Chapter – 5

Metal-free asymmetric synthesis of tetracyclic dibenzo[*b*,*f*][1,4]oxazepine-fused 1,2-dihydropyridines (DHPs)

5.1 Introduction

The synthesis of poly heterocyclic pharmacophores based on privileged structures from ready available building blocks has attracted a great deal of interest over the years.[1-3] In this context, dibenzo[*b*,*f*][1,4]oxazepine (DBO) derivatives have attracted considerable attention due to their importance as privileged scaffolds in medicinal chemistry.[4-5] This subunit is present in marketed tri, and tetracyclic antidepressants drugs and several other related medicinally active compounds such as **I-VI** (Figure 5.1).[6-12] Moreover, oxazepine derivatives also exhibit anti-HIV,[13-15] anti-inflammatory,[16-17] antihistaminics,[18] antidepressant,[19-21] antipsychotics,[22] progesterone receptor agonists,[23-24] and histone deacetylase inhibitors.[25]

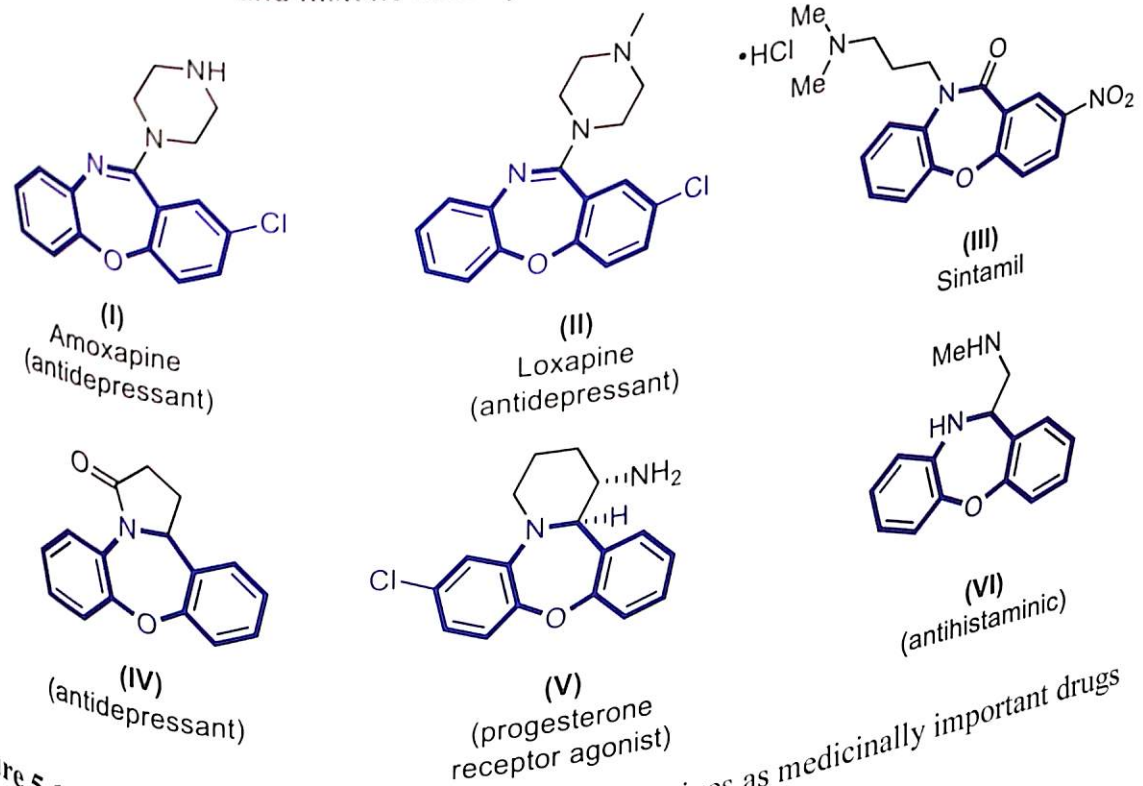


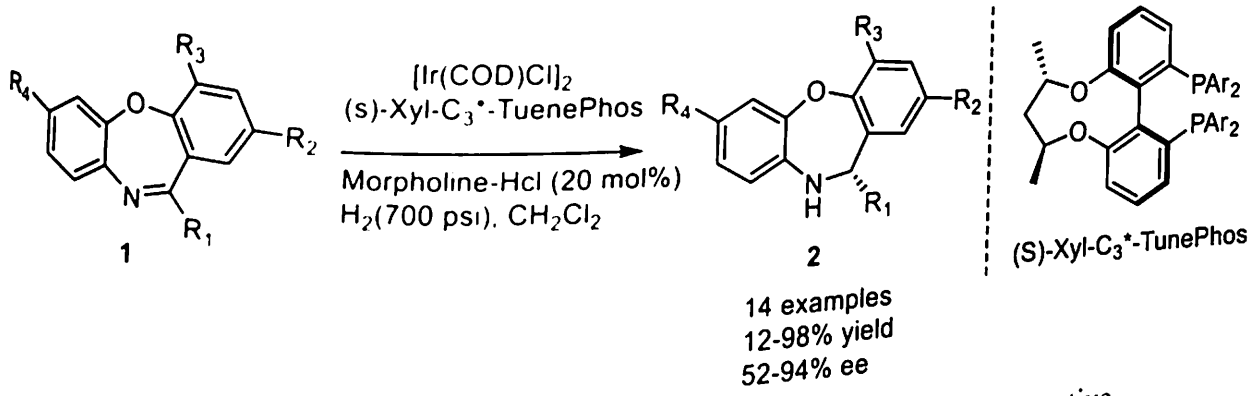
Figure 5.1 Representative fused 1,4-oxazepine derivatives as medicinally important drugs

5.2 Synthetic approaches for 1,4-benzoxazepine derivatives

Despite their widespread prevalence in drug discovery, a limited number of methods exists for the asymmetric synthesis of 1,4-benzoxazepine derivatives.[26] These existing methods mainly involved:

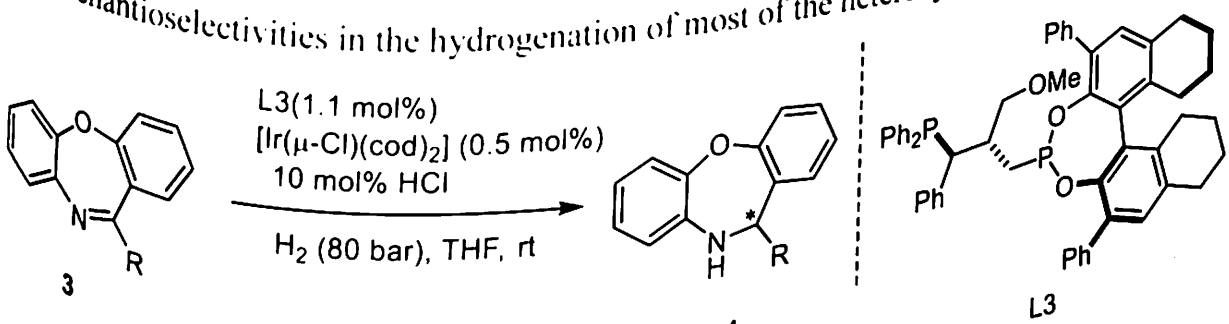
5.2.1 Metal-catalyzed reduction of tricyclic-ketimines:

Zhang and co-workers developed enantioselective hydrogenation for 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepines **2** by using the Ir/(*S*)-Xyl-C_3*-TunePhos catalyst system in the presence of morpholine-HCl with up to 94% ee shown in Scheme 5.1.[27]



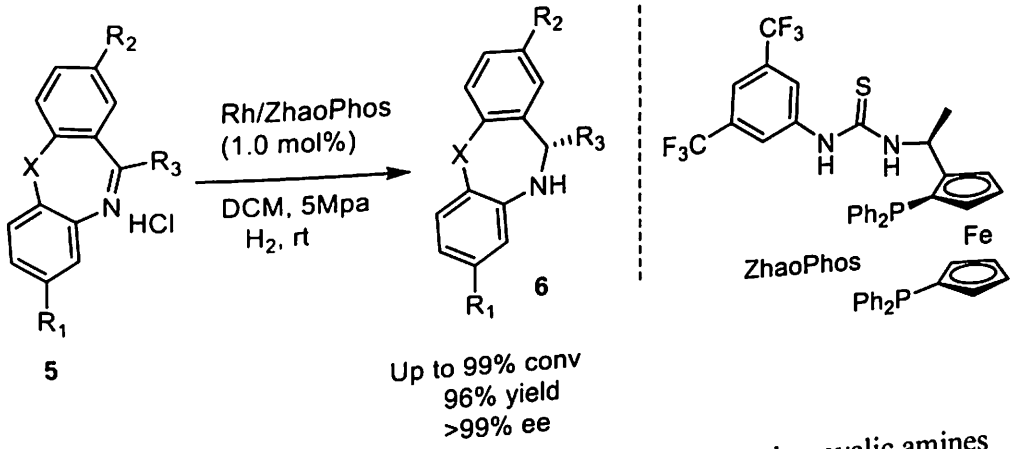
Scheme 5.1 Ir (S)-Xyl-C_3*-TunePhos catalyzed synthesis of optically active dihydrodibenzo[*b,f*][1,4]oxazepines scaffolds

Balakrishna and co-workers developed the enantioselective hydrogenation of diverse seven-membered C=N-containing heterocyclic compounds **3** catalyzed through Iridium (I) complexes with phosphine-phosphite ligands shown in Scheme 5.2.[28] The P-O-P ligand L3, which incorporates an *ortho*-diphenyl substituted octahydrobinol phosphite fragment, provided the highest enantioselectivities in the hydrogenation of most of the heterocyclic compounds studied.



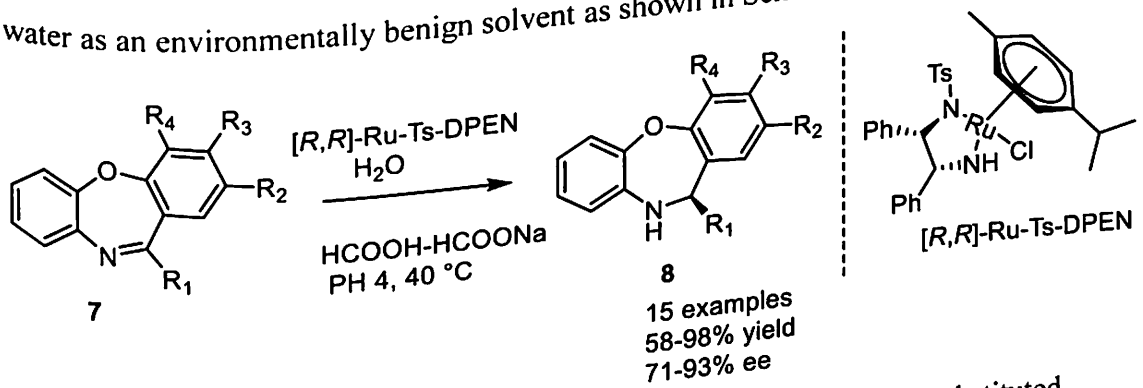
Scheme 5.2 Asymmetric hydrogenation of seven-membered ketimine mediated by [Ir(Cl)(cod)(L3)] as a catalyst

Li and co-workers developed a highly efficient asymmetric hydrogenation of azepine/oxazepine-type seven-membered cyclic imine hydrochlorides **5** using Rh/bisphosphine-thiourea ligand ZhaoPhos, affording various chiral seven-membered cyclic amines with full conversions, high yields, and excellent enantioselectivities (up to 96% yield, >99% ee) as shown in Scheme 5.3.[29]



Scheme 5.3 Rh-catalyzed synthesis of chiral seven-member cyclic amines

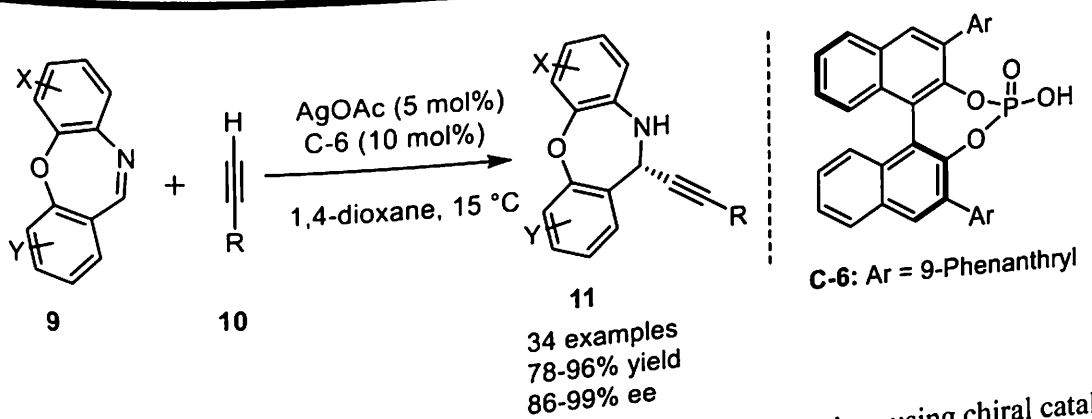
Morewe and co-workers developed a phosphine free, additive free catalytic ATH protocol for dibenzo[*b*,*f*][1,4]oxazepine **7** and its derivatives with an unmodified (*R*, *R*)-Ru-TsDPEN complex. The desired cyclic amines **8** were obtained in good yields with excellent enantioselectivities. In this reaction HCOOH–HCO_2Na was used as a green hydrogen source, atom-economical synthesis, and water as an environmentally benign solvent as shown in Scheme 5.4.[30]



Scheme 5.4 Ru-catalyzed asymmetric transfer hydrogenation of substituted dibenzo[*b*,*f*][1,4]oxazepines in water

