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Synthesis of 1,2- and 1,4-amino alcohols from 1,3-dienes via oxazines. Rearrangements of 1,4-amino alcohol derivatives to oxazolines

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ABSTRACT

Conjugated dienes were converted to 1,2-oxazines by reaction with an acyl nitroso dienophile. The oxazines were reduced to 1,4-*N*-acetylamino alcohols, which were rearranged to the corresponding oxazolines upon treatment with methanesulfonyl chloride or anhydride. The oxazolines yielded 1,2-*N*-acetylamino alcohols upon hydrolysis. Thus either 1,4- or 1,2-*N*-acetylamino alcohols are available from 1,3-dienes via this methodology. Experimental and spectral data are provided for all new compounds.

1. Introduction

In 2009 we published a concise formal synthesis of oseltamivir (Tamiflu) (**1**), in which a key step involved the 1,3-transposition of an allylic alcohol via oxazoline, as outlined in an abbreviated form in Figure 1.[1] The synthesis started with the [4+2] cycloaddition of acyl nitroso dienophile to the diene in acetonide **2**,[2] derived in two steps from ethyl benzoate via enzymatic oxidation.[3] Reduction of oxazine **3** produced the *N*-protected form of 1,4-amino alcohol **4**, which upon exposure to methanesulfonyl chloride rearranged cleanly to oxazoline **5**. Hydrolysis of **5** provided the corresponding 1,2-amino alcohol derivative **6**, which was then converted to oseltamivir in several steps.

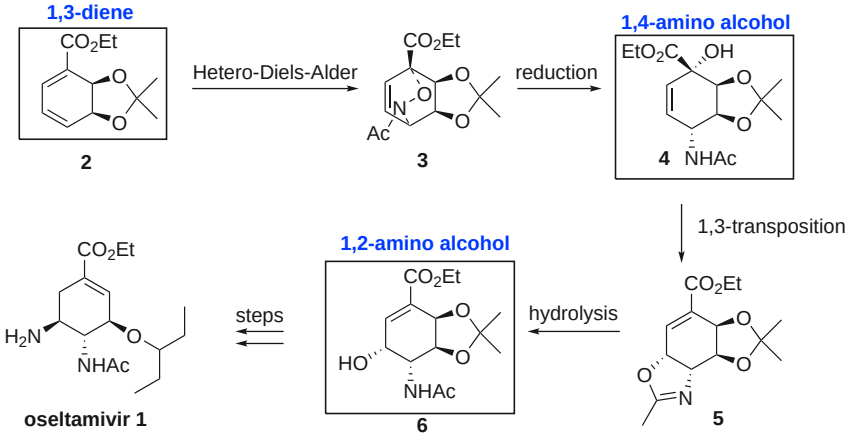

Figure 1. Oseltamivir synthesis via 1,4- and 1,2-amino alcohol derivatives.

When the process pictured in Figure 1 is viewed from the vantage point of functional transformations a possibility emerges of converting conjugated dienes selectively into either 1,4- or 1,2-amino

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alcohol derivatives. The latter group of compounds can also be obtained as either *cis*- or *trans*-isomers by further manipulations of oxazolines of type **5**. The conversion of cyclic as well as acyclic dienes to oxazines with various nitroso dienophiles is amply documented in the literature.[4] The conversion of the oxazines to 1,4-amino alcohol derivatives is also well precedented, especially so in the area of conduramine and amino cyclitol synthesis.[5] We were, however, surprised when the search of the literature revealed very few examples, mostly pertaining to six-membered ring systems, of the conversion of 1,4-*N*-acylamino alcohols to their oxazolines[6] and/or to the corresponding 1,2-derivatives. Olivo reported a convenient and general preparation of vinyl aziridines from 1,4-*N*-acylamino alcohols (obtained by oxazine reduction) via a vinylogous Mitsunobu reaction and observed competing oxazoline formation in some cases.[7] Most of the literature on oxazolines, useful as ligands, is concerned with their synthesis from 1,2-amino alcohols.[8] A recent report described the ruthenuium-catalyzed rearrangement of cyclic oxazines directly to *cis* or *trans* 1,2-amino alcohol derivatives.[9] We therefore chose to investigate the generality of the premise of converting oxazines derived from cyclic and acyclic dienes to both regioisomers of amino alcohols. In this paper we report the details of transforming 1,4-*N*-acylamino alcohols to the corresponding oxazolines via rearrangements of their mesylates.

2. Results and discussion

Based on the observations made during the oseltamivir synthesis we chose to investigate a series of cyclic dienes and their conversion to the corresponding oxazines whose reduction would provide the 1,4-amino alcohols that are suited for oxazoline formation and hence for the generation of 1,2-amino alcohols by hydrolysis.

The results of our study are summarized in Table 1. In each case the hetero Diels–Alder cycloaddition was conducted according to standard protocols (AcNHOH, $NaIO_4$) to prepare 1,2-oxazines **3**,[1] **8**,[10] **13**,[11] **18**, **23**, **28**, **30**, and **36** in the yields indicated. In the case of acyclic diene **22** the yield of the oxazine can be improved by using more equivalents of the nitroso dienophile. Diene **27** provided a mixture of regioisomers **28** and **30** (3:1). Lower yields of oxazine were obtained from diene **35** because of its tendency to aromatize under the reaction conditions to cyclohexyl phenol. Oxazines derived from cyclopentadiene, cyclohexadiene, and cycloheptadiene containing various *N*-acyl groups (*tert*-Boc, Cbz, Bz, etc.) are frequently described in the literature, however, *N*-acetyl derivatives are far less common. An oxazine derived from methyl sorbate was prepared from 1-chloro-1-nitrosocyclohexane providing, after hydrolysis of the iminium ion, the parent system as a hydrochloride salt.[12] The oxazines derived from dienes containing electron withdrawing groups are usually formed regioselectively in an inverse-electron-demand cycloaddition. Cycloadditions with unsymmetrical dienes usually produce mixtures of regioisomers with the major product favoring the placement of oxygen at the more electrophilic site of the diene.

Reduction of the oxazine adducts was performed with $Mo(CO)_6$[13] to afford 1,4-*N*-acetylamino alcohols **4**,[1] **9**,[14] **14**, **19**,[15] **24**, **29**, **31**, and **37**. We found this procedure experimentally more suitable than the usual Na(Hg) or Al(Hg) method[16] that is often used. Conversion of the 1,4-*N*-acetylamino alcohols to the corresponding oxazolines was initially accomplished by treatment with methanesulfonyl chloride at room temperature. Oxazolines **10**, **15**, **20**, and **25** were too volatile to allow for accurate determination of isolated yields and were therefore directly converted to the 1,2-acetylamino alcohols. The less volatile oxazolines **5**, **32**, **34**, and **38** permitted isolation and full characterization prior to their conversion to the 1,2-amino alcohol derivatives by base-catalyzed hydrolysis. We observed several intermediates during monitoring of the reactions by TLC and obtained lower yields of oxazolines at the expense of other products. In the case of alcohol **37** the major product from the reaction performed at room temperature was identified as chloride **39**. The ^{1}H NMR spectrum of compound **39** revealed two equal magnitude coupling constants ($J_{4,5}$=$J_{4,NHAc}$=9.9 Hz) and one small one ($J_{3,4}$=3.3 Hz) for proton H-4 (4.35 ppm, ddd). Even though the ring is not in a perfect chair conformation because of the presence of double bond, these values correspond to standard axial-equatorial coupling (J=3.3 Hz), which indicates cis orientation of the chlorine and acetamido substituents.

