ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

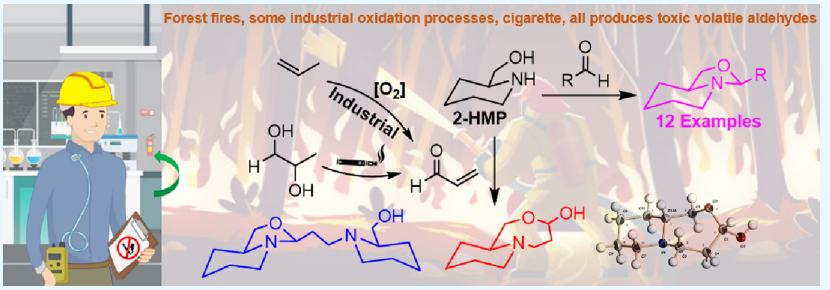
Synthesis of 3-Alkyl Oxazolidines, Derived from 2-Hydroxymethyl Piperidine, as Analytical Standards for the Analysis of Volatile Aldehydes in the Workplace

Amadou R. Yaya,[#] Martin Girard,[#] Karima Belkhadem, Rémi Piard, Andreas Decken, Catherine Choinière, Pierre Luc Cloutier, Jacques Lesage, and Livain Breau*

Cite This: *ACS Omega* 2023, 8, 26793−26805

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



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 ^{1}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.

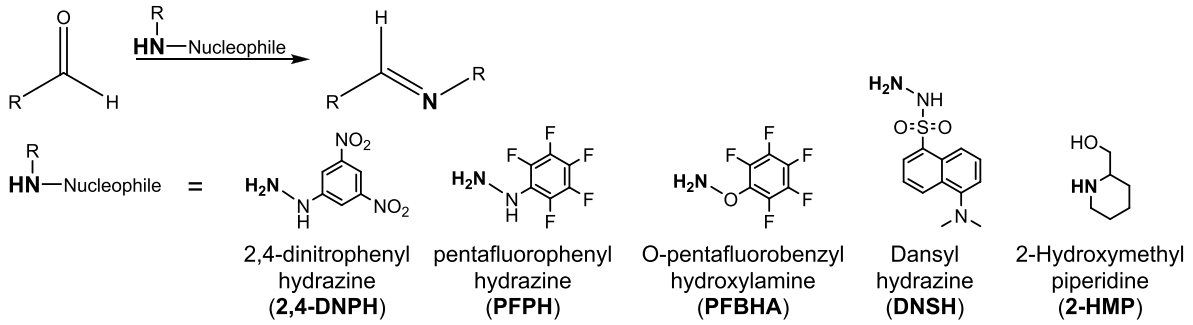
1. INTRODUCTION

The condensation of an aldehyde or ketone with a β-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 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-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.[7−9]

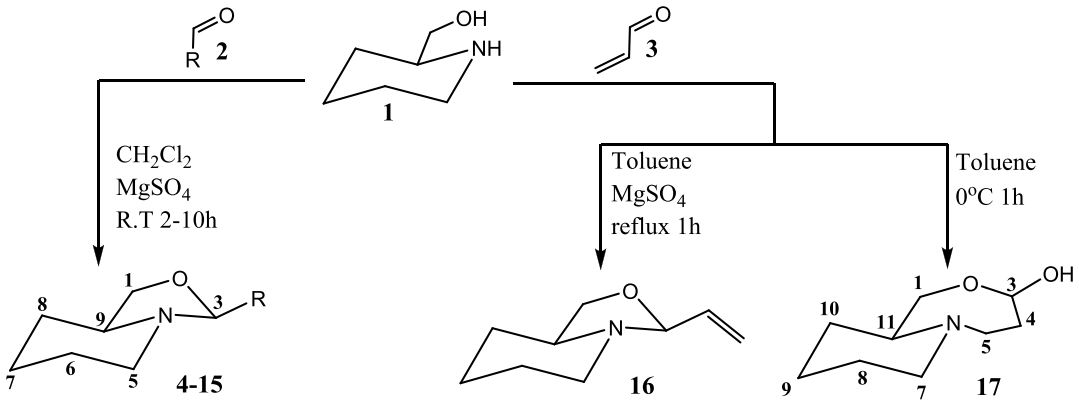
These heterocycles are also of analytical interest. Indeed, volatile aldehydes are reactive in the air and require stabilization *via* chemisorption during sampling for occupational exposure assessment or air quality and to ensure a reliable quantification through instrumental analysis. Such toxic aldehydes are released from forest fires, some industrial oxidation processes, and cigarette smoke.[18b] 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.[10,11] The second most common option is with the use of 2,4-dinitrophenylhydrazine 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] Aldehyde capture methods involving other derivatizing agents are summarized in Scheme 1.[18] The scope of application of a method should be as broad

