A stereoselective aza-Prins reaction: rapid access to enantiopure piperidines and pipecolic acids

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ABSTRACT: The aza-Prins reaction is a widely employed and highly efficient method for the preparation of saturated nitrogen-containing heterocycles. Its major drawback has always been a lack of diastereoselectivity and the formation of racemic products. Herein we address these problems and report, for the first time, the synthesis of both diastereomerically and enantiopure multiply-substituted piperidines via the aza-Prins reaction. This method will be widely applicable for natural product synthesis and is exemplified here by the synthesis of enantiopure pipecolic acid derivatives.

INTRODUCTION

Nitrogen heterocycles are amongst the most important structural component in both natural products and modern pharmaceuticals.[1] For example, 2,6-disubstituted and 2,4,6-trisubstituted piperidines are found widely in alkaloids. Analysis of all F.D.A. approved drugs show that 59% of small molecule drugs contain a nitrogen heterocycle and that 72 drugs contain a piperidine moiety, making it the most prevalent nitrogen heterocycle in approved drugs (Figure 1a).[1] The two most common substitution patterns are *N*- and C(4)-, followed by C(2)- and C(3) (Figure 1b). The vast majority of these drugs require careful stereocontrol of the substitutents around the ring during manufacture. Methods for their synthesis have been widely reviewed[2-5] but the greatest problem has always been the asymmetric construction of the piperidine ring. Furthermore, there is an emerging need for sp^3-rich heterocyclic frameworks, again with both relative and absolute stereocontrol of the substituents.

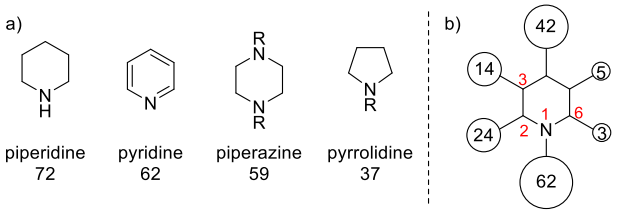
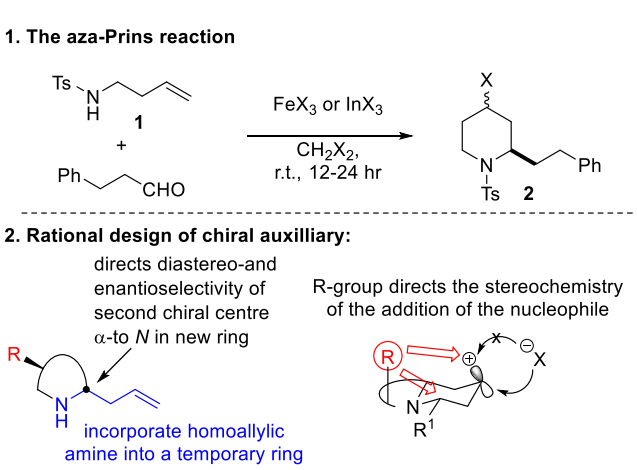


FIGURE 1: a) most abundant nitrogen heterocycles within FDA approved drugs and their occurrence; b) most popular positions of piperidine substitution.[1]

Since it was first reported by Hanschke in 1955, the Prins cyclisation has become one of the leading methods for the preparation of tetrahydropyran rings.[6] For many years this remained a highly diastereoselective but racemic reaction. A limited number of asymmetric cyclisation processes to give enantiopure tetrahydropyrans have been reported, either commencing from enantiopure starting materials[7-9] or employing an asymmetric catalyst approach.[10-13] More recently, the aza-Prins[14-21] (and related aza-silyl-Prins[22-25]) cyclisation – the reaction of a homoallylic amine and aldehyde (or acetal or epoxide) promoted by a Lewis or Brønsted acid (Scheme 1) – has emerged as a highly efficient method for the diastereoselective synthesis of substituted piperidines, albeit in racemic form. While methods for the asymmetric synthesis of heterocycles via chiral iminium ion cyclisations have been extensively reviewed[26], there are only isolated examples of attempts at simple asymmetric aza-Prins reactions and there remains no general catalytic and asymmetric aza-Prins cyclisation reaction and interest in developing enantioselective aza-Prins processes is high and very challenging. Recently we have reported a related asymmetric aza-silyl-Prins reaction[27] and Maruoka has described an aza-Prins *endo*-type cyclisation of 2-(1-phenylvinyl)benzaldehyde and $BocNH_2$ catalysed by a BINOL-derived *N*-triflyl phosphoramide to form 1-aminoindenes.[28]



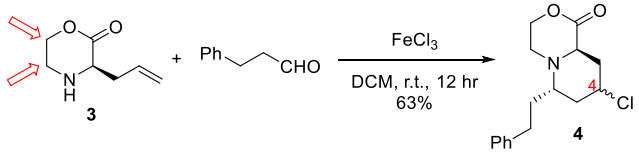
SCHEME 1: 1. The aza-Prins reactions, giving a diastereomeric mixture through non-selective trapping at c-4. 2. Rationale in designing a chiral auxiliary to direct C-4 trapping.

Herein we report for the first time a highly novel, efficient and high yielding diastereo- and enantioselective aza-Prins reaction, offering the ability to access enantiopure multi-substituted sp^3-rich piperidines.

RESULTS AND DISCUSSION

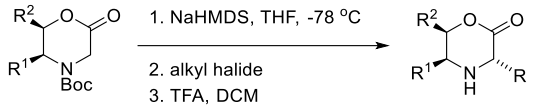
In designing an asymmetric aza-Prins reaction, we were conscious that one of the considerable drawbacks of the aza-Prins cyclisation has been the necessity for an *N*-sulfonamide[14-15] group (Ts, Ns, Bs) in the homoallylic amine component (**1**); groups such as *N*-benzyl or *N*-Boc do not undergo aza-Prins cyclisation.[17, 20, 29] Further, we have recently reported that chiral auxiliaries on nitrogen, for example α-methylbenzyl, in place of the tosyl group, were inefficient for promoting asymmetric aza-silyl-Prins-type reactions.[27] Therefore we have instead focused on developing a novel, easy to prepare and use chiral-auxilliary-containing a homoallylic amine. We have previously shown that the aza-Prins and aza-silyl-Prins reactions are 2,6-*trans* selective across the nitrogen[17, 23, 27, 30-31] and reasoned that this *trans* relationship would be maintained when employing a chiral centre adjacent to nitrogen in the homoallylic amine starting material and thus generating a new chiral centre across the nitrogen after cyclisation.

In order to test this hypothesis, starting from (*R*)-allyl glycine, it was possible to prepare (*R*)-allylmorpholin-2-one (**3**) in a single step. Attempting the aza-Prins reaction using FeCl3 and phenyl propionaldehyde afforded the corresponding piperidine (**4**, Scheme 2) in 63% yield, with the expected exclusive *trans*-relationship of substituents across the nitrogen, but surprisingly with little selectivity at the C-4 position compared with employing (**1**). We reasoned that the introduction of either one or two substituents on the two bridging carbons in (**3**) may improve the C-4 selectivity of the aza-Prins reaction.



SCHEME 2: 2,6-*trans* selective aza-Prins reaction starting from (*R*)-allylmorpholin-2-one generates an equal mixture of adducts at C-4.

Therefore we prepared mono- (**8**)[32] and di-phenyl (**7**)[33-34] allylmorpholin-2-ones in both enantiomeric forms in just 4 steps, as two new chiral platforms containing a homoallylic amine. Following the rationale presented in Scheme 1(2), the phenyl substituents were chosen as these would both facilitate rapid removal of part of the chiral platform post Prins cyclisation and crucially block one face from anion trapping. Treatment of either (**7**) or (**8**) with NaHMDS and an allyl or propargylic bromide gave a small library of enantiomerically pure secondary amines (Table 1).



5 R^1, R^2 = Ph
6 R^1 = Ph, R^2 = H
7 R^1, R^2 = Ph
8 R^1 = Ph, R^2 = H

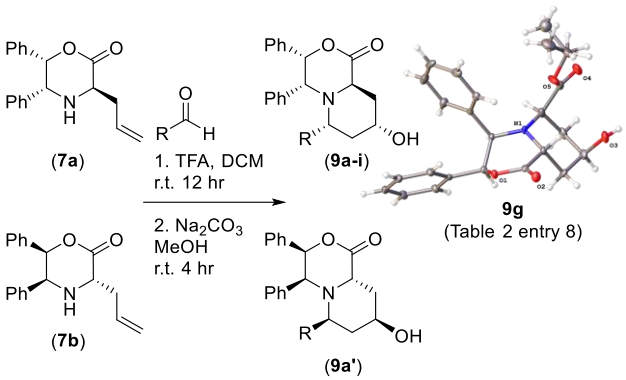
Table 1: Synthesis of chiral homoallylic amines

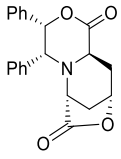
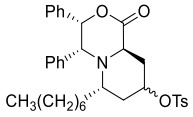
Entry	**R^1**	**R^2**	**Alkyl halide**	**R**	**Product**	**% Yield[a]**
1.	Ph	Ph	Allyl bromide	CH_2CHCH_2	7	81
2.	Ph	H	Allyl bromide	CH_2CHCH_2	8a	85
3.	Ph	H	Propargyl bromide	CH_2CCH	8b	85
4.	Ph	H	Crotyl bromide	$CH_2CHCH(CH_3)$	8c	86
5.	Ph	H	3-Bromo-2-methylprop-1-ene	$CH_2C(CH_3)CH_2$	8d	90
6.	Ph	H	1-Bromo-3-methyl-but-2-ene	$CH_2CHC(CH_3)_2$	8e	80

a) isolated and purified yields. b) all products isolated as a single enantiomer and diastereoisomer.

We attempted aza-Prins reactions utilizing (**7a**) with a range of aldehydes using Brønsted and Lewis acids to promote the reaction. With TFA, the reaction of (**7a**) with butanal proceeded smoothly at room temperature to afford 76% of an enantiomerically pure single diastereoisomer (**9a**), with only traces of the opposite C-4 diastereomer being isolated and which could easily be separated by chromatography (Table 2 Entry 1). Starting from the opposite enantiomer (**7b**) gave the enantiomeric product (Table 2 Entry 2). The same result was observed with a number of other aldehydes, all proceeding in excellent yields and diastereoslectivities and giving the product as a single enantiomer in every case (Table 2, Entries 3-8). The structure of (**9g**) was confirmed by x-ray crystallography and also studied by 2D NMR and NOESY experiments. This data was used to confirm the structural assignments for all compounds (**9a-g**) as they gave almost identical 2D and NOESY spectra to the spectra obtained for (**9g**) where xray crystallography also confirmed the structure. The use of glyoxylic acid gave a tricyclic product, whereby the acid moiety had trapped the intermediate carbocation intramolecularly (Table 2 Entry 9). Replacing TFA with pTSA gave the -OTs trapped adduct but as an inseparable mixture of diastereoisomers (Table 2 Entry 10). Finally, acetals could be employed in place of aldehydes and also gave high yields of a single enantiomerically pure product (Table 2 Entry 11).

Table 2: Asymmetric aza-Prins reactions employing Brønsted acids

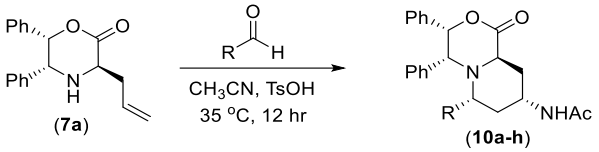


Entry	Starting Material	Aldehyde[a]	Product R =	% Yield[a,b]
1.	7a	Butanal	$CH_2CH_2CH_3$ (**9a**)	76
2.	7b	Butanal	$CH_2CH_2CH_3$ (**9a'**)	82
3.	7a	3-Phenylpropionaldehyde	CH_2CH_2Ph (**9b**)	81
4.	7a	Dodecanal	$CH_2(CH_2)_9CH_3$ (**9c**)	75
5.	7a	Decanal	$CH_2(CH_2)_7CH_3$ (**9d**)	73
6.	7a	Octanal	$CH_2(CH_2)_5CH_3$ (**9e**)	72
7.	7a	Diphenylacetaldehyde	$CHPh_2$ (**9f**)	78
8.	7a	Ethyl glyoxalate	CO_2Et (**9g**)	91[c]
9.	7a	Glyoxylic acid	 (**9h**)	60
10.	7a	Octanal	 (**9i**)	68[d] (65:35)
11.	7a	Butanal diethyl acetal	$CH_2CH_2CH_3$ (**9a**)	73

a) isolated and purified yields. b) all products isolated as a single enantiomer and diastereoisomer. c) structure confirmed by x-ray crystallography.[35] d) using TsOH instead of TFA, giving 65:35 inseperable mixture

In the absence of a suitable nucleophile, it is also known that solvents, such as acetonitrile or benzene, can trap the cyclic secondary carbocation, in an aza-Prins-Ritter or aza-Prins-Friedel-Crafts cascade.[21, 36] Using pTSA in acetonitrile gave good yields of the 4-NHAc trapped products (Table 3), again as a single enantiomer and diastereomer.

Table 3: Asymmetric aza-Prins-Ritter Reactions

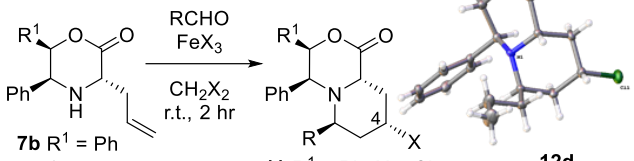


Entry	Starting Material	Aldehyde	Product	% Yield[a,b]
1.	7a	3-Phenylpropionaldehyde	**10a**	83
2.	7b	3-Phenylpropionaldehyde	**10a'**	76
3.	7a	Octanal	**10b**	73
4.	7a	Decanal	**10c**	78
5.	7a	Hexanal	**10d**	75
6.	7a	Butanal	**10e**	74
7.	7a	Butanal diethyl acetal	**10e**	65
8.	7a	Phenylacetaldehyde	**10f**	82
9.	7a	Styrene oxide	**10f**	63
10.	7a	Diphenylacetaldehyde	**10g**	78

a) isolated and purified yields. b) all products isolated as a single enantiomer and diastereoisomer.