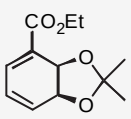
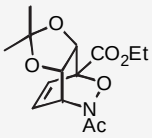
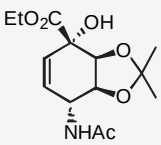
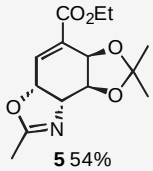
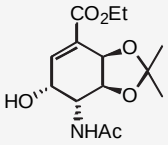
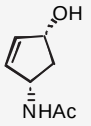
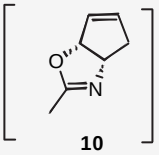
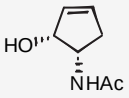
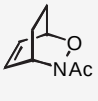
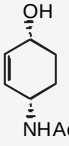
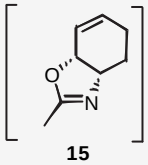
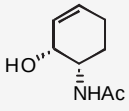
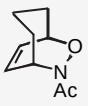
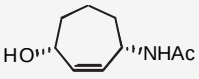
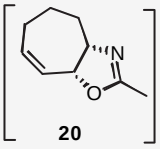
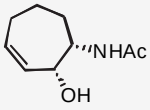
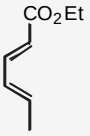
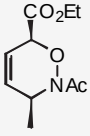
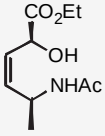
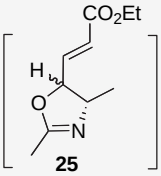
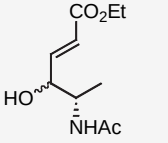
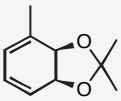
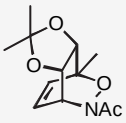
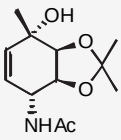
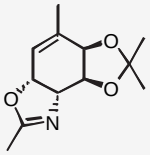
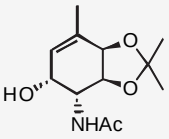
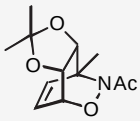
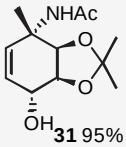
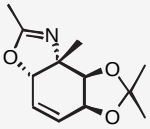
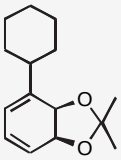
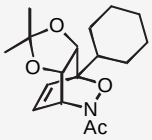
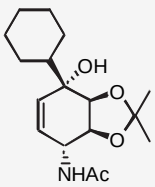
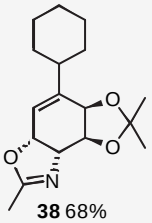
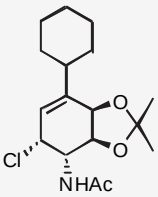
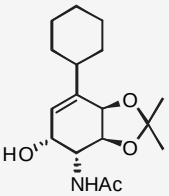
We therefore decided to investigate the reaction process in detail for this particular case. The results of this study are shown in Scheme 1.

The products of the reaction were markedly different depending on the reagents as well as the temperature. With mesyl chloride and triethylamine several intermediates could be observed during the reaction of alcohol **37**. At room temperature the reaction mixture consisted of oxazoline **38** (14%), chloride **39** (32%), and triethyl ammonium salts (either or both **42** and/or **43**) (~30%). However, if the reaction mixture was heated to 40 °C the content of oxazoline **38** increased to 30–40% (vide ^{1}H NMR). This observation indicated that intermediates **39** and **42**/**43** are further transformed to the desired oxazoline. The ^{1}H NMR spectrum of compound **42** showed three equally large couplings for H-4 (4.54 ppm, ddd, $J_{3,4}$=$J_{4,5}$=$J_{4,NHAc}$=9.0 Hz), which indicates trans orientation of substituents at positions C-3/C-4 and C-4/C-5. In a separate experiment chloride **39** was cleanly transformed to oxazoline **38** upon heating at 80 °C in the presence of Et_3N. Without Et_3N present in reaction mixture chloride **39** did not cyclize, which also strongly supports the assigned cis orientation of acetamido and chloro substituents. Similar experiment with triethyl ammonium salts **42**/**43** showed that heating of the ethanolic solution of the salt **42** to 80 °C in the presence of $NaHCO_3$ also led to oxazoline **38** as a major product. We assume that oxazoline **38** is formed from the quarternary salts **42**/**43** via S_N2 process. Chloride **39** cannot undergo such a direct displacement to the oxazoline and must be first transformed by Et_3N via S_N2 process to the quarternary ammonium salts **42**/**43** with trans orientation of the acetamido and triethyl ammonium moieties required for the second S_N2 displacement.

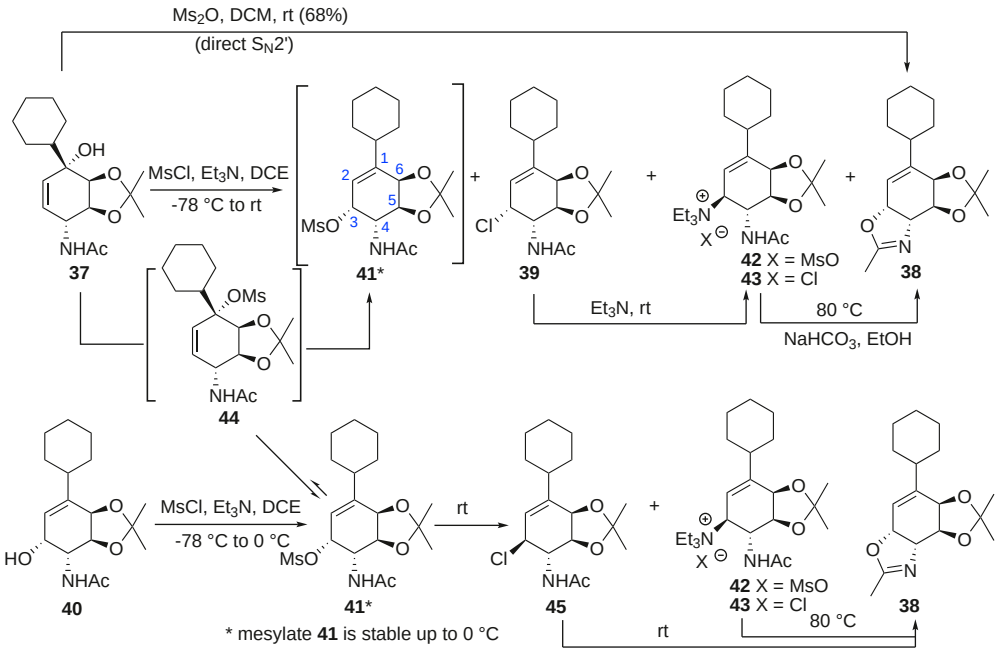
The entire process of transformation of 1,4-*N*-acetylamino alcohols to the oxazolines and the corresponding 1,2-*N*-acetylamino alcohols was optimized and reduced to a one-pot procedure. The use of dichloroethane as solvent allowed the reaction to be heated to 80 °C after the observation of the mesylate **41** at 0 °C. After mesylation the reaction mixture is concentrated, diluted with EtOH and the pH is adjusted to ~8 with 1 M NaOH or with $NaHCO_3$ (the latter conditions were used in the study of mechanism). After 1–2 h at reflux the chloride and the quarternary ammonium salt are transformed to the oxazoline, at which point the pH is adjusted to ~10 and the oxazoline is hydrolyzed to the corresponding 1,2-*N*-acetyl amine after 16 h at reflux. In the case of oxazolines **5** and **25** $CaCO_3$ or acetic acid were used for hydrolysis in order to prevent hydrolysis of the ester moiety. In addition, oxazoline can be cleanly prepared at room temperature. When methanesulfonyl anhydride is used instead of mesyl chloride the allylic alcohol **37** was smoothly transformed to oxazoline **38** in 68% isolated yield.

The reaction of the 1,2-acylamino derivative **40** with mesyl chloride proceeded along a similar pathway with one exception being the generation of the diastereomeric allylic chloride **45** (observed in ^{1}H NMR, not isolated) by a S_N2 reaction of the mesylate **41**. Stereochemistry of these labile compounds **41** and **45** was confirmed by performing the reaction in $CDCl_3$ and measuring the ^{1}H NMR spectra at two different temperatures. Proton H-3 (5.12 ppm, dd) in compound **41** displayed two small interactions ($J_{3,4}$=3.0 Hz, $J_{2,3}$=5.7 Hz), which is in accordance with the similar 'cis coupling' observed in compound **39** ($J_{3,4}$=3.3 Hz) as well as in the acetamido alcohol **40** ($J_{3,4}$=3.6 Hz). Mesylate **41** was reasonably

Table 1
Synthesis of 1,4- and 1,2-amino alcohol derivatives from cyclic dienes

Enrty	Diene	Oxazine	1,4-Amino alcohol	Oxazoline	1,2-Amino alcohol
1	 **2**	 **3** 90%	 **4** 93%	 **5** 54%	 **6** 72% [47%][a]
2	 **7**	 **8** 89%	 **9** 51%	 **10**	 **11** 20%[a]
3	 **12**	 **13** 68%	 **14** 47%	 **15**	 **16** 39%[a]
4	 **17**	 **18** 90%	 **19** 42%	 **20**	 **21** 32%[a]
5	 **22**	 **23** 46%	 **24** 65%	 **25**	 **26** 67% (1:1)[a]
6	 **27**	 **28** 60%	 **29** 68%	 **32** 25%	 **33** 37%[a]
		 **30** 25%	 **31** 95%	 **34** 57%	
7	 **35**	 **36** 43%	 **37** 69%	 **38** 68%	 **39** 32%	 **40** 58%[a]

[a]The yields for 1,2-amino derivatives are reported for the two-step sequence from 1,4-amino alcohols.



