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SYNTHESIS OF 2,3-DIHYDROFURO[3,2-*c*]PYRIDINE-3,4-DICARBOXYLIC ACID, A CONFORMATIONALLY CONSTRAINED ANALOGUE OF THE SUBTYPE SELECTIVE NMDA RECEPTOR AGONIST HOMOQUINOLINIC ACID

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Abstract - 4-Allyloxy- and 4-prop-2-ynyloxy-3-iodopicolinic acid derivatives, obtained by reaction of 4-chloro-2-iodopicolinanilides (**11**,**14**) with the sodium salts of allyl alcohol and propargyl alcohol, respectively, were subjected to tri-*n*-butyltin hydride/AIBN free radical cyclization conditions. While the propargylic compound (**15**) did not cyclize, the allylic compounds (**8**, **28**) cyclized in the presence of diphenyl diselenide, TEMPO or oxygen as radical trapping agents to give the corresponding 2,3-dihydrofuro[3,2-*c*]pyridine-4-carboxylic acid derivatives substituted at C-3 by a phenylselenylmethyl (**20**), 2,2,6,6-tetramethylpiperidin-1-yloxymethyl (**22**) or hydroxymethyl group (**29**), respectively. The latter was oxidized to the 3-carboxylic acid using ruthenium chloride /sodium periodate and the C-4 benzyl ester was hydrogenolyzed to afford the title compound (**5**), a conformationally constrained analogue of the subtype selective NMDA receptor agonist, homoquinolinic acid.

L-Glutamic acid (**1**) is the principal excitatory neuromediator of the central nervous system. It acts at two major classes of receptors, the ionotropic (i.e., voltage gated) glutamate receptors (iGluR) and the

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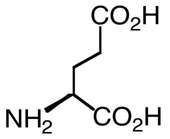
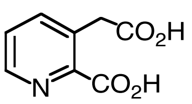
This paper is dedicated to Professor Pierre Potier on the occasion of his 70th birthday.

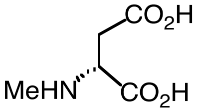
metabotropic (i.e. G-protein coupled) glutamate receptors (mGluR) each in turn comprised of a large number of receptor types and subtypes.[1] Because dysfunction of the glutamatergic system has been associated with a wide variety of syndromes such as Alzheimer's, Parkinson's and Huntington's diseases, the search for subtype selective ligands is currently a major pharmacological goal. One way of obtaining such selectivity is by utilizing rigid analogues of L-glutamic acid. An example of this approach is that of homoquinolic acid (**2**), a conformationally constrained analogue of L-glutamic acid which demonstrates high selectivity for the 2B subtype of the NMDA (*N*-methyl-D-aspartate, **3**) type of iGluRs.[2]



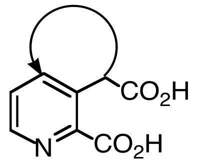
1 : L-Glutamic acid



2 : Homoquinolinic acid



3 : NMDA



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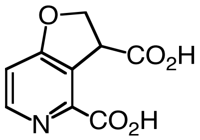

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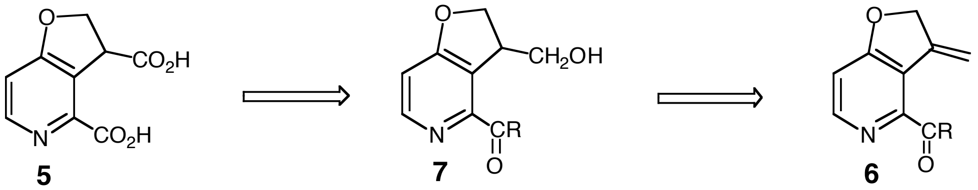
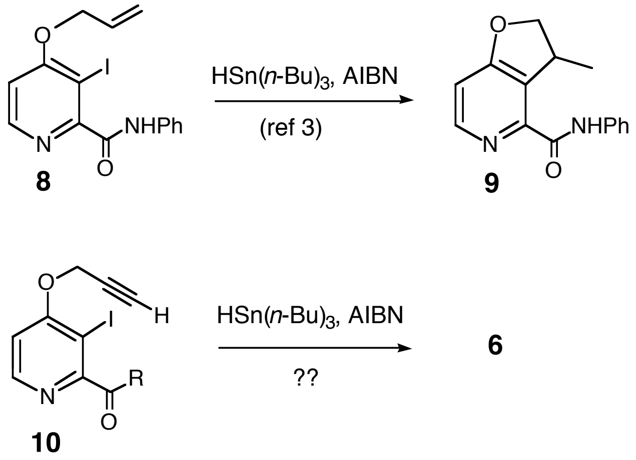
It appeared to us that even greater or different subtype selectivities could be obtained by imposing further conformational rigidity to homoquinolinic acid. This could be achieved by the preparation of molecules of general type (**4**) in which the exocyclic methylene group of homoquinolinic acid is now incorporated into a ring system fused to the pyridine ring. In this paper, then, we describe the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridine-3,4-dicarboxylic acid (**5**), which may be considered as such a conformationally constrained analogue of homoquinolinic acid (**2**).

One approach to the preparation of the target compound would be *via* hydroboration of the exocyclic methylene function of a derivative such as **6** followed by oxidation and deprotection of the resulting product (**7**) to give the dicarboxylic acid (**5**) (Scheme 1). In this context, we have previously described[3] the preparation of a 3-methyl analogue of **6** (i.e., **9**) by way of trialkyltin hydride-promoted free radical cyclization[4] of 4-allyloxy-3-iodopicolinanilide (**8**) (Scheme 2) in turn obtained by ortho-metalation/substitution reactions on picolinanilide. A similar process using the acetylenic version of allyl derivative (**8**) (i.e., **10**) should then give access to the desired 3-methylene derivative (**6**).