In place of TFA or TsOH, the alternative is to use a Lewis acid to promote the aza-Prins cyclisation, with iron and indium trihalides being particularly prevalent in the literature. In these cases, the Lewis acid provides a nucleophile to trap the secondary carbocation. When initially trialing Lewis acids, a disappointing 62:38 ratio of diastereoisomers was obtained when starting from (**7b**) and iron trichloride (Table 4, Entry 1). Somewhat surprisingly, changing to the mono-phenyl amine (**8**) gave much improved results and a single diastereomer product in excellent yield. However, the configuration of the halogen is the opposite to that observed for the diphenyl starting materials (**7a**/**7a'**). Both iron trichloride and iron tribromide gave excellent yields of 4-halo products (**12a-d, 13a-b**), as long as the appropriate halide-containing solvent was employed, to avoid mixed-halogen products (Table 3). The structure of (**12d**) was confirmed by x-ray crystallography and also by 2D NMR and NOESY experiments. This combined knowledge was utilized to confirm the structural assignments for compounds (**11-16b**) as they gave almost identical 2D and NOESY spectra around the ring hydrogens to the spectra obtained for (**12d**) where x-ray crystallography had also confirmed the structure. The methodology was then extended to incorporate other nucleophiles into the mono-phenyl amine (**8**). Reaction of **8** with butanal in the presence of TFA (2 equiv.) surprisingly gave the hydroxy product (**14a**) in 88% yield (Table 4 entry 8). The same outcome was observed with other aldehydes (Table 4 entry 8), and an acetal (Table 4 entry 10). Replacing TFA with pTSA in DCM provided tosyl-substituted derivatives in excellent yields (**15a-b**, Table 4, entries 11-12). Finally, conducting the reaction in acetonitrile and optimized with boron trifluoride etherate, a sequential aza-Prins cyclisation-Ritter reaction was observed, giving single amine products in high yield and selectivity (**16a-b**, Table 4 entries 13-14) but with the opposite stereochemistry at C4 (*c.f.* **10a-h**).

Table 4: Asymmetric aza-Prins reactions employing Lewis acids



7b R^1 = Ph
8 R^1 = H

11 R^1 = Ph; X = Cl
12a-d R^1 = H; X = Cl
13a-b R^1 = H; X = Br
14a-b R^1 = H; X = OH
15a-b R^1 = H; X = OTs
16a-b R^1 = H; X = NHAc

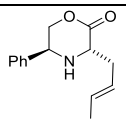
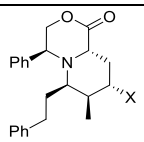
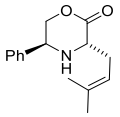
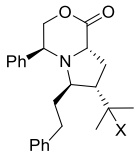
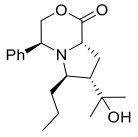
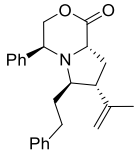
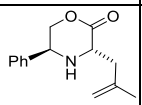
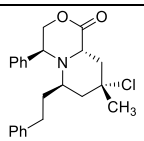
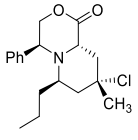
12d

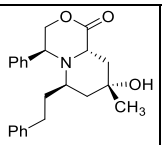
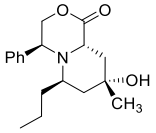
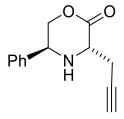
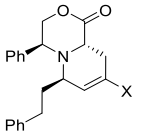
Entry	R^1	Aldehyde	X	Acid[a]	Product	% Yield[b,c]
1.	Ph	3-Phenylpropionaldehyde	Cl	$FeCl_3$	**11**	67 % (62:38)
2.	H	3-Phenylpropionaldehyde	Cl	$FeCl_3$	**12a**	90
3.	H	benzaldehyde	Cl	$FeCl_3$	**12b**	91
4.	H	Diphenylacetaldehyde	Cl	$FeCl_3$	**12c**	89
5.	H	Butanal	Cl	$FeCl_3$	**12d**	89[d]
6.	H	3-Phenylpropionaldehyde	Br	$FeBr_3$	**13a**	90
7.	H	Diphenylacetaldehyde	Br	$FeBr_3$	**13b**	80
8.	H	Butanal	OH	TFA	**14a**	88
9.	H	Dodecanal	OH	TFA	**14b**	90
10.	H	Butanal diethyl acetal	OH	TFA	**14a**	76
11.	H	Decanal	OTs	PTSA	**15a**	80
12.	H	Dodecanal	OTs	PTSA	**15b**	78
13.	H	Decanal	NHAc	$BF_3.OEt_2$	**16a**	75[e]
14.	H	Dodecanal	NHAc	$BF_3.OEt_2$	**16b**	72[e]

a) other halogen containing Lewis acids ($TiCl_4$, $SnCl_4$, $AlCl_3$) gave lower yields and decomposition of starting material; b) isolated and purified yields. c) all products isolated as a single enantiomer and diastereoisomer (except entry 1). d) structure confirmed by x-ray crystallography.[37] e) CH_3CN as solvent.

Substituted allyl and propargylic amines (Table 1) were the next to be employed in the cyclisation and furnished a range of substituted products (Table 5). Using (3*S*,5*S*)-3-((*E*)-But-2-enyl)-5-phenylmorpholin-2-one (8c, Table 5 entry 1) gave very high yields of the methyl-substituted product as a single diastereoisomer and enantiomer under either Lewis or Bronsted acid conditions. When using (3*S*,5*S*)-3-(3-Methyl-but-2-enyl)-5-phenylmorpholin-2-one (**8e**, Table 5 entries 2-4), the formation of a 5-membered ring was observed, presumably *via* the more stable tertiary carbocation, and irrespective of the aldehyde or acid employed.[17] (3*S*,5*S*)-3-(2-Methylallyl)-5-phenylmorpholin-2-one (**8d**, entries 5-8) gave a new single isomer quaternary chiral centre. Finally using (3*S*,5*S*)-5-Phenyl-3-(prop-2-ynyl) morpholin-2-one (**8b**, entry 9) gave a single vinyl halide-containing diastereoisomer and enantiomer where either Cl or Br could be incorporated into the product. The structures of (**17c**) and (**19b**) were additionally confirmed by x-ray crystallography in addition to the 2D NMR and NOESY experiments used to assign all the structures and stereochemistry in Table 5.

Table 5: Asymmetric aza-Prins reactions employing substituted alkenes or alkynes

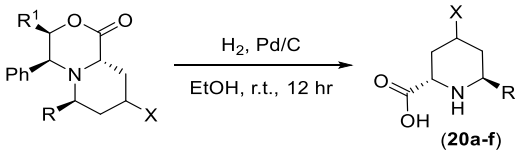
Entry	Amine	Aldehyde	Acid	Product	% Yield[a,b]
1.	 (**8c**)	3-Phenylpropionaldehyde	$FeCl_3$ $FeBr_3$ TFA	 (**17a-c**)	92 (Cl) 91 (Br) 83 (OH)[c]
2.	 (**8e**)	3-Phenylpropionaldehyde	$FeCl_3$ TFA	 (**18a, 18b**)	63 (Cl) 76 (OH)
3.		Butanal	TFA	 (**18c**)	72
4.		3-Phenylpropionaldehyde	Sc(OTf)$_3$	 (**18d**)	51
5.	 (**8d**)	3-Phenylpropionaldehyde	$FeCl_3$	 (**19a**)	76
6.		Butanal		 (**19b**)	72[c]

7.		3-Phenylpropionaldehyde	TFA	 (**19c**)	80
8.		Butanal		 (**19d**)	75
9.	 (**8b**)	3-Phenylpropionaldehyde	$FeCl_3$ $FeBr_3$	 (**20a, 20b**)	70 (Cl) 71 (Br)

a) isolated and purified yields. b) all products isolated as a single enantiomer and diastereoisomer. c) structure confirmed by x-ray crystallography.[38]

The morpholin-2-one has not been considered as a chiral auxillary since part of it remains in the final product; therefore it is seen as a highly efficient chiral platform for controlling the aza-Prins reaction. Partial removal of the chiral platform was easily achieved *via* catalytic hydrogenation, from both the mono- and di-phenyl substituted bicyclic compounds, to afford enantiopure pipecolic acid derivatives. All substituents at the C4-position tolerated these deprotection conditions except in vinyl halo compounds **20a** and **20b** where the halogen was lost along with the alkene during hydrogenation (Table 6 Entry 6). Use of acidified ethanol as the solvent furnished the ethyl ester product.

Table 6: Synthesis of substituted pipecolic acids *via* partial removal of the chiral platform



(**20a-f**)

Entry	R (Starting material)	R^1	X[a]	% Yield[b,c]
1.	$(CH_2)_2CH_3$ (**9a/9a'**)	Ph	OH	95/93[d] (**21a**)
2.	$(CH_2)_6CH_3$ (**9e**)	Ph	OH	92 (**21b**)
3.	$(CH_2)_2Ph$ (**10a/10a'**)	Ph	NHAc	91/89 (**21c/21c'**)
4.	$(CH_2)_2CH_3$ (**14a**)	H	OH	76 (**21d**)
5.	$(CH_2)_2Ph$ (**12a**)	H	Cl	68[e] (**21e**)
6.	$(CH_2)_2Ph$ (**20a/20b**)	H	H	51/57 (**21f**)

a) stereochemistry of X in starting material different depending on if the mono-phenyl or di-phenyl compound was used (Table 2 *c.f.* Table 4); stereochemical integrity of X from the starting material was maintained in all products. b) isolated and purified yields. c) all products isolated as a single enantiomer and diastereoisomer. d) reaction performed on both enantiomers of starting material (93%for (2*S*,4*S*,6*R*)-product and 95% for (2*R*,4*R*,6*S*)-product. e) product isolated as the ethyl ester, using acidified ethanol (EtOH-HCl)

CONCLUSIONS

In summary, we have reported a highly efficient asymmetric aza-Prins reaction, capable of furnishing enantiopure piperidines and pipecolic acid derivatives in excellent yields and as a single enantiomer and diastereomer. We believe that this method will be of great use in total synthesis and the development of novel 3D structures, exploring new chemical space and we shall report our findings in due course.

EXPERIMENTAL SECTION

General methods. All dry solvents were prepared/dried according to standard procedures. Reactions were performed in oven-dried round bottom flasks. The flasks were fitted with rubber septa and the reactions were conducted under nitrogen atmosphere. Reaction mixtures were purified by flash column chromatography on silica gel 100-200 mesh. TLC plates were visualized by exposure to ultraviolet light and/or by exposure to acidic ethanolic solution of ninhydrin followed by heating (<1 min) on a hot gun (~250 °C). Organic solutions were concentrated on rotary evaporator at 35–40 °C. ^{1}H NMR and ^{13}C NMR (proton-decoupled) spectra were recorded on 400 & 500 MHz NMR spectrometers in DMSO-D_6/MeOD/$CDCl_3$/D_2O as solvent as indicated. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). High Resolution Mass Spectrometry (HRMS) data were obtained by using a hybrid quadrupole-orthogonal acceleration time-of-flight system.

(*R*)-Methyl 2-(benzylamino)pent-4-enoate. To a stirred solution of (*R*)-methyl 2-aminopent-4-enoate (500 mg, 3.8 mmol, 1 equiv) and benzaldehyde (1.1 equiv) in MeOH (10 mL) was added $NaBH_3CN$ (2 equiv) at 0 °C and brought to rt. After 12 hrs, the reaction mixture was quenched with 1 mL of water and concentrated to remove methanol. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:5) to afford 800 mg (90%) as a colour less liquid. $[\alpha]_D^{26}$ = +32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 5.80-5.68 (m, 1 H), 5.17-5.04 (m, 2 H), 3.88-3.63 (m, 5 H), 3.37 (t, *J* = 6.4 Hz, 1 H), 2.42 (t, *J* = 8.4 Hz, 2 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.1, 139.7, 133.6, 129.1, 128.4, 128.3, 127.1, 118.0, 77.4, 77.0, 76.7, 60.3, 52.0, 51.7, 37.7 ppm; ν_{max}(neat)/cm^{-1}: 3453, 2950, 1583, 1455, 1321, 1123, 762, 591 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{13}H_{18}NO_2$: 220.1337; found: 220.1332.

(*R*)-Methyl 2-(4-methylphenylsulfonamido)pent-4-enoate. To a stirred solution of (*R*)-methyl 2-aminopent-4-enoate (500 mg, 3.8 mmol, 1 equiv) in DCM (10 mL) was added Et_3N (1 equiv) at 0 °C and TsCl was added followed. After 12 hrs, the reaction mixture was quenched with 1 mL of water. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:5) to afford 910 mg (83%) as a colour less liquid. $[\alpha]_D^{26}$ = -50.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68

(m, 2H), 7.28-7.24 (m, 2 H), 5.65-5.54 (m, 1 H), 5.25 (t, *J* = 9.2 Hz, 1 H), 5.09-5.02 (m, 2 H), 4.02-3.97 (m, 1 H), 3.49 (s, 3 H), 2.43 (t, *J* = 6.8 Hz, 1 H), 2.39 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 143.7, 136.9, 131.4, 129.9, 129.7, 127.5, 127.3, 127.0, 119.7, 55.3, 52.4, 37.6, 21.6 ppm; ν_{max}(neat)/cm^{-1}: 3466, 3013, 1596, 1421, 1335, 1067, 785, 585 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{13}H_{18}NO_4S$ 284.0956; found 284.0950.

