Synthetic strategy studies for a concise access to functionalized pyrano[4,3-b]pyridin-7-ones: An entry to semi-rigid analogs of antihistamines

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Synthetic strategy studies for a concise access to functionalized pyrano[4,3-*b*]pyridin-7-ones: An entry to semi-rigid analogs of antihistamines

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Abstract: We report short and efficient syntheses of polyfunctionalized 5,8-dihydro-7*H*-pyrano[4,3-*b*]pyridin-7-ones and 1,4-dihydro-3*H*-pyrano[4,3-*c*]pyridin-3-ones which can be considered as new aza analogs of 3-isochromanones and as promising scaffolds for medicinal chemistry. Depending on the nature of the substituent, three different and complementary synthetic methodologies were used allowing the introduction of significant diversity in the substituent on the lactone ring of the pyranopyridinones. The selective α-arylation of nitrile (S_NAr) and *tert*-butylester enolate (Pd catalyzed) followed by an acidic mediated lactonisation gives access to original C8-functionalized pyrano[4,3-*b*] pyridin-7-ones and a seleno-mediated cyclization to C1-functionalized pyrano[4,3-*c*]pyridin-3-ones. We have also applied the outlined synthetic methodologies to the preparation of potential semi-rigid analogs of antihistamines.

Introduction

3-isochromanones and derivatives belong to an important class of heterocycle compounds found in several natural products or as useful building blocks to access biological active compounds.[1] Among them, aza analogs of 3-isochromanones or pyranopyridin ones derivatives containing a pyridine ring instead of a phenyl ring are less known heterocycles despite some promising results obtained as medicinal compounds (Figure 1).[2] Efforts have been dedicated to the development of efficient syntheses of 3-isochromanones.[3] However, limited synthetic procedures for the preparation of aza 3-isochromanones analogs are reported.[4] The main synthetic approaches to the construction of the delta lactone ring of 3-isochromanones are based on sigmatropic rearrangement on benzocyclobutenes, on ynamide or Baeyer Villiger oxidation on benzocyclopentanones.[3bdk] These approaches are hardly appropriate to the preparation of pyranopyridinones because pyridine based starting material required in these strategies are not as accessible as their benzo analogs.

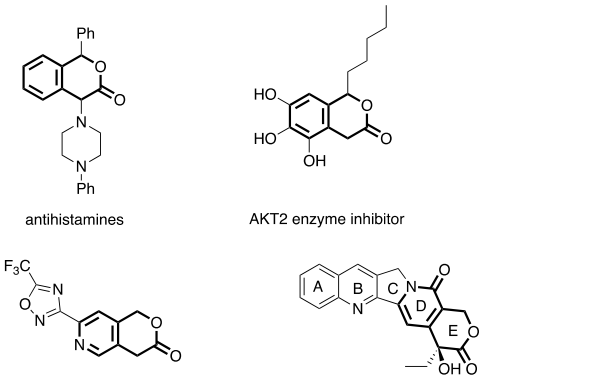


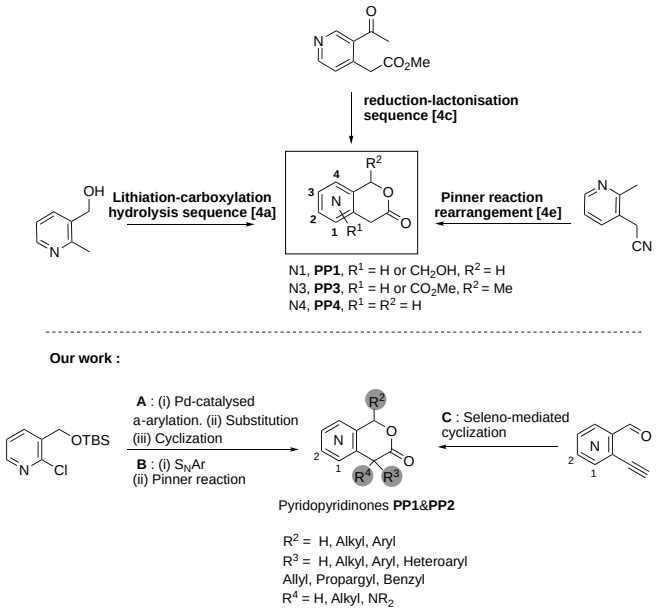
Figure 1. Example of molecules containing (aza) 3-isochromanone scaffold with biological interest.

Among the four possible isomers of pyranopyridinones, three of them, namely **PP1** (N1)[4abc], **PP3** (N3)[4de] and **PP4** (N4)[4f], have been described in the literature, albeit with a narrow range of substituent (Scheme 1). However, the employed strategies narrow the introduction of structural diversity on the lactone ring, a major drawback for potential use in medicinal chemistry. Finally, the lack of effective strategies to access these useful polyfunctionalized lactones makes them still under-explored.

Herein, we present a significant improvement in the synthesis of pyranopyridinones using three different but complementary synthetic methodologies allowing for the first time to easily access polyfunctionalized 5,8-dihydro-7*H*-Pyrano[4,3-*b*]pyridin-7-ones **PP1** and in particular 1,4-dihydro-3*H*-Pyrano[4,3-*c*]pyridin-3-ones **PP2** for which no synthesis has been reported yet. We report an optimized synthetic procedure for selective monoarylation-nucleophilic substitution of *tert*-butylester enolate and α-arylation of various het(aryl)acetonitriles with ortho-substituted chloropyridine followed by acidic mediated lactonisation. We described also an original seleno-mediated cyclization on pyridyl substituted alkynol allowing to construct substituted pyridine fused delta-lactones with efficiency. In the second part of this article, we describe the preparation of original potential semi-rigid analogs of antihistamines using the outlined synthetic methodologies.

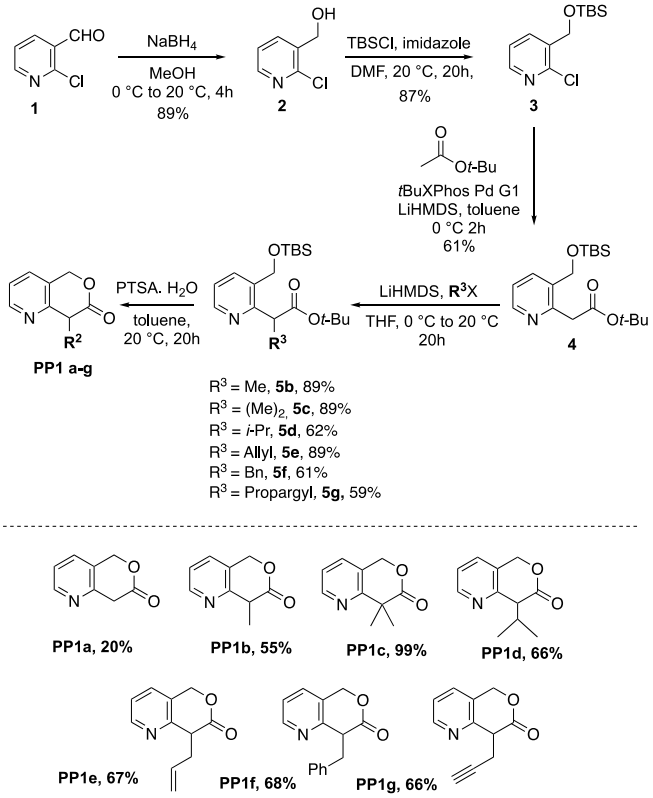
Results and Discussion

Unsubstituted **PP1** was first synthesized in 1957 by Bohlmann *and coll.* from ethyl-2-methyl-pyridine-3-carboxylic acid in two steps via a cyclocondensation of dilithiated intermediate.[4a] Then, in 1991, Alm *and coll.* reported the synthesis of a polyhydroxylated pyridolactone using a [2+2+2] cobalto-catalyzed cycloaddition in 9% global yield with no functionalization of the lactone ring.[4b] Our first approach to functionalized pyranopyridinone **PP1** takes advantage of a Buchwald type pallado-catalyzed α-arylation of *tert*-butyl acetate ester with a TBS protected chloropyridine (**method A**, Scheme 1).[5a] We prepared the required trimethylsilyl protected (2-chloropyridin-3-yl)- methanol **3** from commercially available 2-chloropyridine-3-carboxaldehyde **1** by reduction with sodium borohydride followed by hydroxyl group protection with *tert*-butyltrimethylsilyl chloride (Scheme 2).[6]



Scheme 1. Main synthetic strategies for pyranopyridinones and our approaches

The selective monoarylation reaction of *tert*-butyl acetate with **3** was achieved with *tert*-BuXphosPdCl (1 mol%) as a pre-catalyst and LiHMDS as a base in toluene. The reaction was run at 0°C to prevent the potential formation of bis-arylated by-product. The reaction reached 86% conversion by adding 2 mol % of the pre-catalyst. In our preliminary studies when ethyl acetate was employed instead of *tert*-butyl acetate, less than 30% conversion was observed. However, under these conditions the same α-arylation using substituted esters was not productive. The presence of an α-substituent on the enolate generally leads to the instability of alkali ester enolates or the formation of bis-arylated products. [5b] The use of substituted zinc enolate esters could be required. Besides, such arylation reactions are subsequently substrate-dependent and limited to a small range of substrate.[7] We introduce various substituent such as alkyl/ benzylic/ allylic and propargyl groups on pyrido ester **4** by a deprotonation/ nucleophilic substitution sequence. After optimization, this transformation was achieved successfully by using LiHMDS as a base and a slight excess of the corresponding halide compound as the electrophile. The expected substituted pyridoesters **5** with alkyl, allyl, benzyl and propargyl substituent were thus obtained with yields up to 89%.



Scheme 2. Synthesis of alkyl substituted pyranopyridinones **PP1a-g** following method A

The pyranopyridinones **PP1a-g** are easily obtained from **5** by an acidic deprotection followed by a lactonisation using 4 eq. of PTSA monohydrate. The unsubstituted pyranopyridinone **PP1a** was obtained in 20 % isolated yield whereas substituted pyranopyridinones **PP1b-g** were isolated for the first time in yield from 55% to 99% for gem-dimethyl **PP1c** benefiting from Thorpe Ingold effect for cyclization.[8]

We examined a strategy based on the Pinner reaction (**method B, Scheme 1**) to introduce aromatic substituent on the methylene group of the pyridine ester **4.** It requires the preparation of nitrile analogs of compounds **5** via nucleophilic aromatic substitution of a chloropyridine (Scheme 2 and Scheme 3).[9]

The aryl-substituted 2-pyridyl acetonitrile precursors **7a-e** were prepared from the protected 2-chloropyridine **3** and the corresponding aryl or heteroaryl acetonitrile.

