

# 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 was used, the bicyclic 17 was obtained. This novel compound has suitable physical characteristics for an analytical standard. The hexahydro-3-vinyl-3*H*-oxazolo[3,4-*a*]pyridine 16 can be obtained at higher temperatures using an excess of acrolein (3 equiv). Following the same procedure as for 16, but with an excess of 2-HMP (2 equiv), a diastereomeric mixture of 18/19, which are both bisadducts of 2-HMP with acrolein, was obtained. The latter mixture can be easily converted into pure 18. Mechanistically, a thorough <sup>1</sup>H-NMR study did not show any evidence that the condensation reaction proceeded *via* an enamine. The reaction probably proceeded through an elusive hemiaminal and fleeting iminium ion, which underwent subsequent cyclization to give hexahydro-3-alkyl-3*H*-oxazolo[3,4-*a*]pyridines 4–16. The reaction pathways for the preparation of 4–18 are described.

## **1. INTRODUCTION**

The condensation of an aldehyde or ketone with a  $\beta$ -amino alcohol is of considerable interest in synthetic organic chemistry. Such heterocycles, 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  $\beta$ -amino alcohol pharmacophores.<sup>1–5</sup> 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.<sup>6</sup> The bicyclic octahydro-3*H*-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.<sup>7–9</sup>

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. Such

toxic aldehydes are released from forest fires, some industrial oxidation processes, and cigarette smoke.<sup>18b</sup> One of the options to efficiently stabilize 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.<sup>10,11</sup> The second most common option is with the use of 2,4-dinitrophenylhydrazine derivatives.<sup>12–16</sup> However, some authors reported concerns with unsaturated aldehydes, such as acrolein and crotonaldehyde, due to the presence of by-products and stability issues.<sup>17,18</sup> Aldehyde capture methods involving other derivatizing agents are summarized in Scheme 1.<sup>18</sup> The scope of application of a method should be as broad

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Scheme 1. Summary of the State-of-the-Art Capture of Volatile Aldehydes



Scheme 2. Reactions of 2-HMP with Different Aldehydes<sup>a</sup>



<sup>*a*</sup>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.	<b>Reaction Su</b>	ummary of	4-15	from the	Condensation	of Aldeh	vdes 2	with 2	2-HMP	1
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entry	aldehyde 2 (–R)	ratio <sup><i>a,b</i></sup> equiv	solvent	temp. (°C)	time (h)	product no	yield (%)
1	-Н	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 <sub>3</sub>	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

<sup>*a*</sup>A ratio of 5 g of MgSO<sub>4</sub> was used for 1 g of HMP for formaldehyde at 30%, while a mass ratio of MgSO<sub>4</sub>:HMP of 1:1 was used for the other aldehydes. <sup>*b*</sup>Ratio of aldehyde to HMP.

as possible to include all volatile aldehydes. 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 for NIOSH method 2539 using 2-piperidinemethanol.<sup>10</sup> Therefore, when using the 2-HMP method, these standards must be generated *in situ* from a precise amount of prepurified aldehyde, which adds to the technical difficulties. Furthermore, for acrolein, the reported 2-HMP derivative was erroneous.<sup>11</sup>

Even though bicyclic oxazolidines are well-known fivemembered 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 an iminium intermediate.<sup>19–21</sup> Thus, we were prompted to reinvestigate the reaction involving Scheme 3. Summary of Products Derived from the Reaction of 2-HMP with Acrolein



2-HMP with a series of substituted aldehydes to gain a deeper understanding of its reaction mechanism and to establish optimal conditions for the generation of analytical standards 4-15 and 17.

#### 2. RESULTS AND DISCUSSION

2.1. 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.<sup>22-24</sup> Therefore, we investigated the condensation of various aldehydes with 2-HMP and obtained the corresponding hexahydro-3-alkyl-1,3oxazolopiperidines 4-15 in high yields (see Scheme 2 and Table 1). Solvent and temperature conditions have been reported for similar condensation reactions and may affect the oxazolidine ring formation.<sup>21d,e</sup> Optimization of the reaction conditions was explored, wherein changes in solvent (hexane, benzene, toluene, xylene, DCM, and MeOH), acid present (PPTs, p-TsA, and BF<sub>3</sub>OEt), dehydrating agent (MgSO<sub>4</sub>, 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<sub>3</sub>OEt (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 as follows: anhydrous MgSO<sub>4</sub> in dichloromethane (DCM) or toluene at room temperature. The other solvents investigated led to lower yields (THF, MeOH: Table 1, entries 13 and 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 Schemes 2 and 3 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 (in 93% yield, Table 2, entry 1) with traces of 18 and 19. The use of hexanes at reflux for 1 h 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.

