Studies on Reactive Pyridylketones Formed by Weinreb Transformations

Vegar Stockmann, Svein Jacob Kaspersen, Alexander Nicolaisen, and Anne Fiksdahl*

Department of Chemistry, Norwegian University of Science and Technology, NTNU, N-7491 Trondheim, Norway

*E-mail: anne.fiksdahl@chem.ntnu.no

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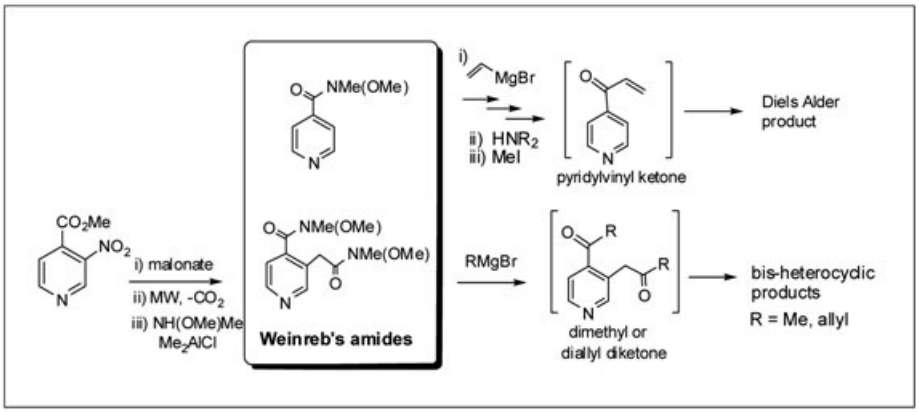

A method has been developed to allow the preparation of reactive pure vinylpyridylketones and activated vinylketones, in general, to be used in further reactions, such as cycloadditions. The process is based on the Weinreb's amide transformation and includes a quarternary ammonium intermediate and subsequent elimination. Additionally, based on our previous results on the malonate alkylation of 3-nitropyridines and subsequent synthetic applications, we present the studies on the transformation of pyridyl malonate derivative **3** *via* the Weinreb's amide **4** and reactive methylpyridyl- (**17**) and allylpyridyl-ketone (**6**) into bis-heterocyclic products **18** and **19**, and **8**, **20**, and **21**, respectively.

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INTRODUCTION

Aromatic alkylation methods are essential in organic synthesis since more complex carbon skeletons can be constructed. We have previously reported the nucleophilic aromatic substitution (NAS) [1–3] of the nitro group in 3-nitropyridyl carboxylate (**1**) with malonate (Scheme 1). The versatility of the 3-pyridylmalonate product **2** was demonstrated by subsequent transformations to give new fused bis-heterocycles.

The initial target of this project was the preparation of the two potentially biological active pyridoisotropolone analogue **7** and cyclopenta[g]isoquinolinol **9** from pyridyl malonate **2** (Scheme 1). Tropolones are widespread natural products with a broad range of anti-bacterial, anti-fungal, anti-tumor, and insecticide effects [4,5], whereas cyclopentaisoquinoline compounds, similar to product **9**, have been prepared as cancer chemotherapeutic agents [6–9]. The acidity and properties of the cyclopentadienide ion of similar cyclopentaphenanthrenes have been studied [10–12]. Thus, derivatives of compound **9** would show pronounced acidity due to the strong anionic stabilizing resonance effect and the electron-withdrawing pyridine moiety.

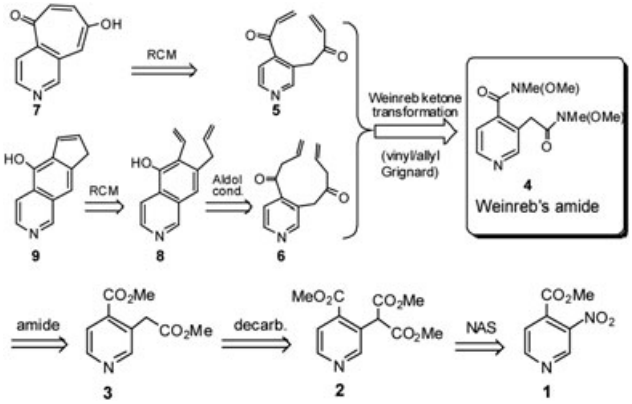
Our approach for the preparation of the seven-membered cyclic products **7** and the tricyclic product **9** was based on RCM of the vinyl-vinyl and vinyl-allyl moieties of compounds **5** and **8**, prepared from pyridyl malonate (**2**) via diester **3**, Weinreb's amide **4** and subsequent Weinreb ketone transformations (Scheme 1) [13,14]. 7-Allyl-6-vinylisoquinolinolol **8** would be obtained by an intramolecular regioselective aldol cyclization of diallylketone **6**.

However, some challenging effects were observed by the transformation of Weinreb's amide **4** into the reactive divinyl- and diallyl-ketones **5** and **6**. Further investigations were needed to identify the formed products and preferably establish suitable methods for the handling and application of such reactive pyridyl ketones. The results of the studies are discussed below.

RESULTS AND DISCUSSION

Weinreb's amides, *N*-methoxy-*N*-methyl amides, formed by ester aminolysis [15], are useful intermediates

Scheme 1

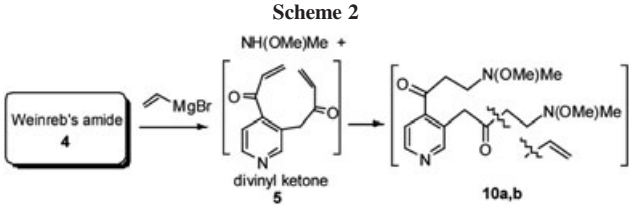


in organic synthesis, as they react efficiently with organometallic agents, such as Grignard reagents, to selectively produce ketones. A corresponding two-step procedure allowed a direct allylation of carboxylic acids [16]. We applied a more efficient process, using the modified Me_2AlCl/MeONHMe·HCl reagent system [17] for the preparation of Weinreb's amide **4** (74%) from homochinchomeric acid dimethyl ester **3**, readily obtained (89%) by microwave (MW) promoted mono-decarboxylation of pyridyl malonate **2** (Scheme 1) [3].