Thus, using the procedure analogous to that used for the preparation of **8**, 4-chloro-3-iodopicolinanilide (**11**) was reacted with sodium propargylate in THF at 80°C for 6 h (Scheme 3). However, only 2% of the desired 4-propynyloxy derivative (**12**) was obtained, the major product being the reduced compound (**13**). In contrast, when the *N*-methyl analogue of **11** (i.e., **14**) was submitted to the same reactions, a good yield (82%) of the desired 4-propynyloxy derivative (**15**) was obtained. Attempted free radical cyclization of the latter by treatment with tri-*n*-butyltin hydride and AIBN in hot toluene failed however to give the desired 3-methylene derivative (**16**). Steric factors may explain this lack of reactivity since, when the same cyclization conditions were applied to the 2-unsubstituted pyridine analogue, that is, compound (**18**) (obtained by treatment of 4-chloro-3-iodopyridine (**17**) with sodium propargylate as before), a high yield of 3-methylenefuropyridine (**19**) was obtained. A final attempt to cyclize compound (**15**) by way of a palladium-catalyzed coupling reaction was also unsuccessful.[5]

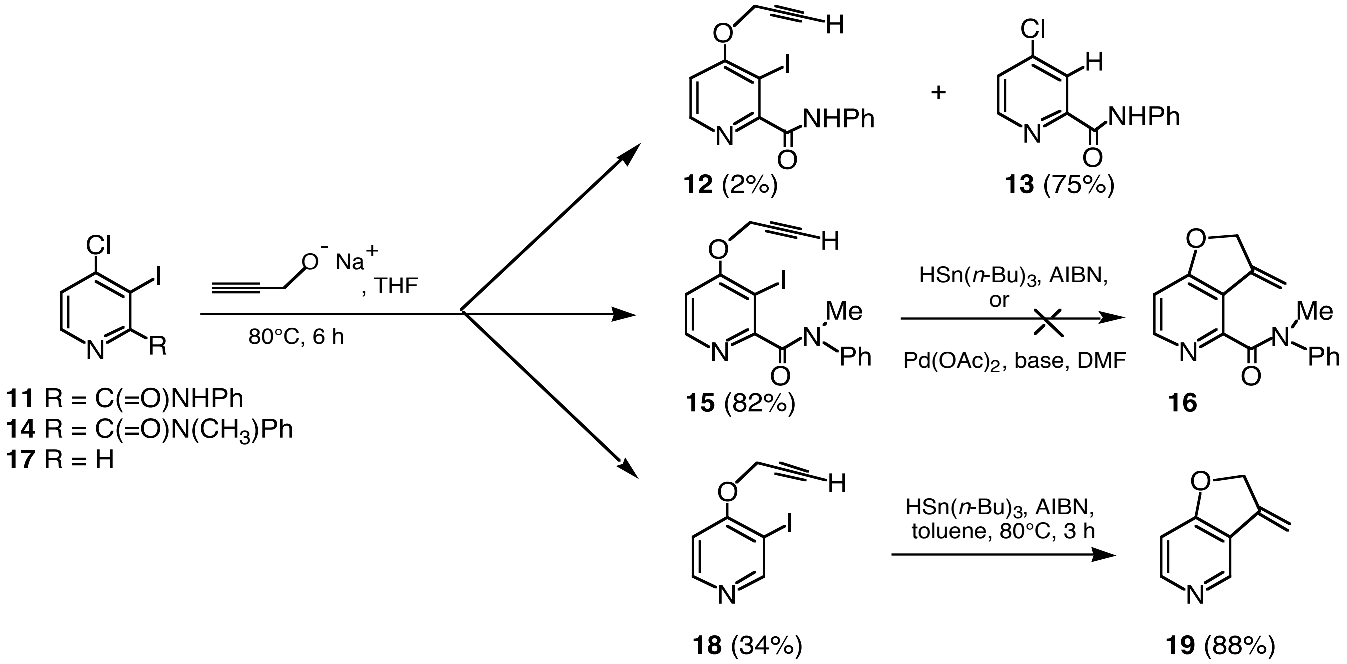


Scheme 1

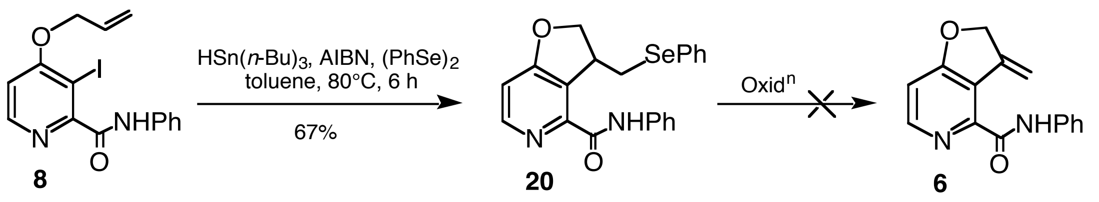


Scheme 2

These disappointing results prompted us to re-evaluate the possibility of utilizing the 4-allyloxy derivative (**8**) to achieve our goal. In particular, use of a radical trapping agent during the cyclization step should permit functionalization of the C-3 methyl group of **9** (Scheme 2). Thus, it was found that compound (**8**) reacts efficiently with diphenyl diselenide in the presence of tri-*n*-butyltin hydride and AIBN to give the 3-phenylselenylfuropyridine derivative (**20**) (Scheme 4). However, various atttempts to effect oxidative elimination of the phenylselenide group to provide the desired 3-methylene function (**21**) failed, decomposition products being consistently observed.