As illustrated in Scheme 2 and Tables 1 and 2, various oxazolopiperidines 4-16 and/or an octahydro-3H-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 furalde-hyde) slightly hydrolyze (aldehyde peaks were detected in the <sup>1</sup>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 hydrolysis or isomerization;

entry	ratio equiv (acrolein:HMP)	solvent	temp. (°C)	time (h)	yield (%)	(purity ratio %) <sup>b</sup>
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 <sup>a</sup>	69	1	ND	<b>16</b> + <b>1</b> 7 (50:50)
5	3	hexane <sup><i>a</i></sup>	69	2	80	<b>16</b> + <b>17</b> (85:15)
6	3	hexane <sup>a</sup>	69	4	50	<b>16</b> + <b>17</b> (85:15)
7	0.5	toluene <sup>a</sup>	111	1	95	18/19 (97)
8	0.8	toluene <sup>a</sup>	111	1	ND	<b>16 + 18/19</b> (90:10)
9	2	toluene <sup>a</sup>	111	0.25	80	<b>16</b> + <b>18/19</b> (95:5)
10	2	toluene <sup>a</sup>	111	0.5	85	<b>16</b> + <b>18/19</b> (95:5)
11	2	toluene <sup>a</sup>	111	1.5	85	<b>16</b> + <b>18</b> / <b>19</b> (95:5)
12	3	toluene <sup>a</sup>	111	1	90	16 (97)
13	2	xylene <sup>a</sup>	139	1	70	<b>16</b> + <b>18/19</b> (85:15)

Table 2. Reaction Summary of 16-19 from the

Condensation of Acrolein 3 with 2-HMP 1

"A mass ratio of MgSO<sub>4</sub>:HMP of 1:1 was used. <sup>b1</sup>H-NMR ratio of products. Diastereoisomers **18/19** were obtained in various proportions. Overall yield undetermined.

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

**2.2. Analytical Standards.** The products 4-15 were obtained (avg yield 80%) in high degrees of purity (>98%) and were suitable as analytical standards. The purities of 2-HMP aldehyde derivatives were assessed annually and were found to be stable after 8 years at -70 °C. In the case of acrolein derivatives 16-18, the relative GC-MS response was equivalent. Although compound 17 can undergo a partial conversion to 18/19 during the analysis, this transformation does not affect the quantitative analysis of acrolein (see the Supporting Information page S46 Table S3, last two entries).

Scheme 4. General Reaction Pathway for the Condensation of Amine 1 with Aldehyde 2 Leading to a Hemiaminal, Iminium, and (A) Enamine and/or (B) Oxazolidine



Scheme 5. Proposed General Mechanism for the Formation of the Oxazolidine Based on <sup>1</sup>H-NMR Monitoring of 6-10-11 Derivatives



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 polymerization 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.). Furthermore, for pure crystalline 17 and 18, we did not observe any degradation by <sup>1</sup>H-NMR analysis after a year of storage in a regular fridge. However, for further protection against any slight degradation, we recommend storage at -20 °C. 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).<sup>19,23</sup>

2.3. Mechanistic Aspects. The reaction of various substituted aldehydes with 2-HMP and other  $\beta$ -amino alcohols was first studied by McCarty et al. in 1957and then by Craab and Newton in 1966 followed by Kennedy and Ashley in 1992.<sup>25,26,19</sup> Based on the interpretation of FT-IR data, Kennedy and Ashley assumed that the reaction proceeded via the formation of an enamine intermediate (Scheme 4A), 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.<sup>20,21</sup> In an attempt to distinguish between one of these two pathways (Scheme 4), we decided to carry out a series of <sup>I</sup>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  $\alpha$ -proton.<sup>19,21a</sup> Isobutyraldehyde was studied because it is less sterically encumbered than pivaldehyde.

