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Rhodium-catalyzed multicomponent synthesis of chiral oxazolopiperidines

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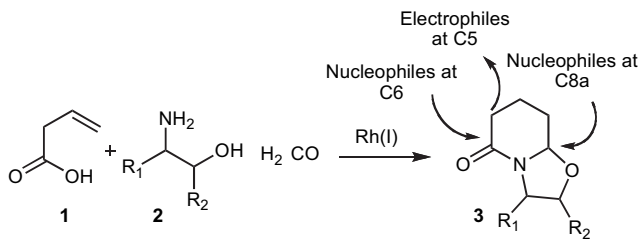
ABSTRACT

A multicomponent reaction that employs an unsaturated carboxylic acid, a 1,2 or 1,3 amino alcohol and gaseous CO and H_2 has been discovered. Thus, hydrocarbonylation of the carboxylic acid double bond generates a linear aldehyde, that is, immediately transformed into an oxazolidine. Further microwave assisted intramolecular lactamization delivers oxazolopiperidines with the generation of six new bonds in a one-pot single step. Bicylic, tricyclic, tetracyclic, and spirocyclic oxazolopiperidines can be prepared in good yields and acceptable stereoselection. The reaction did not occur under conventional heating even at higher temperature and pressure and for longer time, showing that microwave heating is indispensable to the process.

1. Introduction

The diversity oriented synthesis (DOS) approach, developed by S. Schreiber at the beginning of the century,[1] is nowadays a key area for organic chemistry and chemical biology.[2] The ultimate goal of DOS is the understanding of biological problems through the implementation of collections of structurally diverse molecules. For this purpose, multicomponent reactions (MCR) play an important role among the processes employed for diversity generation. In MCR, a complex scaffold (often a cycle) is generated in one step starting from more than two simple reagents.[3] Originally based on few reactions (Ugi, Passerini, Biginelli, Hantsh etc.), the MCR field, is now experiencing a high level of innovation.[4] Recently, many new MCR based on transition metal catalysis have been also discovered.[5]

Oxazolopiperidines are bicyclic heterocycles characterized by the possibility of functionalization at C5 (electrophile), C6 (nucleophile), and C8a (nucleophile) (Scheme 1). They can incorporate a wide range of substituents for functional groups pairing behaving as versatile synthetic intermediates and pluripotent scaffolds in DOS.[6] The oxazolopiperidine ring is also present in several natural products and drug-like molecules,[7] and can be considered as a privileged structure. The synthesis of oxazolopiperidine is generally accomplished by first assembly of the six-membered ring followed by closing of the second or by contemporary formation of the two rings using a bis-electrophile and a bis-nucleophile.[8] Amongst many types of nucleophiles investigated, the aldehyde is often used for its high reactivity with amines. As 1,5-bis-aldehydes (or adehydes carrying a terminal carboxylic functions) are relatively unstable and have a high tendency to polymerize, we projected to use an unsaturated carboxylic acid that, after Rh catalyzed hydrocarbonylation to the homologous aldehyde, could react in situ with amino alcohols as partners. In contrast with the results we recently communicated,[9] we did not want to activate the carboxylic acid in order to avoid an additional step. Thus, we decided to apply microwave dielectric heating to the reaction in order to force the lactamization of the free carboxylic acid[10] and to use exclusively commercially available compounds for a truly MCR strategy. Moreover, the use of microwave heating was preferred (respect to the standard autoclave) in order to carry out the reaction inside a small vial under low gas pressure,[11] limiting the waste of H_2/CO and orienting toward a real atom-economic hydroformylation.[12]



Scheme 1. MCR approach for the synthesis of perhydro-oxazolopyridines.