We first studied the substitution step by using phenylacetonitrile as a model nucleophile (Table 1).[10] When treated with 3 equivalents of LiHMDS in the presence of 2 equivalents of phenylacetonitrile in toluene at room temperature, the chloropyridine **3** gave the expected S_NAr product **7a** in a 62 % isolated yield (Table 1 entry 1). However, these conditions were ineffective when using other substituted arylacetonitriles.

Among the few modifications screened (solvent, base, temperature) to improve the yield, the reaction time and the scope of the S_NAr reaction, the use of a large excess of NaH in THF at 70 °C was found to be the best reaction conditions allowing us to isolate the expected S_NAr product with an optimized yield of 69% (Table 1, entry 5). Interestingly, this protocol (2 equiv. of phenylacetonitrile in

the presence of 5 equiv. of NaH in THF at reflux 3h), was successively extended to other (Het)arylacetonitrile compounds giving the corresponding S_NAr product with yields ranging from 56 to 74% (Scheme 3). The nucleophilic substitution was also performed on the more hindered phenyl substituted chloropyridine **6** giving the expected product **7e** as a 3/1 mixture of diastereoisomers (Scheme 3).

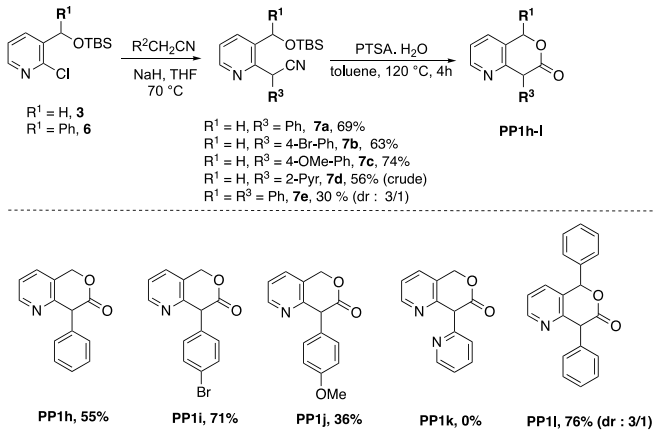
Table 1. Optimization table for nucleophilic substitution of **3**

Entry	Base	Conditions	Yield (%)[a]
1	LiHMDS (3 equiv.)	Toluene, 0 °C to rt, 24h	62
2	$NaNH_2$ (4 equiv.)	Toluene, rt, 24h	20
3	*t*BuOK (3 equiv.)	NMP, 110 °C	-[b]
4	NaH (2 equiv.)	THF, reflux, 2h	59
5	NaH (5 equiv.)	THF, reflux, 3h	69

[a] Isolated yield. [b] The expected product was not observed only starting material was recovered.

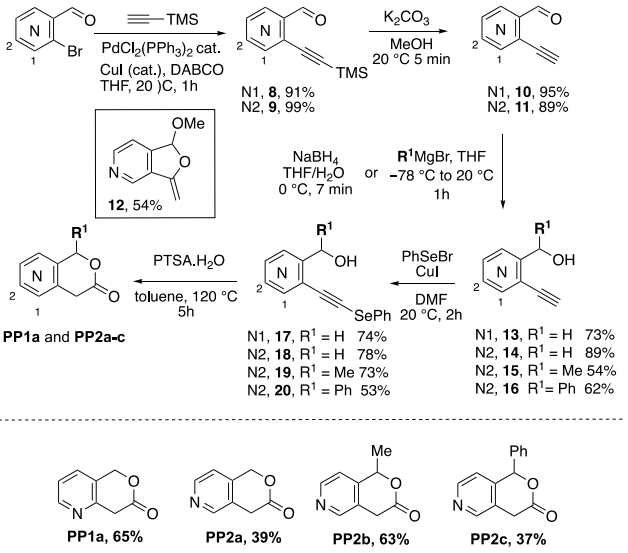
The intramolecular Pinner reaction (PTSA monohydrate at reflux in toluene) was run on five aryl-substituted 2-pyridyl acetonitrile compounds **7a-e**, affording the desired lactones in 39 to 71% isolated yields. Unfortunately, under these acidic conditions a competitive decyanation of the dipyridyl substituted acetonitrile **7d** was observed during the reaction. It is proposed that, under acidic conditions, the protonated electron withdrawing 2-pyridyl substituents activates the benzylic position leading preferentially to decyanation over cyclization.

The high reactivity of the 2-position of the pyridine ring on protected 2-chloropyridylethanol **3** allowed an effective introduction of various substituents on pyranopyridinone **PP1** using S_NAr approach.



Scheme 3. Synthesis of aryl substituted pyranopyridinones **PP1h-l** via method B

Original functionalized pyranopyridinones **PP2** possessing the nitrogen atom at the 3 position of the pyridyl ring were prepared following an unreported selenium-promoted ring closure reaction using pyridoalkynols (Scheme 4). We based our approach on the work of Tiecco et al.[11] who described the conversion of hydroxyl alkynyl phenyl selenides into delta-lactones through proton-induced ring-closure reaction. However, there are limited examples of delta-lactones synthesized using this methodology with only one example of a benzofused lactone and no example containing a heteroaromatic ring. We thus first investigated the possible conversion of alkynylpyridyl derivatives into pyranopyridinones **PP1** and **PP2** using this seleno mediated cyclization. The alkynyl pyridyl carboxaldehydes **8** and **9** were synthesized with good yields from the corresponding bromopyridine derivatives via the Sonogashira reaction using an improved procedure. The best conditions were using $Pd(Cl)_2(PPh_3)_2$ and CuI as catalysts, DABCO as a base instead of Et_3N (Scheme 4).[12] The alkynyl deprotection was carried out with potassium carbonate in methanol in 5 min affording the expected alkynyl pyridyl carboxaldehyde **10** and **11** in 95% and 89% yield respectively.



Scheme 4. Synthesis of pyranopyridinones **PP1a** and **PP2a-c** *via* **method C**

Interestingly, when the TMS deprotection was run for longer reaction time, the furo[3,4,c]pyridine **12** was isolated in 54% yield resulting from an intramolecular 5-*exo*-dig cyclization (Scheme 4).

Reduction of the carbonyl function with $NaBH_4$ in a mixture of THF/ H_2O was performed on both regioisomers **10** and **11** giving the corresponding alkynols **13** and **14** in good yields. In parallel, methyl and phenyl substituted-alkynols **15** and **16** were obtained successfully by the reaction of **10** or **11** with the corresponding Grignard reagent (Scheme 4). The alkynyl pyridyl selenides **17-20** were prepared from the corresponding alkynols **13-16** with phenylselenyl bromide and two equivalent of copper iodide.[13] Finally, the reaction of selenides **17-20** with an excess of PTSA monohydrate proceeds smoothly in toluene at 120 °C in 5 h to give selectively pyranopyridinones **PP1a** and substituted **PP2 a-c** in moderate yield (Scheme 4).

Thus, we have developed a rapid access to diverse isomers of functionalized pyranopyridinones using three complementary strategies. To increase substituent diversity on pyranopyridinones, we have investigated the synthesis of a new class of semi-rigid compounds based on pyranopyridinones scaffolds with potentially interesting properties as an antifungal, enzyme inhibitors or

antihistaminics. The latter are therapeutics targeting the histamine receptors (H1R to H4R) involved in the regulation of many aspects of diseases such as allergic rhinitis, autoimmune diseases and infection.[14] Among these therapeutic agents, antihistamines H1 have long been employed to treat allergy.

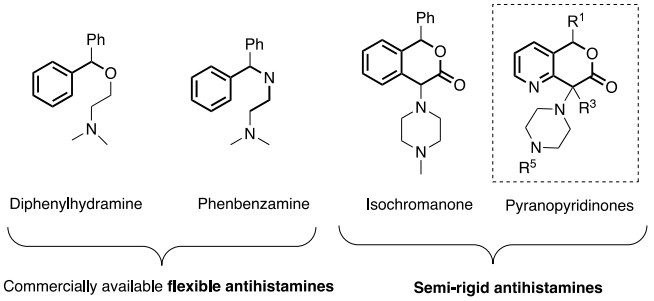
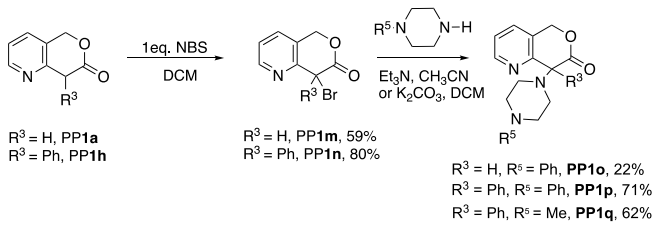


Figure 2. New class of potential semi-rigid antihistamines based on pyranopyridinones scaffold

First and second generations of H1-antihistamines are commonly flexible molecules possessing a diarylmethane moiety i.e. phenbenzamine, cetirizine, doxylamine (Figure 2).[15] However, rotationally constrained molecules of these types are highly desired in order to get more insight to identify the active conformation of histamine itself and thus get more selective H1-receptor antagonists.[16] Semi-rigid piperazine substituted 3-isochromones have proved earlier to possess significant antihistaminic activity (H1) in isolated guinea pig opening the way to develop other semi-rigid molecules with increased antihistaminic properties through structure-activity relationship studies. [1b]

In first instance, we have investigated the synthesis of piperazinyl substituted pyranopyridinones, as starting point to develop other original aza analogs of semi-rigid antihistamines described above. **PP1a** and **PP1h** were converted into the corresponding bromopyranopyridinones **PP1m** (R^3 = H, R^4 = Br) and **PP1n** (R^3 = Ph, R^4 = Br) by reaction with 1 equivalent of N-bromosuccinimide. The title compounds **PP1o**, **PP1p and PP1q** were then synthesized in yields up to 71% by condensation of amines such as *N*-methyl- and *N*-phenyl piperazine in the presence of trimethylamine or potassium carbonate (Scheme 5).



Scheme 5. A new class of potential analogs of anti-histamines

Conclusion

In conclusion, two isomers of functionalized pyranopyridinones were synthesized using three different and complementary synthetic methodologies allowing the introduction of various substituents on the lactone ring. We also applied the outlined synthetic methodologies to prepare semi-rigid analogs of antihistamines with potential biological importance opening the way to develop a new generation of anti-histamines with increased properties. For a future structure-activity relationship studies, other substitution and structural modifications of pyranopyridinones are highly needed and could be easily envisioned based on our developed methodology. The scope of the reaction as well as biological evaluation of these compounds on H1 receptors are underway in the laboratory and will be reported in due course.