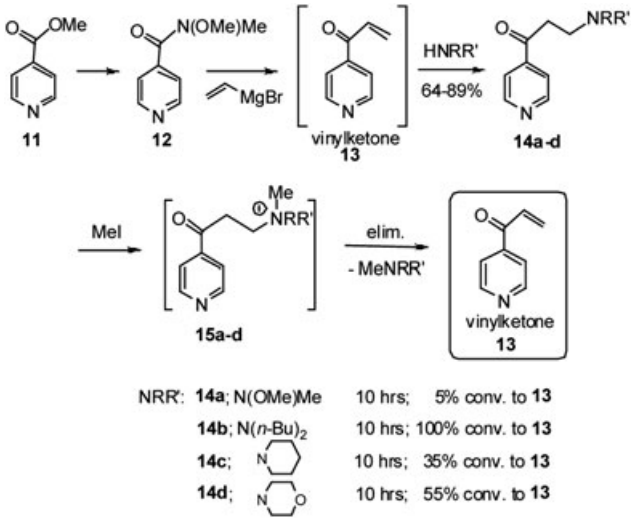
Vinylpyridylketone. The ketone transformation of Weinreb's amide **4** into divinylketone (**5**) intermediate for the preparation of pyridoisotropolone **7** (Scheme 1) did not take place. The reaction resulted in a tarry and hardly soluble material, and no products were isolated or identified. The highly reactive vinylpyridylketone **5** may react in several ways. Because of pyridyl activation, instant mono or double Michael additions of present potential nucleophiles, such as the amine leaving group, NHMe(OMe), to the vinylketone groups of **5** would lead to a mixture of unwanted intermediates and products. Compounds, such as **10a** or **10b**, were not observed, but illustrate the potential reactivity of vinylpyridylketone **5** (Scheme 2). The direct synthesis of such β-aminoketones from Weinreb's amides *via* sequential nucleophilic vinyl substitution and Michael reaction is well known [18,19].

To develop a practical and selective preparation method for reactive vinylpyridylketones and activated vinylketones in general, the transformations of Weinreb's amide **12**, obtained from methyl isonicotinate (**11**, Scheme 3), was

Scheme 2



Scheme 3

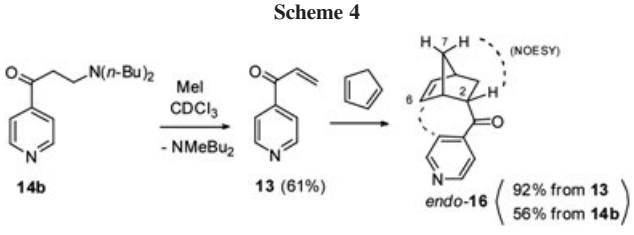


studied. By the conversion of intermediate **12** with vinylMgBr, the formed vinylketone **13** was directly trapped *in situ* by the present amine leaving group and the corresponding —N(OMe)Me Michael product (**14a**) was isolated (70%).

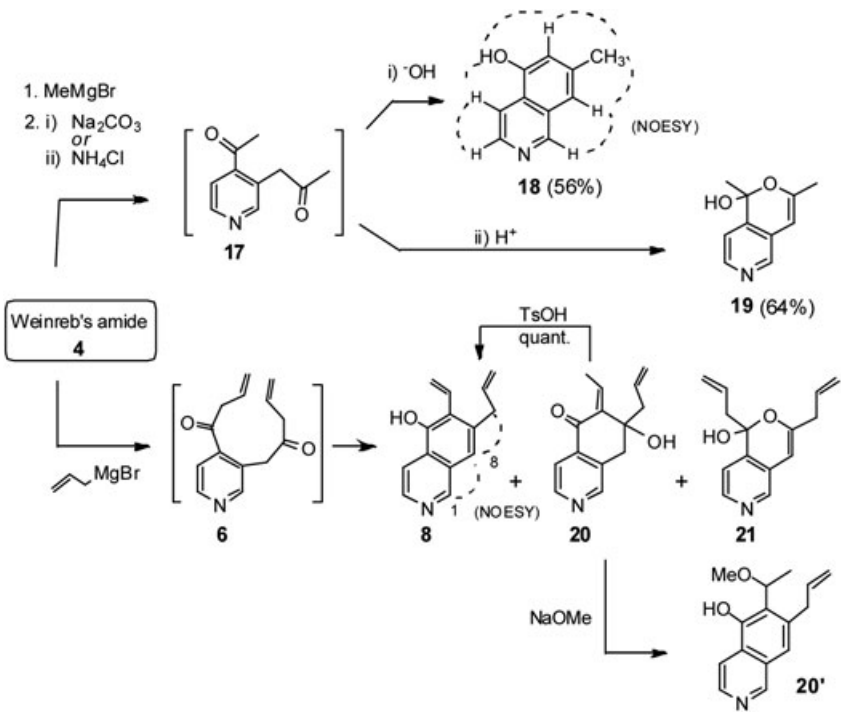
Furthermore, the corresponding amine products **14b—d** (64—89%) were formed by *in situ* trapping of the vinylketone **13** with dibutylamine, piperidine, or morpholine, respectively, added to the reaction mixture. To enable the formation of a stable and pure solution of the reactive vinylpyridylketone **13**, the isolated amine products **14a—d** were converted into quarternary ammonium intermediates (**15a—d**) by reaction with methyl iodide (Scheme 3). *In situ* amine elimination afforded the desired vinylketone **13**. The dibutylamine intermediate **14b** gave full conversion to the vinylketone **13** in 10 h, as shown by NMR of the reaction mixture. A solution of vinylketone **13** in $CDCl_3$ (61%, Scheme 4), pure by ^{1}H-NMR, was obtained after repeated washing with water and final argon-flush to remove excess MeI. The yield was determined by ^{1}H-NMR with 1,2,4,5-tetrachlorobenzene as an internal standard. Low to moderate conversion (5—55%) of amines **14a**,**c**,**d** into vinylketone **13** was obtained through their respective quarternary ammonium compounds **15a**,**c**,**d**.

To demonstrate the utility of the reactive vinylpyridylketone **13** in subsequent synthetic transformations,

Scheme 4



Scheme 5



the stable and pure solution of vinylketone **13** was treated with cyclopentadiene to undergo a Diels-Alder cycloaddition (Scheme 4). The bicyclo[2.2.1]heptenyl product **16** was isolated in excellent yield (92% from vinylketone **13**; 56% from amine **14b**). The endo isomer was exclusively formed, as confirmed by 2D NMR, as NOESY effects between H2 and H7, and between pyridine-H3/-H5 and H6, were observed, excluding the exo product. No traces of the exo-isomer could be observed.

