DOI: 10.1002/ejoc.201001691

Efficient Access to C1- and C3-Functionalized Isoquinolines: Towards Potential Lanthanide Ligands

Fabien Caillé,[a,b] Frédéric Buron,[a] Éva Tóth,[b] and Franck Suzenet*[a]

Keywords: Nitrogen heterocycles / Fused-ring systems / Lanthanides

Highly substituted isoquinolines have been synthesized by two different pathways using either a Pictet–Grams or a Bischler–Napieralski approach. While the first synthesis afforded C1-functionalizable 1,3-dimethylisoquinoline derivatives, the second approach allowed the isolation of isoquinoline derivatives bearing a reactive ester function at the challenging C3 position. Among the large variety of efficient chemistry that can be independently or simultaneously performed at the C1 and C3 positions of the isoquinoline ring, 1,3-dibromomethylisoquinoline derivatives have proven to be efficient intermediates for the synthesis of highly valuable ligands for lanthanide complexation.

Introduction

Isoquinoline derivatives are fundamental heterocyclic compounds, and their abundance in many natural products[1] makes this scaffold a crucial building block for organic chemistry. They already proved to have medicinal importance like the opium alkaloid papaverine.[2] As a result, the synthesis of these heterocycles is of primary interest so that a wide range of mimetics can be prepared for pharmaceuticals. Isoquinoline derivatives have found applications in various types of medicines including anesthetics[3] and anti-infectives[4] but also in other domains.[5,6] Consequently, there has been tremendous interest in the design of this scaffold, and research has focused on finding new routes to synthesize this heteroaromatic core.

Many different routes have been explored to synthesize dihydro- and tetrahydroisoquinolines,[7,8] but the available syntheses of isoquinolines are less diversified,[9] and aromatization is not trivial.[10] Since the early 1950s, various approaches to this heteroaromatic core have been proposed. Among state-of-the-art approaches, the Pomeranz–Fritsch[11] and the Bischler–Napieralki cyclizations[12] appear to be the most widely used reactions to design these scaffolds. Other concerted electrocyclic reactions from allylbenzene,[13] nitrogen ylides,[14] or oximes[15] were also reported. More recently, direct functionalization of the isoquinoline core[16] or metallocatalyzed routes[17] were described. However, although the syntheses of isoquinolines substituted at the C1 position and, to a lesser extent, at the C4 position are quite readily performed, functionalization at the C3 position appears to be much more difficult.

As part of a research project on the development of lanthanide complexes as novel probes for optical and magnetic resonance imaging,[18] access to polysubstituted isoquinolines was of primary interest. Indeed, this scaffold shows interesting luminescence properties,[19] and substitution by electron-donating groups (EDG), like methoxy, on its benzene ring could enhance its capacities.[20] Therefore, the isoquinoline core has to bear highly reactive groups at both the C1 and C3 positions for further functionalization (Figure 1). Herein, we wish to report an efficient route to highly substituted isoquinolines bearing reactive functions at the C1 and challenging C3 positions. The strategy was applied to the synthesis of original ligands for lanthanide complexation.

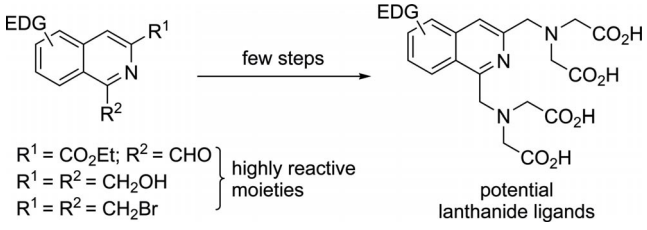


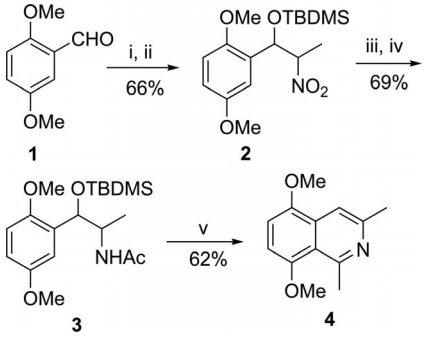
Figure 1. Polysubstituted isoquinolines bearing reactive moieties at both the C1 and C3 positions towards potential lanthanide ligands.

Results and Discussion

Considering that halogens in the benzylic position are common leaving groups involved in many substitution processes, we first focused our interest on the synthesis of a 1,3-dibromomethylisoquinoline intermediate ($R^1 = R^2 =$

[a] Institut de Chimie Organique et Analytique (ICOA), University of Orléans, UMR-CNRS 6005, rue de Chartres, 45063 Orléans cedex 2, France
Tel: +33238494580
E-mail: franck.suzenet@univ-orleans.fr
[b] Centre de Biophysique Moléculaire (CBM), UPR 4301 CNRS, rue Charles Sadron, 45071 Orléans cedex 2, France
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001691.