Received: February 13, 2023
Accepted: May 30, 2023
Published: July 17, 2023

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



Scheme 2. Reactions of 2-HMP with Different Aldehydes[a]



[a]**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[a,b] 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

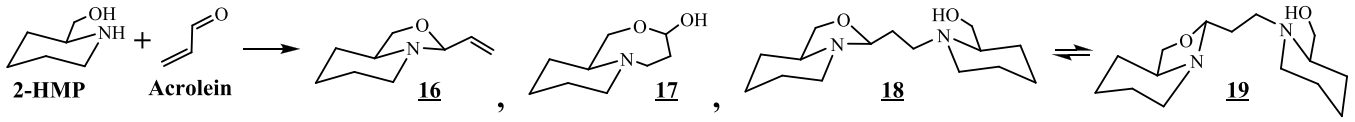
[a]A ratio of 5 g of $MgSO_4$ was used for 1 g of HMP for formaldehyde at 30%, while a mass ratio of $MgSO_4$:HMP of 1:1 was used for the other aldehydes. [b]Ratio of aldehyde to HMP.

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.[10] 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.[11]

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 an iminium intermediate.[19−21] Thus, we were prompted to reinvestigate the reaction involving

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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.[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 Scheme 2 and Table 1). Solvent and temperature conditions have been reported for similar condensation reactions and may affect the oxazolidine ring formation.[21d,e] 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_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 as follows: 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 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-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 hydrolyze (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 hydrolysis or isomerization;

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 %)[b]
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[a]	69	1	ND	**16** + **17** (50:50)
5	3	hexane[a]	69	2	80	**16** + **17** (85:15)
6	3	hexane[a]	69	4	50	**16** + **17** (85:15)
7	0.5	toluene[a]	111	1	95	**18/19** (97)
8	0.8	toluene[a]	111	1	ND	**16** + **18/19** (90:10)
9	2	toluene[a]	111	0.25	80	**16** + **18/19** (95:5)
10	2	toluene[a]	111	0.5	85	**16** + **18/19** (95:5)
11	2	toluene[a]	111	1.5	85	**16** + **18/19** (95:5)
12	3	toluene[a]	111	1	90	**16** (97)
13	2	xylene[a]	139	1	70	**16** + **18/19** (85:15)

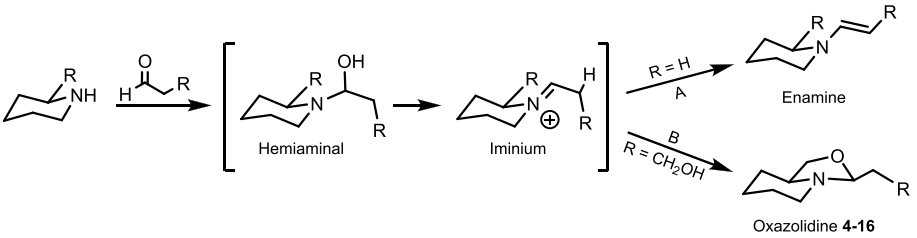
[a]A mass ratio of $MgSO_4$:HMP of 1:1 was used. [b]^{1}H-NMR ratio of products. Diastereoisomers **18/19** were obtained in various proportions. Overall yield undetermined.

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 ^{1}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 (^{1}H and ^{13}C) characterization was deduced from the differential analysis of the mixture of **18/19**.