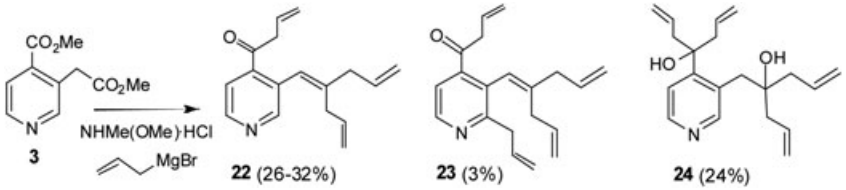
The developed method was not successful for the generation of divinylketone **5** from Weinreb's amide **4**, probably due to competing cyclization reactions, as discussed below for allylpyridylketone **6**.

Allylpyridylketone. The transformation of Weinreb's amide **4** with allylmagnesium bromide (Scheme 5) gave a mixture of cyclization products *via* the initially formed diallylketone (**6**). To identify these new heterocyclic compounds, the MeMgBr conversion of amide **4** and, hence, the formation of dimethyldiketone intermediate **17** (Scheme 5) was chosen as a less complex reaction to study the Grignard transformations of Weinreb's amide **4**. The formed cyclic products were dependant on the workup procedures. The MeMgBr conversion of amide **4** afforded the isoquinolinol product **18** (56%), formed by regioselective intramolecular aldol condensation of diketone **17**, by quenching the reaction with water and subsequent alkalic treatment of the crude product. The hemiketal **19** (64%), formed by *O*-acylation of diketone **17**, was obtained as the main product after NH_4Cl workup. Such cyclocondensations are well known from the preparation of 2*H*- and 4*H*-pyran natural product from 1,5-diketone precursors [20—22].

The reaction of Weinreb's amide **4** with allylMgBr gave a crude mixture mainly affording isoquinolinol **8** (13%), analogues to compound **18** discussed above, and the corresponding aldol precursor, the ethylidene compound **20**, by adding NaOH (5*M*) to the solution and thus extraction from an alkalic solution. Product **8** (11%) was also obtained by quenching with an NH_4Cl solution and final extraction. The aldol precursor compound **20** (26%), and minor amounts of the hemiketal **21** (6%), similar to product **19** above, were isolated as well. The hemiketal **21** was later isolated in higher yield (21%) by quenching with an ice-cold solution of NH_4Cl. The conjugated addition of a methoxy group to the exocyclic double bond in product **20**, giving methoxy-product **20′**, confirmed the keto-ethylidene structure of **20**. Separate experiments showed that aromatization and ethylidene-vinyl isomerization and, hence, full conversion of **20** into **8** could be performed by treatment of **20**in $CDCl_3$ with *p*-TsOH in 10 hours. Alternative treatments with HCl (1—5*M*) or NaOH (3—5*M*) were not successful, mainly affording the elimination product without any ethylidene-vinyl isomerization. We were, however, not able to develop optimized conditions allowing direct conversion of Weinreb's amide **4** into the desired compound **8** as the major product.

The identity of the vinyl-allyl-isoquinolinol product **8** was confirmed by HMBC, HSQC, and NOESY NMR

Scheme 6



experiments. In particular, the NOESY results supported the regioselective aldol reaction and structure **8**, as a through-space proximity of H8 with both H1 and the allylic CH_2 group was observed. The isolation of small amounts of compound **8** was laborious, and the compound was never isolated in sufficient amounts to permit a final RCM for the preparation of **9** (Scheme 1).

The conclusive structure elucidations of isoquinolinol **8** and the cyclic diallylhemiketal **21** were based on comparative studies of the fully characterized products **18** and **19**, respectively. In particular, the unambiguous ^{13}C-NMR data correlations in pairs between **8/18** and **19/21** were significant.

Attempts to develop a one-pot procedure for the formation of allyl-vinyl-isoquinolinol **8**, applying allyl-MgCl both to generate the Me(MeO)NMgCl reagent [15] and to convert the formed Weinreb's amide **4** into di-allyl product **6**, were unsuccessful. Polyallylation of the most reactive carbonyl group mainly took place (**22** and **24**, 24—32%, Scheme 6). Minor amount of the oxidative nucleophilic substitution product **23** was also observed [23].

CONCLUSIONS

A method was developed to enable the preparation of reactive pure vinylpyridylketones (e.g., **13**) from Weinreb's amides (e.g., **4**), including formation of a β-aminoketone (e.g., **14a-d**), quarternary ammonium intermediates (e.g., **15a-d**) and subsequent elimination. The utility of the reactive vinylketone **13** in further synthesis was demonstrated by the application in Diels-Alder cycloaddition with cyclopentadiene to give the *endo*-bicyclo[2.2.1]heptenyl product (**16**, 92% from **13**).

The transformation of pyridyl malonate derivative **2** *via* diester **3**, Weinreb's amide **4** and the reactive allylpyridylketone intermediate **6** into cyclization products was studied. The *in situ* formation of the cyclic aldol products **8** and **20** and the *O*-acylation hemiketal pyrano-compound **21** from diallylketone **6** took place. The analogous dimethyldiketone **17** formed, correspondingly, hemiketal **19** and the aldol cyclization product **18**, essential for the structure elucidation of the analogous products **8** and **21**.

EXPERIMENTAL

General. Solvents: pro analysi quality. Dry solvents were collected from a MB SPS-800 solvent purification system. All air and moisture sensitive reactions were performed under argon atmosphere in predried glassware. NMR: Bruker Avance DPX 300 and 400 MHz spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from TMS. *J* values are given in Hz. ms: Finnigan MAT 95 XL (ei/70 eV). ESI-MS accurate mass determination was performed on a waters QTOF II instrument. IR: Nicolet 20SXC FT-IR spectrophotometer. IR spectra were recorded using a Smart Endurance reflexion cell, unless KBr or film is specified. All melting points are uncorrected and were recorded on a Stuart apparatus. Flash chromatography: SiO_2 (sds, 60 Å, 40—63 μm). Dimethyl homochinchomeric acid diester (**3**) was prepared from methyl 3-nitro-4-pyridinecarboxylate (**1**) according to the ref. 3.

