Synthesis of 3-alkyl oxazolidines, derived from 2-hydroxymethyl piperidine, as analytical standards for the analysis of volatile aldehydes in the workplace

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Abstract: Hexahydro-3-alkyl-3*H*-oxazolo[3,4-a]pyridines **4-15** for the quantitative analysis of various aldehydes were obtained in good yield *via* the condensation reaction of 2-hydroxymethylpiperidine (2-HMP) with aldehydes under mild conditions. When acrolein is used, the bicyclic **17** was obtained. This novel compound has suitable physical characteristic for an analytical standard. The hexahydro-3-vinyl-3*H*-oxazolo[3,4-a]pyridine **16** can be achieve at higher temperature. Using specific conditions, a diastereomeric mixture of **18**/**19** and pure **18**, which are both bisadducts of 2-HMP with acrolein, can be obtained. Mechanistically, a thorough ^{1}H-NMR study did not show any evidence that the condensation reaction proceeded *via* an enamine. The reaction probably proceeds through an elusive hemiaminal and fleeting iminium ion, which underwent subsequent cyclisation to gave hexahydro-3-alkyl-3*H*-oxazolo[3,4-a]pyridines **4-16**. The reaction pathways for the preparation of **4-18** are described.

Key word: 2-hydroxymethylpiperidine (2-HMP); Heterocycle; Oxazolidine; Hexahydro-oxazolopyridine; Octahydro-oxazepanol; Analytical standard; Addition 1,2/1,4-α/β-unsaturated aldehyde.

1. Introduction:

The condensation of an aldehyde or ketone with a β-amino alcohol is of considerable interest in synthetic organic. The cycladducts produced, i.e., oxazolidines are useful in drug development and can act as chiral auxiliaries in various asymmetric transformations such as prodrugs, improving the pharmacokinetic profile of β-amino alcohol pharmacophores.[1-5] They are also known biocides, used to prevent the growth of undesirable algal, barnacle or fungal growth on submerged or partially submerged structures in aquatic environments and to inhibit fungal growth in hydrocarbon fuels.[6] The bicyclic octahydro-3H-pyrido[2,1-c][1,4]oxazepan ring system (similar to **17**) is an important component of the skeleton of some interesting natural products, for example, the neurotoxin batrachotoxin as well as glycosidase enzyme inhibitors.[7-9]

These heterocycles are also of analytical interest. Indeed, volatile aldehydes are reactive in the air and require stabilization via chemisorption during sampling for occupational exposure assessment or air quality, and to ensure a reliable quantification through instrumental analysis. One of the options to efficiently stabilise aldehydes in air was developed by the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) using 2-piperidinemethanol (better known as: 2-hydroxymethyl piperidine or 2-HMP) derivatives.[10-11] The second most common option is with the use of 2,4-dinitrophyenyhydrazine derivatives.[12-16] However, some authors reported concerns with unsaturated aldehydes, such as acrolein and crotonaldehyde, due to the presence of by-products and stability issues.[17-18] As with any reliable analytical method, the availability or information regarding the preparation of stable analytical standards with high purity is imperative, which is actually lacking in the methods using 2-piperidinemethanol.

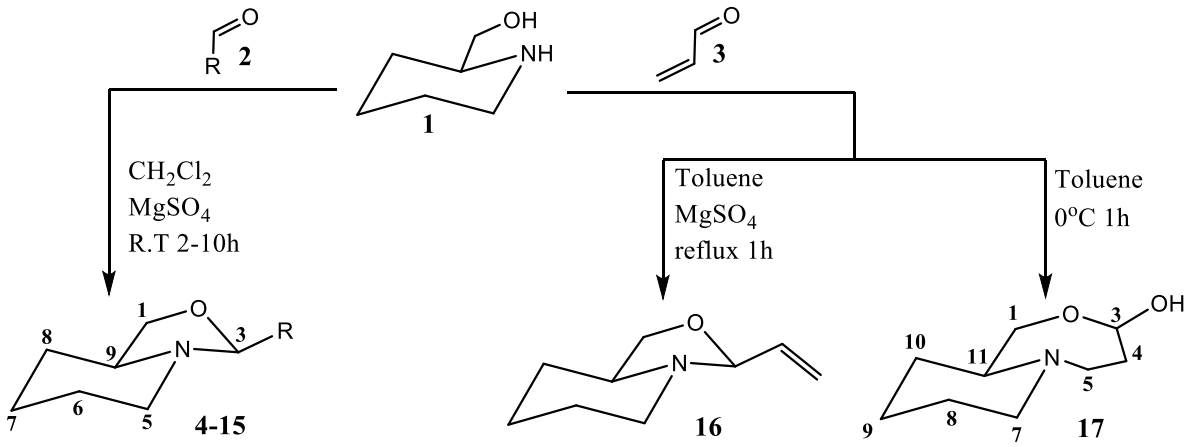
Even though bicyclic oxazolidines are well-known five-membered nitrogen-oxygen heterocycles, a comprehensive review of their generation and mechanism has not been reported. Indeed, conflicting reports of the capture of aldehydes by 2-HMP were found in the literature. Notably, Kennedy and Ashley reported the formation of oxazolopiperidine using 2-HMP and proposed, based on IR studies, that the reaction proceeded via an enamine intermediate while other authors, rather, reported to proceed via an iminium intermediate.[19-21] Thus, we were prompted to reinvestigate the reaction involving 2-HMP with a series of

substituted aldehydes in order to gain a deeper understanding of its mechanism and to establish optimal conditions for the generation of analytical standards **4-15** and **17**.

2. Results and discussion

2.1.1 Synthesis: A potentially attractive approach for the detection of volatile aldehydes would be to capture the aldehyde in question with a binucleophilic agent such as 2-HMP, producing a 1,3-oxazolidine.[22-24] Therefore, we investigated the condensation of various aldehydes with 2-HMP and obtained the corresponding hexahydro-3-alkyl-1,3-oxazolopiperidines **4-15** in high yields (see **Table 1**). Optimization of the reaction conditions was explored, changes in: solvent (hexane, benzene, toluene, xylene, DCM and MeOH); acid present (PPTs, p-TsA and BF_3OEt); dehydrating agent ($MgSO_4$, 4 Å molecular sieves and Dean-Stark trap) and temperature were considered. The condensation occurs best at neutral pH. Indeed, in the case of acetaldehyde, the use of BF_3OEt (5% mole) resulted exclusively in the acetaldehyde trimer (paracetaldehyde). The reaction involving the diethylacetal derivative of acetaldehyde and acrolein in the presence of p-TsA or PPTs in toluene or benzene did not provide the corresponding products **5** nor **16**. Ultimately, the mildest conditions for the condensation reaction were: anhydrous $MgSO_4$ in dichloromethane (DCM), or toluene at room temperature. The other solvents investigated led to lower yields (THF, MeOH: **Table 1** entries 13 - 14); or were more difficult to remove (xylene, **Table 2** entry 13).

The temperature was critical from low to high boiling solvents in the reaction involving acrolein, see **Scheme 1** and **Table 2**. Contrary to that previously reported, the reaction of acrolein with 2-HMP at room temperature in toluene does not give compound **16**.[23] Instead, under these conditions, either in DCM, hexane or toluene, the reaction provides mostly octahydro-3*H*-pyrido[2,1-c][1,4]oxazepin-3-ol **17** with trace of **18**-**19**. The use of hexanes at reflux for 1 hour gave an almost 50/50 mixture of **16** and **17.** Increasing the reflux time pushed the reaction toward **16,** while toluene at reflux produced the oxazolopiperidine **16** in 85% yield.



Scheme 1. Reactions of 2-HMP with different aldehydes

4: R = H; **5**: R = -CH_3; **6**: R = -CH_2CH_3; **7**: R = -$(CH_2)_2CH_3$; **8**: R = -$CH(CH_3)_2$; **9**: R = -$C{=}CHCH_3$; **10**: R = -$(CH_2)_3CH_3$; **11**: R = -$C(CH_3)_3$; **12**: R = -$CH_2CH(CH_3)_2$; **13**: R = -$(CH_2)_4CH_3$; **14**: R = -$(CH_2)_5CH_3$; **15**: R = furyl

Table 1. Reaction summary of **4-15** from the condensation of aldehydes **2** with 2-HMP **1**

Entry	Aldehyde 2 (- R)	Ratio*† Equiv	Solvent	Temp. (°C)	Time (h)	Product No	Yield (%)
1	- H	1.1	CH_2Cl_2	RT	2	**4**	96
2	- CH_3	2.0	CH_2Cl_2	RT	2	**5**	93
3	- CH_2CH_3	1.0	CH_2Cl_2	RT	2	**6**	52
4	- $(CH_2)_2CH_3$	1.0	CH_2Cl_2	RT	3	**7**	65
5	- $CH(CH_3)_2$	1.0	CH_2Cl_2	RT	3	**8**	70
6	- CH=CH-CH_3	1.2	CH_2Cl_2	RT	3	**9**	82
7	- $(CH_2)_3CH_3$	1.35	CH_2Cl_2	RT	4	**10**	88
8	- $C(CH_3)_3$	1.5	CH_2Cl_2	40	6	**11**	81
9	-$CH_2CH(CH_3)_2$	1.0	CH_2Cl_2	RT	4	**12**	68
10	- $(CH_2)_4CH_3$	1.0	CH_2Cl_2	RT	4	**13**	77
11	-$(CH_2)_5CH_3$	1.0	CH_2Cl_2	RT	4	**14**	72
12	- Furyl	1.2	CH_2Cl_2	RT	10	**15**	78
13	- Furyl	1.2	THF	RT	10	**15**	34
14	- Furyl	1.2	MeOH	RT	10	**15**	56
15	- Furyl	1.2	Toluene	RT	10	**15**	86

** A ratio of 5g of $MgSO_4$ was used for 1g of HMP for formaldehyde at 30% while a mass ratio of $MgSO_4$: HMP of 1:1 was used for the other aldehydes*

† Ratio of aldehyde to HMP

Table 2. Reaction summary of **16-19** from the condensation of acrolein **3** with 2-HMP **1**

Entry	Ratio equiv (Acrolein:HMP)	Solvent	Temp. (°C)	Time (h)	Yield (%)	Product No (Purity ratio %)"
1	1.2	DCM	0	1	93	**17** (96)
2	2	DCM	RT	4	82	**17** + **18/19** (90:10)
3	2	Toluene	RT	1	85	**17** + **18/19** (90:10)
4	3	Hexane*	69	1	ND	**16** + **17** (50:50)
5	3	Hexane*	69	2	80	**16** + **17** (85:15)
6	3	Hexane*	69	4	50	**16** + **17** (85:15)
7	0.5	Toluene*	111	1	95	**18/19** (97)
8	0.8	Toluene*	111	1	ND	**16** + **18/19** (90:10)
9	2	Toluene*	111	0.25	80	**16** + **18/19** (95:5)
10	2	Toluene*	111	0.5	85	**16** + **18/19** (95:5)
11	2	Toluene*	111	1.5	85	**16** + **18/19** (95:5)
12	3	Toluene*	111	1	90	**16** (97)
13	2	Xylene*	139	1	70	**16** + **18/19** (85:15)

* *A mass ratio of $MgSO_4$: HMP of 1:1 was used.*
*" ^{1}H-NMR Ratio of products. Diastereoisomers **18/19** were obtain in various proportion. Overall yield undetermined.*

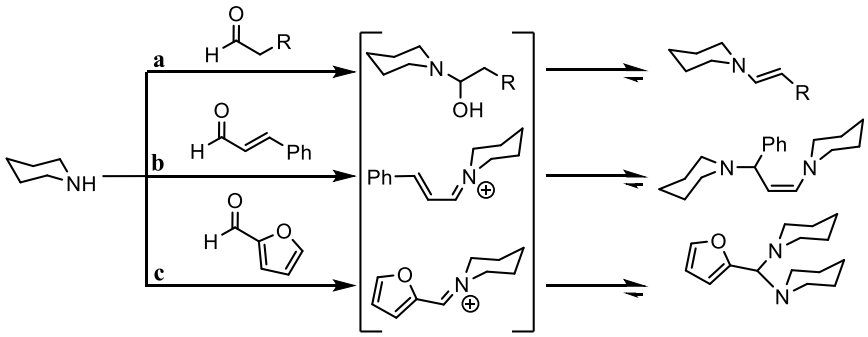
As illustrated in **Scheme 1** and **Tables 1**, **2**, various oxazolopiperidines **4-16** and/or an octahydro-3*H*-pyrido[2,1-c][1,4]oxazepin-3-ol **17** were obtained as mixtures of diastereomers in good yields (avg 80%) from racemic 2-HMP. However, several difficulties were encountered. For example, all the condensation products derived from unsaturated aldehydes (acrolein, crotonaldehyde and furaldehyde) slightly hydrolyse (aldehyde peaks were detected in the ^{1}H-NMR) and thus were difficult to purify. In some cases, a modification of the isolation procedure was required. Furthermore, chromatographic purification must be avoided since some products may undergo hydrolyses or isomerisation, for instance, using silica gel in DCM, compound **16** was transformed progressively into compound **17**. The products of the condensation using formaldehyde, **4,** or acetaldehyde, **5**, were first vacuum distilled in a Kulgelrohr apparatus to remove undesired low boiling impurities and then vacuumed redistilled

from diphenylether. The latter acts as a heat dispersant, suppressing local overheating and decomposition during distillation. All products from **4-16** were purified using vacuum distillation while compounds **17** and **18** were crystalized. **19** could not be isolated in pure form (**Table 2**). Very high degree of purity for all synthesized compounds was achieved. Products **4-18** were rigorously characterised by ^{1}H-NMR and GC-MS. In some cases, further characterization: COSY (**4**, **5**, **9**, **15**, **17-19**), DEPT-HSQC (**18**, **18/19**), NOE (**15**, **17-19**), and X-ray analysis (**17**, **18**) were performed. In the case of **19**, a partial (^{1}H and ^{13}C) characterization was deduced from the differential analysis of mixture of **18/19**.