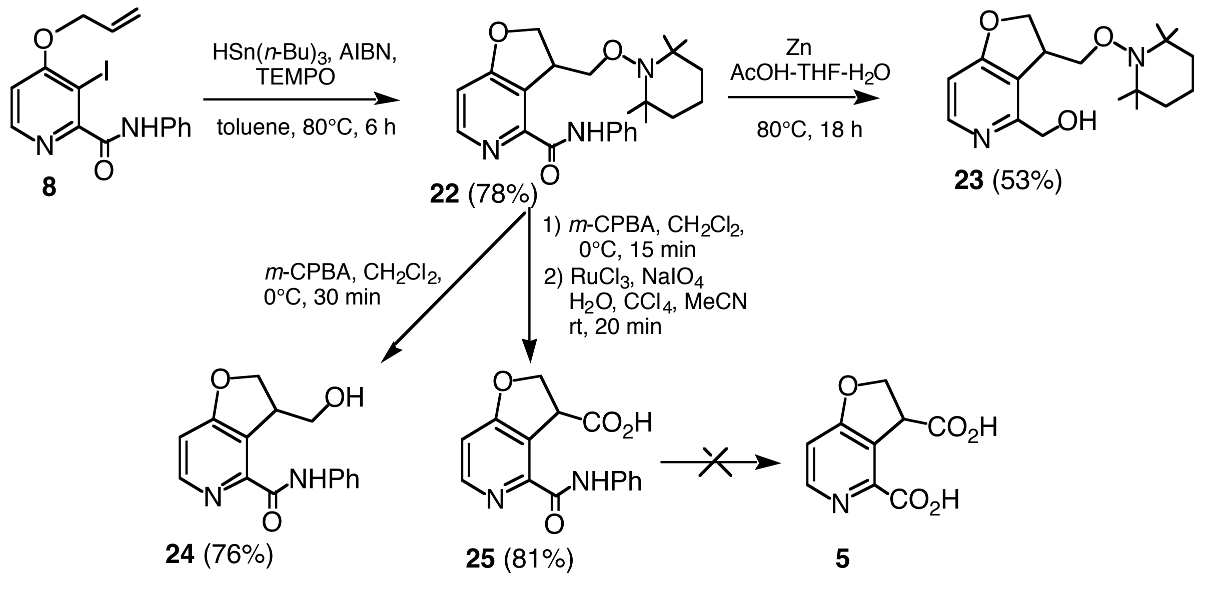


Scheme 3



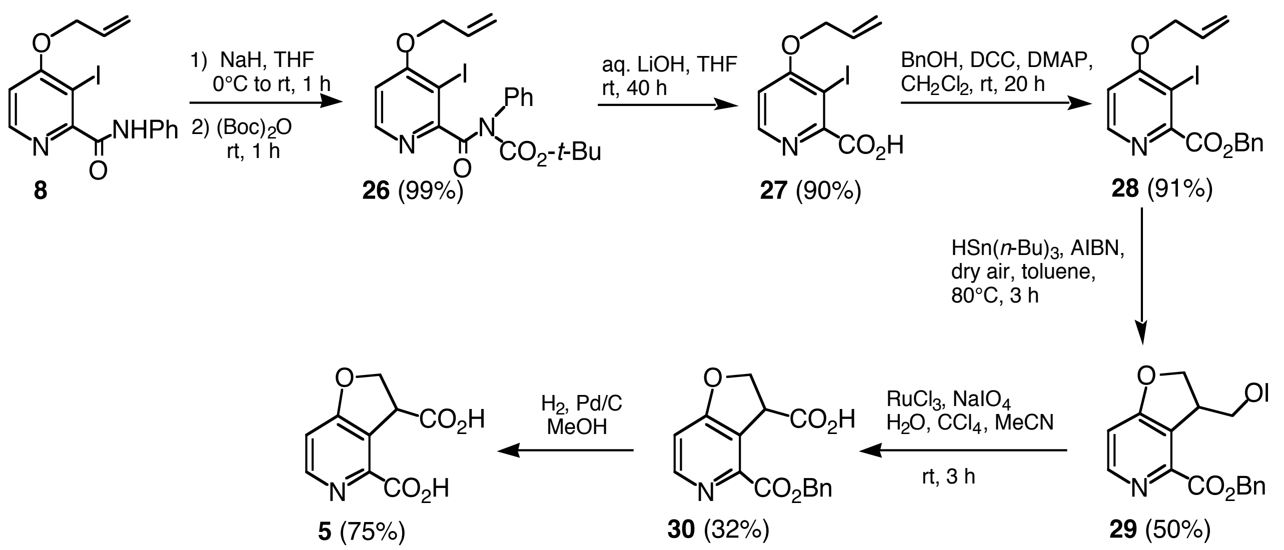
Scheme 4

TEMPO (2,2,6,6-tetramethyl-1-piperidine oxide) has been shown to be an excellent radical trap for free radical cyclizations,[6] providing an N-O bond in the final product which can be cleaved to an alcohol[6c] or an aldehyde[7] depending on the reaction conditions. When the 4-allyloxy derivative (**8**) was treated with tri-*n*-butyltin hydride and AIBN in hot toluene in the presence of TEMPO, the expected 3-piperidinyloxymethylfuropyridine (**22**) was obtained in 78% yield (Scheme 5). Unexpectedly, however, application to compound (**22**) of conditions known to afford the corresponding alcohol by cleavage of the N-O bond[6c,8] (i.e., zinc in acetic acid/THF/water at 80°C) provided exclusively **23**, the product of phenylcarboxamide reduction. Use of alternative methods shown to effect the expected N-O bond scission of the piperidinyl moiety in other systems ($LiAlH_4$[9] ; H_2 on palladium[10] or Raney nickel[11] ; $Mo(CO)_6$[12] ; SmI_2[13]) only led to recovery of starting material. However, when compound (**22**) was treated with *m*-chloroperbenzoic acid in dichloromethane for 30 min at 0°C,[7] a satisfactory yield (76%) of the 3-hydroxymethylfuropyridine (**24**) was obtained. While this latter compound could be isolated and oxidized to the corresponding 3-carboxylic acid (**25**), it was found to be more efficient to perform a Sharpless oxidation[14] directly on the crude alcohol, thereby providing **25** in 81% yield. With compound (**25**) in hand, all that remained was to effect hydrolysis of the carboxamide to the desired carboxylic acid (**5**). Disappointingly, however, all attempts to achieve this seemingly simple transformation, whether by use of strongly acidic or basic conditions, failed.



Scheme 5

The presence of this carboxamide group was originally necessary to allow regioselective iodination *via* the ortho-metalation strategy which ultimately gave access to the starting substrate (**8**).[3] It was thus decided to convert the phenylcarboxamido function of **8** to a more easily cleaved ester function before proceeding with construction of the fused heterocycle system. While again, the carboxamide function of compound (**8**) was resistant to simple aqueous base or acid hydrolysis, the *N*-Boc derivative (**26**), formed quantitatively by treating **8** successively with sodium hydride and Boc anhydride,[15] could now be hydrolyzed under mild conditions (1.5N LiOH, rt), providing the corresponding picolinic acid derivative (**27**) (Scheme 6).