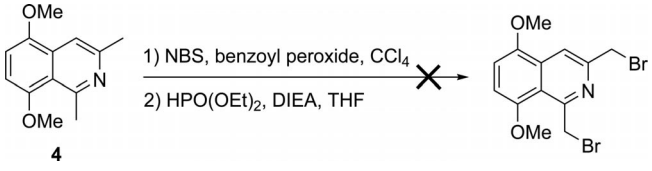
CH_2Br, Figure 1). Benzylic bromination is known to be readily performed under radical conditions from the corresponding methyl groups ($R^1 = R^2 = CH_3$, Figure 1). This approach has also been described for unsubstituted 1,3-dimethylisoquinolines,[13b,21] and we first focused our interest on the synthesis of 1,3-dimethylisoquinoline precursor **4** (Scheme 1). This key intermediate was obtained from the Pictet–Grams modification of the Bischler–Napieralski approach.[22]



Scheme 1. Synthesis of substituted 1,3-dimethylisoquinoline intermediate **4**. Reagents and conditions: (i) $EtNO_2$, $P(nBu)_3$, MeOH, room temp.; (ii) TBDMSCl, imidazole, CH_2Cl_2, reflux; (iii) H_2 (1 atm), Raney Ni, MeOH/NH_3, 50 °C; (iv) Ac_2O, pyridine, CH_2Cl_2, room temp.; (v) $POCl_3$, toluene, reflux.

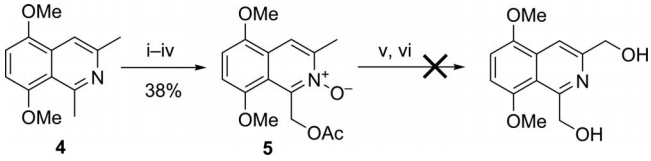
The synthesis starts from commercially available 2,5-dimethoxybenzaldehyde (**1**). Nitroaldolization was carried out smoothly with nitroethane by using a catalytic amount of tri-*n*-butylphosphane according to the method of Weeden and Chilsholm.[23] The hydroxy group was immediately silylated without further purification to easily isolate compound **2** in 66% yield over two steps. The nitro group was then reduced by hydrogenation in the presence of Raney nickel, and the resulting amine was acylated to afford intermediate **3**. Cyclization was carried out by using phosphorus oxychloride in refluxing toluene. These conditions allow both cyclization and elimination of the hydroxy moiety to give desired 1,3-dimethylisoquinoline **4** in 62% yield.

Bromination of the two methyl moieties under radical conditions according to Yin and Tan[13b] was unsuccessful (Scheme 2).



Scheme 2. Attempt at radical benzylic bromination of **4**.

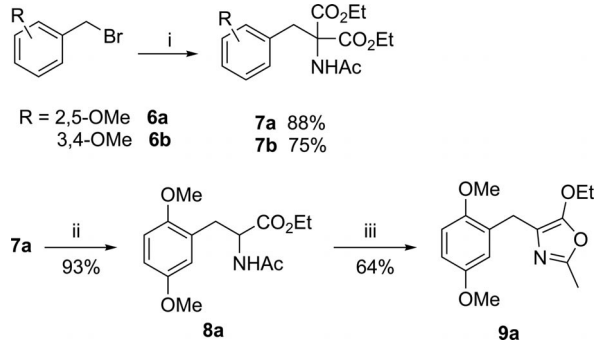
Attempts to oxidize both methyl groups to either aldehyde or carboxylic acid groups with selenium dioxide[24] or potassium permanganate, respectively, were disappointing. Although the C1 methyl group was easily oxidized under mild conditions, the C3 alkyl group was completely unreactive. A few years ago, Janin et al. provided an indirect method to oxidize the C3 position without using toxic selenium dioxide under harsh conditions. After *N*-oxidation of the isoquinoline ring, the *N*-oxide was submitted to rearrangement in the presence of acetic anhydride[25] followed by basic treatment to afford a 1,3-dihydroxymethylisoquinoline (Scheme 3).[26]



Scheme 3. Attempts to oxidize **4**. Reagents and conditions: (i) SeO_2, 1,4-dioxane, reflux; (ii) $NaBH_4$, MeOH, room temp.; (iii) Ac_2O, pyridine, DMAP, THF, room temp.; (iv) *m*-CPBA, CH_2Cl_2, room temp.; (v) Ac_2O, *o*-dichlorobenzene, reflux; (vi) NaOH, EtOH, 50 °C.

