Regiospecific Electrocyclization of β-Arylvinyl Ketenimines. Formal Syntheses of the Alkaloid from Marine Origin Aaptamine

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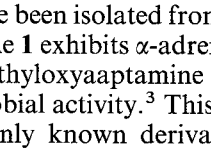
Preparation of 6,7-dimethoxy-1-methyl-8-nitroisoquinoline and 6,7-dimethoxy-1-methylisoquinoline, used as precursors in the synthesis of the alkaloid aaptamine, is reported. The method is based on the regiospecific electrocyclization of the appropriate β-arylvinyl ketenimine available by aza-Wittig reaction of the corresponding vinyl iminophosphorane with (trimethylsilyl)ethenone.

The aqueous ethanol extracts of the Okinawan sea sponge *Aaptos aaptos* afforded a bright yellow substance christened aaptamine and assigned structure **1**.[1] Also demethylaaptamine and demethylated and oxidised variant **2** have been isolated from the same natural source.[2] Aaptamine **1** exhibits α-adrenoceptor blocking activity, while demethyloxyaaptamine **2** possesses antitumor and antimicrobial activity.[3] This novel group of bases represents the only known derivatives of 1*H*-benzo[*de*][1,6]naphthyridine ring system in a naturally occurring substance. This unusual nature of compound **1** has focused considerable attention on its synthesis. From a synthetic viewpoint the 1*H*-benzo[*de*][1,6]naphhyridine ring system can be viewed either as a quinoline or as an isoquinoline, but with an additional fused six-membered nitrogen-containing ring (Figure 1).



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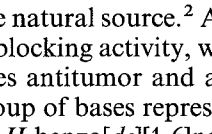

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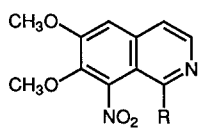
Figure 1

Of the seven syntheses[4-10] of aaptamine **1** previously reported, four took an approach in which the third ring was fused to an existing isoquinoline.[7-10] In this sense, compounds **3** (Joule, Cava and Yamanaka syntheses) and **4** (Tollari synthesis) have been used as suitable building blocks in the synthesis of aaptamine **1** (Figure 2).



