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α-(3-Pyridyl)malonates: preparation and synthetic applications

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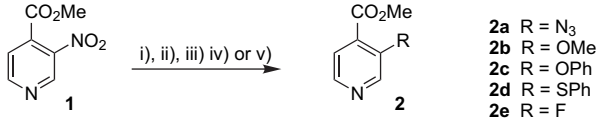
Abstract—Alkylation of aromatic rings is a major challenge in organic syntheses since more complex carbon skeletons can be constructed. The alkylation of pyridine by nucleophilic aromatic substitution of the nitro group in methyl 3-nitro-4-pyridylcarboxylate (**1**) with malonic ester is reported. The versatility of the α-(3-pyridyl) malonic ester product (**3**) is demonstrated by the formation of a number of new 3-alkylated pyridines and new fused bis-heterocycles. *cis* 2-Halomethyl-4-(3-pyridyl)tetrahydrofuran products were selectively prepared. Exact ^{1}H and ^{13}C NMR assignments of practically all products were obtained by a series of NMR experiments.

1. Introduction

As a general fact, aromatic substrates are very unreactive towards nucleophilic substitution. However, substitution is accelerated by electron-withdrawing groups *ortho* or *para* to the leaving group. A nitrogen atom in the ring is also activating. Surprisingly, the nitro group, which is not generally lost in aliphatic systems, is a particularly good leaving group in nucleophilic aromatic substitutions.[1,2]

These effects and the synthetic potential for the replacement of a nitropyridine group have been demonstrated by our results for the nucleophilic aromatic substitution of the nitro group in 3-nitro-4-carboxylate (**1**) since the pyridyl aromatic system in combination with the anion stabilising carbonyl group in *ortho* position makes the 3-nitro substituent a good leaving group. We have previously obtained promising results from the nucleophilic aromatic substitution of the nitro group in methyl 3-nitropyridyl carboxylate **1** by heteroatom nucleophiles, see below.[3] Oxygen, nitrogen, sulfur and fluoride nucleophiles were tested to yield the new products **2a**–**e**.



i) NaN_3 ii) MeOH, NaH iii) PhOH, NaH iv) PhSH, NaH v) CsF, DMSO

Based on the fact that a number of substituted 3-nitropyridines have been readily available through an improved nitration method,[4] an investigation of the chemistry of nitropyridines is now in progress in our laboratories.

The formation of new C–C bonds is a major challenge in organic syntheses since more complex carbon skeletons can be constructed. Alkylation of aromatic rings is therefore an important transformation. The classical malonate arylation is based on the α-arylation of malonic esters followed by hydrolysis and decarboxylation. Activated aryl halides like nitroaryl halides generally give good results. Correspondingly, copper catalysed[5] and palladium catalysed α-arylation of malonic esters[6] have been reported.

Based on our experience with the useful leaving group ability of the nitro group in carboxylate **1**, we have investigated 3-nitropyridyl carboxylate (**1**) as a potential substrate for malonate arylation. The versatility of the α-(3-pyridyl) malonic ester product (**3**) is hereby demonstrated by the formation of new 3-alkylpyridines (**5**–**10**, **16**), and new bis-heterocycles (**11a**, **11b**, **13**, **14**, **15**). *cis* 2,4-(3-Pyridyl)tetrahydrofurano products (**17a**, **17b**) were prepared from the decarboxylated allyl bromide product **8**. Our results are discussed below.

2. Results and discussion

2.1. α-(3-Pyridyl) malonic esters

We have succeeded in carrying out for the first time, the nucleophilic aromatic substitution of the pyridine nitro group in 3-nitropyridyl carboxylate (**1**) with a carbon nucleophile. We thus obtained the methyl α-(3-pyridyl) malonic esters (**3a**, see Scheme 1) in 55% yield by nucleophilic aromatic substitution of **1** with dimethyl malonate and Cs_2CO_3. The ethyl ester product (**3b**) was prepared (24%) by diethyl malonate and NaH. The general experience was that a higher

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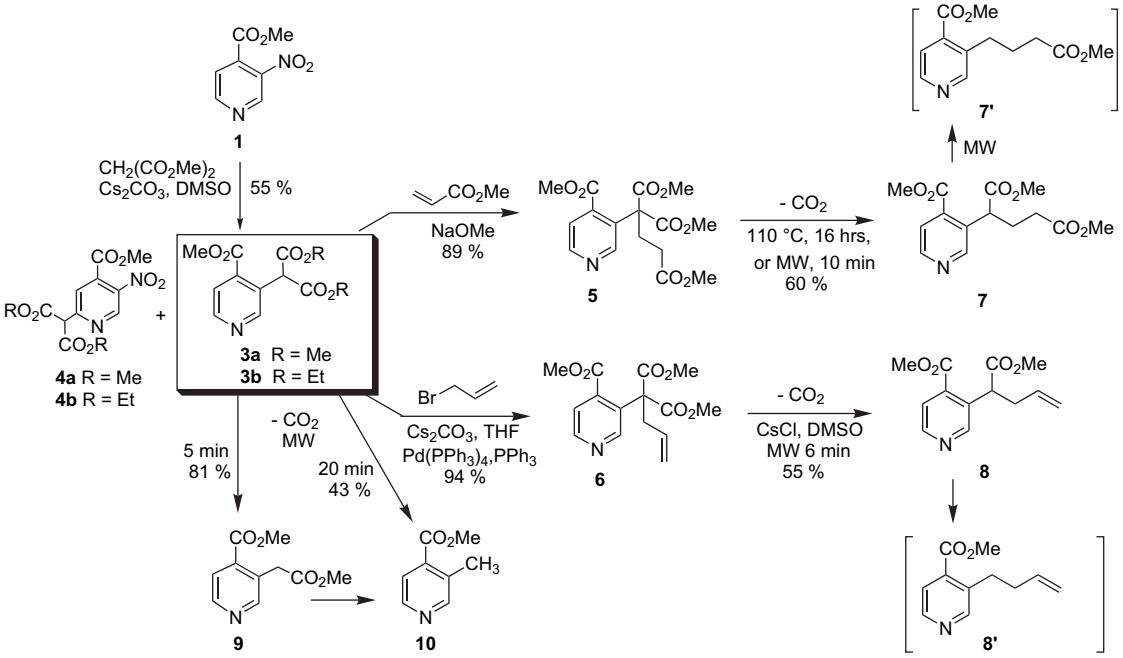


Scheme 1.

yield of **3b** would be expected by using Cs_2CO_3 as a base. Additionally, the formation of minor amounts of the 6-substituted products **4a** and **4b** could be observed. These products may be formed by oxidative nucleophilic substitution, a reaction that is well known for nitroarenes and nucleophiles.[7]

2.2. 3-Alkylpyridines

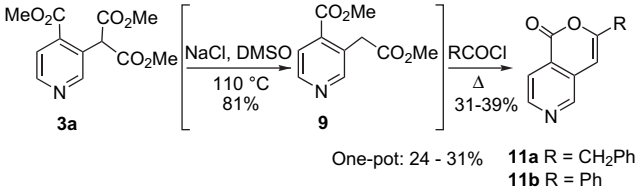
3-Alkylpyridines are related to nicotinic acid (niacin) and nicotinamide, the essential component in the pyridine nucleotides, the NAD and NADP coenzymes. A series of 3-alkylated pyridine compounds have previously been studied for their pharmacological activity. We have used the pyridylmalonate (**3a**) as a key intermediate for the preparation of a series of new 3-alkylpyridines.