[16] The carboxylic acid function of the latter was then protected as the benzyl ester (**28**) by treatment with benzyl alcohol and DCC in the presence of catalytic DMAP. At this point, an alternative and simpler procedure was used for cyclization which obviated the utilization of TEMPO. Thus, treatment of compound (**28**) with tri-*n*-butyltin hydride and AIBN in the presence of air[17] now provided the desired cyclized 3-hydroxymethyl derivative (**29**) directly and in satisfactory yield (50%). Sharpless oxidation of the latter then gave the 3-carboxylic acid (**30**), albeit in modest yield. Finally, hydrogenolysis of the benzyl ester group provided the desired 2,3-dihydrofuro[3,2-*c*]pyridine-3,4-dicarboxylic acid (**5**).



Scheme 6

In conclusion, the 4-allyloxy-3-iodopicolinanilide derivative (**8**), resulting from our previously described ortho-metalation studies of picolinic acid derivatives, has served as a template for the preparation of **5**, a conformationally constrained analogue of the subtype selective NMDA receptor agonist homoquinolinic acid (**2**).

EXPERIMENTAL

General -Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as films or as KBr pellets with a Nicolet 205 FT-IR spectrophotometer. ^{1}H-NMR and

^{13}C NMR spectra were determined on Bruker 250 MHz or 300 MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization MS were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High resolution MS were obtained using a Kratos MS-80 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm). All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). Elemental analyses were performed at the ICSN,CNRS, Gif-sur-Yvette, France.

3-Iodo-4-prop-2-ynyloxypicolinanilide (12). To a suspension of sodium (0.15 g, 6.7 mmol) in anhydrous THF (20 mL) was added propargyl alcohol (0.7 mL, 12.3 mmol). The mixture was stirred at rt until complete disappearance of the sodium. It was then heated to reflux and a solution of 4-chloro-3-iodopicolinanilide[3] (**11**, 2 g, 5.58 mmol) in THF (5 mL) was added dropwise over 10 min. The reaction mixture was stirred and refluxed for 6 h and, after cooling to rt, water (5 mL) was added. The solvents were removed under reduced pressure, the residue was partitioned between water (50 mL) and ethyl acetate and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL), the organic fractions were combined, dried over sodium sulfate and evaporated under reduced pressure leaving a residue which was purified by column chromatography on silica gel (ethyl acetate/heptane 2:8). The minor component, compound (**12**), was first eluted (0.042 g, 2%). mp 169-174°C (heptane). IR (film) 2150, 1649 cm^{-1}. CIMS m/z 379 $(MH)^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 2.62 (s, 1H, ≡ CH), 4.91 (d, 2H, J = 2.3 Hz, OCH_2), 7.00 (d, 1H, J = 5.4 Hz, H-5), 7.14 (t, 1H, J = 7.5 Hz, PhH), 7.37 (t, 2H, J = 7.5 Hz, PhH), 7.75 (d, 2H, J = 7.5 Hz, PhH), 8.39 (d, 1H, J = 5.0 Hz, H-6), 9.99 (s, 1H, exchangeable with D_2O, NH). ^{13}C-NMR (50 MHz, $CDCl_3$) δ : 29.7, 57.2, 78.2, 84.2, 109.0, 119.8, 124.4, 129.0, 137.9, 148.5, 150.7, 161.7, 164.4. Anal. Calcd for $C_{15}H_{11}N_2O_2I.0.8H_2O$: C, 45.90 ; H, 3.24. Found : C, 46.24 ; H, 3.62.