Experimental Section

General: NMR spectra were recorded on Bruker Avance III 300 MHz or 400 MHz spectrometers at room temperature. Chemical shifts (δ) are expressed in part per million (ppm), reported as s = singlet, d = doublet, t = triplet, m = multiplet; and referenced to the solvent peak of respectively $CDCl_3$, CD_2Cl_2, $(CD_3)_2SO$ (^{13}C NMR: δ = 77.23; 53.84; 39.52 ppm; ^1H NMR: δ = 7.26; 5.32; 2.50 ppm). IR spectra were recorded on ThermoNicolet Avatar 330 FT IR on film. Exact mass measurements were obtained on TQ R30-10 HRMS spectrometer by ESI+ ionization and are reported in *m/z* for the major signal.

Experimental procedures and characterization data for new compounds or compounds made by a new method are listed below. For the experimental procedure and characterization data of the remaining compounds see references: Compounds **2**[17], **3**[6], **8**[12], **9**[12], **10**[18] ,**11**[19] were reported in literature, **PP1a**[4a] was reported without full characterization. Reagents were purchased as reagent-grade and used without further purification. All anhydrous reactions were carried out in oven dried glassware and under an inert atmosphere of argon. THF and toluene were dried by purification through activated alumina purification columns. Reactions were monitored by analytical TLC on silica gel 60 F254 plates 0.25 mm, and visualized under UV light (λ = 254 and 354 nm). Silica gel (SDS 60 ACC 35–70 mm) was used for column chromatography. Abbreviations: ℃: degrees Celsius. DCM: dichloromethane. ESI: electrospray ionization. Et_2O: diethyl ether. EtOAc: ethyl acetate. Eq: equivalent(s). Et: Ethyl g: gram. h: hour(s). HRMS: High resolution-mass spectrometry. LiHMDS: Lithium bis(trimethylsilyl)amide. IR: infra-red. M (moles per litre (mol L^{-1}). Me: methyl. MeCN: acetonitrile. mg: milligram. $MgSO_4$: Magnesium sulfate. min: minute(s). mL (milliliter). mm: millimeter. mmol: millimole. mol: mole. *m/z*: mass-to-charge ratio. PTSA: paratoluenesulfonic acid.

N_2: nitrogen (g). NBS. N-bromosuccinimide. Et_3N: triethylamine. NMR: Nuclear magnetic resonance. nm: nanometer. ppm: parts per millions. r.t.: room temperature. tBu: tert-butyl. *t*BuXPhos Pd G1: *tert*-BuXPhos palladium(II) phenethylamine chloride. THF: tetrahydrofuran. TFA: trifluoroacetic acid. TIPS: triisopropylsilane. µL: microliter(s). µm: micrometre(s). µM:micromolar. µmol: micromole(s). UV: ultraviolet.

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)acetate (4)**

Compound **3** (2 g, 7.8 mmol, 1 eq.) and *t*-butyl acetate (1.95 mL, 11.7 mmol, 1.5 eq.) were dissolved in 20 mL of toluene. *t*BuXPhos Pd G1 (107 mg, 0.16 mmol, 2 mol%) was added under argon at 0 °C. Solution was stirred for 5 min. Then, LiHMDS (1M in toluene, 23.4 mL, 3 eq.) was carefully added to the mixture which was allowed to warm up to rt for 2 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with EtOAc (3 x 50 mL).

Organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 9:1 to 8:2). Yellow oil, Yield: 61%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, 1H, *J* = 4.2 Hz, H_5), 7.89 (d, 1H, *J* = 7.3 Hz, H_3), 7.30 (m, 1H, H_4), 4.75 (s, 2H, H_6), 3.90 (s, 2H, H_{13}), 1.45 (s, 9H, $H_{16,17,18}$), 0.95 (s, 9H, $H_{9,10,11}$), 0.12 (s, 6H, $H_{7,8}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3 (C_{14}), 151.8 (C_1), 147.2 (C_5), 135.1 (C_2), 134.4 (C_3), 122.0 (C_4), 80.8 (C_{15}), 61.7 (C_6), 42.2 (C_{13}), 27.8 ($C_{16,17,18}$), 25.6 ($C_{9,10,11}$), 18.1 (C_{12}), -5.5 ($C_{7,8}$) ppm; IR: 2930, 2857, 1731, 1577, 1391, 1254, 1146, 1076, 837, 777 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{31}NNaO_3Si$: 360.1965, found: 360.1976 $[M+Na]^+$

General procedure A for the synthesis of compounds 5b and 5d-g

Compound **4** (300 mg, 0.89 mmol, 1 eq.) was dissolved in 5 mL of THF. LiHMDS (1M in toluene, 0.98 mL, 1.1 eq.) was added at 0 °C. The mixture was stirred at this temperature for 20 min. The appropriate halogenoalkane (1.1 eq.) was added dropwise and the solution was allowed to warm up to rt for 20 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with DCM. Organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 9:1).

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)propanoate (5b)**

From compound **4** according to general **procedure A.** Yellow oil, Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, 1H, *J* = 3.8 Hz, H_5), 7.75 (d, 1H, *J* = 7.7 Hz, H_3), 7.16 (dd, 1H, J_1 = 7.70, J_2 = 4.9 Hz, H_4), 4.82 (d, 1H, *J* = 13.3 Hz, H_{13a}), 4.75 (d, 1H, *J* = 13.5 Hz, H_{13b}), 3.93 (q, 1H, *J* = 6.9 Hz, H_6), 1.49 (d, 3H, *J* = 7.15 Hz, H_7), 1.36 (s, 9H, $H_{10,11,12}$), 0.95 (s, 9H, $H_{17,18,19}$), 0.13 (s, 3H, $H_{14/15}$), 0.11 (s, 3H, $H_{14/15}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 172.5 (C_8), 157.4 (C_1), 147.7 (C_5), 134.6 (C_3), 133.9 (C_2), 121.6 (C_4), 80.4 (C_9), 61.8 (C_{13}), 43.8 (C_6), 27.9 ($C_{10,11,12}$), 25.8 ($C_{17,18,19}$), 18.2 (C_{16}), 15.9 (C_7), -5.3 ($C_{14/15}$), -5.3 ($C_{14/15}$) ppm; IR: 2931, 2857, 1736, 1576, 1458, 1367, 1254, 1150, 1063, 836, 777 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{33}NNaO_3Si$: 374.2122, found: 374.2129 $[M+Na]^+$

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-2-methylpropanoate (5c)**

Compound **4** (300 mg, 0.89 mmol, 1 eq.) was dissolved in 5 mL of THF. LiHMDS (1M in toluene, 1.96 mL, 2.2 eq.) was added at 0 °C. The mixture was stirred at this temperature for 20 min. MeI (166 µL, 2.67 mmol, 3 eq.) was added dropwise and the solution was allowed to warm at rt for 20 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with DCM. Organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 9:1). Yellow oil, Yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J* = 4.4 Hz, H_5), 7.91 (d, 1H, *J* = 7.5 Hz, H_3), 7.25-7.18 (m, 1H, H_4), 4.65 (s, 2H, H_{14}), 1.58 (s, 6H, $H_{7,8}$), 1.42 (s, 9H, $H_{11,12,13}$), 0.96 (s, 9H, $H_{18,19,20}$), 0.13 (s, 6H, $H_{15/16}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 176.0 (C_9), 158.6 (C_1), 146.3 (C_5), 135.1 (C_3), 134.4 (C_2), 121.6 (C_4), 80.4 (C_{10}), 60.8 (C_{14}), 49.9 (C_6), 27.6 ($C_{11,12,13}$), 25.8 ($C_{7,8}$), 25.8 ($C_{18,19,20}$), 18.1 (C_{17}), -5.4 ($C_{15/16}$) ppm; IR: 2930, 2858, 1723, 1569, 1470, 1367, 1255, 1145, 1117, 1068, 839, 776 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{36}NO_3Si$: 366.2459, found: 366.2453 $[M+H]^+$

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-3-methylbutanoate (5d)**

From compound **4** according to general **procedure A.** Yellow oil, Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J* = 3.6 Hz, H_5), 7.80 (d, 1H, *J* = 7.5 Hz, H_3), 7.17 (dd, 1H, J_1 = 7.7, J_2 = 4.7 Hz, H_4), 4.89 (d, 1H, *J* = 13.7 Hz, H_{15a}), 4.81 (d, 1H, *J* = 13.7 Hz, H_{15b}), 3.40 (d, 1H, *J* = 10.4 Hz, H_6), 2.85-2.73 (m, 1H, H_7), 1.36 (s, 9H, $H_{12,13,14}$), 1.12 (d, 3H, *J* = 6.4 Hz, $H_{8/9}$), 0.98 (s, 9H, $H_{19,20,21}$), 0.68 (d, 3H, *J* = 6.7 Hz, $H_{8/9}$), 0.16 (s, 3H, $H_{16/17}$), 0.14 (s, 3H, $H_{16/17}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.9 (C_{10}), 154.8 (C_1), 147.6 (C_5), 135.1 (C_2), 134.0 (C_3), 121.4 (C_4), 80.3 (C_{11}), 61.5 (C_{15}), 57.1 (C_6), 29.4 (C_7), 27.8 ($C_{12,13,14}$), 25.8 ($C_{19,20,21}$), 21.1 ($C_{8/9}$), 20.1 ($C_{8/9}$), 18.2 (C_{18}), -5.4 ($C_{16,17}$) ppm; IR: 2957, 2858, 1739, 1574, 1434, 1367, 1255, 1113, 1073, 837, 777 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{37}NNaO_3Si$: 402.2435, found: 402.2447 $[M+Na]^+$

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)pent-4-enoate (5e)**

From compound **4** according to general **procedure A.** Brown oil, Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (d, 1H, *J* = 3.4 Hz, H_5), 7.78 (d, 1H, *J* = 7.7 Hz, H_3), 7.19 (dd, 1H, J_1 = 7.7, J_2 = 4.7 Hz, H_4), 5.75 (m, 1H, H_8), 5.05 (d, 1H, *J* = 17.0 Hz, H_{9a}), 4.95 (d, 1H, *J* = 10 Hz, H_{9b}), 4.84 (d, 1H, *J* = 13.7 Hz, H_{15a}), 4.79 (d, 1H, *J* = 13.7 Hz, H_{15b}), 3.86 (t, 1H, *J* = 7.3 Hz, H_6), 2.92 (m, 1H, H_{7a}), 2.72 (m, 1H, H_{7b}), 1.36 (s, 9H, $H_{12,13,14}$), 0.96 (s, 9H, $H_{19,20,21}$), 0.14 (s, 3H, $H_{16/17}$), 0.12 (s, 3H, $H_{16/17}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.0 (C_{10}), 155.2 (C_1), 147.5 (C_5), 135.8 (C_3), 134.7 (C_2), 134.5 (C_8), 121.8 (C_4), 116.4 (C_9), 80.8 (C_{11}), 61.6 (C_{15}), 49.2 (C_6), 35.0 (C_7), 27.9 ($C_{12,13,14}$), 25.8 ($C_{19,20,21}$), 18.3 (C_{18}), -5.3 ($C_{16,17}$) ppm; IR: 2930, 2857, 2362, 1737, 1576, 1436, 1367, 1255, 1148, 1076, 837, 777 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{36}NO_3Si$: 378.2459, found: 378.2468 $[M+H]^+$