Alkylation of the malonic ester **3a** by a Michael addition with methyl acrylate afforded the tetraester intermediate **5** in 89% yield, while the allylproduct **6** was obtained in 94% yield by the Pd catalysed reaction with allyl bromide. Similar allyl bromide reactions are known to afford considerably lower yields without palladium catalysis.[8] The following decarboxylation of **5** and **6** gave the 3-pyridylalkylated products **7** and **8**. Depending on the temperature, similar decarboxylation reactions have been reported to give mono- or di-decarboxylated products, selectively.[9] We did not observe any formation of the di-decarboxylation products **7′** and **8′** after 16 h heating at 110 °C.

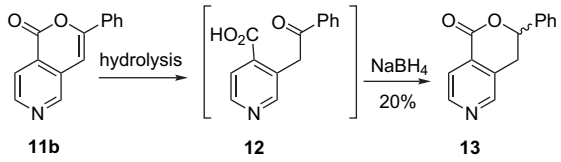
Recent development in microwave-accelerated (MW) organic syntheses has shown that the method offers the great advantage of enhanced reaction rates. The products are often produced in increased yields and in higher purity by such reactions compared to conventional heating methods. We have experienced that MW irradiation has been successful for a number of reactions.[10] In this work, MW promoted decarboxylation reactions were successful and afforded higher yields of **7** and **8** than conventional heating. For the conversion of the tetraester **5** to the triester **7** (60%) the reaction time was drastically reduced from 16 h to 10 min (360 W). Correspondingly, the decarboxylation of **6** to **8** (55%) was carried out in 6 min by MW irradiation (360 W). In contrast to conventional heating, minor amounts of additional products were also isolated. Based on NMR and GC–MS, the new by-products were supposed to be the di-decarboxylated compounds **7′** and **8′**, respectively. MW decarboxylation of the malonic ester intermediate **3a** similarly afforded homochinchomeric acid dimethyl ester (**9**)[11] in 81% yield in 5 min. Irradiation (90 W) of **3a** for 10 min gave a mixture of **9** (34%) and methyl 3-methyl-4-pyridylcarboxylate (**10**, 17%). However, the di-decarboxylated product **10** was the single product after 20 min irradiation and was readily isolated (43%). The decarboxylation products **9**/**10** were never obtained by conventional heating.

2.3. Bis-heterocycles

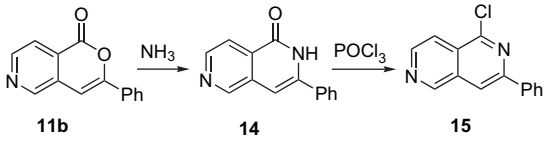
The pyridylmalonate (**3a**) and homochinchomeric acid dimethyl ester (**9**) were key precursors for the preparation of a number of new ring closure products (**11a**, **11b**, **13**, **14**, **15**, **17a**, **17b**), as shown in Schemes 2–5.



Scheme 2.



Scheme 3.



Scheme 4.

An one-pot preparation of the vinylic δ-lactone products **11a/11b** by direct condensation of pyridylmalonate (**3a**) with benzoyl and phenylacetyl chloride and subsequent cyclisation afforded 3-benzyl- and 3-phenyl-pyrano[4,3-*c*]pyridin-1-one (**11a**, **11b**, see Scheme 2) in 24 and 31% yields, respectively. A step-wise procedure was also successful, giving corresponding total yields (25, 32%) but also easier work-up and product isolation compared to the direct condensation of **9** with acyl chloride. The step-wise yields are given in Scheme 2. A similar strategy has been applied, using homophthalic acid, for the preparation of natural products and compounds with biological activity.[12–17] The 3-substituted pyrano[4,3-*c*]pyridin-1-ones (**11a**, **11b**) are *N*-heterocyclic isocoumarin analogues. Similar products have previously been prepared from halopyridines by palladium-catalysed cross-coupling reactions.[18,19]

An one-pot alkaline hydrolysis, hydride reduction and cyclodehydration of **11b** gave the saturated δ-lactone, 3,4-dihydro-1*H*-pyrano[4,3-*c*]pyridin-1-one (**13**, 20%). The reaction proceeds through the 3-(2-oxo-2-phenylethyl)-4-pyridinecarboxylic acid (**12**) intermediate and the reduction product of **12**, which underwent spontaneous cyclisation to **13** (Scheme 3).[15,20]

Several multi-step syntheses of 2,6-naphthyridine (**15**) have been described.[11,21,22] Based on our simple three-step synthesis of homochinchomeric acid (**9**) from methyl 4-pyridinecarboxylate,[3,4] a new procedure is proposed for the preparation of 2,6-naphthyridine derivative (**15**, see Scheme 4).

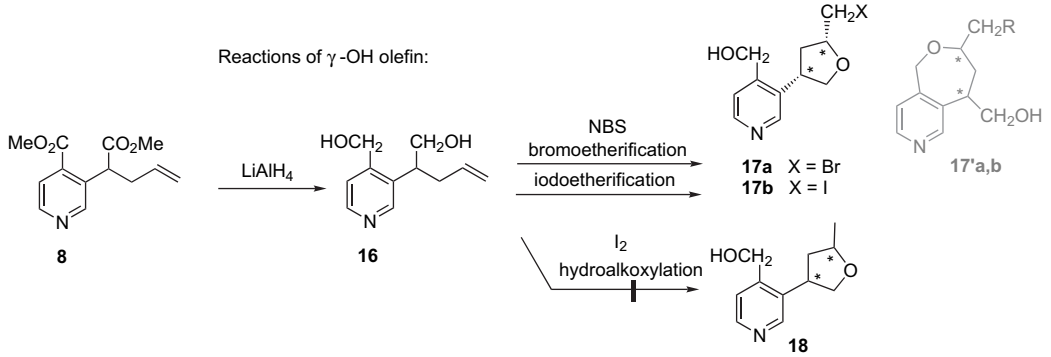
The preparation of the 2,6-naphthyridine derivative **15** includes the amination of the isocoumarine analogue (**11b**) for the formation of 3-phenyl-2,6-naphthyridin-1(2*H*)-one (**14**).[23] We obtained the 2,6-naphthyridin-1(2*H*)-one (**14**) in 43% yield from **11b** and NH_3 and prepared the 2,6-naphthyridine derivative (**15**) (49%) from **14** by $POCl_3$ reaction.[24] The chloro substituent may be removed by hydrogenation or used in subsequent transformations such as amination or palladium catalysed cross-coupling reactions. 1-Halo-2,6-naphthyridines forms α-adducts at C-1 with KNH_2/NH_3 and the method has been used for the preparation of 1-amino-2,6-naphthyridines.[25] The reaction represents an alternative to Chichibabin amination to prepare 1-amino derivatives.[21] 1-Halo-2,6-naphthyridines can now readily be prepared by the present procedure via pyridylmalonate (**3a**). Non-substituted 2,6-naphthyridin-1(2*H*)-one has previously been prepared by cyclisation of 4-pyridylnitrile derivatives[21] or by palladium catalysed cross-coupling reactions.[26]

2.4. Pyridyltetrahydrofurans

Tetrahydrofurans are in general used as intermediates in synthesis of biologically active compounds and the ring system is found in many naturally occuring compounds. Being nicotine-related compounds, the 3-alkylpyridyl systems are of special interest. 5-(3-Pyridyl)tetrahydrofuran-2-yl analogues have been studied as drug candidates and as modulators of smoking or nicotine ingestion and lung cancer.[33] 2-(Aminomethyl)-5-(2-pyridyl)tetrahydrofurans have been patented for treating of central nervous system disorders,[34] while 2-(aminomethyl)-4-phenyltetrahydrofurans are used in the preparation of agrochemical fungicides[35] and have been studied as potential antidepressants.[36]

The decarboxylated allyl bromide product **8** was used as substrate for the preparation of the tetrahydrofuran ring closure products **17a** and **17b**, as shown in Scheme 5.