2.1.2 Analytical standards: The products **4-15** were obtained (avg yield 80%) in high degree of purity (>98%) and were suitable as analytical standards. In the case of acrolein derivatives **16-18**, the relative GC-MS response were equivalent. However, the relative standard deviation was higher for both **16** (10.81%) and **18** (4.63%) than that of **17** (2.73%) (see analytical data for detailed information). Furthermore, while **16** undergoes degradation via slow polymerisation even at -20 ˚C, compound **17** was found to have the best properties as an analytical standard (i.e. ease of synthesis, crystalline state at RT, good stability, etc). Consequently, these results show that the method proposed by Kennedy and Ashley for the determination and the quantification of acrolein in the air must be validated based on the derivatization into **17** at room temperature and not based upon the presumed *in-situ* formed derivative **16** (i.e. UIPAC: 9-vinyl-l-aza-8-oxabicyclo[4.3.0]-nonane).[19, 23]

2.2 Mechanistic aspects: The reaction of various substituted aldehydes with 2-HMP and other β-amino alcohols was first studied by McCarty in 1957, then by Craab and Newton in 1966 and followed by Kennedy and Ashley in 1992.[25-26, 19] Based on the interpretation of FT-IR data, Kennedy and Ashley assumed that reaction proceeded *via* the formation of an enamine intermediate (**Scheme 2a**); that is, leading to an oxazolidine after the reaction was exposed to ultrasound. However, recent work by Gschwind and others, proposed the involvement of an iminium intermediate during the first step of the condensation.[20, 21] In an attempt to distinguish between one of these two pathways, we decided to carry out a series of ^{1}H-NMR studies of the condensation reaction involving 2-HMP or piperidine with the following aldehydes: propanal-, pentanal-, isobutyral-, pival-, furfural- and cinnamal-. These aldehydes were chosen because propanal and pentanal were first used in the IR condensation study, propanal was used in a more recent NMR study and the last three do not have a tautomerisable α-proton.[19, 21a] Isobutyraldehyde was studied because it is less sterically encumbered than pivaldehyde.

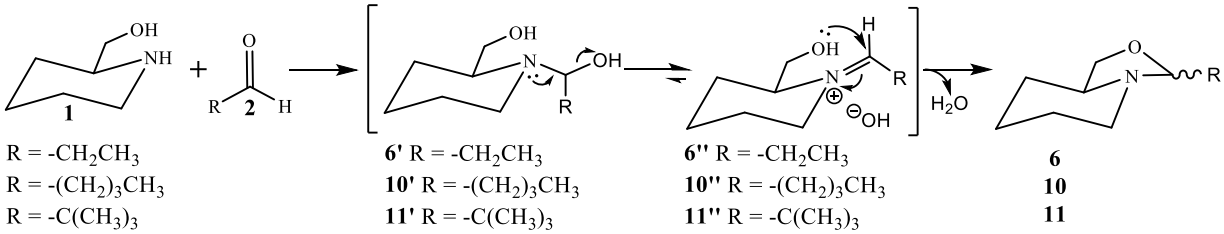
2.2.1 Enamine: Key reference signals for the enamine protons, obtained from the reaction of piperidine with propanal in DMSO-d_6, were at 5.79 ppm (d, N-C**H**=CH-CH_3) and 4.23 ppm (hex-ap, N-CH=C**H**-CH_3) respectively. Similarly, when piperidine was reacted with the more encumbered isobutyraldehyde in $CDCl_3$, over 24hrs at RT, only a progressive increase of an enamine signal at 5.28 ppm (hept-app, N-C**H**=$C(CH_3)_2$) could be observed. It is important to know that a previous study involving prolinol, instead of 2-HMP, with propanal required a polar aprotic solvent such as DMSO-d_6 to allow the observation of low amount of the enamine.[21a] The HMP-propanal (**6**) and HMP-pivaldehyde (**11**) adducts displayed characteristic H-3 protons of the oxazolopiperidine ring system (**Scheme 1**) at 3.81 ppm (t) and 3.51 ppm (s) respectively. 2-HMP was mixed with propanal directly in an NMR tube containing DMSO-d_6 at ambient temperature and the progress of reaction was monitored by ^{1}H-NMR spectroscopy, taking measurement every 5 minute at first and then at every double time interval (up to 3 hrs). In this specific experiment, beside from the initial aldehyde proton and the final oxazolidine **6** proton, the reaction was mostly completed within 20min, we did not observe the above characteristic signals for the enamine intermediate throughout the reaction. In contrast to previous work, the use of ultrasound for the reaction of 2-HMP with one of the following aldehydes: formaldehyde, crotonaldehyde, pivaldehyde and furfuraldehyde, was not required.[19, 22-23] Even though, there is no possibility for enamine intermediate formation, the corresponding oxazolopiperidines (**4**, **9**, **11**, **15**) were obtained at room temperature in DCM. Together, these experiments clearly exclude the necessity of the intermediacy of an enamine (**Scheme 2a**).



Scheme 2: a) Reaction of enamine, b) 1,3-N,N-bis-piperidyl-3-phenylpropene and c) 2-furyl aminal.

2.2.2 Iminium/hemiaminal/Aminal: Key signal at 9.2 ppm for the iminium intermediate derive from proline with 3-methylbutanal was reported by Gschwind while others key iminium peaks were found from 8.4 to 9.3 ppm.[19, 28] The iminium ^{13}C were reported at 166 to 171 ppm.[28] In the reaction of 2-HMP with propanal in DMSO-d_6, we did not observe any signal at

8.6-9.3 ppm expected for an iminium intermediate **6''** (**Scheme 3**). This suggests that the elusive iminium is more rapidly converted into oxazolidine, which is consistent with some previous studies.[21a]



R = -CH_2CH_3	**6'** R = -CH_2CH_3	**6''** R = -CH_2CH_3	**6**
R = -$(CH_2)_3CH_3$	**10'** R = -$(CH_2)_3CH_3$	**10''** R = -$(CH_2)_3CH_3$	**10**
R = -$C(CH_3)_3$	**11'** R = -$C(CH_3)_3$	**11''** R = -$C(CH_3)_3$	**11**

Scheme 3: Proposed mechanism for the formation of the oxazolidine (**6, 10** and **11)** based on ^{1}H-NMR monitoring.

Key values for the ^{1}H and ^{13}C (R_2N-**CH**(OH)-R) signals for hemiaminal intermediates, similar to that of (**Scheme 2a**), but derived from pyrrole/imidazole, were reported at 5.6-6.6 ppm and 77-83 ppm respectively.[29, 30] In the case of 2-HMP with pentanal or pivaldehyde in C_6D_6, we could not observe in the ^{1}H-NMR an iminium intermediate **10''** and **11''** nor an hemiaminal intermediate **10'** and **11'** during these reactions (**Scheme 3**). While for the reaction of 2-HMP with pentanal, we do observe (from 45 sec up to 80 min) new minor signals at 5.75 (vbr s), 3.50 (dd), 3.34-3.28 (br s), 2.94 (br d) and 2.20 (t) ppm, which is probably due to an aminal intermediate (**Scheme 2c**). Further investigations of the reaction of piperidine with cinnamaldehyde or furfuraldehyde were carried out in $CDCl_3$. Two new key proton signals at 3.52 ppm and 3.58 ppm were observed, while the corresponding ^{13}C signals were observed at 72 ppm and 83 ppm. The NMR values are consistent with those reported for the aminal 4,4'-(furan-2-ylmethylene)dipiperidine derive from morpholine[31] and 1,3-*N*,*N*-bis-piperidyl-3-phenylpropene via a 1,2- and 1,4- bis-addition of piperidine on cinnamaldehyde (**Scheme 2b,c**).[32-33]

In line with recent literature, we propose that the condensation reaction of 2-HMP with aldehydes first proceeds via an elusive open hemiaminal such as **10'** or **11'**, which proceed through a fleeting iminium intermediate **10''** or **11''** to give the corresponding oxazolidines (**Scheme 3**).[20-21, 27, 34] In the absence of a proximal hydroxymethyl nucleophile and with a tautomerisable α-proton, it will rearrange rapidly into the more stable enamine structure (**Scheme 2a**).

2.2.3 Oxazolidine formation: In the presence of an intramolecular proximal nucleophile, such as the alcohol function in 2-HMP, it immediately undergoes a rapid nucleophilic attack on the more reactive carbon of the transient iminium ion to form the cyclic oxazolidine as in **6**, **10** or **11** (**Scheme 3**).[21] This can theoretically lead to two diastereomers depending on whether the C-3 substituent is in a pseudo-equatorial or –axial position. Thus, the procedure allows a facile synthesis of a diastereomeric mixture of oxazolopiperidines as oils, for which generally the thermodynamically more stable C-3 pseudo-equatorial diastereomer was observed by NMR. In most cases, except for **9**, two diastereomeric products were obtained (distinguishable by ^{1}H-NMR spectroscopy analysis of the oxazolopiperidine H-3 protons and or GC-MS, generally in a 95:5 ratio and **15** in a 80:20 ratio). The following isomers **15$_M$/15$_m$** and **18**/**19** were characterised by key nOes experiments (**Figure 1**). Products **15** had relaxation issues and required mix nOes and rOes.

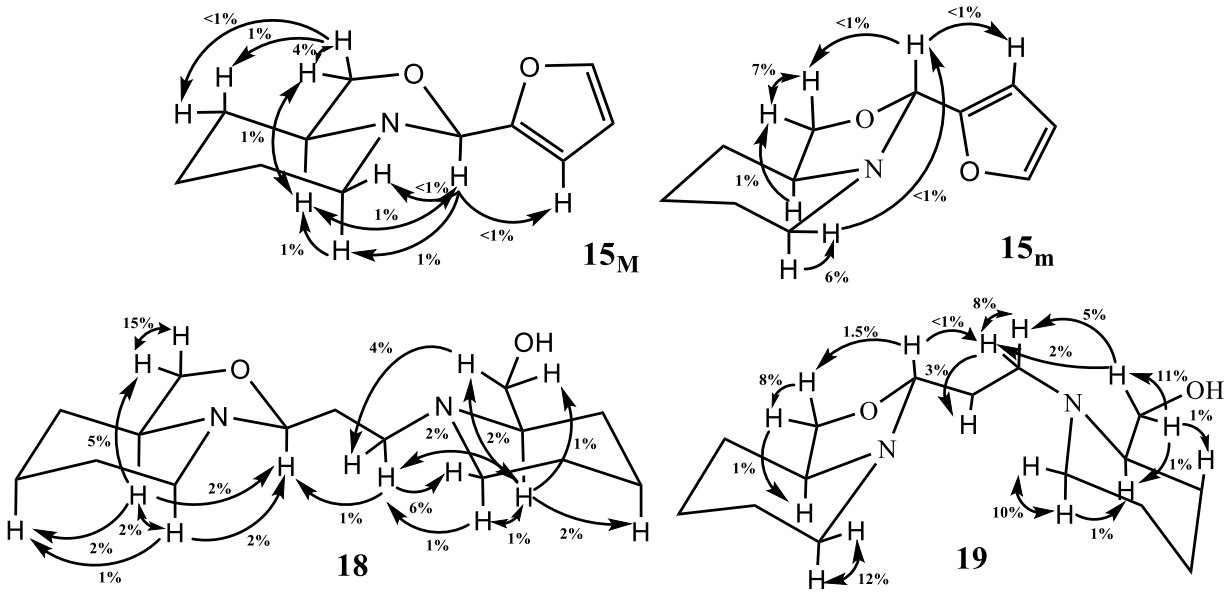


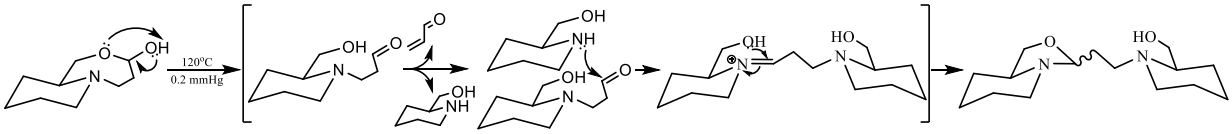
Figure 1: Summary of selected nOes observed for compounds **15$_M$/15$_m$** and **18/19** consistent with the pseudo-equatorial orientation of the C-3 substituents as shown.