2.3.1. Enamine. Key reference signals for the enamine protons, obtained from the reaction of piperidine with

propanal in DMSO-d<sub>6</sub>, were at 5.79 ppm (d, N-C<u>H</u>=CH-CH<sub>3</sub>) and 4.23 ppm (hex-ap, N-CH=CH-CH<sub>3</sub>) respectively. Similarly, when piperidine was reacted with the more encumbered isobutyraldehyde in CDCl<sub>3</sub>, over 24 h at RT, only a progressive increase in an enamine signal at 5.28 ppm (hept-app, N-C<u>H</u>=C(CH<sub>3</sub>)<sub>2</sub>) 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 amounts of enamine.<sup>21a</sup> This is also the case for 1,3oxazolidines derived from 2-amino-2-methyl-propanol.<sup>21d</sup> The HMP-propanal (6) and HMP-pivaldehyde (11) adducts displayed characteristic H-3 protons of the oxazolopiperidine ring system (Scheme 2) 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 <sup>1</sup>H-NMR spectroscopy, taking measurement every 5 min at first and then at every double time interval (up to 3 h). In this specific experiment, beside from the initial aldehyde proton and the final oxazolidine 6 proton, the reaction was mostly completed within 20 min, and 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.<sup>19,22,23</sup>

Even though there is no possibility for enamine intermediate formation, the corresponding oxazolopiperidines (4, 9, 11, and 15) were obtained at room temperature in DCM. Together, these experiments clearly exclude the necessity of the intermediacy of an enamine (Scheme 4A).

2.3.2. Iminium/Hemiaminal/Aminal. The key signal at 9.2 ppm for the iminium intermediate derived from proline with 3-methylbutanal was reported by Gschwind et al., while others key iminium peaks were found from 8.4 to 9.3 ppm.<sup>19,28</sup> The iminium <sup>13</sup>C was reported at 166 to 171 ppm.<sup>28</sup> 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 5). This suggests that the elusive iminium is more

Scheme 6. Reaction of Piperidine with Unsaturated Aldehydes Leading to (a) 1,3-*N*,*N*-Bis-piperidyl-3-phenylpropene and (b) 2-Furyl Aminal





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.

rapidly converted into oxazolidine, which is consistent with a previous study.<sup>21a</sup> It has been previously reported that products from condensation of various 1,2- and 1,3-amino alcohol with carbonyl compounds are exothermic, quantitative at room temperature, and favors a higher ratio of the cyclic form instead of the open chain structures (Schemes 4 and 5).<sup>21d</sup>,e

Key values for the <sup>1</sup>H and <sup>13</sup>C ( $R_2N-CH(OH)-R$ ) signals for hemiaminal intermediates, similar to that of (Scheme 4), but derived from pyrrole/imidazole, were reported at 5.6-6.6 ppm and 77–83 ppm, respectively.<sup>29,30</sup> In the case of 2-HMP with pentanal or pivaldehyde in  $C_6D_6$ , we could not observe in the <sup>1</sup>H-NMR an iminium intermediate 10" and 11" nor a hemiaminal intermediate 10' and 11' during these reactions (Scheme 5). While for the reaction of 2-HMP with pentanal, we do observe (from 45 s 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 6b). Further investigations of the reaction of piperidine with cinnamaldehyde or furfuraldehyde were carried out in CDCl<sub>3</sub>. Two new key proton signals at 3.52 and 3.58 ppm were observed, while the corresponding <sup>13</sup>C signals were observed at 72 and 83 ppm. The NMR values are consistent with those reported for the aminal 4,4'-(furan-2-ylmethylene) dipiperidine derived from morpholine<sup>31</sup> and 1,3-N,N-bispiperidyl-3-phenylpropene via a 1,2- and 1,4-bis-addition of piperidine on cinnamaldehyde (Scheme 6).<sup>32,33</sup>

In line with recent literature studies, 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 (Schemes 4B and 5).<sup>20,21,27,34</sup> In the absence of a proximal hydroxymethyl nucleophile and with a tautomerisable  $\alpha$ -proton, it will

rearrange rapidly into the more stable enamine structure (Scheme 4A).

2.3.3. 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 5).<sup>21</sup> This can theoretically lead to two diastereomers depending on whether the C-3 substituent is in a pseudo-equatorial or pseudo-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 <sup>1</sup>H-NMR spectroscopy analysis of the oxazolopiperidine H-3 protons and or GC-MS, generally in a 95:5 ratio and 15 in an 80:20 ratio). The following isomers  $15_M/15_m$  and 18/19 were characterized by key nOes experiments (Figure 1). Products 15 had relaxation issues and required mix nOes and rOes.