Hydride reduction of **8** afforded the diol **16** (51%). Compound **16** is a γ-hydroxyolefin and underwent NBS bromoetherification to give the brominated 5-ring cyclic ether product (**17a**) in 40% yield. This bromoetherification method has previously been used for the preparation of small and medium-sized cyclic bromomethyl ethers.[27] Due to the presence of two primary alcohol groups in substrate **17**, theoretically, either the 5-ring (**17a**) or the 7-ring product (**17′a**)

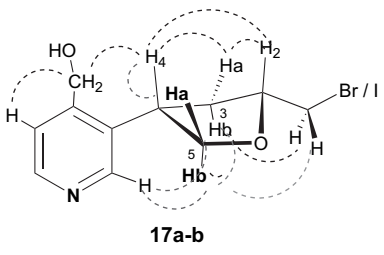


Scheme 5.

could be formed. Neither of the products (**17a**, **17′a**) could be excluded from the ^{1}H and ^{13}C NMR spectra, but HSQC and HMBC experiments showed that the most favourable 5-ring ether product **17a** was formed. A displacement of the halide in **17a** with alkylamine would give the corresponding 2-(aminomethyl)-5-(2-pyridyl)tetrahydrofuran, a well known structural moiety in pharmaceuticals.[34–36]

A second chiral centre is formed by the tetrahydrofuran ring closure. Only one single diastereomer was formed, as shown by NMR. The ring configuration was studied by NOESY NMR experiments. The observed strong interactions between the tetrahydrofuran protons H-2 and H-4, H_a-3 and H-2, H_a-3 and H-4 indicated that a *cis* ring closure had taken place (see Fig. 1). Additional confirmation of the *cis* ring configuration is based on a series of observed NOESY interactions between H-4/H_a-5, H_b-3/H_b-5, H_b-3/CH_2Br and H_b-5/CH_2Br. *cis* H-2/H-4 was stronger than the H_b-3/H_b-5 NOESY interaction, indicating a closer proximity between H-2 and H-4 ('axial') than H_b-3 and H_b-5 ('semi-axial') in the five-membered ring. As a consequence, the *cis* H_a-3 and H_a-5 would be 'equatorial' and thus explain the absence of a NOESY interaction between them. The *cis* configuration was also supported by the absence of any NOESY interaction between H-4 and CH_2Br. A *trans* ring configuration may have been demonstrated by a possible NOESY interaction between H-4 and the protons of the bromomethyl substituent in the 2-position. Interactions between the pyCH_2OH group and H-4 as well as pyridine-H-2 and H_b-3 and H_b-5, respectively, indicate the conformation shown below.

It is well known that γ-hydroxyolefins can undergo hydroalkoxylation by I_2 catalysis.[28] However, for non-sterically hindered double-bonds using stoichiometric amounts of iodine, the competing reaction would be iodoetherification. The two alternative products for substrate **16** would therefore be the 2-methyltetrahydrofuran product **18** or the iodomethyl product **17b**. The outcome of the reaction was that no hydroalkoxylation had taken place, explained by the lack of steric hindrance of the substrate double-bond. Thus the iodo-substituted product **17b** (24%) was isolated and the 7-ring product (**17′b**) was not observed. Hydroalkoxylation may also be carried out with Pt catalysis.[29] However, no 2-methyltetrahydrofuran product (**18**) was obtained by this method either. Except for the predicted effects of the iodine, in particular the characteristic low ^{13}C NMR frequency of the CH_2I carbon (δ 9.4), all NMR data (^{1}H, ^{13}C NMR, HSQC, HMBC) of the iodoproduct **17b** were in accordance with the corresponding data for the bromoproduct **17a**. Detailed NOESY NMR studies of **17b** were also in exact agreement with the data for **17a** discussed above.



17a-b

Figure 1.

Consequently, all the identical NOESY interactions for **17a** and **17b** indicate that both the tetrahydrofuran rings are formed by *cis* ring closure and that the cyclisations for the formation of products **17a** and **17b** are proceeding through similar reaction mechanisms and intermediates. The tetrahydrofuran moiety may be prepared via the bromonium/iodonium ion intermediate followed by an *exo-tet* ring closure. The direct *exo-trig* alcohol intramolecular attack on the double bond by addition of the halide electrophile would represent an alternative mechanism. Radical photochemical mechanisms are reported as well.[30] 2,4-Disubstituted tetrahydrofurans have been reported to be formed by cyclisation reactions as 5:1 mixtures of *cis*/*trans* iodo- and bromomethyl diastereomers.[31] Computational and experimental studies have shown that 5-*exo-trig* cyclisations of sterically hindered 4-penten-1-oxyl radicals form diastereomeric mixtures, but *cis* 2,4-disubstituted tetrahydrofurans are the major products.[32] To the best of our knowledge, there are no reports on diastereospecific formation of single *cis* 2,4-disubstituted tetrahydrofurans.

The observed selective *cis* ring closures would proceed through *cis* intermediates to give the single *cis* products, having both large groups (pyridyl and CH_2X) at the same side of the new tetrahydrofuran ring. This *cis* configuration would be favoured, since the least steric hindrance can be obtained by a di-equatorial arrangement of the two large groups to avoid unfavourable 1,3-diaxial interactions. The fact that the formation of only *cis* tetrahydrofuran rings takes place in our case, may be due to the additional directing effect and the stabilisation affected by the pyridine nitrogen atom on the bromination/iodination agents or bromonium/iodonium intermediates. Such stabilisation would only be enabled by *cis* intermediates and *cis* ring closures to give the *cis* product.

3. Conclusion

Our results demonstrate that the nitropyridine/α-pyridylmalonate pathway may represent a convenient strategy both for the preparation of 3-alkylated pyridines and for the synthesis of more complex carbon skeletons, such as fused bis-heterocycles.

α-(3-Pyridyl)malonic esters (**3a**,**b**) have been prepared by nucleophilic aromatic substitution of the nitro group in methyl 3-nitro-4-pyridylcarboxylate (**1**) by malonate. The versatility of the α-pyridylmalonate product (**3**) has been demonstrated by the simple transformations of **3a** into a series of new 3-alkylpyridines (**5**–**10**, **16**). Furthermore, new bis-heterocycles such as the *N*-heterocyclic isocoumarin analogue 3-substituted-pyrano[4,3-*c*]pyridin-1-one (**11a**, **11b**), the δ-lactone 3,4-dihydro-1*H*-pyrano[4,3-*c*]pyridin-1-one (**13**), the 2,6-naphthyridin-1(2*H*)-one (**14**) and the 2,6-naphthyridine derivative (**15**) were readily prepared from α-pyridylmalonate (**3a**) in few steps by subsequent intramolecular reactions. *cis* 2-Halomethyl-4-(3-pyridyl)tetrahydrofurano products **17a** and **17b** were selectively prepared from the decarboxylated allyl bromide product **8**.

NMR experiments (DEPT, COSY, HMBC, APT, HSQC, NOESY) were used for structure identification and ^{1}H and ^{13}C NMR assignments of practically all products.

Bioassay screening of the products are in progress.