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-3-phenylpropanoate (5f)**

From compound **4** according to general **procedure A.** Brown oil, Yield: 61%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J* = 4.5 Hz, H_5), 7.70 (d, 1H, *J* = 7.5 Hz, H_3), 7.15 (m, 4H), 7.04 (m, 2H), 4.62 (d, 1H, *J* = 13.7 Hz, H_{19a}), 4.31 (d, 1H, *J* = 13.7 Hz, H_{19b}), 4.02 (dd, 1H, J_1 = 8.6 Hz, J_2 = 6.6 Hz, H_6), 3.49 (dd, 1H, J_1 = 13.5 Hz, J_2 = 6.4 Hz, H_{7a}), 3.26 (dd, 1H, J_1 = 13.5 Hz, J_2 = 8.4 Hz, H_{7b}), 1.33 (s, 9H, $H_{16,17,18}$), 0.92 (s, 9H, $H_{23,24,25}$), 0.03 (s, 6H, $H_{20,21}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.0 (C_{14}), 155.1 (C_1), 147.5 (C_5), 139.5 (C_8), 134.9 (C_2), 134.0 (C_3), 128.9 ($C_{9,13}$), 128.0 ($C_{10,12}$), 126.0 (C_{11}), 121.7 (C_4), 80.7 (C_{15}), 61.2 (C_{19}), 51.1 (C_6), 37.1 (C_7), 27.8 ($C_{16,17,18}$), 25.8 ($C_{23,24,25}$), 18.2 (C_{22}), -5.4 ($C_{20,21}$) ppm; IR: 2955, 2857, 1736, 1576, 1435, 1391, 1255, 1143, 837, 777, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{37}NNaO_3Si$: 450.2435, found: 450.2434 $[M+Na]^+$

***tert*-butyl-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)pent-4-ynoate (5g)**

From compound **4** according to general **procedure A.** Brown oil, Yield: 59%.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, 1H, *J* = 4.0 Hz, H_5), 7.82 (d, 1H, *J* = 7.7 Hz, H_3), 7.21 (dd, 1H, J_1 = 7.7, J_2 = 4.7 Hz, H_4), 4.94 (d, 1H, *J* = 13.7 Hz, H_{15a}), 4.88 (d, 1H, *J* = 13.7 Hz, H_{15b}), 4.03 (t, 1H, *J* = 6.9 Hz, H_6), 3.05 (ddd, 1H, J_1 = 16.6 Hz, J_2 = 6.4 Hz, J_3 = 2.3 Hz, H_{7a}), 2.86 (ddd, 1H, J_1 = 16.6 Hz, J_2 = 8.2 Hz, J_3 = 2.3 Hz, H_{7b}), 1.86 (t, 1H, *J* = 2.3 Hz, H_9), 1.36 (s, 9H, $H_{12,13,14}$), 0.97 (s, 9H, $H_{19,20,21}$), 0.15 (s, 3H, $H_{16/17}$), 0.14 (s, 3H, $H_{16/17}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.0 (C_{10}), 154.2 (C_1), 147.6 (C_5), 134.9 (C_2), 134.3 (C_3), 122.0 (C_4), 82.1 (C_{11}), 81.1 (C_8), 69.0 (C_9), 61.6 (C_{15}),

48.3 (C_6), 27.8 ($C_{12,13,14}$), 25.8 ($C_{19,20,21}$), 20.4 (C_7), 18.2 (C_{18}), -5.4 ($C_{16,17}$) ppm; IR: 3313, 2930, 2857, 1736, 1577, 1438, 1368, 1255, 1147, 1080, 838, 777 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{33}NNaO_3Si$: 398.2122, found: 398.2113 $[M+Na]^+$

General procedure B for the synthesis of compounds PP1a-g

The appropriate substrate (**4 and 5bg**) (1 eq.) was dissolved in 10 mL of toluene. PTSA.H_2O (2.5 eq.) was added to the mixture which was stirred at rt for 20 h. 40 mL of a mixture of a saturated aqueous solution of $NaHCO_3$ and EtOAc (1:1) were added to the solution. Organic phase was separated. Aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 5/5).

5H,7H,8H-pyrano[4,3-b]pyridin-7-one PP1a[4a]

From compound **4** according to general **procedure B.** Brown solid, Yield: 20%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1H, *J* = 4.7 Hz, H_5), 7.69 (d, 1H, *J* = 7.5 Hz, H_3), 7.38 (dd, 1H, J_1 = 7.5, J_2 = 5.14 Hz, H_4), 5.39 (s, 2H, H_8), 4.07 (s, 2H, H_6) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 169.5 (C_7), 151.0 (C_1), 149.9 (C_5), 132.3 (C_3), 126.2 (C_2), 122.3 (C_4), 68.2 (C_8), 38.9 (C_6) ppm; IR: 2969, 1732, 1588, 1442, 1391, 1247, 1213, 1151, 1057, 824 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_7NO_2Li$: 156.0632, found : 156.0629 $[M+Li]^+$

8-methyl-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1b)

From compound **5b** according to general **procedure B.** Yellow oil, Yield: 55%.^1H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, 1H, *J* = 4.7 Hz, H_5), 7.5 (d, 1H, *J* = 7.5 Hz, H_3), 7.27 (m, 1H, H_4), 5.3 (d, 1H, *J* = 14.4 Hz, H_{9a}), 5.30 (d, 1H, *J* = 14.3 Hz, H_{9b}), 3.84 (q, 1H, *J* = 6.9 Hz, H_6), 1.73 (d, 3H, *J* = 7.1 Hz, H_7) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 172.7 (C_8), 154.1 (C_1), 149.5 (C_5), 132.1 (C_3), 126.3 (C_2), 121.9 (C_4), 67.2 (C_9), 42.5 (C_6), 11.9 (C_7) ppm; IR: 2994, 2946, 1738, 1595, 1436, 1390, 1240, 1152, 1075, 1008, 804, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_9NNaO_2$: 186.0525, found: 186.0518 $[M+Na]^+$

8,8-dimethyl-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1c)

From compound **5c** according to general **procedure B.** Beige solid, Yield: 99%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, 1H, *J* = 4.4 Hz, H_5), 7.51 (d, 1H, *J* = 7.5 Hz, H_3), 7.25 (dd, 1H, J_1 = 7.5 Hz, J_2 = 4.7 Hz, H_4), 5.40 (s, 2H, H_{10}), 1.66 (s, 6H, $H_{7,8}$) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 175.0 (C_9), 156.9 (C_1), 149.4 (C_5), 132.1 (C_3), 124.6 (C_2), 121.7 (C_4), 66.9 (C_{10}), 44.7 (C_6), 23.7 ($C_{7,8}$) ppm; IR: 3004, 1731, 1585, 1469, 1442, 1396, 1256, 1146, 1108, 1058, 801 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{11}NNaO_2$: 200.682, found: 200.0675 $[M+Na]^+$

8-(propan-2-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1d)

From compound **5d** according to general **procedure B.** Yellow oil, Yield: 66%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1H, *J* = 4.5 Hz, H_5), 7.53 (d, 1H, *J* = 7.7 Hz, H_3), 7.26 (m, 1H, H_4), 5.53 (d, 1H, *J* = 14.8 Hz, H_{11a}), 5.23 (d, 1H, *J* = 14.8 Hz, $H11_b$), 3.68 (d, 1H, *J* = 7.3 Hz, H_6), 2.45-2.29 (m, 1H, H_7), 1.13 (d, 3H, *J* = 6.7 Hz, $H_{8/9}$), 1.07 (d, 3H, *J* = 6.7 Hz, $H_{8/9}$) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 171.1 (C_{10}), 153.8 (C_1), 149.5 (C_5), 132.2 (C_3), 125.7 (C_2), 122.0 (C_4), 67.9 (C_{11}), 55.5 (C_6), 31.6 (C_7), 20.7 ($C_{8/9}$), 20.2 ($C_{8/9}$) ppm; IR: 2966, 1741, 1587, 1444, 1389, 1242, 1183, 1039, 857 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NNaO_2$: 214.0838, found: 214.0840 $[M+Na]^+$

8-(prop-2-en-1-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1e)

From compound **5e** according to general **procedure B.** Brown oil, Yield: 67%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, 1H, *J* = 4.5 Hz, H_5), 7.55 (d, 1H, *J* = 7.5 Hz, H_3), 7.27 (m, 1H, H_4), 6.00-5.86 (m, 1H, H_8), 5.41 (d, 1H, *J* = 14.4 Hz, H_{11a}), 5.30 (d, 1H, *J* = 14.4 Hz, H_{11b}), 5.13 (d, 1H, *J* = 18.5 Hz, H_{9a}), 5.09 (d, 1H, *J* = 11.0 Hz, H_{9b}), 3.92 (t, 1H, *J* = 6.2 Hz, H_6), 3.03-2.84 (m, 2H, H_7) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 171.40 (C_{10}), 153.0 (C_1), 149.6 (C_5), 134.0 (C_3), 132.1 (C_8), 126.0 (C_2), 122.0 (C_4), 117.9 (C_9), 67.5 (C_{11}), 48.0 (C_6), 33.4 (C_7) ppm; IR: 3074, 2924, 1743, 1589, 1438, 1387, 1255, 1058, 919, 797 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}NNaO_2$: 212.0682, found: 212.0676 $[M+Na]^+$

8-benzyl-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1f)

From compound **5f** according to general **procedure B;** Brown solid, Yield: 68%**.** ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, 1H, *J* = 4.2 Hz, H_5), 7.34 (d, 1H, *J* = 7.5 Hz, H_3), 7.25-7.11 (m, 4H, $H_{4,10,11,12}$), 6.91 (dd, 2H, J_1 = 7.7 Hz, J_2 = 1.6 Hz, $H_{9,13}$), 4.92 (d, 1H, *J* = 14.6 Hz, H_{15a}), 4.22-4.13 (m, 2H, $H_{6,15b}$), 3.63 (dd, 1H, J_1 = 13.39 Hz, J_2 = 4.9 Hz, H_{7a}), 3.37 (dd, 1H, J_1 = 13.3 Hz, J_2 = 5.5 Hz, H_{7b}) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 171.8 (C_{14}), 152. (C_1), 149.7 (C_5), 136.9 (C_8), 131.7 (C_3), 129.25 ($C_{9,13}$), 128.3 ($C_{10,12}$), 127.0 (C_{11}), 126.6 (C_2), 122.1 (C_4), 67.5 (C_{15}), 49.5 (C_6), 37.9 (C_7) ppm; IR: 3028, 1742, 1590, 1496, 1452, 1390, 1250, 1149, 1077, 798, 701 cm^{-1}; HRMS (ESI): $C_{15}H_{13}NNaO_2$: 262.0838, found: 262.0849 $[M+Na]^+$