To undertake this rearrangement, we planned to isolate *N*-oxide isoquinoline **5** bearing a protected alcohol at the C1 position. The synthesis was performed from compound **4**; the methyl moiety was oxidized to an aldehyde group, which was then reduced to an alcohol. Protection of the primary alcohol followed by *N*-oxidation of the isoquinoline in the presence of *m*-CPBA rapidly afforded *N*-oxide **5** (Scheme 3). The key rearrangement with acetic anhydride in refluxing *o*-dichlorobenzene followed by basic treatment with potassium hydroxide was unfortunately unsuccessful in our hands.

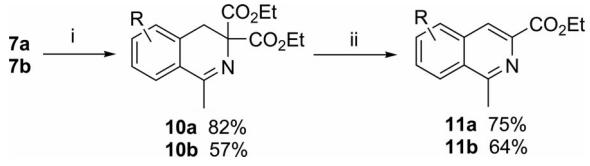
Considering the lack of reactivity of the methyl moiety at the C3 position, we decided to develop an original synthetic pathway to isoquinoline scaffolds already incorporating a reactive ester group at this position. This function could be introduced through diethyl aminomalonate[27] and subsequent decarboxylation (Scheme 4).



Scheme 4. Introduction of an ester moiety via **8a**. Reagents and conditions: (i) Diethyl 2-acetylaminomalonate, K_2CO_3, KI, CH_3CN, reflux; (ii) LiBr, H_2O, DMF, reflux; (iii) $POCl_3$, CH_3CN, reflux.

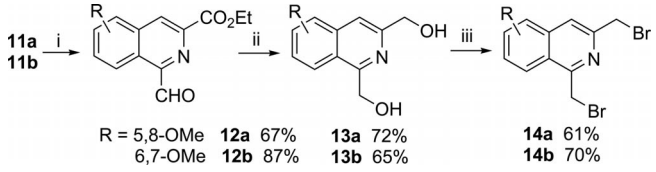
Bromides **6a**[28] and **6b**[29] were submitted to nucleophilic substitution with commercially available diethyl 2-acetylaminomalonate. Ester decarboxylation was successfully initiated with compound **7a** to afford amidoester **8a** in excellent yield. Considering the reported conditions,[10b,30] Bischler–Napieralski cyclization was carried out in the presence of phosphorus oxychloride. Unfortunately, in the case of **7a**, the Robinson–Gabriel reaction was favored to afford

exclusively oxazole **9a**.[31] Therefore, the cyclization step was carried out prior to ester decarboxylation (Scheme 5). Bischler–Napieralski cyclization of compounds **7** in refluxing phosphorus oxychloride afforded 4*H*-isoquinolines **10**, which were submitted to Krapcho decarboxylation. The use of a classical solvent such as DMF or DMSO[32] led to isoquinolines **11** with poor and irreproducible yields. The choice of pyridine as the solvent for the decarboxylation created basic conditions, which promoted the in situ aromatization of the formed dihydroisoquinoline. As a result, desired products **11** were isolated in 75 and 64% yield, respectively, reproducibly.



Scheme 5. Synthesis of isoquinolines **11a** and **11b**. Reagents and conditions: (i) $POCl_3$, reflux; (ii) NaI, pyridine, reflux.

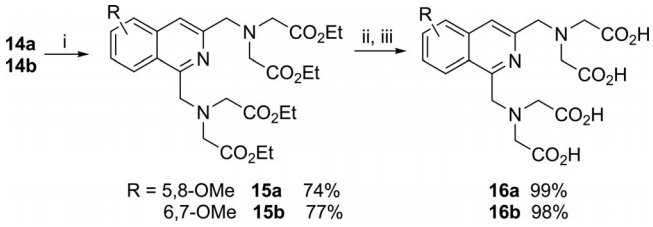
This sequence afforded the isoquinoline scaffold bearing a reactive ester or methyl moiety at the C3 or C1 position, respectively. As expected, these two positions can be easily functionalized into different highly reactive groups (Scheme 6).



Scheme 6. Functionalization of the C1 and C3 positions of **11a** and **11b**. Reagents and conditions: (i) SeO_2, 1,4-dioxane, reflux; (ii) $NaBH_4$, EtOH, reflux; (iii) PBr_3, $CHCl_3$, reflux.

Oxidation of the C1 methyl in the presence of selenium dioxide in refluxing 1,4-dioxane afforded aldehydes **12**. Among the variety of reactions that can be carried out over the two carbonyl moieties,[33] reduction of both groups with sodium borohydride in refluxing ethanol yielded diols **13**. These two highly reactive hydroxy functions can be submitted to various reactions[34] such as bromination with phosphorus tribromide in refluxing chloroform to give compounds **14**. The highly reactive C1 and C3 electrophilic positions of these bromomethylisoquinolines can react with a wide range of nucleophiles.[13b,21] As part of our research project, we functionalized these isoquinoline scaffolds to synthesize ligands for lanthanide complexation (Scheme 7).