***N*-Methoxy-3-(2-(methoxy(methyl)amino)-2-oxoethyl)-*N*-methylisonicotinamide (Weinreb's amide 4).** MeONHMe·HCl (2.30 g, 23.6 mmol) in CH_2Cl_2 (80 mL) was cooled to 0°C and added Me_2AlCl (23.6 mL, 23.6 mmol, 1*M* in hexanes) dropwise. The mixture was stirred for 1.5 h before it was allowed to warm to room temperature. The diester **3** (990 mg, 4.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 8 h, and then quenched with a borate buffer (pH 8, 100 mL). After extraction with CH_2Cl_2 (3× 60 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (5% MeOH/CH_2Cl_2), the title compound **4** was obtained as a transparent oil, 938 mg (74%), pure by ^{1}H-NMR; IR (film): 3535, 2972, 2938, 1672, 1592, 1493, 1419, 1385, 1177, 998, 844 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.55 (s, 1H, H2), 8.52 (d, J = 4.8 Hz, 1H, py-H6), 7.33 (d, J = 4.8 Hz, 1H, py-H5), 3.93 (s, 2H, CH_2), 3.77 (s, 3H, CH_2—CO—N—O*CH*$_3$), 3.56 (s, br, 3H, py—CO—N—O*CH*$_3$), 3.26 (s, br, 3H, py—CO—N—*CH*$_3$), 3.14 (s, CH_2—CO—N—*CH*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 171.6 (CH_2—*C*=O), 168.2 (py—CH_2—*C*=O), 152.4 (C2), 148.1 (C6), 142.6 (C4), 128.5 (C3), 121.4 (C5), 61.8/61.4 (2× N—O*CH*$_3$), 34.0 (CH_2), 32.6 (2× N—*CH*$_3$); NMR assignments are based on HSQC and HMBC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{12}H_{18}N_3O_4$: 268.1297; observed 268.1293.

***N*-Methoxy-*N*-methylisonicotinamide (12).** The title compound was prepared as described above for Weinreb's amide **4**, using MeONHMe·HCl (1.09 g, 11.2 mmol) in CH_2Cl_2 (80 mL), Me_2AlCl (11.2 mL, 11.2 mmol, 1*M* in hexanes) and ester **11** (1.02 g, 7.44 mmol) in CH_2Cl_2 (10 mL). Product **12** was obtained after flash chromatography (2.5% CH_2Cl_2/MeOH) as a yellow oil (1.10 g, 89%), pure by NMR; R_f 0.15 (5% MeOH/CH_2Cl_2); IR: 2936w, 1644s, 1405m, 1382m, 980m, 832m, 702m, 630m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.71 (dd, 2H, J = 4.4, 1.6 Hz, H2/H6), 7.52 (dd, 2H, J = 4.4,

1.6 Hz, H3/H5), 3.54 (s, 3H, OMe), 3.36 (s, 3H, N—Me), ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 167.5 (C=O), 149.8 (C2, C6), 141.6 (C4), 121.9 (C3, C5), 61.3 (OMe), 33.0 (NMe); NMR assignments are based on HMBC and HSQC experiments ESI-HRMS: calcd. for $[M + H]^+$ $C_8H_{11}N_2O_2$: 167.0815; observed 167.0817.

1-(Pyridin-4-yl)prop-2-en-1-one (13). Amine **14b** (40 mg, 0.152 mmol) in $CDCl_3$ (5 mL) was added MeI (95 μL, 1.53 mmol) and stirred for 12 h at room temperature. The solution was washed with water (3× 3 mL) and dried over Na_2SO_4. Argon was bobbled through the solution to remove excess of MeI and the solution was used directly in the next step to form Diels Alder adduct **16**. Quantification was based on 1,2,4,5-tetrachlorobenzene as internal standard; **13** was obtained in 61% yield in a $CDCl_3$ solution, pure by NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.82 (dd, J = 4.4, 1.6 Hz, 2H, py—H2/H6); 7.70 (dd, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 7.07 (dd, J = 17.2, 10.8 Hz, 1H, CO—CH=), 6.48 (dd, J = 17.2, 1.2 Hz, 1H, =CH_aH$_b$), 6.01 (dd, J = 10.8, 1.2 Hz, 1H, =CH$_a$$H_b$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 190.5 (C=O), 150.8 (py—C2/C6), 143.3 (py—C4), 132.2 (—CH=), 131.7 (=CH_2), 121.6 (py—C3/C5); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ C_8H_8NO 134.0600; observed 134.0602.

***endo*-Bicyclo[2.2.1]hept-5-en-2-yl(pyridin-4-yl)methanone (16).** To the stirred solution of vinylketone **13** in $CDCl_3$ was added freshly distilled cyclopentadiene (100 μL) at −10°C. The reaction was stirred for 2 h and allowed to warm to room temperature. Evaporation of solvent and flash chromatography [EtOAc/pentane (1:1)] afforded product **16** as a white solid, 17 mg (56% from **14b**, 92% from **13**), mp: 59—60°C, pure by NMR; R_f 0.30 [EtOAc/pentane (1:1)]; IR: 2972w, 1681s, 1411m, 1227m, 1218m, 848s, 717s, 685s, 654s cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.80 (dd, J = 4.4, 1.6 Hz, 2H, py—H2/H6), 7.72 (dd, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 6.20 (dd, J = 5.6, 3.2 Hz, 1H, H5), 5.78 (dd, J = 5.6, 2.8 Hz, 1H, H6), 3.79 (app. dt, J = 8.8, 4.0 Hz, 1H, H2), 3.25 (app. br s, 1H, H1), 2.99 (app. br s, 1H, H4), 1.98 (ddd, J = 11.6, 8.8, 3.6 Hz, 1H, exo-H3), 1.62 (ddd, J = 11.6, 4.4, 2.4 Hz, 1H, endo-H3), 1.50 (m, 2H, H7); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 200.5 (C=O), 151.1 (py—C2/C6), 143.6 (py—C4), 137.9 (C5), 131.6 (C6), 121.5 (py—C3/C5), 50.2 (C7), 48.2 (C2), 47.1 (C1), 43.1 (C4), 29.0 (C3); NMR assignments are based on HSQC, HMBC, and NOESY experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{13}H_{14}NO$ 200.1070; observed 200.1065.