The separation of these diastereomeric compounds was not feasible due to equilibration (*via* oxazolidine ring opening and closing) and hydrolysis. Some of the compounds, particularly, **9** and **16** (**Scheme 1**) with an alkene functional group, can easily undergo polymerisation. During this investigation, we observed no formation of 3-vinyl-oxazolopiperidine product **16,** from the similar reaction involving acrolein with 2-HMP at room temperature even after prolonged reaction time (78h). Indeed, none of the characteristic chemical shifts for the proton H-3 or for the alkene protons were observed. Instead, new signals at 5.21 (dd) and 2.62-2.78 (br-s) ppm were present, which we attributed to the C-3 hemiacetal and OH group protons respectively. ^{1}H

and ^{13}C NMR analysis of the white crystalline product **17** thus obtained, was consistent with an octahydro-3*H*-pyrido[2,1-c][1,4]oxazepin-3-ol, ring structure formed by a hemiacetal function. The IR spectrum supported the presence of an alcohol by the presence of an absorption band at 3063cm^{-1}. Furthermore, the structure of **17** was established by an X-ray crystal structure analysis (**Figure 2**). Thus, the reaction at room temperature proceeds via a highly regioselective Michael 1,4-addition of 2-HMP on acrolein and leads, in one step, to a seven-membered oxazepan cycle **17** (**Scheme 1**). Other syntheses of 1,4-oxazepanol involving 2-3 steps were reported.[35] The direct formation of **17** only occurs with acrolein. Indeed, when crotonaldehyde was allowed to react with 2-HMP in the same conditions as above, the 3-(propenyl)-oxazolopiperidine **9** was exclusively obtained as pale-yellow oil. The ^{1}H-NMR displayed the anticipated H-3 signal at 4.0 ppm and the vinyl protons were observed at 5.85 and 5.43 ppm. The formation of oxazolopiperidine in this case (i.e. a 1,2-addition on the carbonyl) is due to the combined steric and electronic factors of the methyl group at C-4 position.

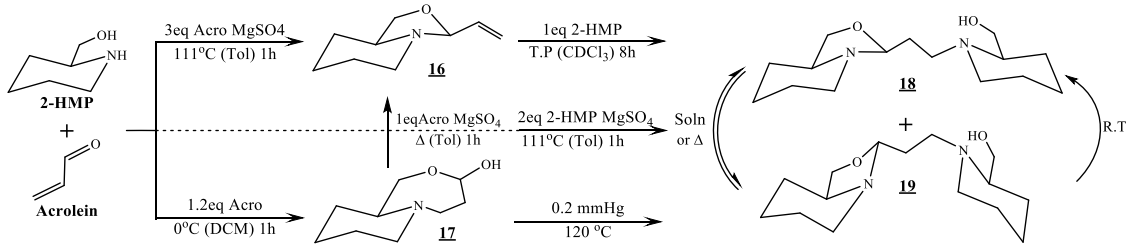
Another benefit as an analytical standard, was the GC-MS behavior of **17** for which the key fragment mass peak was identical to one observed for **16** and **18**. The capture of volatile aldehydes using standard air sampling procedure, involving 2-HMP impregnated on Amberlite XAD-2, is usually done at room temperature.[10] The derived product obtained is extracted and directly analysed by GC-MS. Therefore, in the case of acrolein, the derivative that will most likely be generated is the octahydro-3*H*-pyrido[2,1-c][1,4]oxazepin-3-ol, **17**. When pre-absorbed 2-HMP onto amberlite XAD-2 was allowed to react with acrolein in toluene at room temperature for 1hr, the relative proportion of compounds observed by ^{1}H-NMR was **17** (52%) along with new side products **18**/**19** (48%). However, upon refluxing in toluene for 1h, the adduct **17** underwent partial conversion into the corresponding 3-vinyl-oxazolopiperidine **16** (52%), **18**/**19** (40%), unreacted **17** (7%) and some trace of acrolein (~1%). Furthermore, if 1 eq of acrolein is added to **17**, the conversion leads to almost pure **16** (95%). When the latter was further subjected to column chromatography, it reverts partially to **17** (only 20-30% yield at best), which indicates that **17** is the thermodynamic product. When neat **17** was heated in vacuum (0.2 mmHg, 120ºC), the diastereomeric mixture of bis-adducts **18/19** (70%) is initially obtained as a viscous yellow oil (**Scheme 4**). This mixture slowly crystalizes quantitatively into **18** over 2-3 days. When the latter is melted, it isomerises again into an equal mixture of **18/19**, which reverts slowly to **18** at room temperature as above. Thus, proving that **18**/**19** are diastereomers. We rationalise the formation of **18**/**19** by first an opening of the hemiacetal **17** to the corresponding ring open aldehyde intermediate. Half of it undergoes a reverse Michael

addition generating *in situ* the starting materials 2-HMP of which the volatile acrolein was lost in the vacuum. The residual 2-HMP immediately undergoes a 1,2-addition onto the aldehyde function of the ring open intermediate thus generating **18**/**19**.[36] These can also be generated by the stoichiometric addition of 2-HMP to **16** (RT 8h or after 1hr reflux in toluene). Compounds **18/19** are best obtained starting with 2eq of 2-HMP with acrolein (**Table 2** entry 7, **Scheme 5**).



Scheme 4: Proposed mechanism for the conversion of **17** to **18**/**19** when heated in vacuum

The ^{1}H-NMR of **18** displayed key signals at 3.44(dd), 3.37(dd) 2.90-3.00(m) and 2.45(ddd) ppm and the ^{13}C displayed a doubling of the signals related to 2-HMP. A follow up by ^{1}H-NMR of a solution of **18** in $CDCl_3$ at -20 °C, over a period 3 months, shows a slow, but cleaner, isomerisation of up to 75% of **19**. The following distinct signals of the latter were deduced from the enriched mixture of **19/18** and were observed at 3.97(dd), 3.50(dd), 3.26(dd), 3.15(ddd) and 3.01-3.06(m). Furthermore, the structure of **18** was confirmed by X-ray crystallography analysis (**Figure 2**) and establishes a bisadduct of 2-HMP with acrolein. Both configuration at C3 of **18** (S) and **19** (R) in solution were supported by nOes experiments (**Figure 1**). The flip-flap of C-3 oxazolidine envelope allows the substituent at C-3 to maintain a pseudo-equatorial position.



Scheme 5: Reaction summary for **16-19** involving 2-HMP with acrolein in various conditions

3. X-Ray crystal determination of structure 17 and 18.

The X-ray crystal-structure of **17** is consistent with that anticipated for an oxazepane ring system (**Figure 2**).[37-39] Information for the positional and equivalent thermal isotropic parameters for non-hydrogen atoms, bond distances and angles as well as selected torsional angles can be found in supplementary information and the complete data in the CCDC database.

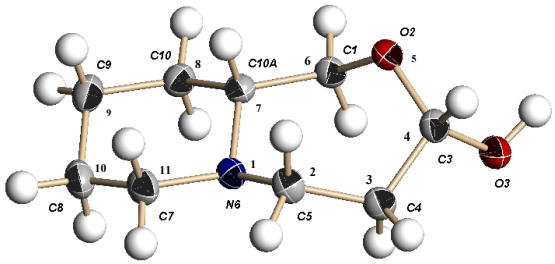


Figure 2: Thermal ellipsoid plot of **17**. Displacement ellipsoids are drawn at the 50% probability level.

The geometry of **17** presents a fused 7,6-membered ring structure with a ring junction essentially *trans*. The alcohol function is in the pseudo axial position to minimize the repulsion between the oxygen lone pairs (anomeric effect).

The X-ray crystal-structure of **18** is shown in **Figure 3**. Information for the positional and equivalent thermal isotropic parameters for non-hydrogen atoms, bond distances and angles as well as selected torsional angles can be found in supplementary information and the complete data in the CCDC database.

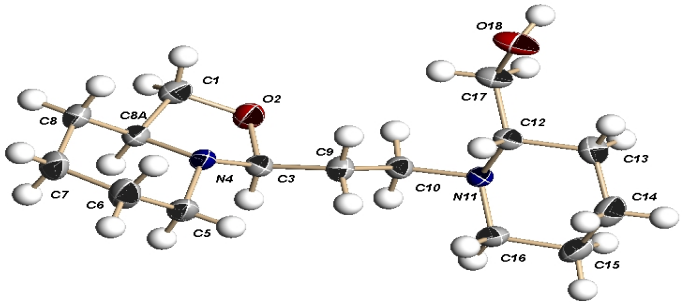


Figure 3 Thermal ellipsoid plot of **18**. Displacement ellipsoids are drawn at the 50% probability level.

The X-ray structure of **18** shows a chair configuration for the six-member ring with a trans ring junction for the 5,6-fused rings. The five-membered ring is in an envelope conformation with atoms C(8A), C(1), O(2) and C(3) in the plane and N(4) forming the flap of the envelope. The C(3) substituent is held in a pseudo equatorial position relative to the fused chair. The other HMP ring is linked on the ethyl C(9)-C(10) in an antiperiplanar fashion.

4. Conclusion

In conclusion, an expedient high yielding route for HMP-aldehydes derivatives as 2-substituted 1,3-oxazolo[4,3-a]piperidines with a high degree of purity suitable for analytical standards was developed. The reaction proceeds even for aldehydes which can't isomerise to an enamine. In the case of acrolein, the path of the reaction is highly temperature dependant and leads to the hemiacetal octahydro-3H-pyrido[2,1-c][1,4]oxazepin-3-ol **17** at room temperature or to the 3-vinyl-1,3-oxazolopiperidine **16** at 111 °C. When further heated under vacuum, compound **17** is transformed into **18/19** which are bisadduct of 2-HMP with acrolein. The diastereomer **18** can be obtained in pure crystalline form. Both structures **17** and **18** were investigated by X-ray crystal analyses. All attempt to observe the hemiaminal or iminium intermediate, lead instead to the observed 2-HMP oxazolidine or aminal derived from piperidine with furfural.

5. Experimental Section

5.1. Equipment and Methods: Melting points were determined in open capillary tube using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT/IR instrument at 25°C. All glassware for reactions under anhydrous conditions was flame-dried prior to use. Heat source was an oil bath. Vacuum distillation was performed using a Kugelrohr apparatus or using a distillation apparatus with a Vigraux Column. For thin layer chromatographies (TLC), silica gel 60 F_{254} plates from Merck were used with detection visualized under UV light and/or iodine chamber. A solution of 5% w/v sulfuric acid in EtOH followed by heat was used as well. Organic phases were dried over anhydrous sodium and magnesium sulphate (Anachemia) and rotary evaporated under reduced pressure. Nuclear magnetic resonance ^{1}H-NMR spectra were recorded using a Varian Gemini 300 BB −300.1 MHz and a Bruker 600 MHz spectrometers. ^{13}C-NMR spectra were recorded at 75 or 125 MHz, respectively. Chemical shifts for observed signals are reported in parts per million downfield from tetramethylsilane. ^{1}H chemical shifts were referenced to the solvents ($CDCl_3$, 7.27 ppm, 77.16 ppm; C_6D_6 7.16 ppm, DMSO-d_6 2.50 ppm or CD_3OD, 3.30 ppm); ^{13}C chemical shifts were referenced to the solvents ($CDCl_3$, 77.03 ppm or CD_3OD, 49.00 ppm). The structure assignment of proton and carbon signals was achieved using NMR methods (^{1}H, ^{13}C and in some cases: nOe, H-COSY and HSQC). The assignments of ^{1}H and ^{13}C NMR chemical shifts for the other compounds were attributed by comparison with those fully characterised. GC-MS were recorded on a Hewlett-Packard - HP G1800A GCD Series II with a

5% Me Ph silicon (30m x 0.25mm x 0.25µm HP part no 19091 J-433). The MS detection mode was EI.