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 2) with an alkene functional group, can easily undergo polymerization. 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 (78 h). 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. <sup>1</sup>H- and <sup>13</sup>C-NMR analysis results of the white crystalline product **17** thus obtained were 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  $3063 \text{ cm}^{-1}$ . Furthermore, the structure of 17 was established by X-ray crystal structure analysis (Figure 2). Thus, the reaction at room temperature



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

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 (Schemes 2 and 3). Other syntheses of 1,4oxazepanol involving two to three steps were reported.<sup>35</sup> 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 <sup>1</sup>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 the 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 a standard air sampling procedure, involving 2-HMP impregnated on Amberlite XAD-2, is usually done at room temperature.<sup>10</sup> The derived product obtained is extracted and directly analyzed by GC-MS. Therefore, in the case of acrolein, the derivative that will most likely be generated is the octahydro-3H-pyrido [2,1-c] [1,4] oxazepin-3-ol, 17. When preabsorbed 2-HMP onto amberlite XAD-2 was allowed to react with acrolein in toluene at room temperature for 1 h, the relative proportion of compounds observed by <sup>1</sup>H-NMR was 17 (52%) along with new side products 18/19 (48%). However, upon refluxing in toluene for 1 h, the adduct 17 underwent partial conversion into the corresponding 3-vinyloxazolopiperidine 16 (52%), 18/19 (40%), unreacted 17 (7%), and some trace of acrolein ( $\sim$ 1%). Furthermore, if 1 equiv 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, 120 °C), the diastereomeric mixture of bisadducts 18/19 (70%) is initially obtained as a viscous yellow oil (Scheme 7). This mixture slowly crystallizes quantitatively into 18 over 2-3 days. When the latter is melted, it isomerizes 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 rationalize the formation of 18/19 by first an opening of the hemiacetal 17 to the corresponding ring open aldehyde intermediate 17'. 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 17', leading to 18'' and thus generating 18/19.<sup>36</sup> These can also be generated by the stoichiometric addition of 2-HMP to 16 (RT 8 h or after 1 h reflux in toluene). Compounds 18/19 are best obtained (95% yield) starting with 2 equiv of 2-HMP with acrolein (Table 2, entry 7, Schemes 3 and 8).

The <sup>1</sup>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 <sup>13</sup>C displayed a doubling of the signals related to 2-HMP. A follow up by <sup>1</sup>H-NMR of a solution of **18** in CDCl<sub>3</sub> at -20 °C, over a period 3 months, shows a slow, but cleaner, isomerization 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 established a bisadduct of 2-HMP with acrolein. Both configurations 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.

### 3. X-RAY CRYSTAL DETERMINATION OF STRUCTURES 17 AND 18

The X-ray crystal structure of 17 is consistent with that anticipated for an oxazepane ring system (Figure 2).<sup>37–39</sup> 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 the Supporting Information and the complete data in the CCDC database.

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 Supporting Information and the complete data in the CCDC database.

Scheme 7. Proposed Mechanism for the Conversion of 17 to 18/19 when Heated in Vacuum









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-membered 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. CONCLUSIONS

In conclusion, an expedient high yielding route for HMPaldehyde 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 that cannot isomerize to an enamine. In the case of acrolein, the path of the reaction is highly temperaturedependent and leads to the novel hemiacetal octahydro-3Hpyrido [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 attempts 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 tubes using a Gallenkamp melting point apparatus and were 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. The 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 chromatography (TLC), silica gel 60 F254 plates from Merck were used with detection visualized under UV light and/or an 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 sulfate (Anachemia) and rotary evaporated under reduced pressure. Nuclear magnetic resonance <sup>1</sup>H-NMR spectra were recorded using a Varian Gemini 300 BB -300.1 MHz and a Bruker 600 MHz spectrometers. <sup>13</sup>C-NMR spectra were recorded at 75 or 125 MHz. Chemical shifts for observed signals are reported in parts per million downfield from tetramethylsilane. <sup>1</sup>H chemical shifts were referenced to the solvents (CDCl<sub>3</sub>, 7.27 ppm, 77.16 ppm; C<sub>6</sub>D<sub>6</sub>, 7.16 ppm; DMSO- $d_{6i}$  2.50 ppm; or CD<sub>3</sub>OD, 3.30 ppm); <sup>13</sup>C chemical shifts were referenced to the solvents (CDCl<sub>3</sub>, 77.03 ppm or CD<sub>3</sub>OD, 49.00 ppm). The structure assignment of proton and carbon signals was achieved using NMR methods (1H, 13C, and in some cases: nOe, H-COSY, and HSQC). The assignments of <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts for the other compounds were attributed by comparison with those fully characterized. GC-MS were recorded on a Hewlett-Packard - HP G1800A GCD Series II with a 5% Me Ph silicon  $(30 \text{ m} \times 0.25 \text{ mm} \times 0.25 \ \mu\text{m}$  HP part no 19091J-433). The MS detection mode was EI.