3-(Methoxy(methyl)amino)-1-(pyridin-4-yl)propan-1-one (14a). A solution of Weinreb's amide **12** (323 mg, 1.94 mmol) in dry THF (15 mL) was added vinylmagnesium bromide (3.89 mL, 3.89 mmol, 1*M* in THF) dropwise at −78°C under argon atmosphere. The reaction mixture was stirred for 60 min before it was allowed to warm to room temperature, and stirred for an additional 2 h. Quenching with an NH_4Cl solution (15 mL, sat.), extraction with EtOAc (3× 50 mL), drying over Na_2SO_4, evaporation of solvent and flash chromatography (5% MeOH/CH_2Cl_2) afforded product **14a** as a light brown oil, 263 mg (70%), pure by NMR; R_f 0.24 (5% MeOH/CH_2Cl_2); IR: 2938w, 1694s, 1408m, 1209m, 1045s, 991m, 787m, 656m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.82 (dd, J = 4.4, 1.6 Hz, 2H, py—H2/H6), 7.74 (dd, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 3.45 (s, 3H, OMe), 3.24 (t, J = 6.8 Hz, 2H, CO—CH_2), 3.08 (t, J = 6.8 Hz, 2H, CH_2—N), 2.62 (s, 3H, NMe); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 198.5 (C=O), 150.9 (py—C2/C6), 142.8 (py—C4), 121.0 (py—C3/C5), 59.8 (OMe), 55.2 (*C*H$_2$—N), 45.0 (N—Me), 36.6 (CO—*C*H$_2$); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{10}H_{15}N_2O_2$ 195.1128; observed 195.1126.

3-(Dibutylamino)-1-(pyridin-4-yl)propan-1-one (14b). A stirred solution of Weinreb's amide **12** (400 mg, 2.41 mmol) in dry THF (15 mL) at −78°C was added vinylmagnesium bromide (3.61 mL, 3.61 mmol, 1*M* in THF). The reaction was allowed to warm to room temperature and stirred for 1 h. Dibutylamine (4.1 mL, 24 mmol) was added to the mixture, followed by the dropwise addition of H_2O (1 mL) over 10 min. Addition of water (50 mL), extraction with diethyl ether (3× 30 mL), drying over Na_2SO_4, evaporation of solvent, and flash chromatography [4% Et_3N in EtOAc/pentane (1:2)] afforded the title compound **14b** as a pale yellow oil, 453 mg (72%), pure by NMR; R_f 0.24 [4% Et_3N in EtOAc/pentane (1:2)]; IR: 2955m, 2930m, 1694s, 1407m, 1220w, 773w, 655m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.81 (dd, J = 4.4, 1.6 Hz, 2H, py—H2/H6), 7.72 (dd, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 3.10 (t, J = 7.6 Hz, 2H, CO—CH_2), 2.90 (t, J = 7.6 Hz, 2H, CH_2—N), 2.43 (t, J = 7.2 Hz, 4H, Bu—H1), 1.39 (m, 4H, Bu—H2), 1.27 (m, 4H, Bu—H3), 0.90 (t, J = 7.2 Hz, 6H, Bu—H4); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 199.4 (C=O), 150.9 (py—C2/C6), 142.9 (py—C4), 121.0 (py—C3/C5), 53.8 (Bu—C1), 48.9 (*C*H$_2$—N), 37.0 (CO—*C*H$_2$), 29.2 (Bu—C2), 20.6 (Bu—C3), 14.0 (Bu—C4); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{16}H_{27}N_2O$ 263.2118; observed 263.2114.

3-(Piperidin-1-yl)-1-(pyridin-4-yl)propan-1-one (14c). The title compound was prepared as described above for **14b**, using Weinreb's amide **12** (106.6 mg, 0.641 mmol) in dry THF (5 mL), vinylmagnesium bromide (1.22 mL, 1.22 mmol, 1*M* in THF) and piperidine (1.21 mL, 12.2 mmol). Flash chromatography (5% MeOH/CH_2Cl_2) afforded the title compound **14c** as a pale brown oil, 124.5 mg (89%), pure by NMR; R_f 0.15 (5% MeOH/CH_2Cl_2); IR (film): 3044w, 2935s, 2852m, 2799m, 1697s, 1555w, 1408s, 735m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.81 (d, J = 4.4, 1.6 Hz, 2H, py—H2/H6), 7.73 (d, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 3.18 (t, J = 7.2 Hz, 2H, CO—CH_2), 2.79 (t, J = 7.2 Hz, 2H, CH_2—pip), 2.44 (s, 4H, pip—H2/H6), 1.58 (m, 4H, pip—H3/H5), 1.44 (m, 2H, pip—H4); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 198.9 (C=O), 150.9 (py—C2/C6), 142.8 (py—C4), 121.0 (py—C3/C5), 54,6 (pip—C2/C6), 53.4 (*C*H$_2$—pip), 36.8 (CO—CH$_2$), 25.9 (pip—C3/C5), 24.2 (pip—C4); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{13}H_{19}N_2O$: 219.1492; observed 219.1495.

3-(Morpholino)-1-(pyridin-4-yl)propan-1-one (14d). The title compound was prepared as described above for **14b**, using Weinreb's amide **12** (240 mg, 1.45 mmol) in dry THF (10 mL), vinylmagnesiumbromide (2.12 mL, 2.17 mmol, 1*M* in THF) and morpholine (1.26 mL, 14.5 mmol). After flash chromatography (10% MeOH/CH_2Cl_2), the title compound **14d** was obtained as a yellow oil, 229.3 mg (72%), pure by NMR; R_f 0.30 (10% MeOH/CH_2Cl_2); IR: 2953w, 2852w, 1694s, 1408m, 1114s, 988m, 870m, 769m, 663m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.82 (dd, J = 4.4, 1.6 Hz, 2H, py—H2/H6),

7.72 (dd, J = 4.4, 1.6 Hz, 2H, py—H3/H5), 3.70 (t, J = 4.4 Hz, 4H, morph-H2/H6), 3.19 (t, J = 7.2 Hz, 2H, CO—CH_2), 2.83 (t, J = 7.2 Hz, 2H, CH_2—N-morph), 2.50 (t, J = 4.0 Hz, 4H, morph-H3/H5); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 198.4 (C=O), 150.9 (py—C2/C6), 142.6 (py—C4), 120.9 (py—C3/C5), 66.8 (morph-C2/C6), 53.6 (morph-C3/C5), 53.0 (*C*H_2—N-morph), 36.3 (CO—*C*H_2); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{12}H_{17}N_2O_2$ 221.1285; observed 221.1288.