3a R = CH_3

3b R = CH_2CO_2Et

3c R = $CH_2CH(OCH_3)_2$

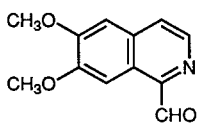


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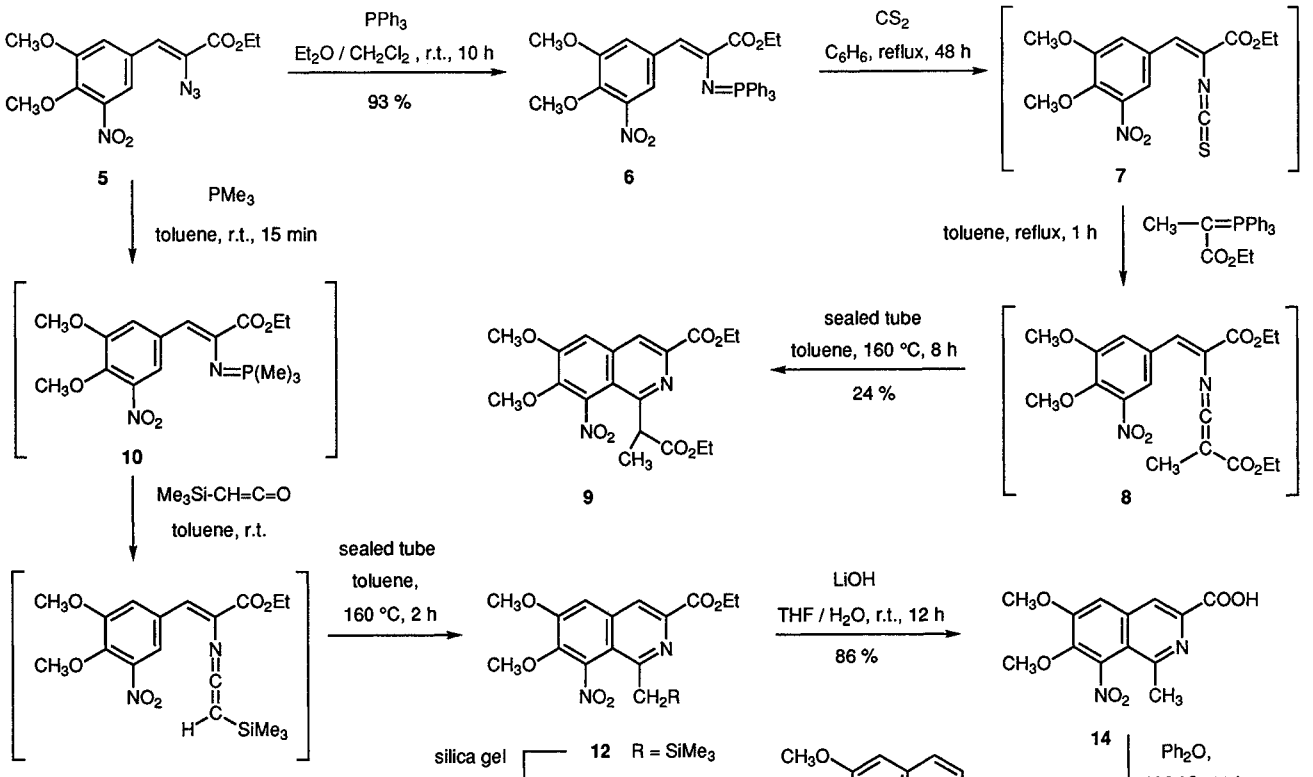
Figure 2

In connection with the synthesis of a number of isoquinoline and β-carboline-containing alkaloids,[11] we sought to find methods that could provide convenient entries to highly functionalized isoquinoline derivatives. It occured to us that an iminophosphorane-based approach could be suitably applied to the synthesis of the key intermediates **3** and **4**, successfully used in the above mentioned syntheses of the alkaloid aaptamine **1**.

Condensation of 3,4-dimethoxy-5-nitrobenzaldehyde[5] with ethyl azidoacetate in the presence of NaOEt at −10 °C provided the vinyl azide **5** in 47% yield, which was converted into the iminophosphorane **6** in 93% yield by Staudinger reaction[12] with triphenylphosphane in dichloromethane/diethyl ether at room temperature. Iminophosphorane **6** was converted into the 1-substituted isoquinoline **9** in 24% overall yield by an one-flask process involving sequential treatment with carbon disulfide, (carbethoxyethylidene)triphenylphosphorane and further heating at 160 °C. The conversion **6** → **9** probably involves an initial aza-Wittig-type reaction[13] between the iminophosphorane **6** and carbon disulfide to give the vinyl isothiocyanate **7**, which reacts with (carbethoxyethylidene)triphenylphosphorane to afford the ketenimine[14] **8** (as evidenced by IR). Eventually thermally induced electrocyclic ring closure of the vinyl ketenimine **8**, involving the aryl ring as a 2π-component, yields the isoquinoline derivative **9**. This compound may be converted into the 3-methylaaptamine in a straightforward manner[8] (Scheme 1).