**5.2.** X-ray Crystallography. For compounds 17 and 18, crystallization was obtained from a 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  $\omega$  and  $\theta$  scans with a scan width of 0.3° and 10 s (17) and 60 s (18) exposure times. The detector distance was 5 cm. The data were reduced (SAINT)<sup>37</sup> and corrected for absorption (SA-DABS).<sup>38</sup> The structure was solved by direct methods and refined by full-matrix least squares on F<sup>2</sup>(SHELXTL).<sup>39</sup> 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 for 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

5.3.1. Preparation of Hexahydro-3H-oxazolo[3,4-a]pyridine (4).<sup>10,22</sup> Formaldehyde (0.72 mL, 37% aqueous solution, 9.67 mmol) was added dropwise via a syringe to a solution of 2-HMP (1.00 g, 8.68 mmol) in DCM (10 mL), the whole mixture was stirred for 10 min at room temperature, anhydrous MgSO4 (5 gr) was added, and the mixture was stirred for 2 h while being monitored by TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH (9:1)). The reaction mixture was filtered, and the solvent was removed under reduced pressure to afford a crude product that was then treated with solution of sodium hydroxide (5%). The aqueous solution was extracted with ether  $(3 \times 20 \text{ mL})$ . The combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. Filtration and removal of solvents afforded 1.056 g (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 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 °C (1.2 torr). GC:  $R_T$  = 3.22 min. MS (EI, 70 eV, m/z): 127 (M<sup>+</sup>, 32%), 126 (M<sup>+</sup>-H, 47%), 97 (M<sup>+</sup>-H<sub>2</sub>C=O, 100%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): Peak 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,  $J^3$  = 4.9 Hz, 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-Seq), 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.2. General Procedure for the Preparation of Hexahydro-3-alkyl-3H-oxazolo[3,4-a]pyridines.<sup>10,23,24,40</sup> Freshly distilled aldehyde (1-2 equiv, see Table 1) was stirred with a solution of 2-HMP (1 equiv) in DCM (1 mL per mmole of 2-HMP) for 30 min. Anhydrous MgSO<sub>4</sub> (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 h). 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  $(3 \times 20 \text{ mL})$ . The combined organic phases were dried with brine and over MgSO<sub>4</sub>. 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 giving a colorless or pale-yellow liquid. A fractional collector (cow) was used, which allowed four fractions to be collected without disturbing the vacuum.

5.3.3. Synthesis of Hexahydro-3-methyl-3H-oxazolo[3,4a]pyridine (5). Using the general procedure, freshly distilled acetaldehyde (1.46 mL, 26.1 mmol, 2 equiv) was added to a cooled (0 °C) solution of 2-HMP (1.50 g, 13.0 mmol), DCM (12 mL), and anhydrous MgSO<sub>4</sub> (1.5 g) that gave 1.7 g (93%) of crude mass. The product was first vacuum (3 Torr) distilled in a Kulgelrohr apparatus 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 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<sup>+</sup>, 5%), 140 (M<sup>+</sup>-H, 13%), 126 (M<sup>+</sup>-CH<sub>3</sub>, 100%), 98 (M<sup>+</sup>-H<sub>3</sub>CC=O, 18%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): Peak 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.4. Synthesis of Hexahydro-3-ethyl-3H-oxazolo[3,4a]pyridine (6). Using the general procedure, an equimolar mixture of freshly distilled propionaldehyde (1.00 g, 17.2 mmol), 2-HMP (2 g, 17.4 mmol) in DCM (20 mL), and anhydrous MgSO4 (2 g) afforded 1.4 g (52%) of crude oil. Fractional vacuum distillation gave pure 6 (1.04 g) 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%),  $126(M+-C_2H_5, 100\%)$ ,  $98(M+-C_2H_5C=O, 7.5\%)$ . <sup>1</sup>H-NMR (300 MHz,  $CDCl_3$ ): 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-7H)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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.5. Synthesis of Hexahydro-3-propyl-3H-oxazolo[3,4a]pyridine (7). Using the general procedure, an equimolar mixture of freshly distilled butyraldehyde (1.56 mL, 1.25 g, 17.3 mmol), 2-HMP (2.00 g, 17.4 mmol) in DCM (15 mL), and anhydrous MgSO4 (2.0 g) was stirred for 3 h. Usual workup afforded 1.92 g (65.5%) of crude product. Subsequent fractional distillation under reduced pressure (1.2 torr) gave 7 as a colorless liquid.