Nucleophilic substitution at the C1 and C3 positions with diethyl iminodiacetate in the presence of potassium carbonate and potassium iodide in refluxing acetonitrile gave tetraesters **15**. Final saponification with lithium hydroxide followed by purification on Dowex ion-exchange resin afforded desired isoquinoline ligands **16** in almost quantitative yields.



Scheme 7. Synthesis of isoquinoline ligands **16a** and **16b**. Reagents and conditions: (i) $HN(CH_2CO_2Et)_2$, K_2CO_3, KI, CH_3CN, reflux; (ii) LiOH, THF/H_2O, room temp.; (iii) Dowex 1X2 100(Cl), HCOOH.

Conclusions

To conclude, we have developed efficient routes to highly substituted isoquinoline scaffolds from readily accessible starting materials. We have overcome the lack of reactivity of the challenging C3 position by introducing an ester function before isoquinoline ring formation. This approach allows very easy access to a wide range of C1 and C3 polysubstituted isoquinolines starting from three complementary synthons of type **12**, **13**, and **14**. We have functionalized 1,3-dibromomethylisoquinoline derivatives **14** to build new ligands for lanthanide complexation. These ligands are currently being tested for lanthanide complexation properties.

Experimental Section

General Information: All solvents used were analytical grade. All reactions were monitored by thin-layer chromatography, which was performed on aluminum sheets covered with silica gel 60 F_{254}. Visualization was realized by UV-light irradiation (254 and 365 nm) or with a cerium molybdate stain. Purification by flash chromatography was realized on silica gel 40–70 nm (230–400 mesh). Melting points were measured with a Kofler bench. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with $CDCl_3$ or CD_3OD as solvent and tetramethylsilane (TMS) as reference. Infrared analysis were carried out on a diamond crystal (ATR-D). High-resolution mass spectrometry was recorded at the Centre Régionale de Mesure Physique, Clermont-Ferrand University, with the electrospray ionization (ESI) technique. Mass spectroscopy (ESI) was recorded with a Perkin–Elmer SCIEX AOI 300 spectrometer.

***tert*-Butyl[1-(2,5-dimethoxyphenyl)-2-nitropropoxy]dimethylsilane (2):** To a solution of aldehyde **1** (1 g, 1 equiv.) in methanol (10 mL) was added nitroethane (2.2 mL, 5 equiv.) and a catalytic amount of $P(n\text{Bu})_3$ (150 μL, 0.1 equiv.), and the resulting mixture was stirred for 14 h at room temperature. The solvent was evaporated, and the resulting orange oil was purified by flash chromatography on silica gel (petroleum ether/dichloromethane, 1:4) to give the aldol adduct (1.31 g, 90%) as a yellow solid. The crude product was used without further purification in the next step. To a solution of the aldol adduct (1.31 g, 1 equiv.) in dichloromethane (30 mL) was added TBDMSCl (1.23 g, 1.5 equiv.) and imidazole (740 mg, 2 equiv.). The resulting mixture was heated at reflux for 16 h, and after being cooled to room temperature, the medium was hydrolyzed with water (10 mL), the organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concen-

trated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to give silyl ether **2** (1.9 g, 73%) as a colorless oil of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 1) = 6.97 (m, 1 H, ArH), 6.82 (m, 1 H, ArH), 6.79 (m, 1 H, ArH), 5.51 (d, J = 12 Hz, 1 H, CHOSi), 4.7 (m, 1 H, $CHNO_2$), 3.81 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.27 (d, J = 8 Hz, 3 H, CH_3), 0.8 (s, 9 H, 3 CH_3), –0.01 (s, 3 H, $SiCH_3$), –0.23 (s, 3 H, $SiCH_3$) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 2) = 7.05 (m, 1 H, ArH), 6.82 (m, 1 H, ArH), 6.79 (m, 1 H, ArH), 5.80 (d, J = 4 Hz, 1 H, CHOSi), 4.76 (m, 1 H, $CHNO_2$), 3.84 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.31 (d, J = 8 Hz, 3 H, CH_3), 0.91 (s, 9 H, 3 CH_3), 0.01 (s, 3 H, $SiCH_3$), –0.11 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 1) = 153.5 (C^{IV}), 150.5 (C^{IV}), 128.6 (C^{IV}), 114.7 (ArCH), 113.2 (ArCH), 111.6 (ArCH), 89.7 ($CHNO_2$), 69.8 (CHOSi), 55.8 (OCH_3), 55.6 (OCH_3), 25.4 (3 CH_3), 17.9 (C^{IV}), 15.3 (CH_3), –5.1 (CH_3Si), –5.9 (CH_3Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 2) = 153.7 (C^{IV}), 149.3 (C^{IV}), 128.9 (C^{IV}), 114.7 (ArCH), 113.6 (ArCH), 110.9 (ArCH), 84.8 ($CHNO_2$), 70.5 (CHOSi), 55.6 (OCH_3), 55.6 (OCH_3), 25.6 (3 CH_3), 17.9 (C^{IV}), 10.3 (CH_3), –4.9 (CH_3Si), –5.9 (CH_3Si) ppm. IR (ATR-D): $\tilde{\nu}$ = 2930, 1551, 1498, 1389, 1215, 1046, 836, 778 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{29}NO_5NaSi$ $[M + Na]^+$ 378.1713; found 378.1714.