(*R*)-3-Allylmorpholin-2-one (3): To a stirred solution of (*R*)-2-aminopent-4-enoic acid (500 mg, 3.8 mmol, 1 equiv) and dibromoethane (1.0 equiv) in CH_3CN (10 mL) was added K_2CO_3 (2 equiv) at 0 °C and brought to reflux. After 12 hrs, the reaction mixture was cooled to RT and concentrated to remove CH_3CN. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:1) to afford 92 mg (15%) as a semi solid. $[\alpha]_D^{26}$ = -126.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.91-5.78 (m, 1 H), 5.20-5.05 (m, 2 H), 4.51 (bs, 1 H), 4.45 (t, *J* = 6.0 Hz, 1 H), 3.52 (t, *J* = 6.4 Hz, 2 H), 2.66-2.54 (m, 1 H), 2.17 (dd, *J* = 0.8, 6.0 Hz, 2 H), 1.88 (t, *J* = 6.0 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 133.5, 118.2, 72.8, 64.1, 37.2, 28.6 ppm; ν_{max}(neat)/cm^{-1}: 3302, 3016, 2995, 1564, 1521, 1376, 1093, 785, 643 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_7H_{12}NO_2$ 142.0868; found 142.0869.

(3*R*,5*R*,6*S*)-3-allyl-5,6-diphenylmorpholin-2-one (7, Table 1, Entry 1). To a stirred solution of *tert*-butyl (2*S*,3*R*)-6-oxo-2,3-diphenylmorpholine-4-carboxylate[1] (300 mg, 0.849 mmol, 1 equiv) and allyl iodide (388 µL, 4.243 mmol, 5 equiv) in THF (5 mL) was added lithium bis(trimethylsilyl)amide (1019 µL, 1.019 mmol, 1.2 equiv, 1 M solution in THF) dropwise *via* syringe at -78 °C. After 40 min, the reaction mixture was quenched with sat. NH_4Cl solution. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 286 mg (85%) as a white solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture was removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture cooled to 0 °C and adjust pH (neutral) using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 199 mg (81% overall two steps) of **7** as a white solid. $[\alpha]_D^{26}$ = +260.0 (*c* 1.0, $CHCl_3$); M.pt. 118-120 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.15 (m, 6H), 7.00-6.95 (m, 2 H), 6.92-6.88 (m, 2 H), 5.88-5.80 (m, 1 H), 5.67 (d, *J* = 3.2 Hz, 1 H), 5.19-5.13 (m, 2 H), 4.73-4.63 (m, 1H), 4.08-4.01 (m, 1H), 2.84-2.69 (m, 2H), 2.00 (bs, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 137.0, 135.0, 133.9, 128.4, 128.2, 128.1, 127.7, 127.7, 127.2, 119.6, 85.2, 77.5, 77.1, 76.8, 56.8, 56.0, 37.9 ppm; ν_{max}(neat)/cm^{-1}: 3331, 2981, 1700, 1456, 1196, 1036, 703 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{19}H_{20}NO_2$ 294.1494; found 294.1491.

(3*S*,5*S*)-3-allyl-5-phenylmorpholin-2-one (8a, Table 1, Entry 2). To a stirred solution of (*S*)-*tert*-butyl 2-oxo-5-phenylmorpholine-4-carboxylate[2] (300 mg, 1.08 mmol, 1 equiv) in THF (5 mL) and DME (5 mL) was added sodium bis(trimethylsilyl) amide (594 µL, 1.19 mmol, 1.1 equiv, 2 M solution in THF) dropwise *via* syringe at -78 °C. After 20 min, neat allyl bromide (2.16 mmol, 2 equiv) was added drop wise. The reaction was quenched with sat. NH_4Cl after 1.5 h. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 305 mg (90%) as a white solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture was removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture was cooled to 0 °C and the pH adjusted to neutral using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 200 mg (85% overall two steps) of **8a** as a white solid. $[\alpha]_D^{26}$ = −7.6 (*c* 1.0, $CHCl_3$); M.pt. 64-66 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.31 (m, 5H), 5.88-5.80 (m, 1 H), 5.24-5.15 (m, 2 H), 4.44-4.28 (m, 3 H), 3.86 (dd, *J* = 3.6 Hz, 1 H), 2.72-2.62 (m, 2H), 1.97 (bs, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 133.6, 129.0, 126.9, 119.7, 77.3, 77.1, 76.8, 73.2, 54.7, 53.1, 36.4 ppm; ν_{max}(neat)/cm^{-1}: 3323, 2992, 1733, 1464, 1182, 1025, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{13}H_{16}NO_2$ 218.1176; found 218.1175.

(3*S*,5*S*)-5-Phenyl-3-(prop-2-ynyl) morpholin-2-one (8b, Table 1, Entry 3). To a stirred solution of (*S*)-*tert*-butyl 2-oxo-5-phenylmorpholine-4-carboxylate[2] (300 mg, 1.08 mmol, 1 equiv) in THF (5 mL) and DME (5 mL) was added sodium bis(trimethylsilyl) amide (594 µL, 1.19 mmol, 1.1 equiv, 2 M solution in THF) dropwise *via* syringe at -78 °C. After 20 min, 80% propargyl bromide (2.16 mmol, 2 equiv) in toluene was added drop wise. The reaction was quenched with sat. NH_4Cl after 1.5 h. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 315 mg as a semi solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture was removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture cooled to 0 °C and adjust pH (neutral) using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 210 mg (85% overall two steps) of **8b** as a white solid. $[\alpha]_D^{26}$ = +152.0 (*c* 1.0, $CHCl_3$); M.pt. 96-98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.30 (m, 5H), 4.49-4.28 (m, 3 H), 4.01-3.92 (m, 1 H), 2.91-2.78 (m, 2 H), 2.38 (bs, 1 H), 2.08 (s, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 138.1, 129.1, 128.6, 127.1, 77.4, 77.1, 76.8, 73.5, 72.1, 54.3, 53.1, 22.5 ppm; ν_{max}(neat)/cm^{-1}: 2970, 2890, 1603, 1456, 1314, 1225, 1039, 757, 646 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{13}H_{14}NO_2$ 216.1025; found 216.1029.

(3*S*,5*S*)-3-((*E*)-But-2-enyl)-5-phenylmorpholin-2-one (8c, Table 1, Entry 4). To a stirred solution of (*S*)-*tert*-butyl 2-oxo-5-phenylmorpholine-4-carboxylate[2] (300 mg, 1.08 mmol, 1 equiv) in THF (5 mL) and DME (5 mL) was added sodium bis(trimethylsilyl) amide (594 µL, 1.19 mmol, 1.1 equiv, 2 M solution in THF) dropwise *via* syringe at -78 °C. After 20 min, neat crotyl bromide (2.16 mmol, 2 equiv) was added drop wise. The reaction was quenched with sat. NH_4Cl after 1.5 h. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 315 mg as a white solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture *was* removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture cooled to 0 °C and adjust pH (neutral) using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 216 mg (86% overall two steps) of **8c** as a white solid. $[\alpha]_D^{26}$ = +82.0 (*c* 1.0,

$CHCl_3$); M.pt. 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.29 (m, 5H), 5.66-5.43 (m, 2 H), 4.41-4.23 (m, 3 H), 3.84-3.74 (m, 1 H), 2.63-2.53 (m, 2 H), 1.98 (bs, 1 H), 1.69-1.63 (m, 2 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.2, 138.6, 130.5, 128.9, 128.5, 127.1, 126.0, 77.5, 77.2, 76.8, 73.2, 55.1, 53.1, 35.2, 18.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1603, 1453, 1164, 912, 647 cm^{-1}; HRMS (ESI) *m/z*: [M]$^+$ calcd for $C_{14}H_{18}NO_2$ 232.1338; found 232.1337.

(3*S*,5*S*)-3-(2-Methylallyl)-5-phenylmorpholin-2-one (8d, Table 1, Entry 5). To a stirred solution of (*S*)-*tert*-butyl 2-oxo-5-phenylmorpholine-4-carboxylate[2] (300 mg, 1.08 mmol, 1 equiv) in THF (5 mL) and DME (5 mL) was added sodium bis(trimethylsi1yl) amide (594 µL, 1.19 mmol, 1.1 equiv, 2 M solution in THF) dropwise *via* syringe at -78 °C. After 20 min, neat 3-bromo-2-methylprop-1-ene (2.16 mmol, 2 equiv) was added drop wise. The reaction was quenched with sat. NH_4Cl after 1.5 h. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 315 mg as a white solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture was removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture cooled to 0 °C and adjust pH (neutral) using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 225 mg (90% overall two steps) of **8d** as a solid. $[\alpha]_D^{26} = -106.8$ (*c* 1.0, $CHCl_3$); M.pt. 92-94 °C; $[\alpha]_D^{25}$ −12.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.31 (m, 5H), 4.92-4.81 (m, 1 H), 4.80-4.75 (m, 1 H), 4.36-4.27 (m, 3 H), 3.97-3.94 (m, 1 H), 2.66-2.59 (m, 1 H), 1.99 (bs, 1 H), 1.75 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.1, 141.1, 138.1, 128.9, 128.6, 127.2, 115.2, 77.43, 77.1, 76.8, 73.9, 53.6, 52.4, 40.4, 21.6 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1648, 1455, 1216, 1039, 898, 596 cm^{-1}; HRMS (ESI) *m/z*: [M]$^+$ calcd for $C_{14}H_{18}NO_2$ 232.1338; found 232.1338.

(3*S*,5*S*)-3-(3-Methylbut-2-enyl)-5-phenylmorpholin-2-one (8e, Table 1, Entry 6). To a stirred solution of (*S*)-*tert*-butyl 2-oxo-5-phenylmorpholine-4-carboxylate[2] (300 mg, 1.08 mmol, 1 equiv) in THF (5 mL) and DME (5 mL) was added sodium bis(trimethylsilyl) amide (594 µL, 1.19 mmol, 1.1 equiv, 2 M solution in THF) dropwise *via* syringe at -78 °C. After 20 min, neat 1-bromo-3-methylbut-2-ene (2.16 mmol, 2 equiv) was added drop wise. The reaction was quenched with sat. NH_4Cl after 1.5 h. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford 315 mg as a white solid. The crude compound was diluted with DCM (10 mL) and added TFA (2 mL) at 0 °C. The reaction mixture was removed from ice bath and continued stirring at RT. After 4 hrs, the reaction mixture cooled to 0 °C and adjust pH (neutral) using triethylamine. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 212 mg (80% overall two steps) of **8e** as a solid. $[\alpha]_D^{26} = -263.2$ (*c* 1.0, $CHCl_3$); M.pt. 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.30 (m, 5H), 5.20-5.12 (m, 1 H), 4.92-4.81 (m, 1 H), 4.80-4.75 (m, 1 H), 4.36-4.27 (m, 3 H), 3.97-3.94 (m, 1 H), 3.83-3.77 (m, 1 H), 2.74-2.51 (m, 2 H), 1.91 (bs, 1 H), 1.71 (s, 3 H), 1.64 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.3, 138.5, 136.9, 128.9, 128.5, 127.1, 119.3, 77.4, 77.1, 76.8, 73.5, 55.8, 53.2, 30.8, 25.9, 18.1 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1746, 1387, 1174, 1050, 697, 607 cm^{-1}; HRMS (ESI) *m/z*: [M]$^+$ calcd for $C_{15}H_{20}NO_2$ 246.1494; found 246.1498.

General procedure A: the TFA mediated aza-Prins reaction: A round-bottomed flask was charged with aldehyde (0.5 eq.) and dichloromethane (10 mL). To the resulting suspension was added neat TFA (1 mmol, 2 eq.). After stirring the mixture for 15 min at room temperature, corresponding amine derivative (0.5 mmol, 1.00 eq.) in dichloromethane (3 mL) was added and the resulting mixture stirred for 12 hrs. After this time, the solvent was concentrated completely. The resulting material was diluted with methanol (15 mL) and K_2CO_3 (excess, 5 equiv.) added and stirred for 3 hrs. The solvent was removed and diluted with DCM. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*, and purified by chromatography (silica gel 100-200 mesh, 30:70 EtOAc/Hexane).

(3*S*,4*R*,6*S*,8*R*,9*aR*)-8-hydroxy-3,4-diphenyl-6-propylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9a, Table 2 Entry 1). Following the general procedure, **A**, the *title compound* **9a** was prepared from compound **7a** (146 mg) and butanal as a white solid (138 mg, 76 %). $[\alpha]_D^{26} = -40.0$ (*c* 1.0, $CHCl_3$); M.pt. 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2 H), 7.18-7.13 (m, 5 H), 7.10-7.05 (m, 2 H), 6.96-6.91 (m, 2 H), 6.79-6.74 (m, 2 H), 5.53 (d, *J* = 4.4 Hz, 1 H), 4.59 (d, *J* = 4.4 Hz, 1 H), 4.17 (dd, *J* = 3.6, 8.8 Hz, 1 H), 4.05 (sep, *J* = 6.4 Hz, 1 H), 3.04-2.96 (m, 1H), 2.30-2.23 (m, 1 H), 2.09-1.94 (m, 1 H), 1.58-1.40 (m, 6 H), 1.34-1.19 (m, 3 H), 1.15-1.10 (m, 1 H), 0.78 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.9, 135.7, 135.5, 129.8, 128.3, 128.1, 128.0, 127.9, 127.6, 83.7, 77.4, 77.2, 77.0, 76.7, 64.9, 61.9, 54.5, 54.2, 34.6, 33.5, 33.2, 19.9, 14.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1730, 1355, 1044, 921, 655 cm^{-1}; HRMS (ESI) *m/z*: [M]+ calcd for $C_{23}H_{28}O_3N$: 366.2064; found: 366.2064. Compound **9a** was also prepared using the same method starting from **7a** (146 mg) and butanal diethyl acetal (73 mg) in 132 mg, 73% yield (**Table 2 Entry 11**). All data was in agreement with that presented above.