Scheme 1.

stable at 0 °C, thus allowing for the determination of its structure. However, warming the NMR tube to room temperature led to the transformation of mesylate **41** to chloride **45**, with the latter compound exhibiting the typical 'trans coupling' for proton H-4 (3.94 ppm, ddd, $J_{3,4}=J_{4,5}=J_{4,NHAc}=9.6$ Hz), in accordance with the previously assigned configuration of the quarternary salt **42** ($J_{3,4}=J_{4,5}=J_{4,NHAc}=9.0$ Hz).

All intermediates converged to oxazoline **38** with increasing temperature of the reaction. A standard sample of the pure quarternary salt **42** was also prepared by this method because reaction with mesyl chloride provides quarternary salt as a mixture of chloride and mesylate counter ions.

Finally, we should point out the distinct probability of a rearrangement of **44** to **41**, as shown in Scheme 1. Mesylate **44**, derived form the allylic alcohol **37**, may rearrange to mesylate **41** at temperatures above 0 °C, as shown in Scheme 1. While we did not directly observe the putative [3,3] sigmatropic rearrangement of **44**–**41** we obtained evidence of this rearrangement (vide NMR) for the case of the substrate containing the ethyl ester moiety: the mesylate prepared form **4** partially rearranged to the mesylate derived from **6** (this mesylate was isolated and matched with the corresponding mesylate prepared earlier during in synthesis of oseltamivir[1]) before the conversion to either a chloride or an ammonium salt and ultimately to oxazoline **5**.

3. Conclusions

We have demonstrated that 1,3-dienes can be effectively converted to either 1,4- or 1,2-*N*-acetylamino alcohols via their oxazines obtained by hetero Diels–Alder cycloaddition with an acyl nitroso dienophile. This approach is stereoselective and general for 5-, 6-, and seven-membered rings, however, in cases of acyclic dienes affords mixture of diastereoisomers. The cycloadditions proceed via inverse-electron-demand and are completely regioselective when the diene is suitably polarized by an electron withdrawing group. With non-polarized dienes regioisomers may be formed with substrates that do not exhibit additional steric bias. The 1,4-acylamino alcohol derivatives yield 1,2-acylamino derivatives via hydrolysis of the corresponding oxazolines.

Finally, it should be noted that 1,2-amino alcohol derivatives containing the allylic olefin moiety and prepared by this method could also be obtained by nucleophilic opening of vinyl aziridines where such aziridines are available regioselectively from 1,3-dienes. The opposite regiochemistry of 1,2-amino alcohol derivatives, in which the acyl amine is allylicaly disposed, is easily accessible by the reaction of the Burgess reagent with vinyl oxiranes as previously demonstrated.[17] Thus the current method provides a good complement to the existing methodology especially in cases where regioslective aziridination or epoxidation of conjugated dienes might be problematic or non-selective while the oxazine formation of polarized dienes proceeds with excellent regioslectivity.

4. Experimental section

4.1. General procedure for the preparation of oxazines

To a stirred solution of the diene in MeOH (10 mL/g of diene) at room temperature was added freshly grounded $NaIO_4$ (1.5 equiv) followed by the addition of a solution of acetohydroxamic acid (1.5 equiv) in MeOH (10 mL) dropwise over 5 min. The resulting suspension was stirred for 20 h, quenched by the slow addition of satd $NaHCO_3$ (~5 mL), diluted with methylene chloride (100 mL) and filtered through filterpaper. The filtrate was washed with $NaHCO_3$ (2×10 mL) and the combined aqueous layer re-extracted with methylene chloride (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude oxazine was purified by column chromatography with a solvent system of hexanes/ethyl acetate.

*4.1.1. 2-Oxa-3-azabicyclo[2.2.1]hept-5-ene, 3-acetyl (**8**)*[10]. Compound **7**: (4.55 g, 68.86 mmol), ($NaIO_4$: 20.01 g, 93.51 mmol), ($CH_3CONHOH$: 8.14 g, 108.46 mmol); yield of **8** (8.52 g, 61.27 mmol, 89%) as a yellow oil. R_f=0.25 (hexane/ethyl acetate 1:1).

*4.1.2. 2-Oxa-3-azabicyclo[2.2.2]oct-5-ene, 3-acetyl (**13**)*[11]. Compound **12**: (1.63 g, 20.34 mmol), ($NaIO_4$: 6.53 g, 30.53 mmol),

($CH_3CONHOH$: 2.29 g, 30.50 mmol); yield of **13** (2.10 g, 13.72 mmol, 68%) as a yellow oil. R_f=0.30 (hexane/ethyl acetate 1:1).

*4.1.3. 2-Oxa-3-azabicyclo[3.2.1]non-5-ene, 3-acetyl (**18**).* Compound **17**: (1.00 g, 10.62 mmol), ($NaIO_4$ 3.41 g, 15.93 mmol), ($CH_3CONHOH$: 1.2 g, 15.99 mmol); yield of **18** (1.59 g, 90%) as a brown liquid: R_f=0.30 (hexane/ethyl acetate 1:1); IR (KBr, cm^{-1}) ν 3476, 2938, 2360, 1646, 1454, 1379, 1157, 1113; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (dd, 1H, J=7.2, 8.7 Hz), 6.15 (dd, 1H, J=6.9, 6.9 Hz), 5.18 (m, 1H), 4.67–4.63 (m, 1H), 1.99 (s, 3H), 1.91–1.28 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 129.5, 127.2, 76.3, 50.2, 29.7, 28.6, 20.8, 18.4 ppm; MS (EI^+) m/z %: 167 (M^+): 125 (26), 79 (20), 75 (19), 57 (17), 43 (100). HRMS calcd for $C_9H_{13}NO_2$: 167.09407 found: 167.09463.

*4.1.4. 1-Oxa-2-aza-3-methyl-6-carboethoxycyclohex-4-ene (**23**).* Compound **22**: (5.00 g, 35.67 mmol), ($NaIO_4$: 22.88 g, 107.00 mmol), ($CH_3CONHOH$: 8.04 g, 107.00 mmol); yield of **23** (3.49 g, 16.41 mmol, 46%) as a yellow oil: R_f=0.20 (hexane/ethyl acetate 3:1); IR (KBr, cm^{-1}) ν 3491, 2984, 2937, 2360, 1755, 1669, 1412, 1276, 1203, 1078, 1030; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, 1H, J=10.2, 2.4, 3.9 Hz), 5.79 (d, 1H, J=10.2 Hz), 4.97–4.93 (m, 1H), 4.70–4.68 (m, 1H), 4.16 (q, 2H, J=7.2 Hz), 2.03 (s, 3H), 1.23 (t, 6H, J=7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 166.6, 130.6, 121.4, 77.2, 61.8, 47.2, 20.1, 17.5, 14.0 ppm; MS (EI^+) m/z %: 213 (M): 171 (76), 156 (33), 141 (23), 98 (62), 43 (100); HRMS Calcd for $C_{10}H_{15}NO_4$: 213.10042 found: 213.10011. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.47; H, 7.18.