8-(prop-2-yn-1-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1g)

From compound **5g** according to general **procedure B.** Brown solid, Yield: 66%.^1H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, 1H, *J* = 4.40Hz, H_5), 7.57 (d, 1H, *J* = 7.5 Hz, H_3), 7.30 (m, 1H, H_4), 5.47 (d, 1H, *J* = 14.4 Hz, H_{11a}), 5.35 (d, 1H, *J* = 14.4 Hz, H_{11b}), 3.96 (t, 1H, *J* = 5.3 Hz, H_6), 3.29 (ddd, 1H, J_1 = 16.8 Hz, J_2 = 5.1 Hz, J_3 = 2.5 Hz, H_{7a}), 3.15 (ddd, 1H, J_1 = 16.8 Hz, J_2 = 5.50 Hz, J_3 = 2.5 Hz, H_{7b}), 1.97 (t, 1H, *J* = 2.5 Hz, H_9) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 170.5 (C_{10}), 151.4 (C_1), 149.6 (C_5), 132.1 (C_4), 126.4 (C_2), 122.3 (C_4), 81.1 (C_8), 69.8 (C_9), 67.6 (C_{11}), 46.4 (C_6), 18.06(C_7) ppm; IR: 3282, 1746, 1586, 1440, 1386, 1262, 1145, 1063, 1031, 797, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_9NNaO_2$: 210.0525, found: 210.0523 $[M+Na]^+$

2-chloro-(3-{[(tert-butyldimethylsilyl)oxy](phenyl)methyl}pyridine (6)

2-Chloropyridin-3-yl)-phenylmethanol[20] (18,2 mmol, 1 eq.), *tert*-butyldimethylchlorosilane (20,2 mmol, 1.1 eq.) and imidazole (36,4 mmol, 2 eq.) were added to 20 mL of dry DMF. The reaction mixture was stirred at rt for 18 h. 200 mL of Et_2O were added and the reaction mixture was washed three time with water (3 x 100 mL). The combined aqueous layers were extracted with Et_2O (100 mL) and the combined organic layers washed with an aqueous saturated solution of LiCl and brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound. The residue was purified by silica gel chromatography (DCM 100%). White solid, Yield: 79%. ^1H NMR (300 MHz, DMSO-*d6*): δ 8.30 (d, 1H, *J* = 4.2 Hz, H_5), 8,03 (d, 1H, J_1 = 7,7 Hz, J_2 = 1.6Hz, H_3), 7.40 (d, 1H, *J* = 7,7 Hz, H_4), 7.27 (m, 5H, $H_{8\text{-}12}$), 6,14 (s, 1H, H_6), 0.91 (s, 9H, $H_{15,16,17}$), 0.01 (d, 6H, *J* = 6,4 Hz, $H_{13,14}$) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 148.5 (C_1), 148.3 (C_5), 142.7 (C_2), 139.4 (C_7), 137.2 (C_3), 128.3 ($C_{8,12}$), 127. 5 (C_{10}), 126.4 ($C_{9,11}$), 122.9 (C_4), 72.3 (C_6), 25.7 ($C_{15,16,17}$), 18.1 (C_{18}), -4.9 ($C_{13,14}$); HRMS (ESI): *m/z* calcd for $C_{18}H_{25}ClNOSi$: 334.1388, found: 334.1389 $[M+H]^+$

General procedure C for the synthesis of compounds 7a-7e

NaH (60% in oil, 17 mmol) was added portionwise to a solution of compound **3** or **6** (3.4 mmol) in THF (10 mL) at room temperature. The corresponding arylacetonitrile (4.12 mmol) was added to the mixture and the reaction mixture was stirred à 70 °C for 12 h. Water

(20 mL) was added slowly to stop the reaction. EtOAc (20 mL) was added and the two layers were separated. The aqueous layer was extracted three times with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography to afford the pure product.

2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-2-phenylacetonitrile (7a) From compound **3** and phenylacetonitrile according to general **procedure C**. The residue was purified by silica gel chromatography (Cyclohexane/Ether: 8/2, 7/3 to 5/5). Yellow oil, 69 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (dd, 1H, *J* = 4.6 Hz, *J* = 1.2 Hz, H_5), 7.76 (d, 1H, *J* = 7.7 Hz, H_3), 7.42-7.28 (m, 6H, $H_{4,\ 8,\ 9,\ 10,\ 11,\ 12}$), 5.66 (s, 1H, H_6), 4.68 (d, 1H, *J* = 13.7 Hz, H_{14a}), 4.61 (d, 1H, *J* = 13.7 Hz, H_{14b}), 0.91 (s, 9H, $H_{18,\ 19,\ 20}$), 0.05 (s, 6H, $H_{15,16}$), ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 152.2 (C_1), 148.5 (C_5), 136.0 (C_3), 134.2 (C_2), 134.0 (C_7), 129.0 ($C_{8,12}$), 128.3 (C_{10}), 127.8 ($C_{9,11}$), 123.3 (C_4), 118.6 (C_{13}), 61.7 (C_{14}), 42.3 (C_6), 25.8 ($C_{18,19,20}$), 18.2 (C_{17}), -5.45 ($C_{15,16}$) ppm; IR: 2954, 2857, 2250, 1576, 1435, 1257, 1117, 1076-837 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{26}N_2NaOSi$: 361.1707, found: 361.1694 $[M+Na]^+$

2-(4-bromophenyl)-2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2- yl)acetonitrile (7b)
From compound **3** and 4-bromophenylacetonitrile according to general **procedure C**. The residue was purified by silica gel chromatography (Cyclohexane/Et_2O: 8/2, 7/3 to 5/5). Yellow oil, 63 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, 1H, *J* = 4.6 Hz, *J* = 1.8 Hz, H_1), 7.73 (d, 1H *J* = 7.5 Hz, H_3), 7.49 (d, 2H, *J* = 7.5 Hz, $H_{18,19}$), 7.29-7.27 (m, 3H, $H_{16,17,2}$), 5.64 (s, 1H, H_{13}), 4.68 (d, 1H, *J* = 13.4 Hz, H_{6a}), 4.63 (d, 1H, *J* = 13.3 Hz, H_{6b}), 0.90 (s, 9H, $H_{10,11,12}$), 0.05 (s, 6H, $H_{7,8}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 152.1 (C_5), 148.8 (C_1), 136.4 (C_3), 134.0 (C_{20}), 133.2 (C_4), 132.1 ($C_{16,17}$), 129.6 ($C_{18,19}$), 123.5 (C_2), 122.5 (C_{15}), 118.3 (C_{14}), 62.0 (C_6), 41.4 (C_{13}), 25.8 ($C_{10,11,12}$), 18.28 (C_9), -5.38 ($C_{7,8}$) ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{25}N_2NaOSi$: 439.0811, found: 439.0813 $[M+Na]^+$

2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-2-(4-methoxyphenyl)acetonitrile (7c)
From compound **3** and 4-methoxyphenylacetonitrile according to general **procedure C**. The residue was purified by silica gel chromatography (Cyclohexane/ Et_2O: 8/2, 7/3 to 5/5). Yellow oil, 74 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, 1H, *J* = 6.3 Hz, H_1), 7.76 (d, 1H, *J* = 8.1 Hz, H_3), 7.30-7.27 (m, 3H, $H_{2,16,17}$), 6.88 (d, 2H, *J* = 8.1 Hz, $H_{18,\ 19}$), 5.6 (s, 1H, H_{13}), 4.64 (d, 1H, *J* = 13.5 Hz, H_{6a}), 4.62 (d, 1H, *J* = 13.8 Hz, H_{6b}), 3.80 (s, 3H, H_{21}), 0.92 (s, 9H, $H_{10,11,12}$), 0.05 (s, 6H, $H_{7,8}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 159.7 (C_{20}), 152.6 (C_5), 148.6 (C_1), 136.2 (C_3), 134.27(C_4), 129.2 ($C_{16,17}$), 126.1 (C_{15}), 123.4 (C_2), 119.1 (C_{14}), 114.6 ($C_{18,19}$), 61.9 (C_6), 55.5 (C_{21}), 41.7 (C_{13}), 25.9 ($C_{10,11,12}$), 18.4 (C_9), -5.1 ($C_{7,8}$) ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{28}N_2NaO_2Si$: 391.1812, found: 391.1814 $[M+Na]^+$

2-(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)-2-(pyridine-2-yl)acetonitrile (7d)
From compound **3** and 2-pyridylacetonitrile according to general **procedure C**. The residue was purified by silica gel chromatography (Cyclohexane/ Et_2O: 8/2, 7/3 to 5/5). Purification of the compound led to degradation. So, the crude was used directly in the next step. Yellow oil (impure product, 56 % estimated yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (d, 1H, 5Hz, H_5), 8.46 (d, 1H, 4Hz, H_{18}), 7.72 (m, 1H, H_3), 7.65 (m, 1H, H_{16}), 7.52 (d, 1H, *J* = 8 Hz, H_{15}), 7.20 (m, 1H, H_{17}), 7.15 (m, 1H, H_4), 5.69 (s, 1H, H_{13}), 4.83 (d, 1H, *J* = 13 Hz, H_{6a}), 4.76 (d, 1H, *J* = 13 Hz, H_{6b}), 0.85 (s, 1H, $H_{10,11,12}$), 0. 02 (s, 3H, H_7), 0.00 (s, 3H, H_8) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 154.5 (C_1), 151.4 (C_{19}), 149.5 (C_5), 148.4 (C_{18}), 137.3 (C_3), 135.8 (C_{16}), 135.3 (C_2), 123.4 (C_{15}), 123.0 (C_{17}), 122.4 (C_4), 118.2 (C_{14}), 61.8 (C_6), 44.9 (C_{13}), 25.8 ($C_{11,12,13}$), 18.3 (C_9), -5.3 ($C_{7,8}$) ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{26}N_3OSi$: 340.1840, found: 340.1842 $[M+H]^+$

