5.0 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (3% MeOH in DCM) to afford 205 as a white solid (0.01 g, 91%).

$^1$H NMR (400MHz, CDCl₃) δ 6.87 (s, 1 H), 6.72 (s, 2 H), 5.87 (s, 2 H), 4.84 (d, $J$ = 7.1 Hz, 1 H), 4.65 - 4.42 (m, 2 H), 4.33 - 4.04 (m, 4 H), 3.94 - 3.78 (m, 3 H), 3.05 (d, $J$ = 11.8 Hz, 1 H), 1.28 (br. s., 9 H)

$^1$H NMR (800MHz, CD₃OD) δ = 6.93 (s, 1 H), 6.78 (d, $J$ = 7.8 Hz, 1 H), 6.70 (d, $J$ = 7.8 Hz, 1 H), 5.87(s, 1H), 5.85 (s, 1 H), 4.27 (t, $J$ = 11.2 Hz, 1 H), 4.05 - 4.03 (t, $J$ = 3.1 Hz, 1 H), 4.01 (br. s., 1 H), 3.76 (br. s., 1 H), 3.76 - 3.73 (dd, $J$ = 3.1, 10.6 Hz, 1 H), 3.11 (dd, $J$ = 1.6, 12.1 Hz, 1 H), 1.29 (s, 9 H)

$^{13}$C NMR (201MHz, CD₃OD) δ = 159.0, 148.7, 147.6, 135.2, 124.0, 111.3, 108.6, 102.1, 79.8, 77.5, 76.2, 73.5, 72.0, 50.8, 49.0, 28.8

5-(benzo[d][1,3]dioxol-5-yl)-6-((tert-butoxycarbonyl)amino)cyclohexane-1,2,3,4-tetrayl tetraacetate (206):

To a solution of 205 (0.034 g, 0.088 mmol, 1 equiv.) and DMAP (0.005 g, 0.044 mmol, 0.5 equiv.) in 5 mL of pyridine at 0°C was added acetic anhydride (0.084 mL, 0.88 mmol, 10 equiv.). The reaction mixture was stirred at that temperature for 1 h after which it was quenched with the addition of ice and extracted with (3 x 6 mL) DCM. The crude material was purified with flash chromatography (EtOAc: Hexane 1:1) to get 206 (0.042 g, 85%) as a white crystalline solid.

IR (neat) \( \nu_{\text{max}} \) cm\(^{-1} \) 1704, 1366, 1177, 1141, 1007, 968, 868.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \( \delta \) : 6.78 (s, 1 H), 6.73 (s, 2 H), 5.92 (d, \( J = 10.6 \) Hz, 2 H), 5.35 (br. s., 1 H), 5.18 (dd, \( J = 2.6, 10.4 \) Hz, 1 H), 5.11 (t, \( J = 2.8 \) Hz, 1 H), 5.01 (br. s., 1 H), 4.71 (q, \( J = 11.1 \) Hz, 1 H), 4.18 (d, \( J = 10.3 \) Hz, 1 H), 3.15 (d, \( J = 10.8 \) Hz, 1 H), 2.19 (s, 3 H), 2.17 (s, 3 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.30 (br. s., 9 H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) : 169.4, 168.9, 168.3, 155.4, 147.7, 146.9, 129.7, 122.3, 109.2, 108.1, 101.0, 79.5, 72.1, 71.1, 68.8, 68.1, 47.5, 47.1, 28.1, 20.9, 20.7, 20.6

HRMS (ESI): \( m/z \) calcd. for C\(_{26}\)H\(_{34}\)NO\(_{12}\) ([M+H]+): 552.2076, found: 552.2075.
6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2,3,4-tetrayl tetraacetate(207):

To a solution of 206 (0.02 g, 0.036 mmol, 1 equiv.) and 2-chloropyridine (0.145 mL of 0.5 M solution in DCM, 2 equiv.) in anhydrous DCM (1.0 mL) was added freshly distilled triflic anhydride (0.218 mL of 0.5 M solution in DCM, 3 equiv.) at -84℃. After 20 min BF₃·OEt₂ (0.1 mL) was added at the same temperature. The reaction mixture was allowed to come to ambient temperature in 4 h after which the reaction mixture was stirred at that temperature for another 8 h. It was diluted with 2 mL of DCM and quenched at 0℃ by slow addition of saturated aqueous NaHCO₃ solution (1 mL). The mixture was extracted with (3 x 5 mL) DCM concentrated and chromatographed using flash silica gel (EtOAc:Hexane 1:1) to get 207 (0.011g, 63%) as a yellowish solid.

IR (chloroform) υ max cm⁻¹ 2934, 1704,1697, 1366, 1177, 1141, 1007, 965.

¹H NMR (400 MHz, CDCl₃) δ : 7.61 (s, 1 H), 6.58 (s, 1 H), 6.04 (dd, J = 1.3, 7.3 Hz, 2 H), 5.83 (s, 1 H), 5.60 (t, J = 2.6 Hz, 1 H), 5.48 (t, J = 2.8 Hz, 1 H), 5.24 (t, J = 2.8 Hz, 1 H), 5.19 (dd, J = 3.4, 10.9 Hz, 1 H), 4.31 (dd, J = 10.9, 12.9 Hz, 1 H), 3.53 - 3.43 (dd, J = 2.3, 12.9 Hz, 1 H), 2.18 (s, 3 H), 2.09 (d, J = 1.2 Hz, 6 H), 2.05 (s, 3 H)

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[Chemical shift spectra diagram]
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\[ \text{H NMR (500MHz, CHLOROFORM-d)} \delta = 6.76 (d, J = 7.9 Hz, 4 H), 6.68 - 6.59 (m, 7 H), 5.99 - 5.91 (m, 8 H), 4.37 - 4.32 (m, 3 H), 4.31 - 4.27 (m, 4 H), 4.20 (br. s., 4 H), 4.16 - 4.11 (m, 4 H), 3.54 (br. s., 4 H), 2.24 (br. s., 3 H), 1.94 - 1.86 (m, 4 H), 1.59 (s, 11 H), 1.41 (s, 11 H), 1.36 (s, 33 H) \]
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