*4.1.5. 1-Methyl-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol, 3-acetyl (**28**).* To a stirred solution of 1-methyl-(2*R*,3*S*)-2,3-dihydroxy-1-methylcyclohexa-4,6-diene[18] (2.29 g, 18.18 mmol) in 2,2-dimethoxypropane (25 mL) was added *p*-toluenesulfonic acid (catalytic amount) at room temperature. After complete consumption of starting material (TLC analysis), a spatula tip of solid $NaHCO_3$ was added. The intermediate acetonide **27** was not isolated. Then $NaIO_4$ (5.83 g, 27.27 mmol) and MeOH (20 mL) was added to the reaction mixture prior to the dropwise addition of a solution of acetohydroxamic acid (2.05 g, 27.27 mmol) in MeOH (20 mL) over 5 min. The resulting solution was stirred for 20 h, quenched by the slow addition of satd $NaHCO_3$ (~5 mL), diluted with methylene chloride (100 mL) and filtered through filterpaper. Filtrate was washed with $NaHCO_3$ (2×10 mL) and combined aqueous layer re-extracted with methylene chloride (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude material was purified by column chromatography with a solvent system of hexanes/ethyl acetate (4:1) to yield **28** (720 mg, 60% over two steps); mp=79–81 °C; $[\alpha]_D^{20}$=−27.5 (c 1, $CHCl_3$); R_f=0.75 (ethyl acetate); IR (KBr, cm^{-1}) ν 3448, 2991, 2922, 2360, 1656, 1618, 1410, 1387, 1276, 1209, 1184, 1162, 1087, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (dd, 1H, J=6.3, 8.1 Hz), 6.14 (d, 1H, J=8.4 Hz), 5.48 (m, 1H), 4.49 (dd, 1H, J=4.2, 6.9 Hz), 4.18 (d, 1H, J=6.9 Hz), 2.01 (s, 3H), 1.57 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 133.4, 130.8, 110.6, 78.5, 78.0, 73.2, 49.2, 25.6, 25.4, 21.4, 19.9 ppm; MS (EI^+) m/z %: 239 (M): 224 (15), 109 (24), 97 (19), 92 (26), 85 (13), 43 (100); HRMS calcd for $C_{12}H_{17}NO_4$: 239.11579 found: 239.11576.

*4.1.6. 1-Methyl-5,6-O-isopropylidene-3-oxa-2-azabicyclo[2.2.2]oct-7-ene-5,6-diol, 2-acetyl (**30**).* Regioisomer **30** (25%) as white solid; mp=93–94 °C (ethyl acetate/hexane); R_f=0.5 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ +60.1 (c 1, $CHCl_3$); R_f=0.82 (ethyl acetate 1); IR (KBr, cm^{-1}) 3066, 2997, 2977, 2939, 2926, 2907, 1687, 1612, 1431, 1382, 1365, 1260, 1212, 1160, 1084, 1064, 1007, 974, 889, 850, 727, 691; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.36 (d, 1H, J=8.1 Hz), 6.31 (dd, 1H, J=5.7, 8.4 Hz), 4.87 (ddd, 1H, J=1.8, 4.8, 5.4 Hz), 4.58 (dd, 1H, J=4.8, 6.9 Hz), 4.19 (d, 1H, J=7.2 Hz), 2.02 (s, 3H), 1.98 (s, 3H), 1.32 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.0, 137.7, 127.0, 110.8, 77.6, 74.0, 71.0, 60.9, 25.7, 25.5, 24.5, 21.3 ppm; MS (EI^+) m/z %: 239 (8), 224 (11), 208 (6), 139 (9); HRMS (EI^+) calcd for $C_{12}H_{17}N_1O_4$ 239.11591 found 239.11576.

*4.1.7. 1-Cyclohexyl-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol, 3-acetyl (**36**).* To a stirred solution of (2*R*,3*S*)-2,3-dihydroxy-1-cyclohexylcyclohexa-4,6-diene[19] (500 mg, 2.58 mmol) in 2,2-dimethoxypropane (10 mL) was added *p*-toluenesulfonic acid (catalytic amount) at room temperature. After complete consumption of starting material (TLC analysis), a spatula tip of solid $NaHCO_3$ was added. The intermediate acetonide **35** was not isolated. Then $NaIO_4$ (825 mg, 3.86 mmol), MeOH (5 mL) was added to the reaction mixture followed by the dropwise addition of a solution of acetohydroxamic acid (290 mg, 3.86 mmol) in MeOH (5 mL) over 5 min. The resulting solution was stirred for 20 h, quenched by the slow addition of satd $NaHCO_3$ (~2 mL), diluted with methylene chloride (50 mL) and filtered through filterpaper. Filtrate was extracted with $NaHCO_3$ (2×5 mL) and combined aqueous layer re-extracted with methylene chloride (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuo. The crude material was purified by column chromatography with a solvent system of hexanes/ethyl acetate (4:1) to yield **36** (340 mg, 43% over two steps); mp=104–107 °C (ethyl acetate/hexane); $[\alpha]_D^{20}$ −51.4 (c 1, $CHCl_3$); R_f=0.85 (hexane/ethyl acetate 1:1); IR (KBr, cm^{-1}) ν 3449, 2932, 2859, 1654, 1620, 1457, 1414, 1387, 1272, 1211, 1162, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (dd, 1H, J=6.0, 8.1 Hz), 6.15 (d, 1H, J=8.4 Hz), 5.27 (br s, 1H), 4.34 (m, 2H), 1.93–1.87 (m, 5H), 1.74 (s, 3H), 1.65–1.62 (m, 1H), 1.28–1.05 (m, 11H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 131.5, 131.0, 110.3, 82.3, 75.9, 73.3, 49.1, 41.3, 26.9, 26.6, 26.4, 26.3, 26.2, 25.6, 25.2, 21.6 ppm; MS (EI^+) m/z %: 307 (M) (55), 292 (16), 249 (13), 232 (31), 190 (17), 175 (18), 160 (21), 83 (45), 55 (40), 43 (100); HRMS calcd for $C_{17}H_{25}NO_4$: 307.17840 found: 307.17836.

*4.1.8. 1-Carboethoxy-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol, 3-acetyl (**3**)*[20]. For complete experimental and spectral data see Ref. 20a.

4.2. General procedure for oxazine reduction with $Mo(CO)_6$

To a stirred solution of oxazine in 15:1/CH_3CN/H_2O (10 mL/3 mmol) was added molybdenum hexacarbonyl (2 equiv). The reaction was brought to reflux for 4–16 h, cooled to room temperature, filtered through a plug of Celite, and concentrated. The crude material was purified by column chromatography with ethyl acetate as the solvent.

*4.2.1. 1-Hydroxy-4-acetylamino-cyclopent-2-ene (**9**).* Compound **8**: (4.0 g, 28.76 mmol), ($Mo(CO)_6$: 11.39 g, 43.11 mmol); yield of **9** (2.05 g, 14.53 mmol, 51%). R_f=0.40 (ethyl acetate/ethanol 5:1).

*4.2.2. 1-Hydroxy-4-acetylamino-cyclohex-2-ene (**14**).* Compound **13**: (1.98 g, 12.94 mmol), ($Mo(CO)_6$: 4.44 g, 16.81 mmol); yield of **14** (937 mg, 6.05 mmol, 47%). R_f=0.10 (ethyl acetate).

*4.2.3. 1-Hydroxy-4-acetylamino-cyclohept-2-ene (**19**).* Compound **18**: (500 mg, 2.99 mmol), ($Mo(CO)_6$: 1.19 g, 4.49 mmol); yield of **19** (211 mg, 42%); mp=146–148 °C (ethyl acetate/hexane); R_f=0.10 (ethyl acetate); IR (KBr, cm^{-1}) ν 3358, 3287, 3086, 2929, 2851, 1638, 1555, 1450, 1372, 1297, 1125, 1058, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 2H), 5.56 (ddd, 1H, J=1.8, 3.9,

13.5 Hz), 4.55 (m, 1H), 4.42 (d, 1H, J=5.1 Hz), 2.00 (s, 3H), 1.89–1.64 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 137.5, 133.0, 71.3, 50.0, 36.0, 33.6, 23.8, 23.5 ppm; MS (EI$^+$) m/z %: 169 (M): 167 (19), 151 (34), 149 (41), 110 (40), 109 (47), 82 (39), 70 (46), 56 (88), 43 (100). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.60; H, 8.88.