2-(3-{[(tert-butyldimethylsilyl)oxy](phenyl)methyl}pyridin-2-yl)-2-phenylacetonitrile (7e)
From compound **6** and phenylacetonitrile according to general **procedure C**. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 9:1) and trituration with petroleum ether. White solid, Yield: 30%.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H, *J* = 3,9 Hz, H_1), 8,04 (d, 1H, *J* = 7.5 Hz, H_3), 7.30 (m, 9H, $H_{16,}$ $H_{17,}$ $H_{18,}$ $H_{19,}$ $H_{20,}$ $H_{24,}$ $H_{25,}$ $H_{26,}$ H_2), 7,03 (m, 2H, $H_{22,23}$), 5,82 (s, 1H, H_6), 5,55 (s, 1H, H_{13}), 0,94 (s, 9H, $H_{10,11,12}$), 0.00 (s, 3H, $H_{7,8}$), -0.09 (s, 3H, $H_{7,8}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 152,3 (C_5), 148,8 (C_1), 142,0 (C_4), 136,5 (C_3), 134,4 (C_{21}), 128,8-128,8-127,9-126,5-123,0 ($C_{16,17,18,19,20,22,23,24,25,26}$), 119, 1 ($C_{14}$), 74,1 ($C_6$), 41,4 ($C_{13}$), 25,8 ($C_{10,11,12}$), -4,8 ($C_{7,8}$), -5,0 ($C_{7,8}$) ppm; HRMS (ESI): *m/z* calcd for $C_{26}H_{31}N_2OSi$: 415.2200, found 415.2201 [M+H+]

General procedure D for the synthesis of compounds PP1h to PP1l
Compound **7a-7e** (3.25 mmol, 1 eq.) was dissolved in 20 mL of toluene. PTSA.H_2O (19.5 mmol, 6 eq.) was added and the mixture was vigorously stirred and refluxed at 120 °C for 4 h. The reaction mixture was cooled to room temperature and poured into a mixture of a saturated aqueous solution of $NaHCO_3$ and EtOAc (1/1) (50 mL + 50 mL). Water was added and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with water (100 mL), a saturated aqueous solution of Na_2CO_3 (50 mL) and brine (50 mL). Finally, the organic layer was dried over $MgSO_4$ and concentrated to afford the title compound. The residue was purified by silica gel chromatography.

8-phenyl-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1h)
From compound **7a** according to general **procedure D**. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 5:5). Yellow oil, Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 8.68 (d, 1H, *J* = 4.5 Hz, H_5), 7.62 (d, 1H, *J* = 7.5 Hz, H_3), 7.39-7.28 (m, 4H, $H_{4,9,10,11}$), 7.19 (d, 2H, *J* = 6.7 Hz, $H_{8,12}$), 5.32 (s, 1H, H_6), 5.29 (d, 1H, *J* = 14.4 Hz, H_{14a}), 5.21 (d, 1H, *J* = 14.4 Hz, H_{14b}) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.1 (C_{13}), 153.5 (C_1), 149.9 (C_5), 133.2 (C_2), 133.1 (C_3), 129.08 ($C_{8,12}$), 128.0 (C_{10}), 127.5 ($C_{9,11}$), 127.0 (C_7), 122.7 (C_4), 67.7 (C_{14}), 54.3 (C_6) ppm; IR: 3060, 2364, 1744, 1539, 1442, 1242, 1039, 761 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{11}NNaO_2$: 248.0677, found: 248.0682 $[M+Na]^+$

4-(4-bromophenyl)-3,4-dihydro-1H-2-benzopyran-3-one (PP1i)
From compound **7b** according to general **procedure D**. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 5:5). Yellow oil, 71 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, 1H, *J* = 4.1 Hz, H_1), 7.87 (d, 1H, *J* = 7.5 Hz, H_3), 7.56 (d, 2H, *J* = 8.7 Hz, $H_{10/11}$), 7.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.9 Hz, H_2), 7.13 (d, 2H, *J* = 8.7 Hz, $H_{12/13}$), 5.52 (d, 1H, *J* = 14.6 Hz, H_{6a}), 5.42 (d, 1H, *J* = 14.3 Hz, H_{6b}), 5.41 (s, 1H, H_8) ppm; ^{13}C {^{1}H} NMR

(75 MHz, $CDCl_3$) : δ = 169.5 (C_7), 153.0 (C_5), 150.4 (C_1), 132.8 (C_3), 132.6 (C_4), 132.1 ($C_{10/11}$), 129.5 ($C_{12/13}$), 126.7 (C_9), 122.8 (C_2), 122.2 (C_{14}), 67.7 (C_6), 53.9 (C_8) ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{11}BrNO_2$: 303.9894, found: 303.9969 $[M+H]^+$

8-(4-methoxyphenyl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1j)

From compound **7c** according to general **procedure D**. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 5:5). Yellow oil, 36 % yield. ^1H NMR (400 MHz, $CDCl_3$) : δ = 8.65 (dd, 1H, J_1 = 4.9 Hz, J_2 = 1.7 Hz, H_1), 7.60 (dd, 1H, J_1 = 8.1, J_2 = 1.2 Hz, H_3), 7.33 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz, H_2), 7.06 (d, 2H, J = 8.4 Hz, $H_{10,11}$), 6.86 (d, 2H, J = 8.2 Hz, $H_{12,13}$), 5.28 (d, 1H, J = 14.2 Hz, H_{6a}), 5.21 (s, 1H, H_8), 5.18 (d, 1H, J = 14.2 Hz, H_{6b}), 3.77 (s, 3H, H_{15}) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): 171.0 (C_7), 159.7 (C_5), 154.5 (C_{14}), 150.7 (C_1), 133.1 (C_3), 129.2 ($C_{10/11}$), 127.2 (C_9), 125.7 (C_4), 123.0 (C_2), 114.9 ($C_{12/13}$), 68.2 (C_6), 55.7 (C_{15}), 54.3 (C_8) ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}NNaO_3$: 278.0789, found: 278.0788 $[M+Na]^+$

5,8-diphenyl-5H, 7H, 8H-pyrano[4,3-b]pyridin-7-one. (PP1l)

From compound **7e** according to general **procedure D**.

The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 7:3) and trituration with petroleum ether. Yellow solid, 76% yield. Mixture of 2 inseparable diasteroisomers 3/1; ^1H NMR (400 MHz, $CDCl_3$) of the major diasteroisomer: δ = 8.69 (d, 1H, J = 4,8 Hz, H_1), 7,49-7,27 (m, 11H, $H_{3,\ H8,9,10,11,12,16,17,18,19,20}$), 7,08 (d, 1H, J = 7,5 Hz, H_2), 6,23 (s,1H, H_6), 5.50 (s, 1H, H_{14}); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): 170,1 (C_{13}), 154,0 (C_5), 150,3 (C_1), 135,5 (C_4), 134,0 (C_3), 133,4 (C_7 or C_{15}), 131,1 (C_{15} or C_7), 129,4-129,1-128,9-128,1-128,0-127,5 ($C_{8,9,10,11,12,\ 6,17,18,19,20}$), 122,6 ($C_2$), 79,9 ($C_4$), 54.9 ($C_{13}$) ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}NO_2$: 302.1176, found: 302.1176 $[M+H]^+$

1-methoxy-3-methylidene-1H,3H-furo[3,4-c]pyridine (12)

Compound **9** (300 mg, 1.48 mmol, 1 eq.) was dissolved in 5 mL of MeOH. K_2CO_3 (409 mg, 2.96 mmol, 2 eq.) was added to the mixture, which was stirred at room temperature for 4 h. Water (12 mL) was added and the mixture was extracted with DCM (3 x 15 mL). Organic phase was washed brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 7:3 to 6:4) to afford the title compound as a white solid. White solid, Yield: 54%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H, H_1), 8.65 (d, 1H, J = 4.9 Hz, H_5), 7.38 (d, 1H, J = 4.9 Hz, H_4), 6.36 (s, 1H, H_6), 4.78 (d, 1H, J = 2.5 Hz, H_{9a}), 4.76 (d, 1H, J = 2.5 Hz, H_{9b}), 3.51 (s, 3H, H_7) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 156.3 (C_8), 149.3 (C_5), 145.5 (C_3), 142.9 (C_1), 129.9 (C_2), 117.5 (C_4), 105.5 (C_6), 82.8 (C_9), 55.0 (C_7) ppm; IR: 3008, 2941, 1675, 1426, 1373, 1340, 1204, 1101, 972, 914, 811 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{10}NO_2$: 164.0706, found: 164.0709 $[M+H]^+$

(2-ethynylpyridin-3-yl)methanol (13)

Compound **10** (200 mg, 1.53 mmol, 1 eq.) was dissolved in a mixture of 10 mL of THF and 1 mL of water. At 0 °C, $NaBH_4$ (58 mg, 1.53 mmol, 1 eq.) was added. Mixture was stirred at 0 °C for 7 min. Water (10 mL) was added and mixture was extracted with DCM (3 x 20 mL). Organic phase was dried over $MgSO_4$ and concentrated. The title compound was obtained in pure form without any further purification.

Brown solid, Yield: 73%. ^1H NMR (300 MHz, DMSO-d_6): δ 8.44 (d, 1H, J = 4.7 Hz, H_5), 7.88 (d, 1H, J = 7.7 Hz, H_3), 7.4 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.77 Hz, H_4), 5.45 (t, 1H, J = 5.6 Hz, H), 4.63 (d, 2H, J = 5.5 Hz, H_6), 4.54 (s, 1H, H_8) ppm; ^{13}C {^1H} NMR (75 MHz, DMSO-d_6): δ 148.0 (C_5), 140.4 (C_1), 139.0 (C_2), 134.1 (C_3), 123.7 (C_4), 84.5 (C_8), 80.6 (C_7), 59.7 (C_6) ppm; IR: 3207, 2915, 2104, 1585, 1432, 1048, 695 cm^{-1}; HRMS (ESI): *m/z* calcd for C_8H_8NO: 134.0600, found: 134.0599 $[M+H]^+$

(3-ethynylpyridin-4-yl)methanol (14)

From compound **11** using the same experimental procedure as for the preparation of **13.** Brown solid, Yield: 90%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H, H_1), 8.58 (d, 1H, J = 4.9 Hz, H_5), 7.52 (d, 1H, J = 5.1 Hz, H_4), 4.89 (d, 1H, J = 2.5 Hz, H_6), 3.47 (s, 1H, H_8), ~~2.87 (bt, 1H, J = 5.3 Hz, OH)~~ ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.5 (C_3), 151.8 (C_1), 148.6 (C_5), 120.3 (C_4), 116.5 (C_2), 85.5 (C_8), 77.5 (C_7), 61.2 (C_6) ppm; IR: 3286, 3166, 2834, 1597, 1404, 1062, 836, 670, 615 cm^{-1}; HRMS (ESI): *m/z* calcd for C_8H_8NO: 134.0600, found: 134.0597 $[M+H]^+$

1-(3-ethynylpyridin-4-yl)ethan-1-ol (15)