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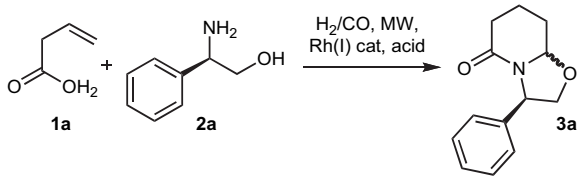
2. Results and discussion

We began the exploration and optimisation process by using a modified version of our unsaturated amide hydroformylation[13] applied to a mixture of 3-butenoic acid (**1a**), (*R*)-phenylglycinol (**2a**) in the presence of Rh(I) catalyst and a chelating ligand. The initial reaction conditions in the presence of $HRh(CO)(PPh_3)_3$ with different ligands, such as xantphos or biphephos gave the expected product exclusively in the presence of TsOH (entries 1–3 in Table 1). Therefore, TsOH was used as an additive to investigate the best pair of catalyst/ligand (entries 4–8 in Table 1). Xantphos at 110 °C gave high conversion but low yields due to the formation of several by-products. Using $Rh(CO)_2$acac/biphephos the reaction was cleaner and we also found that the yield of **3a** increased working at lower temperature (75 °C) for longer time (60 min). At the same time, the nature of the acid was investigated. Increasing the acid strength did not give any improvement (entries 9–10 in Table 1), whereas the less acid and more soluble PPTS (pyridinium *p*-toluenesulfonate), (entry 11) gave better results. Increasing the reaction time to 90 min, the yield of **3a** increased further. The use of toluene as the solvent did not modify the yield of **3a** (entry 8 in Table 1) whereas with CH_2Cl_2 or EtOH, **3a** was not formed at all. It is worth noticing that, if the reaction was carried under conventional heating (autoclave) compound **3a** was not formed even at higher temperature and pressure (entry 13), showing that microwave heating was essential for the process. A possible explanation for this effect is the more efficient heating provided in a microwave vial respect to the stainless steel autoclave (heated outside with an oil bath). With this apparatus, the starting materials start to degradate before reacting.

Table 1
Optimisation of the MCR between 3-butenoic acid, (*R*)-phenylglycinol, H_2, and CO[a]

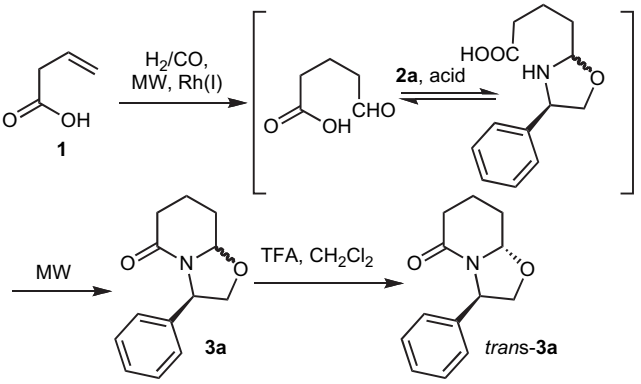


Entry	Catalyst/ligand	Acid	Time, temperature	**3a**[b] [%]
1	$HRh(CO)(PPh_3)_3$/xantphos		60 min, 70 °C	0
2	$HRh(CO)(PPh_3)_3$/biphephos		60 min, 70 °C	0
3	$Rh(CO)_2$acac/xantphos	TsOH	30 min, 70 °C	15
4	$Rh(CO)_2$acac/xantphos	TsOH	30 min, 110 °C	35
5	$Rh(CO)_2$acac/biphephos	TsOH	30 min, 70 °C	45
6	$Rh(CO)_2$acac/biphephos	TsOH	30 min, 110 °C	25
7	$Rh(CO)_2$acac/biphephos	TsOH	60 min, 75 °C	56
8	$Rh(CO)_2$acac/biphephos	TsOH	60 min, 75 °C	60[c]
9	$Rh(CO)_2$acac/biphephos	AcOH	60 min, 75 °C	50
10	$Rh(CO)_2$acac/biphephos	TFA	60 min, 75 °C	60
11	$Rh(CO)_2$acac/biphephos	BF_3. Et_2O	60 min, 75 °C	58
12	$Rh(CO)_2$acac/biphephos	PPTS	90 min, 75 °C	78
13	$Rh(CO)_2$acac/biphephos	PPTS	12 h, 75 °C	0[d]

[a] 3-Butenoic acid (1.0 equiv), (*R*)-phenylglycinol (1.1 equiv), H_2/CO (1:1) at 6.89 10^5 Pa, Rh catalyst (0.01 equiv), ligand (0.04 equiv), acid (0.1 equiv), THF, microwave dielectric heating at 150 W.
[b] Yields of **3a** isolated by column chromatography.
[c] Toluene was used as the solvent.
[d] Reaction carried out under conventional heating inside to a stainless steel autoclave.