*4.2.4. Ethyl 2-hydroxy-4-acetylamino-hex-3-enoate (**24**).* Compound **23**: (1.00 g, 4.69 mmol), ($Mo(CO)_6$: 1.86 g, 7.04 mmol); yield of **24** (653 mg, 65%); mp=113–115 °C (ethyl acetate/hexane); R_f=0.10 (ethyl acetate); IR (KBr, cm^{-1}) ν 3361, 3240, 2983, 1725, 1644, 1541, 1384, 1215, 1108, 1024; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, 1H, J=6.6 Hz), 5.50 (dd, 1H, J=8.1, 10.8 Hz), 5.40 (dd, 1H, J=9.9, 9.9 Hz), 5.11 (d, 1H, J=7.8 Hz), 4.81–4.73 (m, 1H), 4.27 (br s, 1H), 4.20 (q, 2H, J=7.2 Hz), 1.91 (s, 3H), 1.26–1.21 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.4, 135.3, 127.6, 67.5, 61.4, 43.1, 23.1, 20.3, 14.1 ppm; MS (EI$^+$) m/z %: 215 (M): 156 (21), 142 (56), 112 (36), 100 (84), 82 (100), 60 (47), 43 (73). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96. Found: C, 55.82; H, 8.11.

*4.2.5. (1S, 2R, 3S, 6R)-6-Acetylamino-1,2-O-isopropylidene-3-methylcyclohex-4-ene, 1,2,3-triol (**29**).* Compound **28**: (720 mg, 3.01 mmol), ($Mo(CO)_6$: 1.19 g, 4.52 mmol); yield of **29** (494 mg, 68%); mp=148–151 °C (ethyl acetate/hexane); $[\alpha]_D^{20}$ −119.7 (c 1, $CHCl_3$); R_f=0.23 (ethyl acetate); IR (KBr, cm^{-1}) ν 3433, 3379, 2991, 2924, 2907, 2856, 1741, 1650, 1512, 1460, 1382, 1308, 1252, 1211, 1166, 1109, 1063, 1045, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (d, 1H, J=8.4 Hz), 5.92–5.89 (m, 2H), 4.47 (ddd, 1H, J=2.1, 4.8, 9.0 Hz), 4.41 (dd, 1H, J=2.1, 6.6 Hz), 4.25 (d, 1H, J=6.6 Hz), 3.04 (br s, 1H), 1.95 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 135.8, 128.9, 108.3, 81.3, 77.3, 68.4, 47.6, 26.6, 26.1, 24.6, 23.5 ppm; MS (EI$^+$) m/z %: 226 (M−Me), 182 (32), 141 (57), 124 (27), 112 (29), 99 (44), 81 (22), 56 (21), 43 (100); HRMS calcd for $C_{12}H_{19}NO_4$: 241.13141 found: 226.10793. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94. Found: C, 59.91; H, 8.04.

*4.2.6. N-((3aR,4S,7R,7aS)-7-Hydroxy-2,2,4-trimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)acetamide (**31**).* Compound **30**: (70 mg, 0.29 mmol), ($Mo(CO)_6$: 165 mg, 0.63 mmol); yield of **31** (67 mg, 95%); $[\alpha]_D^{20}$ +47.6 (c 1, $CHCl_3$); R_f=0.26 (ethyl acetate); IR (KBr, cm^{-1}) 3321, 3074, 2989, 2938, 2900, 2875, 1657, 1548, 1456, 1446, 1383, 1303, 1265, 1212, 1163, 1136, 1070, 1028, 879, 781, 705, 607; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89 (br s, 1H), 5.82 (dd, 1H, J=2.1, 9.9 Hz), 5.72 (dd, 1H, J=2.1, 9.6 Hz), 4.68 (d, 1H, J=7.8 Hz), 4.32 (dd, 1H, J=4.5, 8.1 Hz), 4.28 (m, 1H), 1.96 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H), 1.20 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 134. 6, 128.2, 108.6, 80.7, 69.4, 55.6, 26.4, 24.6, 24.0, 22.0 ppm; MS (FAB$^+$) m/z %: 242 (99), 224 (100), 184 (57), 124 (35); HRMS (FAB$^+$) calcd for $C_{12}H_{20}N_1O_4$ 242.13671 found 242.13923.

*4.2.7. (1S, 2R, 3S, 6R)-6-Acetylamino-1,2-O-isopropylidene-3-cyclohexylcyclohex-4-ene, 1,2,3-triol (**37**).* Compound **36**: (2.961 g, 9.63 mmol), ($Mo(CO)_6$: 7.63 g, 28.90 mmol); yield of **37** (2.05 g, 69%); mp=162–165 °C (ethyl acetate); $[\alpha]_D^{20}$ −132.4 (c 1, $CHCl_3$); R_f=0.35 (ethyl acetate); IR (KBr, cm^{-1}) ν 3386, 3345, 2990, 2936, 2853, 1730, 1631, 1534, 1452, 1383, 1300, 1252, 1215, 1099, 1064, 1052, 1018 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (d, 1H, J=9.0 Hz), 6.13 (d, 1H, J=9.6 Hz), 6.02 (dd, 2H, J=6.3, 9.9 Hz), 4.55 (m, 1H), 4.39 (m, 2H), 2.47 (br s, 1H), 1.94 (s, 3H), 1.88–1.62 (m, 5H), 1.35 (s, 3H), 1.30 (s, 3H), 1.27–1.14 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 133.5, 130;.4, 108.0, 78.5, 77.6, 71.8, 47.3, 43.3, 26.6, 26.5, 26.4, 25.7, 25.6, 24.3, 23.5 ppm; MS (EI$^+$) m/z %: 294 (M−Me), 250 (38), 209 (90), 183 (49), 163 (51), 83 (85), 55 (47), 43 (100); HRMS calcd for $C_{17}H_{27}NO_4$: 309.19401 found: 294.17053. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80. Found: C, 66.27; H, 8.92.

*4.2.8. (1S, 2R, 3S, 6R)-6-Acetylamino-1,2-O-isopropylidene-3-carboethoxycyclohex-4-ene, 1,2,3-triol (**4**)*[20]. For complete experimental and spectral data see Ref. 20a.

4.3. General procedure for the conversion of 1,4-amino alcohols to 1,2-isomers via oxazolines

To the pre-cooled (4 °C) solution of 1,4-amino alcohols (2 mL dichloroethane/100 mg of substrate) was added MsCl or Ms_2O (5 equiv) followed by dropwise addition of Et_3N (10 equiv). Reaction mixture was then stirred in cooling bath and spontaneously allowed to room temperature. After reached room temperature the mixture was heated 4 h to 60 °C. On preparative scale the oxazoline was directly hydrolyzed without isolation. Reaction mixture was concentrated, dissolved in EtOH (4 mL) and the pH of the ethanolic solution was adjusted to ~8 with NaOH (1 M). The mixture was then heated to 90 °C for 1 h, the pH was then adjusted to ~10 with NaOH (1 M), and the heating continued for the next 16 h. After complete disappearance of intermediary oxazoline was reaction mixture concentrated and washed between dichloromethane (20 mL) and H_2O (2×3 mL). Aqueous layer was re-extracted with dichloromethane (10 mL) and combined organic layer dried over $MgSO_4$ and concentrated under vacuum. Chromatography of crude [10 mL SiO_2, ethyl acetate/hexane] afforded corresponding 1,2-isomers.

*4.3.1. 1-Hydroxy-2-acetylaminocyclopent-4-ene (**11**).* Compound **9**: (300 mg, 2.13 mmol), (MsCl: 823 μL, 10.63 mmol), (Et_3N: 2.96 mL, 21.26 mmol); yield of **11** (59 mg, 0.419 mmol, 20%); R_f=0.45 (ethyl acetate/ethanol 5:1); IR (KBr, cm^{-1}) ν 3425, 3335, 2362, 1645, 1554, 1384, 1046; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (br s, 1H), 6.00–5.97 (m, 1H), 5.88–5.84 (m, 1H), 4.63–4.61 (m, 1H), 4.34 (dddd, 1H, J=4×6.3 Hz), 3.04 (br s, 1H), 2.77–2.68 (m, 1H), 2.28–2.18 (m, 1H), 2.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 134.5, 131.8, 74.3, 51.2, 37.4, 23.3 ppm; MS (EI$^+$) m/z %: 141 (M): 98 (9), 85 (10), 82 (38), 70 (14), 60 (26), 56 (15), 43 (100); HRMS calcd for $C_7H_{11}NO_2$: 141.07867 found: 141.07898.