Continued elution of the chromatography column afforded compound (**13**) (0.96 g, 75%) identical in all respects to the compound previously described.[3]

3-Iodo-4-prop-2-ynyloxy-*N*-methylpicolinanilide (15). Following the same procedure as for the preparation of compound (**12**), 4-chloro-3-iodo-*N*-methylpicolinanilide[3] (**14**, 2 g, 5.37 mmol) in THF (5 mL) was treated with sodium propargylate (prepared from sodium (0.12 g, 5.37 mmol) and propargyl alcohol (0.6 mL, 10.75 mmol) in THF (20 mL) as before). After work-up, the crude product was purified by column chromatography on silica gel (ethyl acetate/heptane 7:3) providing compound (**15**) as a white solid (1.72 g, 82%). mp 172-174°C (heptane). IR (film) 2152, 1652 cm^{-1}. CIMS m/z 393 (MH)$^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 2.57 (s, 1H, ≡CH), 3.53 (s, 3H, CH_3), 4.73 (d, 2H, J = 2.0 Hz, OCH_2), 6.65 (d, 1H, J = 5.0 Hz, H-5), 7.09-7.21 (m, 3H, PhH), 7.29 (d, 2H, J = 7.0 Hz, PhH), 8.22 (d, 1H, J = 5.0 Hz, H-6). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 29.7, 37.0, 56.8, 77.5, 83.5, 107.0, 127.0, 127.2, 128.8, 142.6, 149.8, 160.8, 162.6, 168.2. Anal. Calcd for $C_{16}H_{13}N_2O_2I$. 0.6 H_2O: C, 47.69; H, 3.55; N, 6.95. Found : C, 47.41 ; H, 3.59 ; N, 6.73.

3-Iodo-4-prop-2-ynyloxypyridine (18). Following the same procedure as for the preparation of compound (**12**), 4-chloro-3-iodopyridine[18] (**17**, 2 g, 8.37 mmol) in THF (5 mL) was treated with sodium propargylate (prepared from sodium (0.23 g, 10 mmol) and propargyl alcohol (1.12 mL, 20 mmol) in THF (20 mL) as before). After work-up, the crude product was purified by column chromatography on silica gel (ethyl acetate/heptane 1:1), providing starting material (**17**) (700 mg, 35%) followed by compound (**18**) (730 mg, 34%) obtained as a white powder. mp 82-85°C (heptane). IR (film) 2105 cm^{-1}. CIMS m/z 260 (MH)$^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 2.60 (s, 1H, ≡CH), 4.83 (d, 2H, J = 2.4 Hz, OCH_2), 6.91 (d, 1H, J = 5.0 Hz, H-5), 8.40 (d, 1H, J = 5.0 Hz, H-6), 8.78 (s, 1H, H-2). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 29.4, 56.2, 76.3, 84.9, 108.0, 150.3, 157.9, 161.9. Anal. Calcd for C_8H_6NOI : C, 37.09 ; H, 2.33 ; N, 5.41. Found : C, 37.31 ; H, 2.46 ; N, 5.29.

2,3-Dihydro-3-methylenefuro[3,2-*c*]pyridine (19). A solution of compound (**18**) (0.5 g, 1.93 mmol) in anhydrous toluene (20 mL) was degassed by bubbling argon for 15 min and then heated to 80°C. A solution of tri-*n*-butyltin hydride (0.62 mL, 2.3 mmol) and AIBN (0.038 g, 0.23 mmol) in toluene (10 mL) was added slowly over 1.5 h and the reaction mixture was stirred for 3 h at 80°C. After cooling, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (ethyl acetate/heptane 1:9) affording compound (**19**) as a colorless oil (230 mg, 88%). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.13-5.17 (m, 3H, H-2, =CH_a), 5.57 (m, 1H, =CH_b), 6.81 (d, 1H, J = 5.0 Hz, H-5), 8.34 (d, 1H, J = 5.0 Hz, H-6), 8.61 (s, 1H, H-2). ^{13}C -NMR (62.5 MHz, $CDCl_3$) δ : 76.0, 102.2, 106.8, 123.3, 128.3, 140.8, 143.3, 151.3. HRCIMS calcd for C_8H_8NO m/z 134.0606 found 134.0603.

(±)-2,3-Dihydro-*N*-phenyl-3-phenylselenylmethylfuro[3,2-*c*]pyridine-4-carboxamide (20). A mixture of compound (**8**) (0.5 g, 1.32 mmol) and diphenyl diselenide (1.43 g, 4.62 mmol) in anhydrous toluene (30 mL) was degassed by bubbling argon for 15 min and then heated to 80°C. A solution of tri-*n*-butyltin hydride (0.46 mL, 1.58 mmol) in anhydrous toluene (70 mL) was slowly added and the reaction mixture was stirred for 6 h at 80°C. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate/heptane 6:4) affording compound (**20**) as a yellow solid (360 mg, 67%). mp 127-130°C (heptane). IR (film) 1687 cm^{-1}. CIMS m/z 410 $(MH)^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ :4.26 (d, 2H, J = 4.3 Hz, CH_2Se), 5.07 (t, 2H, J = 9.0 Hz, H-2), 5.24-5.35 (m, 1H, H-3), 6.76 (d, 1H, J = 5.6 Hz, H-7), 7.11-7.47 (m, 8H, PhH), 7.78 (d, 2H, J = 8.0 Hz, PhH), 8.32 (d, 1H, J = 5.2 Hz, H-6), 9.89 (s, 1H, exchangeable with D_2O, NH). Anal. Calcd for $C_{21}H_{18}N_2O_2Se.0.7\ H_2O$: C, 59.78 ; H, 4.63 ; N, 6.64. Found : C, 59,65 ; H, 4,65 ; N, 6.37.