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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%),  $126(M+-C_3H_7, 100\%)$ ,  $98(M+-C_3H_7C=O, 12\%)$ . <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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 = 7.5Hz, 1H, H-1eq), 4.54 (6%, t, J = 4.5 Hz, 1H, H-3). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.6. Synthesis of Hexahydro-3-isopropyl-3H-oxazolo-[3,4-a]pyridine (8). Using the general procedure, an equimolar mixture of freshly distilled isobutyraldehyde (1,19 mL, 0.940 g, 13.0 mmol), 2-HMP (1.50 g, 13.0 mmol) in DCM (10 mL), and anhydrous MgSO<sub>4</sub> (1.5 g) was stirred for 3 h, and a general workup afforded a crude yellow oil. Fractional vacuum distillation gave 8 (1.54 g, 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%),  $126(M+-C_3H_7, 100\%)$ ,  $98(M+-C_3H_7C=O, 6.25\%)$ . <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.7. Synthesis of Hexahydro-3-(1-propenyl)-3H-oxazolo-[3,4-a]pyridine (9). Using the general procedure, a mixture of the freshly distilled crotonaldehyde (0.84 mL, 10.22 mmol, 1.2 equiv), 2-HMP (1.00 g, 8.68 mmol), DCM (10 mL), and anhydrous MgSO<sub>4</sub> (1.0 g) was added and stirring was continued for 3 h. A general workup afforded a crude yellow oil. Fractional vacuum distillation over sodium carbonate (100 mg) and using a Vigraux column using a wood boiling stick to avoid formation of froth during distillation afforded 9 (1.18 g, 82%) as a colorless oil.

B.p. = 126 °C (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<sub>3</sub>, 8.75%), 126 (M+-C<sub>3</sub>H<sub>5</sub>, 100%), 98 (M+-C<sub>4</sub>H<sub>5</sub>O, 20%), 84 (C<sub>5</sub>H<sub>8</sub>O+, 3.75%), 69 (C<sub>4</sub>H<sub>5</sub>O+, 18.75%). IR/TF (NaCl): 2939 (F, *ν*(C-H des CH<sub>2</sub>)); 2782 (m, *ν*(C-H de CHO)); 1546 (F,  $\nu$ (C=C)); 1256 (m,  $\nu$ (C-O)). <sup>1</sup>H-NMR (300 MHz,  $CDCl_3$ ): Peak 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<sup>3</sup> = 10.2, 6.5, 2.7 Hz, 1H, H-9), 2.93  $(dt, J^2 = 10.4, J^3 = 3.3 \text{ Hz}, 1\text{H}, \text{H-Seq}), 3.49 (dd, J^3 = 10.2, J^2 =$ 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.8. Synthesis of Hexahydro-3-butyl-3H-oxazolo[3,4a]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 (15 mL), and anhydrous MgSO<sub>4</sub> (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 (2.81 g, 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<sub>4</sub>H<sub>9</sub>, 100%), 98 (M+-C<sub>4</sub>H<sub>9</sub>C=O, 7.5%). <sup>1</sup>H-NMR (300 MHz,  $CDCl_3$ ): 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<sup>2,3</sup> = 7.5 Hz, 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.9. Synthesis of Hexahydro-3-t-butyl-3H-oxazolo[3,4a]pyridine (11). Using the general procedure, a mixture of the freshly distilled pivaldehyde (0.70 mL, 0.56 g, 6.4 mmol, 1.5 equiv), 2-HMP (0.500 g, 4.34 mmol, 1 equiv), DCM (10 mL), anhydrous MgSO<sub>4</sub> (0.50 g) were stirred and heated to reflux for 6 h. A general workup afforded a crude product 11 as a yellow oil. Fractional 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<sub>3</sub>, 1.2%), 126 (M+-C<sub>4</sub>H<sub>9</sub>, 100%), 98 (M +-C<sub>4</sub>H<sub>9</sub>C=O, 5%). <sup>1</sup>H-NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>): 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.10. 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 (12 mL), and anhydrous MgSO<sub>4</sub> (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 (1.61 g, 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<sub>4</sub>H<sub>9</sub>, 100%), 98 (M+-C<sub>4</sub>H<sub>9</sub>C=O, 9.5%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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<sup>3</sup> = 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  $(7\%, dd, J^3 = 8.0, J^3 = 4.3 \text{ Hz}, 1\text{H}, \text{H-3})$ . <sup>13</sup>C-NMR (75 MHz, CDCl<sub>2</sub>): 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).