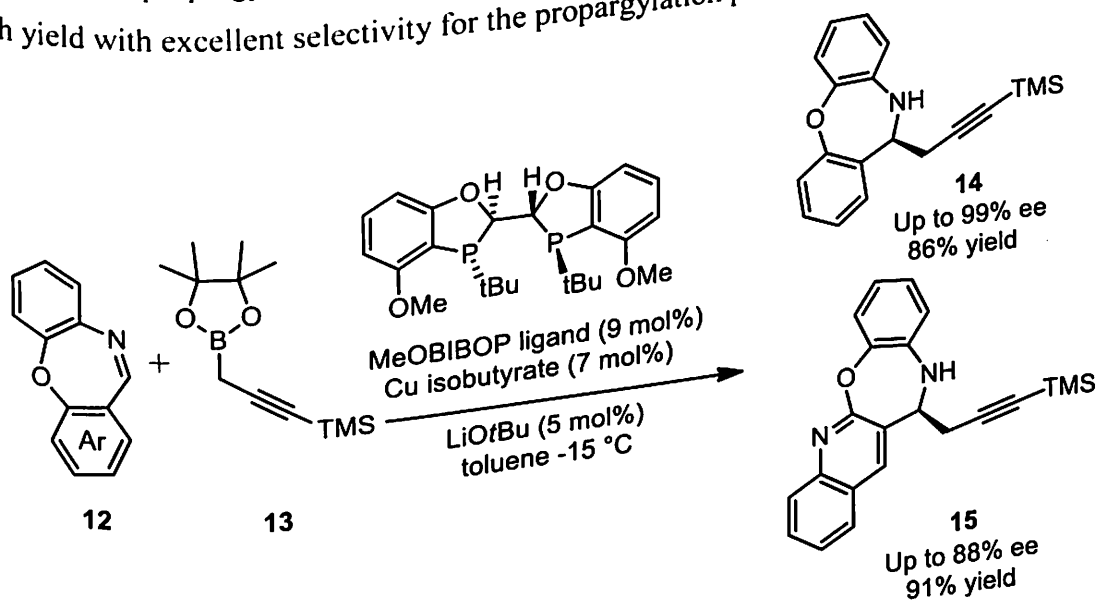
5.2.2 Nucleophilic addition of organometallic reagents to tricyclic-aldimines:

Ren and co-workers developed the asymmetric alkynylation of seven-membered cyclic imines **9** catalyzed by combining chiral phosphoric acids and silver salts. This approach has provided a new method to synthesize optically active 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine **11** derivatives containing a carbon-carbon triple bond with excellent enantioselectivities and yields shown in Scheme 5.5.[31]



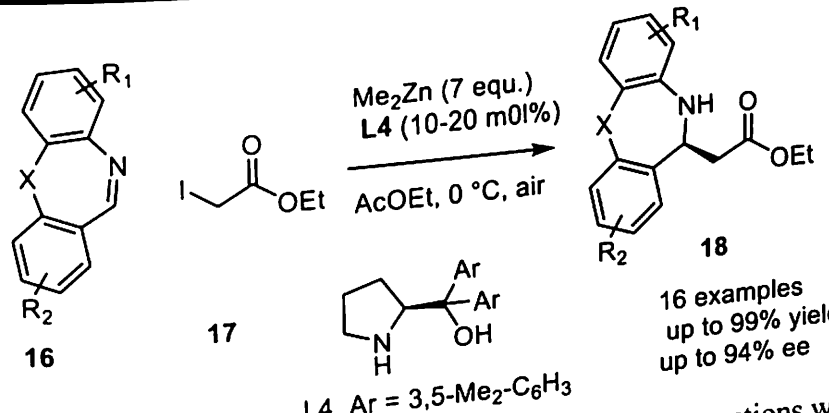
Scheme 5.5 Asymmetric alkynylation of seven-membered cyclic imines using chiral catalysts

Fandrick and co-workers reported the copper-catalyzed asymmetric propargylation of aldimines **12** with use of a propargylborolane **13** as a propargylic agent. The reactions generally proceeded in high yield with excellent selectivity for the propargylation pathway shown in Scheme 5.6.[32]



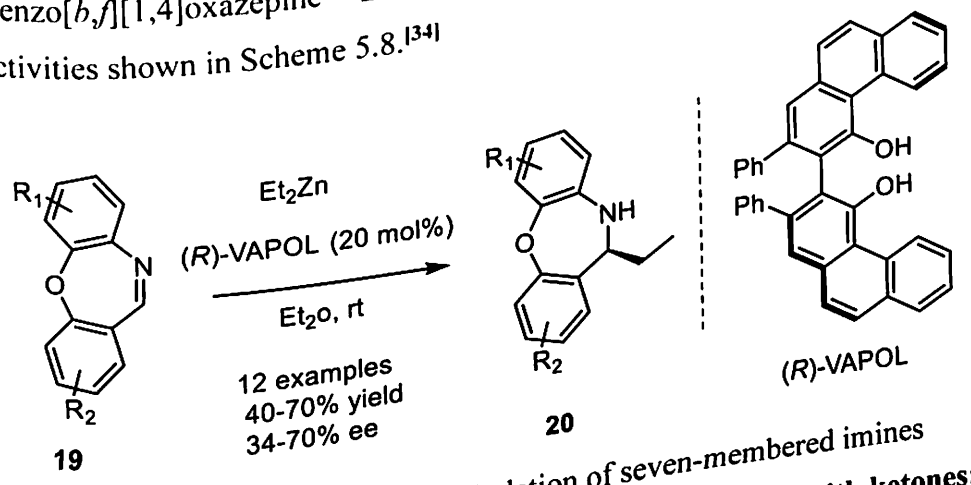
Scheme 5.6 Enantioselective propargylation of dibenzo[*b*,*f*][1,4]oxazepine

Pedro and Vila described catalytic enantioselective aza-Reformatsky reactions with dibenzo[*b*,*f*][1,4]oxazepines **16** as electrophiles and ethyl iodoacetate **17** as a nucleophile. This reaction proceeded by diarylprolinol as a chiral ligand and $ZnMe_2$ as a zinc source for the synthesis of chiral ethyl 2-(10,11-dihydrodi-benzo[*b*,*f*][1,4]oxazepin-11-yl)acetate **18** derivatives with excellent yields and high enantioselectivities shown in Scheme 5.7.[33]



Scheme 5.7 Catalytic enantioselective aza-Reformatsky reactions with di-benzo[*b*,*f*][1,4]oxazepine derivatives

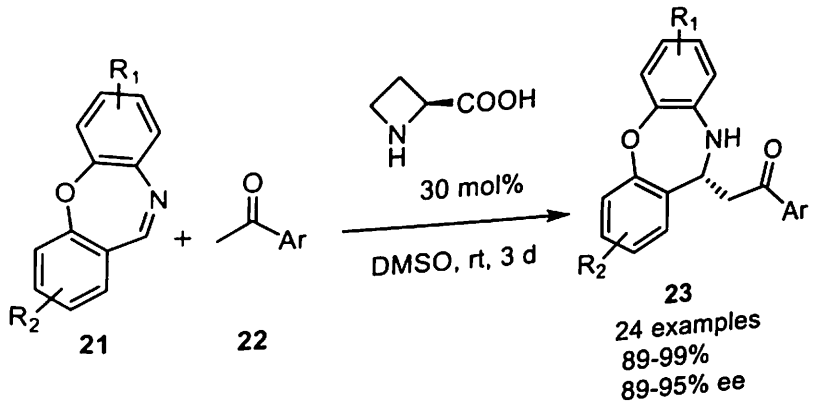
Munck and co-workers reported the enantioselective alkylation of dibenzo[*b*,*f*][1,4]oxazepine **19** derivatives with Et_2Zn catalyzed by (*R*)-VAPOL-Zn(II) furnished optically active 11-ethyl-10,11-dihy-drodibenzo[*b*,*f*][1,4]oxazepine **20** derivatives with good yields and moderate enantioselectivities shown in Scheme 5.8.[134]



Scheme 5.8 Enantioselective alkylation of seven-membered imines

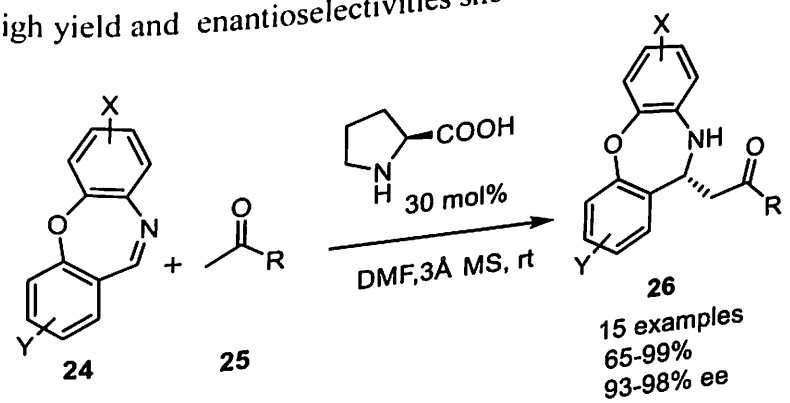
5.2.3 Direct organocatalytic Mannich reaction of tricyclic-aldimines with ketones:

Wang and collaborators described the highly enantioselective direct Mannich reaction of acetophenone **22** derivatives with dibenzo[*b*,*f*][1,4]oxazepine **21** using (*S*)-azetidine-2-carboxylic acid as an organocatalyst for the synthesis of optically active 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine **23** derivatives with high yield and enantioselectivities shown in Scheme 5.9.[135]



Scheme 5.9 Enantioselective Mannich addition of acetophenone derivatives to dibenzo[*b*,*f*][1,4]oxazepine derivatives

In 2015, the same group described a highly enantioselective direct Mannich reaction of seven-membered cyclic imines dibenzo[*b*,*f*][1,4]oxazepines **24** with acetone **25** using proline as the catalyst for the synthesis of 11-substituted-10, 11-dihydro-dibenzo[*b*,*f*][1,4]oxazepine **26** derivatives with high yield and enantioselectivities shown in Scheme 5.10.[36]

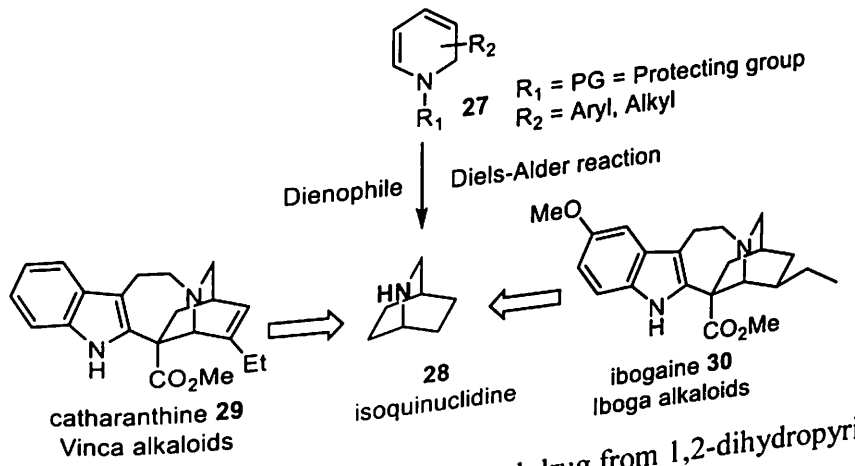


Scheme 5.10 Enantioselective Mannich reaction between acetone and dibenzoxazepines

Clearly, these existing approaches are mainly restricted to produce chiral tricyclic 10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine (Scheme 1a). Interestingly, structurally similar *ortho*-fused dibenz[*b*,*f*][1,4]-oxazepines that resemble the tetracyclic antidepressants (TeCAs), have received restricted attention.[37-41] This polycyclic-frameworks often carry a chiral center with similar bioactivities are attractive targets to explore further as drugs candidates.[42-43] However, the catalytic asymmetric synthesis of these tetracyclic scaffolds remained unexplored, to the best of our knowledge. Thus, the development of new methods to access chiral tetracyclic-oxazepines that could serve as suitable drug-candidates for CNS and other comorbid-disorders from easily available starting materials is highly desired.

5.3 Importance of 1,2-dihydropyridines (DHPs)

Dihydropyridine **27** is a pyridine-based scaffold, which belongs to the class of compounds that have been semi-saturated with two substituents replacing one double bond. They are particularly well known in pharmacology as L-type calcium channel blockers, used in the treatment of hypertension.