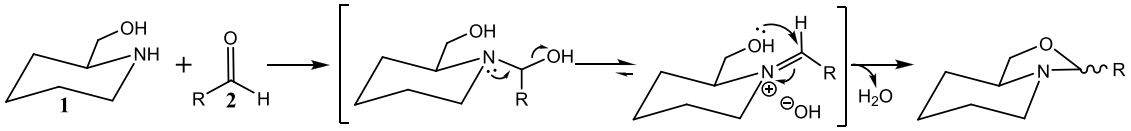
2.2. Analytical Standards. The products **4**−**15** were obtained (avg yield 80%) in high degrees of purity (>98%) and were suitable as analytical standards. The purities of 2-HMP aldehyde derivatives were assessed annually and were found to be stable after 8 years at −70 °C. In the case of acrolein 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).

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 ^{1}H-NMR Monitoring of 6-10-11 Derivatives



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**

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 ^{1}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).[19,23]

2.3. Mechanistic Aspects. The reaction of various substituted aldehydes with 2-HMP and other *β*-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.[25,26,19] 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.[20,21] In an attempt to distinguish between one of these two pathways (Scheme 4), 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.

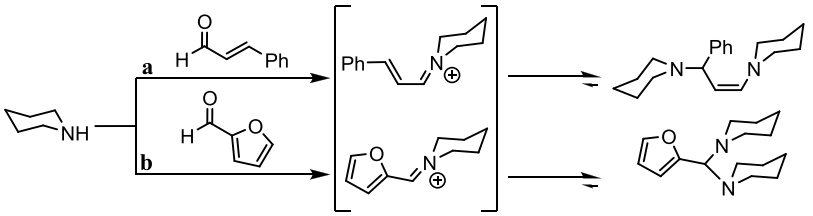
2.3.1. Enamine. Key reference signals for the enamine protons, obtained from the reaction of piperidine with propanal in DMSO-d_6, were at 5.79 ppm (d, N-C**H**=CH-CH_3) and 4.23 ppm (hex-ap, N-CH=C**H**-CH_3) respectively. Similarly, when piperidine was reacted with the more encumbered isobutyraldehyde in $CDCl_3$, over 24 h at RT, only a progressive increase in 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 amounts of enamine.[21a] This is also the case for 1,3-oxazolidines derived from 2-amino-2-methyl-propanol.[21d] 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 ^{1}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.[19,22,23]

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.[19,28] The iminium ^{13}C was 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 5). This suggests that the elusive iminium is more

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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



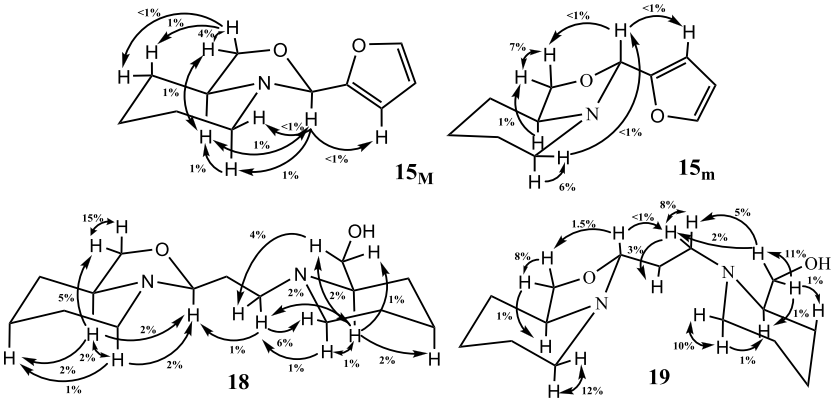


Figure 1. Summary of selected nOes observed for compounds $\mathbf{15_M/15_m}$ and **18**/**19** consistent with the pseudo-equatorial orientation of the C-3 substituents as shown.

rapidly converted into oxazolidine, which is consistent with a previous study.[21a] 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).[21d,e]