Likewise, vinyl azide **5** was converted into 3-ethoxycarbonyl-6,7-dimethoxy-1-methyl-8-nitroisoquinoline **(13)** in 62% overall yield by a one-flask process involving sequential treatment with trimethylphosphane, (trimethylsilyl)ethenone,[15] heating at 160 °C and chromatographic separation using a silica gel column. The conversion **5** → **13** can be understood by an initial Staudinger reaction between the vinyl azide **5** and trimethylphosphane to give the iminophosphorane **10**, which was used without purification for the next step. The aza-Wittig-type reaction of **10** with (trimethylsilyl)ethenone provides the ketenimine[16] **11** (evidenced by a strong band at 2004 cm^{-1} in the IR), which undergoes electrocyclic ring closure to give **12** and, finally, carbon–silicon bond cleavage in compound **12** by the action of silica gel affords **13** (Scheme 1). The later assumption is supported by the fact that compound **12** was isolated and fully characterized. In addition, when a solution of **12** was stirred in the presence of silica gel at room temperature, compound **13** was obtained in almost quantitative yield. Compound **13** was converted into the desired 6,7-dimethoxy-1-methyl-8-ni-

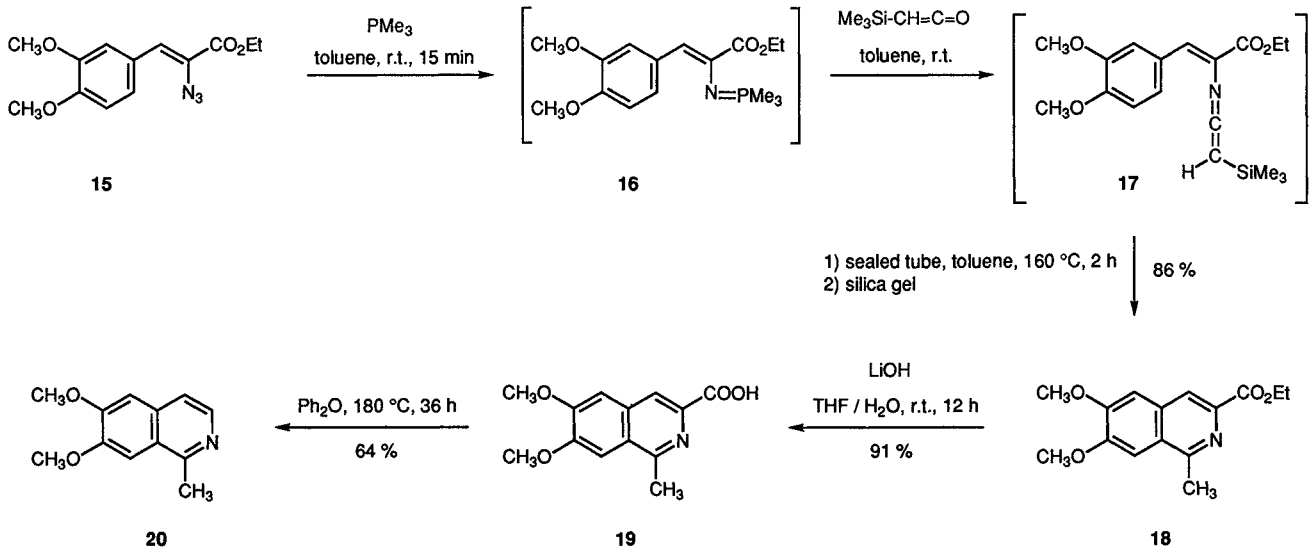


Scheme 1

troisoquinoline (**3a**) by hydrolysis with LiOH in THF/H_2O (86%) followed by thermal decarboxylation (68%).

This constitutes a formal total synthesis of aaptamine since **3a** is the isoquinoline derivative of the Joule synthesis[10] of aaptamine, and may be easily converted into the target molecule.

On the other hand, condensation of 3,4-dimethoxybenzaldehyde with ethyl azidoacetate under standard conditions afforded the vinyl azide **15** in 72% yield. This compound was transformed into the 3-ethoxycarbonyl-6,7-dimethoxy-1-methylisoquinoline (**18**) in 86% overall yield as previously described for the conversion **5** → **13**. When, in this reaction sequence, acetaldehyde was used instead of (trimethylsilyl)ethenone isoquinoline derivative **18** was also obtained, although the completion of the reaction required a longer period of time (48 h) and the yield was dramatically lower (25%). Conversion of the isoquinoline derivative **18** into the key intermediate **20** was achieved by hydrolysis with LiOH in THF/H_2O



Scheme 2

(91%) followed by decarboxylation in diphenyl ether at 180°C (64%) (Scheme 2).