Compound **11** was dissolved in 5 mL of dry THF. At −78 °C, a methylmagnesium chloride solution (3 M in THF, 330 µL, 0.99 mmol, 1.3 eq.) was carefully added. The reaction mixture was allowed to warm at room temperature for 1 h. A saturated aqueous solution of NH_4Cl was added, followed by a saturated aqueous solution of $NaHCO_3$. EtOAC was added to the mixture and the two layers decanted. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 1:1) to afford the title compound as a white solid. White solid, Yield: 54%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H, H_1), 8.58 (d, 1H, J = 5.1 Hz, H_5), 7.6 (d, 1H, J = 5.1 Hz, H_4), 5.30 (q, 1H, J = 6.4 Hz, H_6), 3.51 (s, 1H, H_9), 1.54 (d, 3H, J = 6.6 Hz, H_7) ppm; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 157.7 (C_3), 152.5 (C_1), 149.0 (C_5), 119.3 (C_4), 116.2 (C_2), 85.2 (C_9), 78.0 (C_8), 66.8 (C_6), 23.7 (C_7) ppm; IR: 3210, 3100, 2961, 2103, 1595, 1326, 1230, 1103, 1059, 845, 691, 627 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{10}NO$: 148.0757, found: 148.0755 $[M+H]^+$

1-(3-phenylpyridin-4-yl)ethan-1-ol (16)

Compound **11** (314 mg, 2.39 mmol) was dissolved in 15 mL of dry THF. At -78°C, a solution of phenylmagnesium chloride (3M in THF, 1,14mL, 5,26 mmol) was carefully added. The reaction mixture was allowed to warm at room temperature for 1 h. An aqueous saturated solution of NH4Cl was added, followed by an aqueous saturated solution NaHCO3. EtOAc was added (20 mL) and the two layers decanted. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over MgSO4 and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 7/3 → 5/5) to afford the title compound as a white solid. White solid, 62% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H, H_1), 8.59 (d, J = 4 Hz, 1H, H_5), 7.74 (d, J = 4 Hz, 1H, H_4), 7.43 – 7.27 (m, 5H, $H_{8\text{-}12}$), 6.24 (s, 1H, H_6), 3.50 (s, 1H, H_{15}); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 155.3 (C_3), 152.5 (C_1), 148.8 (C_5), 141,7 (C_7), 128.4 ($C_{9,11}$),127.9 (C_{10}), 126.7 ($C_{8,12}$), 120.4 (C_4), 117. 0 (C_2), 85.5 (C_{14}), 78, 5 (C_{13}), 72, 3(C_6). ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}NO$: 210.0913, found: 210.0914 $[M+H]^+$

{2-[2-(phenylselanyl)ethynyl]pyridin-3-yl}methanol (17)

General procedure E: Compound **13** (18.8 mmol, 1 eq.) was dissolved in 30 mL of DMF. PhSeBr (18.8 mmol, 1 eq.) and CuI (37.6 mmol, 2 eq.) were then added to the mixture. The reaction mixture was stirred at room temperature for 2 h. Et_2O (200 mL) was added and the mixture was washed with ammonia solution (20% wt.) (4 x 100 mL). The layers were decanted and the aqueous layer extracted with Et_2O (1 x 100 mL). Combined organic layers were washed with water, brine (1 x 100 mL) and then dried over $MgSO_4$. After evaporation, the resulting residue was purified by silica gel chromatography (DCM/MeOH: 100/0 to 95/5) to afford the title compound as a brown solid, Yield: 74%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.46 (d, 1H, *J* = 4.5 Hz, H_5), 7.89 (d, 1H, *J* = 7.7 Hz, H_3), 7.73-7.67 (m, 2H, $H_{10,14}$), 7.48-7.32 (m, 4H, $H_{4,11,12,13}$), 5.46 (t, 1H, *J* = 5.5 Hz, OH), 4.65 (d, 2H, *J* = 5.5 Hz) ppm; ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6): δ 148.1 (C_5), 139.6, 139.5, 134.3, 129.8, 129.1, 127.8 (C_9), 127.5, 123.3, 100.4 (C_8), 75.3 (C_7), 59.9 (C_6) ppm; IR: 3224, 3872, 2159, 1577, 1424, 1045, 734, 666 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}NOSe$: 290.0074, found: 290.0079 $[M+H]^+$

{3-[2-(phenylselanyl)ethynyl]pyridin-4-yl}methanol (18)
From compound **14** according to general **procedure E**.
Brown solid, Yield: 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H, H_1), 8.56 (d, 1H, *J* = 5.1 Hz, H_5), 7.60 (d, 2H, *J* = 6.7 Hz, $H_{10,14}$), 7.49 (d, 1H, *J* = 5.1 Hz, H_4), 7.35 (m, 3H, $H_{11,12,13}$), 4.88 (d, 2H, *J* = 4.5 Hz, H_6), 2.26 (bt, 1H, *J* = 5.1 Hz, OH) ppm; ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6): δ 152.8 (C_5), 151.2 (C3), 149.0 (C_1), 129.8 ($C_{10,14}$), 128.9 ($C_{11,13}$), 127.4 (C_9), 120.3 (C_4), 116.5 (C_2), 97.1 (C_7), 78.1 (C_8), 60.3 (C_6) ppm; IR : 3197, 2161, 1578, 1475, 1439, 1398, 1335, 1233, 1064, 843, 730, 688 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}NOSe$: 290.0079, found: 290.0089 $[M+H]^+$

1-{3-[2-(phenylselanyl)ethynyl]pyridin-4-yl}ethan-1-ol (19)
From compound **15** according to general **procedure E**. The reaction mixture was stirred at room temperature for 20 h. The resulting residue was purified by silica gel chromatography (DCM/MeOH: 1:0 to 97:3) to afford the title compound. Yellow oil, Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H, H_1), 8.53 (d, 1H, *J* = 4.4 Hz, H_5), 7.63-7.56 (m, 3H), 7.41-7.31 (m, 3H), 5.26 (q, 1H, *J* = 6.4 Hz, H_6), 1.51 (d, 3H, *J* = 6.6 Hz, H_7) ppm. ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6): δ 157.4 (C_3), 151.5 (C_1), 149.1 (C_5), 129.8 ($C_{11,15}$), 129.1 ($C_{12,14}$), 128.0 (C_{10}), 127.5 (C_{13}), 119.5 (C_4), 116.4 (C_2), 97.3 (C_9), 78.0 (C_8), 65.6 (C_6), 24.1 (C_7) ppm; IR: 3166, 2972, 2162, 1477, 1099, 731, 687 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}NOSe$: 304.0236, found: 304.0227 $[M+H]^+$

1-{3-[2-(phenylselanyl)phenyl]pyridin-4-yl}ethan-1-ol (20)
From **16** according to **the general procedure E:** The reaction mixture was stirred at room temperature for 20h. The resulting residue was purified by silica gel chromatography (DCM/EtOAc 9/1 → 7/3) to afford the title compound as a yellow oil, Yield: 55%.
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (s, 1H, H_1), 8.58 (d,1H, *J* = 4 Hz, H_5), 7.68 (d, 1H, *J* = 4 Hz, H_4), 7.58 (m, 2H, $H_{8,12}$), 7.40 – 7.22 (m, 8H, $H_{9,10,\ 11,\ 16,\ 17,\ 18,\ 19,\ 20}$), 6.24 (d, 1H, *J* = 4 Hz, H_6).^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 155.2 (C_3), 152.0 (C_1), 149.3 (C_5), 142.8 (C_7), 129.8, 129.4, 128.1, 127.5, 127.3, 126.6, 120.4 (C_4), 117. 1 (C_2), 97.5 (C_{14}), 78, 5 (C_{13}), 71,4 (C_6). ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{15}NNaOSe$: 388.0212, found: 388.0204 $[M+Na]^+$

5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1a)

Procedure F: Compound **17** (2.76 mmol, 1 eq) was dissolved in 40 mL of toluene. PTSA. monohydrate (11.04 mmol, 4 eq.) was then added and the reaction mixture was refluxed at 120 °C for 20 h. The reaction mixture was cooled to room temperature and basified with a saturated aqueous solution of $NaHCO_3$. EtOAc was added and the two layers decanted. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (DCM/MeOH: 95:5) to afford the title compound. Beige solid, Yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1H, *J* = 4.7 Hz, H_5), 7.69 (d, 1H, *J* = 7.5 Hz, H_3), 7.38 (dd, 1H, J_1 = 7.5, J_2 = 5.1 Hz, H_4), 5.39 (s, 2H, H_8), 4.07 (s, 2H, H_6) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.5 (C_7), 151.0 (C_1), 149.9 (C_5), 132.3 (C_3), 126.2 (C_2), 122.3 (C_4), 68.2 (C_8), 38.9 (C_6) ppm; IR: 2969, 1732, 1588, 1442, 1391, 1247, 1213, 1151, 1057, 824 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_7NO_2Li$: 156.0632, found : 156.0629 $[M+Li]^+$

1,4-dihydro-3*H*-pyrano[4,3-*c*]pyridin-3-one (PP2a)
From compound **18** according to general **procedure F**.
Beige solid, Yield: 39%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, 1H, *J* = 4.7 Hz, H_5), 8.50 (s, 1H, H_1), 7.19 (d, 1H, *J* = 4.9 Hz, H_4), 5.33 (s, 2H, H_6), 3.75 (s, 2H, H_8) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.8 (C_7), 148.8 (C_5), 148.0 (C_1), 139.7 (C_3), 126.4 (C_2), 119.0 (C_4), 68.8 (C_6), 32.8 (C_8) ppm; IR: 2969, 1731, 1392, 1256, 1146, 1032, 829, 707 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_8NO_2$: 150.0550, found: 150.0553 $[M+H]^+$

1-methyl-1H,3H,4H-pyrano[4,3-c]pyridin-3-one (PP2b)
From compound **19** according to general **procedure F**. The reaction mixture was refluxed at 120°C for 5 h. The resulting residue was purified by silica gel chromatography (100% EtOAc) to afford the title compound. Beige solid, Yield: 63%.^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, 1H, *J* = 4.9 Hz, H_5), 8.50 (s, 1H, H_1), 7.38 (d, 1H, *J* = 4.9 Hz, H_4), 5.64 (q, 1H, *J* = 6.7 Hz, H_6), 3.92 (d, 1H, *J* = 18.5 Hz, H_{8a}), 3.85 (d, 1H, *J* = 18.5 Hz, H_{8b}), 1.65 (d, 3H, *J* = 6.6 Hz, H_7) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.9 (C_9), 148.9 (C_1), 147.8 (C_5), 143.9 (C_3), 126.1 (C_2), 118.0 (C_4), 75.2 (C_6), 32.7 (C_8), 18.7 (C_7) ppm; IR: 2950, 1740, 1410, 1340, 1250, 1165, 1077, 651 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{10}NO_2$: 164.0706, found: 164.0706 $[M+H]^+$