4. Experimental

4.1. General

Chemicals: Cs_2CO_3 (99.9%), NaH (95%), $POCl_3$ (99%), $LiAlH_4$ (95%), methyl isonicotinate (98%) (Aldrich); methyl acrylate, $Pd(PPh_3)_4$, phenylacetylchloride, benzoylchloride, $NaBH_4$ (Fluka); allyl bromide (99%), acetic anhydride (99%) (Acros); diethyl malonate (99%) (Acros); PPh_3, NaCl (*p.a.*), CsCl (*p.a.*), NBS (Merck); NH_3 (25% in water, VWR), I_2 (Acf chemiefarma); NaS_2O_3 (*p.a.*, KeboLab); dimethyl malonate (97%, Janssen Chimica). Solvents: DMSO, Et_2O, THF, EtOAc, CH_2Cl_2, pentane, (*p.a.* VWR). $^{1}H/^{13}C$ NMR: Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in parts per million downfield from TMS. *J* values are given in hertz. MS: Finnigan MAT 95 XL (EI/70 eV). IR: Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured on a Griffin apparatus. Flash chromatography: Silica (SDS, 60 Å, 40–63 μm). Microwave irradiation was performed in a household microwave oven (Elram M8017NP-CF), modified with a reflux condenser, at '*Low*' (90 W) or '*Medium*' (360) power of max 800 W output. Methyl 3-nitro-4-pyridinecarboxylate (**1**) was prepared from methyl 4-pyridinecarboxylate by nitration according to the literature.[4]

4.1.1. 2-(4-Methoxycarbonyl-3-pyridyl)-propanedioic acid dimethyl ester (3a). A solution of **1** (600 mg, 3.3 mmol), in DMSO (25 mL) was added drop-wise to a stirred solution of Cs_2CO_3 (1.21 g, 3.7 mmol, 1.1 equiv) and diethyl malonate (0.60 mL, 5.25 mmol, 1.6 equiv) in DMSO (15 mL) under nitrogen atmosphere during 30 min at 150 °C. After additional stirring at 150 °C a saturated solution of NH_4Cl (100 mL) was added and the product was extracted by diethyl ether. Flash chromatography (Et_2O) afforded two products, the 3-substituted (**3a**) and the 6-substituted (**4a**). Compound **3a**: 484 mg, 55%; R_f 0.35 (Et_2O); mp 78.2–78.5 °C; IR (film) ν_{max}: 3019 (m), 1735 (m), 1437 (w), 1282 (w), 1215 (s), 1221 (s), 1092 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.80 (6H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.56 (1H, s, malonate-CH), 7.80 (1H, d, *J* 4.9 Hz, H-5), 8.69 (1H, s, H-2), 8.73 (1H, d, *J* 4.9 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 52.8 (py-ester-OCH_3), 53.0 (malonate-CH), 53.1 (malonate-OCH_3), 123.5 (C-5), 128.2 (C-4), 136.6 (C-3), 150.2 (C-6), 151.9 (C-2), 166.0 (py-C═O), 168.0 (malonate-C═O); NMR assignments are based on DEPT, HMBC and HSQC experiments; MS: *m/z* 267 (M^+, 6%), 235 (100), 207(79), 204 (89), 180 (41), 164 (55), 150 (21), 134 (39), 106 (12); HRMS: calcd for $C_{12}H_{13}NO_6$: 267.0743; obsd 267.0699. Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.73; H, 4.94; N, 5.26.

4.1.2. 2-(4-Methoxycarbonyl-3-pyridyl)-propanedioic acid diethyl ester (3b). The title product was prepared from **1** and diethyl malonate as described above for the preparation of **3a** from **1** and dimethyl malonate. However, Cs_2CO_3 was replaced by NaH. As for **3a**/**4a**, flash chromatography (Et_2O) afforded two products, the 3-substituted (**3b**) and the 6-substituted (**4b**). Compound **3b** was obtained as a crystalline product (220 mg, 24%), pure by ^{1}H and ^{13}C NMR. R_f 0.35 (Et_2O); mp 64–65 °C; IR ν_{max}: 3019 (m), 2960 (w), 1732 (s), 1282 (w), 1216 (s), 758 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (6H, t, *J* 7.1 Hz, CH_3), 3.92 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1 Hz, CH_BH), 4.26 (2H, q, *J* 7.1 Hz, CH_AH), 5.52 (1H, s, CH), 7.80 (1H, dd, *J* 5.0, 0.5 Hz, H-5), 8.71 (1H, s, H-2), 8.72 (1H, d, *J* 5.0 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.1, 52.8, 53.5, 62.1, 123.5, 128.4, 136.7, 150.0, 151.8, 166.0, 167.6; MS: *m/z* 295 (M^+, 2%), 263 (11), 249 (96), 235 (10), 221 (61), 218 (41), 204 (46), 189 (51), 177 (20), 163 (26), 149 (69), 134 (100), 120 (14), 106 (53), 92 (13); HRMS: calcd for $C_{14}H_{17}NO_6$: 295.1056; obsd 295.1055.

4.1.3. 2-(4-Methoxycarbonyl-3-nitro-6-pyridyl)-propanedioic acid dimethyl ester (4a). Minor amounts of the title compound, pure by NMR, were isolated by flash chromatography (Et_2O) from the crude product mixture of **4a** and **3a** described above (186 mg, 18%). R_f 0.2 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.82 (6H, s, OCH_3), 3.99 (3H, s, OCH_3), 5.10 (1H, s, CH), 7.85 (1H, s, H-5), 9.16 (1H, s, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 53.4 (malonate-OCH_3), 53.8 (py-ester-OCH_3), 59.6 (malonate-CH), 123.3 (C-5), 135.7 (C-4), 142.3 (C-3), 144.7 (C-2), 158.2 (C-6), 163.7 (py-C═O), 166.4 (malonate-C═O); NMR assignments are based on COSY, HMBC and HSQC experiments; MS: *m/z* 312 (M^+, 7%), 307 (17), 280 (40), 269 (65), 254 (67), 222 (52), 209 (55), 181 (60); HRMS: calcd for $C_{12}H_{12}N_2O_8$: 312.0504; obsd 312.0601.

4.1.4. 2-(4-Methoxycarbonyl-3-nitro-6-pyridyl)-propanedioic acid diethyl ester (4b). Minor amounts of **4b** were isolated by flash chromatography (Et_2O) from the crude product mixture of **4b** and **3b** described above (67 mg, 7.5%). R_f 0.2 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (6H, t, *J* 7.1 Hz, CH_3), 3.99 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1 Hz, CHH_B), 4.26 (2H, q, *J* 7.1 Hz, CH_AH), 5.07 (1H, s, CH), 7.87 (1H, s, H-5), 9.16 (1H, s, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0, 53.8, 60.2, 62.7, 123.5, 135.8, 142.3, 144.7, 158.6, 163.9, 166.1.

4.1.5. Trimethyl 1-(4-(methoxycarbonyl)pyridin-3-yl)-propane-1,1,3-tricarboxylate (5). A solution of **3a** (52 mg, 0.2 mmol), methyl acrylate (51 mL, 0.57 mmol) and NaOMe (0.15 M, 13 mL, 0.02 mmol) in MeOH (2 mL) was stirred at room temperature for 68 h. Flash chromatography (Et_2O) afforded an oily product (61 mg, 89%), pure by ^{1}H and ^{13}C NMR. R_f 0.25 (Et_2O); IR (film) ν_{max}: 3003 (w), 2955 (m), 1735 (s), 1588 (w), 1436 (s), 1363 (w), 1283 (s), 1218 (m), 1174 (m), 1106 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.37 (2H, t, *J* 8.0 Hz, propyl 3-CH_2), 2.79 (2H, t, *J* 8.0 Hz, propyl 2-CH_2), 3.53 (3H, s, terminal ester OCH_3), 3.69 (6H, s, malonate esters OCH_3), 3.81 (3H, s, py-ester OCH_3), 7.65 (1H, d, *J* 5.0 Hz, H-5), 8.37 (1H, s, H-2), 8.62 (1H, d, *J* 5.0 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 30.3 (C-2, CH_2), 30.5 (C-3, CH_2), 51.7 (terminal ester OCH_3), 52.8 (py-ester OCH_3), 53.2 (malonate esters OCH_3), 61.3 (C-1, quart. C), 123.9 (C-5), 131.4 (C-3), 138.4 (C-4), 149.8 (C-6), 150.3 (C-2), 166.9

(py-ester C=O), 169.8 (malonate ester C=O), 172.9 (terminal ester C=O); NMR assignments are based on DEPT, COSY, HMBC, APT and HSQC experiments; MS (CI): *m/z* 354 (M+1, 77%), 322 (45), 267 (37), 236 (100), 230 (40), 202 (28); MS (EI) *m/z* 353 (M^+, 2%), 322 (78), 294 (53), 267 (86), 262 (38), 236 (100), 235 (92), 202 (88), 174 (62), 162 (74); HRMS: calcd for $C_{16}H_{19}NO_8$: 353.1111; obsd 353.1107.