This constitutes a second formal total synthesis of aaptamine **1**. Compound **20** may be easily transformed into **1** either by the sequence oxidation, condensation with nitromethane and further nitrene insertion,[9] or by nitration, oxidation, condensation with nitromethane and finally reduction.[10]

A final word about the thermal behaviour of ketenimines **8, 11** and **17** is relevant. These compounds underwent electrocyclization to give the isoquinoline derivatives **9, 13** and **18** respectively in a regiospecific fashion. NOE difference experiments confirmed the proposed structures of **9** and **13**. Thus, in compound **13** irradiation of the H-4 proton signal induced a 14% enhancement of the H-5 signal, whereas irradiation of the H-5 proton induced in addition a 5% enhancement of the methoxy group signal at position 6.

In conclusion, we have demonstrated that the tandem aza-Wittig/electrocyclic ring closure of vinyl ketenimines affords a convenient entry to the preparation of polysubstituted isoquinolines, used as building blocks in the synthesis of the alkaloid aaptamine.

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spetra were obtained as Nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 (200 MHz) or a Varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Microanalyses were performed on a Perkin-Elmer 240C instrument.

Ethyl α-Azido-3,4-dimethoxy-5-nitrocinnamate (5):
A mixture of ethyl azidoacetate (10.32 g, 80 mmol) and 3,4-dimethoxy-5-nitrobenzaldehyde (4.22 g, 20 mmol) in anhyd THF (25 mL) was added dropwise under N_2 at −10°C to a well-stirred solution containing Na (1.84 g, 80 mmol) in anhyd EtOH (100 mL). The mixture was stirred for 6 h, poured into aqueous NH_4Cl (200 mL) and then extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O, brine and dried ($MgSO_4$). The $MgSO_4$ was removed by filtration and the solvent concentrated to dryness. The resulting solid was recrystallized from EtOH to give **5** (3.02 g, 9.4 mmol); yield 47%; mp 114–116°C.

MS (EI, 70 eV): m/z (%) = 322 (M^+, 7), 160 (100).

IR (Nujol): ν = 2121, 1709, 1537, 1382 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.41 (t, 3H, J = 7.1 Hz), 3.96 (s, 3H), 4.00 (s, 3H), 4.38 (q, 2H, J = 7.1 Hz), 6.77 (s, 1H), 7.60 (d, 1H, J = 2.1 Hz), 7.77 (d, 1H, J = 2.1 Hz).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 14.11, 56.47, 62.01, 62.56, 117.24, 118.17, 121.92, 127.00 (s), 129.00 (s), 143.06 (s), 144.65 (s), 153.63 (s), 162.90 (s).

$C_{13}H_{14}N_4O_6$	calc.	C 48.45	H 4.38	N 17.38
(322.3)	found	48.37	4.45	17.24

Ethyl 3,4-Dimethoxy-5-nitro-α-[(triphenylphosphoranylidene)amino]-cinnamate (6):
To a solution of PPh_3 (1.05 g, 4 mmol) in anhyd Et_2O (25 mL) was added, dropwise at r.t. and under N_2, a solution of **5** (1.29 g, 4 mmol) in anhyd CH_2Cl_2 (25 mL). The mixture was stirred at r.t. for 10 h, the solvent was concentrated to dryness and the solid residue was recrystallized from benzene/hexane to give **6** (2.07 g, 3.72 mmol); yield 93%; mp 152–153°C.

MS (EI, 70 eV); m/z (%) = 556 (M^+, 13), 201 (100).