(3*R*,4*S*,6*R*,8*S*,9*aS*)-8-Hydroxy-3,4-diphenyl-6-propylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9a', Table 2, Entry 2). Following the general procedure, **A**, the *title compound* **9a'** was prepared from compound **7b** (146 mg) (opposite isomer of **7a**) and butanal as a white solid (150 mg, 82 %). $[\alpha]_D^{26}$ = +360.00 (c 1.0, MeOH); M.pt. 124-126 oC; 1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2 H), 7.18-7.13 (m, 5 H), 7.10-7.05 (m, 2 H), 6.96-6.91 (m, 2 H), 6.79-6.74 (m, 2 H), 5.53 (d, *J* = 4.4 Hz, 1 H), 4.59 (d, *J* = 4.4 Hz, 1 H), 4.17 (dd, *J* = 3.6, 8.8 Hz, 1 H), 4.05 (sep, *J* = 6.4 Hz, 1 H), 3.04-2.96 (m, 1H), 2.30-2.23 (m, 1 H), 2.09-1.94 (m, 1 H), 1.58-1.40 (m, 6 H), 1.34-1.19 (m, 3 H), 1.15-1.10 (m, 1 H), 0.78 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.0, 135.7, 135.5, 129.9, 128.3, 128.1, 127.9, 127.6, 83.8, 77.4, 77.1, 76.8, 64.9, 61.8, 54.5, 54.3, 34.6, 33.5, 33.2, 19.9, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1767, 1455, 1130, 1042, 753, 658 cm^{-1}; HRMS (ESI) *m/z*: [M]$^+$ calcd for $C_{23}H_{28}O_3N$ 366.2064; found 366.2064.

(3*S*,4*R*,6*S*,8*R*,9*aR*)-8-hydroxy-6-phenethyl-3,4-diphenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9b, Table 2 Entry 3). Following the general procedure, **A**, the *title compound* **9b** was prepared from compound **7a** (146 mg) and 3-phenyl propionaldehyde as a white solid (173 mg, 81 %). $[\alpha]_D^{26}$ = -421.0 (*c* 1.0, $CHCl_3$); M.pt. 136-138 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.27-7.09 (m, 7 H), 7.04 (t, *J* = 7.2 Hz, 2 H), 6.94 (d, *J* = 7.2 Hz, 4 H), 6.73 (d, *J* = 8.0 Hz, 2 H), 5.55 (d, *J* = 4.0 Hz, 1 H), 4.52 (dd, *J* = 4.0, 14.4 Hz, 2 H), 4.20 (dd, *J* = 2.4, 10 Hz, 1 H), 4.01-3.92 (m, 1 H), 3.01-2.94 (m, 1H), 2.90 (bs, 1 H), 2.66-2.53 (m, 1 H), 2.38-2.20 (m, 2 H), 2.02-1.77 (m, 2 H), 1.62-1.39 (m, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 141.6, 135.6, 135.5, 129.6, 128.1, 128.1, 128.0, 128.0, 127.8, 127.6, 127.3, 125.6, 83.4, 77.9, 77.6, 77.2, 63.6, 62.0, 54.6, 54.3, 34.8, 33.2, 32.7, 32.6 ppm; ν_{max}(neat)/cm^{-1}: 2933, 1738, 1626, 1221, 953, 732 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{28} H_{30} O_3 N 428.2220; found 428.2219.

(3*S*,4*R*,6*S*,8*R*,9*aR*)-8-hydroxy-3,4-diphenyl-6-undecylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9c, Table 2 Entry 4). Following the general procedure, **A**, the *title compound* **9c** was prepared from compound **7a** (146 mg) and dodecanal as a white solid (179 mg, 75%). $[\alpha]_D^{26}$ = +78.0 (*c* 1.0, $CHCl_3$); M.pt. 126-128 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23-7.13 (m, 4 H), 7.10-7.05 (m, 2 H), 6.96-6.91 (m, 2 H), 6.77-6.73 (m, 2 H), 5.54 (d, *J* = 4.0 Hz, 1 H), 4.57 (d, *J* = 4.0 Hz, 1 H), 4.17 (dd, *J* = 3.2, 8.8 Hz, 1 H), 4.04 (sep, *J* = 6.0 Hz, 1 H), 3.02-2.93 (m, 1H), 2.32-2.24 (m, 1 H), 2.03-1.93 (m, 1 H), 1.61-1.38 (m, 3 H), 1.33-1.02 (m, 22 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.9, 135.7, 135.5, 129.9, 128.3, 128.1, 127.9, 127.5, 83.7, 77.4, 77.0, 76.7, 64.9, 61.9, 54.6, 54.2, 34.6, 33.3, 32.0, 31.2, 29.7, 29.6, 29.4, 26.6, 22.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1712, 1457, 1152, 885, 730 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{31} H_{44} O_3 N 478.3316; found 478.3309.

(3*S*,4*R*,6*S*,8*R*,9*aR*)-8-hydroxy-6-nonyl-3,4-diphenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9d, Table 2 Entry 5). Following the general procedure, **A**, the *title compound* **9d** was prepared from compound **7a** (146 mg) and decanal as a white solid (164 mg, 73%). $[\alpha]_D^{26}$ = −52.0 (*c* 1.0, $CHCl_3$); M.pt. 124-126 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23-7.13 (m, 4 H), 7.10-7.04 (m, 2 H), 6.96-6.90 (m, 2 H), 6.77-6.72 (m, 2 H), 5.52 (d, *J* = 4.0 Hz, 1 H), 4.57 (d, *J* = 4.0 Hz, 1 H), 4.17 (dd, *J* = 3.2, 8.8 Hz, 1 H), 4.09-4.00 (m, 1 H), 3.00-2.93 (m, 1H), 2.30-2.24 (m, 1 H), 2.02-1.93 (m, 1 H), 1.46-1.38 (m, 1 H), 1.35-1.06 (m, 15 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.9, 135.7, 135.5, 129.9, 128.3, 128.1, 127.9, 127.5, 83.7, 77.4, 77.1, 76.8, 64.9, 61.9, 54.6, 54.2, 34.6, 33.3, 31.9, 31.2, 29.6, 29.3, 26.7, 22.8, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2983, 1738, 1454, 1224, 703 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{29} H_{40} O_3 N 450.3003; found 450.3001.

(3*S*,4*R*,6*S*,8*R*,9*aR*)-6-heptyl-8-hydroxy-3,4-diphenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9e, Table 2 Entry 6). Following the general procedure, **A**, the *title compound* was prepared from compound **5** (146 mg) and octanal as a white solid (151 mg, 72 %). $[\alpha]_D^{26}$ = +124.0 (*c* 1.0, $CHCl_3$); M.pt. 108-110 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.13 (m, 4 H), 7.07 (t, *J* = 8 Hz, 2 H), 6.97-6.93 (m, 2 H), 6.79-6.73 (m, 2 H), 5.53 (d, *J* = 4.0 Hz, 1 H), 4.57 (d, *J* = 4.0 Hz, 1 H), 4.17 (dd, *J* = 3.2, 8.8 Hz, 1 H), 4.04 (sep, *J* = 6.0 Hz, 1 H), 3.02-2.94 (m, 1H), 2.31-2.22 (m, 1 H), 2.03-1.93 (m, 1 H), 1.87 (bs, 1 H), 1.58-1.38 (m, 3 H), 1.32-1.05 (m, 12 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 135.7, 135.5, 129.9, 128.3, 128.1, 127.9, 127.6, 83.8, 77.4, 77.3, 77.1, 76.8, 64.8, 61.9, 54.6, 54.2, 34.6, 33.3, 31.8, 31.2, 29.5, 29.3, 26.7, 22.7, 14.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1740, 1382, 1071, 956, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{27} H_{36} O_3 N 422.2690; found 422.2688.

(3*S*,4*R*,6*R*,8*R*,9*aR*)-6-benzhydryl-8-hydroxy-3,4-diphenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (9f, Table 2 Entry 7). Following the general procedure, **A**, the *title compound* **9e** was prepared from compound **7a** (146 mg) and diphenyl acetaldehyde as a white solid (191 mg, 78 %). $[\alpha]_D^{26}$ = +125.0 (*c* 1.0, $CHCl_3$); M.pt. 140-142 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.01 (m, 14 H), 6.93-6.85 (m, 2 H), 6.53-6.49 (m, 4 H), 5.32 (d, *J* = 4.0 Hz, 1 H), 4.65 (d, *J* = 4.0 Hz, 1 H), 4.46 (dd, *J* = 4.0 Hz, 1 H), 4.16 (d, *J* = 12.0 Hz, 1 H), 3.76-3.73 (m, 1H), 2.41-2.32 (m, 1 H), 2.14-2.03 (m, 1 H), 1.58-1.51 (m, 1 H), 1.41-1.32 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 142.5, 141.9, 135.3, 134.3, 130.3, 129.0, 128.5, 128.3, 127.8, 127.7, 127.7, 126.9, 126.8, 84.1, 77.4, 77.1, 76.7, 63.9, 61.8, 58.3, 54.8, 52.7, 33.4, 29.3 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1726, 1382, 1073, 957, 695 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{33} H_{32} O_3 N 490.2377; found 490.2369.

(3*S*,4*R*,6*R*,8*R*,9*aR*)-Ethyl 8-hydroxy-1-oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazine-6-carboxylate (9g, Table 2 Entry 8). Following the general procedure, **A**, the *title compound* was prepared from compound **7a** (146 mg) and ethyl glyoxylate (0.5 mmol) as a white solid (175 mg, 91 %). $[\alpha]_D^{26}$ = -226.0 (*c* 1.0, $CHCl_3$); M.pt. 196-198 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.03 (m, 8H), 6.88 (d, *J* = 7.2 Hz, 2 H), 5.79 (d, *J* = 3.6 Hz, 1 H), 4.89 (dd, *J* = 2.8, 8.8 Hz, 1 H), 4.27 (m, 2H), 3.83-3.66 (m, 2H), 3.57-3.48 (m, 1H), 3.42 (d, *J* = 7.6 Hz, 1 H), 3.56 (d, *J* = 12.8 Hz, 1 H), 2.20-2.19 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.6, 170.8, 135.4, 134.2, 129.5, 128.1, 128.0, 128.0, 128.0, 127.8, 126.7, 83.5, 77.3, 77.0, 76.6, 64.6, 64.2, 61.1, 57.4, 50.1, 35.4, 31.7, 13.6, 13.6, 13.6 ppm; ν_{max}(neat)/cm^{-1}: 3481, 2932, 1699, 1232, 1052, 697 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{23} H_{26} O_5 N 396.1805; found 396.1806.

(3*S*,4*R*,6*R*,8*R*,9*aR*)-1-Oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazine-6,8-carboxylic anhydride (9h, Table 2 entry 9). Following the general procedure, **A**, the *title compound* was prepared prepared from compound**7a** (146 mg) and glyoxylic acid as a white solid (104 mg, 60 %). $[\alpha]_D^{26}$ = +40.0 (c 1.0, MeOH); M.pt. 240-242 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.05 (m, 6 H), 6.95-6.88 (m, 4 H), 5.72 (d, *J* = 5.6 Hz, 1 H), 5.00 (t, *J* = 5.6 Hz, 1 H), 4.47 (d, *J* = 4.8 Hz, 1 H), 4.12 (dd, *J* = 5.6 Hz, 1 H), 3.35 (d, *J* = 4.8 Hz, 1 H), 2.62-2.54 (m, 1 H), 2.30-2.18 (m, 2 H), 1.93 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.4, 170.6, 136.1, 134.2, 129.1, 128.2, 128.2, 127.9, 127.9, 126.7, 126., 79.6, 77.4, 77.1, 76.7, 76.5, 65.8, 57.8, 52.8, 36.9, 31.2 ppm; ν_{max}(neat)/cm^{-1}: 2825, 1756, 1218, 1049, 956, 771, 678 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for C_{21} H_{20} O_4 N 350.1387; found 350.1390.

General procedure-B for the aza-Prins- Ritter reaction: A round-bottomed flask was charged with an aldehyde (0.5 eq.) and CH_3CN (10 mL). To the resulting suspension was added anhydrous pTSA (0.75 mmol, 1.5 eq.). After stirring the mixture for 15min at room temperature, an amine derivative (**7a** or **7b**, 0.5 mmol, 1.00 eq.) in CH_3CN (3 mL) was added and the resulting mixture stirred for 12 hrs at 35 ºC using a solid heating block. The solvent was removed and diluted with DCM (20 mL) followed by sat. $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*, and purified by chromatography (silica gel 100-200 mesh, 50:49:1 EtOAc/Hexane/Et_3N).

***N*-((3*S*,4*R*,6*S*,8*R*,9*aR*)-1-oxo-6-phenethyl-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10a, Table 3 Entry 1).** Following the general procedure **B**, the *title compound* **10a** was prepared from compound **7a** (146 mg) and 3-phenylpropionaldehyde as a white solid (194 mg, 83 %). $[\alpha]_D^{26}$ = -560.00 (c 1.0, CHCl3); M.pt. 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.02 (m, 10 H), 6.97-6.92 (m, 3 H), 6.74-6.70 (m, 2 H), 5.51 (d, *J* = 4.0 Hz, 1 H), 5.37 (d, *J* = 8.3 Hz, 1 H), 4.53 (d, *J* = 4.0 Hz, 1 H), 4.38-4.18 (m, 2 H), 3.05-2.97 (m, 1 H), 2.67-2.57 (m, 1 H), 2.46-2.32 (m, 1 H), 1.96 (s, 3H), 1.90-1.78 (m, 1 H), 1.70-1.55 (m, 3 H), 1.71.37 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 169.3, 141.6, 141.5, 135.5, 135.4, 129.8, 128.4, 128.4, 128.3, 128.3, 128.3, 128.1, 127.9, 127.7, 125.9, 84.1, 77.4, 77.3, 77.1, 76.8, 62.6, 54.4, 42.9, 32.8, 32.4, 31.8, 31.2, 23.6 ppm; ν_{max}(neat)/cm^{-1}: 2980, 1738, 1544, 1373, 1235, 1020, 694 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{30}H_{33}O_3N_2$ 469.2486; found 469.2481.