4.1.6. 1-(4-Methoxycarboxyl-3-pyridyl)-1,1-di(methoxycarbonyl)-3-butene (6). A solution of **3a** (1.34 g, 5.02 mmol, 1 equiv) and Cs_2CO_3 (1.96 g, 6.93 mmol, 1.2 equiv) in dry THF (20 mL) was stirred for 15 min under nitrogen atmosphere. Allyl bromide (0.60 mL, 6.0 mmol, 1.4 equiv), $Pd(PPh_3)_4$ (0.28 g, 0.25 mmol, 0.05 equiv) and PPh_3 (0.12 g, 0.61 mmol, 0.1 equiv) in dry THF (20 mL) was stirred for 15 min. The allyl bromide solution was transferred to the malonate solution by syringe in an inert pressure system and the reaction was stirred for 1 h at room temperature before a saturated solution of NH_4Cl (30 mL) was added. The product was extracted by ethyl acetate. Flash chromatography (Et_2O) afforded an oily product (1.45 g, 94%), pure by ^1H and ^{13}C NMR. R_f 0.4 (Et_2O); IR (film) ν_{max}: 3004 (w), 2954 (s), 1735 (s), 1638 (w), 1588 (w), 1435 (s), 1284 (s), 1215 (s), 1105 (m), 963 (m), 928 (m), 858 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.66 (1H, d, *J* 5.0 Hz, H-6), 8.50 (1H, s, H-2), 7.7 (1H, d, *J* 5.0 Hz, H-5), 5.77 (1H, m, H-3′, –CH=), 5.00 (2H, d, *J* 12.8 Hz, H-4′, terminal $=CH_2$), 3.87 (3H, s, py-ester OCH_3), 3.74 (6H, s, 2×malonate OCH_3), 3.27 (2H, dd, *J* 7.2, 0.8 Hz, H-2′, $–CH_2–$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 39.6 (CH_2), 52.6 (py-*Me*-ester), 52.9 (two malonate-*Me*-ester), 62.0 (quart. C), 119.3 (terminal $=CH_2$), 123.5 (C-5), 131.7 (C-3), 133.0 (allyl –CH=), 138.8 (C-4), 149.3 (C-6), 150.7 (C-2), 167.6 (py-ester-C=O), 169.7 (two malonate-ester-C=O); NMR assignments are based on DEPT, COSY, HMBC and HSQC experiments; MS: *m/z* 307 (M^+, 5%), 275 (59), 247 (77), 216 (100), 188 (89), 156 (90). HRMS: calcd for $C_{15}H_{17}NO_6$: 307.1056; obsd 307.1069. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.18; H, 5.77; N, 4.44.

4.1.7. Dimethyl 2-(4-(methoxycarbonyl)pyridin-3-yl)-pentanedioate (7). The title product was preferentially prepared by MW irradiation. A solution of **5** (130 mg, 0.37 mmol) and NaCl (64 mg, 1.11 mmol) in DMSO (4 mL) was irradiated at '*medium*' power (360 W) for 10 min to afford an oily product (87 mg, 60%), pure by ^1H and ^{13}C NMR. Alternatively, some lower yields were obtained by conventional heating of the reaction mixture for 16 h at 110 °C; IR (film) ν_{max}: 3001 (w), 2954 (s), 1731 (s), 1590 (w), 1437 (s), 1281 (s), 1171 (m), 1104 (m), 1003 (w), 853 (w), 724 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.16 (1H, m, H-2′), 2.36 (2H, m, H-3′), 2.55 (1H, m, H-2′), 3.64 (3H, s, terminal ester OCH_3), 3.67 (3H, s, 'malonate ester' OCH_3), 3.93 (3H, s, py-ester OCH_3), 4.51 (1H, t, *J* 7.6 Hz, H-1′), 7.71 (1H, d, *J* 4.8 Hz, H-5), 8.65 (1H, d, *J* 4.8 Hz, H-6), 8.68 (1H, s, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.9 (C-2′), 31.9 (C-3′), 44.9 (C-1′), 51.7 (terminal ester O*C*H_3), 52.4 ('malonate ester O*C*H_3'), 52.8 (py-ester O*C*H_3), 123.6 (C-5), 133.6 (C-3), 136.8 (C-4), 149.3 (C-6), 151.4 (C-2), 166.3 (py-ester C=O), 172.9 ('malonate' ester C=O), 173.1 (terminal ester C=O); NMR assignments are based on DEPT, COSY, HMBC, APT and HSQC experiments; MS: *m/z* 295 (M^+, 2%), 263 (75), 235 (31), 217 (21), 203 (15), 190 (31), 176 (22), 162 (44), 160 (23), 150 (31), 144 (37), 134 (20), 111 (26), 99 (19); HRMS: calcd for $C_{14}H_{17}NO_6$: 295.1056; obsd 295.1058.

4.1.8. Methyl 3-(4-methoxy-4-oxobutyl)isonicotinate (7′). Minor amounts of **7′** (3–5%) were isolated by flash chromatography (Et_2O/*n*-pentane 4:1) from a mixture with **7**, pure by NMR; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.95 (2H, t, *J* 7.6 Hz, CH_2-2′), 2.39 (2H, t, *J* 7.6 Hz, CH_2-3′), 2.99 (2H, t, *J* 7.6 Hz, CH_2-1′), 3.67 (3H, s, terminal ester OCH_3), 3.93 (3H, s, py-ester-OCH_3), 7.67 (1H, d, *J* 5.2 Hz, py-H-5), 8.58 (1H, *J* 5.2 Hz, py-H-6), 8.58 (1H, s, py-H-2).

4.1.9. 2-(4-Methoxycarboxyl-3-pyridyl)-4-pentenoic acid methyl ester (8). The title product was preferentially prepared by MW irradiation. A solution of **6** (860 mg, 2.80 mmol), CsCl (1.42 g, 8.4 mmol, 3 equiv) in water (0.6 mL, 12 equiv) and DMSO (25 mL) was irradiated at '*medium*' power (360 W) for 6 min. The solution was cooled, added water (30 mL) and extracted with ethyl acetate (3×30 mL). An oily product was obtained (382 mg, 55%), pure by ^1H and ^{13}C NMR; IR (film) ν_{max}: 3019 (s), 2954 (m), 1732 (s), 1642 (w), 1436 (m), 1412 (w), 1280 (s), 1215 (s), 1170 (m), 1103 (m), 924 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.69 (1H, s, py-H-2), 8.63 (1H, d, *J* 5.2 Hz, py-H-6), 7.69 (1H, dd, *J* 5.2, 1.3 Hz, py-H-5), 5.7 (1H, m, H-4, –CH=), 5.05 (2H, m, H-5, terminal $=CH_2$), 4.54 (1H, t, *J* 7.4 Hz, H-2), 3.87 (3H, s, py-ester OCH_3), 3.74 (3H, s, 'malonate' OCH_3), 2.96 (1H, m, H-3, $–CH_2–$), 2.60 (1H, m, H-3, $–CH_2–$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 36.4 (CH_2), 45.2 (methin CH), 51.3 ('malonate ester' O*C*H_3), 52.2 (pyridyl ester O*C*H_3), 117.2 (terminal $=CH_2$), 122.8 (py-C-5), 133.0 (py-C-3), 134.2 (penten-C-4; –CH=), 136.2 (py-C-4), 148.4 (py-C-6), 150.9 (py-C-2), 165.9 (py-ester C=O), 172.4 ('malonate' ester C=O); NMR assignments are based on COSY, HMBC and APT experiments; MS: *m/z* 249 (M^+, 7%), 248 (29), 247 (63), 216 (89), 189 (66), 188 (95), 156 (100), 144 (34), 130 (97), 128 (42) 103 (30). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 6.13; N, 5.65.