Compound **3a** was obtained as a 1:1 mixture of diastereomers, suggesting a pathway of first regioselective hydrocarbonylation of the terminal double bond, probably followed by the acid catalyzed formation of the intermediate oxazolidine assisted by the Rh coordination to the amino alcohol. This process does not provide any stereoselectivity giving a cis/trans mixture. The ultimate lactamization promoted by microwaves gave the product with the same diastereomer composition.

However, the above mixture can be equilibrated with TFA in CH_2Cl_2 toward the thermodynamically more stable *trans*-**3a**.[14] Indeed a 85:15 mixture of trans/cis diastereomers was obtained and pure *trans*-**3a** could be isolated by column chromatography in 65% yield (Scheme 2).



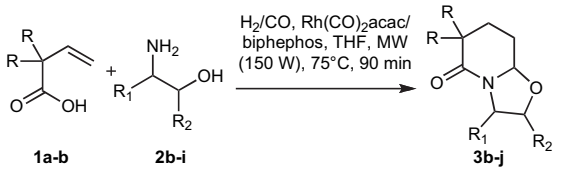
Scheme 2. Process for the formation of *trans*-**3a**.

This result prompted us to extend the procedure to other commercially available 1,2-amino-alcohols (**2b**–**i**) (Table 2) giving the expected lactams **3b**–**j** in moderate to good yields. Starting from chiral amino alcohols **2b**–**d**, the corresponding oxazolopiperidines **3b**–**d** were always obtained as a mixture of diastereomers. However, TFA mediated equilibration was operative on compounds **3b**,**c** allowing isolation of the trans isomers by column chromatography (entries 1 and 2 in Table 2). Compound **3d**, not stable under the equilibration conditions, was isolated only as a mixture of diastereomers. With more hindered amino alcohols **2e**–**g**, the cyclisation occurred with higher stereoselectivity (entries 3–5, 7 in Table 2) and *trans*-**3e**–**g** were isolated without the resort of equilibration. Compound **3f**, obtained with high diastereoselectivity, is the demethylated analog of Meyers' (2*R*,3*R*,(8*aS*)-3-(hydroxymethyl)-8*a*-methyl-2-phenyl-hexahydro-5*H*-[1,3]oxazolo[3,2*a*]-pyridin-5-one)[15] employed as a key intermediate in several natural product syntheses.[16] Our procedure is compatible with the presence of different functional groups potentially useful to increase diversity, such as in the case of compounds **3d**, **3f**, and **3h** and tricyclic, tetracyclic, and spirocyclic compounds were prepared in acceptable yields. Few variations are possible on the side of the unsaturated carboxylic acid as very few compounds with this structural connection are commercially available. Using acid **1b** and amino alcohol **2g**, the corresponding tetracyclic oxazolopyridine was formed and the *trans*-isomer **3j** was isolated in acceptable yields after column chromatography (entry 8 in Table 2). Using 1,3 amino alcohols **4a**–**c**, the 6,6-bicyclic lactams **5a**–**c** were obtained in fairly good yields under comparable reaction conditions. However, a lower stereoselectivity was observed, as **5a**–**c** were always isolated as a mixture of the cis and trans isomers Table 3.

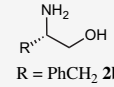
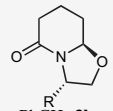
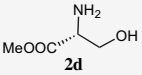
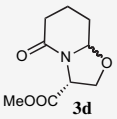
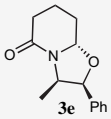
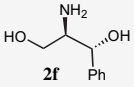
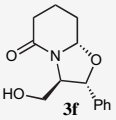
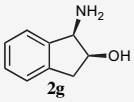
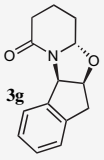
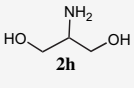
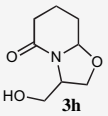
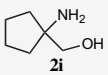
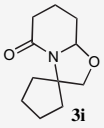
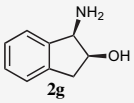
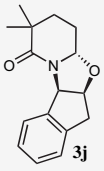
3. Conclusions