***N*-((3*R*,4*S*,6*R*,8*S*,9*aS*)-1-Oxo-6-phenethyl-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10a', Table 3 Entry 2).** Following the general procedure **B**, the *title compound* **10a'** (enantiomer of **10a**) was prepared from compound **7b** (146 mg) and 3-phenylpropionaldehyde as a white solid (178 mg, 76 %). $[\alpha]_D^{26}$ = +120.00 (c 1.0, MeOH); M.pt. 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.02 (m, 10 H), 6.97-6.92 (m, 3 H), 6.74-6.70 (m, 2 H), 5.51 (d, *J* = 4.0 Hz, 1 H), 5.37 (d, *J* = 8.3 Hz, 1 H), 4.53 (d, *J* = 4.0 Hz, 1 H), 4.38-4.18 (m, 2 H), 3.05-2.97 (m, 1 H), 2.67-2.57 (m, 1 H), 2.46-2.32 (m, 1 H), 1.96 (s, 3H), 1.90-1.78 (m, 1 H), 1.70-1.55 (m, 3 H), 1.71-1.37 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.4, 168.3, 140.5, 134.5, 134.4, 128.7, 127.4, 127.4, 127.3, 127.2, 127.1, 126.9, 126.6, 124.9, 83.0, 76.3, 76.1, 75.8, 61.6, 53.4, 53.3, 41.9, 31.8, 31.4, 30.7, 30.2, 22.6 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1733, 1355, 1114, 751, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{30}H_{33}O_3N_2$ 469.2486; found 469.2481.

***N*-((3*S*,4*R*,6*R*,8*S*,9*aR*)-6-Heptyl-1-oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10b, Table 3 Entry 3).** Following the general procedure **B**, the *title compound* was prepared from compound **7a** (146 mg) and octanal as a white solid (168 mg, 73 %). $[\alpha]_D^{26}$ = −54.0 (*c* 1.0, $CHCl_3$); M.pt. 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.06 (m, 6 H), 6.94-6.91 (m, 2 H), 6.77-6.72 (m, 2 H), 5.49 (d, *J* = 4.0 Hz, 1 H), 5.32 (bs, 1 H), 4.54 (d, *J* = 4.0 Hz, 1 H), 4.31-4.16 (m, 2 H), 2.96-2.92 (m, 1 H), 2.36-2.31 (m, 1 H), 1.96 (s, 3H), 1.81-1.77 (m, 1 H), 1.55-1.49 (m, 2 H), 1.40-1.08 (m, 11 H), 0.86 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 169.2, 135.6, 135.5, 129.8, 128.3, 128.2, 128.1, 127.9, 127.6, 84.2, 77.4, 77.1, 76.7, 62.3, 54.6, 54.3, 42.9, 32.2, 31.8, 31.0, 30.3, 29.5, 29.3, 26.7, 23.6, 22.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1733, 1373, 1132, 702 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{29}H_{39}O_3N_2$ 463.2955; found 463.2951.

***N*-((3*S*,4*R*,6*S*,8*R*,9*aR*)-6-nonyl-1-oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10c, Table 3 Entry 4).** Following the general procedure **B**, the *title compound* **10c** was prepared from compound **7a** (146 mg) and decanal as a white solid (191 mg, 78 %). $[\alpha]_D^{26}$ = −132.0 (*c* 1.0, $CHCl_3$); M.pt. 173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.03 (m, 6 H), 6.95-6.90 (m, 2 H), 6.78-6.72 (m, 2 H), 5.47 (d, *J* = 4.0 Hz, 1 H), 5.38 (d, *J* = 8.4 Hz, 1 H), 4.54 (d, *J* = 4.0 Hz, 1 H), 4.28-4.18 (m, 2 H), 2.98-2.93 (m, 1 H), 2.38-2.30 (m, 1 H), 1.97 (s, 3H), 1.83-1.77 (m, 1 H), 1.57-1.49 (m, 1 H), 1.40-1.02 (m, 16 H), 0.87 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 169.2, 135.6, 135.5, 129.8, 128.3, 128.2, 128.1, 127.9, 127.6, 84.2, 77.4, 77.1, 76.7, 62.3, 54.6, 54.3, 42.9, 32.2, 31.9, 31.0, 30.3, 29.6, 29.4, 26.7, 23.6, 22.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1733, 1319, 1053, 954, 768 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{31}H_{43}O_3N_2$ 491.3268; found 491.3259.

***N*-((3*S*,4*R*,6*S*,8*R*,9*aR*)-1-Oxo-6-pentyl-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10d, Table 3 Entry 5).** Following the general procedure **B**, the *title compound* **10d** was prepared from compound **7a** (146 mg) and hexanal as a white solid (163 mg, 75 %). $[\alpha]_D^{26}$ = −120.0 (*c* 1.0, $CHCl_3$); M.pt. 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.06 (m, 6 H), 6.96-6.91 (m, 2 H), 6.78-6.72 (m, 2 H), 5.49 (d, *J* = 4.0 Hz, 1 H), 5.32 (bs, 1 H), 4.55 (d, *J* = 4.0 Hz, 1 H), 4.31-4.16 (m, 2 H), 2.98-2.92 (m, 1 H), 2.38-2.29 (m, 1 H), 1.96 (s, 3H), 1.87-1.83 (m, 1 H), 1.55-1.49 (m, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 169.2, 135.6, 135.4, 129.8, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.6, 84.2, 77.4, 77.3, 77.1, 76.7, 62.3, 54.6, 54.3, 42.9, 32.2, 31.7, 31.0, 30.2, 26.4, 23.6, 22.6, 22.6, 14.0 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1717, 1237, 1042, 753, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{27}H_{35}O_3N_2$ 435.2642; found 435.2641.

***N*-((3*S*,4*R*,6*S*,8*R*,9*aR*)-1-oxo-3,4-diphenyl-6-propyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10e, Table 3 Entry 6).** Following the general procedure B, the *title compound* 10e was prepared from compound **7a** (146 mg) and butanal as a white solid (152 mg, 74 %). $[\alpha]_D^{26}$ = −63.0 (*c* 1.0, $CHCl_3$); M.pt. 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.03 (m, 6 H), 6.95-6.90 (m, 2 H), 6.78-6.72 (m, 2 H), 5.49 (d, *J* = 4.0 Hz, 1 H), 5.32 (bs, 1 H), 4.55 (d, *J* = 4.0 Hz, 1 H), 4.31-4.16 (m, 2 H), 2.98-2.92 (m, 1 H), 2.38-2.20 (m, 1 H), 1.96 (s, 3H), 1.81-1.77 (m, 1 H), 1.40-1.22 (m, 4 H), 0.75 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 169.2, 135.6, 135.5, 129.8, 128.3, 128.2, 128.0, 128.0, 127.6, 84.1, 77.4, 77.2, 77.1, 76.7, 62.3, 54.5, 54.3, 42.9, 32.6, 32.2, 30.9, 23.6, 19.9, 14.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1732, 1232, 1035, 912, 694 cm^{-1}; HRMS (ESI) *m/z*: [M]+ calcd for $C_{25}H_{31}O_3N_2$: 407.2329; found: 407.2325. Compound **10e** was also prepared using the same method starting from **7a** (146 mg) and butanal diethyl acetal (73 mg) in 131 mg, 65% yield (**Table 3 Entry 7**). All data was in agreement with that presented above.

***N*-((3*S*,4*R*,6*S*,8*R*,9*aR*)-6-benzyl-1-oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10f, Table 3 Entry 8).** Following the general procedure **B**, the *title compound* **10f** was prepared from compound **7a** (146 mg) and phenylacetaldehyde as a white solid (186 mg, 82%). $[\alpha]_D^{26}$ = -200.00 (c 1.0, MeOH); M.pt. 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-6.99 (m, 12 H), 6.84-6.79 (m, 2 H), 6.63-6.53 (m, 1 H), 5.47 (d, *J* = 4.0 Hz, 1 H), 5.35 (bs, 1 H), 4.53 (d, *J* = 4.0 Hz, 1 H), 4.46-4.34 (m, 1 H), 3.31-3.21 (m, 1 H), 2.72-2.66 (m, 1H), 2.52-2.44 (m, 1 H), 1.95 (s, 3H), 1.88-1.77 (m, 1 H), 1.38-1.28 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.1, 169.2, 139.1, 135.4, 135.3, 129.7, 129.3, 128.4, 128.2, 128.1, 128.1, 127.8, 127.7, 126.3, 84.5, 77.4, 77.3, 77.1, 76.8, 62.7, 57.4, 54.4, 42.9, 36.3, 32.9, 30.5, 23.5 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1734, 1653, 1454, 1381, 1239, 1071, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{29}H_{31}O_3N_2$ 455.2329; found 455.2323 . Compound **10f** was also prepared using the same method starting from **7a** (146 mg) and

styrene oxide (60 mg) in 142 mg, 63% yield (**Table 3 Entry 9**). All data was in agreement with that presented above.

***N*-((3*S*,4*R*,6*R*,8*R*,9*aR*)-6-benzhydryl-1-oxo-3,4-diphenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (10g, Table 3 Entry 10).** Following the general procedure **B**, the *title compound* **10g** was prepared from compound **7a** (146 mg) and diphenyl acetaldehyde as a white solid (207 mg, 78 %). $[\alpha]_D^{26} = -113.0$ (*c* 1.0, $CHCl_3$); M.pt. 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.02 (m, 15 H), 6.88 (t, *J* = 7.6 Hz, 2 H), 6.59-6.45 (m, 3 H), 5.30-5.19 (m, 2 H), 4.67 (d, *J* = 4.1 Hz, 1 H), 4.51-4.46 (m, 1 H), 4.33 (d, *J* = 12.8 Hz, 1 H), 3.74-3.61 (m, 1 H), 2.52-2.43 (m, 1 H), 2.05-1.94 (m, 1H), 1.89 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.6, 169.3, 142.3, 141.8, 135.3, 134.3, 130.4, 128.9, 128.6, 128.38, 128.0, 127.9, 127.9, 127.8, 127.7, 126.9, 126.8, 84.1, 77.4, 77.1, 76.7, 61.9, 57.7, 54.8, 52.2, 42.2, 30.8, 26.4, 23.5 ppm; ν_{max}(neat)/cm^{-1}: 2982, 1796, 1412, 1096, 978, 693 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{35}H_{35}O_3N_2$ 531.2642; found 531.2637.

General procedure C: for the $FeCl_3$ or $FeBr_3$ catalysed aza-Prins reaction: A round-bottomed flask was charged with aldehyde (0.5 eq.) and solvent (DCM for $FeCl_3$ and DBE for $FeBr_3$) (10 mL). To the resulting suspension was added $FeCl_3$ or $FeBr_3$ (0.75 mmol, 1.5 eq.) at 0 °C. After stirring the mixture for 15 min at same temperature, the corresponding amine derivative (0.5 mmol, 1.00 eq.) in the appropriate solvent (DCM/DBE) (3 mL) was added and the resulting mixture stirred for 6 hrs. After completion of the reaction, resulting solution treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel 100-200 mesh; 5: 95 EtOAc/Hexane).

General procedure D: for the O-tosyl azabicyclic derivatives *via* aza-Prins reaction: A round-bottomed flask was charged with aldehyde (0.5 eq.) and CH_3CN (10 mL). To the resulting suspension was added anhydrous PTSA (0.75 mmol, 1.5 eq.). After stirring the mixture for 15min at room temperature, the corresponding amine derivative (0.5 mmol, 1.00 eq.) in CH_3CN (3 mL) was added and the resulting mixture stirred for 12 hrs. After completion of the reaction, the solvent was concentrated. The resulting crude compound was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel 100-200 mesh; 5: 95 EtOAc/Hexane).

General procedure E: for the aza-Prins-Ritter reaction: a) Using $BF_3.OEt_2$: a round-bottomed flask was charged with aldehyde (0.5 eq.) and CH_3CN (10 mL). To the resulting suspension was added $BF_3.OEt_2$ (0.75 mmol, 1.5 eq.). After stirring the mixture for 15min at room temperature, the corresponding amine derivative (0.5 mmol, 1.00 eq.) in CH_3CN (3 mL) was added and the resulting mixture stirred for 12 hrs. After completion of the reaction, the solvent was concentrated. The resulting crude compound was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel 100-200 mesh; 50: 49: 1 EtOAc/Hexane/Et_3N).

b) Using $Sc(OTf)_3$: a round-bottomed flask was charged with aldehyde (0.5 eq.) and DCM (10 mL). To the resulting suspension was added $Sc(OTf)_3$ (0.75 mmol, 1.5 eq.). After stirring the mixture for 15min at room temperature, the corresponding amine derivative (3, 0.5 mmol, 1.00 eq.) in DCM (3 mL) was added and the resulting mixture stirred for 12 hrs. After completion of the reaction, the solvent was concentrated. The resulting crude compound was treated with aqueous sodium bicarbonate (5 mL) and the product was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to leave the crude product, which was purified by column chromatography (silica gel 100-200 mesh; 50: 49: 1 EtOAc/Hexane/Et_3N).