Key values for the ^{1}H and ^{13}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.[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 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 $CDCl_3$. Two new key proton signals at 3.52 and 3.58 ppm were observed, while the corresponding ^{13}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[31] and 1,3-*N*,*N*-bis-piperidyl-3-phenylpropene *via* a 1,2- and 1,4-bis-addition of piperidine on cinnamaldehyde (Scheme 6).[32,33]

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).[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 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).[21] 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 ^{1}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 $\mathbf{15_M/15_m}$ 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. ^{1}H- and ^{13}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-

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 cm^{-1}. Furthermore, the structure of **17** was established by X-ray crystal structure analysis (Figure 2). Thus, the reaction at room temperature

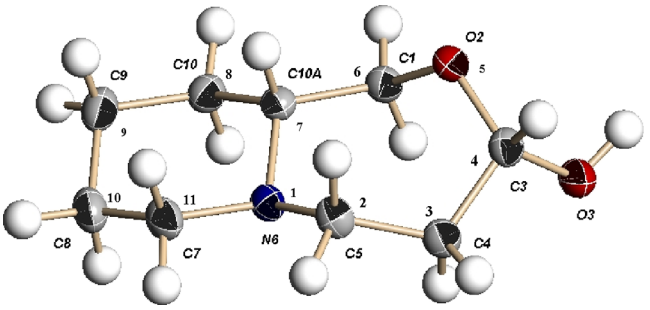


Figure 2. Thermal ellipsoid plot of **17**. Displacement ellipsoids are drawn at the 50% probability level.

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 1,4-oxazepanol involving two to three 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 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.[10] 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-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 1 h, 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 1 h, 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 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 bis-adducts **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**.[36] 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 ^{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, 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.

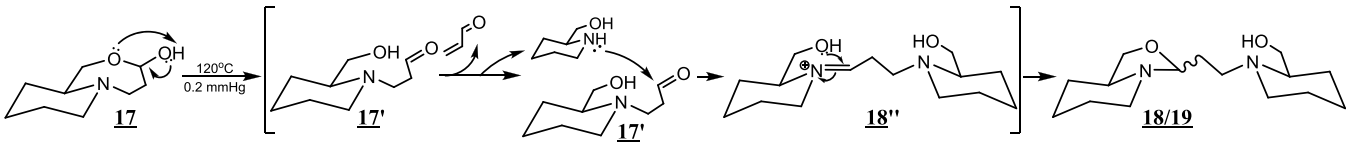
3. X-RAY CRYSTAL DETERMINATION OF STRUCTURES 17 AND 18

The X-ray crystal structure of **17** is consistent with that anticipated for an oxazepane ring system (Figure 2).[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 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).

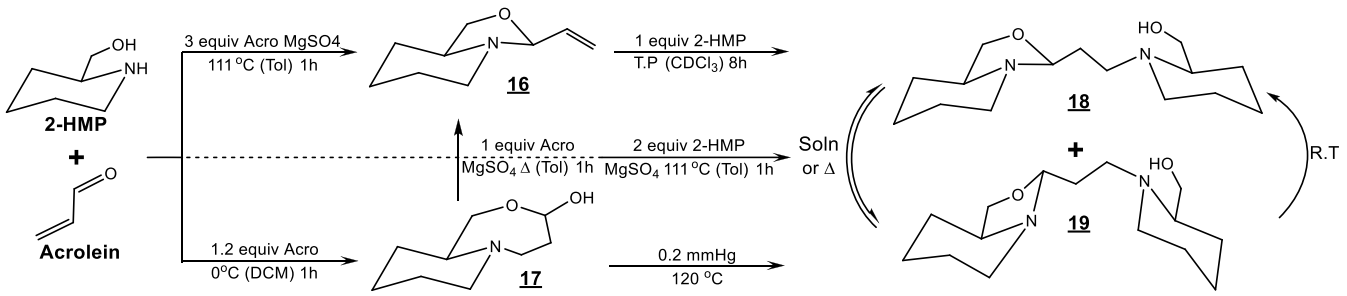
The X-ray crystal structure of **18** is shown in Figure 3. Information for the positional and equivalent thermal isotropic parameters for non-hydrogen atoms, bond distances, and angles as well as selected torsional angles can be found in Supporting Information and the complete data in the CCDC database.