In conclusion, a new microwave assisted MCR has been discovered employing a latent bi-electrophile and a bi-nucleophile. A sequence of linear hydrocarbonylation, intermolecular formation of an oxazolidine followed by nucleophilic attack occurred under microwave heating with the creation of six *new bonds in a single step*. It has to be emphasized that as the starting compounds

Table 2
Reaction with 1,2-amino alcohols



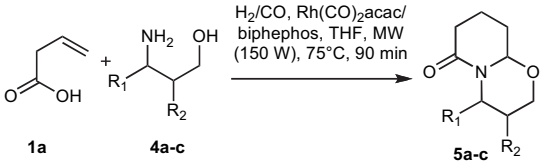
1a-b 2b-i 3b-j

Entry	Acid	Amino alcohol	Product	Yield [%]
1	**1a** R=H	 R = $PhCH_2$ **2b** R = Me_2CH **2c**	 R = $PhCH_2$ **3b**. R = Me_2CH **3c**	56[a] 65[a]
2	**1a** R=H	 **2d**	 **3d**	46[b]
3	**1a** R=H	 **2e**	 **3e**	62[c]
4	**1a** R=H	 **2f**	 **3f**	70[d]
5	**1a** R=H	 **2g**	 **3g**	63[c]
6	**1a** R=H	 **2h**	 **3h**	50[b]
7	**1a** R=H	 **2i**	 **3i**	65
8	**1b** R=Me	 **2g**	 **3j**	56[c]

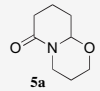
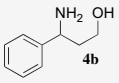
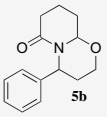
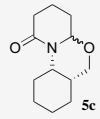
[a] Isolated yield of the trans isomer after TFA mediated equilibration (24 h at rt).
[b] Isolated yield before equilibration.
[c] Obtained as a 4:1 mixture of trans/cis diastereomers. Yields of the trans isomer isolated by column chromatography.
[d] Obtained as a 8:1 mixture of trans/cis diastereomers. Yields of the trans isomer isolated by column chromatography.

(vinylacetic acid and the amino alcohols) are commercially available, the preparation of oxazolopiperidines is now very competitive in respect to the previous reported methods. Finally this process

Table 3
Reaction with 1,3 amino alcohols



1a 4a-c 5a-c

Entry	Acid	Amino alcohol	Product	Yield[a] [%]
1	**1a**	 **4a**	 **5a**	65
2	**1a**	 **4b**	 **5b**	66
3	**1a**	 **4c**	 **5c**	62

[a] Isolated yield as a mixture of diastereomers approximatively 1:1.

represents a combination of DOS and MCR involving gaseous reagents (CO and H_2) that are scarcely exemplified, but have great potentialities.

4. Experimental

4.1. General procedure for the Rh catalyzed multicomponent synthesis of oxazolopiperidine, (3*R*,8a*S*)-3-Phenyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridin-5(3*H*)-one *trans*-3a