4.1.10. Methyl 3-(but-3-enyl)isonicotinate (8′). Minor amounts of **8′** (2–3%) were isolated by flash chromatography (Et_2O/*n*-pentane 4:1) from a mixture with **8**, pure by ^1H NMR and GC–MS. R_f 0.5 (Et_2O/*n*-pentane 4:1), ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.37 (2H, q, *J* 6.8 Hz, CH_2-2′), 3.04 (2H, t, *J* 7.2 Hz, CH_2-1′), 3.93 (3H, s, py-ester-OCH_3), 5.02 (2H, m, C-4′; terminal $=CH_2$), 5.82 (1H, m, C-3′; –CH=), 7.66 (1H, d, *J* 5.2 Hz, py-H-5), 8.56 (1H, d, *J* 5.2 Hz, py-H-6), 8.57 (1H, s, py-H-2); GC–MS: *m/z* 291 (M^+, 13%), 176 (6), 159 (100), 150 (34), 131 (19), 92 (36).

4.1.11. Methyl (4-methoxycarboxyl-3-pyridine)acetate (homochinchomeric acid dimethyl ester) (9).[11] MW decarboxylation was carried out as described above for the preparation of **8**. Irradiation of the solution of **3a** (150 mg, 0.54 mmol) and CsCl (3 equiv) in water (12 equiv) and DMSO (10 mL) at '*low*' power (90 W) for 5 min afforded **9** in 81% yield, pure by ^1H and ^{13}C NMR, after flash

chromatography (ethyl acetate/*n*-pentane 4:1). R_f 0.5 (Et_2O); IR (film) ν_{max}: 3002 (w), 2954 (m), 1732 (s), 1591 (w), 1437 (m), 1281 (s), 1105 (m), 1001 (m), 997 (m), 724 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.71 (3H, s, side chain OCH_3), 3.91 (3H, s, py-ester OCH_3), 4.01 (2H, s, CH_2), 7.80 (1H, d, *J* 5.2 Hz, H-5), 8.58 (1H, s, H-2); 8.69 (1H, d, *J* 5.2 Hz, H-6), ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 37.5 (CH_2), 52.4 (side chain OCH_3), 52.8 (py-ester OCH_3), 123.8 (C-5), 130.0 (C-3), 137.0 (C-4), 150.0 (C-6), 153.3 (C-2), 166.3 (pyr-ester C═O), 171.3 (side chain C═O); NMR assignments are based on DEPT, HSQC and HMBC experiments; MS: *m*/*z* 209 (M^+, 2%), 177 (100), 149 (53), 120 (22), 92 (27). HRMS: calcd for $C_{10}H_{11}NO_4$: 209.0688; obsd 209.0688. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 56.76; H, 5.39; N, 6.66.

4.1.12. Methyl 3-methyl-4-pyridinecarboxylate (10).[30] By prolonged MW irradiation time (10 min, 90 W, see preparation of **9** above), **9** and methyl 3-methyl-4-pyridylcarboxylate (**10**) were isolated in 34 and 17% yields, respectively. Irradiation for 20 min afforded only **10**. Purification by chromatography (Et_2O) afforded 30% yield, pure by ^{1}H NMR. Compound **10**: R_f 0.55 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.55 (3H, s, py-CH_3), 3.90 (3H, s, OCH_3), 7.66 (1H, d, *J* 5.2 Hz, H-5), 8.53 (1H, d, *J* 5.2 Hz, H-6), 8.55 (1H, s, H-2); MS: *m*/*z* 151 (M^+, 10%), 150 (31), 149 (100), 134 (121), 125 (11), 123 (10), 119 (13), 111 (19), 97 (27).

4.1.13. 3-Benzylpyrano[4,3-*c*]pyridin-1-one (11a). A solution of **3a** (140 mg, 0.52 mmol) and phenylacetyl chloride (416 mL, 3.14 mmol, 6 equiv) was stirred at 200 °C for 2 h. To the solution were added $NaHCO_3$ (saturated solution, 30 mL) and ethyl acetate (30 mL) and the mixture was stirred for additional 5 min before the product was isolated by extraction. Flash chromatography (CH_2Cl_2) afforded an off-white crystalline product (CH_2Cl_2) (30 mg, 24%), pure by ^{1}H and ^{13}C NMR. R_f 0.05 (CH_2Cl_2); mp 72–72.5 °C; IR ν_{max}: 3019 (m), 2918 (w), 1740 (s), 1654 (m), 1560 (w), 1480 (w), 1454 (m), 1417 (m), 1262 (w), 1215 (s), 1139 (w), 1054 (m), 850 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.86 (2H, s, benzylic CH_2), 6.21 (1H, t, *J* 0.7 Hz, pyrano-CH═), 7.28–7.38 (5H, m, Ph), 7.98 (1H, d, *J* 5.4 Hz, py-H-5), 8.69 (1H, d, *J* 5.4 Hz, py-H-6), 8.77 (1H, s, py-H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 40.1 (benzylic *C*H_2), 100.9 (pyrano-C-4, –CH═), 121.3 (py-C-5), 125.6 (py-C-4), 127.6 (*p*-Ph-CH), 129.1/129.5 (*o*-/*m*-Ph-CH), 131.4 (py-C-3), 135.2 (Ph-C-1), 148.4 (py-C2/C-6), 159.5 (pyrano-C-3), 161.3 (pyrano-C═O); NMR assignments are based on APT, HSQC and HMBC experiments; MS: *m*/*z* 237 (M^+, 100%), 209 (30), 208 (15), 180 (12), 146 (30), 118 (15), 91 (39); HRMS: calcd for $C_{15}H_{11}NO_2$: 237.0790; obsd 237.0790.

4.1.14. 3-Phenylpyrano[4,3-*c*]pyridin-1-one (11b).[18] The title compound was prepared from **3a** and benzoyl chloride as described above for **11a**. afforded the pale yellow crystalline product (CH_2Cl_2, 31%), pure by ^{1}H and ^{13}C NMR. R_f 0.05 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H7.01 (1H, s, pyrano-C-4, –CH═), 7.48 (3H, m, *m*/*p*-Ph-H), 7.87 (2H, dd, *J* 1.7, 5.1 Hz, *o*-Ph-H), 8.06 (1H, d, *J* 4.9 Hz, py-H-5), 8.76 (1H, d, *J* 4.9 Hz, py-H-6), 8.98 (1H, s, py-H-2); corresponding data in DMSO-d_6: δ_H 7.55 (4H, m, H-4 and *m*/*p*-Ph-H), 7.67 (2H, dd, *J* 0.7, 5.5 Hz, *o*-Ph-H), 8.06 (1H, dd, *J* 5.1, 0.8 Hz, py-H-5), 8.88 (1H, d, *J* 5.1 Hz, py-H-6), 9.11 (1H, s, py-H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 98.7 (pyrano-C-4, –CH═), 121.6 (py-C-5), 125.6 (py-C-4), 127.6 (*p*-Ph-CH), 129.1/129.5 (*o*-/*m*-Ph-CH), 131.4 (py-C-3), 135.2 (Ph-C-1), 148.4 (py-C-6), 149.0 (py-C2), 155.9 (pyrano-C-3), 160.9 (pyrano-C═O); NMR assignments are based on DEPT, COSY and HMBC experiments; MS: *m*/*z* 223 (M^+, 100%), 195 (70), 167 (11), 166 (11), 139 (17), 105 (17).