5.2. X-ray Crystallography: For compounds **17** and **18** crystallization was obtain from minimum amount of diethylether and by cooling the solution at -15 to -18˚C. Another way to induce crystallization as leaflet on the side walls of the vial is from slow evaporation of an ether solution at room temperature.

Single crystals were coated with Paratone-N oil, mounted using a 20-micron cryo-loop and frozen in the cold nitrogen stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and θ scans with a scan width of 0.3˚ and 10s (**17**) and 60s (**18**) exposure times. The detector distance was 5 cm. The data were reduced (SAINT)[37] and corrected for absorption (SADABS).[38] The structure was solved by direct methods and refined by full-matrix least squares on F^2(SHELXTL)[39]. All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were found in Fourier difference maps and refined using isotropic displacement parameters.
Data for both compounds have been deposited with the Cambridge Crystallographical Data Centre, CCDC 2212006 for **17** and 2212007 **18**. Structural data is accessible via the CCDC web site https://www.ccdc.cam.ac.uk/.

5.3. Chemicals: Common solvents were obtained from Aldrich and used as received. Hydroxymethylpiperidine (2-HMP, from Aldrich 97% or from TCI 98%) and formaldehyde (Aldrich 37% Aqueous solution) were used without further purification. Other aldehydes were obtained from Aldrich or Anachemia and were distilled prior to use. Amberlite XAD-2 BDH Chemical.

5.4.1 Preparation of hexahydro-3H-oxazolo[3,4-a]pyridine (4)[10, 22]
Formaldehyde (0.72 mL, 37% aqueous solution, 9.67 mmol) was added dropwise via syringe to a solution of 2-HMP (1.00 gr., 8.68 mmol) in DCM (10 mL), the whole mixture was stirred for 10 min at room temperature, anhydrous $MgSO_4$ (5 gr) was added, and the mixture was stirred for 2h while being monitored by TLC (CH_2Cl_2:MeOH (9:1)). The reaction mixture was filtered, and the solvent was removed under reduced pressure to afford a crude product which was then treated with solution of sodium hydroxide (5%). The aqueous solution was extracted with ether (3x20 mL). The combined organic phases were washed with brine and dried over

$MgSO_4$. Filtration and removal of solvents afforded 1.056 gr. (96%) of product. Vacuum fractional distillation using a Vigreaux column under reduced pressure (1.2 torr.) gave a colorless liquid. A wood splint was placed vertically in the flask in order to prevent material bumping and decomposition. A fractional collector (cow) was used, which allowed four fractions to be collected without disturbing the vacuum.

B.p. = 65 ^oC (1.2 torr). GC: R_T = 3.22 min. MS (EI, 70 eV, m/z): 127 (M^+, 32%), 126 (M^+-H, 47%), 97 (M^+-H_2C=O, 100%). ^{1}H-NMR (300MHz, $CDCl_3$): Peaks assignments were supported by a COSY spectrum. 1.26-1.52 (m, 2H, H-7ax, H-8ax), 1.58-1.78 (m, 3H, H-6eq, H-6ax, H-7eq), 1.82-1.92 (dq app, J^2=12.7, J^3=3.2 Hz, 1H, H-8eq), 2.25-2.36 (ddd, J^2=11.1, J^3=6.3, J^3=4.9Hz, 1H, H-5ax), 2.56-2.65 (tdd, J^3=10.4, J^3=6.9, J^3=3.5 Hz, 1H, H-9), 2.87-2.95 (dt, J^2=10.5, J^3=5.3 Hz, 1H, H-5eq), 3.50 (dd, J^3= 10.2, J^2=7.2 Hz, 1H, H-1ax), 3.86 (t, J^2=J^3=6.9 Hz, 1H, H-1eq), 3.99 (d, J^2=3.0 Hz, 1H, H-3ax), 4.56 (d, J^2=3.0 Hz, 1H, H-3eq). ^{13}C-NMR (75MHz, $CDCl_3$): 22.08 (C-7), 24.80 (C-6), 25.35 (C-8), 47.56 (C-5), 60.51 (C-9), 68.69 (C-1), 86.83 (C-3).

5.4.2 **General** *procedure for the preparation of hexahydro-3-alkyl-3H-oxazolo[3,4-a]pyridines*[10, 23-24, 40]

Freshly distilled aldehyde (1-2 equiv. see table 1) was stirred with a solution of 2-HMP (1eq) in DCM (1 mL per mmole of 2-HMP) for 30 min. Anhydrous $MgSO_4$ (a mass ratio of 1:1 with HMP) was added and the mixture was stirred for the time indicated in table 1 (generally 2 to 10 hours). The reaction mixture was filtered, and the solvent was removed under reduced pressure to afford a crude product which was then added to a solution of sodium hydroxide (5%, 2 mL). The aqueous mixture was extracted with ether (3x20 mL). The combined organic phases were dried with brine and over $MgSO_4$. Filtration and removal of solvents afforded a crude product. The product was purified by vacuum fractional distillation using a Vigraux column under reduced pressure (1.2 torr.), usually gave a colorless or pale-yellow liquid. A fractional collector (cow) was used, which allowed four fractions to be collected without disturbing the vacuum.

5.4.3 Synthesis of hexahydro-3-methyl-3H-oxazolo[3,4-a]pyridine (5).

Using the general procedure, freshly distilled acetaldehyde (1.46 mL, 26.1 mmol, 2 equiv.) was added to a cooled (0^{o}C) solution of 2-HMP (1.50 gr., 13.0 mmol), DCM (12 mL) and anhydrous $MgSO_4$ (1.5g) gave 1.7 gr. (93%) of crude mass. The product was first vacuum (3 Torr) distilled in a Kulgelrohr apparatus in order to remove undesired low boiling impurities

and 2-HMP. A subsequent vacuum (2 Torr) distillation from diphenylether (which acts as a heat dispersant) using a Vigraux column gave a colorless liquid. A wood splint was also placed vertically in the flask in order to prevent material bumping and decomposition.

B.p. = 85 °C (2 torr). GC: R_T = 3.17 min major isomer; 3.54 min minor isomer. MS (EI, 70 eV, m/z): 141 (M^+, 5%), 140 (M^+-H, 13%),126 (M^+-CH_3, 100%), 98 (M^+ -H_3CC=O, 18%). ^{1}H-NMR (300MHz, $CDCl_3$): Peaks assignments were supported by a COSY spectrum. 1.17 (4%, d, J^3=6 Hz, 3H, H-10), 1.24 (96%, d, J^3=5.4 Hz, 3H, H-10), 1.22-1.35 (m 2H, H-7ax, H-8ax), 1.51-1.65 (qt app, $J^{2,3}$=12.0, J^3=4.3 Hz, 1H, H-6ax), 1.65-1.71 (m, 1H, H-6eq), 1.72-1.84 (m, 2H, H-7eq, H-8eq), 1.96 (96%, td, $J^{2,3}$= 11.0, J^3= 3.2 Hz, 1H, H-5ax), 2.23-2.33 (96%, tdd, J^3=9.7, 6.0, 2.8 Hz, 1H, H-9), 2.59-2.72 (4%, m, 1H, H-5ax), 2.78-2.88 (4%, m, 1H, H-9), 2.96 (96%, dt, J^2= 10.3, J^3= 3.3 Hz, 1H, H-5eq), 3.05-3.20 (4%, m, 1H, H-5eq), 3.37-3.44 (4%, m, 1H, H-1), 3.46 (96%, dd, J^3= 10.2, J^2= 6.7 Hz, 1H, H-1ax), 3.52-3.61 (4%, m, 1H, H-1), 3.85 (96%, q, J^3= 5.4 Hz, 1H, H-3), 3.90 (96%, t, J^2=J^3= 6.7 Hz, 1H, H-1eq), 4.80 (4%, q app, J^3= 6.6 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 18.62(96%, C-10), 18.90(4%, C-10), 22.38 (4%, C-7) 23.42 (96%, C-7), 23.62 (4%, C-6) 24.79 (96%, C-6), 25.49 (4%, C-8), 26.73 (96%, C-8), 46.35 (4%, C-5), 47.69 (96%, C-5), 56.31 (4%, C-9), 63.12 (96%, C-9), 69.03 (4%, C-1), 69.88 (96%, C-1), 90.61 (4%, C-3), 91.71 (96%, C-3).

5.4.4 Synthesis of hexahydro-3-ethyl-3H-oxazolo[3,4-a]pyridine (6).

Using the general procedure, an equimolar mixture of freshly distilled propionaldehyde (1.00 g, 17.2 mmol), 2-HMP (2g, 17.4 mmol) in DCM (20 mL) and anhydrous $MgSO_4$ (2g) afforded 1.4g (52%) of a crude oil. Fractional vacuum distillation gave pure **6** (1.04g) as a colorless liquid.

B.p. = 89 °C (1.5 torr). GC: R_T = 3.73 min major isomer; 4.15 min minor isomer. MS (EI, 70 eV, m/z): 154(M+-H, 2.5%), 126(M+-C_2H_5, 100%), 98(M+-C_2H_5C=O, 7.5%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.73 (6%, t, J= 7.5 Hz, 3H, H-11), 0.96 (94%, t, J= 7.5 Hz, 3H, H-11), 1.12-1.31 (m, 2H, H-7ax, H-8ax), 1.46 (sex app, J=7.2 Hz, 2H, H-10), 1.50-1.64 (qt app, J=12, 3.9 Hz, 1H, H-6ax), 1.64-1.84 (m, 3H, H-6eq, H-7eq, H-8eq), 2.00 (94%, td, $J^{2,3}$= 11, J^3=3 Hz, 1H, H-5ax), 2.23-2.38 (94%, tdd, J^3=10.2, 6.3, 2.4 Hz, 1H, H-9), 2.59-2.70 (6%, td, $J^{2,3}$= 11, J^3=3 Hz, 1H, H-5ax), 2.70-2.85 (6%, m, 1H, H-9), 2.94 (94%, dt, J^2= 10.5, J^3= 3.5 Hz, 1H, H-5eq), 3.14-3.24 (6%, m, 1H, H-5eq), 3.39 (94%, dd, $J^{2,3}$= 10.2, 6.6 Hz, 1H, H-1ax), 3.55 (6%, t, $J^{2,3}$= 7.3, 1H, H-1ax), 3.71 (94%, dd, J^3= 7.5, J^2= 2.5 Hz, 1H, H-3), 3.84 (6%, t, $J^{2,3}$= 6.7 Hz, 1H, H-1eq), 3.90 (94%, t, J^3= 6.5 Hz, 1H, H-1eq), 4.48 (6%, dd, J^3= 7.5, J^3= 4.2 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 8.83 (95%, C-11), 9.65 (5%, C-11), 22.03, (5%, C-7 or 6), 23.48,

(5%, C-6 or 7), 23.55 (95%, C-7), 24.89 (95%, C-6), 25.06, (5%, C-10 or 8), 25.81 (95%, C-10), 26.47 (5%, C-8 or 10), 26.75 (95%, C-8), 46.92 (5%, C-5), 47.83 (95%, C-5), 56.68 (5%, C-9), 63.09 (95%, C-9), 68.45 (5%, C-1), 70.11 (95%, C-1), 96.23 (5%, C-3), 96.44 (95%, C-3).

5.4.5 Synthesis of hexahydro-3-propyl-3H-oxazolo[3,4-a]pyridine (7).

Using the general procedure, an equimolar mixture of freshly distilled butyraldehyde (1.56 mL, 1.25g, 17.3 mmol), 2-HMP (2.00g, 17.4 mmol) in DCM (15 mL) and anhydrous $MgSO_4$ (2.0 g) was stirred for 3h. Usual work-up afforded 1.92 g (65.5%) of crude product. Subsequent fractional distillation under reduced pressure (1.2 torr) gave **7** as a colorless liquid.