(4*S*,6*R*,8*R*,9*aS*)-8-chloro-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6H)-one (12a, Table 4 Entry 2). Following the general procedure **C** the *title compound* **12a** was prepared from compound **8a** (109 mg) and 3-phenylpropionaldehyde as a white solid (166 mg, 90 %). $[\alpha]_D^{26}$ = +143.0 (*c* 1.0, $CHCl_3$); M.pt. 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.14 (m, 8 H), 7.11-7.08 (m, 2 H), 4.37-4.17 (m, 4 H), 4.11 (dd, *J* = 3.2, 9.2 Hz, 1 H), 2.89-2.70 (m, 2 H), 2.45-2.20 (m, 3 H), 1.95-1.65 (m, 3H), 1.61-1.54 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.2, 141.5, 135.4, 129.4, 129.2, 128.6, 128.6, 128.2, 126.1, 77.4, 77.1, 76.7, 73.9, 55.8, 55.6, 54.2, 53.6, 34.9, 33.9, 33.1, 32.8 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1726, 1249, 1133, 1020, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{22}H_{25}{}^{35}ClNO_2$ 370.1574; found 370.1570; calcd for $C_{22}H_{25}{}^{37}ClNO_2$ 372.1544; found 372.1536.

(4*S*,6*S*,8*R*,9a*S*)-8-Chloro-4,6-diphenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (12b, Table 4 Entry 3). Following the general procedure **C**, the *title compound* **12b** was prepared from compound **8a** (109 mg) and benzaldehyde as a white solid (155 mg, 91 %). $[\alpha]_D^{26}$ = +78.0 (*c* 1.0, $CHCl_3$); M.pt. 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.23 (m, 10 H), 4.59-4.51 (m, 2 H), 4.38-4.36 (m, 1 H), 4.25-4.16 (m, 2 H), 3.86 (dd, *J* = 4.0 Hz, 1 H), 2.55-2.39 (m, 2 H), 2.28-2.21 (m, 1 H), 2.10-2.03 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.3, 139.3, 136.0, 129.4, 129.1, 129.0, 128.0, 127.5, 126.7, 71.5, 56.2, 55.2, 54.6, 53.6, 34.4, 33.8 ppm; ν_{max}(neat)/cm^{-1}: 3031, 1783, 1202, 1163, 1104, 784 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{20}H_{21}{}^{35}ClNO_2$ 342.1261; found 342.1256; calcd for $C_{20}H_{21}{}^{37}ClNO_2$ 344.1231; found 344.1234.

(4*S*,6*S*,8*R*,9*aS*)-6-Benzhydryl-8-chloro-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6H)-one (12c, Table 4 Entry 4). Following the general procedure **C**, the *title compound* was prepared from compound **8a** (109 mg) and diphenyl acetaldehyde as a white solid (192 mg, 89 %). $[\alpha]_D^{26}$ = +132.0 (*c* 1.0, $CHCl_3$); M.pt. 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.32 (m, 3 H), 7.26-7.13 (m, 6 H), 7.09-7.00 (m, 4 H), 6.92-6.86 (m, 2 H), 4.37-4.19 (m, 3 H), 4.13-3.97 (m, 3 H), 3.47-3.38 (m, 1 H), 2.53-2.48 (m, 1 H), 2.29 (q, *J* = 13.2 Hz, 1 H), 1.82-1.65 (m, 2H), 1.61-1.54 (m, 1 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.0, 142.1, 140.9, 134.5, 129.4, 129.2, 129.1, 128.3, 128.1, 128.0, 127.1, 126.7, 77.4, 77.1, 76.7, 73.4, 58.0, 56.0, 55.7, 53.0, 51.6, 34.2, 30.8 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1733, 1245, 1141, 1031, 697 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{27}H_{27}{}^{35}ClNO_2$ 432.1730; found 432.1726; calcd for $C_{27}H_{27}{}^{37}ClNO_2$ 434.1701; found 434.1696.

(4*S*,6*R*,8*R*,9*aS*)-8-bromo-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6H)-one (13a, Table 4 Entry 6).

Following the general procedure **C**, the *title compound* **13a** was prepared from compound **8a** (109 mg) and phenyl propionaldehyde as a white solid (186 mg, 90 %). $[\alpha]_D^{26}$ = +225.0 (*c* 1.0, $CHCl_3$); M.pt. 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.14 (m, 8 H), 7.11-7.05 (m, 2 H), 4.40-4.24 (m, 4 H), 4.11 (dd, *J* = 3.2, 9.2 Hz, 1 H), 2.82-2.70 (m, 2 H), 2.51-2.27 (m, 3 H), 2.20-1.80 (m, 3H), 1.63-1.54 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 141.4, 135.3, 129.3, 128.6, 128.5, 128.2, 126.1, 77.3, 77.1, 76.8, 73.9, 56.3, 55.8, 54.7, 44.7, 35.0, 34.7, 33.0, 32.6 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1726, 1453, 1242, 1133, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{22}H_{25}{}^{79}BrNO_2$ 414.1063; found 414.1063; calcd for $C_{22}H_{25}{}^{81}BrNO_2$ 416.1043; found 416.1042.

(4*S*,6*S*,8*R*,9*aS*)-6-Benzhydryl-8-bromo-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (13b, Table 4 Entry 7). Following the general procedure **C**, the *title compound* **13b** was prepared from compound **8a** (109 mg) and diphenyl acetaldehyde as a white solid (211 mg, 80 %). $[\alpha]_D^{26}$ = +183.0 (*c* 1.0, $CHCl_3$); M.pt. 201-203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.30 (m, 4 H), 7.28-7.13 (m, 6 H), 7.09-7.00 (m, 3 H), 6.98-6.90 (m, 2 H), 4.44-4.31 (m, 3 H), 4.13-3.97 (m, 3 H), 3.38-3.32 (m, 1 H), 2.61-2.43 (m, 2 H), 1.93-1.84 (m, 2 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.7, 142.0, 140.9, 134.5, 129.9, 129.4, 129.2, 129.1, 128.3, 128.1, 128.0, 127.1, 126.7, 77.3, 77.1, 76.8, 76.5, 73.3, 58.6, 56.4, 56.0, 51.3, 44.0, 34.9, 31.7 ppm; ν_{max}(neat)/cm^{-1}: 2933, 1738, 1454, 1228, 1021, 702 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{27}H_{27}{}^{79}BrNO_2$ 476.1220; found 476.1216; calcd for $C_{27}H_{27}{}^{81}BrNO_2$ 478.1200; found 478.1195.

(4*S*,6*R*,8*R*,9*aS*)-8-Hydroxy-4-phenyl-6-propylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6H)-one (14a, Table 4 Entry 8). Following the general procedure, **D**, the *title compound* **14a** was prepared from compound **8a** (109 mg) and butanal as a colourless liquid (127 mg, 88 %). $[\alpha]_D^{26}$ = +65.0 (*c* 1.0, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 5 H), 4.35-4.22 (m, 3 H), 4.02-3.95 (m, 2 H), 2.83-2.75 (m, 1 H), 2.46 (bs, 1 H), 2.16-1.96 (m, 2H), 1.54-1.35 (m, 4 H), 1.22-1.09 (m, 2 H), 0.77 (t, *J* = 5.6 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 135.7, 128.2, 127.9, 127.6, 76.5, 76.3, 76.0, 72.6, 63.6, 55.5, 53.6, 52.9, 33.2, 32.1, 31.9, 18.8, 13.2 ppm; ν_{max}(neat)/cm^{-1}: 2955, 2870, 1732, 1456, 1330, 1228, 1138, 761, 647 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{24}O_3N$ 290.1751; found 290.1750. Compound **14a** was also prepared using the same method starting from **8a** (109 mg) and butanal diethyl acetal (73 mg) in 170 mg, 76% yield (**Table 4 Entry 10**). All data was in agreement with that presented above.

(4*S*,6*R*,8*R*,9*aS*)-8-hydroxy-4-phenyl-6-undecylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6H)-one (14b, Table 4 Entry 9). Following the general procedure, **D**, the *title compound* **14b** was prepared from compound **8a** (109 mg) and dodecanal as a colourless liquid (172 mg, 90 %). $[\alpha]_D^{26}$ = +187.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5 H), 4.35-4.21 (m, 3 H), 4.02-3.96 (m, 2 H), 2.83-2.76 (m, 1 H), 2.19-1.96 (m, 2H), 1.54-1.45 (m, 2 H), 1.38-1.05 (m, 22 H), 0.87 (t, *J* = 5.6 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 136.6, 129.0, 128.7, 128.4, 77.3, 77.1, 76.8, 73.4, 64.5, 56.6, 54.4, 53.9, 32.9, 31.9, 29.6, 29.4, 26.4, 22.7, 14.1 ppm; ν_{max}(neat)/cm^{-1}: 2923, 2853, 1739, 1456, 1230, 1044, 762 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{25}H_{40}O_3N$ 402.3003; found 402.2999.

(4*S*,6*R*,8*R*,9*aS*)-6-Nonyl-1-oxo-4-phenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl 4-methylbenzenesulfonate (15a, Table 4 Entry 11). Following the general procedure **C**, the *title compound* **15a** was prepared from compound **8a** (109 mg) and decanal as a white solid (211 mg, 80 %). $[\alpha]_D^{26}$ = +65.0 (*c* 1.0, $CHCl_3$); M.pt. 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.74 (m, 2 H), 7.41-7.28 (m, 7 H), 4.78-4.71 (m, 1 H), 4.33-4.17 (m, 3 H), 4.00-3.94 (m, 1 H), 2.77-2.71 (m, 1 H), 2.44 (s, 3 H), 2.10-2.02 (m, 1 H), 1.65-1.42 (m, 3 H), 1.34-1.02 (m, 15 H), 0.88 (t, *J* = 5.2 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 144.9, 135.4, 134.3, 130.0, 129.2, 128.6, 127.6, 77.3, 77.1, 76.8, 76.2, 73.8, 55.7, 54.3, 53.6, 31.9, 31.0, 29.9, 29.6, 29.4, 26.5, 22.7, 21.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1733, 1456, 1232, 940, 816, 698, 551 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{30}H_{42}O_5NS$ 528.2778; found 528.2768.

(4*S*,6*R*,8*R*,9*aS*)-1-oxo-4-phenyl-6-undecyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl 4-methylbenzenesulfonate (15b, Table 4 Entry 12). Following the general procedure **C**, the *title compound* **15b** was prepared from compound **8a** (109 mg) and dodecanal as a white solid (216 mg, 78 %). $[\alpha]_D^{26}$ = +223.0 (*c* 1.0, $CHCl_3$); M.pt. 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.74 (m, 2 H), 7.41-7.28 (m, 7 H), 4.78-4.68 (m, 1 H), 4.33-4.17 (m, 3 H), 4.00-3.93 (m, 1 H), 2.77-2.70 (m, 1 H), 2.44 (s, 3 H), 2.10-2.01 (m, 1 H), 1.65-1.43 (m, 3 H), 1.34-1.02 (m, 20 H), 0.88 (t, *J* = 5.2 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 143.9, 134.4, 133.3, 129.0, 128.2, 127.5, 126.6, 76.3, 76.0, 75.8, 75.2, 72.8, 54.7, 53.3, 52.6, 30.9, 30.0, 28.9, 28.6, 28.4, 25.5, 21.7, 20.7, 13.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1734, 1456, 1190, 1037, 751, 698 cm^{-1}; HRMS (ESI) *m/z:* $[M]^+$ calcd for $C_{32}H_{46}O_5NS$ 556.3091; found 556.3081.

***N*-((4*S*,6*R*,8*R*,9*aS*)-6-nonyl-1-oxo-4-phenyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (16a, Table 4 Entry 13).** Following the general procedure **E**, the *title compound* **16a** was prepared from compound **8a** (109 mg) and decanal as a semi solid (155 mg, 75 %). $[\alpha]_D^{26}$ = +74.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.30 (m, 5 H), 5.94 (bs, 1 H), 4.27-4.08 (m, 5 H), 2.72-2.63 (m, 1 H), 2.21-2.19 (m, 1H), 1.95 (s, 3 H), 1.62-1.49 (m, 2 H), 1.44-1.02 (m, 17 H), 0.87 (t, *J* = 6.8 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 169.4, 137.0, 129.1, 128.7, 128.1, 77.4, 77.1, 76.7, 73.0, 57.6, 54.4, 54.1, 42.6, 31.9, 31.7, 31.0, 29.6, 29.3, 26.1, 23.6, 22.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2980, 1739, 1549, 1233, 1021, 702 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{25}H_{39}O_3N_2$ 415.2955; found 415.2952.

***N*-((4*S*,6*R*,8*R*,9*aS*)-1-oxo-4-phenyl-6-undecyloctahydropyrido[2,1-*c*] [1,4] oxazin-8-yl) acetamide (16b, Table 4 Entry 141).** Following the general procedure **E**, the *title compound* **16b** was prepared from compound **8a** (109 mg) and dodecanal as a semi solid (159 mg, 72 %). $[\alpha]_D^{26}$ = +94.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.30 (m, 5 H), 5.94 (bs, 1 H), 4.27-4.08 (m, 5 H), 2.72-2.63 (m, 1 H), 2.21-2.14 (m, 1H), 1.95 (s, 3 H), 1.47-1.02 (m, 20 H), 0.87 (t, *J* = 6.8 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 169.3, 137.0, 129.0, 128.7, 128.1, 77.4, 77.1, 76.7, 72.9, 57.7, 54.4, 54.1, 42.6, 31.9, 31.8, 31.1, 29.7, 29.6, 29.4, 26.0, 23.6, 22.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1742, 1381, 1152, 958, 600 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{27}H_{43}O_3N_2$ 443.3268; found 443.3264.

(4*S*,6*R*,7*S*,8*S*,9*aS*)-8-Chloro-7-methyl-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (17a, Table 5 Entry 1). Following the general procedure **C**, the *title compound* **16a** was prepared from compound **8c** (116 mg) and 3-phenylpropionaldehyde as a white solid (176 mg, 92 %).