7-Methylisoquinolin-5-ol (18). To a stirred solution of Weinreb's amide **4** (60.0 mg, 0.224 mmol) in dry THF at −78°C MeMgBr (1.0 mL, 1.0 mmol, 1*M* in butyl ether) was added dropwise. The reaction was allowed to heat to room temperature and stirred for 2 h. Then, EtOAc (10 mL), brine (10 mL), and H_2O (5 mL) were added. After extraction with EtOAc (3× 10 mL), the combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. An aqueous solution of Na_2CO_3 (15 mL, sat.) was added to the brown oil and the mixture was stirred over night. Extraction with EtOAc (3× 10 mL), drying over Na_2SO_4, concentration under reduced pressure and flash chromatography (gradient; 2.5—5% MeOH/CH_2Cl_2) gave the title compound **18** as a white solid, 20 mg (56%), mp > 215°C (decomp), pure by NMR; R_f 0.18 (5% MeOH/CH_2Cl_2); IR: 3400—2400br, 1588m, 1396s, 1350m, 1281s, 1037m, 832s cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 10.39 (s, 1H, OH), 9.10 (s, 1H, H1), 8.36 (d, J = 5.6 Hz, 1H, H3), 7.84 (d, J = 5.6 Hz, 1H, H4), 7.30 (s, 1H, H8), 6.93 (s, 1H, H6), 2.43 (s, 3H, —CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_C 152.1 (C5), 151.1 (C1), 141.1 (C3), 137.7 (C7), 129.5 (C8a), 125.3 (C4a), 116.6 (C8), 114.8 (C4), 113.9 (C6), 21.6 (—CH_3); NMR assignments are based on HMBC, HSQC, and NOESY experiments; ESI-HRMS: calcd. for $[M + H]^+$ $C_{10}H_{10}NO$ 160.0757; observed 160.0759.

1,3-Dimethyl-1*H*-pyrano[4,3-c]pyridin-1-ol (19). A solution of Weinreb's amide **4** (36 mg, 0.14 mmol) in dry THF (2 mL) was added methylmagnesium bromide (0.4 mL, 0.4 mmol, 1*M* in butyl ether) dropwise at −78°C. The reaction mixture was allowed to heat to room temperature and stirred for 3 h before a solution of NH_4Cl (10 mL) was added. The aqueous solution was extracted with diethyl ether (3× 15 mL). After drying over Na_2SO_4, evaporation of solvent and flash chromatography (2.5% MeOH/CH_2Cl_2), the title compound **19** was obtained as a yellow oil, 15 mg (64%), pure by NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.20 (s, 1H, py—H2), 8.63 (d, J = 5.6 1H, py—H6), 7.81 (d, 1H J = 5.6 Hz, py—H5), 7.45 (s, 1H, pyran—C*H*=C), 2.94 (s, 3H, CH_3), 2.71 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 158.0/152.4/131.2/127.4 (py—C3, —C4, pyran—C1, —C3), 151.9 (py—C2), 143.7 (py—C6), 117.6 (py—C5), 115.5 (pyran—*C*H=), 24.4 (Me), 21.7 (Me); NMR assignments are based on HMBC and HSQC experiments; ESI-HRMS: calcd. for $[M + H]^+$ $H_2O{\cdot}C_{10}H_{10}NO$ 160.0757; observed 160.0758.

Preparation of 8, 20, and 21. A solution of Weinreb's amide **4** (355 mg, 1.328 mmol) in dry THF (5 mL) was cooled to −78°C, and allylmagnesium bromide (3.45 mL, 3.45 mmol, 1*M* in ether) was added dropwise. The reaction was stirred for 2 h at −78°C and allowed to heat to room temperature. NH_4Cl (15 mL, sat.) was added and the mixture was extracted with EtOAc (3× 40 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography [EtOAc/pentane (1:1)] allowed the isolation of compounds **8**, **20**, and **21**.

7-Allyl-6-vinylisoquinolin-5-ol (8). The title compound **8** was obtained as a yellow oil, 31 mg (11%), pure by ^{1}H-NMR; R_f 0.26 [EtOAc/pentane (1:1)]; IR (KBr): 3074w, 2976w, 2922w, 2800w br, 1623m, 1579s, 1566m, 1394s, 1260s, 1180s, 1038s, 1024m, 921s, 847m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.12 (s, 1H, H1), 8.49 (d, J = 5.6 Hz, 1H, H3), 7.95 (d, J = 5.6 Hz, 1H, H4), 7.35 (s, 1H, H8), 6.84 (dd, J = 18.4, 11.6 Hz, 1H, vinyl; C*H*=CH_2), 6.31 (br s, 1H, OH), 6.01 (m, 1H, allyl; C*H*=CH_2), 5.88 (dd, J = 11.6, 1.6 Hz, 1H, vinyl; CH=CH_aH$_b$), 5.71 (dd, J = 18.4, 1.6 Hz, 1H, vinyl; CH=CH_aH$_b$), 5.14 (m, 1H, allyl; CH=CH_aH$_b$), 5.04 (m, 1H, allyl; CH=CH_aH$_b$), 3.49 (m, 2H, allyl —CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 151.3 (C1), 147.3 (C5), 142.2 (C3), 137.8 (C7) 135.8 (allyl; *C*H=), 132.1 (vinyl; *C*H=), 128.5 (C8a), 125.7 (C4a), 122.4 (vinyl; =*C*H_2), 122.2 (C6), 118.5 (C8), 116.8 (allyl; =*C*H_2), 115.4 (C4), 38.2 (allyl; *C*H_2—); NMR assignments are based on NOESY, HSQC, and HMBC experiments; EI-MS: m/z 212 (M^+, 100%).