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



https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

Scheme 8. Reaction Summary for 16−19 Involving 2-HMP with Acrolein in Various Conditions



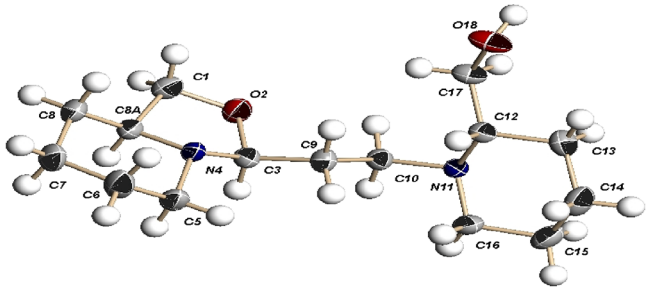


Figure 3. Thermal ellipsoid plot of **18**. Displacement ellipsoids are drawn at the 50% probability level.

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 HMP-aldehyde 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 temperature-dependent and leads to the novel hemiacetal octahydro-3*H*-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 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 F_{254} 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 ^{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. 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 characterized. GC−MS were recorded on a Hewlett-Packard - HP G1800A GCD Series II with a 5% Me Ph silicon (30 m × 0.25 mm × 0.25 μm 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 ω and θ 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)[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 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

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

(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 was obtained from BDH Chemical.

*5.3.1. 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* 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 $MgSO_4$ (5 gr) was added, and the mixture was stirred for 2 h 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 that was then treated with solution of sodium hydroxide (5%). The aqueous solution was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. 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^+, 32%), 126 (M^+-H, 47%), 97 (M^+-H_2C=O, 100%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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-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 (75 MHz, $CDCl_3$): 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).

5.3.2. 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 (1 equiv) 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 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 × 20 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 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[3,4-a]pyridine (**5**).* Using the general procedure, freshly distilled acetaldehyde (1.46 mL, 26.1 mmol, 2 equiv) was added to a cooled (0 °C) solution of 2-HMP (1.50 g, 13.0 mmol), DCM (12 mL), and anhydrous $MgSO_4$ (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^+, 5%), 140 (M^+-H, 13%), 126 (M^+-CH_3, 100%), 98 (M^+-H_3CC=O, 18%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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).

*5.3.4. 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 (2 g, 17.4 mmol) in DCM (20 mL), and anhydrous $MgSO_4$ (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%). ^{1}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-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 (75 MHz, $CDCl_3$): 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).

*5.3.5. 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, 1.25 g, 17.3 mmol), 2-HMP (2.00 g, 17.4 mmol) in DCM (15 mL), and anhydrous $MgSO_4$ (2.0 g) was stirred for 3 h. 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.

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 (300 MHz, $CDCl_3$): 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 (75 MHz, $CDCl_3$): 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).

*5.3.6. 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 $MgSO_4$ (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%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (75 MHz, $CDCl_3$): 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).

*5.3.7. 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 $MgSO_4$ (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_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 (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^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 (75 MHz, $CDCl_3$): 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).

*5.3.8. 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 (15 mL), and 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** (2.81 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_4H_9, 100%), 98 (M+-C_4H_9C=O, 7.5%). ^{1}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, $J^{2,3}$ = 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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).

*5.3.9. 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 equiv), 2-HMP (0.500 g, 4.34 mmol, 1 equiv), DCM (10 mL), 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. 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_3, 1.2%), 126 (M+-C_4H_9, 100%), 98 (M+-C_4H_9C=O, 5%). ^{1}H-NMR (300 MHz, 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 =

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 (75 MHz, $CDCl_3$): 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).

*5.3.10. 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 $MgSO_4$ (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** (1.61 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_4H_9, 100%), 98 (M+-C_4H_9C=O, 9.5%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (75 MHz, $CDCl_3$): 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).

*5.3.11. 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 (1.07 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 °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 (300 MHz, $CDCl_3$): 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; 3 Hz, 1H, H-3). ^{13}C-NMR (75 MHz, $CDCl_3$): 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).