$[\alpha]_D^{26}$ = +64.0 (*c* 1.0, $CHCl_3$); M.p. 128-130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 5 H), 7.28-7.25 (m, 2 H), 7.21-7.16 (m, 1 H), 7.14-7.10 (m, 2 H), 4.44-4.34 (m, 2 H), 4.27 (dd, *J* = 2.4, 6.0 Hz, 1 H), 4.15 (dd, *J* = 2.4, 6.0 Hz, 1 H), 3.96 (dt, *J* = 4.4, 4.8 Hz, 1 H), 2.94-2.88 (m, 1 H), 2.70-2.65 (m, 1 H), 2.45-2.28 (m, 3 H), 1.98-1.92 (m, 1 H), 1.67-1.59 (m, 1 H), 0.86(d, *J* = 5.2 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 141.9, 135.2, 129.3, 129.2, 128.8, 128.6, 128.3, 126.1, 77.4, 77.1, 76.7, 73.9, 61.2, 59.3, 55.5, 55.3, 36.0, 35.0, 33.1, 26.6, 15.7 ppm; ν_{max}(neat)/cm^{-1}: 2980, 1604, 1452, 1042, 909, 595 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{23}H_{27}{}^{35}ClNO_2$ 384.1730; found 384.1734; calcd for $C_{23}H_{27}{}^{37}ClNO_2$ 386.1701; found 386.1709.

(4*S*,6*R*,7*S*,8*S*,9*aS*)-8-Bromo-7-methyl-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (17b, Table 5 Entry 1). Following the general procedure **C**, the *title compound* **16b** was prepared from compound **8c** (116 mg) and 3-phenylpropionaldehyde as a white solid (194 mg, 91 %). $[\alpha]_D^{26}$ = +183.0 (*c* 1.0, $CHCl_3$); M.p. 136-138 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.26 (m, 7 H), 7.21-7.16 (m, 1 H), 7.13-7.08 (m, 2 H), 4.51-4.35 (m, 2 H), 4.27 (dd, *J* = 3.6, 7.2 Hz, 1 H), 4.19-4.10 (m, 2 H), 2.96-2.84 (m, 1 H), 2.70-2.50 (m, 2 H), 2.35-2.26 (m, 1 H), 2.11-2.01 (m, 1 H), 1.71-1.58 (m, 2 H), 0.87 (d, *J* = 6.8 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.8, 141.9, 135.1, 129.3, 128.8, 128.6, 128.3, 126.1, 77.4, 77.1, 76.7, 73.9, 59.4, 55.9, 55.5, 54.3, 36.3, 36.2, 33.0, 26.4, 17.6 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1739, 1235, 1064, 766, 635, 528 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{23}H_{27}{}^{79}BrNO_2$ 428.1225; found 428.1221; calcd for $C_{23}H_{27}{}^{81}BrNO_2$ 430.1205; found 430.1201.

(4*S*,6*R*,7*S*,8*S*,9*aS*)-8-Hydroxy-7-methyl-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (17c, Table 5 Entry 1). Following the general procedure, **C**, the *title compound* **16c** was prepared from compound **8c** (116 mg) and phenyl propionaldehyde as a white solid (151 mg, 83 %). $[\alpha]_D^{26}$ = +82.0 (*c* 1.0, $CHCl_3$); M.p. 132-134 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 5 H), 7.28-7.25 (m, 2 H), 7.19-7.16 (m, 1 H), 7.14-7.08 (m, 2 H), 4.44-4.34 (m, 2 H), 4.27 (dd, *J* = 2.8, 5.6 Hz, 1 H), 4.13 (dd, *J* = 2.8, 5.6 Hz, 1 H), 3.65 (dt, *J* = 4.0, 4.4 Hz, 1 H), 2.94-2.87 (m, 1 H), 2.67-2.60 (m, 1 H), 2.34-2.27 (m, 1 H), 2.20-2.15 (m, 1 H), 2.06-1.98 (m, 1 H), 1.76-1.66 (m, 1 H), 1.62-1.57 (m, 1 H), 0.81(d, *J* = 5.6 Hz, 3 H), ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 142.3, 135.7, 129.2, 129.0, 128.7, 128.5, 128.3, 125.9, 77.3, 77.1, 76.8, 73.9, 70.01 59.0, 55.6, 54.6, 34.9, 33.3, 33.1, 27.4, 13.9 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1701, 1245, 1059, 699 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{23}H_{28}NO_3$ 366.2069; found 366.2072.

(4*S*,6*R*,7*S*,8*aS*)-7-(2-Chloropropan-2-yl)-6-phenethyl-4-phenylhexahydro-1H-pyrrolo[2,1-*c*] [1,4] oxazin-1-one (18a, Table 5 Entry 2).Following the general procedure **C**, the *title compound* **17a** was prepared from compound **8e** (123 mg) and phenyl propionaldehyde as a white solid (125 mg, 63 %). $[\alpha]_D^{26}$ = +32.0 (*c* 1.0, $CHCl_3$); M.p. 152-154 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.32 (m, 5 H), 7.21-7.08 (m, 3 H), 6.86-6.81 (m, 2 H), 4.40-4.33 (m, 1 H), 4.28-4.160 (m, 4 H), 3.10-3.04 (m, 1 H), 2.60 (q, *J* = 4.8, 8 Hz, 1 H), 2.44-2.37 (m, 3 H), 2.23-2.11 (m, 3 H), 1.73-1.64 (m, 1 H), 1.57 (s, 3 H), 1.48 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.2, 142.3, 137.4, 129.1, 128.8, 128.4, 128.3, 128.2, 125.7, 77.4, 77.1, 76.7, 72.9, 72.3, 66.2, 60.6, 59.6, 56.5, 39.0, 32.8, 32.5, 32.1, 32.0 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1752, 1384, 1156, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{24}H_{29}{}^{35}ClNO_2$ 398.1886; found 398.1884; calcd for $C_{24}H_{29}{}^{37}ClNO_2$ 400.1857; found 400.1861.

(4*S*,6*R*,7*S*,8*aS*)-7-(2-Hydroxypropan-2-yl)-6-phenethyl-4-phenylhexahydro-1H-pyrrolo[2,1-*c*] [1,4] oxazin-1-one (18b, Table 5 Entry 2). Following the general procedure, **A**, the *title compound* **17b** was prepared from compound **8e** (123 mg) and 3-phenylpropionaldehyde as a white solid (144 mg, 76 %). $[\alpha]_D^{26}$ = +136.0 (*c* 1.0, $CHCl_3$); M.p. 134-136 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.34 (m, 5 H), 7.21-7.08 (m, 3 H), 6.77-6.69 (m, 2 H), 4.35-4.12 (m, 3 H), 4.06 (dd, *J* = 4.0, 7.6 Hz, 1 H), 3.06 (q, *J* = 5.2 Hz, 1 H), 2.52-2.25 (m, 2 H), 2.01-1.94 (m, 1 H), 1.71-1.44 (m, 3 H), 1.28 (s, 3 H), 1.14 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 142.5, 138.8, 128.8, 128.4, 128.2, 125.6 77.42, 77.1, 76.8, 72.1, 71.2, 66.6, 61.4, 60.2, 52.7, 37.8, 31.2, 29.4, 28.9 ppm; ν_{max}(neat)/cm^{-1}: 2980, 1667, 1453, 1155, 1029, 646 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{24}H_{30}NO_3$ 380.2225; found 380.2221.

(4*S*,6*R*,7*S*,8*aS*)-7-(2-Hydroxypropan-2-yl)-4-phenyl-6-propylhexahydro-1H-pyrrolo[2,1-*c*] [1,4] oxazin-1-one (18c, Table 5 Entry 3). Following the general procedure, **A**, the *title compound* **17c** was prepared from compound **8e** (123 mg) and butanal as a white solid (114 mg, 72 %). $[\alpha]_D^{26}$ = +182.0 (*c* 1.0, $CHCl_3$); M.p. 140-142 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.28 (m, 5 H), 4.29-4.15 (m, 2 H), 4.07-4.02 (m, 2 H), 2.96 (q, *J* = 5.2 Hz, 1 H), 2.40-2.25 (m, 2 H), 1.87-1.81 (m, 1 H), 1.41 (bs, 1 H), 1.33-1.06 (m, 10 H), 0.54 (t, *J* = 7.2 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.8, 138.5, 128.6, 128.5, 128.3, 77.4, 77.1, 76.7, 72.4, 71.1, 65.9, 60.7, 60.5, 53.3, 38.5, 30.1, 29.5, 29.0, 18.3, 13.9 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1733, 1355, 1111, 1017, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{19}H_{28}NO_3$ 318.2069; found 318.2079.

(4*S*,6*R*,7*R*,8*aS*)-6-Phenethyl-4-phenyl-7-(prop-1-en-2-yl) hexahydro-1H-pyrrolo[2,1-*c*] [1,4] oxazin-1-one: (18d, Table 5, Entry 4). Following the general procedure **E**, the *title compound* **17d** was prepared from compound **8e** (123 mg) and phenyl propionaldehyde in presence of catalytic amount of Sc $(OTf)_3$ as a white solid (90 mg, 51 %). $[\alpha]_D^{26}$ = -63.0 (*c* 1.0, $CHCl_3$); M.p. 168-170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51-7.32 (m, 5 H), 7.16-7.04 (m, 3 H), 6.58-6.53 (m, 2 H), 4.87-4.82 (m, 2 H), 4.28-4.16 (m, 3 H), 3.91-3.84 (m, 1 H), 2.83-2.70 (m, 2 H), 2.44-2.32 (m, 3 H), 1.73-1.62 (m, 2 H), 1.55 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.4, 144.2, 142.3, 139.3, 128.9, 128.3, 128.1, 128.1, 127.8, 125.5, 113.1, 77.4, 77.1, 76.7, 71.2, 68.1, 63.1, 58.5, 49.8, 33.4, 31.0, 29.8, 19.2. ppm; ν_{max}(neat)/cm^{-1}: 2981, 1756, 1454, 1137, 1071, 699 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{24}H_{28}NO_2$ 362.2120; found 362.2122.

(4*S*,6*R*,8*R*,9*aS*)-8-Chloro-8-methyl-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (19a, Table 5 Entry 5). Following the general procedure **C**, the *title compound* **18a** was prepared from compound **8d** (116 mg) and 3-phenylpropionaldehyde as a white solid (145 mg, 76 %). $[\alpha]_D^{26}$ = +162.0 (*c* 1.0, $CHCl_3$); M.p. 138-140 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.42 (m, 2 H), 7.40-7.24 (m, 5 H), 7.22-7.15 (m, 1 H), 7.14-7.08 (m, 2 H), 4.75-4.55 (m, 2 H), 4.40 (t, *J* = 4.4 Hz, 1 H), 3.76 (t, *J* = 5.6 Hz, 1 H), 3.30-3.23 (m, 1 H), 2.88-2.80 (m, 1 H), 2.66 (t, *J* = 8.8 Hz, 1 H), 2.17-2.11 (m, 1 H), 1.98-1.71 (m, 3 H), 1.70 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 141.7, 137.3, 129.1, 128.6, 128.5, 128.3, 127.9, 126.2, 67.6, 67.4, 54.9, 53.5, 52.9, 43.4, 38.9, 35.2, 33.0, 31.6 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1740, 1382, 1151,

953, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{23}H_{27}{}^{35}ClNO_2$ 384.1730; found 384.1734; calcd for $C_{23}H_{27}{}^{37}ClNO_2$ 386.1701; found 386.1709.

(4*S*,6*R*,8*R*,9*aS*)-8-Chloro-8-methyl-4-phenyl-6-propylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (19b, Table 5 Entry 6). Following the general procedure **C**, the *title compound* **18b** was prepared from compound **8d** (116 mg) and butanal as a white solid (115 mg, 72 %). $[\alpha]_D{}^{26}$ = +126.0 (*c* 1.0, $CHCl_3$); M.pt. 126-128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.42 (m, 2 H), 7.40-7.27 (m, 3 H), 4.80 (dd, *J* = 4.4, 7.6 Hz, 1 H), 4.62 (dd, *J* = 4.8, 7.7 Hz, 1 H), 4.39 (t, *J* = 4.4 Hz, 1 H), 3.72 (t, *J* = 5.6 Hz, 1 H), 3.23-3.13 (m, 1 H), 2.88-2.79 (m, 1 H), 2.10-2.03 (m, 1 H), 1.87 (dd, *J* = 6.0 Hz, 1 H), 1.67 (s, 3 H), 1.65-1.59 (m, 2 H), 1.48-1.36 (m, 3 H), 0.87 (t, *J* = 7.2 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 137.6, 129.0, 128.3, 127.8, 77.4, 77.1, 76.7, 67.7, 67.6, 54.8, 53.5, 52.9, 43.5, 38.9, 35.4, 33.0, 18.4, 14.4 ppm; ν_{max}(neat)/cm^{-1}: 2965, 1723, 1367, 1148, 948, 688 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{18}H_{25}{}^{35}ClNO_2$ 322.1573; found 322.1572; calcd for $C_{18}H_{25}{}^{37}ClNO_2$ 324.1544; found 324.1551.

(4*S*,6*R*,8*R*,9*aS*)-8-Hydroxy-8-methyl-6-phenethyl-4-phenylhexahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (19c, Table 5 Entry 7). Following the general procedure, **A**, the *title compound* **18c** was prepared from compound **8d** (116 mg) and phenyl propionaldehyde as a white solid (146 mg, 80 %). $[\alpha]_D{}^{26}$ = +56.0 (*c* 1.0, $CHCl_3$); M.pt. 136-134 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46-7.29 (m, 5 H), 7.19-7.07 (m, 3 H), 6.79-6.74 (m, 2 H), 4.52 (q, *J* = 10.8 Hz, 1 H), 4.29-4.20 (m, 2 H), 3.99 (dd, *J* = 2.4, 4.0 Hz, 1 H), 3.25 (bs, 1 H), 3.12-3.05 (m, 1 H), 2.51-2.40 (m, 2 H), 1.94-1.47 (m, 3 H), 1.32 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.1, 142.1, 139.4, 129.0, 128.3, 128.2, 128.1, 127.1, 125.8, 77.4, 77.1, 76.7, 69.6, 66.5, 60.1, 55.3, 53.8, 43.2, 36.3, 35.6, 31.3, 30.5 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1732, 1391, 1115, 751, 697 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{23}H_{28}NO_3$ 366.2069; found 366.2071.