5.3.11. Synthesis of Hexahydro-3-pentyl-3H-oxazolo[3,4a]pyridine (13). Using the general procedure, an equimolar mixture of the freshly distilled of hexanal (1.07 mL, 0.87 g, 8.69 mmol), 2-HMP (1.000 g, 8.68 mmol), DCM (10 mL), and anhydrous  $MgSO_4$  (1.0 g) was added and stirred for 4 h. A usual workup afforded 1.67 g 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. =  $111 \degree C$ (1.2 torr). GC:  $R_T = 5.74$  min. MS (EI, 70 eV, m/z): 196 (M +-H, 1.3%), 126 (M+-C<sub>5</sub>H<sub>11</sub>, 100%), 98 (M+-C<sub>5</sub>H<sub>11</sub>C=O, 7.5%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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,  $J^3 = 6.6$ ; 3 Hz, 1H, H-3). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.12. Synthesis of Hexahydro-3-hexyl-3H-oxazolo[3,4a]pyridine (14). Using the general procedure, an equimolar mixture of freshly distilled heptanal (1.22 mL, 0.99 g, 8.69 mmol), 2-HMP (1.000 g, 8.68 mmol), DCM (10 mL), and anhydrous MgSO<sub>4</sub> (1.0 g) was added and stirred for 4 h. A usual workup afforded a crude pale-yellow oil. Fractional vacuum distillation using a Vigreaux column gave 14 (1.31 g, 72%) as a colorless liquid.

B.p. = 126 °C (2 torr). GC:  $R_T$  = 6.39 min. MS (EI, 70 eV, m/z): 210 (M+-H, 1.3%), 126 (M+-C<sub>6</sub>H<sub>13</sub>, 100%), 98 (M +-C<sub>6</sub>H<sub>13</sub>C=O, 8.75%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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<sup>2</sup> = 10.6,  $J^3 = 3.5$  Hz, 1H, H-Seq), 3.15-3.25 (6%, m, 1H, H-Seq), 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.13. 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, 0.998 g, 10.4 mmol), 2-HMP (1.000 g, 8.68 mmol), toluene (15 mL, for other solvents, see Table 1), and anhydrous MgSO<sub>4</sub> (1.0 g) was added and stirred for 10 h. A usual workup afforded 1.44 g of a crude yellow oil. Fractional vacuum distillation using a Vigreaux column gave 15 (1.39 g, 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<sup>+</sup>, 33%), 192 (M<sup>+</sup>-H, 100%), 163 (M<sup>+</sup>-CH<sub>2</sub>O, 60%), 126 (M<sup>+</sup>-C<sub>4</sub>H<sub>3</sub>O-furyl, 23%). <sup>1</sup>H-NMR (300 MHz,  $CDCl_3$ ): Peak 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<sup>3</sup> = 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-Seq), 3.14.-3.23 (20%, m, 1H, H-9), 3.63  $(20\%, t, I^{2,3} = 7.4 \text{ Hz 1H}, \text{H-1ax}), 3.65 (80\%, \text{dd}, I^3 = 10.0, I^2 =$ 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'). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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').