*5.3.12. Synthesis of Hexahydro-3-hexyl-3H-oxazolo[3,4-a]pyridine (**14**).* Using the general procedure, an equimolar mixture of freshly distilled heptanal (1.22 mL, 0.99 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 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_6H_{13}, 100%), 98 (M+-$C_6H_{13}C$=O, 8.75%). ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (75 MHz, $CDCl_3$): 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).

*5.3.13. 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 $MgSO_4$ (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^+, 33%), 192 (M^+-H, 100%), 163 (M^+-CH_2O, 60%), 126 (M^+-C_4H_3O-furyl, 23%). ^{1}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^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 =

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 (75 MHz, $CDCl_3$): 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′).

*5.3.14. 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 $MgSO_4$ (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. ^{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 (300 MHz, $CDCl_3$):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 (75 MHz, $CDCl_3$): 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).

*5.3.15. Synthesis of Bicyclic Octahydro-3H-pyrido[2,1-c][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 ^{1}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 pale-yellow 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 ($C_5H_{11}N^+$, 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 (300 MHz, $CDCl_3$): 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, 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 (75 MHz $CDCl_3$): 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).

*5.3.16. Synthesis of Hexahydro-3-[2-N-(2-hydroxymethyl)piperidyl-1-ethyl]-3H-oxazolo[3,4-a]pyridine (**18**).* Freshly distilled acrolein (48.6 mg, 58 μL, 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%). ^{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 °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 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. ^{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 °C. GC: R_T = 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 (600 MHz, $CDCl_3$): 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-

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805

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 (150 MHz, $CDCl_3$): 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 $CDCl_3$ at −20 °C over a 3 month period.

^{1}H-NMR (600 MHz, $CDCl_3$): 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). ^{13}C-NMR **19** (150 MHz, $CDCl_3$): 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).

■ 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)

■ AUTHOR INFORMATION

Corresponding Author

Livain Breau − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada*; Email: breau.livain@uqam.ca

Authors

Amadou R. Yaya − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada*; orcid.org/0000-0001-7440-1673

Martin Girard − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada*

Karima Belkhadem − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada; Department of Chemistry, University of Sciences and Technology Mohamed Boudiaf, 31000 Oran, Algeria*

Rémi Piard − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada*

Andreas Decken − *Department of Chemistry, University of New Brunswick, Fredericton, NB E3A 6E2, Canada*

Catherine Choinière − *Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montréal, Québec H3A 3C2, Canada*

Pierre Luc Cloutier − *Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montréal, Québec H3A 3C2, Canada*

Jacques Lesage − *Département de chimie, Université du Québec à Montréal, Montreal, PQ H3C 3P8, Canada*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c00961

Author Contributions

#A.R.Y. and M.G. contributed equally.

Notes

The authors declare no competing financial interest.

The unmodified article is available on preprint repository ChemRxiv via the following link: https://chemrxiv.org/engage/chemrxiv/article-details/63573008cf6de9bcaa20cea6.

■ ACKNOWLEDGMENTS

We thank Simon Aubin and Marielle Carrier for the preliminary determination of purity of **4**−**15**. This work was partially supported by the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST). Also, A.R.Y. acknowledges the financial contribution of UQAM for a fellowship. Several 600 MHz spectra were recorded *via* the NanoQAM. Special thanks to K. Walsh for providing assistance with the editing of the manuscript and G. Landry for help with the graphic modification of the Cover-Art.

■ REFERENCES

(1) Scolastico, C. Asymmetric synthesis via nor-ephedrine derived 2-alkenyloxazolidines. *Pure Appl. Chem.* **1988**, *60*, 1689−1698.

(2) Hoppe, I.; Hoffmann, H.; Gärtner, I.; Krettek, 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*, 8783−8796.

(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 Lett.* **1994**, *35*, 8333−8336.

(8) Clark, S. M.; Osborn, H. M. I. Synthetic entry to functionalised morpholines and [1,4]-oxazepanes via reductive amination reactions of carbohydrate derived dialdehydes. *Tetrahedron: Asymmetry* **2004**, *15*, 3643−3652.