*4.3.2. 1-Hydroxy-2-acetylaminocyclohex-5-ene (**16**).* Compound **14**: (297 mg, 1.910 mmol), (MsCl: 743 μL, 9.570 mmol), (Et_3N: 2.67 mL, 19.14 mmol); yield of **16** (116 mg, 39%); mp=108–110 °C (ethyl acetate/EtOH); R_f=0.15 (ethyl acetate); IR (KBr, cm^{-1}) ν 3281, 3178, 3082, 2905, 2835, 1643, 1562, 1433, 1384, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (br s, 1H), 5.91 (ddd, 1H, J=2×3.6, 10.2 Hz), 5.82 (dddd, 1H, J=1.8, 2.1, 4.5, 10.2 Hz), 4.09 (dd, 1H, J=2×4.2 Hz), 4.01 (dddd, 1H, J=3.6, 7.2, 11.7, 15.3 Hz), 2.01 (s, 3H), 1.82–1.74 (m, 1H), 1.70–1.60 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 131.8, 127.2, 65.0, 48.9, 24.7, 23.5, 23.1 ppm; MS (FAB$^+$) m/z %: 156 (M$^+$+H): 96 (34), 81 (43), 69 (82), 60 (57), 55 (71), 43 (78); HRMS calcd for $C_8H_{13}NO_2$: 155.09463 found: 156.10245. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.08; H, 8.44; N, 8.96.

*4.3.3. 1-Hydroxy-2-acetylaminocyclohept-6-ene (**21**).* Compound **19**: (86 mg, 0.509 mmol), (MsCl: 228 μL, 2.96 mmol), (Et_3N: 0.82 mL, 5.91 mmol); yield of **21** (28 mg, 0.163 mmol, 32%); R_f=0.15 (ethyl acetate); IR (KBr, cm^{-1}) ν 3391, 3284, 3034, 2925, 2843, 1655, 1549, 1383, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.85 (m, 2H), 5.65–5.60 (m, 1H), 4.52–4.51 (m, 1H), 4.24–4.20 (m, 1H), 3.24 (br s, 1H), 2.26–2.17 (m, 1H), 2.02 (s, 3H), 2.13–1.98 (m, 2H), 1.88–1.77 (m, 1H), 1.66–1.54 (m, 1H), 1.49–1.34 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 133.8, 132.0, 72.9, 52.5, 32.0, 28.2, 23.4, 21.5 ppm; MS (FAB$^+$) m/z %: 170 (M$^+$+H): 152 (59), 110 (66), 69 (56), 55 (94), 43 (87); HRMS calcd for

$C_9H_{16}NO_2$: 170.11803 found: 170.11810. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.66; H, 8.80.

*4.3.4. (syn and anti)-Ethyl 4-hydroxy-5-acetylamino-hex-2-enoate (**26**).* Compound **24**: (72 mg, 0.334 mmol), (Ms_2O: 146 mg, 0.836 mmol), (Et_3N: 233 μL, 1.672 mmol); yield of **26** (upper R_f isomer: 20 mg, 28%) as a yellow oil; R_f=0.60 (dichloromethane/MeOH 10:1); IR (KBr, cm^{-1}) ν 3444, 2982, 1711, 1658, 1548, 1448, 1383, 1282, 1182, 1038, 983; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, 1H, J=4.5, 15.6 Hz), 6.28 (d, 1H, J=8.1 Hz), 6.09 (dd, 1H, J=1.5, 15.6 Hz), 4.26 (dd, 1H, J=1.8, 2×4.5 Hz), 4.16 (q, 2H, J=7.2 Hz), 4.06–3.99 (m, 1H), 3.30 (br s, 1H), 1.95 (s, 3H), 1.26 (t, 3H, J=7.2 Hz), 1.19 (d, 3H, J=6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.5, 147.3, 122.0, 73.5, 60.6, 49.7, 23.2, 17.0, 14.2 ppm; MS (FAB^+) m/z %: 216 (100), 198 (20), 156 (35); HRMS calcd for $C_{10}H_{18}NO_4$: 216.12094 found: 216.12358.

Yield of **26** (lower R_f isomer (28 mg, 39%)) as a yellow oil; R_f=0.5 (dichloromethane/MeOH 10:1); IR (KBr, cm^{-1}) ν 3473, 2983, 2936, 1756, 1724, 1661, 1523, 1383, 1309, 1222, 1205, 1057, 1044, 983, 785; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, 1H, J=6.3, 15.6 Hz), 6.13 (d, 1H, J=15.6 Hz), 5.50 (dd, 1H, J=6.9, 6.9 Hz), 4.21 (q, 2H, J=7.2 Hz), 3.50 (m, 1H), 2.19 (s, 3H), 1.39 (d, 3H, J=6.3 Hz), 1.30 (t, 3H, J=7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.3, 139.7, 126.0, 73.9, 60.9, 49.8, 20.9, 14.9, 14.2 ppm; MS (FAB^+) m/z %: 216 (100), 156 (30); HRMS calcd for $C_{10}H_{18}NO_4$: 216.12358 found: 216.12038.

*4.3.5. (1S, 2R, 5R, 6R)-6-Acetylamino-1,2-O-isopropylidene-3-methyl-cyclohex-3-ene, 1,2,5-triol (**33**).* Compound **29**: (174 mg, 0.722 mmol), (MsCl: 321 μL, 4.15 mmol), (Et_3N: 1.15 mL, 8.29 mmol); yield of **33** (65 mg, 0.270 mmol, 37%); mp=91–94 °C (ethyl acetate); $[\alpha]_D^{20}$ −74.8 (c 1, $CHCl_3$); R_f=0.30 (ethyl acetate); IR (KBr, cm^{-1}) ν 3342, 2986, 2360, 1655, 1551, 1384, 1219, 1076; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (br s, 1H), 5.65 (m, 1H), 4.37 (d, 1H, J=5.4 Hz), 4.31–4.26 (m, 2H), 4.14 (ddd, 1H, J=3.6, 2×8.4 Hz), 1.99 (s, 3H), 1.83 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 135.4, 125.9, 109.6, 75.2, 73.9, 65.1, 52.1, 27.8, 26.1, 23.4, 20.5 ppm; MS (EI^+) m/z %: 226 (M−Me), 208 (15), 142 (61), 124 (53), 84 (86), 43 (100); HRMS calcd for $C_{12}H_{16}NO_4$: 226.10738 found: 226.10793.

*4.3.6. (3aR,4S,5R,7aR)-2,6-Dimethyl-4–5-O-isopropyliden-3a,4,5,7a-tetrahydrobenzo[d]oxazole-4,5-diol (**32**).* A stirred solution of **29** (55 mg, 0.178 mmol) in methylene chloride (1 mL) was cooled to −78 °C prior to the addition of methanesulfonyl chloride (69 μL, 0.890 mmol) and triethylamine (0.248 mL, 1.78 mmol). The reaction was spontaneously brought to −10 °C, then diluted with methylene chloride (20 mL), and washed with 5% citric acid (2 mL) and satd $NaHCO_3$ (2 mL). The organic layer was dried over $MgSO_4$ with a spatula tip of solid $NaHCO_3$, filtered, and concentrated under vacuo The crude material was purified via column chromatography in a solvent system of hexane/ethyl acetate (1:1) to yield **32** (10 mg, 25%); $[\alpha]_D^{20}$ +34.8 (c 0.5, $CHCl_3$); R_f=0.60 (ethyl acetate); IR (film) ν 3443, 2985, 2933, 2360, 2340, 1667, 1452, 1438, 1383, 1312, 1236, 1226, 1175, 1073, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (m, 1H), 4.99 (m, 1H), 4.72 (dd, 1H, J=2.4, 5.1 Hz), 4.49 (ddd, 1H, J=1.5, 1.5, 8.7 Hz), 4.38 (d, 1H, J=4.8 Hz), 1.95 (d, 3H, J=1.5 Hz), 1.84 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 138.0, 118.8, 108.8, 74.3, 74.3, 72.9, 63.9, 27.8, 26.6, 19.5, 14.3 ppm; MS (EI^+) m/z %: 223 (M) 208 (100), 166 (29), 124 (41), 107 (14), 95 (17), 43 (67); HRMS calcd for $C_{12}H_{17}NO_3$: 223.12133 found: 223.12084.