A solution of dicarbonylacetylacetonato rhodium(I) (2.5 mg, 0.01 mmol) and biphephos (6.3 mg, 0.02 mmol) in anhydrous degassed THF (2 mL), was introduced into a microwave vial containing a THF solution (2 mL) of the acid **1a** (183 mg, 1.0 mmol), (*R*)-2-amino-2-phenylethanol **2a** (137 mg, 1.0 mmol) and PPTS (25 mg, 0.2 mmol) under inert atmosphere. The solution was submitted to pressurized syngas (H_2/CO 1:1) (Discover microwave synthesizer equipped with the gas addition kit)[17] at 6.89 10^5 Pa and heated at 75 °C by microwave irradiation at 150 W (value previously settled on the microwave oven) for 90 min. The flask was cooled and the internal gas released. Aqueous saturated Na_2CO_3 solution was added and the aqueous layer was extracted three times with EtOAc. The organic layer was dried over Na_2SO_4. After filtration and concentration in vacuo the crude mixture was dissolved in dry CH_2Cl_2 (1 mL) and TFA (193 mg, 1.7 mmol) was added at 0 °C. The mixture was stirred at rt for 24 h, then aqueous saturated Na_2CO_3 solution was added and the mixture was extracted three times with EtOAc. The organic layer was dried over Na_2SO_4 and the crude was purified by flash chromatography (98:2 EtOAc–MeOH) to give *trans*-**3a** as a pale yellow solid (103 mg, 65%). Mp 87–89 °C (lit.[14] 88–90 °C); IR (neat) 2930, 2871, 1650, 1443, 1307, 996, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.32 (m, 2H), 7.28–7.24 (m, 3H), 5.27 (t, *J*=7.8 Hz, 1H), 5.02 (dd, *J*=9.0, 4.6 Hz, 1H), 4.48 (dd, *J*=8.9, 8.0 Hz, 1H), 3.76 (dd, *J*=9.0, 7.8 Hz, 1H), 2.52 (ddt, *J*=18.0, 5.7, 1.7 Hz, 1H), 2.39–2.29 (m, 1H), 2.34 (ddd, *J*=18.0, 11.4, 6.4 Hz, 1H), 2.0–1.93 (m, 1H), 1.77 (tddd, *J*=13.8, 11.4, 5.9, 2.8 Hz, 1H), 1.54 (dddd, *J*=13.6, 12.7, 9.1, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9 (C), 139.6 (C), 128.8 (CH), 127.5 (CH), 126.1

(CH), 88.7 (CH), 72.4 (CH_2), 58.1 (CH), 31.3 (CH_2), 28.4 (CH_2),17.1 (CH_2); $[\alpha]_D^{20}$ −87.5 (*c* 0.6, CH_2Cl_2) {lit.[14] $[\alpha]_D^{22}$ −88.0 (*c* 0.6, CH_2Cl_2)}; LRMS-ESI (*m*/*z*): 218 $(M+H)^+$, 240 (M+Na). HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 218.1176; found 218.1169.

*4.1.1. (3S,8aS)-3-Benzylhexahydro-5H-[1,3]oxazolo[3,2-a]pyridin-5-one trans-**3b**.* Compound **3b** was prepared following the general procedure starting from (*R*)-2-amino-3-phenyl-1-propanol **2b** (100 mg, 0.66 mmol), **1a** (68 mg, 0.79 mmol), and PPTS (8.3 mg, 0,03 mmol) in THF. The residue was purified by flash chromatography on silica gel (98:2 EtOAc–MeOH) to give **3b** as a white solid (85 mg, 56%). Mp 65–66 °C. IR (neat) 1637, 1450, 1412, 999, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.28 (m, 2H), 7.25–7.20 (m, 3H), 4.54–4.47 (m, 2H), 4.03 (dd, *J*=9.0, 7.6 Hz, 1H), 3.62 (dd, *J*=9.0, 7.6 Hz, 1H), 3.28 (dd, *J*=13.4, 3.7 Hz, 1H), 2.80 (dd, *J*=13.4, 9.2 Hz, 1H), 2.50 (ddt, *J*=18.1, 6.0, 1.8 Hz, 1H), 2.31 (ddd, *J*=18.1, 11.8, 6.7 Hz, 1H), 2.25–2.19 (m, 1H), 1.94–1.87 (m, 1H), 1.64 (tddd, *J*=13.8, 11.6, 6.0, 2.8 Hz, 1H), 1.40 (dddd, *J*=13.8, 12.6, 9.2, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.7 (C), 136.9 (C), 129.6 (CH), 128.6 (CH), 126.7 (CH), 87.3 (CH), 69.3 (CH_2), 55.1 (CH), 37.8 (CH_2), 31.4 (CH_2), 28.2 (CH_2), 17.2 (CH_2); $[\alpha]_D^{20}$ −30.7 (*c* 1.0, $CHCl_3$). HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 232.1332; found 220.1330.