4.1.15. 3-Phenyl-3,4-dihydro-1*H*-pyrano[4,3-*c*]pyridin-1-on (13). A solution of **11b** (34 mg, 0.15 mmol) in a solution of KOH (5%, 5 mL) and ethanol (2.5 mL) was heated to reflux for 4 h, cooled and $NaBH_4$ (23 mg, 0.60 mmol) was added. The reaction was stirred at room temperature for 24 h. After the addition of acetic anhydride (0.3 mL, 3 mmol) the solution was heated to reflux for further 2 h, cooled, water was added (15 mL) and the mixture stirred for 24 h. Dichloromethane extraction (3×15 mL) and flash chromatography (ethyl acetate/pentane added 2.5% NEt_3; 1:2) yielded the product (7 mg, 20%), pure by ^{1}H and ^{13}C NMR; IR (film) ν_{max}: 3064 (w), 2918 (w), 1724 (s), 1572 (m), 1494 (m), 1453 (m), 1425 (m), 1413 (m), 1349 (s), 1286 (s), 1244 (s), 1200 (m), 1160 (w), 1101 (m), 1007 (s), 883 (w), 852 (m) cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.78 (1H, d, *J* 5.0 Hz, py-H-6), 8.72 (1H, s, py-H-2), 7.96 (1H, d, *J* 5.0 Hz, py-H-5), 7.44 (5H, m, Ph-H), 5.61 (1H, dd, *J* 12.0, 3.0 Hz, pyrano-H-3), 3.35 (1H, dd, *J* 16.5, 12.0 Hz, pyrano-H-4), 3.32 (1H, dd, *J* 1.5, 3.0 Hz, pyrano-C-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 32.4 (pyrano-H-4; *C*H_2), 80.4 (pyrano-C-3, *C*H), 122.6 (py-C-5), 126.1 (*o*-Ph-C), 128.4 (*p*-Ph-C), 128.9 (*m*-Ph-C), 130.1 (py-C-3), 132.6 (py-C-4), 137.7 (Ph-C-1), 149.2 (py-C-6), 149.8 (py-C-2), 163.6 (pyrano-C═O); NMR assignments are based on HSQC and HMBC experiments; MS: *m*/*z* 225 (M^+, 17%), 119 (100), 105 (13), 91 (42); HRMS: calcd for $C_{14}H_{11}NO_2$: 225.0790; obsd 225.0794.

4.1.16. 3-Phenyl-2,6-naphthyridin-1(2*H*)-one (14).[21] The title compound was prepared in 43% yield from **11b** and NH_3 as described in literature,[23,24] pure by ^{1}H and ^{13}C NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.85 (1H, s, H-4), 8.14 (1H, d, *J* 5.2 Hz, H-8), 8.68 (1H, d, *J* 5.2 Hz, H-7), 9.06 (1H, d, *J* 0.8 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 101.4 (C-4), 119.5 (C-8), 126.2 (*o*-Ph-C), 129.4 (*p*-Ph-C), 129.5 (C-4a), 130.1 (*m*-Ph-C), 133.2 (Ph-C-1),133.7 (C-8a), 141.6 (C-3), 146.2 (C-7), 150.1 (C-5), 162.7 (C-1); NMR assignments are based on DEPT, COSY, APT, HSQC and HMBC experiments.

4.1.17. 1-Chloro-3-phenyl-2,6-naphthyridine (15). The title compound was prepared from **14** and $POCl_3$ as described in literature[25] to afford an off-white crystalline product (EtOAc) (49%), pure by ^{1}H and ^{13}C NMR; mp 145.0–145.4 °C; IR ν_{max}: 3063 (w), 1615 (w), 1566 (s), 1478 (s), 1453 (m), 1317 (s), 1257 (s), 1224 (m), 1150 (s), 989 (m), 876 (m), 850 (m), 827 (m) cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6): δ_H 9.50 (1H, s, H-5), 8.78 (1H, d, *J* 5.4 Hz, H-7), 8.55 (1H, d, *J* 1.0 Hz, H-4), 8.21 (2H, m, Ph-*o*-H), 8.06 (1H, dd, *J* 5.4, 1.0 Hz, H-8), 7.52–7.55 (2H, m, Ph-*m*-H), 7.47–7.49 (1H, m, Ph-*p*-H); ^{13}C NMR (150 MHz, acetone-d_6): δ_C 153.5 (C-5), 152.4 (C-3), 150.7 (C-1), 146.7 (C-7),

138.0 (Ph-C-1), 134.1 (C-4′), 130.4 (Ph-C-4), 129.8 (Ph-C-3/5), 128.9 (C-8′), 127.5 (Ph-C-2/6), 118.1 (C-8), 115.9 (C-4); NMR assignments are based on HSQC and HMBC experiments; MS: *m/z* 242/240 (M^+, 32/100%), 105 (46), 177 (14), 151 (18), 102 (14); HRMS: calcd for $C_{14}H_9N_2Cl$: 240.0454; obsd 240.0449.

4.1.18. 2-(4-Hydroxymethyl-3-pyridyl)-4-penten-1-ol (16). A solution of **8** (725 mg, 2.9 mmol) in dry THF (12 mL) was drop-wise added to a solution of $LiAlH_4$ (165 mg, 4.38 mmol) in dry THF (13 mL) at 0 °C. The reaction was stirred at room temperature for 2 h, cooled to 0 °C and diethyl ether (25 mL) was added, followed by a NH_4Cl solution (saturated, 40 mL) and water (40 mL). The product was extracted from basic solution by diethyl ether (3×50 mL) and yielded **17** (287 mg, 51%), pure by ^1H and ^{13}C NMR; IR (film) ν_{max}: 3682 (w), 3620 (w), 3400 (br), 3019 (s), 2976 (m), 1523 (w), 1421 (m), 1216 (s), 1046 (m), 928 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ_H 8.32 (1H, s, py-H-2), 8.22 (1H, d, *J* 5.4 Hz, py-H-6), 7.24 (1H, d, *J* 5.4, 1.3 Hz, py-H-5), 5.65 (1H, dd, *J* 17.0, 10.2 Hz, H-4, –CH═), 5.15 (1H, dd, *J* 17.0, 1.8 Hz, H-5, terminal ═C*H*$_a$H$_b$), 4.98 (1H, dd, *J* 10.2, 1.8 Hz, H-5, terminal ═CH$_a$*H*$_b$), 4.78 (1H, d, *J* 13.0 Hz, py-*CH*$_a$H$_b$OH), 4.47 (1H, d, *J* 13.0 Hz, py-CH$_a$*H*$_b$*OH*), 3.90 (1H, dd, *J* 10.0, 4.8 Hz, 'malonate'-C*H*$_a$H$_b$OH), 3.62 (1H, dd, *J* 10.0, 9.4 Hz, 'malonate'-CH$_a$*H*$_b$OH), 3.46 (2H, s, 2×OH), 3.19 (1H, m, H-2), 2.46 (1H, m, H-3, –C*H*$_a$H$_b$-C), 2.39 (1H, m, H-3, –CH$_a$*H*$_b$-C); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 36.0 (C-3), 40.9 (C-2), 61.6 (py-CH_2OH), 66.5 (C-1, CH_2OH), 117.2 (C-5, ═CH_2), 123.0 (py-C-5), 135.2 (C-4, –CH═), 136.5 (py-C-3), 147.2 (py-C-6), 147.7 (py-C-2), 148.8 (py-C-4); NMR assignments are based on APT, HSQC and HMBC experiments; MS: *m/z* 193 (M^+, 1%), 180 (6), 170 (4), 164 (13), 157 (14), 145 (66), 134 (39), 130 (49), 117 (66), 106 (100), 91 (68); HRMS: calcd for $C_{11}H_{15}NO_2$: 193.1103; obsd 193.1094. Anal. Calcd for $C_{11}H_{15}NO_2$; C, 68.37; H, 7.82; N, 7.25. Found: C, 68.10; H, 7.68; N, 7.15.