***N*-[1-(*tert*-Butyldimethylsilyloxy)-1-(2,5-dimethoxyphenyl)propan-2-yl]acetamide (3):** To a solution of compound **2** (250 mg, 1 equiv.) in a mixture of methanol/ammoniac (99:1, 10 mL) was added Raney nickel (25 mg, 10%). The flask was placed under a hydrogen atmosphere (1 atm), and the mixture was vigorously stirred at 50 °C for 3 h. After being cooled, the medium was filtered through a pad of Celite, and the filtrate was evaporated to yield the crude amine as a colorless oil. This amine was directly used without further purification in the next step. To a solution of the crude amine (150 mg, 1 equiv.) in dichloromethane (10 mL) was added pyridine (190 μL, 5 equiv.) and acetic anhydride (870 μL, 20 equiv.), and the mixture was stirred for 3 h at room temperature. The organic phase was then washed with water (5 mL), dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (ethyl acetate) to give intermediate **3** (150 mg, 69% over two steps) as a white powder of two diastereoisomers. M.p. 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 1) = 6.93 (m, 1 H, ArH), 6.74 (m, 1 H, ArH), 6.72 (m, 1 H, ArH), 5.73 (br., 1 H, NH), 5.02 (d, J = 4 Hz, 1 H, CHOSi), 4.15 (m, 1 H, CHN), 3.8 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 1.83 (s, 3 H, $COCH_3$), 0.95 (m, 12 H, CH_3, 3 CH_3), 0.06 (s, 3 H, $SiCH_3$), –0.13 (s, 3 H, $SiCH_3$) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 2) = 7.01 (m, 1 H, ArH), 6.74 (m, 1 H, ArH), 6.72 (m, 1 H, ArH), 5.73 (br., 1 H, NH), 5.07 (d, J = 4 Hz, 1 H, CHOSi), 4.25 (m, 1 H, CHN), 3.78 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 1.93 (s, 3 H, $COCH_3$), 1.2 (d, J = 4 Hz, 3 H, CH_3), 0.95 (m, 9 H, 3 CH_3), 0.08 (s, 3 H, $SiCH_3$), –0.11 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 1) = 169.0 (C=O), 153.6 (C^{IV}), 150.1 (C^{IV}), 131.3 (C^{IV}), 113.6 (ArCH), 113.1 (ArCH), 111.1 (ArCH), 70.8 (CHOSi), 56.0 (OCH_3), 55.9 (OCH_3), 49.8 (CHN), 26.1 (3 CH_3), 26.1 (C^{IV}), 23.6 ($COCH_3$), 18.6 (CH_3), –4.5 (CH_3Si), –5.0 (CH_3Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (diastereoisomer 2) = 169.0 (C=O), 153.4 (C^{IV}), 150.1 (C^{IV}), 131.3 (C^{IV}), 113.5 (ArCH), 112.6 (ArCH), 111.1 (ArCH), 71.2 (CHOSi), 56.0 (OCH_3), 55.9 (OCH_3), 49.4 (CHN), 26.1 (3 CH_3), 26.1 (C^{IV}), 23.8 ($COCH_3$), 18.5 (CH_3), –4.4 (CH_3Si), –4.9 (CH_3Si) ppm. IR (ATR-D): $\tilde{\nu}$ = 3269, 2953, 1642, 1498, 1214, 1044, 862, 776 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{33}NO_4NaSi$ $[M + Na]^+$ 390.2077; found 390.2068.

5,8-Dimethoxy-1,3-dimethylisoquinoline (4): To a solution of compound **3** (150 mg, 1 equiv.) in toluene (5 mL) was added phosphorus oxychloride (380 μL, 10 equiv.), and the mixture was heated at reflux for 5 h. After being cooled to 0 °C, the medium was hydrolyzed with a saturated solution of sodium hydrogencarbonate (30 mL) to pH 8. The phases were separated, and the aqueous phase was extracted with ethyl acetate (10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to give isoquinoline **4** (55 mg, 62%) as pale yellow needles. M.p. 60 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (s, 1 H, ArH), 6.83 (d, J = 8 Hz, 1 H, ArH), 6.69 (d, J = 8 Hz, 1 H, ArH), 3.96 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.07 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.7 (C^{IV}), 152.2 (C^{IV}), 150.7 (C^{IV}), 148.3 (C^{IV}), 131.6 (C^{IV}), 119.0 (C^{IV}), 111.1 (ArCH), 107.6 (ArCH), 104.6 (ArCH), 56.1 (OCH_3), 55.8 (OCH_3), 28.7 ($ArCH_3$), 24.5 ($ArCH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2931, 1574, 1260, 1242, 1093, 1048, 730 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1181; found 218.1178.