B.p. = 94 °C (1.2 torr). GC: R_T = 4.41 min major isomer; 4.81 min minor isomer. MS (EI, 70 eV, m/z): 168(M+-H, 2.5%), 126(M+-C_3H_7, 100%), 98(M+-C_3H_7C=O, 12%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.91 (6%, t, J= 7.5 Hz, 3H, H-11), 0.92 (94%, t, J= 7.1 Hz, 3H, H-12), 1.15-1.33 (m, 2H, H-7ax, H-8ax), 1.34-1.85 (m, 8H, H-6eq, H-6ax, H-7eq, H-8eq, H-10, H-11), 1.98 (96%, td, $J^{2,3}$= 12, J^3= 3 Hz, 1H, H-5ax), 2.23-2.34 (96%, tdd, J^3=10.1, 6.7, 2.6 Hz, 1H, H-9), 2.60-2.84 (6%, m, 2H, H-5ax, H-9), 2.95 (94%, dt, J^2= 10.5, J^3= 3.8 Hz, 1H, H-5eq), 3.11-3.24 (6%, m, 1H, H-5eq), 3.41 (94%, dd, J^3= 10.0, J^2= 7.5 Hz, 1H, H-1ax), 3.54 (6%, t, J= 7.5, 1H, H-1ax), 3.74 (96%, dd, J^2= 7.5, J^3= 1.5 Hz, 1H, H-3), 3.81 (6%, dd, J^2=7.2, J^3= 6.3 Hz, 1H, H-1eq), 3.87 (94%, t, J= 7.5 Hz, 1H, H-1eq), 4.54 (6%, t, J= 4.5 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 14.15 (6%, C-12), 14.34 (94%, C-12), 18.73 (94%, C-11), 18.75 (6%, C-11), 22.06 (6%, C-7), 23.54 (94%, C-7), 24.87 (94%, C-6), 25.00 (6%, C-6), 26.75 (C-8), 35.22 (94%, C-10), 35.84 (6%, C-10), 46.98 (6%, C-5), 47.84 (94%, C-5), 56.59 (6%, C-9), 63.07 (94%, C-9), 68.29 (6%, C-1), 70.05 (94%, C-1), 95.04 (6%, C-3), 95.42 (94%, C-3).

5.4.6 Synthesis of hexahydro-3-isopropyl-3H-oxazolo[3,4-a]pyridine (8).

Using the general procedure, an equimolar mixture of freshly distilled isobutyraldehyde (1,19mL, 0.940g, 13.0 mmol), 2-HMP (1.50g, 13.0 mmol) in DCM (10 mL) and of anhydrous $MgSO_4$ (1.5 g). The mixture was stirred for 3h and a general workup afforded a crude yellow oil. Fractional vacuum distillation gave **8** (1.54g, 70%) as a colorless liquid.

B.p. = 91 °C (1.2 torr). GC: R_T = 4.05 min major isomer; 4.48 min minor isomer. MS (EI, 70 eV, m/z): 168(M+-H, 1.25%), 126(M+-C_3H_7, 100%), 98(M+-C_3H_7C=O, 6.25%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.83 (95 %, d, J= 7.1 Hz, 3H, H-11a or 11b), 0.85 (5 %, d, J= 7.0 Hz, 3H, H-11a or 11b), 0.87 (5 %, d, J= 7.0 Hz, 3H, H-11b or 11a), 0.94 (95 %, d, J= 7.1 Hz, 3H, H-11b or 11a), 1.14-1.31 (m, 2H, H-7ax, H-8ax), 1.43-1.58 (qt app, J=12.1, 4.3 Hz, 1H, H-6ax),

1.58-1.66 (dt app, J=13.2, 2.7 Hz, 1H, H-6eq), 1.69-1.74 (dt app, J=14.1, 2.4 Hz, 1H, H-7eq), 1.71-1.78 (dd app, J=14.7, 3.0 Hz, 1H, H-8eq), 1.67-1.81 (m, 1H, H-10), 1.96 (td, $J^{2,3}$= 10.5, J^{2}= 3 Hz, 1H, H-5ax), 2.28 (tdd, J^{3}= 10.2, 6.3, 2.4 Hz, 1H, H-9), 2.73 (5%, m, 2H, H-5eq, H-9), 2.87 (95%, dt, J^{2}=11, J^{3}= 3.8 Hz, 1H, H-5eq), 3.28 (95%, dd, J^{3}= 10.2, J^{2}= 7.5 Hz, 1H, H-1ax), 3.54 (5%, t, $J^{2,3}$= 7.5, 1H, H-1ax), 3.64 (95%, d, J^{3}= 2.4 Hz, 1H, H-3), 3.71 (5%, dd, J^{3}= 7.5, J^{2}= 6 Hz, 1H, H-1eq), 3.84 (95%, t, $J^{2,3}$= 6.3 Hz, 1H, H-1eq), 4.15 (5%, d, J^{3}= 6.6 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 14.84 (95%, C-11b or 11a), 17.13 (5%, C-11b or 11a), 18.77 (95%, C-11a or 11b), 19.29 (5%, C-11a or 11b), 21.72 (5%, C-7 or 6), 23.08 (5%, C-6 or 7), 23.68 (95%, C-7), 25.09 (95%, C-6), 24.35 (5%, C-8), 26.79 (95%, C-8), 29.67 (95%, C-10), 31.90 (5%, C-10), 47.72 (5%, C-5), 47.84 (95%, C-5), 56.65 (5%, C-9), 62.87 (95%, C-9), 67.94 (5%, C-1), 70.59 (95%, C-1), 98.82 (95%, C-3), 100.37 (5%, C-3).

5.4.7 Synthesis of hexahydro-3-(1-propenyl)-3H-oxazolo[3,4-a]pyridine (9).

Using the general procedure, an mixture of the freshly distilled crotonaldehyde (0.84 mL, 10.22 mmol, 1.2 eq), 2-HMP (1.00g, 8.68 mmol), DCM (10mL) and anhydrous $MgSO_4$ (1.0 g) was added and stirring was continued for 3 h. A general workup, afford a crude yellow oil. Fractional vacuum distillation over sodium carbonate (100mg) and using a vigraux column using a wood boiling stick to avoid formation of froth during distillation, afforded **9** (1.18g, 82%) as a colorless oil.

B.p. = 126 ºC (2 torr). GC: R_T = 4.65 min. MS (EI, 70 eV, m/z): 167 (M+, 11%), 166 (M+-H, 53.75%), 152 (M+-CH_3, 8.75%), 126 (M+-C_3H_5, 100%), 98 (M+ -C_4H_5O, 20%), 84 (C_5H_8O+, 3.75%), 69 (C_4H_5O+, 18.75%). IR/TF (NaCl): 2939 (F, ν(C-H des CH_2); 2782 (m, ν(C-H de CHO)); 1546 (F, ν(C=C)); 1256 (m, ν(C-O)). ^{1}H-NMR (300MHz, $CDCl_3$): Peaks assignments were supported by a COSY spectrum. 1.22-1.38 (m, 2H, H-7ax, H-8ax), 1.50-1.64 (m, 2H, H-6), 1.64-1.88 (m, 2H, H-7eq, H-8eq), 1.74 (dd, J^{3}=6.6, J^{4}= 1.6 Hz, 3H, H-12), 1.96 (td, J^{2}= 10.5, J^{3}= 3.0 Hz, 1H, H-5ax), 2.22-2.38 (tdd, J^{3}=10.2, 6.5, 2.7 Hz, 1H, H-9), 2.93 (dt, J^{2}= 10.4, J^{3} =3.3 Hz, 1H, H-5eq), 3.49 (dd, J^{3}= 10.2, J^{2}= 6.6 Hz, 1H, H-1ax), 3.95 (t, $J^{2,3}$= 6.6 Hz, 1H, H-1eq), 3.99 (d, J^{3}= 7.1 Hz, 1H, H-3), 5.45 (ddq, J^{3}= 15.2, J^{3}= 7.1 Hz, J^{4}= 1.6 Hz, 1H, H-10), 5.82 (dq, J^{3}= 15.2, J^{3}= 6.6 Hz, 1H, H-11). ^{13}C-NMR (75MHz, $CDCl_3$): 17.64 (C-12), 23.60 (C-7), 24.74 (C-6), 27.04 (C-8), 47.41 (C-5), 62.76 (C-9), 70.59 (C-1), 96.59 (C-3), 129.90 (C-10), 132.51 (C-11).

*5.4.8 Synthesis of hexahydro-3-butyl-3H-oxazolo[3,4-a]pyridine (***10***).*

Using the general procedure, a mixture of the freshly distilled valeraldehyde (2.019 g, 23.4 mmol, 1.35), 2-HMP (2.003 g, 17.4 mmol), DCM (15mL), anhydrous $MgSO_4$ (2.00 g) was added and stirring was continued for 4 h. A usual workup afforded a crude product **10**. Fractional vacuum distillation using a Vigreaux column and a wood boiling stick to avoid formation of frothing during distillation, gave pure **10** (2.81g, 88%) as a colorless oil.

B.p. = 105 °C (1.5 torr). GC: R_T = 5.05 min major isomer; 5.46 min minor isomer. MS (EI, 70 eV, m/z): 182 (M+-H, 2.5%), 126 (M+-C_4H_9, 100%), 98 (M+-C_4H_9C=O, 7.5%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.90 (t, J= 7.5 Hz, 3H, H-13), 1.18 -1.54 (m, 7H, H-6ax, H-7ax, H-8ax, H-11, H-12), 1.55-1.85 (m, 5H, H-6eq, H-7eq, H-8eq, H-10), 2.00 (93%, td, J^3= 10, J^2= 3.2 Hz, 1H, H-5ax), 2.23-2.36 (93%, tdd, J^3=10.0, 6.6, 2.4 Hz, 1H, H-9), 2.72-2.84 (7%, m, 2H, H-5ax, H-9), 2.97 (93%, dt, J^2=10.3, J^3= 3.3 Hz, 1H, H-5eq), 3.17-3.26 (7%, m, 1H, H-5eq), 3.43 (93%, dd, J^3= 12, J^2= 6.8 Hz, 1H, H-1ax), 3.56 (7%, t, $J^{2,3}$= 7.5Hz, 1H, H-1ax), 3.75 (93%, dd, J^3= 7.5, J^2= 2.5 Hz, 1H, H-3), 3.84 (7%, dd, J^2= 7.2, J^3=3.3, Hz, 1H, H-1eq), 3.90 (93%, t, J^3= 6.6 Hz, 1H, H-1eq), 4.55 (7%, dd, J^3= 6.9, J^3= 4.2 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 14.02(C-13), 22.06, (7%, C-12 or 11), 22.77 (7%, C-11 or 12), 22.92 (93%, C-12), 23.53 (93%, C-11), 24.86 (93%, C-7), 24.99 (7%, C-7), 26.73 (93%, C-6), 26.95 (93%, C-8), 27.62 (7%, C-8 or 6), 32.74 (93%, C-10), 33.38 (7%, C-10), 46.93 (7%, C-5), 47.82 (93%, C-5), 56.58 (7%, C-9), 63.06 (93%, C-9), 68.30 (7%, C-1), 70.02 (93%, C-1), 95.19 (7%, C-3), 95.59 (93%, C-3).

5.4.9 Synthesis of hexahydro-3-t-butyl-3H-oxazolo[3,4-a]pyridine (11)

Using the general procedure, a mixture of the freshly distilled pivaldehyde (0.70 mL, 0.56 g, 6.4 mmol, 1.5 eq), 2-HMP (0.500 g, 4.34 mmol, 1eq), DCM (10mL), anhydrous $MgSO_4$ (0.50 g) were stirred and heated to reflux for 6 h. A general workup afforded a crude product **11** as a yellow oil. Fractionnal vacuum distillation using a Vigreaux column and a wood boiling stick to avoid formation of froth during distillation gave pure **11** (0.59, 81%).

B.p. = 95 °C (1.2 torr). GC: R_T = 4.42 min major isomer; 4.97 min minor isomer (ratio 96.4% :3.6%). MS (EI, 70 eV, m/z): 168 (M+-CH_3, 1.2%), 126 (M+-C_4H_9, 100%), 98 (M+-C_4H_9C=O, 5%). ^{1}H-NMR (300MHz, C_6D_6): 0.68 (s, 9H, H-11), 0.98-1.15 (m, 2H, H-7ax, H-8ax), 1.16-1.20 (m, 1H, H-6ax), 1.27-1.50 (m, 3H, H-6eq, 7eq, 8eq), 1.84 (td, J^2= 11.0, J^3= 3.0 Hz, 1H, H-5ax), 2.02-2.12 (96%, tdd, J^3=10.4, 5.6, 2.0 Hz, 1H, H-9), 2.50-2.59 (4%, m, 1H, H-9), 2.95 (96%, dt, J^2= 10.4, J^3= 3.0 Hz, 1H, H-5eq), 3.00-3.06 (4%, m, 1H, H-5eq), 3.19 (96%, dd, J^3= 10.3, J^2= 6.5 Hz, 1H, H-1ax), 3.33 (4%, t, J= 7.5, Hz, 1H, H-1ax), 3.50 (4%, dd, J^3= 10.3, J^2= 4.8 Hz, 1H, H-1eq), 3.53 (96%, s, 1H, H-3), 3.62 (96%, dd, 1H, J^2= 6.5, J^3= 5.8 Hz, 1H, H-

1eq), 3.98 (4%, s, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 21.25 (4%, C-7, or 6 or 8), 23.68 (4%, C-6 or 7 or 8), 23.85 (94%, C-7 or 6), 24.05 (4%, C-8 or 6 or 7), 25.60 (C-6 or 7), 25.76 (96%, 3C, C-11), 25.89 (4%, 3C, C-11), 27.03 (C-8), 36.45 (96%, C-10), 36.81 (4%, C-10), 50.25 (4%, C-5) 51.76 (96%, C-5), 64.75 (96%, C-9), 66.47 (4%, C-9), 68.12 (4%, C-1), 70.52 (96%, C-1), 101.50 (96%, C-3), 104.65 (4%, C-3).