(±)-2,3-Dihydro-*N*-phenyl-3-(2,2,6,6-tetramethylpiperidin-1-yloxymethyl)furo[3,2-*c*]-pyridine-4-carboxamide (**22**). Using the same procedure as for the preparation of **19**, a solution of compound (**8**) (1.0 g, 2.63 mmol) and TEMPO (1.61 g, 9.2 mmol) in toluene (30 mL) was treated with tri-*n*-butyltin hydride (1.14 mL, 3.16 mmol) in toluene (70 mL). After work-up, the residue was purified by column chromatography on silica gel (ethyl acetate/heptane 0.5:9.5) to provide compound (**22**) as a colorless oil (835 mg, 78%). IR (film) 1687 cm^{-1}. CIMS m/z 410 $(MH)^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 0.87-1.63 (m, 18H, $4xCH_3$, $3xCH_2$ of TEMPO), 4.00 (pseudo t, 1H, J = 6.8 Hz, $NOCH_a$), 4,14 (dd, J_{gem} = 8.2 Hz, J = 3.5 Hz, $NOCH_b$), 4.34-4.40 (m, 1H, H-3), 4.64 (pseudo t, 1H, J = 8.6 Hz, H-2a), 4.90 (dd, 1H, J = 8.6 Hz, J = 2.8 Hz, H-2b), 6.89 (d, 1H, J = 5.0 Hz, H-7), 7.14 (t, 1H, J = 8.2 Hz, PhH), 7.36 (t, 2H, J = 8.2 Hz, PhH), 7.73 (d, 2H, J = 8.2 Hz, PhH), 8.31 (d, 1H, J = 5.0 Hz, H-6), 10.10 (s, 1H, exchangeable with D_2O, NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 17.6-41.8, 60.4, 76.9, 77.0, 108.2, 120.1, 124.6, 127.3, 129.5, 138.4, 146.4, 149.0, 152.7, 170.2. Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39 ; H, 7.63 ; N, 10.26. Found : C, 70.71 ; H, 7.79 ; N, 9.86.

(±)-2,3-Dihydro-4-hydroxymethyl-3-(2,2,6,6-tetramethylpiperidin-1-yloxymethyl)furo-[3,2-*c*]pyridine (23). Zinc (0,12 g, 1.84 mmol) was added to a solution of compound (**22**) (50 mg, 0.12 mmol) in a mixture of acetic acid (3 mL), water (1 mL) and THF (1 mL). The mixture was stirred at 70°C for 18 h, cooled and evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous sodium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (2 x 10 mL), the organic fractions were combined, dried over sodium sulfate and the solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/heptane 6:4) affording compound (**23**) as an amorphous white solid (21 mg, 53%). IR (film) 3136 cm^{-1}. CIMS m/z 321 (MH)$^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.06-1.60 (m, 18H, 4 x CH_3, 3 x CH_2 of TEMPO), 3.65-3.96 (m, 3H, N-O-$C\underline{H}_2C\underline{H}$), 4.25 (br s, 1H, exchangeable with D_2O, OH), 4.65 (d, 2H, J = 5.7 Hz, H-2), 4.75 (s, 2H, $C\underline{H}_2OH$), 6.71 (d, 1H, J = 5.0 Hz, H-7), 8.28 (d, 1H, J = 5.0 Hz, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 16.8, 20.0, 29.5, 32.7, 32.9, 39.1, 39.4, 59.8, 61.8, 75.9, 76.3, 104.9, 120.6, 148.9, 155.3, 167.5. Anal. Calcd for $C_{18}H_{28}N_2O_3$.0.5 H_2O : C, 65.63 ; H, 8.81. Found : C, 65.57 ; H, 8.87.

(±)-2,3-Dihydro-3-hydroxymethyl-*N*-phenylfuro[3,2-*c*]pyridine-4-carboxamide (24). To a olution of compound (**22**) (0.1 g, 0.24 mmol) in dichloromethane (10 mL) was added dropwise at -78°C a solution of *m*-chloroperbenzoic acid (80% purity, 50 mg, 0.24 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 30 min at 0°C, water (10 mL) was added, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, washed with 15% aqueous sodium hydrogen sulfite (2 x 5 mL) and with saturated aqueous sodium hydrogen carbonate (2 x 5 mL) and then dried over sodium sulfate. Evaporation of the solvents under reduced pressure left a residue which was purified by column chromatography on silica gel (ethyl acetate/heptane 1:1) affording compound (**24**) as an oil (50 mg, 76%). IR (film) 3341, 1687 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 3.22 (br s, 1H, exchangeable with D_2O, OH), 3.84-3.96 (m, 2H, $C\underline{H}_2OH$), 4.32 (m, 1H, H-3), 4.66 (m, 2H, H-2), 6.92 (br s, 1H, H-7), 7.15 (t, 1H, J = 7.4 Hz, PhH), 7.38 (t, 2H, J = 7.4 Hz, PhH), 7.72 (d, 2H, J = 7.4 Hz, PhH), 8.34 (br s, 1H, H-6), 10.26 (s, 1H, exchangeable with D_2O, NH). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 45.1, 64.6, 77.2, 109.0, 121.1, 125.5, 127.0, 129.9, 139.1, 147.4, 150.2, 164.4, 171.2. HRCIMS calcd for $C_{15}H_{15}N_2O_3$ m/z 271.1082 found 271.1086.