*4.1.2. (3S,8aR)-3-Isopropylhexahydro-5H-[1,3]oxazolo[3,2-a]pyridin-5-one trans-**3c**.* Compound **3c** was prepared following the general procedure starting from (*S*)-(+)-2-amino-3-methyl-1-butanol **2c** (100 mg, 0.97 mmol), **1a** (83 mg, 0.97 mmol), and PPTS (21 mg, 0.9 mmol) in THF. The residue was purified by flash chromatography (97:3 EtOAc–MeOH) to give **3c** as a yellow oil (115 mg, 65%). IR (neat) 2957, 2873, 1648, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.73 (dd, *J*=8.6, 4.7 Hz, 1H), 4.18 (td, *J*=7.5, 6.4 Hz, 1H), 4.03 (dd, *J*=8.3, 8.0 Hz, 1H), 3.66 (dd, *J*=8.6, 6.9 Hz, 1H), 2.49 (br ddt, *J*=17.9, 5.8, 1.9 Hz, 1H), 2.34–2.10 (m, 3H), 1.95–1.85 (m, 1H), 1.66 (tddd, *J*=13.7, 11.0, 6.1, 2.6 Hz, 1H), 1.42 (tdd, *J*=13.0, 8.6, 3.3 Hz, 1H), 0.92 (d, *J*=6.5 Hz, 3H), 0.89 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.3 (C), 87.7 (CH), 66.6 (CH_2), 59.2 (CH), 31.7 (CH_2), 30.1 (CH), 28.5 (CH_2), 19.1 (CH_2), 17.0 (CH_3); $[\alpha]_D^{20}$ +3.2 (*c* 1.0, $CHCl_3$) {lit.[18] $[\alpha]_D^{20}$ +13 (*c* 1.1, EtOH)}. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 184.1332; found 184.1328.

*4.1.3. (3R,8aR)-methy-l5-oxohexahydro-2H-oxazolo[[3,2-a]pyridine-3-carboxylate **3d**.* Compound **3d** was prepared following the general procedure starting from L-Serine methylester (131 mg, 0.85 mmol), **1a** (73 mg, 0.85 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (95:5 CH_2Cl_2–MeOH) to give **3d** as a colorless oil (78 mg 46%). IR (neat) 2953, 1720, 1645, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.75–4.68 (m, 1H), 4.39 (t, *J*=6.3, 1H), 4.09 (q, *J*=6.8, 1H), 3.77–3.61 (m, 4H), 2.25–2.17 (m, 2H), 1.81–1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1 (C), 167.5 (C), 87.1 (CH), 66.9 (CH), 53.2 (CH_3), 52.6 (CH_2), 33.2 (CH_2), 32.7 (CH_2), 19.6 (CH_2); $[\alpha]_D^{20}$ +19.8 (*c* 1.0, $CHCl_3$). ES-MS (*m*/*z*): 200.09 $[M+1]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 200.0917; found 200.0935.

*4.1.4. (2S,3R,8aS)-3-Methyl-2-phenylhexahydro-5H-[1,3]oxazolo[3,2-a]pyridin-5-one trans-**3e**.* Compound **3e** was prepared following the general procedure starting from D-(+)-norephedrine **2e** (100 mg, 0.66 mmol), **1a** (56 mg, 0.66 mmol), and PPTS (15 mg, 0.6 mmol) in THF. The residue was purified by flash chromatography (98:2 EtOAc–MeOH) to give **3e** as a colorless oil (94 mg, 62%). IR (neat) 2958, 1628, 1448, 1329 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.26 (m, 5H), 5.28 (dd, *J*=9.3, 4.2 Hz, 1H), 5.14 (d, *J*=6.1 Hz, 1H), 4.87 (dq, *J*=6.6, 6.6 Hz, 1H), 2.53–2.44 (m, 1H), 2.41–2.29 (m, 2H), 1.99–1.90 (m, 1H), 1.78–1.63 (m, 1H), 1.61–1.48 (m, 1H), 0.81 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.6 (C), 137.4 (C), 128.4 (CH), 127.8 (CH), 126.1 (CH), 86.0 (CH), 80.0 (CH), 53.4 (CH), 30.9 (CH_2), 29.3 (CH_2), 16.7 (CH_2), 14.1 (CH_3); $[\alpha]_D^{20}$ +77.3 (*c* 1.0, $CHCl_3$). HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 232.1332; found 232.1330.