Scheme 5.11 Synthesis of the pharmaceutical drug from 1,2-dihydropyridines

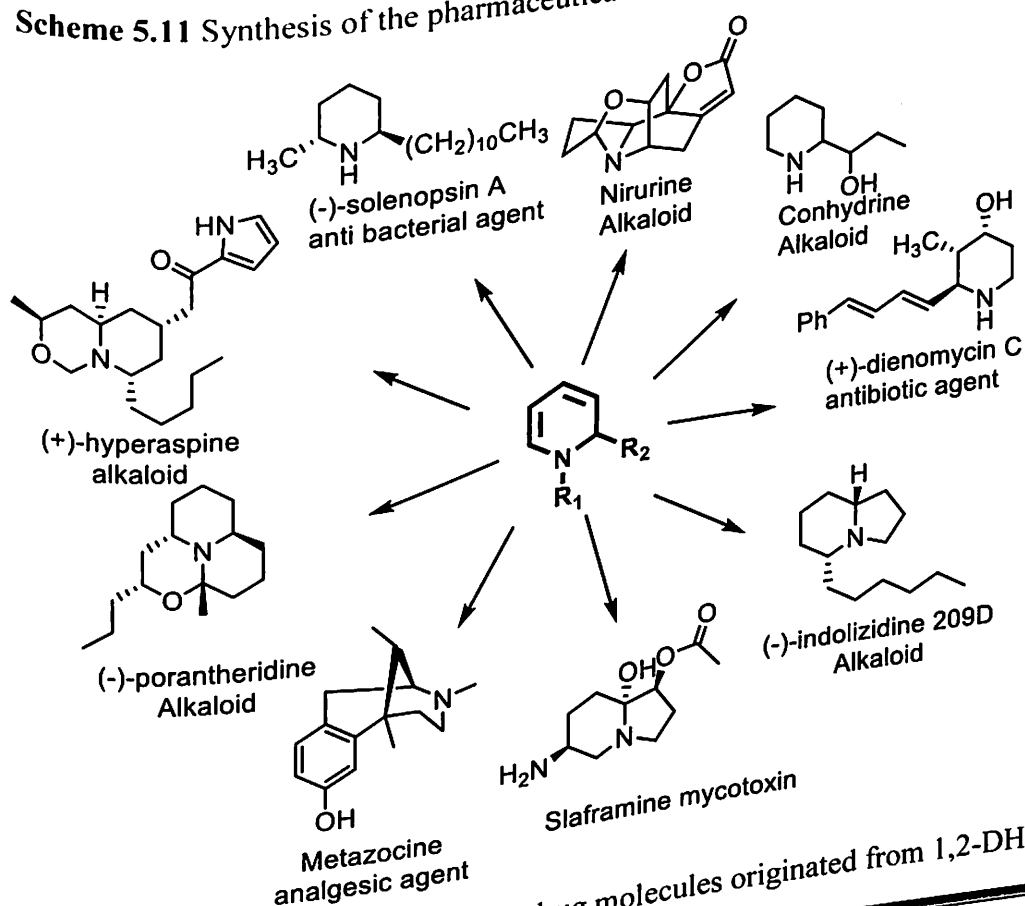


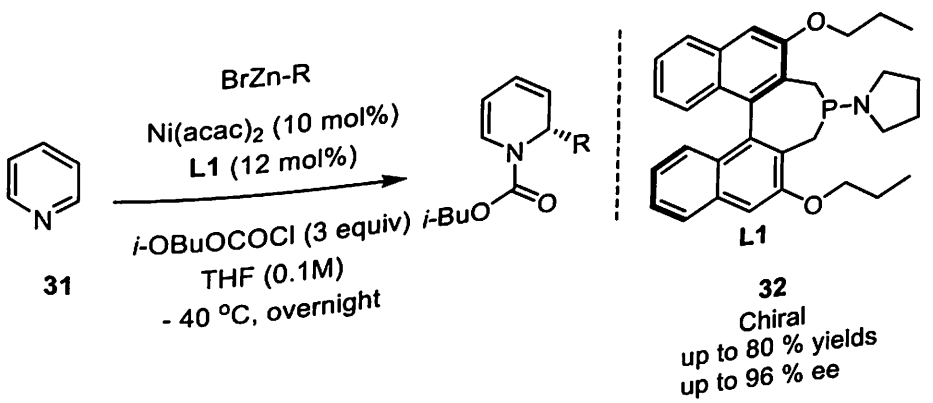
Figure 5.2 Few alkaloids and drug molecules originated from 1,2-DHPs

In particular, 1,2-dihydropyridines (DHPs) **27**, a key structural motif that is either present-in,[44-46] or utilized to synthesize a wide range of organic molecules as well as functionalized bioactive compounds such as: piperidines,[47-50] indolizidines,[51-55] and quinolizidines,[56-59] as well as act as suitable substrate to achieve isoquinuclidine **28** ring system and related complex bioactive alkaloids like catharanthine vinca alkaloids **29** and iboga type alkaloids **30** through Diels-Alder reaction.[60-66]

5.4 Synthetic approaches of 1,2-dihydropyridines (DHPs)

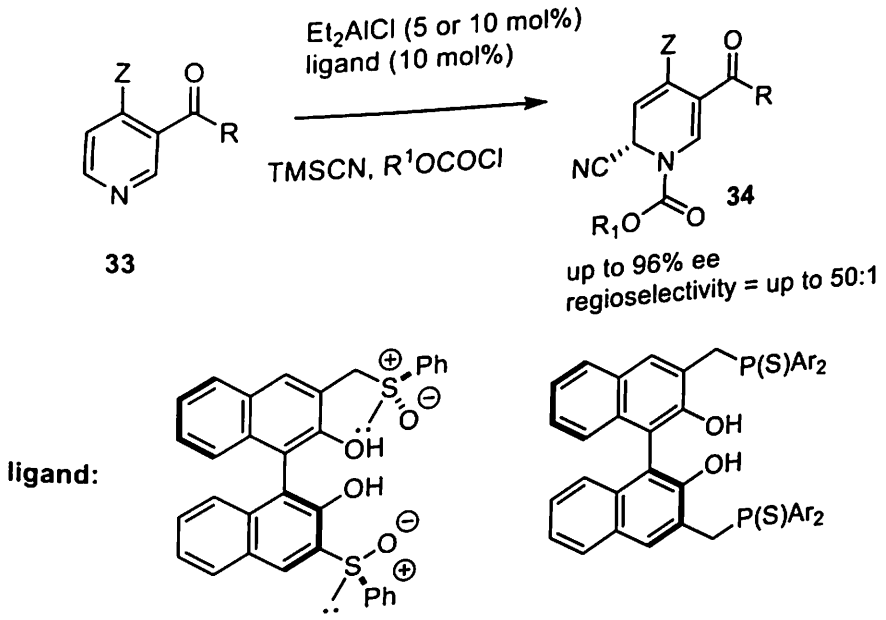
Despite high significance, a limited number of methods exist to access chiral 1,2-DHPs. [67-68] Few graceful asymmetric synthetic methods for the synthesis of chiral 1,2-DHPs were reported, although they possess experimental limitations like tedious pre-activation.

In this direction, Doyle and co-workers developed enantioselective Ni-catalyzed cross-coupling between aryl zinc reagents and pyridine **31** to the synthesis of chiral 1,2-DHP **32** in high yields and enantioselectivities showed in Scheme 5.12.[69] But, this method too demands pre-activation experimental limitations.



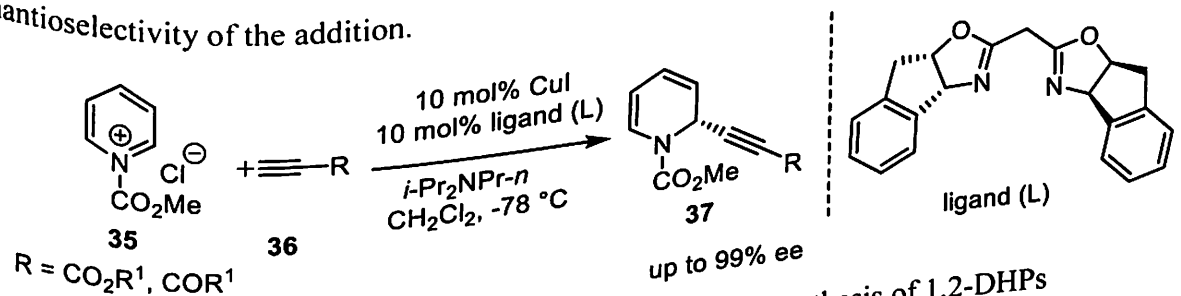
Scheme 5.12 Activation of pyridine for 1,2-DHPs synthesis

Ichikawa and co-workers described the first catalytic enantioselective Reissert reaction of pyridine derivatives **33** for the synthesis of chiral 1,2-DHPs **34** with excellent regio and enantioselectivity. This reaction proceeded through Lewis-acid-base bifunctional asymmetric catalysts containing an aluminum as a Lewis acid and sulfoxides or phosphine sulfides as a Lewis base as shown in Scheme 5.13.[70]



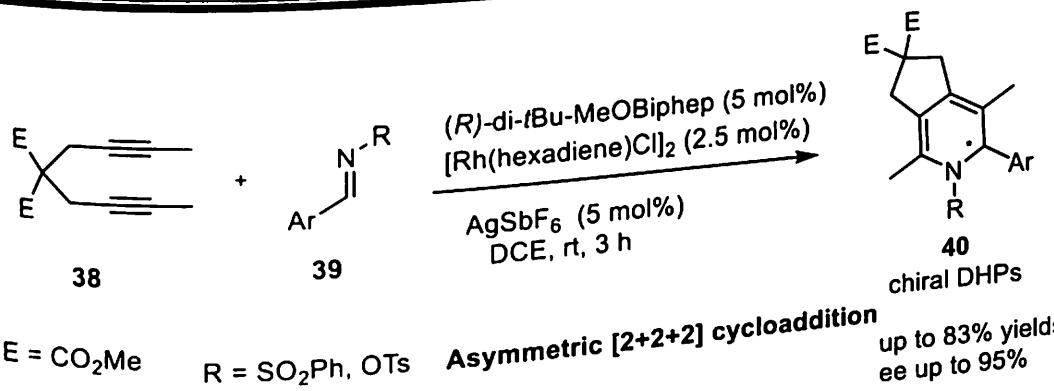
Scheme 5.13 Lewis acid-base catalyzed the synthesis of 1,2-DHPs

Sun and co-workers developed an enantioselective synthesis of dihydropyridines **37** in the presence of CuI/bis(oxazoline)-catalyzed addition of propiolates and terminal ynones **36** to 1-acylpyridinium salt produced excellent enantioselectivity and yield shown in Scheme 5.14.[71] It was found that the carbonyl group adjacent to the alkyne moiety is essential for the enantioselectivity of the addition.



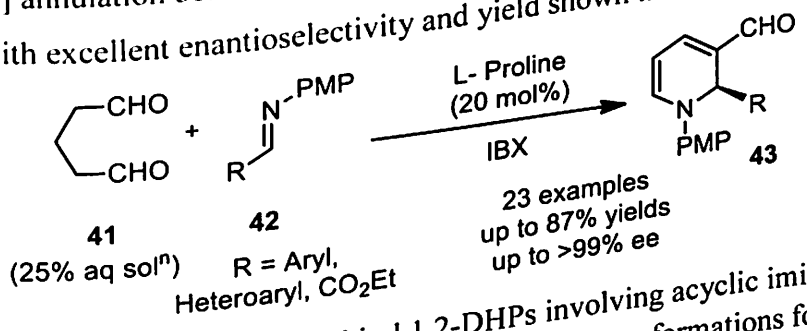
Scheme 5.14 CuI/bis (oxazoline) catalyzed the synthesis of 1,2-DHPs

Gandon and co-workers reported the metal-catalyzed asymmetric [2+2+2] cycloaddition between diynes **38** and *N*–sulfonimines **39** as well as with *N*–tosyl imines for the asymmetric synthesis of 1,2-DHPs **40** in excellent enantioselectivity and yield shown in Scheme 5.15.[72] The tedious procedure to prepare diyne starting material and the necessity to have an electron-withdrawing group on nitrogen is the main drawback of this methodology.



Scheme 5.15 Synthesis of chiral DHPs involving imine and diynes

Recently, Kumar and co-workers have reported an organocatalytic protocol to access chiral 1,2-DHPs **43** *via* [4+2] annulation between glutaraldehyde **41** and acyclic *N*-PMP-aldimines **42** under mild conditions with excellent enantioselectivity and yield shown in Scheme 5.16.[73]



Scheme 5.16 Synthesis of chiral 1,2-DHPs involving acyclic imine

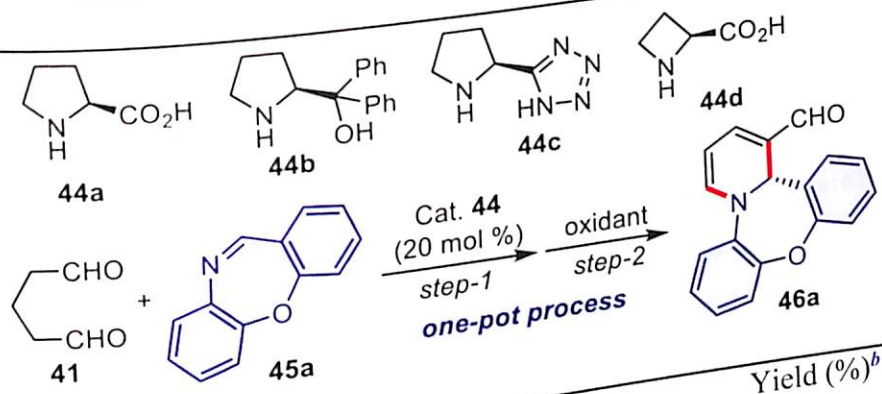
Interestingly, cyclic-imines have not been explored for similar transformations for the synthesis of structurally fused chiral 1,2-DHPs **46**. Here, we envisioned that seven-membered dibenzoxazepines **45** would be attractive partners for similar transformation to access chiral tetracyclic fused-1,2-DHPs **46** that might exhibit interesting bioactivities. Here, the synthesis of 1,2-fused 1,2-DHPs **46** seems essential as there is no report to these scaffolds in an asymmetric fashion. Thus, we extended our study to develop a simple, and efficient method, that overcomes earlier limitations, for the first asymmetric synthesis of 1,4-oxazepines fused 1,2-dihydropyridines (DHPs) **46** in one pot operation from glutaraldehyde **41** and cyclic imine **45** under metal-free conditions.

5.5 Results and discussion:

Having experience in this direction, we quickly established the reaction protocol as [4+2] annulation, which proceeds through L-proline-catalyzed **44** direct Mannich/cyclization sequence, followed by IBX-mediated site-selective dehydrogenative-oxidation and results as shown in **Table 5.1**. Initially, dibenzoxazepine **45a** was taken as a model substrate with aqueous glutaraldehyde **41**

(25% solution) in DMSO as the choice of solvent and obtained fused 1,2-DHPs **46a** with good yield (68%) and moderate enantioselectivity (83:17 er) (entry 1, Table 5.1).