(±)-2,3-Dihydro-4-(phenylcarbamoyl)furo[3,2-*c*]pyridine-3-carboxylic acid (25). To a solution of compound (**22**) (0.2 g, 0.48 mmol) in dichloromethane (10 mL) was added dropwise over 5 min at 0°C a solution of *m*-chloroperbenzoic acid (80% purity, 0.1 g, 0.48 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 10 min at rt, water (5 mL) was added, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, washed with 15% aqueous sodium hydrogen sulfite (2 x 5 mL) and with saturated aqueous sodium hydrogen carbonate (2 x 5 mL) and then dried over sodium sulfate. The solvents were removed under reduced pressure and the residue was partitioned between carbon tetrachloride (8 mL) and water (12 mL). Ruthenium trichloride (12 mg, 0.056 mmol) and sodium periodate (0.42 g, 1.94 mmol) were added, the mixture was stirred vigorously for 20 min at rt, diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried over sodium sulfate and the solvents were removed under reduced pressure. Trituration of the residue with heptane-ethyl acetate (95:5) provided compound (**25**) as an oil (105 mg, 81%). IR (film) 1729, 1675 cm^{-1}.^{1}H-NMR (250 MHz, $CDCl_3$) δ:4.63 (t, 1H, J = 8.7 Hz, H–3), 4.86 (dd, 1H, J = 8.7 Hz, J=2.4 Hz, H-2a), 5.62 (dd, 1H, J = 8.7 Hz, J = 2.4 Hz, H-2b), 7.02 (d, 1H, J = 5.4 Hz, H-7), 7.27 (t, 1H, J = 7.7 Hz, PhH), 7.38 (t, 2H, J = 7.7 Hz, PhH), 7.45 (d, 2H, J = 7.7 Hz, PhH), 8.43 (d, 1H, J = 5.4 Hz, H-6), 10.41 (s, 1H, exchangeable with D_2O, NH). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 46.7, 75.2, 109.6, 120.7, 123.3, 126.1, 129.5, 136.3, 145.1, 150.0, 164.8, 169.5, 169.7. HRCIMS calcd for $C_{15}H_{13}N_2O_4$ m/z 285.0875 found 285.0876.

4-Allyloxy-*N*-*t*-butyloxycarbonyl-3-iodopicolinanilide (26). To a solution of compound (**8**) (6.4 g, 16.8 mmol) in anhydrous THF (40 mL) was added sodium hydride (2.0 g, 50.0 mmol of a 60% dispersion in oil) in small portions over 30 min at 0°C. The reaction mixture was stirred at rt for 30 min and a solution of di-*t*-butyl dicarbonate (15.0 g, 68.8 mmol) in anhydrous THF (20 mL) was added. Stirring was maintained for 1 h at rt, the solution was cooled to 0°C and saturated aqueous ammonium chloride (30 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL), the organic extracts were combined, dried over magnesium sulfate and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (heptane/ethyl acetate 9:1 followed by 1:1) providing compound (**26**) as a white powder (8.0 g, 99%). mp 151-153°C (ethyl acetate). IR (KBr) 1740, 1690 cm^{-1}. CIMS m/z 481 (MH)$^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 1.22 (s, 9H, 3 x CH_3), 4.71 (m, 2H, OCH_2), 5.38 (dd, 1H, J = 1.2 Hz, J = 10.7 Hz, $CH=CH_a$), 5.53 (dd, 1H, J = 1.2 Hz, J = 17.5 Hz, $CH=CH_b$), 6.02 (m, 1H, $C\underline{H}=CH_2$), 6.72 (d, 1H, J = 5.5 Hz, H-5), 7.40 (m, 5H, PhH), 8.38 (d, 1H, J = 5.5 Hz, H-6). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 27.5, 69.8, 81.8, 84.0, 107.4, 118.7, 128.4, 129.0, 131.1, 139.0, 150.0, 151.5, 161.0, 163.0. Anal. Calcd for $C_{20}H_{21}N_2O_4I$: C, 50.00 ; H, 4.37 ; N, 5.83. Found : C, 49.61 ; H, 4.41 ; N, 5.47.

4-Allyloxy-3-iodopicolinic acid (27). A solution of compound (**26**) (8.0 g, 16.7 mmol) in THF (100 mL) was treated with aqueous lithium hydroxide solution (75 mL of a 1.5 N solution ; 113 mmol) for 40 h at rt. The organic solvent was removed under reduced pressure and the residual aqueous phase was washed with ethyl acetate (40 mL). The aqueous fraction was acidified to pH 2-3 by addition of aqueous 1N HCl solution and the mixture was extracted with ethyl acetate (12 x 30 mL). The organic extracts were combined, dried over magnesium sulfate and the solvents were removed under reduced pressure leaving compound (**27**) as a white solid (4.6 g, 90%). mp 151-153°C (ethyl acetate). IR (KBr) 3410, 1663 cm^{-1}. EIMS m/z 305 (M^+). ^{1}H-NMR (250 MHz, CD_3OD) δ : 4.48 (m, 2H, OCH_2), 5.35 (dd, 1H, J = 1.0 Hz, J = 10.7 Hz, $CH{=}C\underline{H}_a$), 5.55 (dd, 1H, J = 1.6 Hz, J = 19.0 Hz, $CH{=}C\underline{H}_b$), 6.08 (m, 1H, $C\underline{H}{=}CH_2$), 7.11 (d, 1H, J = 6.0 Hz, H-5), 8.34 (d, 1H, J = 6.0 Hz, H-6). ^{13}C-NMR (62.5 MHz, CD_3OD) δ : 71.7, 83.2, 109.5, 118.9, 132.5, 148.8, 157.7, 167.7, 168.4. Anal. Calcd for $C_9H_8NO_3I.0.5H_2O$: C, 34.39 ; H, 2.54 ; N, 4.46. Found : C, 34.66 ; H, 2.82 ; N, 4.07.