5,8-Dimethoxy-3-methylisoquinoline-1-carbaldehyde (4a): To a solution of compound **4** (300 mg, 1 equiv.) in 1,4-dioxane (10 mL) was added selenium dioxide (300 mg, 2 equiv.), and the mixture was heated at reflux for 1 h. After being cooled to room temperature, the solution was filtered through a pad of Celite, the solvent was evaporated, and the residue was dissolved in ethyl acetate (10 mL). The organic phase was then washed with water (10 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to give the aldehyde (220 mg, 70%) as a yellow powder. M.p. 100 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.85 (s, 1 H, CHO), 7.98 (s, 1 H, ArH), 6.89 (d, J = 8 Hz, 1 H, ArH), 6.79 (d, J = 8 Hz, 1 H, ArH), 3.97 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 2.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.1 (CHO), 153.1 (C^{IV}), 152.3 (C^{IV}), 149.8 (C^{IV}), 148.6 (C^{IV}), 131.6 (C^{IV}), 118.2 (C^{IV}), 115.9 (ArCH), 107.7 (ArCH), 105.4 (ArCH), 56.1 (OCH_3), 56.0 (OCH_3), 24.4 ($ArCH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2929, 1693, 1239, 1097, 804, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{18}NO_4$ $[M + H + CH_3OH]^+$ 264.1236; found 264.1227.

(5,8-Dimethoxy-3-methylisoquinolin-1-yl)methyl Acetate (4b): To a solution of aldehyde (200 mg, 1 equiv.) in methanol (10 mL) was added sodium borohydride (50 mg, 2 equiv.) in portions, and the mixture was stirred for 3 h at room temperature. The medium was then hydrolyzed with water (10 mL), and the solvent was evaporated. The residue was dissolved in ethyl acetate (10 mL) and washed with water (5 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to yield a crude alcohol (180 mg, 90%) as a white solid. This compound was used without further purification in the next step. To a solution of the crude alcohol (170 mg, 1 equiv.) in THF (10 mL) was successively added pyridine (720 μL, 12 equiv.), acetic anhydride (700 μL, 10 equiv.), and a catalytic amount of DMAP. The mixture was stirred at room temperature for 24 h, and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to give the ester (120 mg, 60%) as a pale yellow solid. M.p. 109 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.80 (s, 1 H, ArH), 6.86 (d, J = 8 Hz, 1 H, ArH), 6.72 (d, J = 8 Hz, 1 H, ArH), 5.79 (s, 2 H, CH_2O), 3.94 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 2.66 (s, 3 H, CH_3), 2.18 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.3 (C=O), 153.0 (C^{IV}), 151.0 (C^{IV}), 150.9 (C^{IV}), 148.4 (C^{IV}), 131.9 (C^{IV}), 118.1 (C^{IV}), 113.1 (ArCH), 107.6 (ArCH), 104.8 (ArCH), 68.9 (CH_2O), 56.1 (OCH_3), 55.8 (OCH_3), 24.5 ($ArCH_3$), 21.3 ($COCH_3$) ppm. IR (ATR-D): $\tilde{\nu}$

= 2942, 1735, 1235, 1028, 814 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.1236; found 276.1235.

1-(Acetoxymethyl)-5,8-dimethoxy-3-methylisoquinoline 2-Oxide (5): To a solution of the ester (100 mg, 1 equiv.) in dichloromethane (10 mL) was added *m*-CPBA (190 mg, 3 equiv.), and the mixture was stirred at room temperature for 14 h. The medium was washed successively with a solution of sodium hydroxide (1 M, 10 mL) and water (10 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to afford isoquinoline *N*-oxide **5** (105 mg, quantitative) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.07 (s, 1 H, ArH), 6.8 (m, 2 H, ArH), 6.12 (s, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 2.65 (s, 3 H, CH_3), 2.11 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.2 (C=O), 157.4 (C^{IV}), 148.4 (C^{IV}), 145.7 (C^{IV}), 138.5 (C^{IV}), 122.2 (C^{IV}), 121.6 (C^{IV}), 118.4 (ArCH), 108.1 (ArCH), 106.4 (ArCH), 60.0 (CH_2O), 56.2 (OCH_3), 56.1 (OCH_3), 21.2 ($COCH_3$), 18.8 ($ArCH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2941, 1732, 1230, 1026, 730 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{17}NO_5Na$ $[M + Na]^+$ 314.1004; found 314.0995.