Table 5.1: Optimization of reaction conditions for **46a**



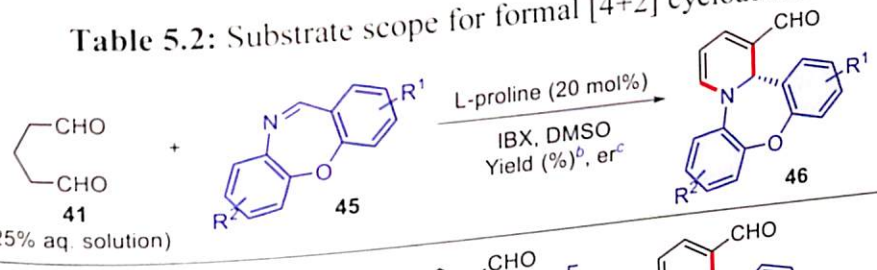
Entry	Catalyst	Step-1	Step-2	Yield (%)[b]	er[c]
1	**44a**	DMSO, rt, 3 h	IBX, rt, 3 h	68	83:17
2	**44a**	DMF, rt, 4 h	IBX, 40 °C, 3 h	48	91:9
3	**44a**	toluene, rt, 9 h	IBX, 70 °C, 3 h	<10	n.d.
4	**44a**	CH_3CN, rt, 4 h	IBX, 50 °C, 3 h	45	80:20
5	**44b**	DMSO, rt, 6 h	IBX, rt, 3 h	48	80:20
6	**44c**	DMSO, rt, 5 h	IBX, rt, 3 h	65	86:14
7	**44d**	DMSO, rt, 3 h	IBX, rt, 3 h	61	89:11
8	**44d**	DMSO, 10 °C, 3 h	IBX, 40 °C, 3 h	74	89:11
9	**44a**	**DMSO, 10 °C, 3 h**	**IBX, 40 °C, 3 h**	**88**	**92:8**
10[d]	**44a**	DMSO, 10 °C, 3 h	IBX, 65 °C, 3 h	85	92:8
11	**44a**	DMSO, 10 °C, 3 h	IBX, 40 °C, 3 h	75	92:8

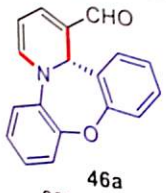
(a) Unless otherwise indicated, the reaction was carried out at (*i*) **45a** (0.3 mmol), **41** (25% aqueous sol., 0.9 mmol), L-proline **44** (20 mol%), solvent (3.0 mL); (*ii*) oxidant (120 mol%). (b) Isolated yield of **46a** refer to **45a**. (c) Determined using stationary chiral columns. (d) Catalyst **44a** (10 mol%).

With this initial success, we quickly screened other solvents, while DMF gave improved enantioselectivity (91:9 er) with a lower yield (entry 2, Table 5.1), and reaction in other solvents was poor (entries 3-4, Table 5.1). Next, the feasibility of other amine-catalysts (**44b**, **44c**, and **44d**, entries 5-7, Table 5.1) was screened in DMSO, followed by IBX (2-Iodoxybenzoic acid) oxidation at room temperature. An improved result in terms of yield (74%) and enantioselectivity (89:11 er) was obtained with catalyst **44d** at 10 °C, and warming the reaction to 40 °C during IBX-oxidation (entry 8, Table 5.1). Next, **46a** was obtained with high yield (88%) and enantioselectivity (92:8 er) when the reaction was performed with L-proline **44a** following similar reaction conditions (entry 9, Table 5.1). Any further improvement in the reaction outcome was not observed either by increasing reaction temperature during IBX-oxidation (entry 10, Table 5.1) or by decreasing catalyst loading (entry 11, Table 5.1). Thus, this overall [4+2] annulation between aqueous glutaraldehyde **41** and cyclic-imine **45** to yield **46** was preferred to perform under the optimized conditions (entry 9, Table 5.1). Interestingly, this one-pot protocol became highly feasible due to the high solubility of IBX in DMSO as well as its ability to dehydrogenate carbonyls to the corresponding α,β-unsaturated moieties.[74]

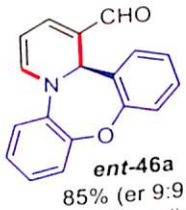
Next, we explored the generality of this protocol with variously substituted dibenzoxazepine imines **45** under optimized conditions. It was observed that the reaction was quite general with respect to the substituents on both arene rings of **45**. Initially, the generality was tested with imines **45a-45h** derived from 2-aminophenol and variously substituted 2-fluorobenzaldehydes and resulting products **46a-46h** (Table 5.2) were obtained with high yields (92%) and excellent enantioselectivity (up to >99:1 er). Moreover, opposite enantiomer *ent*-**46a** was also synthesized with high yield and enantioselectivity (9:91 er) by altering the amine-catalyst from L- (for **46a**) to D-proline (for ent-**46a**) under standardized conditions. Later, the scope of the protocol was explored for suitably substituted cyclic-imines **45i-45s** decorated with F, Cl, Br, CF_3, and CH_3 at different positions of the two aryl rings also afforded products **46i-47s** (Table 5.2) with good to high yields and excellent enantioselectivity (up to >99:1 er). Moreover, oxazepine-imines **45s-45t**, densely substituted at different positions of the two aryl rings, also furnished corresponding **46s-46t** (Table 5.2) with high yields and excellent enantioselectivity. Unexpectedly, reaction failed to give desired products, when oxazepine-imines **45v** and **45w** substituted with CF_3 groups at *ortho*-position were employed under standardized conditions (Table 5.2) and this could be due to an unfavorable steric hindrance employed by this CF_3-group.

Table 5.2: Substrate scope for formal [4+2] cycloaddition **46**

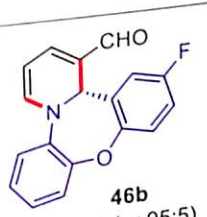




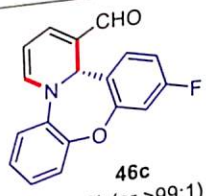
46a
88% (er 92:8)



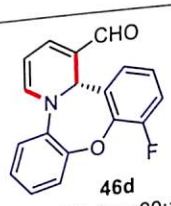
***ent*-46a**
85% (er 9:91)
(with D-proline)



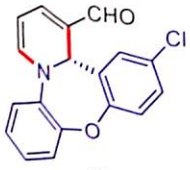
46b
80% (er 95:5)



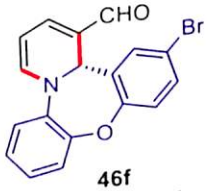
46c
78% (er >99:1)



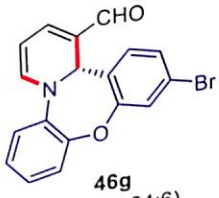
46d
83% (er >99:1)



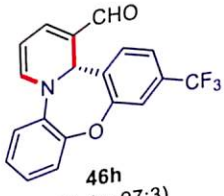
46e
92% (er >99:1)



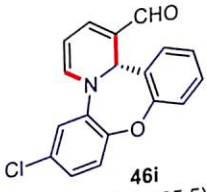
46f
83% (er 99:1)



46g
85% (er 94:6)

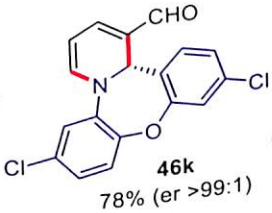


46h
80% (er 97:3)



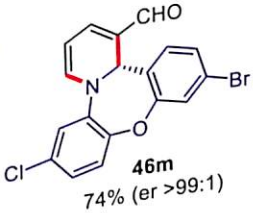
46i
78% (er 95:5)

46j
76% (er 97:3)

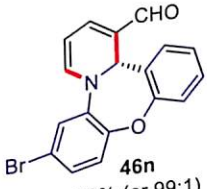


46k
78% (er >99:1)

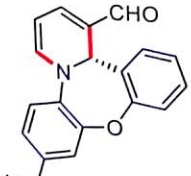
46l
83% (er 98:2)



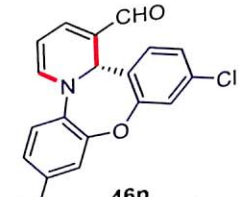
46m
74% (er >99:1)



46n
68% (er 99:1)

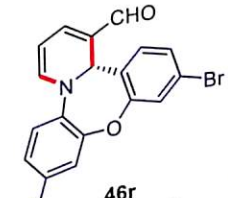


46o
85% (er 98:2)

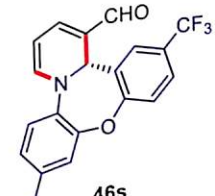


46p
87% (er 95:5)

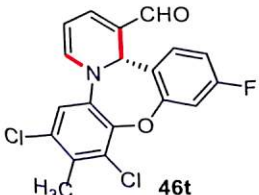
46q
85% (er 95:5)



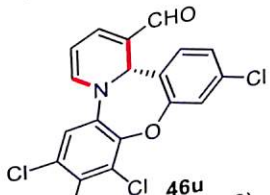
46r
86% (er 97:3)



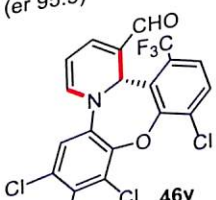
46s
81% (er 95:5)



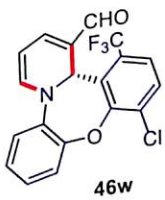
46t
72% (er >99:1)



46u
70% (er 97:3)

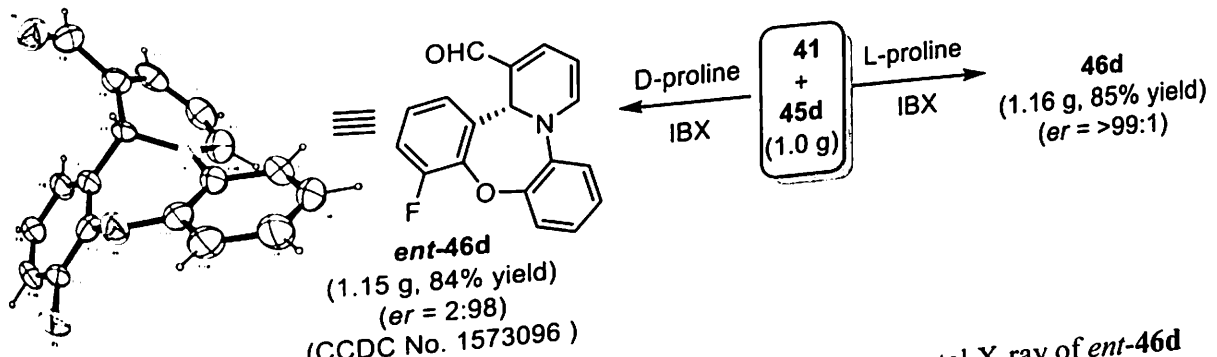


46v
n.r.



46w
n.r.

(a) Unless otherwise indicated, the reaction was carried out at (*i*) **45** (0.3 mmol), **41** (25% aqueous sol., 0.9 mmol), catalyst **44a** (20 mol%), DMSO (3.0 mL), 3 h; (*ii*) IBX (120 mol%), 40 °C, 3h. (b) Isolated yield of **46** refers to **45**.
(c) Determined using stationary chiral columns.



Scheme 5.17: Gram-scale synthetic of both enantiomers and single crystal X-ray of *ent*-**46d**

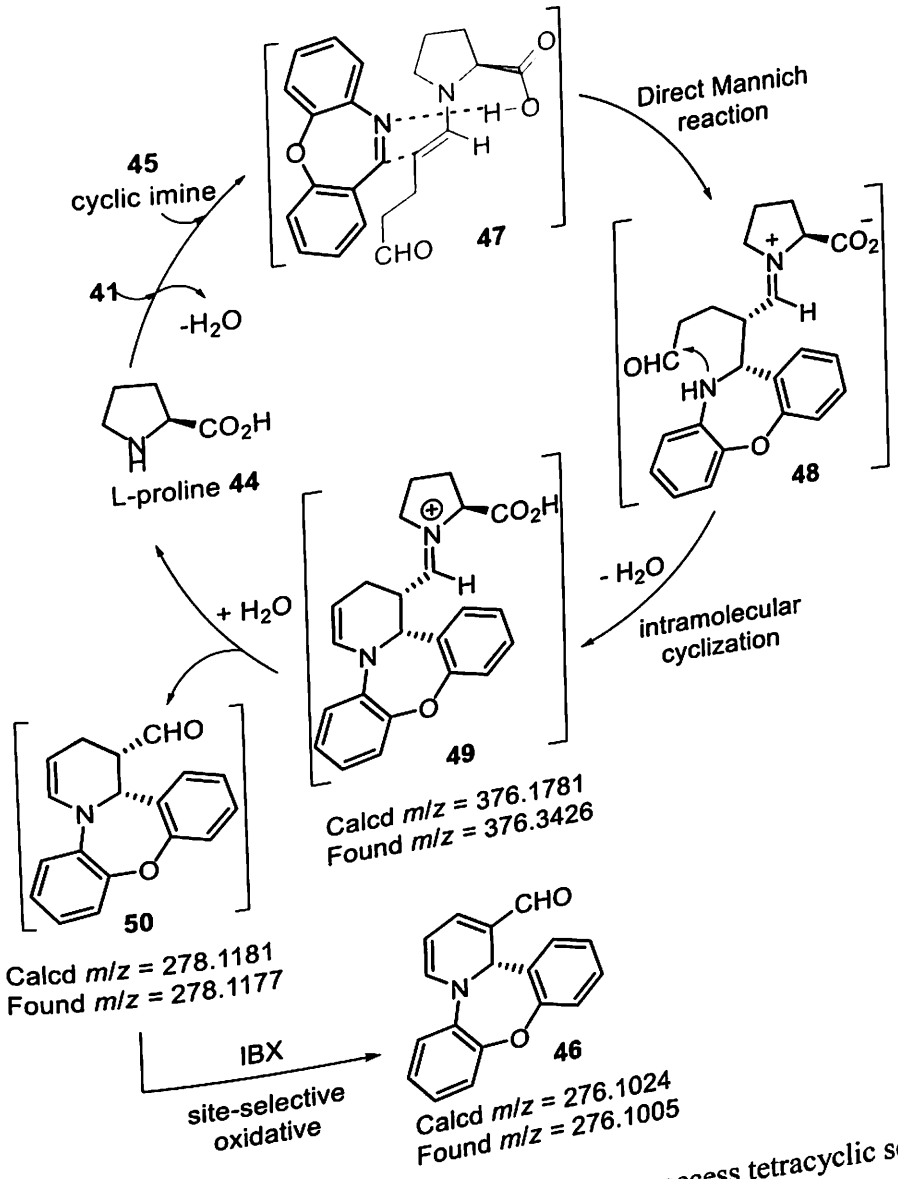
Thermal ellipsoids are drawn at the 40% probability level.