(9) Malki, Y.; Martinez, J.; Masurier, N. 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*; NIOSH 1994

(11) (a) Occupational Safety and Health Administration (OSHA), *Acrolein, Formaldehyde - Method 52*; OSHA 1989 (b) National Institute for Occupational Hygiene (NIOSH), *Acrolein - Method 2501*; NIOSH 1994

(12) (a) National Institute for Occupational Hygiene (NIOSH). (2003a). *Aliphatic aldehydes*; NIOSH 2018 (b) National Institute for Occupational Hygiene (NIOSH). (2003b). *Formaldehyde*; NIOSH, 2016
(13) (a) Occupational Safety and Health Administration (OSHA). (1990a). *Crotonaldehyde - Method 81*; OSHA (b) Occupational Safety and Health Administration (OSHA). (1990b). *Valeraldehyde - Method 85*; OSHA 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.; Kunugita, N. Derivatization of carbonyl compounds with 2,4-dinitrophenylhydrazine and their subsequent determination by high-performance liquid chromatography. *J. Chromatogr., B* **2011**, *879*, 1282−1289.
(16) Compendium Method TO-11A, *Determination of Formaldehyde in Ambient Air Using Adsorbent Cartridge Followed by High Performance Liquid Chromatography (HPLC)*; US EPA [Active Sampling Methodology], 1999
(17) Ho, S. S. H.; Ho, K. F.; Liu, W. D.; Lee, S. C.; Dai, W. T.; Cao, J. J.; Ip, H. S. S. Unsuitability of using the DNPH-coated solid sorbent cartridge for determination of airborne unsaturated carbonyls. *Atmos. Environ.* **2011**, *45*, 261−265.
(18) (a) Herrington, J. S.; Hays, M. D. Concerns regarding 24-h sampling for formaldehyde, acetaldehyde, and acrolein using 2,4-dinitrophenylhydrazine (DNPH)-coated solid sorbents. *Atmos. Environ.* **2012**, *55*, 179−184. (b) Schieweck, A.; Uhde, E.; Salthammer, T. Determination of acrolein in ambient air and in the atmosphere of environmental test chambers. *Environ. Sci.: Processes Impacts* **2021**, *23*, 1729−1746.
(19) Kennedy, E. R.; Ashley, K. Fourier Transform Infrared Spectrometry/Attenuated Total Reflectance Study of the Reaction of Pentanal and Propanal with 2-(Hydroxymethyl)Piperidine. *Appl. Spectrosc.* **1992**, *46*, 266−272.
(20) Yan, L.-H.; Dagorn, F.; Gravel, E.; Séon-Méniel, B.; Poupon, E. Synthesis and reactivity of pelletierine-derived building blocks and pelletierine analogs. *Tetrahedron* **2012**, *68*, 6276−6283.
(21) (a) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. 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) Haindl, M. H.; Hioe, J.; Gschwind, R. M. The proline enamine formation pathway revisited in dimethyl sulfoxide: rate constants determined via NMR. *J. Am. Chem. Soc.* **2015**, *137*, 12835−12842. (c) Renzi, P.; Hioe, J.; Gschwind, R. M. 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. (d) Fülöp, F.; Mattinen, J.; Pihlaja, R. Ring-chain tautomerism in 1,3-triazolidines. *Tetrahedron* **2017**, *50*, 6545−2948. (e) Fülöp, F.; Pihlaja, K.; Mattinen, J.; Bernáth, G. Ring-Chain Tautomerism in 1,3-Oxazines. *J. Org. Chem.* **1987**, *52*, 3821−3825.
(22) Eugene, R. K.; Hill, R. H., Jr. Determination of formaldehyde in air as an oxazolidine derivative by capillary gas chromatography. *Anal. Chem.* **1982**, *54*, 1739−1742.