*4.3.7. (3aS,4R,5S,7aS)-2,3a-Dimethyl-4-5-O-isopropyliden-3a,4,5,7a-tetrahydrobenzo[d]oxazole-4,5-diol (**34**).* Compound **31**: (38 mg, 0.16 mmol), (MsCl: 55 mg, 0.32 mmol), (Et_3N: 110 μL, 0.79 mmol); yield of **34** (20 mg, 57%); mp=56–59 °C ($CHCl_3$); $[\alpha]_D^{20}$ −92.5 (c 1, $CHCl_3$); R_f=0.40 (hexane/ethyl acetate 1:1); IR (KBr, cm^{-1}) 2986, 2966, 2926, 2879, 1667, 1450, 1384, 1315, 1239, 1227, 1164, 1092, 1039, 927, 867, 769, 638; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.79 (d, 1H, J=10.2 Hz), 5.59 (ddd, 1H, J=1.2, 3.3, 10.2 Hz), 4.61 (d, 1H, J=3.3 Hz), 4.55 (m, 1H), 4.45 (dd, 1H, J=0.9, 4.8 Hz), 1.94 (s, 3H), 1.37 (s, 6H), 1.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 130.6, 122.4, 109.2, 78.9, 77.6, 71.4, 67.8, 28.1, 26.8, 24.8, 14.5 ppm; MS (EI^+) m/z %: 223 (1), 208 (100), 165 (34), 124 (49); HRMS (EI^+) calcd for $C_{11}H_{14}N_1O_3$ 208.09758 found 208.09737.

*4.3.8. (3aR,5aR,8aR,8bS)-2,2,7-Trimethyl-4-cyclohexyl-3a,5a,8a,8b-tetrahydro[1,3]dioxolo[4,5-e][1,3]benzoxazole (**38**).* To the pre-cooled (4 °C) solution of **37** (100 mg, 0.32 mmol) in dichloroethane (2 mL) was added Ms_2O (28 mg, 1.61 mmol) in one portion followed by dropwise addition of Et_3N (450 μL, 3.23 mmol). Reaction mixture was then stirred in cooling bath and spontaneously allowed to 15 °C. TLC showed almost complete disappearance of the starting alcohol. The mixture was then diluted with ethyl acetate (30 mL) and washed with 5% solution of citric acid (2×3 mL) and then with satd solution of $NaHCO_3$ (3 mL). Organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Chromatography of crude [5 mL SiO_2, hexane/ethyl acetate 4:1→2:1] afforded oxazoline **38** as a white solid (64 mg, 68%); mp=46–49 °C (ethyl acetate); $[\alpha]_D^{20}$ +92.4 (c 0.5, $CHCl_3$); R_f=0.35 (hexane/ethyl acetate 3:1); IR (KBr, cm^{-1}) ν 3448, 2926, 2854, 1668, 1450, 1384, 1236, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (d, 1H, J=3.3 Hz), 5.10 (dd, 1H, J=3.0, 8.4 Hz), 4.73 (dd, 1H, J=2.4, 5.1 Hz), 4.57 (d, 1H, J=5.1 Hz), 4.50 (m, 1H), 2.32–2.18 (m, 1H), 1.98 (d, 3H, J=1.5 Hz), 1.91–1.65 (m, 4H), 1.41 (s, 3H), 1.33 (s, 3H), 1.48–1.10 (m, 5H), 1.00 (dddd, 1H, J=3.0, 3×12.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 146.4, 115.9, 108.6, 74.7, 74.2, 70.8, 63.6, 39.4, 33.2, 30.9, 27.9, 26.7, 26.6, 26.5, 26.3, 14.3 ppm; MS (EI^+) m/z %: 276 (M -Me): 234 (18), 192 (18), 175 (57), 55 (19), 43 (61), 41 (20); HRMS calcd for $C_{17}H_{25}NO_3$: 276.15997 found: 276.16038.

*4.3.9. Ethyl (3aR,5aR,8aR,8bS)-2,2,7-trimethyl-3a,5a,8a,8b-tetrahydro[1,3]dioxolo[4,5-e][1,3]benzoxazole-4-carboxylate (**5**)*[1]. To a stirred solution of allylic alcohol **4** (400 mg, 1.33 mmol) in methylene chloride (5 mL) was added NEt_3 (0.74 mL, 4.0 mmol), DMAP (catalytic amount), and methanesulfonyl chloride (0.16 mL, 1.4 mmol) at room temperature. The resulting solution was stirred for 4 h before being quenched by the slow addition of satd $NaHCO_3$ (5 mL), and then extracted into ethyl acetate (3×5 mL). The combined organic layers were washed with brine (1×2 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of hexanes/ethyl acetate (1:2) to yield **5** (204 mg, 54%) as a white-yellow solid: R_f 0.40 (hexanes/ethyl acetate 1:4); mp=54–55 °C (ethyl acetate/hexanes); $[\alpha]_D^{23}$ +150.4 (c 1.25, $CHCl_3$); R_f=0.25 (hexane/ethyl acetate 4:1); IR (film) ν 3543, 2986, 1722, 1667, 1372, 1218 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, J=3.0 Hz, 1H), 5.14 (dd, J=2.9, 8.5 Hz, 1H), 4.93 (d, J=5.2 Hz, 1H), 4.86 (dd, J=2.7, 5.1 Hz, 1H), 4.58 (d, J=8.4 Hz, 1H), 4.27–4.34 (m, 2H), 1.97 (d, J=1.3 Hz, 3H), 1.42 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 165.6, 133.3, 130.5, 109.1, 73.6, 73.2, 68.9, 64.3, 61.2, 27.8, 26.3, 14.2, 14.1 ppm; MS (EI) m/z (%): 266 ($M-CH_3^+$), 43(52), 136(19), 266(100); HRMS calcd for $C_{13}H_{16}NO_5$ 266.1028 found 266.1032.

*4.3.10. (1S, 2R, 5R, 6S)-6-Acetylamino-1,2-O-isopropylidene-5-chloro-3-cyclohexylcyclohex-3-ene-1,2-diol (**39**).* To the pre-cooled (4 °C) solution of **37** (300 mg, 0.97 mmol) in dichloroethane (6 mL) was added MsCl (375 μL, 4.85 mmol) followed by dropwise addition of Et_3N (1.35 mL, 9.70 mmol). Reaction mixture was then stirred in

cooling bath and spontaneously allowed to warm up. The mixture was then heated to 60 °C. After 4 h TLC showed complete disappearance of starting alcohol, and new spots of oxazoline **38** (R_f=0.75 ethyl acetate), chloride **39** (R_f=0.80 ethyl acetate), quarternary ammonium salts **42** and/or **43** (R_f=0.60 dichloromethane/MeOH 5:1) and couple others byproducts were seen. The mixture was then concentrated and the crude material was purified via column chromatography in a solvent system of hexane/ethyl acetate (4:1→3:1) to yield **39** (128 mg, 45%) and white solid of **39** (100 mg, 32%); mp=163–165 °C (ethyl acetate/hexanes); $[\alpha]_D^{20}$ −160.2 (*c* 1, $CHCl_3$); R_f=0.80 ethyl acetate; IR (KBr, cm^{-1}) ν 3325, 2993, 2926, 2876, 2854, 1645, 1536, 1457, 1383, 1220, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (d, 1H, *J*=7.8 Hz), 5.81 (d, 1H, *J*=6.0 Hz), 4.70 (dd, 1H, *J*=3.6, 4.0 Hz), 4.65 (d, 1H, *J*=5.7 Hz), 4.35 (ddd, 1H, *J*=3.3, 9.9, 9.9 Hz), 4.27 (dd, 1H, *J*=5.7, 9.9 Hz), 2.18–2.10 (m, 1H), 2.08 (s, 3H), 1.89–1.71 (m, 5H), 1.50 (s, 3H), 1.41 (s, 3H), 1.36–1.17 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 145.1, 122.9, 109.6, 73.4, 73.3, 57.6, 50.5, 41.8, 32.6, 31.4, 27.8, 26.6, 26.4, 26.1, 25.9, 23.5 ppm; MS (EI^+) *m*/*z* %: 312 (M−Me) 276 (98), 234 (38), 192 (38), 175 (68), 43 (100); HRMS calcd for $C_{17}H_{26}ClNO_3$: 327.1601 found: 312.13665. Anal. Calcd for $C_{17}H_{26}ClNO_3$: C, 62.28; H, 7.99. Found: C, 62.44; H, 8.06.