The practical use of this method was also demonstrated to access both enantiomers of fused 1,2-DHPs (**46d**/*ent*-**46d**) on a gram-scale without much variation in yield and selectivity by altering the catalysts **44a**/*ent*-**44a** under the standardized conditions (Scheme 5.17). The single-crystal X-ray analysis of *ent*-**46d** confirm the stereochemical outcome at C2 with D-proline (Scheme 5.17), and absolute configuration of other products with L-proline as the catalyst was tentatively assigned by analogy and based on previous reports on the proline-catalyzed Mannich reaction on cyclic-imines.[75-77] Similarly, all the new compounds were well characterized by ^{1}H and ^{13}C-NMR and Mass-analysis.

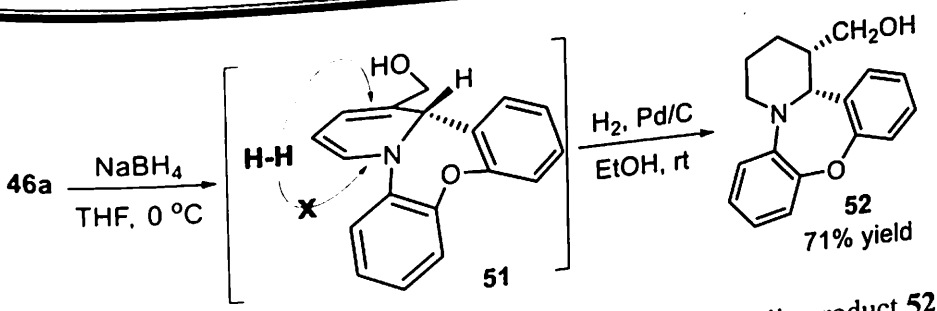
Based on our study and literature examples on proline-catalyzedMannich reaction, a stepwise detailed mechanism has been proposed by predicting the intermediate structures and their confirmation through *in situ* HRMS. As shown in Scheme 5.18, the enamine-intermediate *47 in situ* generated from glutaraldehyde **41** and catalyst **44**, reacts with seven-membered imine **45** via a direct Mannich reaction model **47** to give *anti*-Mannich intermediate **48**. This intermediate **48** underwent intramolecular cyclization with the removal of H_2O to intermediate **49**, which was in situ confirmed by HRMS (m/z= 376.3426 M + H^+). The subsequent release of catalyst **44** from tetracyclic enamine-intermediate **49** to **50**, which was also in situ confirmed by HRMS (m/z = 278.1177, M + H^+). In the same pot, the intermediate **50** underwent IBX-mediated site-selective oxidation to afford desired 1,4-dibenzoxazepine-fused 1,2-DHPs **46** in high yield and selectivity. It is noteworthy to mentions that the presence of a –CHO group, an electron-withdrawing substituent, at 1,2-DHPs skeleton provides additional stabilization to DHPs and resulted in a suitable Ramachary's *push-pull* dienamine[78-79] precursor. Easy availability of starting materials

and metal-free access to both enantiomers of tetracyclic fused 1,2-DHPs **46** makes this approach quite appealing.

Next, the synthetic application was established through the rapid synthesis of oxazepine-fused piperidine **52** (71% yields) in a two-step process from compound **46a** via $NaBH_4$-reduction followed by diastereoselective hydrogenation of crude alcohol **51** with H_2/Pd-C (Scheme 5.19), as similar saturated piperidines scaffolds are present in many biologically active synthetic and natural products.[80-82]



Scheme 5.18: Detailed proposed reaction mechanism to access tetracyclic scaffolds



Scheme 5.19: Synthetic transformations of **46a** to polycyclic product **52**

5.6 Conclusion

In summary, we have developed a simple and straightforward method for the asymmetric synthesis of dibenzoxazepine fused 1,2-dihydropyridines (DHPs) **46** through direct Mannich/cyclization and IBX-mediated dehydrogenative-oxidation sequence between several 1,4-oxazepines **45** and aqueous glutaraldehyde **41**. This metal-free process was successful with a variety of substituted dibenzo[*b*,*f*][1,4]oxazepines and smoothly converted to the desired products with high yield and excellent enantioselectivity. A detailed mechanism was proposed for this protocol and supported by the HRMS data of *in situ* intermediate structures. The resulting tetracyclic fused 1,2-DHPs **46** provide a suitable alternation to stoichiometric push-pull dienamines. The advantage of this protocol was shown through (i) gram-scale access to both enantiomers of tetracyclic 1,2-DHPs **46**, and (ii) rapid conversion to piperidine-fused alkaloid scaffold. Additional investigations of this strategy to other relevant heterocyclic systems are currently ongoing in our laboratory and will be presented later.

5.7 General Experimental Methods

Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100–200 mesh) using a mixture of hexane/EtOAc. Chemical yields refer to pure isolate substances. ^{1}H, ^{13}C-NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a BRUKER-AV400 (100MHz) spectrometer with complete proton decoupling. High-resolution mass spectra were recorded using the quadrupole

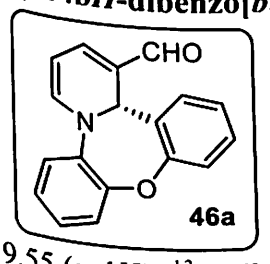
electrospray ionization (ESI) technique. Melting points were determined by EZ–Melt, Automated Melting Point Apparatus, and Specific rotation was measured through RUDOLPH Polarimeter. Enantiomeric ratio (er) was determined on Water- 2998-instrument with CHIRALPAK-IA columns using hexane/2-propanol.

5.8 Typical procedure for the enantioselective synthesis of 1,2-Dihydropyridine-fused dibenzo[*b,f*][1,4]oxazepines 46:

To a stirred solution of dibenzo[*b,f*][1,4]oxazepines **45** (0.3 mmol) in DMSO (3.0 mL) was added glutaraldehyde **41** (25% in water, 0.274 mL, 0.9 mmol) and L-Proline **44** (6.8 mg, 0.06 mmol) at 10 °C. The reaction mixture was further stirred at the same temperature until the dibenzo[*b,f*][1,4]oxazepines **45** was consumed as monitored by TLC. IBX (1.2 equiv, 0.35 mmol) was added to the same flask and further stirred at 40 °C for 3 hrs. The reaction was quenched with saturated $NaHCO_3$ (20% sol., 6.0 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine once and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification was performed by a silica-gel column and eluted with EtOAc/hexane to yield tetracyclic oxazepine-fused 1,2-DHPs **46**. The enantiomeric ratios (er) of the products were determined by stationary chiral phase HPLC analysis.

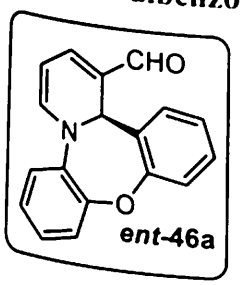
5.9 Analytical data of (46a-46u)

(*S*)-14b*H*-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46a): yellow solid, (72 mg, 88% yield, M.P = 180-182 °C), $[\alpha]_D^{25} = -106.6$ (*c* 0.3, CH_2Cl_2, er = 92:8); ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (t, *J* = 6.5 Hz, 1H), 6.65 (s, 1H), 6.67 (s, 1H), 6.94 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.98 –7.05 (m, 2H), 7.08 (td, *J* = 1.3 Hz, 7.3 Hz, 1H), 7.14 – 7.25 (m, 3H), 7.28 (d, *J* = 3.6 Hz, 2H), 9.55 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.1, 98.5, 118.9, 120.9, 121.7, 122.2, 123.1, 124.0, 126.0, 126.6, 129.2, 132.0, 133.8, 139.9, 144.3, 150.1, 156.4, 188.3. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{13}NO_2$ 276.1024, Found 276.1005. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 10.03 min, major enantiomer t_R = 11.93 min.



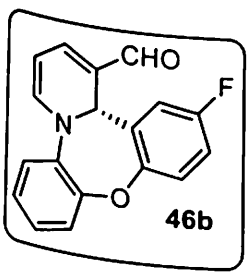
46a

(*R*)-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (*ent*-46a): yellowish solid, (70 mg, 85% yield, M.P = 180-182 °C), $[\alpha]_D^{25}$ = +104.2 (*c* 0.3, CH_2Cl_2, er = 9:91); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 9.35 min, minor enantiomer t_R = 11.79 min.



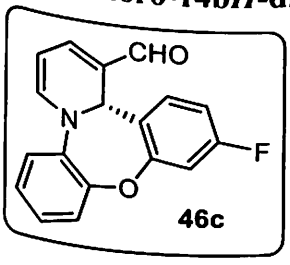
ent-46a

(*S*)-13-fluoro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46b): Red solid, (70 mg, 80% yield, M.P = 175-178 °C), $[\alpha]_D^{25}$ = –120.3 (*c* 0.2, CH_2Cl_2, er = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.39 Hz, 1H), 6.62 (s, 1H), 6.67 (d, *J* = 6.9 Hz, 1H), 6.73 (dd, *J* = 8.4 Hz, 3.1 Hz, 1H), 6.93 (ddd, *J* = 8.4 Hz, 5.9 Hz, 3.2 Hz, 2H), 7.00 – 7.05 (m, 1H), 7.14 – 7.20 (m, 2H), 7.24 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.28 (d, *J* = 5.9 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.7, 98.7, 113.1, 115.5, 118.7, 121.7, 122.2, 122.4, 123.3, 126.7, 133.7, 140.0, 144.2, 149.9, 152.1, 157.9, 160.3, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{12}FNO_2$ 294.0930, Found 294.0922. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 9.02 min, major enantiomer t_R = 7.95 min.



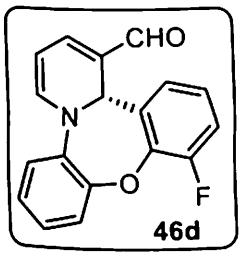
46b

(*S*)-12-fluoro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46c):Red solid, (69 mg, 78% yield, M.P = 200-202 °C), $[\alpha]_D^{25}$ = –120 (*c* 0.24, CH_2Cl_2, er = >99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (t, *J* = 6.5 Hz, 1H), 6.56 (s, 1H), 6.65 (d, *J* = 6.9 Hz, 1H), 6.78 (td, *J* = 2.5, 8.3 Hz, 1H), 6.91 – 6.95 (m, 2H), 6.96 – 6.99 (m, 1H), 7.00 – 7.05 (m, 1H), 7.13 – 7.19 (m, 1H), 7.23 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.24 (s, 1H), 9.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.6, 98.5, 108.9, 110.5, 118.7, 121.6, 122.3, 123.4, 126.7, 127.1, 128.1, 133.5, 139.7, 144.2, 149.7, 157.2, 162.6, 188.1. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{12}FNO_2$ 294.0930, Found 294.0928. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 10.02 min, minor enantiomer t_R = 11.59 min.



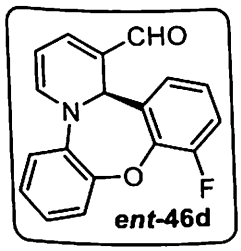
46c

(*S*)-11-fluoro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46d): Red solid, (73 mg, 83% yield, M.P = 174-176 °C), $[\alpha]_D^{25} = -124$ (*c* 0.2, CH_2Cl_2, er = >99:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, *J* = 6.35 Hz, 1H), 6.66 (d, *J* = 6.9 Hz, 1H), 6.70 (s, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.94 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 – 7.04 (m, 1H), 7.04–7.08 (m, 2H), 7.15–7.21 (m, 1H), 7.24 – 7.27 (m, 1H), 7.34 (dd, *J* = 1.4, 8.2 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.0, 98.8, 116.3, 116.5, 119.0, 120.9, 121.9, 122.2, 123.7, 124.3, 126.8, 133.8, 134.97, 139.9, 144.1, 149.6, 154.6, 188.2. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{12}FNO_2$ 294.0930, Found 294.0933. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 8.00 min, minor enantiomer t_R = 9.14 min.



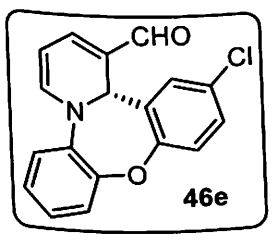
46d

(*R*)-11-fluoro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (*ent*-46d): Red solid, (70 mg, 80% yield, M.P = 174-176 °C), $[\alpha]_D^{25} = +123$ (*c* 0.2, CH_2Cl_2, er = 2:98); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 7.95 min, major enantiomer t_R = 8.65 min.



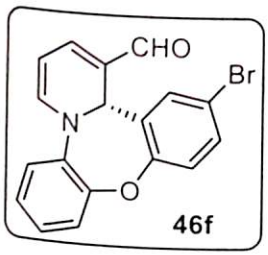
ent-46d

(*S*)-13-chloro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46e): Red oily liquid ,(85 mg, 92% yield), $[\alpha]_D^{25} = -97.6$ (*c* 0.3, CH_2Cl_2,er = 99:1);^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.5 Hz, 1H), 6.59 (s, 1H), 6.66 (d, *J* = 6.9 Hz, 1H), 6.93 (dd, *J* = 2.0, 9.8 Hz, 2H), 7.00 – 7.05 (m, 1H), 7.13 – 7.15 (m, 1H), 7.17 (dd, *J* = 1.6, 7.1 Hz, 1H), 7.22 (ddd, *J* = 2.0, 6.4, 8.6 Hz, 2H), 7.26 – 7.29 (m, 1H), 9.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.7, 98.7, 118.3, 121.6, 122.3, 122.4, 123.3, 126.2, 126.7, 129.1, 129.3, 133.5, 133.7, 139.8, 144.3, 149.7, 154.8, 188.1. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{12}ClNO_2$ 310.0635, Found 310.0637. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 7.61 min, major enantiomer t_R = 8.19 min.