*4.1.5. (2R,3R,8aS)-3-(Hydroxymethyl)2-phenylhexahydro-oxazolo[3,2-a]pyridin-5-one **3f**.* Compound **3f** was prepared following the general procedure starting from (1*R*,2*R*)-2-amino-1-phenyl-propane-1,3-diol **2f** (70 mg, 0.77 mmol), **1a** (66 mg, 0.77 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (95:5 CH_2Cl_2–MeOH to give **3f** as a colorless oil (133 mg, 70%); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.34–7.20 (m, 5H), 4.94 (dd, *J*=10.0, 3.2 Hz, 1H), 4.63 (br s, 1H), 4.60–4.58 (d, *J*=8.0 Hz, 1H), 4.01 (td, *J*=12.0, 8 Hz, 1H), 3.82–3.79 (m, 1H), 3.69–3.64 (m, 1H), 2.25–2.17 (m, 2H), 1.81–1.52 (m, 4H). ES-MS (*m*/*z*): 270.1 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 247,2897; found 247,2894.

*4.1.6. (4aS,5aS,10bR)-2,3,4,4a,6,10b-Hexahydro-1H,5aH-indeno[1′,2′:4,5][1,3]oxazolo[3,2-a]pyridin-1-one **3g**.* Compound **3g** was prepared following the general procedure starting from (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **2g** (123 mg, 0.85 mmol), **1a** (156 mg, 0.85 mmol), and TsOH (16 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **3h** as a white solid (148 mg, 76%). IR (neat) 3010, 2950, 1655, 1450, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J*=8, 1H), 7.27–7.16 (m, 3H), 5.89 (d, *J*=6.4, 1H), 5.05–5.01 (m, 1H), 4.68–4.65 (m, 1H), 3.34–3.28 (m, 1H), 3.13–3.09 (m, 1H), 2.43–2.42 (m, 1H), 2.36–2.32 (m, 1H), 2.21–2.18 (m, 1H), 1.87–1.84 (m, 1H), 1.60–1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7 (C), 141.5 (C), 139.6 (C), 128.7 (CH), 127.5 (CH), 126.6 (CH), 124.7 (CH), 84.8 (CH), 79.1 (CH), 62.4 (CH), 38.7 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 17.2 (CH_2); $[\alpha]_D^{20}$ +43.2 (*c* 1.0, $CHCl_3$). ES-MS (*m*/*z*): 252.1 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 230.1176; found 230.1169.

*4.1.7. 3-(Hydroxymethyl)-hexahydrooxazol[3-2a]pyridin-5-one **3h**.* Compound **3h** was prepared following the general procedure starting from serinol **2h** (70 mg, 0.77 mmol), **1a** (66 mg, 0.77 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (95:5 CH_2Cl_2–MeOH) to give **3h** as a colorless oil (65 mg 50%); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.75–4.68 (m, 1H), 4.27–4.21 (m, 1H), 3.66–3.57 (m, 2H),3.42–3.37 (m, 2H), 2.51–2.40 (m, 2H), 1.70–1.63 (m, 2H), 1.49–1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 89.5, 67.9, 56.8, 32.8, 33.2, 20.9. ES-MS (*m*/*z*): 194.3 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 171.0895; found 171.0899.

*4.1.8. Tetrahydrospiro[cyclopentane-1,3′-oxazolo[3,2-a]pyridin]-5′(2′H)-one **3i**.* Compound **3i** was prepared following the general procedure starting from (1-aminocyclopentyl)methanol **2i** (88 mg, 0.77 mmol), **1a** (66 mg, 0.77 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **3i** as a white solid (97 mg, 65%); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.69 (dd, *J*=10.0, 3.2 Hz, 1H), 3.89 (d, *J*=8 Hz, 1H), 3.56 (d, *J*=8 Hz, 1H), 2.51–2.21 (m, 6H), 1.52–1.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.76, 87.4, 76.4, 57.9, 34.5, 31.0, 23.4, 19.6. ES-MS (*m*/*z*): 218.2 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 195.1259; found 195.1263.