Benzyl 4-allyloxy-3-iodopicolinate (28). A solution of compound (**27**) (2.0 g, 6.6 mmol) and benzyl alcohol (1.08 g, 10.0 mmol) in anhydrous dichloromethane (60 mL) was treated with DCC (1.76 g, 8.5 mmol) and DMAP (122 mg, 1.0 mmol) at rt under argon for 20 h. The reaction mixture was filtered, the filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, affording compound (**28**) as a colorless oil (2.37 g, 91%). IR (film) 1738, 1567 cm^{-1}. CIMS m/z 396 $(MH)^+$. ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 4.68 (m, 2H, OCH_2), 5.31 (dd, 1H, J = 1.3 Hz, J = 10.7 Hz, $CH{=}C\underline{H}_a$), 5.44 (s, 2H, $C\underline{H}_2Ph$), 5.51 (dd, 1H, J = 1.3 Hz, J = 17.5 Hz, $CH{=}C\underline{H}_b$), 5.99 (m, 1H, $C\underline{H}{=}CH_2$), 6.73 (d, 1H, J = 5.6 Hz, H-5), 7.23-7.43 (m, 5H, PhH), 8.36 (d, 1H, J = 5.6 Hz, H-6). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 67.9, 69.9, 83.5, 108.5, 118.5, 128.5, 128.6, 128.8, 130.9, 135.1, 150.4, 156.0, 163.9, 165.0. Anal. Calcd for $C_{16}H_{14}NO_3I$: C, 48.60 ; H, 3.54 ; N, 3.54. Found : C, 48.64 ; H, 3.61 ; N, 3.41.

Benzyl (±)-2,3-dihydro-3-hydroxymethylfuro[3,2-*c*]pyridine-4-carboxylate (29). To a solution of compound (**28**) (54 mg, 0.13 mmol) in anhydrous toluene (5 mL) maintained at 80°C and through which dry air was bubbled continually was slowly added over 3 h a solution of tri-*n*-butyltin hydride (150 µL, 0.55 mmol) and AIBN (49 mg, 0.3 mmol) in toluene (1 mL). After completion of the addition, the reaction mixture was cooled, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (heptane/ethyl acetate 5:1 to 3:1)affording compound (**29**) as an oil which was used in the following step without further purification (21 mg, 50%). IR (film) 3400, 1718, 1577 cm^{-1}. EIMS m/z 285 (M$^+$). ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 3.70 (d, 2H, J = 5.5 Hz, $C\underline{H}_2OH$), 3.95 (m, 1H, H-3), 4.58 (m, 1H, H-2a), 4.78 (dd, 1H, J = 3.2 Hz, J = 8.7 Hz, H-2b), 5.34 (2d, 2H, J = 12 Hz, $C\underline{H}_2Ph$), 6.79 (d, 1H, J = 5.2 Hz, H-7), 7.31-7.43 (m, 5H, PhH), 8.28 (d, 1H, J = 5.2 Hz, H-6). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ : 43.8, 65.3, 68.2, 76.0, 108.5, 128.4, 128.6, 128.7, 128.8, 135.3, 144.1, 150.2, 164.8, 169.1.

(±)-4-Benzyloxycarbonyl-2,3-dihydrofuro[3,2-*c*]pyridine-3-carboxylic acid (30). To a biphasic mixture of compound (**29**) (66 mg, 0.23 mmol) in acetonitrile (2 mL), carbon tetrachloride (2 mL) and water (3 mL) were added successively at rt sodium periodate (190 mg, 40.9 mmol) and ruthenium chloride (2.1 mg, 0.01 mmol). The reaction mixture was stirred vigorously for 3 h, and after addition of water (10 mL), it was extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over magnesium sulfate, evaporated to dryness under reduced pressure and the residue purified by preparative tlc on silica gel (dichloromethane/methanol 10:1), providing compound (**30**) as an amorphous solid (22 mg, 32%). IR (KBr) 3380, 1720, 1603 cm^{-1}. EIMS m/z 299 (M$^+$). ^{1}H-NMR (250 MHz, CD_3OD) δ : 4.56 (m, 1H, H-2a), 4.82 (m, 1H, H-2b), 4.86 (m, 1H, H-3), 5.24 (d, 1H, J = 12.0 Hz, $C\underline{H}_aPh$), 5.29 (d, 1H, J = 12.0 Hz, $C\underline{H}_bPh$), 6.96 (d, 1H, J = 8.0 Hz, H-7), 7.32-7.49 (m, 5H, PhH), 8.29 (d, 1H, J = 8.0 Hz, H-6). ^{13}C-NMR (62.5 MHz, CD_3OD) δ : 30.3, 51.7, 68.4, 78.4, 109.5, 129.3, 129.5, 129.7, 137.1, 146.3, 150.6, 166.5, 170.6. Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21 ; H, 4.35 ; N, 4.68. Found : C, 64.01 ; H, 4.25 ; N, 5.02.

(±)-2,3-Dihydrofuro[3,2-*c*]pyridine-3,4-dicarboxylic acid (5). A solution of compound (**30**) (15 mg, 0.05 mmol) in methanol (6 mL) was stirred for 4 h at rt under an atmosphere of hydrogen in the presence of 10% palladium on carbon (20 mg). The reaction mixture was filtered through celite, the filter pad was washed with warm methanol, the filtrate and washings were combined and evaporated to dryness under reduced pressure, affording compound (**5**) as a white solid (8 mg, 75%). mp 180-182°C (methanol).

CIMS m/z 210 $(MH)^+$. ^{1}H-NMR (250 MHz, D_2O) δ : 4.92 (m, 1H, H-3), 5.15 (m, 2H, H-2), 7.40 (d, 1H, J = 5.7 Hz, H-7), 8.47 (d, 1H, J = 5.7 Hz, H-6). ^{13}C-NMR (62.5 MHz, CD_3OD/D_2O) δ : 47.0, 78.2, 117.0, 125.1, 143.8, 144.8, 162.0, 172.7, 175.2. Anal. Calcd for $C_9H_7NO_5.H_2O$: C, 47.58 ; H, 3.96 ; N, 6.17. Found : C, 47.52 ; H, 4.10 ; N, 6.15.

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