7-Allyl-6-ethylidene-7-hydroxy-7,8-dihydroisoquinolin-5(6H)-one (20). The title compound **20** was obtained as a red solid 80 mg (26%), pure by ^{1}H-NMR; R_f 0.20 [EtOAc/pentane (1:1)]; IR (KBr): 3400br, 3074w, 2931w, 1678s, 1615m, 1416s, 1354m, 1247m, 1067m, 917m, 846m, 729m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.65 (d, J = 5.2 Hz, 1H, H3), 8.60 (s, 1H, H1), 7.84 (d, J = 5.2 Hz, 1H, H4), 6.63 (q, J = 7.2 Hz, 1H, =C*H*—CH_3), 5.85—5.73 (m, 1H, C*H*=CH_2), 5.19 (m, 1H, allyl =CH_aH$_b$), 5.06 (m, 1H, allyl =CH_aH$_b$), 3.16 (br s, 1H, H8; CH_aH$_b$), 3.15 (br s, 1H, H8; CH_aH$_b$), 2.4—2.2 (m, 2H, allyl—CH_2), 2.17 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 188.5 (C=O), 150.9 (C1), 148.7 (C3), 140.9/138.7/133.3 (C4a, C6, C8a), 137.9 (=C*H*—CH_3),132.1 (allyl—C*H*=CH_2), 120.4/119.6 (C4, allyl =*C*H_2), 74.6 (C7), 43.9 (allyl—CH_2—CH=), 39.7 (C8), 15.8 (=CH—CH_3); NMR assignments are based on HSQC and HMBC experiments.

1,3-Diallyl-1H-pyrano[4,3-c]pyridin-1-ol (21). The title compound **21** was obtained as a yellow oil, 20 mg (6%), pure by ^{1}H-NMR. Product **21** was, correspondingly, obtained in 21% by addition of a precooled NH_4Cl solution to the reaction mixture kept at −78°C. R_f 0.40 [EtOAc/pentane (1:1)]; IR (film): 3404br, 3076w, 2977w, 2918w, 1744w, 1638m, 1618w, 1572s, 1481m, 1427w, 1376w, 1152w, 995m, 915s, 859m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.24 (s, 1H, py—H2), 8.62 (d, J = 6.0 Hz, 1H, py—H6), 7.85 (d, J = 6.0 Hz, 1H, py—H5), 7.49 (s, 1H, pyrano—H4), 6.2—6.1 (m, 2H, 2× allyl C*H*=CH_2), 5.25—5.15 (m, 4H, 2× allyl CH=CH_2), 4.07 (m, 2H, 1-pyrano-allyl; CH(OH)—CH_aH$_b$—CH=), 3.77 (m, 2H, 3-pyrano-allyl; =C—CH_aH$_b$=CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.2/154.6/131.5/127.4 (py—C3, —C4, pyran—C1, —C3), 152.3 (py—C2), 143.9 (py—C6), 135.5/135.0 (2× allyl —CH=), 117.4 (py—C5), 117.2/117.1 (2× allyl=*C*H_2), 115.5 (pyran—*CH*=C), 42.5 (3-pyran-allyl; =C—*C*H_2—CH=), 39.9 (1-pyran-allyl; CH(OH)—*C*H_2—CH=); NMR assignments are based on HSQC and HMBC experiments.

Formation of 8 by isomerization of 20. An NMR sample of **20** (10 mg) in $CDCl_3$ was added crystalline *p*-TsOH (2 mg) and left at room temperature. The isomerization was monitored by ^{1}H-NMR and TLC. Full conversion of **20** into **8**, pure by ^{1}H-NMR, was obtained after 10 h.

7-Allyl-6-(1-methoxyethyl)isoquinolin-5-ol (20′). A sample of **20** (20 mg, 0.08 mmol) in MeOH (5 mL) was added crystalline NaOMe (~30 mg) and stirred over night at room temperature. Quenching with an NH_4Cl solution (15 mL), extraction with EtOAc (3× 20 mL), drying over Na_2SO_4, and evaporation of solvent afforded product **20′** (20 mg, 98%), pure by NMR; IR (film): 3271br, 2928s, 1635m, 1581s, 1462m, 1403s, 1286m, 1109m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.26 (br s, OH), 9.15 (s, 1H, H1), 8.50 (br s, 1H, H3), 8.00 (br s, 1H, H4), 7.29 (s, 1H, H8), 6.0—6.1 (m, 1H, allyl—CH=), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1H, allyl=C*H*$_a$H$_b$), (d, *J* = 17.2, 1.6 Hz, 1H, allyl—CH$_a$*H*$_b$), 4.91 (q, *J* = 6.8 Hz, 1H, C*H*—OMe), 3.48 (d, *J* = 5.6 Hz, 2H, allyl—CH_2), 3.41 (s, 3H, OMe), 1.58 (d, *J* = 6.8 Hz, 1H, CH—*Me*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 150.9 (C1), 141.9 (C3), 136.5 (allyl—CH=), 151,2/136.6/129.0/127.2/122.6 (C4a, C5, C6, C7, C8a), 119.2 (C8), 116.9 (allyl=CH_2), 115.1 (C4), 78.0 (*C*H—OMe), 57.4 (OMe), 37.4 (allyl—CH_2—), 20.8 (Me); NMR assignments are based on HSQC and HMBC experiments.

Preparation of 22, 23, and 24. A solution of diester **3** (300 mg, 1.44 mmol) and Me(MeO)NH·HCl (330 mg, 3.3 mmol) in dry THF (30 ml) at −5°C was added allylMgCl (6 mL, 12 mmol, 2*M* in THF) over 2 h. The reaction mixture was kept stirring for 20 h, and then HCl (10 mL, 10%) was added. pH 9 was obtained by addition of a $NaHCO_3$ solution. The products **22** (94 mg, 26%), **23** (12 mg, 3%), and **24** (108 mg, 24%) were isolated by extraction and flash chromatography [EtOAc/pentane (1:6)]. Correspondingly, only product **22** (32%) was isolated from an experiment carried out at −15°C for only 2 h, using **3** (200 mg, 0.95 mmol), Me(MeO)NH·HCl (220 mg, 2.2 mmol), and allylMgCl (1.1 mL, 2.2 mmol, 2*M* in THF) in dry THF (30 mL).