5.4.10 Synthesis of hexahydro-3-isobutyl-3H-oxazolo[3,4-a]pyridine (12).

Using the general procedure, an equimolar mixture of the freshly distilled isovaleraldehyde (1.42 mL, 1.11 g, 12.9 mmol), 2-HMP (1.50 g, 13.0 mmol), DCM (12mL), anhydrous $MgSO_4$ (1.50 g) was added and stirring was continued for 4 h. A general workup afforded a crude product **12**. Fractional vacuum distillation using a Vigreaux column and a wood boiling stick to avoid formation of froth during distillation gave **12** (1.61g, 68%) as a colorless oil.

B.p. = 99 °C (1.2 torr). GC: R_T = 4.81 min major isomer; 5.17 min minor isomer. MS (EI, 70 eV, m/z): 182 (M+-H, 2.5%), 126 (M+-C_4H_9, 100%), 98 (M+-C_4H_9C=O, 9.5%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.87 (d, J^3= 7.5 Hz, 3H, H-12a), 0.97 (d, J^3= 7.5 Hz, 3H, H-12b), 1.19 – 1.35 (m, 2H, H-7ax, H-8ax), 1.41-1.85 (m, 7H, H-6, H-7eq, H-8eq, H-10, H-11), 1.99 (93%, td, $J^{2,3}$= 10.5, J^2= 4 Hz, 1H, H-5ax), 2.27 (93%, tdd, J^3=10.2, 6.5, 2.7 Hz, 1H, H-9), 2.69-2.78 (7%, m, 1H, H-9), 2.93 (93%, dt, J^2=10.4, J^2= 3.4 Hz, 1H, H-5eq), 3.22-3.32 (7%, m, 1H, H-5eq), 3.41 (93%, dd, J^3= 10.1, J^2= 6.8 Hz, 1H, H-1ax), 3.55 (7%, t, J= 7.5, Hz, 1H, H-1ax), 3.67 (7%, dd, J^3= 10.5, J^2= 4.5 Hz, 1H, H-1eq), 3.81 (93%, dd, J^3= 7.3, J^2= 2.9 Hz, 1H, H-3), 3.91 (93%, t, J^3= 6.6 Hz, 1H, H-1eq), 4.61 (7%, dd, J^3= 8.0, J^3= 4.3 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 21.87 (7%, C-11 or 12 or 13), 22.25, (7%, C-12 or 11 or 13), 22.45 (93%, C-11), 22.66 (7%, C-13 or 12 or 11), 23.54 (93%, C-12), 23.87 (93%, C-13), 24.66 (7%, C-7 or 6 or 8), 24.81 (93%, C-7), 24.85 (93%, C-6), 26.75 (93%, C-8), 42.14 (93%, C-10), 42.45 (7%, C-10), 47.05 (7%, C-5), 47.82 (93%, C-5), 56.37 (7%, C-9), 63.04 (93%, C-9), 67.94 (7%, C-1), 69.92 (93%, C-1), 94.00 (7%, C-3), 94.26 (93%, C-3).

5.4.11 Synthesis of hexahydro-3-pentyl-3H-oxazolo[3,4-a]pyridine (13).

Using the general procedure, an equimolar mixture of the freshly distilled of hexanal (1.07mL, 0.87g, 8.69mmol), 2-HMP (1.000g, 8.68mmol), DCM (10 mL), anhydrous $MgSO_4$ (1.0g) was added and stirred for 4h. A usual workup afforded 1.67g of a crude pale-yellow oil. Fractional vacuum distillation using a Vigreaux column gave the pure **13** (1.31, 77%) as a colorless liquid.

B.p. = 111 °C (1.2 torr). GC: R_T = 5.74 min. MS (EI, 70 eV, m/z): 196 (M+-H, 1.3%), 126 (M+-C_5H_{11}, 100%), 98 (M+-$C_5H_{11}C$=O, 7.5%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.88 (t, J= 7.5

Hz, 3H, H-14), 1.23-1.55 (m, 9H, H-6ax, H-7ax, H-8ax, H-11, H-12, H-13), 1.55-1.88 (m, 5H, H-6eq, H-7eq, H-8eq, H-10), 2.00 (td, $J^{2,3}$= 10.5, J^{3}=4 Hz, 1H, H-5ax), 2.22-2.36 (93%, tdd, J^{3}10.2; 6.5; 2.7 Hz, 1H, H-9), 2.68-2.85 (7%, m, 2H, H-5ax, H-9), 2.96 (94%, dt, J^{2}= 11.5, J^{3}= 3 Hz, 1H, H-5eq), 3.13-3.26 (6%, m, 1H, H-5eq), 3.43 (94%, dd, J^{3}= 10.1, J^{2}= 7.4 Hz, 1H, H-1ax), 3.56 (6%, t, $J^{2,3}$= 7.5 Hz, 1H, H-1ax), 3.75 (94%, dd, J^{3}= 7.4; 3 Hz, 1H, H-3), 3.84 (6%, dd, J^{3}= 8.4, J^{2}=6.3, Hz, 1H, H-1eq), 3.90 (94%, t, $J^{2,3}$= 7.5 Hz, 1H, H-1eq), 4.55 (6%, dd, J^{3}= 6.6; 3Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 14.07 (C-14), 22.09 (6%, C-11 or 13), 22.66 (94%, C-11), 23.55 (94%, C-13), 24.56 (94%, C-7), 24.89 (94%, C-6), 25.02 (6%, C-7 or 6), 25.19 (6%, C-6 or 7), 26.75 (C-8), 31.96 (6%, C-12), 32.11 (94%, C-12), 33.06 (94%, C-10), 33.69 (4%, C-10), 46.97 (6%, C-5), 47.85 (94%, C-5), 56.62 (6%, C-9), 63.09 (94%, C-9), 68.34 (6%, C-1), 70.04 (96%, C-1), 95.22 (6%, C-3), 95.66 (94%, C-3).

5.4.12 Synthesis of hexahydro-3-hexyl-3H-oxazolo[3,4-a]pyridine (14).

Using the general procedure, an equimolar mixture of freshly distilled heptanal (1.22mL, 0.99g, 8.69mmol), 2-HMP (1.000g, 8.68mmol), DCM (10 mL), anhydrous $MgSO_4$ (1.0g) was added and stirred for 4h. A usual workup afforded a crude pale-yellow oil. Fractional vacuum distillation using a Vigreaux column gave **14** (1.31g, 72%) as a colorless liquid.

B.p. = 126 ºC (2 torr). GC: R_T = 6.39 min. MS (EI, 70 eV, m/z): 210 (M+-H, 1.3%), 126 (M+-C_6H_{13}, 100%), 98 (M+-C_6H_{13}C=O, 8.75%). ^{1}H-NMR (300MHz, $CDCl_3$): 0.86 (t, J= 7.5 Hz, 3H, H-15), 1.19-1.53 (m, 11H, H-6ax, H-7ax, H-8ax, H-11, H-12, H-13, H-14), 1.53-1.83 (m, 5H, H-6eq, H-7eq, H-8eq, H-10), 1.98 (94%, td, $J^{2,3}$= 10.7, J^{3}= 3.3 Hz, 1H, H-5ax), 2.22-2.35 (94%, tdd, J^{3}=10.2, 6.5, 2.7 Hz, 1H, H-9), 2.65-2.85 (6%, m, 2H, H-5ax, H-9), 2.95 (94%, dt, J^{2}= 10.6, J^{3}= 3.5 Hz, 1H, H-5eq), 3.15-3.25 (6%, m, 1H, H-5eq), 3.41 (94%, dd, J^{3}= 10.5, J^{2}= 7.5 Hz, 1H, H1ax), 3.54 (6%, t, $J^{2,3}$= 7.5, 1H, H-1ax), 3.73 (94%, dd, J^{3}= 7.5; 3.0 Hz 1H, H-3), 3.82 (6%, t, $J^{2,3}$= 7.5 Hz, 1H, H-1eq), 3.88 (94%, t, $J^{2,3}$= 7.5 Hz, 1H, H-1eq), 4.53 (6%, dd, J^{3}= 7.5, J^{3}=4.5 Hz, 1H, H-3). ^{13}C-NMR (75MHz, $CDCl_3$): 14.11 (C-15), 22.09 (6%, C-11 or 14), 22.61 (94%, C-11), 23.55 (94%, C-14), 24.81 (94%, C-7), 24.88 (94%, C-6), 25.02 (6%, C-7 or 6), 25.45 (6%, C-6 or 7), 26.75 (94%, C-8), 29.40 (6%, C-12), 29.55 (94%, C-12), 31.84 (C-13), 33.09 (94%, C-10), 33.72 (4%, C-10), 46.96 (6%, C-5), 47.85 (94%, C-5), 56.61 (6%, C-9), 63.08 (94%, C-9), 68.33 (6%, C-1), 70.04 (96%, C-1), 95.21 (6%, C-3), 95.63 (94%, C-3).

5.4.13 Synthesis of hexahydro-3-(2-furyl)-3H-oxazolo[3,4-a]pyridine (15).

Using the general procedure, a mixture of freshly distilled furfural (0.86 mL, 0.998g, 10.4mmol), 2-HMP (1.000g, 8.68 mmol), toluène (15 mL, for other solvents see Table 1),

anhydrous $MgSO_4$ (1.0 g) was added and stirred for 10h. A usual workup afforded 1.44g of a crude yellow oil. Fractional vacuum distillation using a Vigreaux column gave **15** (1.39g, 86%) as a pale-yellow oil.

B.p. = 90 °C (2 torr). GC: R_T = 6.25 min. MS (EI, 70 eV, m/z): 193 (M^+, 33%), 192 (M^+-H, 100%), 163 (M^+-CH_2O, 60%), 126 (M^+-C_4H_3O-furyl, 23%). ^{1}H-NMR (300MHz, $CDCl_3$): Peaks assignments were supported by a COSY spectrum. 1.21-1.39 (m, 1H, H-7ax), 1.42-1.57 (m, 1H, H-8ax), 1.60-1.73 (m, 2H, H-6), 1.80-1.90 (m, 2H, H-7eq, H-8eq), 2.08 (td, $J^{2,3}$=10.7, J^3= 3.8 Hz, 1H, H-5ax), 2.34-2.40 (20%, m, 1H, H-5ax), 2.47 (80%, tdd, J^3=10.2, 6.0, 2.3 Hz, 1H, H-9), 2.82 (20%, m, 1H, H-5eq), 2.85 (80%, dt, J^2= 10.2, J^3= 3.3 Hz, 1H, H-5eq), 3.14.-3.23 (20%, m, 1H, H-9), 3.63 (20%, t, $J^{2,3}$= 7.4 Hz 1H, H-1ax), 3.65 (80%, dd, J^3= 10.0, J^2= 6.7 Hz, 1H, H-1ax), 4.05 (80%, t, $J^{2,3}$= 6.5 Hz, 1H, H-1eq), 4.10 (20%, t, $J^{2,3}$ 6.6 Hz, 1H, H-1eq), 4.71 (80%, s, 1H, H-3), 5.58 (20%, s, 1H, H-3), 6.32 (20%, dd, J^3= 3.3; J^4= 1.8 Hz, 1H, H-4'), 6.34 (20%, dd, J^3= 3.8; J^4= 1.1 Hz, 1H, H-3'), 6.36 (80%, dd, J^3= 3.2; J^4= 1.8 Hz 1H, H-4'), 6.47 (80%, dd, J^3= 3.2, J^4= 0.7 Hz, 1H, H-3'), 7.40 (20%, dd, J^3= 1.7, J^4= 0.8 Hz, 1H, H-5'), 7.46 (80%, dd, J^3= 1.6, J^4= 1.0 Hz, 1H, H-5'). ^{13}C-NMR (75MHz, $CDCl_3$): 22.43 (20%, C-7), 23.54 (80%, C-7), 24.10 (20%, C-6), 24.69 (80%, C-6), 25.77 (20%, C-8), 26.71 (80%, C-8), 46.29 (20%, C-5), 47.83 (80%, C-5), 56.90 (20%, C-9), 62.83 (80%, C-9), 70.05 (20%, C-1), 70.92 (80%, C-1), 88.79 (20%, C-3), 89.69 (80%, C-3), 108.45 (20%, C-3'), 109.63 (80%, C-3'), 109.87 (20%, C-4'), 110.09 (80%, C-4'), 142.52 (20%, C-5'), 143.32 (80%, C-5'), 151.83 (80%, C-2'), 153.51 (20%, C-2').