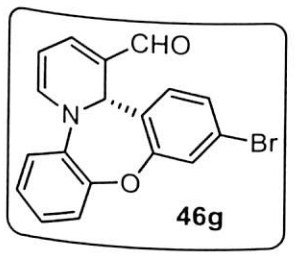
46e

(*S*)-13-bromo-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46f): Orange solid, (96 mg, 83% yield, M.P = 180-182 °C), $[\alpha]_D^{25} = -113$ (*c* 0.1, CH_2Cl_2, er = 99:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.6 Hz, 1H), 6.59 (s, 1H), 6.66 (d, *J* = 6.9 Hz, 1H), 6.93 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.00 – 7.05 (m, 1H), 7.06 – 7.08 (m, 1H), 7.10 (s, 1H), 7.13 – 7.19 (m, 1H), 7.23 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.28 (d, *J* = 6.3 Hz, 1H), 7.36 (dd, *J* = 2.5, 8.5 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.8, 98.8, 117.0, 118.3, 121.6, 122.38, 122.88, 123.4, 126.8, 129.1, 132.2, 133.5, 134.1, 139.8, 144.3, 149.7, 155.5, 188.2. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{12}BrNO_2$ 354.0129, Found 354.0130. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 7.64 min, major enantiomer t_R = 9.61 min.



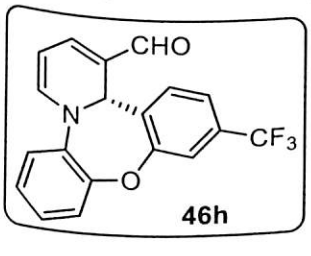
46f

(*S*)-12-bromo-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46g): Orange solid, (99 mg, 85% yield, M.P = 184-186 °C), $[\alpha]_D^{25} = -126.6$ (*c* 0.2, CH_2Cl_2, er = 94:6); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, *J* = 6.67 Hz 1H), 6.56 (s, 1H), 6.66 (d, *J* = 6.9 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.94 (dd, *J* = 1.5, 8., Hz, 1H), 7.00 – 7.06 (m, 1H), 7.18 (ddd, *J* = 1.7, 5.8, 9.8 Hz, 2H), 7.22 (d, *J* = 1.7 Hz, 1H), 7.23 – 7.26 (m, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.8, 98.6, 118.6, 121.6, 122.10, 122.43, 123.5, 124.4, 126.8, 127.0, 127.4, 131.1, 133.6, 139.9, 144.2, 149.8, 156.9, 188.2. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{12}BrNO_2$ 354.0129, Found 354.0133. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 11.67 min, minor enantiomer t_R = 12.58 min.



46g

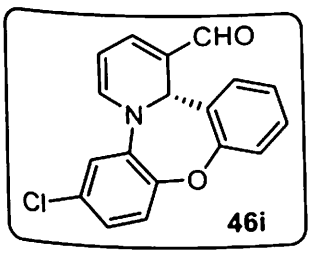
(*S*)-12-(trifluoromethyl)-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46h): Red solid, (64 mg, 80% yield, M.P = 160-162 °C), $[\alpha]_D^{25} = -140.3$ (*c* 0.1, CH_2Cl_2, er = 97:3); ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (t, *J* = 6.5 Hz , 1H), 6.64 (s, 1H), 6.68 (d, *J* = 6.9 Hz, 1H), 6.96 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.05 (td, *J* = 1.5, 7.6 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.17 – 7.23 (m, 1H), 7.29 (dd, *J* = 3.8, 7.1 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.9, 98.8, 118.5, 120.7, 120.8, 121.7, 122.4, 123.6, 126.8, 127.0, 131.47, 131.80, 133.6, 135.5, 139.9, 144.2, 149.7, 156.5, 188.1. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{19}H_{12}F_3NO_2$ 344.0898, Found 344.0906. Enantiomeric excess was



46h

determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 6.87 min, minor enantiomer t_R = 7.61 min.

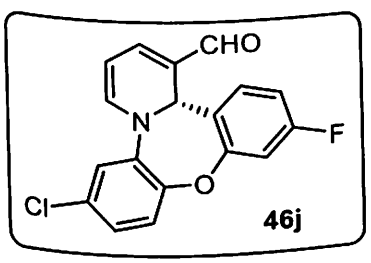
(*S*)-7-chloro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46i): Orange



46i

pasty liquid, (72 mg, 78% yield), $[\alpha]_D^{25}$ = –102 (*c* 0.1, CH_2Cl_2, er = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.39 Hz, 1H), 6.59 (d, *J* = 7.0 Hz, 1H), 6.62 (s, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 7.6 Hz, 1.6 Hz,1H), 7.10 (dd, *J* = 2.1 Hz, 6.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 1.2 Hz, 1H), 7.25 (s, 1H), 9.55 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.7, 99.3, 119.9, 120.9, 121.9, 122.9, 124.3, 126.0, 126.2, 128.04, 129.4, 132.0, 134.6, 139.1, 144.0, 148.6, 156.2, 188.3. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{12}ClNO_2$ 310.0635, Found 310.0639. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 6.05 min, major enantiomer t_R = 6.64 min.

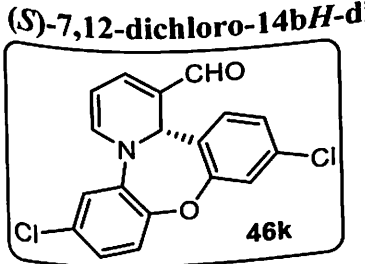
(*S*)-7-chloro-12-fluoro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46j):



46j

Orange solid, (75 mg, 76% yield, M.P = 180-183 °C), $[\alpha]_D^{25}$ = –92.3 (*c* 0.2, CH_2Cl_2, er = 97:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (t, *J* = 6.39 Hz, 1H), 6.54 (s, 1H), 6.60 (d, *J* = 7.0 Hz, 1H), 6.79 (td, *J* = 2.5, 8.3 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 2H), 6.95 – 6.98 (m, 1H), 7.11 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.25 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 99.3, 109.1, 110.9, 119.8, 122.4, 126.4, 127.16, 127.26, 128.0, 128.4, 134.4, 139.0, 143.9, 148.3, 157.0, 162.7, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}ClFNO_2$ 328.0540, Found 328.0546. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 6.034 min, major enantiomer t_R = 6.63 min.

(*S*)-7,12-dichloro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46k):

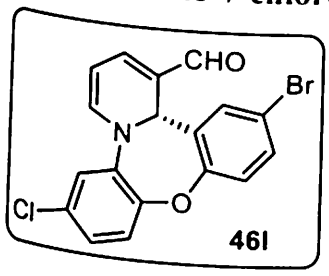


46k

Reddish oily liquid, (79 mg, 78% yield), $[\alpha]_D^{25}$ = –82.6 (*c* 0.1, CH_2Cl_2, er = >99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (t, *J* = 6.31 Hz, 1H), 6.54 (s, 1H), 6.60 (d, *J* = 7.0 Hz, 1H), 6.91 – 6.93 (m, 2H), 7.06 – 7.10 (m, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.15 (s, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.25 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 99.4, 119.7, 121.6, 122.0, 122.8, 124.40, 126.5, 127.1, 128.5, 130.5, 134.4, 134.6, 139.0, 143.9, 148.3, 156.6, 188.2. HRMS (ESI-

TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}Cl_2NO_2$ 344.0245, Found 344.0238. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 11.86 min, minor enantiomer t_R = 12.96 min.

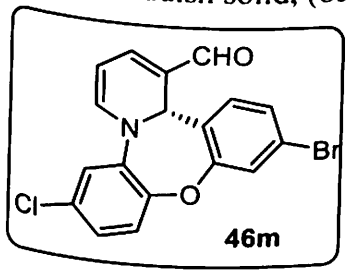
(*S*)-13-bromo-7-chloro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46l):



46l

Reddish solid, (95 mg, 83% yield, M.P = 175-177 °C), $[\alpha]_D^{25}$ = –76.4 (*c* 0.2, CH_2Cl_2, er = 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (t, *J* = 6.31 Hz, 1H), 6.56 (s, 1H), 6.60 (d, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 7.05 – 7.07 (m, 1H), 7.11 (dd, *J* = 9.3 Hz, 3.0 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 5.9 Hz, 1H), 7.38 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.4, 99.6, 117.3, 119.4, 122.03, 122.85, 122.8, 126.4, 128.4, 129.1, 132.4, 134.03, 134.44, 139.0, 144.0, 148.3, 155.3, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}BrClNO_2$ 387.9740, Found 387.9736. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 7.98 min, major enantiomer t_R = 8.66 min.

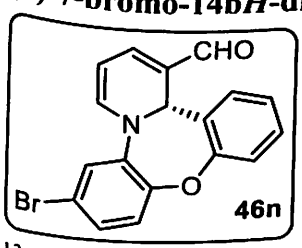
(*S*)-12-bromo-7-chloro-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46m): Reddish solid, (85 mg, 74% yield, M.P = 180-182 °C), $[\alpha]_D^{25}$ = –79 (*c* 0.2, CH_2Cl_2, er = > 99:1);^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (t, *J* = 6.31 Hz, 1H), 6.53 (s, 1H), 6.59 (d, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 7.11 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.14 – 7.17 (m,1H), 7.22 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.25 (s, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.4, 99.4, 119.6, 122.06, 122.29, 122.8, 124.4, 126.5, 127.35, 127.42, 128.5, 131.0, 134.4, 139.1, 143.9, 148.3, 156.6, 188.2.



46m

HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}BrClNO_2$ 387.9740, Found 387.9744. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 12.25 min, minor enantiomer t_R = 13.14 min.

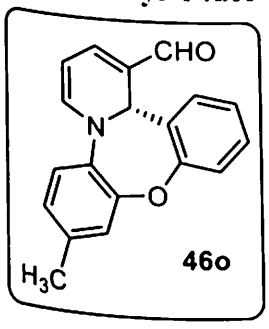
(*S*)-7-bromo-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46n): Orange solid, (79 mg, 68% yield, M.P = 173-175 °C), $[\alpha]_D^{25}$ = –128 (*c* 0.1, CH_2Cl_2, er = 99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.6 Hz, 1H), 6.58 (s, 1H), 6.60 (d, *J* = 1.3 Hz, 1H), 7.00 – 7.03 (m, 1H), 7.09 (m, 3H), 7.13 (s, 1H), 7.20 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.22 – 7.25 (m, 2H), 9.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 99.3, 115.2, 119.9, 120.9, 123.2, 124.34, 124.84, 126.0,



46n

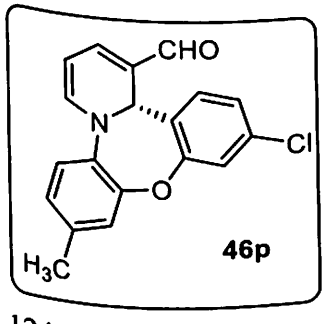
129.2, 129.4, 131.9, 135.0, 139.1, 144.0, 149.2, 156.1, 188.3. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{12}BrNO_2$ 354.0129, Found 354.0135. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 10.26 min, minor enantiomer t_R = 12.91 min.

(*S*)-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46o): Reddish solid, (74 mg, 85% yield, M.P = 183-185 °C), $[\alpha]_D^{25}$ = –93.3 (*c* 0.15, CH_2Cl_2, er = 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 5.24 (t, *J* = 6.5 Hz, 1H), 6.59 (s, 1H), 6.61 (d, *J* = 6.9 Hz, 1H), 6.80 (s, 2H), 7.01 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.04 – 7.09 (m, 2H), 7.18 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.21 – 7.25 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 53.2, 98.0, 118.3, 120.9, 121.9, 122.0, 123.7, 123.9, 126.0, 129.1, 131.2, 132.0, 136.9, 140.1, 144.3, 149.7, 156.3, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{19}H_{15}NO_2$ 290.1181, Found 290.1187. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 7.95 min, major enantiomer t_R = 8.65 min.



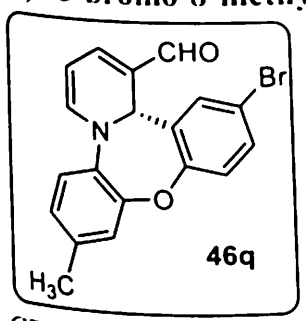
46o

(*S*)-12-chloro-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46p): Dark red solid, (84 mg, 87% yield, M.P = 180-182 °C), $[\alpha]_D^{25}$ = –96 (*c* 0.25, CH_2Cl_2, er = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.27 (t, *J* = 6.6 Hz, 1H), 6.53 (s, 1H), 6.63 (d, *J* = 6.8 Hz, 1H), 6.82 (s, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.04 (dd, *J* = 6.7 Hz, 3.2 Hz, 2H), 7.22 (d, *J* = 1.9 Hz, 1H), 7.24 (d, *J* = 6.3 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6, 52.9, 98.1, 118.0, 121.5, 121.8, 122.1, 123.9, 124.1, 127.1, 130.6, 131.1, 134.2, 137.2, 140.0, 144.2, 149.4, 156.7, 188.1. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{19}H_{14}ClNO_2$ 324.0791, Found 324.0795. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 5.83 min, major enantiomer t_R = 6.26 min.



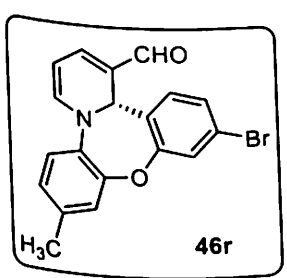
46p

(*S*)-13-bromo-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde



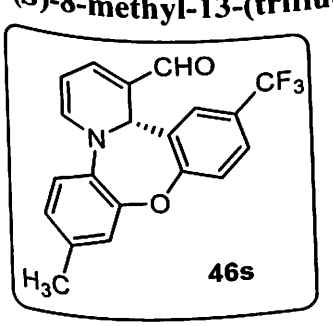
(46q): Dark red solid, (93 mg, 85% yield, M.P = 182-184 °C), $[\alpha]_D^{25} = -106.6$ (*c* 0.12, CH_2Cl_2, er = 95:5); ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.31 (t, *J* = 6.6 Hz, 1H), 6.55 (s, 1H), 6.65 (d, *J* = 6.9 Hz, 1H), 6.82 (d, *J* = 1.0 Hz, 2H), 7.04 – 7.06 (m, 2H), 7.08 (s, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 7.36 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 52.9, 98.4, 116.9, 117.8, 121.9, 122.1, 122.8, 124.0, 129.1, 131.1, 132.1, 134.0, 137.2, 140.0, 144.4, 149.4, 155.4, 188.2. HRMS (ESI-TOF) *m/z*: $[M + H^+]$ Calcd for $C_{19}H_{14}BrNO_2$ 368.0286, Found 368.0275. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 10.45 min, major enantiomer t_R = 11.98 min.