1-(3-(2-Allylpenta-1,4-dienyl)pyridin-4-yl)but-3-en-1-one (22). *^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.31 (d, J* = 5.2 Hz, 1H, py—H6), 8.15 (s, 1H, py—H2), 6.81 (d, *J* = 5.2 Hz, 1H, py—H5), 5.88 (m, 1H, C*H*=CH_2), 5.72 (m, 1H, 4-py-side-chain; C*H*=CH_2), 5.52 (s, 2H, 3-py-side-chain; 2× CH=C), 5.20 (m, 1H, 4-py-side-chain; =CH*H*), 5.16 (m, 1H, 4-py-side-chain; =CH*H*), 5.07 (m, 2H, 3-py-side-chain; =CH*H*), 5.06 (m, 1H, 3-py-side-chain; =CH*H*), 5.03 (m, 1H, 3-py-side-chain; =CH*H*), 2.92 (dd, *J* = 6.0, 1.2 Hz, 2H, 4-py-side-chain; C—CH_2), 2.65 (dd, *J* = 7.2, 1.0 Hz, 4H, 3-py-side-chain; 2× C—CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 156.2 (C=O), 148.3 (py—C6), 144.9 (py—C2), 140.1 (py—C4), 133.4 (4-py-side-chain; *C*H=C), 133.2 (3-py-side-chain; 2× *C*H=C), 127.8 (py—C3), 120.1 (py—C5), 119.3 (3-py-side-chain; 2× *C*H_2=C), 118.5 (4-py-side-chain; *C*H_2=C), 96.3 (3-py—*C*H=), 81.8 (3-py—CH=*C*), 42.6 (3-py-side-chain; 2× *C*H_2—CH=CH_2), 38.8 (4-py-side-chain; *C*H_2—CH=CH_2); NMR assignments are based on APT, HMBC, and HSQC experiments; EI-MS: *m/z* 253 (M^+, 4%), 212 (100), 193 (9), 170 (14), 167 (9), 154 (8), 142 (33), 130 (8), 115 (17); EI-HRMS: calcd. for $C_{17}H_{19}NO$; 253.1467; observed 253.1469.

1-(2-Allyl-3-(2-allylpenta-1,4-dienyl)pyridin-4-yl)but-3-en-1-one (23). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.27 (d, *J* = 4.8 Hz, 1H, py—H6), 6.72 (d, *J* = 4.8 Hz, 1H, py—H5), 6.04 (m, 1H, C*H*=CH_2), 5.90 (m, 1H, C*H*=CH_2), 5.73 (m, 2H, 2× C*H*=CH_2), 5.60 (s, 1H, 3-py—CH=C), 5.22 (m, 1H, =CH*H*), 5.17 (m, 1H, =CH*H*), 5.13 (m, 1H, =CH*H*), 5.09 (m, 1H, =CH*H*), 5.07 (m, 2H, 2× =CH*H*), 5.04 (m, 1H, =CH*H*), 5.02 (m, 1H, =CH*H*), 3.56 (d, *J* = 7.0 Hz, 2H, 4-py-side-chain, C—CH_2), 2.94 (d, *J* = 6.0 Hz, 2H, 2-py-side-chain, C—CH_2), 2.64 (d, *J* = 8.0 Hz, 4H, 3-py-side-chain; 2× C—CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.6 (C=O), 152.1 (py—C2), 146.3 (py—C6), 139.9 (py—C4), 135.6 (4-py-side-chain; *C*H=C), 133.2 (2-py-side-chain; *C*H=C), 129.8 (3-py-side-chain; 2× *C*H=C), 125.3 (py—C3), 119.3 (3-py-side-chain; 2× *C*H_2=C), 118.5 (py—C5), 118.4 (2-py-side-chain; *C*H_2=C), 118.4 (4-py-side-chain; *C*H_2=C), 96.5 (3-py—*C*H=), 81.6 (3-py—CH=*C*), 42.4 (3-py-side-chain; 2× *C*H_2—CH=CH_2), 38.8 and 39.2 (2- and 4-py-side-chain; *C*H_2—CH=CH_2); NMR assignments are based on HMBC experiments; EI-MS: *m/z* 293 (M^+, 3%), 268 (2), 252 (100), 234 (3), 210 (5), 167 (9), 154 (5); EI-HRMS: calcd. for $C_{20}H_{23}NO$; 293.1780; observed 293.1764.

4-(3-(2-Allyl-2-hydroxypent-4-enyl)pyridin-4-yl)hepta-1,6-dien-4-ol (24). IR: 3346m, 3000s (br), 3071w, 2976w, 2924w, 2840w 1640s, 1598s, 1490w, 1438s, 1405s, 1270s, 1150m, 1075m, 1045s, 987s, 912s, 845m cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.36 (d, *J* = 5.2 Hz, 1H, py-H6), 8.27 (s, 1H, py-H2), 7.06 (d, *J* = 5.2 Hz, 1H, py-H5), 5.86 (m, 2H, 3-py-side-chain; 2× C*H*=CH_2), 5.68 (m, 2H, 4-py side-chain; 2× C*H*=CH_2), 5.38 (s, br, 1H, 3-py side-chain; OH), 5.21 (m, 1H, 3-py-side-chain; =CH*H*), 5.19 (m, 1H, 3-py-side-chain; =CH*H*), 5.18 (m, 1H, 3-py-side-chain; =CH*H*), 5.16 (m, 1H, 3-py-side-chain; =CH*H*), 5.02 (m, 2H, 4-py side-chain; 2× =CH*H*), 5.00 (m, 1H, 4-py-side-chain; =CH*H*), 4.98 (m, 1H, 4-py-side-chain; =CH*H*), 3.26 (s, 2H, 3-py—CH_2), 2.77 (s, br, 1H, 4-py side-chain; OH), 2.65 (dd, *J* = 14.0, 7.2 Hz, 2H, 4-py side-chain; 2× CH*H*), 2.54 (dd, *J* = 14.0, 7.6 Hz, 2H, 4-py side-chain; 2× CH*H*), 2.38 (dd, *J* = 14.0, 7.2 Hz, 2H, 3-py side-chain; 2× CH*H*), 2.23 (dd, *J* = 14.0, 7.6 Hz, 2H, 3-py side-chain; 2× CH*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.1 (py—C2), 154.4 (py—C4), 147.5 (py—C6), 133.4 (4-py-side-chain; 2× *C*H=C), 133.2 (3-py-side-chain; 2× *C*H=C), 131.0 (py—C3), 122.6 (py—C5), 119.9 (3-py-side-chain; 2× *C*H_2=C), 119.0 (4-py-side-chain; 2× *C*H_2=C), 78.4 (4-py—*C*—OH), 73.8 (3-py—CH_2—*C*—OH), 48.1 (3-py-side-chain; 2× *C*H_2—CH=CH_2), 43.9 (4-py-side-chain; 2× *C*H_2—CH=CH_2), 39.6 (3-py—*C*H_2); NMR assignments are based on APT, HMBC, and HSQC experiments and D_2O exchange; ms: *m/z* 313 (M^+, 22%), 273 (8), 246 (10), 186 (57), 171 (18), 157 (29), 127 (31), 125 (83), 91 (34), 44 (100).

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