5.4.14 Synthesis of hexahydro-3-(ethynyl)-3H-oxazolo[3,4-a]pyridine (16).

Freshly distilled acrolein (1.74mL, 1.46g, 26mmol, 3eq) in toluene (10 mL) was added (approx. 2mL/min) to a solution of 2-HMP (1.00g, 8.68mmol, 1eq) in toluene (10 mL), anhydrous $MgSO_4$ (1.0g), and the mixture heated at reflux for 1h, then was cooled to an ambient temperature. The reaction mixture was filtered, and the solvent was removed under rotary evaporation at 30-35°C to afford a crude pale-yellow oil. ^{1}H NMR analysis show to be mainly (> 95%) of both isomers of ***16***. The latter can be further purified by a vacuum distillation to give pure (***16***) as a colorless oil, 1.17 g, 90% recovery yield.

B.p. = 65°C (0.05 torr). GC: R_T = 3.67 min major isomer; 4.11 min minor isomer; purity 98%. MS (EI, 70 eV, m/z): 153(M^+, 15%,), 152 (M^+-H, 36%), 126 (M^+-C_2H_3, 100%), 98 (M^+-C_3H_3O, 17%). ^{1}H-NMR (300MHz, $CDCl_3$):1.20-1.38 (m, 2H, H-7ax, 8ax), 1.45-1.62 (qt app, J=12.2, 4.4 Hz, 1H, H-6ax), 1.63-1.75 (dt app, J=13.4, 1.1 Hz, 1H, H-6eq), 1.78-1.88 (tl app, J=9.5 Hz, 2H, H-7eq, H-8eq), 1.99 (90%, td, J^3= 11.8, J^2= 10.7, J^3= 3.0 Hz, 1H, H-5ax), 2.31

(90%, tdd, J^3=10.2, 6.6, 3.2 Hz, 1H, H-9), 2.62 (10%, ddd, J^2=13.1, J^3= 8, 4 Hz, 1H, H-5ax), 2.84 (10%, dt, J^2=13.2, J^3= 5 Hz, 1H, H-5eq), 2.94 (90%, dt, J^2= 10.7, J^3= 3.3 Hz, 1H, H-5eq), 3.06-3.16 (10%, m, 1H, H-9), 3.51 (90%, dd, J^3= 10.2, J^2= 6.8 Hz, 1H, H-1ax), 3.58 (10%, t, $J^{2,3}$= 6.8 Hz, 1H, H-1ax), 3.85 (10%, t, $J^{2,3}$= 6.8 Hz, 1H, H-1eq), 3.97 (90%, t, J^2=J^3=6.6 Hz, 1H, H-1eq), 4.01 (90%, d, 1H, J^3= 7.5 Hz, 1H, H-3), 4.85 (10%, d, 1H, J^3= 6.6 Hz, 1H, H-3), 5.22 (10%, ddd, J^3=10.0, J^2= 1.7, J^4= 0.8 Hz, 1H, H-11c), 5.29 (10%, ddd, J^3=17, J^2= 1.7, J^4= 0.8 Hz, 1H, H-11t), 5.32 (90%, ddd, J^3=10.0, J^2= 1.6, J^4= 0.5 Hz, 1H, H-11c), 5.38 (90%, ddd, J^3=17.3, J^2= 1.6, J^4= 0.5 Hz, 1H, H-11t), 5.76 (90%, ddd, J^3=17.3, J^3= 10.0, J^3= 7.7 Hz, 1H, H-10),5.78 (10%, m, 1H, H10). ^{13}C-NMR (75MHz, $CDCl_3$): 22.37 (10%, C-7), 23.55 (90%, C-7), 23.80 (10%, C-6), 24.76 (90%, C-6), 25.51 (10%, C-8), 26.86 (90%, C-8), 46.20 (10%, C-5), 47.36 (90%, C-5), 56.71 (10%, C-9), 62.73 (90%, C-9), 69.46 (10%, C-1), 70.84 (90%, C-1), 94.65 (10%, C-3), 96.64 (90%, C-3), 118.13 (10%, C-10), 120.45 (90%, C-10), 136.17 (10%, C-11), 136.79 (90%, C-11).

5.4.15 Synthesis of bicyclic octahydro-3H-pyrido[2,1-c][1,4]oxazepin-3-ol (17)

A solution of freshly distilled acrolein (0.875g, 1.043 mL, 15.6mmol, 1.2 eq) in toluene was added dropwise, via syringe, to a solution of 2-HMP (1.50 g, 13.0mmol) in toluene (10 mL) and the mixture was stirred at 0 °C. The reaction was monitored by ^{1}H-NMR. Once completed after 1hr, the solvent was removed under reduced pressure at room temperature to afford **17** as a crude thick oil. Ether (1 mL) and a few drops of hexane were added, and the solution was again evaporated, which induced solidification to afford 2.07g (***17, 93%***). The crude pale-yellow product was taken up in a minimal volume of ether, transferred into a small, tall vial and the ether was allowed to slowly evaporate at room temperature until a residual volume was left. The white crystals on the walls of the vial were washed with small portions of cool ether. The mother liquor at the bottom of the vial was transferred into another vial to be recrystallized. The crystals thus obtain were again recrystallized once more using this process to finally give 2.00g of **17** as pure frostlike crystals (90%) suitable for X-ray analysis.

M.p. 77-78°C. GC: R_T = 5.85 min, purity 99%. MS (EI, 70 eV, m/z): 84 ($C_5H_{11}N^+$, 100%).

IRTF ν_{max} (KBr)/cm^{-1} 3063 (OH), 2940, 2838, 2797, 1310 (C-O), 1279(m), 1125, 1089 and 1033 (C-O). ^{1}H-NMR (300MHz, $CDCl_3$): Peaks assignments were supported by a COSY and nOe spectrum. 1.02-1.20 (qd, $J^{2,3}$=11.8, 3,6 Hz 1H, H10ax), 1.20-1.34 (m, 1H, 8ax), 1.45 (br d, J^2=12.6 Hz 1H, H10eq), 1.48-1.68 (m, 2H, H8eq + H9ax), 1.76 (br d, J^2=12.6 Hz 1H, H9eq), 1.98-2.08 (br. td, J^3=10.2, J^3=2.2 Hz, 1H, H11ax), 2.10-2.24 (m, 3H, 2H4, H7ax), 2.48 (ddd, J^2= 13.1, J^3= 9.4, J^3= 2.3 Hz, 1H, H5ax), 2.58 (ddd, J^2= 13.0 J^3= 6.7, J^3= 2.6 Hz, 1H, H5eq),

2.82 (br.d, J^2= 11.2 Hz, 1H, H7eq),3.30 (dd, J^2=13.4, J^3= 1.8 Hz, 1H, H1eq), 3.94 (dd, J^2= 13.4, J^3= 9.2 Hz, 1H, H1ax), 5.21 (dd, J^3= 8.4, 6.2 Hz, 1H, H3). ^{13}C-NMR (75MHz $CDCl_3$): 24.07 (C-9 or 10), 25.92 (C-8), 28.64 (C-10 or 9), 35.92 (C-4), 52.88 (C-5), 56.99 (C-7), 65.98 (C-11), 66.52 (C-1), 95.34 (C-3).

5.4.16 Synthesis of hexahydro-3-[2-N-(2-hydroxymethyl)piperidyl)-1-ethyl]-3H-oxazolo[3,4-a]pyridine (18).

Freshly distilled acrolein (48.6mg, 58µL, 0.87mmol, 1eq) in toluene (1 mL) was added (approx. 1min) to a solution of 2-HMP (200mg, 1.74mmol, 2eq) in toluene (1 mL), anhydrous $MgSO_4$ (200mg), and the mixture heated at reflux for 1h, then was cooled to an ambient temperature. The reaction mixture was filtered, and the solvent was removed under rotary evaporator at 30-35^{o}C to afford a crude thick yellow oil (222mg, 95%). ^{1}H-NMR analysis shows this to be an equal mixture of both diastereoisomers **18** and **19** having the characteristic ddd at 2.45 ppm for **18** and the ddd at 3.10 ppm for **19**. The mixture can be further completely converted into **18** by allowing the thick oil to solidify over a period of 2 days at 4^{o}C. The ^{1}H-NMR analysis of the pale-yellow solid thus obtained showed only the characteristic ddd 2.45 ppm. The latter was washed with minimal amount of precooled ether and then dissolved in a minimum amount of ether at room temperature and cooled to 4^{o}C overnight to finally give pure white solid (**18**) as an analytical standard (175 mg, 75%) of which an X-ray structure was obtained.

Alternatively

The solid (**17**) (200 mg, 1.17 mmole) was then vacuumed distilled in a Kugelrohr apparatus (0.3 torr, 125 ^{o}C) to afford 107 mg of a colorless thick liquid. A ^{1}H-NMR analysis showed this to be a mixture of both isomers **18** and **19**. This thick oil slowly and partly crystallized into colorless crystals of isomeric **18** (ddd, 2.45 ppm). Crystals were further purified as described above to give a pure white solid (**18**), 68 mg, 43%.

M.p. 94-95^{o}C. GC: RT=8.33 min. MS (EI, 70 eV, m/z) 267 (M^+-H, 0.5%), 207 ($C_{12}H_{19}N_2O^+$, 2%), 152 ($C_9H_{14}NO^+$, 47%), and 126 ($C_7H_{12}NO^+$, 100%). HRMS calcd for $C_{15}H_{28}N_2O_2$: *m/z* 268.2151; found 268.2152. IRTF ν_{max} (KBr)/cm^{-1}: 3440, 3151 (OH), 2931, 2849, 2792, 1274(s, C-N), 1130 (C-O) and 1044 (C-O). ^{1}H-NMR (600MHz, $CDCl_3$): Peaks assignments were supported by a COSY, DEPT-HSQC and nOe spectrum. 1,20-1.35 (m, 3H, H-7ax, H-8ax, H-15ax), 1.37-1.50 (qt app, J=11.8, 3.7 Hz, 1H, H-16ax), 1.53-1.61 (m, 5H, H-6ax, H-10a, H-14ax, H-14eq, H-16eq), 1.63-1.70 (m, 2H, H-6eq, H-15eq), 1.72-1.80 (m, 2H, H-7eq, H-8eq),

1.90 (dtd, J^2= 12.6 J^3= 7.9, J^3= 2.5 Hz 1H, H-10b), 2.04 (td, $J^{2,3}$= 10.8, J^3= 3.3 Hz, 1H, H-5ax), 2.15 (td, $J^{2,3}$= 11.2, J^3= 2.8 Hz, 1H, H-17ax), 2.18 (s, 1H, OH), 2.23-2.30 (m, 1H, H-13), 2.30-2.40 (m, 1H, H-9), 2.45 (ddd, J^2= 12.9, J^3= 8.3, J^3= 4.5 Hz, 1H, H-11a), 2.88-3.00 (dt, J^2= 11.0, J^3= 3.3 Hz, 1H, H-5eq), 2.90-3.00 (m, 1H, H-11b), 2.95-3.05 (dt, J^2= 11.4, J^3= 2.1 Hz, 1H, H-17eq), 3.37 (dd, J^2= 11.5, J^3= 3.5 Hz, 1H, H-18a), 3.43 (dd, J^2= 10.2, J^3= 6.9 Hz, 1H, H-1ax), 3.84 (dd, J^2= 11.5, J^3= 3.8 Hz, 1H, H-18b), 3.89 (t, J^3= 6.5, 1H, H-3), 3.90 (dd, J^2= 8.6, J^3= 2.1 Hz 1H, H-1eq), ^{13}C-NMR (150MHz, $CDCl_3$): Peaks assignments were supported by a DEPT/HSQC spectrum. 23.41 (C-7 or 8), 24.00 (C-15), 24.65 (C-16), 24.74 (C-6), 26.53 (C-8 or 7), 27.98 (C-14), 29.08 (C-10), 47.60 (C-11), 47.66 (C-5), 51.38 (C-17), 61.34 (C-13), 62.91 (C-9), 62.95 (C-18), 69.95 (C-1), 93.99 (C-3)