Compound **3j**. Compound **3j** was prepared following the general procedure starting from (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **2g** (123 mg, 0.85 mmol), **1b** (176 mg, 0.85 mmol), and TsOH (16 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **3j** as a white solid (128 mg, 56%). IR (neat) 3010, 2950, 1655, 1450, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J*=8, 1H), 7.27–7.16 (m, 3H), 5.89 (d, *J*=6.4, 1H), 5.05–5.01 (m, 1H), 4.68–4.65 (m, 1H), 3.34–3.28 (m, 1H), 3.13–3.09 (m, 1H), 2.21–2.18 (m, 1H), 1.87–1.84 (m, 1H), 1.56 (s, 6H), 1.60–1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7 (C), 141.5 (C), 139.6

(C), 128.7 (CH), 127.5 (CH), 126.6 (CH), 124.7 (CH), 84.8 (CH), 79.1 (CH), 62.4 (CH), 38.7 (CH_2), 36.6 (C), 28.2 (CH_2), 17.2 (CH_2), 12.1 (CH3) $[\alpha]_D^{20}$ +73.2 (*c* 1.0, $CHCl_3$). ES-MS (*m*/*z*): 280.1 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 257.3276; found 257.3256.

4.1.9. Hexahydropyrido[2,1b][1,3]oxazin-6(2H)-one ***5a***. Compound **5a** was prepared following the general procedure as described above from 3-amino-1-propanol **4a** (63 mg, 0.85 mmol), **1a** (73 μL, 0.85 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **5a** as a colorless oil (99 mg, 65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.73–4.65 (m, 2H), 4.06–4.02 (m, 1H), 3.72–3.66 (m, 1H), 2.71–2.64 (m, 1H), 2.35–2.29 (m, 2H), 1.98–1.73 (m, 4H), 1.63–1.60 (m, 1H), 1.47–1.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) 169.4 (C), 86.2 (CH), 67.8 (CH_2), 40.9 (CH_2), 32.7 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 17.3 (CH_2). ES-MS (*m*/*z*): 178.1 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd 155.0946; found 155.0942.

4.1.10. 4-Phenylhexahydro-2H,6H-pyrido[2,1-b][1,3]oxazin-6-one ***5b***. Compound **5b** was prepared following the general procedure as described above from 3-amino-3-phenylpropan-1-ol **4a** (128 mg, 0.85 mmol), **1a** (73 μL, 0.85 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **5b** as a colorless oil (129 mg, 66%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 2H), 7.30 (m, 1H), 7.17 (m, 2H), 4.83 (dd, J^A=J^B=7 Hz, 1H), 4.38 (dd, J^A=J^B=8 Hz, 1H), 4.16 (m, 1H), 3.79 (m, 1H), 2–42–1.69 (m, 8H); ^{13}C NMR ($CDCl_3$, 400 MHz) 168.4 (C), 132.2 (C), 127.8 (CH), 126.4 (2CH), 125.6 (2CH), 86.2 (CH), 68.1 (CH_2), 58.4 (CH), 33.5 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 19.5 (CH_2). ES-MS (*m*/*z*): 254.1 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd 254.2801; found 254.2810.

4.1.11. (4aRS,6aR,10aS)-decahydro-1H,6H-pyrido[1,2-a][3,1]benzoxazin-1-one ***5c***. Compound **5c** was prepared following the general procedure as described above from **4c** (109 mg, 0.85 mmol), **1a** (73 μL, 0.85 mmol), and PPTS (20 mg, 0.08 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give **5b** as a colorless oil (104 mg, 62%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68 (m, 1H), 3.70 (m, 3H), 2.32–1.79 (m, 7H), 1.60–1.48 (m, 3H), 1.30–1.05 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) 170.2 (C), 85.9 (CH), 68.5 (CH_2), 57.5 (CH), 34.4 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 28.7 (CH_2), 24.8 (CH_2), 23.6 (CH_2), 22.6 (CH_2), 19.5 (CH_2). ES-MS (*m*/*z*): 231.2 $[M+Na]^+$. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd 232.2764; found 232.2761.

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