Diethyl 2-Acetylamido-2-(2,5-dimethoxybenzyl)malonate (7a): To a solution of bromide **6a**[28] (12 g, 1 equiv.) in acetonitrile (500 mL) was successively added diethyl 2-acetylaminomalonate (12.3 g, 1.1 equiv.), potassium carbonate (13.9 g, 2 equiv.), and potassium iodide (8.6 g, 1 equiv.). The mixture was heated at reflux for 14 h, and after being cooled to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane (200 mL), and the organic phase was washed with water (100 mL), dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 7:3) to give compound **7a** (16.7 g, 88%) as a white solid. M.p. 85 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.72 (m, 2 H, ArH), 6.56 (m, 1 H, ArH), 6.48 (br., 1 H, NH), 4.25 (m, 4 H, CO_2CH_2), 3.70 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.63 (s, 2 H, $ArCH_2$), 1.94 (s, 3 H, $COCH_3$), 1.29 (m, 6 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.1 (C=O), 168.1 (C=O), 166.6 (C=O), 153.5 (C^{IV}), 152.4 (C^{IV}), 125.0 (C^{IV}), 118.3 (ArCH), 113.2 (ArCH), 111.5 (ArCH), 66.4 (C^{IV}), 62.6 (CO_2CH_2), 62.5 (CO_2CH_2), 56.1 (OCH_3), 55.8 (OCH_3), 33.1 ($ArCH_2$), 23.1 ($COCH_3$), 14.2 ($CO_2CH_2CH_3$), 14.1 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 3255, 2985, 1740, 1639, 1219, 1039 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}NO_7$ $[M + H]^+$ 368.1709; found 368.1709.

Diethyl 2-Acetylamido-2-(3,4-dimethoxybenzyl)malonate (7b): Same procedure as for compound **7a** starting from bromide **6b**.[29] Yield: 75%. White solid. M.p. 100 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.74 (d, J = 8 Hz, 1 H, ArH), 6.52 (m, 3 H, 2 ArH, NH), 4.26 (m, 4 H, CO_2CH_2), 3.83 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.58 (s, 2 H, $ArCH_2$), 2.01 (s, 3 H, $COCH_3$), 1.28 (t, J = 8 Hz, 6 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.1 (C=O), 167.7 (C=O), 148.8 (C^{IV}), 148.4 (C^{IV}), 127.8 (C^{IV}), 122.1 (ArCH), 113.3 (ArCH), 111.2 (ArCH), 67.5 (C^{IV}), 62.8 (2 CO_2CH_2), 56.0 (OCH_3), 55.9 (OCH_3), 37.6 ($ArCH_2$), 23.3 ($COCH_3$), 14.2 (2 $CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 3279, 2979, 1744, 1646, 1513, 1257, 1238, 1188, 1157, 1136, 1027 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}NO_7Na$ $[M + Na]^+$ 390.1529; found 390.1538.

Ethyl 2-Acetamido-3-(2,5-dimethoxyphenyl)propanoate (8a): To a solution of compound **7a** (480 mg, 1 equiv.) in DMF (10 mL) was added lithium bromide (125 mg, 1.1 equiv.) and water (52 µL, 2.2 equiv.), and the mixture was heated at reflux for 16 h. After being cooled to room temperature, the residue was dissolved in dichloromethane (10 mL). The organic phase was washed with a saturated solution of sodium chloride (10 mL), dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 6:4) to give compound **8a** (360 mg, 93%) as a pale yellow solid. M.p. 73 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.73 (m, 2 H, ArH), 6.66 (m, 1 H, ArH), 6.34 (br., 1 H, NH), 4.70 (m, 1 H, CH), 4.14 (m, 2 H, CO_2CH_2), 3.78 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.05 (m, 2 H, $ArCH_2$), 1.92 (s, 3 H, $COCH_3$), 1.25 (m, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.1 (C=O), 170.0 (C=O), 153.8 (C^{IV}), 151.9 (C^{IV}), 126.0 (C^{IV}), 117.4 (ArCH), 113.0 (ArCH), 111.7 (ArCH), 61.4 (CO_2CH_2), 55.9 (OCH_3), 53.5 (OCH_3), 41.6 (CHN), 32.7 ($ArCH_2$), 23.2 ($COCH_3$), 14.3 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 3286, 2935, 1737, 1654, 1501, 1224, 1042, 1025 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{21}NO_5Na$ $[M + Na]^+$ 318.1317; found 318.1323.