(4*S*,6*R*,8*R*,9*aS*)-8-Hydroxy-8-methyl-4-phenyl-6-propylhexahydropyrido[2,1-c] [1,4] oxazin-1(6H)-one (19d, Table 5 Entry 8). Following the general procedure, **A**, the *title compound* **18d** was prepared from compound **8d** (116 mg) and butanal as a white solid (114 mg, 75 %). $[\alpha]_D{}^{26}$ = +320.0 (*c* 1.0, $CHCl_3$); M.pt. 128-130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46-7.25 (m, 4 H), 7.31-7.26 (m, 1 H), 4.60-4.51 (m, 1 H), 4.33-4.20 (m, 2 H), 3.95-3.90 (m, 1 H), 3.24 (m, 1 H), 2.96-2.90 (m, 1 H), 2.462.38 (m, 1 H), 1.881.70 (m, 2 H), 1.50-1.36 (m, 2 H), 1.28 (s, 3 H), 1.22-1.12 (m, 2 H), 1.32 (t, *J* = 6.8 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.2, 139.7, 128.8, 127.9, 127.0, 77.4, 77.1, 76.8, 69.6, 66.5, 59.9, 55.4, 53.7, 43.3, 36.3, 35.8, 31.3, 17.7, 14.2 ppm; ν_{max}(neat)/cm^{-1}: 2956, 2872, 1717, 1399, 1123, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{18}H_{26}NO_3$ 304.1912; found 304.1917.

(4*S*,6*R*,9*aS*)-8-chloro-6-phenethyl-4-phenyl-3,4,9,9a-tetrahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (20a, Table 5 Entry 9). Following the general procedure **C**, the *title compound* **19a** was prepared from compound **8b** (107 mg) and 3-phenylpropionaldehyde as a semi solid (128 mg, 70 %). $[\alpha]_D{}^{26}$ = -83.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5 H), 7.23-7.11 (m, 3 H), 7.04-6.98 (m, 2 H), 5.77-5.73 (m, 1 H), 4.37-4.22 (m, 3 H), 4.11 (dd, *J* = 5.2 Hz, 1 H), 3.13-3.05 (m, 1 H), 2.90-2.79 (m, 1 H), 2.72-2.41 (m, 3 H), 1.78-1.62 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 141.4, 135.9, 129.2, 129.0, 128.5, 128.5, 128.2, 127.5, 126.0, 125.6, 77.4, 77.1, 76.7, 73.4, 57.2, 56.0, 53.8, 35.9, 32.4, 30.1 ppm; ν_{max}(neat)/cm^{-1}: 2958,1746, 1454, 1121, 1040, 747, 660 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{22}H_{23}{}^{35}ClNO_2$ 368.1417; found 368.1418; calcd for $C_{22}H_{23}{}^{37}ClNO_2$ 370.1388; found 370.1397.

(4*S*,6*R*,9*aS*)-8-bromo-6-phenethyl-4-phenyl-3,4,9,9a-tetrahydropyrido[2,1-*c*] [1,4] oxazin-1(6*H*)-one (20b, Table 5 Entry 9). Following the general procedure **C**, the *title compound* **19b** was prepared from compound **8b** (107 mg) and 3-phenylpropionaldehyde as a semi solid (146 mg, 71 %). $[\alpha]_D{}^{26}$ = -232.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5 H), 7.23-7.11 (m, 3 H), 7.04-6.98 (m, 2 H), 6.01-5.92 (m, 1 H), 4.37-4.26 (m, 3 H), 4.11 (dd, *J* = 5.2 Hz, 1 H), 3.05-2.91 (m, 2 H), 2.74-2.66 (m, 2 H), 2.47-2.40 (m, 1 H), 1.78-1.64 (m, 2 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 141.4, 135.9, 129.2, 129.1, 128.5, 128.5, 128.2, 127.5, 126.0, 125.6, 77.4, 77.1, 76.7, 73.4, 57.1, 56.0, 53.8, 35.9, 32.4, 30.1 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1727, 1454, 1249, 1137, 700, 594 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{22}H_{23}{}^{79}BrNO_2$ 412.0912; found 414.0907; calcd for $C_{22}H_{23}{}^{81}BrNO_2$ 414.0892; found 414.0918.

General procedure F: Hydrogenation reaction: The compound (0.5 mmol) was dissolved in ethanol (10mL) and exhaustively (14 h) hydrogenated with double pressured balloon over 10% Pd-C (0.1 g). The catalyst was removed by filtration and the filtrate concentrated. The resulting crude compound was washed with Ether twice for removal of non-polar impurities and dried to give pure white solid.

General procedure G: Hydrogenation reaction: The compound (0.5 mmol) was dissolved in ethanol (10 mL) containing TFA (1 equiv) at room temperature and exhaustively (14 h) hydrogenated with double pressured balloon over 10% $Pd(OH)_2$ (0.1 g). The catalyst was removed by filtration and the filtrate concentrated. The resulting crude compound was washed with Ether twice for removal of non-polar impurities and dried to give pure white solid.

General procedure H: Hydrogenation reaction: The compound (0.5 mmol) was dissolved in ethanolic HCl (10 mL) at room temperature and exhaustively (14 h) hydrogenated with double pressured balloon over 10% $Pd(OH)_2$ (0.1 g). The catalyst was removed by filtration and the filtrate concentrated. The resulting crude compound was washed with diethyl ether twice for removal of non-polar impurities and dried to give pure semi solid.

(2*R*,4*R*,6*S*)-4-Hydroxy-6-propylpiperidine-2-carboxylic acid (Table 6 Entry 1): (21a, Starting material is 9b, Table 2, entry). Following the general procedure **F**, the *title compound* was prepared from compound **9b** (183 mg) as a white solid (88 mg, 95 %). $[\alpha]_D{}^{26}$ +40.0 (*c* 1.0, MeOH); M.pt. 260-262 °C; ^1H NMR (400 MHz, D_2O): δ 4.18-4.10 (m, 1 H), 3.88-3.72 (m, 2 H), 2.28-2.16 (m, 1 H), 2.04-1.72 (m, 3 H), 1.71-1.56 (m, 2 H), 1.50-1.20 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.6, 64.7, 56.0, 53.1, 36.0, 35.6, 35.2, 21.0, 15.6 ppm; ν_{max}(neat)/cm^{-1}: 2971, 2489, 1596, 1393, 1096, 836, 576 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_9H_{18}NO_3$ 188.1286; found 188.1290.

(2*S*,4*S*,6*R*)-4-Hydroxy-6-propylpiperidine-2-carboxylic acid (Table 6 Entry 1): (21a',Starting material is 9b', Table 2, Entry 8). Following the general procedure **F**, the *title compound* was prepared from compound **9b'** (183 mg) as a white solid (83 mg, 93 %). $[\alpha]_D{}^{26}$ = -64.0 (c 1.0, MeOH); M.pt. 280-282 °C; ^1H NMR (400 MHz, D_2O): δ 4.06-3.98 (m, 1 H),

3.75-3.68 (m, 2 H), 2.17-2.06 (m, 1 H), 1.90-1.63 (m, 3 H), 1.60-1.46 (m, 2 H), 1.35-1.21 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.8, 61.9, 53.2, 50.2, 33.2, 32.8, 32.4, 18.2, 12.8 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1616, 1381, 1085, 940, 586 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_9H_{18}NO_3$ 188.1286; found 188.1290.

(2*R*,4*R*,6*S*)-6-Heptyl-4-hydroxypiperidine-2-carboxylic acid: (21b, Table 6 Entry 2). Following the general procedure **F**, the *title compound* **20b** was prepared from compound **9e** (211 mg) as a white solid (110 mg, 92 %). $[\alpha]_D^{26}$ = -63.0 (*c* 1.0, $CHCl_3$); M.pt. 164-166 ºC; ^1H NMR (400 MHz, D_2O): δ 4.10-4.03 (m, 1 H), 3.98 (t, *J* = 4.4 Hz, 1 H), 3.72-3.64 (m, 1 H), 2.09 (t, *J* = 4.0 Hz, 3 H), 1.83-1.65 (m, 2 H), 1.58-1.50 (m, 2 H), 1.34-1.15 (m, 10 H), 0.72 (t, *J* = 5.6 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.5, 61.7, 52.1, 49.7, 33.5, 31.8, 31.2, 31.1, 28.2, 24.4, 22.1, 13.5 ppm; ν_{max}(neat)/cm^{-1}: 2971, 1740, 1382, 1151, 953, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{13}H_{26}NO_3$ 244.1913; found 244.1912.

(2*R*,4*R*,6*S*)-4-Acetamido-6-phenethylpiperidine-2-carboxylic acid (21c, Table 6, Entry 3). Following the general procedure **F**, the *title compound* was prepared from compound **10a** (234 mg) as a white solid (133 mg, 91 %). $[\alpha]_D^{26}$ = -80.0 (c 1.0, H2O); M.pt. 182-184 ºC; ^1H NMR (400 MHz, D_2O): δ 7.45-7.21 (m, 5 H), 4.16-3.97 (m, 2 H), 3.78-3.60 (m, 1 H), 2.88-2.67 (m, 2 H), 2.39-2.24 (m, 1 H), 2.34-2.02 (m, 4 H), 1.92 (s, 3 H), 1.78-1.71 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.9, 140.6, 129.0, 128.6, 126.7, 51.4, 41.3, 31.1, 30.9, 30.4, 30.1, 22.0 ppm; ν_{max}(neat)/cm^{-1}: 2980, 1587, 1379, 1085, 586 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1708; found 291.1711.

(2*S*,4*S*,6*R*)-4-Acetamido-6-phenethylpiperidine-2-carboxylic acid (21c', Table 6 Entry 3). Following the general procedure **F**, the *title compound* was prepared from compound **10a'** (234 mg) as a white solid (121 mg, 89 %). $[\alpha]_D^{26}$ = +40.00 (c 1.0, MeOH); M.pt. 170-172 ºC; ^1H NMR (400 MHz, D_2O): δ 7.32-7.03 (m, 5 H), 4.00-3.89 (m, 1 H), 3.78-3.69 (m, 1 H), 3.60-3.52 (m, 1 H), 2.73-2.54 (m, 2 H), 2.22-2.17 (m, 1 H), 2.06-1.87 (m, 3 H), 1.81 (s, 3 H), 1.71-1.60 (m, 2 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.6, 173.3, 140.6, 128.9, 128.5, 126.6, 53.6, 51.4, 41.3, 31.1, 30.9, 30.5, 30.0, 22.0 ppm; ν_{max}(neat)/cm^{-1}: 2981, 1627, 1371, 749, 516 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1708; found 291.1711.

(2*S*,4*R*,6*R*)-4-Hydroxy-6-propylpiperidine-2-carboxylic acid (21d, Table 6, Entry 4). Following the general procedure **G**, the *title compound* **20d** was prepared from compound **14a** (145 mg) as a white solid (73 mg, 76 %). $[\alpha]_D^{26}$ = -116.0 (*c* 1.0, $CHCl_3$); M.pt. 246-248 ºC; ^1H NMR (400 MHz, D_2O): δ 4.28-3.98 (m, 2 H), 3.75-3.68 (m, 1 H), 2.38-2.15 (m, 1 H), 2.13-2.00 (m, 1 H), 1.92-1.79 (m, 1 H), 1.70-1.46 (m, 3 H), 1.35-1.28 (m, 2 H), 0.81 (t, *J* = 6.0 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ^{13}C 170.5, 61.5, 53.4, 51.3, 48.9, 33.5, 31.0, 17.8, 12.7 ppm; ν_{max}(neat)/cm^{-1}: 2973, 1656, 1451, 1032, 956, 593 cm^{-1}; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_9H_{18}NO_3$ 188.1286; found 188.1290.

(2*S*,4*R*,6*R*)-Ethyl 4-chloro-6-phenethylpiperidine-2-carboxylate: (21e, Table 6, entry 5). Following the general procedure **H**, the *title compound* **20e** was prepared from compound **12a** (185 mg) as a semi solid (99 mg, 68 %). $[\alpha]_D^{26}$ = -26.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, D_2O): δ 7.37-7.24 (m, 5 H), 4.67-4.56 (m, 1 H), 4.47-4.38 (m, 1 H), 4.28-4.17 (m, 1 H), 3.85-3.75 (m, 1 H), 3.60 (q, *J* = 7.2 Hz, 2 H), 2.87-2.48 (m, 4 H), 2.32-2.27 (m, 1 H), 2.13-1.97 (m, 3 H), 1.12 (t, *J* = 6.0 Hz, 3 H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, D_2O): δ 162.6, 138.6, 129.1, 128.4, 126.3, 103.7, 74.4, 71.3, 55.2, 52.2, 36.1, 35.4, 33.9, 18.6, 13.8 ppm; ν_{max}(neat)/cm^{-1}: 2956, 1732, 1424, 1133, 983, 673 cm-1; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{23}{}^{35}ClNO_2$ 296.1417; found 296.1410; calcd for $C_{16}H_{23}{}^{37}ClNO_2$ 298.1388; found 298.1385.

ASSOCIATED CONTENT

Supporting Information. Preparation, screening results, characterization data, NMR spectra.
This material is available free of charge via the Internet at http://pubs.acs.org.
Accession Codes: CCDC 2014403, 1950084, 2014404 and 1950070 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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