IR (Nujol): ν = 1697, 1529, 1330, 1106 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 0.98 (t, 3H, J = 7.2 Hz), 3.66 (s, 3H), 3.84 (q, 2H, J = 7.2 Hz), 3.93 (s, 3H), 6.57 (d, 1H, J = 7.5 Hz), 7.40–7.49 (m, 9H), 7.65–7.74 (m, 7H), 8.43 (d, 1H, J = 1.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.94, 56.09, 60.99, 61.89, 112.78 (d, J_{P-C} = 20.1 Hz), 116.81 (d, J_{P-C} = 4.5 Hz), 128.27 (d, J_{P-C} = 12.1 Hz), 131.13 (d, J_{P-C} = 3.0 Hz), 132.24 (d, J_{P-C} = 9.6 Hz), 132.34 (d, J_{P-C} = 103.7 Hz), 134.74 (s), 138.42 (d, J_{P-C} = 7.6 Hz), 139.78 (s), 144.63 (s), 153.07 (s), 167.32 (d, J_{P-C} = 8.1 Hz), one carbon was not observed.

^{31}P NMR (121 MHz, $CDCl_3/H_3PO_4$ 85%): δ = 10.69.

$C_{31}H_{29}N_2O_6P$	calc.	C 66.90	H 5.25	N 5.03
(556.5)	found	66.78	5.18	5.19

Ethyl 2-(3-Ethoxycarbonyl-6,7-dimethoxy-8-nitro-1-isoquinoline)-propanoate (9):
To a solution of **6** (0.28 g, 0.5 mmol) in anhyd benzene (25 mL), CS_2 (5 mL) was added. The mixture was stirred at reflux temperature for 48 h. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in anhyd toluene (25 mL) and (carbethoxyethylidene)triphenylphosphorane (0.18 g, 0.5 mmol) was added at once. The mixture was heated at reflux temperature for 1 h and then 8 h at 160°C in a sealed tube. The solvent was evaporated and the crude mixture was chromatographed on a silica gel column using EtOAc/hexane (1 : 1) as eluent to give **9** (0.049 g, 0.12 mmol); yield 24%.

MS (EI, 70 eV): m/z (%) = 406 (M^+, 7), 360 (100).

IR (Nujol): ν = 1737, 1537, 1360, 1268 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.11 (t, 3H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz), 1.52 (d, 3H, J = 6.8 Hz), 3.95 (s, 3H), 3.99 (s, 3H), 4.04–4.19 (m, 3H), 4.28–4.41 (m, 2H), 7.25 (s, 1H), 8.23 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.91, 14.13, 17.65, 44.21, 56.47, 60.87, 61.52, 62.65, 109.70, 114.86 (s), 121.42, 134.80 (s), 141.21 (s), 141.39 (s), 144.27 (s), 154.73 (s), 155.90 (s), 164.98 (s), 172.43 (s).

3-Ethoxycarbonyl-6,7-dimethoxy-1-methyl-8-nitroisoquinoline (13):
To a solution of **5** (0.64 g, 2 mmol) in anhyd toluene (20 mL), PMe_3 (2 mL of a 1 M solution) was added dropwise at r.t. and the mixture was stirred for 15 min. Then, (trimethylsilyl)ethenone (0.23 g, 2 mmol) was added and the new mixture was heated in a sealed tube at 160°C for 2 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc as eluent to give **13** (0.39 g, 1.23 mmol); yield 62%; mp 140°C (EtOAc/hexane).

MS (EI, 70 eV): m/z (%) = 320 (M^+, 11), 248 (100).

IR (Nujol): ν = 1712, 1535, 1359 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.47 (t, 3H, J = 7.2 Hz), 2.86 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 4.51 (q, 2H, J = 7.2 Hz), 7.33 (s, 1H), 8.35 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 14.30, 22.76, 56.49, 61.93, 62.74, 109.29, 115.76 (s), 121.32, 134.16 (s), 141.30 (s), 144.20 (s), 154.38 (s), 154.99 (s), 165.20 (s), one carbon was not observed.