(*S*)-12-bromo-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde



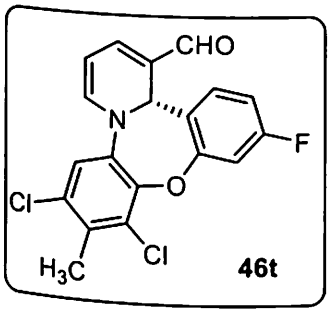
(46r): Dark solid, (94 mg, 86% yield, M.P = 181-182 °C), $[\alpha]_D^{25} = -96$ (*c* 0.2, CH_2Cl_2, er = 97:3); ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.27 (t, *J* = 6.6 Hz, 1H), 6.52 (s, 1H), 6.64 (d, *J* = 6.8 Hz, 1H), 6.82 (s, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 7.04 (s, 1H), 7.20 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6, 52.9, 98.2, 118.0, 121.9, 122.02, 122.08, 122.1, 124.1, 124.4, 126.9, 127.5, 131.1, 137.3, 140.1, 144.3, 149.4, 156.8, 188.1. HRMS (ESI-TOF) *m/z*: $[M + H^+]$ Calcd for $C_{19}H_{14}BrNO_2$ 368.0286, Found 368.0277. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 10.98 min, minor enantiomer t_R = 12.79 min.

(*S*)-8-methyl-13-(trifluoromethyl)-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46s): Dark red solid, (87 mg, 81% yield, M.P = 185-187 °C), $[\alpha]_D^{25} = -127.8$ (*c* 0.28, CH_2Cl_2, er = 95:5); ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 5.32 (t, *J* = 6.6 Hz, 1H), 6.56 (s, 1H), 6.67 (d, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 1.0 Hz, 2H), 7.09 (s, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 6.3 Hz, 1H), 7.53 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 53.0, 98.4, 117.6, 121.6, 121.9, 122.3, 124.2, 125.8, 126.1, 126.6, 126.6, 131.1, 132.5, 137.4, 140.0, 144.4, 149.3, 159.1, 188.2. HRMS (ESI-TOF) *m/z*: $[M + H^+]$ Calcd for $C_{20}H_{14}F_3NO_2$ 358.1055,



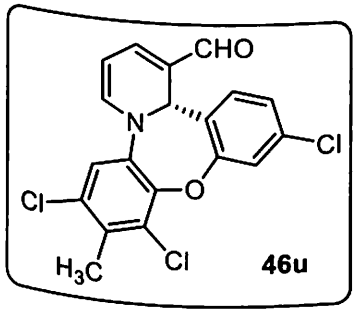
Found 358.1051. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 5.78 min, major enantiomer t_R = 6.16 min.

(*S*)-7,9-dichloro-12-fluoro-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46t):



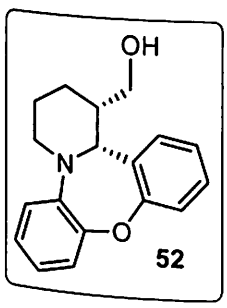
Orange solid, (82 mg, 72% yield, M.P = 176-178 °C), $[\alpha]_D^{25}$ = –67 (*c* 0.3, CH_2Cl_2, er = >99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 5.35 (t, *J* = 6.6 Hz, 1H), 6.54 (s, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.78 – 6.85 (m, 1H), 6.90 (s, 1H), 6.95 (dd, *J* = 8.3 Hz, 6.5 Hz, 1H), 7.06 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.24 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 52.1, 99.6, 109.6, 109.9, 111.3, 111.5, 120.06 120.2, 126.9, 127.0, 128.6, 133.0, 133.06, 139.0, 143.8, 144.5, 156.7, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{19}H_{12}Cl_2FNO_2$ 376.0307, Found 376.0295. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 5.82 min, minor enantiomer t_R = 6.40 min.

(*S*)-7,9,12-trichloro-8-methyl-14b*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde (46u):



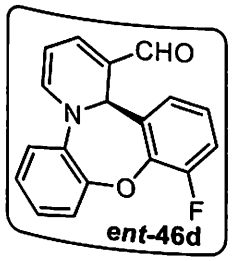
Orange viscous liquid, (82 mg, 70% yield), $[\alpha]_D^{25}$ = –99 (*c* 0.2, CH_2Cl_2, er = 97:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 5.35 (t, *J* = 6.33 Hz, 1H), 6.52 – 6.58 (m, 2H), 6.89 (s, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.10 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 7.24 (s, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 52.2, 99.7, 119.8, 119.9, 120.2, 122.2, 124.8, 126.9, 128.6, 130.7, 133.03, 133.07, 134.6, 139.1, 143.8, 156.3, 160.0, 188.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{19}H_{12}Cl_3NO_2$ 392.0012, Found 392.0019. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 9.18 min, minor enantiomer t_R = 10.03 min.

5.10 General procedure for the synthesis of ((1S,14bR)-1,3,4,14b-tetrahydro-2H-dibenzo[*b,f*]pyrido[1,2-d][1,4]oxazepin-1-yl)methanol (52): To a stirred solution of 45a (55 mg, 0.2 mmol) dried THF (4.0 mL) was added $NaBH_4$ (1.0equiv) at 5 °C. The combined solution was further stirred for 2 hr at rt and concentrated underreduced pressure. The crude mass was taken in dry EtOH (5 mL) and Pd/C (10 wt %) (10 mol%) was added, purged with H_2. The combined solution was additionally stirred under H_2 atmosphere (1 atm) at room temperature for 4.0 hrs. Mixture was filtered through celite andwashed with ethanol. Solvent was evaporated under vacuo and resulting residue was purifiedby column chromatography to afforded single diastereomer **52** (40 mg, 71% yield) as light blueoily liquid. $[\alpha]_D^{25} = -95.8$ (c 0.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.72 (m, 1H), 1.90 (dd, *J* = 10.4 Hz, 4.5 Hz, 2H), 2.20 (dd, *J* = 14.6 Hz, 6.9 Hz, 2H), 3.10 (td, *J* = 11.7 Hz, 3.1 Hz, 1H), 3.51 (d, *J* = 10.2 Hz, 1H), 3.69 (dd, *J* = 11.3 Hz, 2.9 Hz, 1H), 3.87 (dd, *J* = 11.3Hz, 6.2 Hz, 1H), 4.22 (s, 1H), 6.87 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.04–7.00 (m, 2H), 7.09–7.03(m, 2H), 7.11 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 7.19–7.14 (m, 1H), 7.24 (d, *J* = 7.7 Hz, 1H); ^{13}CNMR (101 MHz, CDCl3) δ 22.6, 28.7, 30.2, 52.3, 45.1, 63.4, 119.4, 120.2, 120.6, 122.2, 124.4,124.7, 125.5, 128.3, 129.6, 131.4, 143.7, 157.3; HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{18}H_{19}NO_2$ 282.1494, Found 282.1487.



52

5.11 Crystal structure of *ent*-46d (*R*)-11-fluoro-14b*H*-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1-carbaldehyde(*ent*-46d) (CCDC NO. – 1573096)



ent-46d

The title compound (R)-11-fluoro-14b*H*-dibenzo[*b,f*]pyrido[1,2-*d*][1,4]oxazepine-1 carbaldehyde (*ent*-**46d**),$C_{18}H_{12}FNO_2$, crystallizes in the Orthorhombic space group $P2_12_12_1$ with unit cell parameters: a = 4.9570(8), b = 14.3567(19), c = 19.4567 (3) Å, and Z= 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.1259 for 1031 observed reflections.

Crystal Structure Determination and Refinement

X-ray intensity data of 2249 reflections (of which 1172 unique) were collected at 293(2) K *X'calibur system–Oxford diffraction make, U.K.* equipped with graphite monochromated MoKαradiation (λ=0.71073 Å). The crystal used for data collection was of dimensions 0.3 x 0.2 x 0.1 mm. The intensities were measured byωscan mode forθ ranges 4.155 to 26.966°. 1031 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for absorption, Extinction and

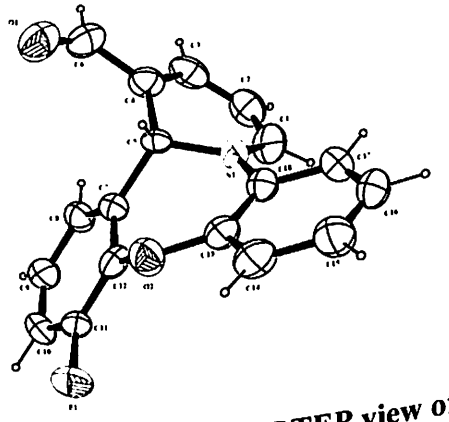
Lorentz and polarisation factors. The structure was solved by direct methods using SHELXS97. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97. All the hydrogen atoms were geometrically fixed and allowed to ride on their parent carbon atoms with C-H= 0.93-0.97 Å.The final refinement cycles converged to an R = 0.1259 and wR(F^2) = 0.2524 for the observed data. Residual electron densities ranged from - 0.347 to 0.274 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in **Table 4.3**. The crystallographic data are summarized in

Table 4.3. CCDC – 1573096.

Table 5.3 Crystal and experimental data for ***ent*-46d**

CCDC No.	**1573096**
Crystal description	block
Crystal colour	transparent
Crystal size	0.30 x 0.20 x 0.10 mm
Empirical formula	C_{18} H_{12} F N O_2
Formula weight	293.29
Radiation, Wavelength	Mo *Kα*, 0.71073 Å
Unit cell dimensions	a=4.9570(8), b=14.3567(19), c=19.457(3)Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell volume	1384.7(4)
No. of molecules per unit cell, Z	4
Temperature	293(2)
Absorption coefficient	0.101 mm^{-1}
F(000)	608
Scan mode	ω scan
θ range for entire data collection	4.15<θ< 26.97 º
Range of indices	h= -5 to 5, k= -14 to 17, l= -23 to 14
Reflections collected / unique	3625 / 2249
Absorption correction	Multi-scan Crys Alis RED
Reflections observed (I > 2σ(I))	1031

R_{int}	0.1170
R_{sigma}	0.1885
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	199
No. of Restraints	0
Final R	0.1259
$wR(F^2)$	0.2524
Weight	$1/[\sigma^2(F_o^2)+(0.0376\ P)^2+0.0000P]$ where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	1.049
$(\Delta/\sigma)_{max}$	0.00
Final residual electron density	$-0.347 < \Delta\rho < 0.274\ eÅ^{-3}$
Measurement	*X'calibur system – Oxford diffraction make, U.K.*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 2012) PLATON (Spek, 2009)



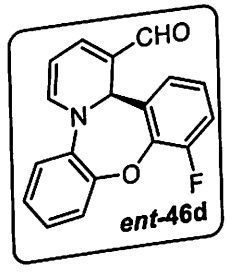


Figure 5.3 Showing ORTEP view of the molecule (CCDC NO. 1573096)