4.1.19. *cis*-Tetrahydro-2-bromomethyl-4-(4-hydroxymethyl-3-pyridyl)-furan (17a). A solution of the diol **16** (88 mg, 0.45 mmol) in THF (2 mL) and water (0.15 mL) was cooled to −78 °C and NBS (89 mg, 0.50 mmol, 1.1 equiv) was added.[37] After 2 h of stirring, the temperature was raised to room temperature. Water (30 mL) was added and the crude product was extracted with ethyl acetate (3×15 mL). Flash chromatography (10% methanol in dichloromethane) yielded the product (50 mg, 40%), pure by ^1H and ^{13}C NMR. R_f 0.1 (acetone/*n*-pentane 1:1); IR (film) ν_{max}: 3682 (w), 3619 (w), 3018 (s), 2975 (m), 1600 (m), 1521 (w), 1477 (w), 1419 (m), 1215 (s), 1046 (m), 928 (m), 877 (w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ_H 8.53 (1H, s, py-H-2), 8.38 (1H, d, *J* 4.8 Hz, py-H-6), 7.10 (1H, d, *J* 4.8 Hz, py-H-5), 4.77 (2H, s, py-C*H*$_2$OH), 4.32 (1H, m, H-2), 4.18 (1H, dd, *J* 8.4, 7.8 Hz, H-5, C*H*$_a$H$_b$, *cis* to H-4, *trans* to –CH_2Br), 3.92 (1H, dd, *J* 8.4, 8.2 Hz, H-5, CH$_a$*H*$_b$, *trans* to H-4, *cis* to –CH_2Br), 3.71 (1H, m, H-4), 3.57 (1H, dd, *J* 11.0, 5.5 Hz, side chain C*H*$_a$H$_b$ Br), 3.54 (1H, dd, *J* 11.0, 5.5 Hz, side chain CH$_a$*H*$_b$ Br), 2.55 (1H, m, H-3, C*H*$_a$H$_b$, *cis* to H-4, *trans* to –CH_2Br), 1.94 (1H, m, H-3, CH$_a$*H*$_b$, *trans* to H-4, *cis* to –CH_2Br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 36.3 (*C*H_2Br), 38.8 (C-3), 39.0 (C-4), 61.3 (py-*C*H_2OH), 74.0 (C-5), 78.8 (C-2), 122.0 (py-C-5), 134.4 (py-C-3), 147.1 (py-C-6), 147.8 (py-C-2), 148.4 (py-C-4); NMR assignments are based on APT, HSQC, HMBC and NOESY experiments. The following NOESY NMR interactions were observed: H-2/H-4, H$_a$-3/H-2, H$_a$-3/H-4, H-4/H$_a$-5, H$_b$-3/H$_b$-5, H$_b$-3/*CH*$_2$Br, H$_b$-5/*CH*$_2$Br, C*H*$_2$OH/H-4, py-H-2/H$_b$-3, py-H-2/H$_b$-5. MS: *m/z* 273/271 (M^+, 1%), 252/254 (4), 234/236 (5), 208/210 (2), 178 (10), 174 (13), 160 (44), 156 (31), 143 (100), 132 (95), 117 (98), 106 (44), 91 (25); HRMS: calcd for $C_{11}H_{14}NO_2{}^{79}Br$: 271.0208; obsd 271.0202. Anal. Calcd for $C_{11}H_{14}NO_2Br$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.45; H, 5.04; N, 5.23.

4.1.20. *cis*-Tetrahydro-2-iodomethyl-4-(4-hydroxymethyl-3-pyridyl)-furan (17b). A solution of the diol **16** (80 mg, 0.4 mmol) in dichloromethane (5 mL) was stirred at room temperature for 24 h after the addition of I_2 (50 mg, 0.2 mmol, 0.5 equiv).[31] The solvent was decanted and the solid precipitate was dissolved in dichloromethane (5 mL) and acetone (10 mL) and $Na_2S_2O_3$ (5% solution, 25 mL) was added. The crude product was extracted with dichloromethane (5×30 mL)) and flash chromatography (1% methanol in dichloromethane) yielded the product (32 mg, 24%), pure by ^1H and ^{13}C NMR. R_f 0.05 (acetone/*n*-pentane 1:2); IR (film) ν_{max}: 3682 (w), 3620 (w), 2975 (m), 1520 (w), 1422 (w), 1215 (s), 1046 (m), 929 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, s, py-H-2), 8.41 (1H, d, *J* 4.8 Hz, py-H-6), 7.39 (1H, d, *J* 4.8 Hz, py-H-5), 4.76 (2H, s, py-C*H*$_2$OH), 4.21 (1H, dd, *J* 8.4, 7.7 Hz, H-5, C*H*$_a$H$_b$), 4.13 (1H, m, H-2), 3.96 (1H, dd, *J* 8.4, 8.2 Hz, H-5, CH$_a$*H*$_b$), 3.72 (1H, m, H-4), 3.35 (1H, dd, *J* 11.6, 5.8 Hz, side chain C*H*$_a$H$_b$ I), 3.38 (1H, dd, *J* 11.6, 5.8 Hz, side chain CH$_a$*H*$_b$ I), 2.59 (1H, m, H-3, C*H*$_a$H$_b$), 1.88 (1H, m, H-3, CH$_a$*H*$_b$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 9.4 (*C*H_2I), 39.3 (C-3), 40.6 (C-4), 61.3 (py-*C*H_2OH), 74.0 (C-5), 79.0 (C-2), 121.7 (py-C-5), 134.4 (py-C-3), 147.3 (py-C-6), 147.9 (py-C-2), 148.0 (py-C-4); NMR assignments are based on APT, HSQC, HMBC and NOESY experiments. The following NOESY NMR interactions were observed: H-2/H-4, H$_a$-3/H-2, H$_a$-3/H-4, H-4/H$_a$-5, H$_b$-3/H$_b$-5, H$_b$-3/*CH*$_2$I, H$_b$-5/*CH*$_2$I, C*H*$_2$OH/H-4, py-H-2/H$_b$-3, py-H-2/H$_b$-5. MS: *m/z* 319 (M^+, 5%), 271 (3), 192 (12), 178 (22), 178 (22), 160 (30), 143 (100), 91 (13); HRMS: calcd for $C_{11}H_{14}NO_2I$: 319.0069; obsd 319.0061. Anal. Calcd for $C_{11}H_{14}NO_2I$: C, 41.40; H, 4.42; N, 4.39. Found: C, 41.49; H, 4.51; N, 4.29.

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