1-phenyl-1H,3H,4H-pyrano[4,3-c]pyridin-3-one (PP2c)
From compound **20** according to general **procedure F**. The reaction mixture was refluxed at 120°C for 6 h. The resulting residue was purified by silica gel chromatography (Cyclohexane/Et_2O 1/9) to afford the title compound. Beige solid, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (m, 2H, $H_{1,5}$), 7.35 (m, 3H, H_4, $H_{9,11}$), 7.23 – 7.19 (m, 2H, $H_{8,12}$), 6.98 (m, 1H, H_{10}), 6.33 (s, 1H, H_6), 3.72 (dd, *J* = 16 Hz, 1H, H_{14a}), 3.64 (dd, *J* = 16 Hz, 1H, H_{14b}). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.7 (C_{13}), 148.6 (C_1), 147.8 (C_5), 143.4 (C_3), 135.3 (C_2), 129.5 (C_{10}), 129.1 ($C_{8,12}$), 127.3 ($C_{9,11}$), 126.7 (C_7), 120.3 (C_4), 81.0 (C_6), 33.2 (C_{14}). IR: 1737, 1421, 1308, 1237, 1182, 1008, 760, 699 cm^{-1}, HRMS (ESI+): calcd for $C_{14}H_{11}NO_2$: 225,08; found *m/z* 226,08 $[M+H]^+$

8-bromo-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1m)
Compound **PP1a** (100 mg, 0.67 mmol, 1 eq.) was dissolved in 10 mL of DCM. NBS (119 mg, 0.67 mmol, 1 eq.) was then added and

the reaction mixture was stirred at room temperature for 10 min. DCM was added and the resulting organic layer was washed twice with an aqueous saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound in pure form. Brown solid, Yield: 59%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, 1H, *J* = 6 Hz, H_5), 7.65 (d, 1H, *J* = 9 Hz, H_3), 7.38 (dd, 1H, J_1 = 9 Hz, J_2 = 6 Hz, H_4), 5.63 (d, 1H, *J* = 12 Hz, H_{6a}), 5.51 (s, 1H, H_7), 5.30 (d, 1H, *J* = 12 Hz, H_{6b}) ppm; ^{13}C {^{1}H} NMR (100 MHz, CD_3OD): δ 167.4 (C_8), 151.6 (C_1), 151.3 (C_5), 135.7 (C_3), 130.6 (C_2), 126.0 (C_4), 69.4 (C_6), 49.3 (C_7) ppm; IR: 2935, 1755, 1432, 1207, 1182, 1023, 779 cm^{-1}; HRMS (ESI): m/ z calcd for $C_8H_6BrNNaO_2$: 249.9474, found: 249.9480 $[M+Na]^+$

8-bromo-8-phenyl-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1n)

Compound **PP1h** (100 mg, 0.44 mmol, 1 eq.) was dissolved in 10 mL of DCM. NBS (79 mg, 0.44 mmol, 1 eq.) was then added and the reaction mixture was stirred at room temperature for 5 minutes. DCM was added and the resulting organic layer was washed twice with an aqueous saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound in pure form. Orange solid, Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, 1H, *J* = 3 Hz, H_5), 7.62 (d, 1H, *J* = 6Hz, H_3), 7.41-7.33 (m, 6H, $H_{4,10,11,12,13,14}$), 5.46 (d, 1H, *J* = 15 Hz, H_{6a}), 5.16 (d, 1H, *J* = 15 Hz, H_{6b}) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.9 (C_8), 152.7 (C_1), 150.0 (C_5), 135.7 (C_2), 132.7 (C_3), 128.7 (C_{12}), 128.3 ($C_{10,14}$), 128.3 ($C_{11,13}$), 126.5 (C_9), 123.5 (C_4), 67.2 (C_6), 63.4 (C_7) ppm; IR : 3092, 1732, 1439, 1388, 1240, 1176, 1049, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}BrNNaO_2$: 325.9787, found: 325.9797 $[M+Na]^+$

8-(4-phenylpiperazin-1-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1o)

Compound **PP1m** (130 mg, 0.6 mmol, 1 eq.) was dissolved in 5 mL of acetonitrile. N-phenylpiperazine (229 µL, 1.5 mmol, 2.5 eq.) was then added. The reaction mixture was stirred at room temperature for 20 hours. An aqueous saturated solution of Na_2CO_3 was added to the mixture, followed by DCM (20 mL) The two layers were decanted and the aqueous layer extracted with DCM (2 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 1:1) to afford the title compound in pure form. White solid, Yield: 22%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, 1H, *J* = 6 Hz, H_5), 7.63 (d, 1H, *J* = 6 Hz, H_3), 7.35 (d, 1H, *J* = 6 Hz, H_4), 7.30-7.20 (m, 2H, $H_{15,17}$), 6.94-6.82 (m, 3H, $H_{14,16,18}$), 5.92 (d, 1H, *J* = 15 Hz, H_{6a}), 5.14 (d, 1H, *J* = 15 Hz, H_{6b}), 4.27 (s, 1H, H_7), 3.23-3.07 (m, 4H,$H_{9/10/11/12}$), 2.94-2.83 (m, 2H, $H_{9/10/11/12}$), 2.70-2.57 (m, 2H, $H_{9/10/11/12}$) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.8 (C_8), 152.3 (C_1), 150.9 (C_{13}), 149.6 (C_5), 133.1 (C_3), 129.1 ($C_{15,17}$), 128.8 (C_2), 123.4 (C_4), 119.8 (C_{16}) 116.0 ($C_{14,18}$), 70.8 (C_6), 68.1 (C_7), 51.2 ($C_{9/10/11/12}$), 49.0 ($C_{9/10/11/12}$) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}N_3O_2$: 310.1550, found: 310.1557 $[M+H]^+$

8-phenyl-8-(4-phenylpiperazin-1-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1p)

Compound **PP1n** (100 mg, 0.33 mmol, 1 eq.) was dissolved in 5 mL of acetonitrile. Et_3N (92 µL, 0.66 mmol, 2 eq.) and *N*-phenylpiperazine (75 µL, 0.49 mmol, 1.5 eq.) were successively added. The solution was stirred at room temperature for 20 h. Water (10 mL) was added, followed by DCM (30 mL). The two layers were decanted and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were washed with an aqueous saturated solution of Na_2CO_3, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (Cyclohexane/EtOAc: 8:2 to 6:4) to afford the title compound. Brown oil, Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, 1H, *J* = 4 Hz, H_5), 7.41 (d, 1H, *J* = 7 Hz, H_3), 7.40-7.16 (m, 8H, $H_{4,16,17,20,21,22,23,24}$), 7.00-6.94 (m, 2H, $H_{14,15}$), 6.86 (t, 1H, *J* = 7 Hz, H_{18}), 5.09 (d, 1H, *J* = 12 Hz, H_{6a}), 4.89 (d, 1H, *J* = 12 Hz, H_{6b}), 3.35-3.18 (m, 6H, $H_{9/10/11/12}$), 3.00-2.91 (m, 2H, $H_{9/10/11/12}$) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.5 (C_7), 155.4 (C_1), 149.8 (C_5), 134.8 (C_{13}), 132.5 (C_3), 128.8 ($C_{14,15}$), 128.7 ($C_{16,17,20,21}$), 128.6 ($C_{22,23,24}$), 127.7 (C_{19}), 122.2 (C_4), 116.1 (C_{18}), 75.2 (C_8), 66.5 (C_6), 47.4 ($C_{9,10,11,12}$) ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{24}N_3O_2$: 386.1863, found: 386.1865 $[M+H]^+$

8-phenyl-8-(4-methylpiperazin-1-yl)-5H,7H,8H-pyrano[4,3-b]pyridin-7-one (PP1q)

Compound **PP1n** (300 mg, 0.99 mmol, 1 eq.) was dissolved in 5 mL of DCM. K_2CO_3 (274 mg, 1.98 mmol, 2 eq.) and *N*-methylpiperazine (121µL, 1.09 mmol, 1.1 eq.) were successively added. The solution was stirred at room temperature for 6 h. Water (10 mL) was added, followed by an aqueous saturated solution of Na_2CO_3 (10 mL) and DCM (30 mL). The two layers were decanted and the aqueous layer extracted with DCM (2 x 30 mL). The combined organic layers were washed with an aqueous saturated solution of Na_2CO_3, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (DCM/ NEt_3: 99/1 to DCM/MeOH/NEt_3 97/2/1) to afford the title compound. Yellow oil: 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, 1H, *J* = 6 Hz, H_5), 7.45 (d, 1H, *J* = 6 Hz, H_3), 7.41-7.18 (m, 6H, $H_{4,15,16,17,18,19}$), 5,05 (d, 1H, *J* = 12 Hz, H_{6a}), 4.84 (d, 1H, *J* = 12 Hz, H_{6b}), 3.03 (m, 2H, H_9), 2,81 (m, 2H, H_{12}), 2,50 (m, 4H, $H_{10,11}$), 2,31 (s, 3H, H_{13}) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.4 (C_8), 155.7 (C_1), 149.9 (C_5), 135.1(C_2),132.4 (C_3), 128.7 ($C_{15,19}$), 128.6 ($C_{16,18}$), 127.8 (C_{14}), 122.1 (C_4), 75.2 (C_7), 66.5 (C_6), 55.9 ($C_{9/12}$), 47.3 ($C_{10/11}$), 46.0 (C_{13}) ppm; HRMS (ESI): calcd for $C_{19}H_{22}N_3O_2$: 324.1707, found: *m/z* 324.1707 $[M+H]^+$

Keywords: pyridopyridinones • antihistamines • delta-lactone • Pinner reaction • seleno-mediated cyclization

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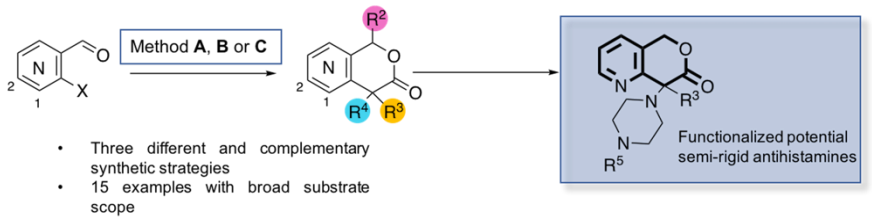

Original pyranopyridinones containing polyfunctionalized delta-lactones ring have been synthesized using three concise and efficient synthetic methodologies. Potential semi-rigid analogs of antihistamines containing a pyranopyridinone scaffold have also been prepared using the outlined synthetic methodologies.

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