5.3.14. Synthesis of Hexahydro-3-(ethynyl)-3H-oxazolo-[3,4-a]pyridine (16). Freshly distilled acrolein (1.74 mL, 1.46 g, 26 mmol, 3 equiv) in toluene (10 mL) was added (approx. 2 mL/min) to a solution of 2-HMP (1.00 g, 8.68 mmol, 1 equiv) in toluene (10 mL) and anhydrous MgSO<sub>4</sub> (1.0 g), the mixture was heated at reflux for 1 h, 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. <sup>1</sup>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<sup>+</sup>, 15%), 152 (M<sup>+</sup>-H, 36%), 126 (M<sup>+</sup>-C<sub>2</sub>H<sub>3</sub>, 100%), 98 (M<sup>+</sup>-C<sub>3</sub>H<sub>3</sub>O, 17%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):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, I = 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<sup>2</sup> = 13.2, J<sup>3</sup> = 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<sup>3</sup> = 10.2, J<sup>2</sup> = 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,  $J^3 = 17$ ,  $J^2 = 1.7$ ,  $J^4 = 1.7$ 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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).

5.3.15. Synthesis of Bicyclic Octahydro-3H-pyrido[2,1c][1,4]oxazepin-3-ol (17). A solution of freshly distilled acrolein (0.875 g, 1.043 mL, 15.6 mmol, 1.2 equiv) in toluene was added dropwise, via a syringe, to a solution of 2-HMP (1.50 g, 13.0 mmol) in toluene (10 mL), and the mixture was stirred at 0 °C. The reaction was monitored by <sup>1</sup>H-NMR. Once completed after 1 h, 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 2.07 g (17, 93%). The crude paleyellow product was taken up in a minimal volume of ether and 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 2.00 g 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<sub>5</sub>H<sub>11</sub>N<sup>+</sup>, 100%).

IRTF  $\nu_{max}$  (KBr)/cm<sup>-1</sup> 3063 (OH), 2940, 2838, 2797, 1310 (C-O), 1279(m), 1125, 1089, and 1033 (C-O). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): Peak 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, 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). <sup>13</sup>C-NMR (75 MHz CDCl<sub>3</sub>): 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).

5.3.16. Synthesis of Hexahydro-3-[2-N-(2hydroxymethyl)piperidyl-1-ethyl]-3H-oxazolo[3,4-a]pyridine (18). Freshly distilled acrolein (48.6 mg, 58  $\mu$ L, 0.87 mmol, 1 equiv) in toluene (1 mL) was added (approx. 1 min) to a solution of 2-HMP (200 mg, 1.74 mmol, 2 equiv) in toluene (1 mL) and anhydrous  $MgSO_4$  (200 mg), the mixture was heated at reflux for 1 h, and then it was cooled to ambient temperature. The reaction mixture was filtered, and the solvent was removed under a rotary evaporator at 30-35 °C to afford a crude thick yellow oil (222 mg, 95%). <sup>1</sup>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 °C. The <sup>1</sup>H-NMR analysis of the pale-yellow solid thus obtained showed only the characteristic ddd 2.45 ppm. The latter was washed with a minimal amount of precooled ether and then dissolved in a minimum amount of ether at room temperature and cooled to 4 °C overnight to finally give a 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 vacuum distilled in a Kugelrohr apparatus (0.3 torr, 125 °C) to afford 107 mg of a colorless thick liquid. <sup>1</sup>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 °C. GC:  $R_T = 8.33$  min. MS (EI, 70 eV, m/z) 267 (M<sup>+</sup>-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  $\nu_{max}$ (KBr)/cm<sup>-1</sup>: 3440, 3151 (OH), 2931, 2849, 2792, 1274 (s, C-N), 1130 (C-O), and 1044 (C-O). <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): Peak 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), <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): Peak 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<sub>3</sub> at -20 °C over a 3 month period.

<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): Partial peak 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). <sup>13</sup>C-NMR **19** (150 MHz, CDCl<sub>3</sub>): 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).

## ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00961.

NMR spectral data ( ${}^{1}$ H,  ${}^{13}$ C) of all the products 4–19 and COSY (for 4, 5, 9, 15, 17–19), DEPT-HSQC (for 18, 18/19), NOE (for 15, 17–19), X-ray data (for 17 and 18), and analytical data (PDF)

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Notes

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