*4.3.11. N-((3aS,4R,5R,7aR)-7-Cyclohexyl-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)acetamide (**40**).* To the pre-cooled (4 °C) solution of **37** (300 mg, 0.97 mmol) in dichloroethane (6 mL) was added MsCl (375 μL, 4.85 mmol) followed by dropwise addition of Et_3N (1.35 mL, 9.70 mmol). Reaction mixture was then stirred in cooling bath and spontaneously allowed to reach ambient temperature. The mixture was then heated for 4 h at 60 °C. TLC showed complete disappearance of starting alcohol, and new spots of oxazoline **38** (R_f=0.75 ethyl acetate), chloride **39** (R_f=0.80 ethyl acetate), quarternary ammonium salts **42** and/or **43** (R_f=0.60, dichloromethane/MeOH (5:1)) and a couple of other byproducts were observed. The mixture was then concentrated and the residue dissolved in EtOH (8 mL). After addition of NaOH (4 mL, 1 M) the mixture was heated 1 h to 90 °C. Then mostly presence of oxazoline **38** was observed by TLC, and pH of reaction mixture was changed from ~8 to ~10 with NaOH (4 mL, 1 M) and mixture was heated to 90 °C additional 16 h. After complete disappearance of intermediary oxazoline was reaction mixture concentrated and partitioned between dichloromethane (40 mL) and H_2O (2×4 mL). Aqueous layer was re-extracted with dichloromethane (20 mL) and combined organic layer dried over $MgSO_4$ and concentrated under vacuum. Chromatography of crude [15 mL SiO_2, ethyl acetate] afforded **40** as a white solid (173 mg, 58%); mp=158–160 °C (ethyl acetate/hexane); $[\alpha]_D^{20}$ −48.1 (*c* 1, $CHCl_3$); R_f=0.35 (ethyl acetate); IR (KBr, cm^{-1}) ν 3382, 3276, 2931, 2853, 1646, 1534, 1384, 1218, 1063; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (d, 1H, *J*=7.9 Hz), 5.72 (d, 1H, *J*=4.8 Hz), 4.60 (d, 1H, *J*=5.7 Hz), 4.41 (dd, 1H, *J*=3.9, 3.9 Hz), 4.32 (dd, 1H, *J*=5.4, 8.4 Hz), 4.24 (ddd, 1H, *J*=3.6, 8.4, 8.4 Hz), 2.19–2.08 (m, 1H), 2.05 (s, 3H), 1.90–1.70 (m, 5H), 1.46 (s, 3H), 1.40 (s, 3H), 1.35–1.10 (m, 5H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 144.5, 123.6, 109.5, 74.0, 73.1, 65.6, 52.1, 41.6, 32.9, 31.5, 27.9, 26.7, 26.4, 26.2, 26.1, 23.6 ppm; MS (EI^+) *m*/*z* %: 309 (M): 294 (18), 276 (23), 192 (44), 142 (75), 84 (100), 43 (63); HRMS calcd for $C_{17}H_{27}NO_4$: 309.19449 found: 309.19401. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80. Found: C, 65.79; H, 8.93.

*4.3.12. Ethyl (3aR,6R,7R,7aS)-7-(acetylamino)-6-hydroxy-2,2-dimethyl-3a,6,7,7a-tetra-hydro-1,3-benzodioxole-4-carboxylate (**6**)*[1]. To a stirred solution of oxazoline **5** (800 mg, 2.86 mmol) in 1:1/ethanol/water (8 mL) was added calcium carbonate (570 mg, 5.69 mmol) at room temperature. The reaction mixture was brought to reflux for 48 h and then concentrated. The crude residue was dissolved in ethyl acetate and then filtered through a plug of Celite and concentrated. The crude material was purified via flash column chromatography with a solvent system of hexanes/ethyl acetate(1:4) to yield **6** (616 mg, 72%) as a white solid: R_f 0.23 (dichloromethane/MeOH 96:4); mp=115–118 °C (ethyl acetate/hexanes); $[\alpha]_D^{23}$ −54.3 (*c* 1.7, $CHCl_3$); IR (film) ν 3307, 2624, 2247, 1718, 1655, 1541, 1247, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J*=3.1 Hz, 1NH), 5.76 (br s, 1NH), 5.01 (d, *J*=5.6 Hz, 1H), 4.73 (t, *J*=3.4 Hz, 1H), 4.53 (q, *J*=5.9 Hz, 1H), 4.47 (t, *J*=5.8 Hz, 1H), 4.26–4.31 (m, 2H), 3.07 (br s, 1OH), 2.04 (s, 3H), 1.42 (s, 6H), 1.36 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 165.4, 141.0, 130.3, 109.9, 73.8, 69.8, 68.8, 61.3, 52.3, 27.48, 25.7, 23.4, 14.2 ppm; MS (FAB) *m*/*z* (%): 299 (M^+), 29(34), 43(71), 136(29), 182(23), 242(100); MS (EI) *m*/*z* (%): 284 ($M-CH_3^+$), 43(100), 84(25), 142(23), 284(17); HRMS calcd for $C_{13}H_{18}NO_6$ 284.1134 found 284.1132. Anal. Calcd C, 56.18; H, 7.07. Found: C, 56.22; H, 7.17.

*4.3.13. (3aS,4R,5S,7aR)-4-Acetamido-7-cyclohexyl-N,N,N-triethyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ammonium methanesulfonate (**42**).* A solution of **41** (53 mg; 0.17 mmol) in dry dichloromethane (2 mL) was stirred under argon and cooled in liquid N_2/acetone bath to −78 °C. Then Ms_2O (60 mg; 0.34 mmol) was added in one portion and the mixture was stirred again at −78 °C. After 5 min Et_3N (0.71 mL; 5.12 mmol) was added dropwise but quickly to the flask and the stirring continued for additional 2.5 h, during, which the temperature of the cooling bath raised slowly to −5 °C. Then the reaction mixture was stirred at room temperature for 20 h. TLC (ethyl acetate) did not show any starting alcohol, but there was a significant spot at the baseline. The solvents were evaporated and the chromatography of residue (ethyl acetate→ethyl acetate/MeOH 7:1) afforded salt **42** (40 mg) as a yellowish oil and oxazoline **39** (10 mg).

R_f=0.6 (dichloromethane/MeOH 5:1); $[\alpha]_D^{20}$ −36.5 (*c* 1, MeOH); IR (KBr, cm^{-1}) 3589, 3440, 3429, 3302, 3285, 3238, 3190, 3051, 2989, 2976, 2929, 2879, 2853, 2756, 2739, 2677, 2627, 2603, 2492, 1661, 1644, 1551, 1523, 1475, 1453, 1435, 1427, 1398, 1383, 1328, 1289, 1241, 1209, 1140, 1009, 979, 927, 891, 874, 851, 804, 567; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.99 (d, 1H, *J*=9.0 Hz), 5.61 (d, 1H, *J*=1.2 Hz), 4.97 (dd, 1H, *J*=1.2, 9.0 Hz), 4.54 (ddd, 1H, *J*=9.0, 9.0, 9.0 Hz), 4.50 (d, 1H, *J*=5.4 Hz), 4.39 (dd, 1H, *J*=5.4, 7.5 Hz), 3.68–3.48 (m, 6H), 2.80 (s, 3H), 2.19 (m, 1H), 2.09 (s, 3H), 1.88–1.68 (m, 5H), 1.37–1.15 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 147.9, 115.7, 110.2, 71.5, 69.7, 53.8, 46.9, 46.0, 42.8, 39.5, 32.5, 31.3, 27.8, 26.5, 26.3, 26.2, 25.9, 23.4, 9.3, 8.6 ppm; MS (FAB^+) *m*/*z* %: 393 (45), 292 (14), 234 (11), 175 (31); HRMS (FAB^+) calcd for $C_{23}H_{41}N_2O_3$ (cation without methanesulfonate counterion); 393.31172 found 393.30982.

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