$C_{15}H_{16}N_2O_6$	calc.	C 56.25	H 5.03	N 8.74
(320.3)	found	56.37	5.19	8.89

In this reaction can be isolated and identified *3-ethoxycarbonyl-6,7-dimethoxy-8-nitro-1-(trimethylsilyl)methylisoquinoline* **(12)**; mp 128–130°C (Et_2O).

MS (EI, 70 eV): m/z (%) = 392 (M^+, 7), 248 (100).

IR (Nujol): ν = 1711, 1536, 1359 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$/TMS): δ = 0.01 (s, 9H), 1.42 (t, 3H, J = 7.1 Hz), 2.56 (s, 2H), 3.99 (s, 3H), 4.03 (s, 3H), 4.43 (q, 2H, J = 7.1 Hz), 7.27 (s, 1H), 8.19 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/TMS): δ = 1.16, 14.30, 26.20, 56.46, 61.58, 62.74, 109.42 (s), 109.54, 115.39 (s), 119.47, 134.62 (s), 141.29 (s), 143.82 (s), 154.72 (s), 157.84 (s), 165.56 (s).

$C_{18}H_{24}N_2O_6Si$	calc.	C 55.08	H 6.16	N 7.14
(392.5)	found	55.29	6.02	7.25

6,7-Dimethoxy-1-methyl-8-nitroisoquinoline-3-carboxylic Acid (14):
To a stirred solution of **13** (0.32 g, 1 mmol) in THF (20 mL) was added in one portion $LiOH \cdot H_2O$ (0.13 g, 3 mmol) in H_2O (6 mL). The mixture was stirred at r.t. for 12 h. After removing the THF under reduced pressure, H_2O (10 mL) was added to the remaining aqueous solution. Then HCl (2 M) was added until pH = 5. The precipitate which formed was filtered off, washed with H_2O, dried and recrystallized from toluene to give **14** (0.25 g, 0.86 mmol); yield 86%; mp 204–205°C.

MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 22), 115 (100).

IR (Nujol): ν = 1718, 1535, 1359 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6/TMS): δ = 2.66 (s, 3H), 3.98 (s, 3H), 4.08 (s, 3H), 7.98 (s, 1H), 8.48 (s, 1H), 10.39 (br s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ = 21.98, 57.00, 62.61, 111.18, 114.42 (s), 121.26, 134.17 (s), 140.57 (s), 141.20 (s), 143.54 (s), 152.36 (s), 154.38 (s), 165.95 (s).

$C_{13}H_{12}N_2O_6$	calc.	C 53.43	H 4.14	N 9.58
(292.2)	found	53.59	4.21	9.37

6,7-Dimethoxy-1-methyl-8-nitroisoquinoline (3a):
A solution of **14** (0.146 g, 0.5 mmol) in Ph_2O (4 mL) was heated at 180°C for 12 h. After cooling, the mixture was chromatographed directly on a silica gel column using EtOAc/hexane (7 : 3) as eluent to give **3a** (0.084 g, 0.34 mmol); yield 68%.

Ethyl α-Azido-3,4-dimethoxycinnamate (15):
A mixture of ethyl azidoacetate (10.32 g, 80 mmol) and 3,4-dimethoxybenzaldehyde (3.32 g, 20 mmol) in anhyd EtOH (25 mL) was added dropwise under N_2 at −10°C to a well-stirred solution containing Na (1.84 g, 80 mmol) in anhyd EtOH (100 mL). The mixture was stirred for 6 h, poured into aq NH_4Cl (200 mL), and then extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O, brine and dried ($MgSO_4$). The $MgSO_4$ was removed by filtration, the solvent concentrated to dryness and the resulting solid was recrystallized from EtOH to give **15** (3.99 g, 14.40 mmol); yield 72%; mp 93°C.

MS (EI, 70 eV); *m/z* (%) = 277 (M^+, 4), 176 (100).