(23) Kennedy, E. R.; O'Connor, P. F.; Gagnon, Y. T. Determination of acrolein in air as an oxazolidine derivative by gas chromatography. *Anal. Chem.* **1984**, *56*, 2120−2123.
(24) Gilbert, C. A.; Christine, S. A.; Pauline, C. A.; Samantha, H. 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) McCarty, F. J.; Tilford, C. H.; Van Campen, M. C. Central Stimulants. α,α-Disubstituted 2-Piperidinemethanols and 1,1-Disubstituted Heptahydroöxazolo [3,4-a]pyridines. *J. Am. Chem. Soc.* **1957**, *79*, 472−480.
(26) Crabb, T. A.; Newton, R. F. Stereochemical studies on 7-substituted 8-oxa-1-azabicyclo [4.3. 0] nonanes. *J. Heterocyclic Chem.* **1966**, *3*, 418.
(27) Lokesh, N.; Seegerer, A.; Hioe, J.; Gschwind, R. M. 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) Lakhdar, S.; Tokuyasu, T.; Mayr, H. Electrophilic Reactivities of α, β-Unsaturated Iminium Ions. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723−8726.
(29) David, A. E.; Borg, G.; Scheidt, K. A. Remarkably Stable Tetrahedral Intermediates: Carbinols from Nucleophilic Additions to N−Acylpyrroles. *Angew. Chem., Int. Ed.* **2002**, *41*, 17. [Supporting Information]
(30) Kwiecień, A.; Barys, M.; Ciunik, Z. Stable hemiaminals with a cyano group and a triazole ring. *Molecules* **2014**, *19*, 11160−11177.
(31) Juliana, G. P.; António, J. P. M.; Mendonça, R.; Gomes, R. F. A.; Afonso, C. A. M. Rediscovering aminal chemistry: copper(ii) catalysed formation under mild conditions. *Green Chem.* **2020**, *22*, 7484−7490.
(32) Dirat, O.; Bibb, A. J.; Burns, C. M.; Checksfield, G. D.; Dillon, B. R.; Field, S. E.; Fussell, S. J.; Green, S. P.; Mason, C.; Mathew, J.; Mathew, S.; Moses, I. B.; Nikiforov, P. I.; Pettman, A. J.; Susanne, F. 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.; Mouslouhouddine, M. Reaction of trimethylsilylamines with α, β-unsaturated aldehydes: a convenient synthesis of 1, 3-bis [dialkylamino]-1-alkenes. *Synthesis* **1984**, *6*, 493−495.
(34) Dalessandro, E. V.; Collin, H. P.; Guimarães, L. G. L.; Valle, M. S.; Pliego, J. R., 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) Miiller, V. W.; Stauss, U. Synthese von 1, 2-annelierten 1, 4-Benzodiazepinen und 4, 1-Benzoxazepinen. *Helv. Chim. Acta* **1982**, *65*, Nr.209. (b) Martens, T.; Billon-Souquet, F.; Gauthierb, L.; Royerb, J. Anodically induced cycloaddition of vinylethylether to N-cyanomethyl-oxazolidine system. Stereoselective synthesis of β-amino ketal compounds. *Tetrahedron Lett.* **1997**, *38*, 4075−4078. (c) Gandon, L. A.; Russell, A. G.; Snaith, J. S. 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) Fülöp, F.; Pihlaja, K.; Neuvonen, K.; Bernáth, G.; Argay, G.; Kálmán, A. Ring-chain tautomerism in oxazolidines. *J. Org. Chem.* **1993**, *58*, 1967−1969.
(37) *SAINT 7.23A*; Bruker AXS, Inc.: Madison, Wisconsin, USA, 2006.
(38) *SADABS 2004*; Sheldrick, G., Bruker AXS, Inc.: Madison,Wisconsin, USA, 2004.
(39) *SHELXTL 6.14*; Sheldrick, G., Bruker AXS, Inc.: Madison,-Wisconsin, USA, 2000.
(40) Andrew, G. B.; Broady, S.; Davies, C. E.; Heightman, T. D.; et al. Enantiopure bicyclic piperidinones: stereocontrolled conjugate additions leading to substituted piperidinones. *Org. Biomol. Chem.* **2004**, 1031−1043.

https://doi.org/10.1021/acsomega.3c00961
ACS Omega 2023, 8, 26793−26805