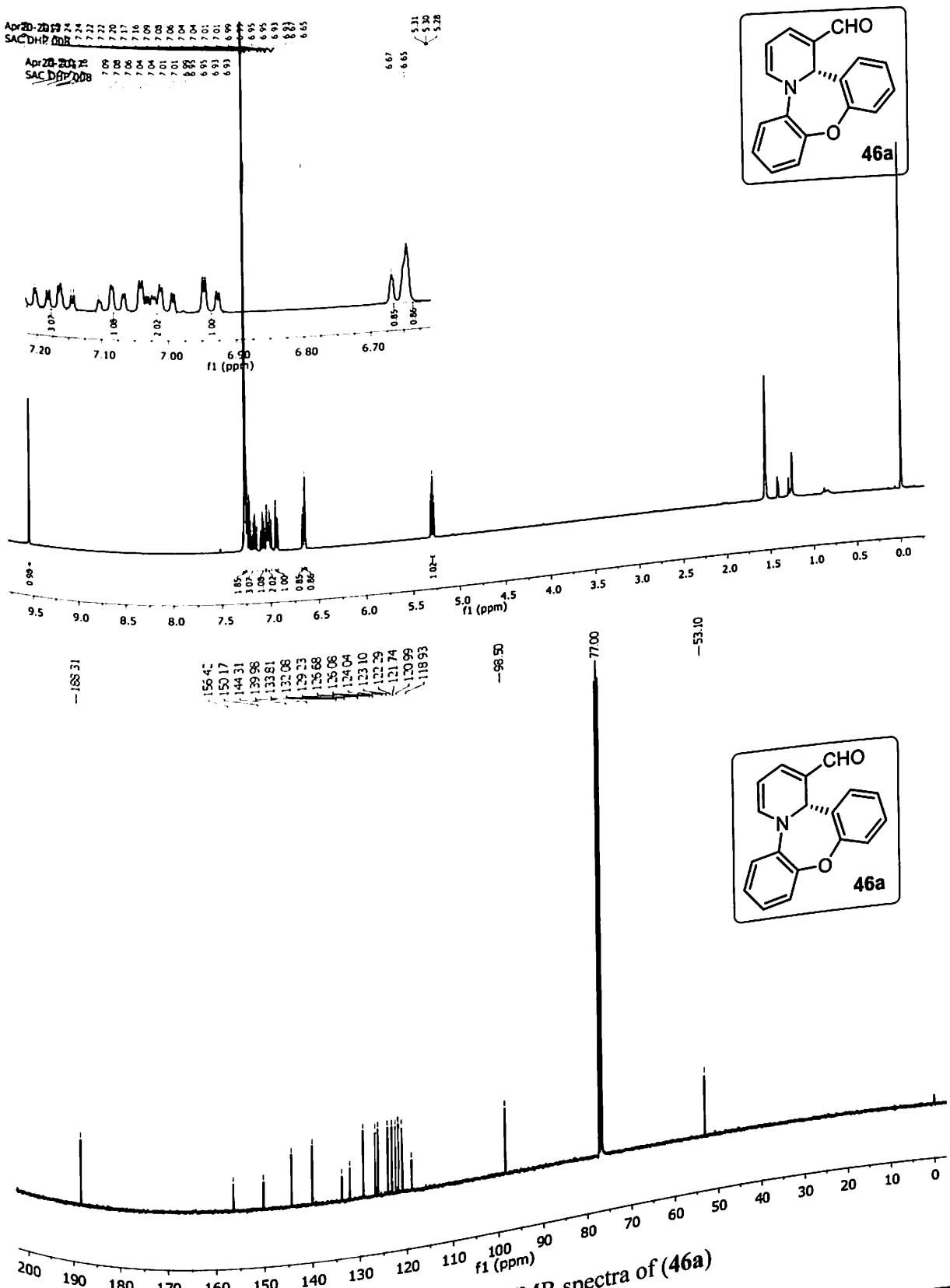
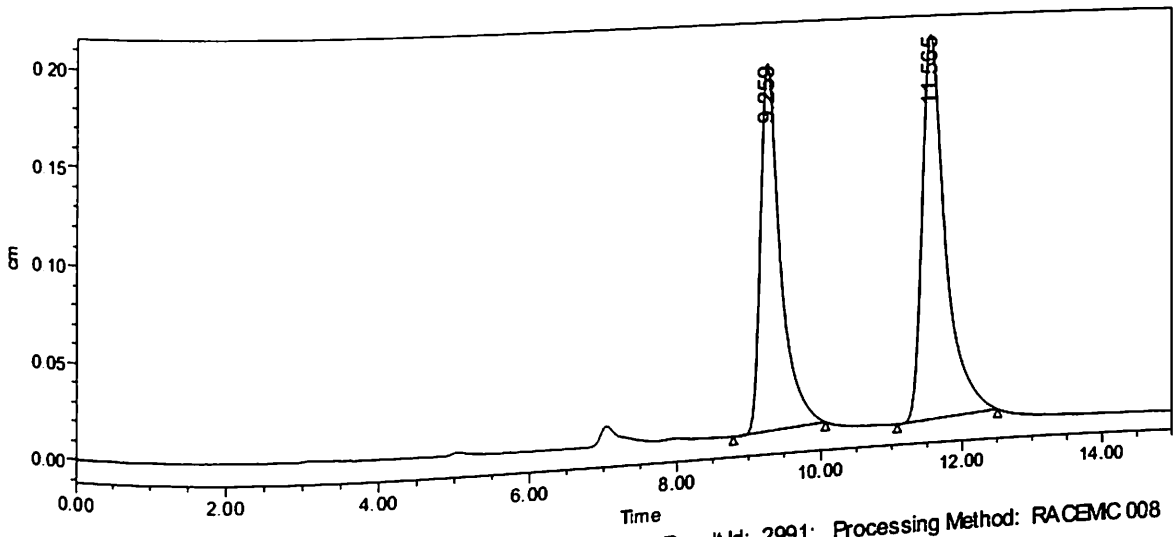


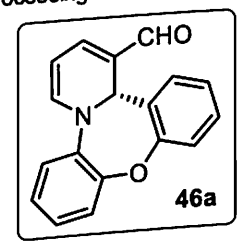
Figure 5.4 ^{1}H and ^{13}C NMR spectra of (**46a**)



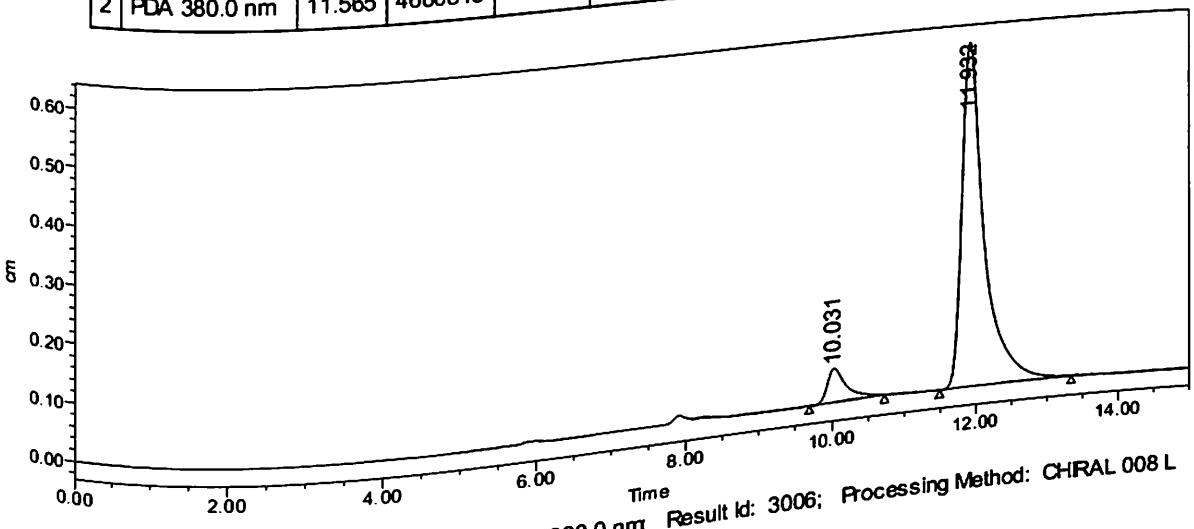
Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 2991; Processing Method: RACEMIC 008

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	9.259	3743465	44.44	193017
2	PDA 380.0 nm	11.565	4680815	55.56	204001



46a

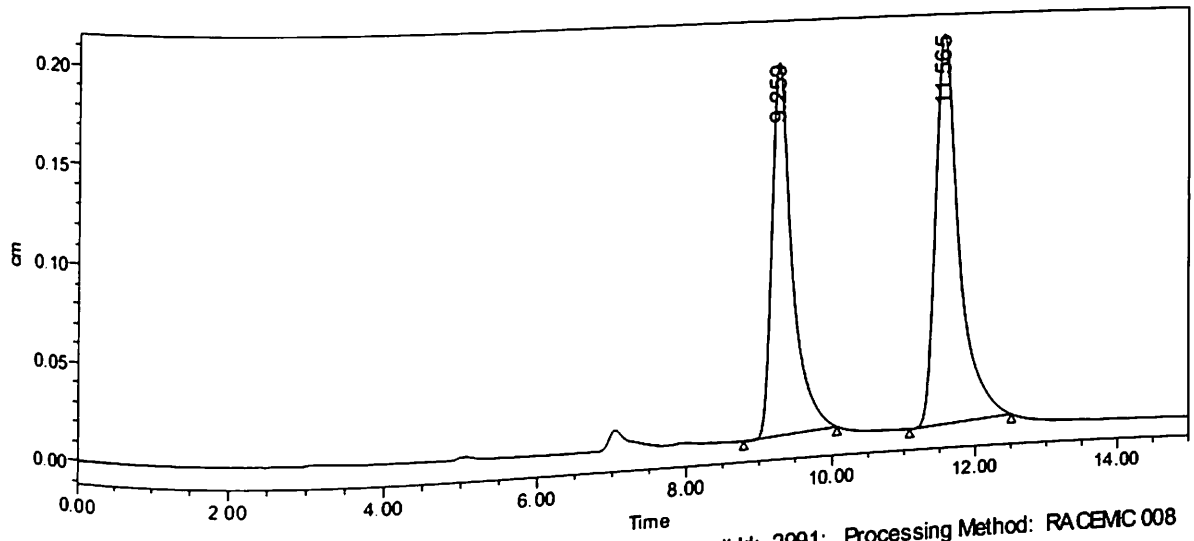


Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 3006; Processing Method: CHIRAL 008 L PROLINE

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	10.031	1069485	7.53	59010
2	PDA 380.0 nm	11.932	13125464	92.47	608931

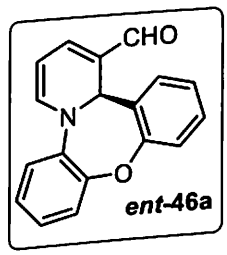
Figure 5.5 HPLC chromatogram of **46a**



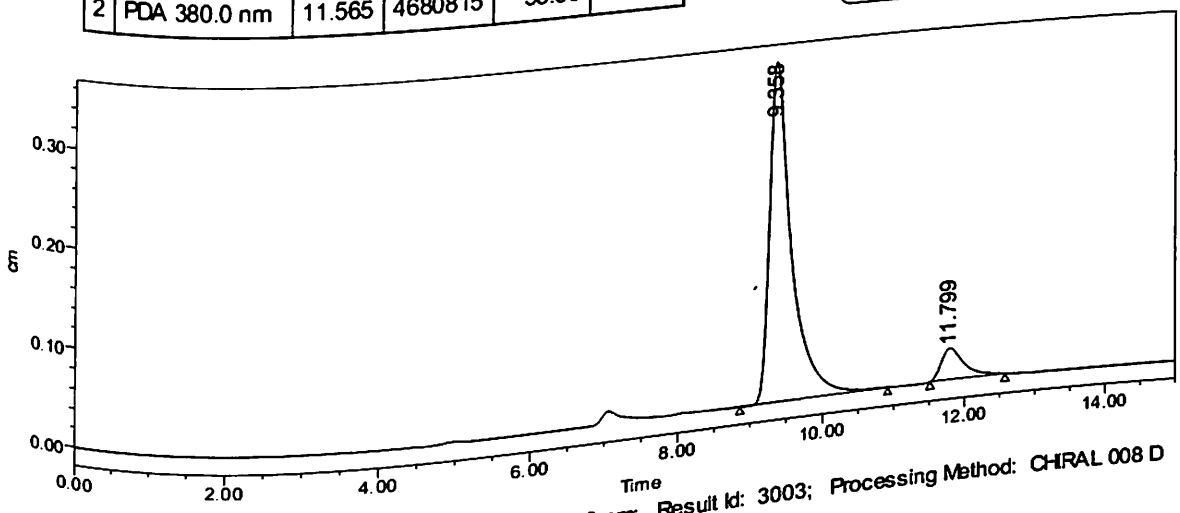
Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 2991; Processing Method: RACEMIC 008

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	9.259	3743465	44.44	193017
2	PDA 380.0 nm	11.565	4680815	55.56	204001



***ent*-46a**

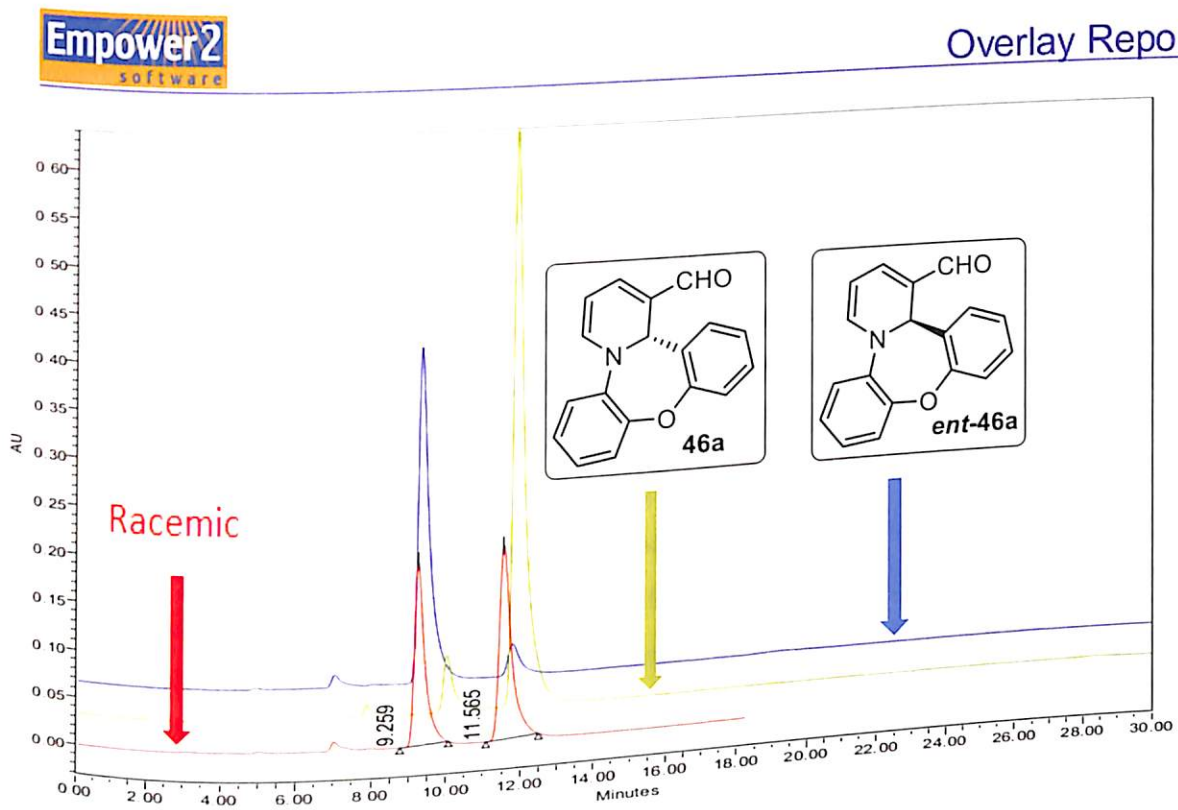


Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 3003; Processing Method: CHIRAL 008 D PROLINE

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	9.358	7399375	91.08	350497
2	PDA 380.0 nm	11.799	724301	8.92	32124

Figure 5.6 HPLC chromatogram of *ent*-**46a**



D-Proline was used as catalyst

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	9.358	7399375	91.08	350497
2	PDA 380.0 nm	11.799	724301	8.92	32124

L-Proline was used as catalyst

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	10.031	1069485	7.53	59010
2	PDA 380.0 nm	11.932	13125464	92.47	608931

Racemic

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	9.259	3743465	44.44	193017
2	PDA 380.0 nm	11.565	4680815	55.56	204001

Figure 5.7 HPLC chromatogram of **46a** and *ent*-**46a**

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