The following distinct signals attributed to **19** were deduced from an enriched mixture of **19/18** (75:25) obtained from a solution of **18** in $CDCl_3$ at -20 °C over a 3-month period.
^{1}H-NMR (600MHz, $CDCl_3$): Partial peaks assignments were supported by a COSY, DEPT-HSQC and nOe spectrum. 1.98 (td, J^2=11.6, J^3=11.6 J^3=2.6 Hz, 1H, 17ax), 2.01 (td, J^2=13.1, J^3=9.6 J^3=4.1 Hz, 1H H11a), 2.10 (dq, J^3=10.5, J^3=3.8 J^3=2.4 Hz, 1H, H13ax), 3.02-3.06 (m, 2H, H17eq, H5eq), 3.16 (ddd, J^2=13.1, J^3=8.8 J^3=4.4 Hz 1H, H11b), 3.26 (dd, J^2=11.7, J^3=2 Hz, 1H, H18a), 3.50 (dd, J^2=10.4, J^3=6.7 Hz, 1H, H1ax), 3.80-3.85 (dd J^3=9.0, J^3=3.0, 1H, H3), 3.86-3.91 (dd J^2=11.6, J^3=3.2, 1H, H1eq), 3.98 (dd, J^2=11.7, J^3=3.5 Hz 1H, H18b). ^{13}C-NMR **19** (150MHz, $CDCl_3$): 23.46 (C-7 or 8) 24.08 (C-15) 24.50 (C-16) 25.56 (C-6) 25.82 (C-8 or 7) 27.82 (C-14) 28.90 (C-10) 45.58 (C-11) 47.56 (C-5) 52.38 (C-17) 62.12 (C-13) 63.02 (C-9) 63.26 (C-18) 70.32 (C-1) 94.54 (C-3)

Supporting information

Experimental procedures and the NMR spectral data of all the products can be found free of charge in the supplementary information…

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References:
(1) Scolastico, C. *Asymmetric synthesis via nor-ephedrine derived 2-alkenyloxazolidines,* Pure Appl. Chem. **1988**, 60, 1689-1698.
(2) Hoppe, I.; Hoffmann, H.;Gartner, I.; Kretek, T.; Hoppe, D. *Diastereoselective Synthesis of Enantiomerically Pure 3-Organosulfonyl-2-(2-oxocycloalkyl)-1,3-oxazolidines from 2-Formylcycloalkanones and ß-Aminoalkanols,* Synthesis **1991**, 1157-1162.
(3) Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *A new access to enantiopure β-hydroxylated piperidines from N-Boc-2-acyloxazolidines. Application to the synthesis of (−)-desoxoprosopinine and (+)-pseudoconhydrine,* Tetrahedron **1998**, 54, 8783 – 8786.
(4) Agami, C.; Dechoux, L.; Melaimi, M. *An Efficient Synthesis of Pyrimidines from β-Amino Alcohols,* Org. Lett. **2000**, 2, 633 - 634

(5) Moloney, G. P.; Craig, D. J.; Iskander, M. N.; Nero, T. L. J. *Synthesis, NMR studies and conformational analysis of oxazolidine derivatives of the β-adrenoreceptor antagonists metoprolol, atenolol and timolol* Chem.Soc, Perkin Trans. 2. **1998**, 199 – 206
(6) Herreros, E.; Almela, M. J.; Lozano, S.; De Las Heras, F. G.; Gargallo-Viola, D. *Antifungal Activities and Cytotoxicity Studies of Six New Azasordarins,* Antimicrob. Agents Chemother. **2001**, 45, 3132
(7) Grinsteiner, T. J.; Kishi, Y. *Synthetic studies towards batrachotoxin 1. A furan-based intramolecular diels-alder route to construct the a-d ring system*, Tetrahedron letter **1994**, 45, 8333-8337
(8) Stuart M. Clark and Helen M. I. Osborn, *Synthetic entry to functionalised morpholines and [1,4]-oxazepanes via reductive amination reactions of carbohydrate derived dialdehydes*, Tetrahedron: Asymmetry 15 (**2004**) 3643–3652
(9) Yohan Malki, Jean Martinez, Nicolas Masurier, *1, 3-Diazepine: A privileged scaffold in medicinal chemistry*, Med Res Rev. **2021**;41:2247–2315.
(10) National Institute for Occupational Hygiene (NIOSH), *Aldehydes, Screening* - Method 2539 **1994**
(11) Occupational Safety and Health Administration (OSHA), *Acrolein, Formaldehyde* - Method 52 **1989**
(12) (a) National Institute for Occupational Hygiene (NIOSH). (2003a). *Aliphatic aldehydes*, **2018** (b) National Institute for Occupational Hygiene (NIOSH). (2003b). *Formaldehyde*, **2016**
(13) (a) Occupational Safety and Health Administration (OSHA). (1990a). *Crotonaldehyde* - Method 81 (b) Occupational Safety and Health Administration (OSHA). (1990b). *Valeraldehyde* - Method 85. **1990**
(14) ASTM. D5197-16 *Standard Method for Determination of Formaldehyde and Other Carbonyl compounds in Air,* Active Sampler Methodology, **2016**
(15) Uchiyama, S., Inaba, Y. et Kunugita, N. *Derivatization of carbonyl compounds with 2,4-dinitrophenylhydrazine and their subsequent determination by high-performance liquid chromatography*, J. Chromatogr. B 879, **2011**, 1282–1289
(16) Compendium Method TO-11A, *Determination of Formaldehyde in Ambient Air Using Adsorbent Cartridge Followed by High Performance Liquid Chromatography (HPLC)* [Active Sampling Methodology], **1999**
(17) Steven Sai Hang Ho, K.F. Ho, W.D. Liu, S.C. Lee, W.T. Dai, J.J. Cao, H.S.S. Ip, *Unsuitability of using the DNPH-coated solid sorbent cartridge for determination of airborne unsaturated carbonyls*, Atmospheric Environment 45, 261-265, **2011**

(18) Jason S. Herrington, Michael D. Hays, *Concerns regarding 24-h sampling for formaldehyde, acetaldehyde, and acrolein using 2,4-dinitrophenylhydrazine (DNPH)-coated solid sorbents*, Atmospheric Environment 55, 179-184, **2012**

(19) Eugene R. Kennedy, and Kevin Ashley. *Fourier Transform Infrared Spectrometry/Attenuated Total Reflectance Study of the Reaction of Pentanal and Propanal with 2-(Hydroxymethyl)Piperidine*, Applied Spectroscopy.**1992**, 46, No-2, 266-272

(20) Lok-Hang Yan, Flore Dagorn, Edmond Gravel, Blandine Séon-Méniel, Erwan Poupon, *Synthesis and reactivity of pelletierine-derived building blocks and pelletierine analogs*, *Tetrahedron,* **2012,** 68, 6276-6283

(21) (a) Markus B. Schmid, Kirsten Zeitler, and Ruth M. Gschwind, *Formation and stability of prolinol and prolinol ether enamines by NMR: delicate selectivity and reactivity balances and parasitic equilibria*, *J. Am. Chem. Soc*. **2011**, 133, 7065–7074; (b) Michael H. Haindl, Johnny Hioe, and Ruth M. Gschwind, *The proline enamine formation pathway revisited in dimethyl sulfoxide: rate constants determined via NMR*, *J. Am. Chem. Soc*. **2015**, 137, 12835−12842; (c) Polyssena Renzi, Johnny Hioe, and Ruth M. Gschwind, *Enamine/dienamine and Brønsted acid catalysis: elusive intermediates, reaction mechanisms, and stereoinduction modes based on in situ NMR spectroscopy and Computational Studies*, *Acc. Chem. Res.* **2017**, 50, 2936−2948

(22) Eugene R. Kennedy and Robert H. Hill, Jr. *Determination of formaldehyde in air as an oxazolidine derivative by capillary gas chromatography*, Anal. Chem. **1982**, 54, 1739-1742

(23) Eugene R. Kennedy, Paula Fey O'Connor, and Yvonne T. Gagnon. *Determination of acrolein in air as an oxazolidine derivative by gas chromatography*, Anal. Chem. **1982**, 56, 2120-2123

(24) Gilbert Cook A., Christine Schering A., Pauline Campbell A., and Samantha Hayes S. *Pyrolysis of perhydro [1, 2-c][1, 3] oxazines: a green method of synthesizing 2, 3-dehydropiperidine enamines*, Tetrahedron Lett. **2005**, 46, 5451-5454

(25) F. J. McCarty. C. H. Tilford and M. C. Van Campen, *Central Stimulants. α,α-Disubstituted 2-Piperidinemethanols and 1,1-Disubstituted Heptahydroöxazolo [3,4-a]pyridines*, J. Am. Chem. Soc. **1956**, 79, 2, 472–480.

(26) T. A. Craab, and R. F. Newton. *Stereochemical studies on 7-substituted 8-oxa-1-azabicyclo [4.3. 0] nonanes*, J. Heterocyclic Chem. **1966**, Vol. 3, 418

(27) N. Lokesh, Andreas Seegerer, Johnny Hioe, and Ruth M. Gschwind, *Chemical exchange saturation transfer in chemical reactions: a mechanistic tool for NMR detection and characterization of transient intermediates*, J. Am. Chem. Soc. **2018**, 140, 1855−1862

(28) Sami Lakhdar, Takahiro Tokuyasu, and Herbert Mayr, *Electrophilic Reactivities of α, β-Unsaturated Iminium Ions*, Angew. Chem. Int. Ed. **2008**, 47, 8723 –8726

(29) David A. Evans, George Borg, and Karl A. Scheidt, *Remarkably Stable Tetrahedral Intermediates: Carbinols from Nucleophilic Additions to N–Acylpyrroles*, Angew, Chem. Int. Ed. **2002**, 41, No. 17 [Supporting Information]

(30) Anna Kwiecień, Maciej Barys and Zbigniew Ciunik, *Stable hemiaminals with a cyano group and a triazole ring*, Molecules **2014**, 19, 11160-11177

(31) Juliana G. Pereira, João P. M. António, Ricardo Mendonça, Rafael F. A. Gomes and Carlos A. M. Afonso, *Rediscovering aminal chemistry: copper(ii) catalysed formation under mild conditions*, Green Chemistry **2020** 22(21):7484-7490

(32) Olivier Dirat, Andrew J. Bibb, Colin M. Burns, Graham D. Checksfield, Barry R. Dillon, Stuart E. Field, Steven J. Fussell, Stuart P. Green, Clive Mason, Jinu Mathew, Suju Mathew, Ian B. Moses, Petar I. Nikiforov, Alan J. Pettman, and Flavien Susanne, *The Lactol Route to Fesoterodine: An Amine-Promoted Friedel–Crafts Alkylation on Commercial Scale*, Org. Process Res. Dev. **2011**, 15, 1010–1017

(33) Combret, J. C; Klein, J. L; Mohamed Mouslouhouddine, *Reaction of trimethylsilylamines with α, β-unsaturated aldehydes: a convenient synthesis of 1, 3-bis [dialkylamino]-1-alkenes*, Synthesis (Stuttgart). **1984**, Num 6, pp 493-495

(34) Ellen V. Dalessandro, Hugo P. Collin, Luiz Gustavo L. Guimarães, Marcelo S. Valle and Josefredo R. Pliego, Jr, *Mechanism of the piperidine-catalyzed Knoevenagel condensation reaction in methanol: the role of iminium and enolate ions*, J. Phys. Chem. B **2017**, 121, 5300−5307

(35) (a) Von Werner Miiller and Urs Stauss, *Synthese von 1, 2-annelierten 1, 4-Benzodiazepinen und 4, 1-Benzoxazepinen*, Helvetica Chimica Acta- Vo1.65, Fasc.7 (**1982**) - Nr.209; (b) Thierry Martens, Florence Billon-Souquet, Lsabelle Gauthierb and Jacques Royerb, *Anodically induced cycloaddition of vinylethylether to N-cyanomethyl-oxazolidine system. Stereoselective synthesis of β-amino ketal compounds*, Tetrahedron Letters, Vol. 38, No. 23. pp. 4075-4078, **1997**; (c) Lucile A. Gandon, Alexander G. Russell and John S. Snaith, *Tris(trimethylsilyl)silane: an unprecedented enhancement in the diastereoselectivity of radical cyclisations to give 2,4-disubstituted piperidines*, Org Biomol. Chem. **2004**, 2, 2270 – 2271

(36) Ferenc Fulop, Kalevi Pihlaja, Kari Neuvonen, Gabor Bernath, Gyula Argay, and Alajos Kàlman, *Ring-chain tautomerism in oxazolidines*, J. Org. Chem., **1993**, 1967-1969

(37) SAINT 7.23A, **2006**, Bruker AXS, Inc., Madison, Wisconsin, USA.

(38) SADABS 2004, George Sheldrick, **2004**, Bruker AXS, Inc., Madison,Wisconsin, USA.

(39) SHELXTL 6.14, George Sheldrick, **2000**, Bruker AXS, Inc., Madison,Wisconsin, USA.

(40) Andrew G. Brewster, Simon Broady, Catherine E. Davies, Thomas D. Heightman et el. *Enantiopure bicyclic piperidinones: stereocontrolled conjugate additions leading to substituted piperidinones*, Org. Biomol. Chem., **2004**, 1031-1043