IR (Nujol): ν = 2105, 1696 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$/TMS): δ = 1.39 (t, 3H, J = 7.2 Hz), 3.91 (s, 3H), 3.92 (s, 3H), 4.35 (q, 2H, J = 7.2 Hz), 6.86 (s, 1H), 6.87 (d, 1H, J = 8.4 Hz), 7.35 (dd, 1H, J = 1.9, 8.4 Hz), 7.51 (d, 1H, J = 1.9 Hz).

^{13}C NMR (50 MHz, $CDCl_3$/TMS): δ = 14.23, 55.86, 55.98, 62.08, 110.74, 113.04, 123.42 (s), 124.82, 125.54, 126.27 (s), 148.57 (s), 150.19 (s), 163.69 (s).

$C_{13}H_{15}N_3O_4$	calc.	C 56.31	H 5.45	N 15.15
(277.3)	found	56.09	5.33	15.09

3-Ethoxycarbonyl-6,7-dimethoxy-1-methylisoquinoline (18):
To a solution of **15** (0.55 g, 2 mmol) in anhyd toluene (20 mL), PMe_3 (2 mL of a 1 M solution) was added dropwise at r.t. and the mixture was stirred for 15 min. Then, (trimethylsilyl)ethenone (0.23 g, 2 mmol) was added and the new mixture was heated in a sealed tube at 160°C for 2 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc as eluent to give **18** (0.47 g, 1.70 mmol); yield 86%; mp 171–173°C (EtOAc/hexane).

MS (EI, 70 eV): *m/z* (%) = 275 (M^+, 5), 203 (100).

IR (Nujol): ν = 1722, 1509, 1255 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.47 (t, 3H, J = 7.2 Hz), 2.97 (s, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 4.50 (q, 2H, J = 7.2 Hz), 7.18 (s, 1H), 7.32 (s, 1H), 8.32 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 14.40, 22.77, 56.07, 56.13, 61.54, 103.96, 106.49, 121.63, 125.00 (s), 132.09 (s), 139.75 (s), 151.59 (s), 152.87 (s), 156.44 (s), 166.18 (s).

$C_{15}H_{17}NO_4$	calc.	C 56.25	H 5.03	N 8.74
(275.3)	found	56.44	5.10	8.89

6,7-Dimethoxy-1-methylisoquinoline-3-carboxylic Acid (19):
To a stirred solution of **18** (0.27 g, 1 mmol) in THF (20 mL) was added in one portion $LiOH \cdot H_2O$ (0.13 g, 3 mmol) in H_2O (6 mL). The mixture was stirred at r.t. for 12 h. After removing the THF under reduced pressure, H_2O (10 mL) was added to the remaining aqueous solution. Then HCl (2 M) was added until pH = 5. The precipitate which formed was filtered off, washed with H_2O, dried and recrystallized from toluene to give **19** (0.22 g, 0.89 mmol); yield 91%; mp 249–250°C.

MS (EI, 70 eV): *m/z* (%) = 247 (M^+, 13), 203 (100).

IR (Nujol): ν = 1643, 1507, 1345 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6/TMS): δ = 2.87 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 7.45 (s, 1H), 7.56 (s, 1H), 8.31 (s, 1H), 11.05 (br s, 1H).

^{13}C NMR (50 MHz, DMSO-d_6/TMS): δ = 21.94, 55.81, 55.82, 104.23, 106.92, 120.75, 124.20 (s), 131.80 (s), 139.15 (s), 151.35 (s), 152.68 (s), 155.54 (s), 166.55 (s).

$C_{13}H_{13}NO_4$	calc.	C 63.15	H 5.30	N 5.66
(247.2)	found	63.04	5.21	5.51

6,7-Dimethoxy-1-methylisoquinoline (20):
A solution of **19** (0.123 g, 0.5 mmol) in Ph_2O (4 mL) was heated at 180°C for 36 h. After cooling, the mixture was chromatographed directly on a silica gel column using EtOAc as eluent to give **20** (0.065 g, 0.32 mmol); yield 64%.

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