4-(2,5-Dimethoxybenzyl)-5-ethoxy-2-methyloxazole (9a): To a solution of compound **8a** (100 mg, 1 equiv.) in chloroform (10 mL) was added phosphorus oxychloride (0.4 mL, 10 equiv.), and the mixture was heated at reflux for 2 h. After being cooled to 0 °C, the solution was hydrolyzed with a saturated solution of sodium hydrogencarbonate (30 mL) until pH 8. The phases were separated, and the aqueous one was extracted with dichloromethane (10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to give oxazole **9a** (60 mg, 64%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.75 (m, 2 H, ArH), 6.68 (m, 1 H, ArH), 4.05 (m, 2 H, OCH_2), 3.78 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.69 (s, 2 H, $ArCH_2$), 2.31 (s, 3 H, CH_3), 1.29 (m, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 154.5 (C^{IV}), 153.8 (C^{IV}), 152.6 (C^{IV}) 151.9 (C^{IV}), 129.2 (C^{IV}), 116.6 (ArCH), 115.2 (C^{IV}), 111.5 (ArCH), 111.5 (*C*HOEt), 70.6 (OCH_2), 56.3 (OCH_3), 55.9 (OCH_3), 25.1 ($ArCH_2$), 15.2 ($ArCH_3$), 14.6 ($COCH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2937, 1669, 1498, 1218, 1024 cm^{-1}. MS (ESI): m/z = 278 $[M + H]^+$. Oxazole **9a** decomposes even when it is kept under an atmosphere of argon at –20 °C.

Diethyl 5,8-Dimethoxy-1-methylisoquinoline-3,3(4*H*)-dicarboxylate (10a): A solution of compound **7a** (14 g) in phosphorus oxychloride (250 mL) was heated at reflux for 2 h, and after being cooled to room temperature, the solvent was evaporated. The residue was hydrolyzed at 0 °C with a saturated solution of sodium hydrogencarbonate (1 L) to pH 8, and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated. The crude solid was purified by flash chromatography on silica gel (petroleum ether/ethyl, 6:4) to give compound **10a** (10.9 g, 82%) as a white solid. M.p. 112 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.91 (d, J = 8 Hz, 1 H, ArH), 6.78 (d, J = 8 Hz, 1 H, ArH), 4.2 (m, 4 H, CO_2CH_2), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.25 (s, 2 H, $ArCH_2$), 2.58 (s, 3 H, CH_3), 1.18 (m, 6 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.7 (2 C=O), 167.9 (C^{IV}), 152.1 (C^{IV}), 150.3 (C^{IV}), 125.2 (C^{IV}), 120.1 (C^{IV}), 114.7 (ArCH), 110.9 (ArCH), 69.9 (C^{IV}), 62.1 (2 CO_2CH_2), 56.5 (OCH_3), 56.2 (OCH_3), 28.1 (N=C*C*H$_3$), 26.0 ($ArCH_2$), 14.2 (2 $CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2992, 1733, 1272, 1239, 1099, 1059 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{24}NO_6$ $[M + H]^+$ 350.1604; found 350.1588.

Diethyl 6,7-Dimethoxy-1-methylisoquinoline-3,3(4*H*)-dicarboxylate (10b): Same procedure as for compound **10a** starting from **7b**. Yield: 57%. White solid. M.p. 107 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.00 (s, 1 H, ArH), 6.70 (s, 1 H, ArH), 4.21 (m, 4 H, CO_2CH_2), 3.91 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.28 (s, 2 H, $ArCH_2$), 2.50 (s, 3 H, CH_3), 1.22 (t, J = 8 Hz, 6 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ =

169.8 (2 C=O), 167.3 (C^{IV}), 151.9 (C^{IV}), 148.1 (C^{IV}), 127.8 (C^{IV}), 122.1 (C^{IV}), 110.6 (ArCH), 109.2 (ArCH), 70.4 (C^{IV}), 62.3 (2 CO_2CH_2), 56.4 (OCH_3), 56.2 (OCH_3), 31.5 ($ArCH_2$), 23.9 ($ArCH_3$), 14.2 (2 $CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2986, 1734, 1300, 1267, 1161, 1062 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{24}NO_6$ $[M + H]^+$ 350.1604; found 350.1588.

Ethyl 5,8-Dimethoxy-1-methylisoquinoline-3-carboxylate (11a): To a solution of compound **10a** (5.5 g, 1 equiv.) in pyridine (250 mL) was added sodium iodide (6.7 g, 3 equiv.), and the mixture was heated at reflux for 24 h. After being cooled to room temperature, the solvent was evaporated, and the residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude solid was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 5:5) to give isoquinoline **11a** (3.1 g, 75%) as a yellow solid. M.p. 85 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.72 (s, 1 H, ArH), 6.91 (m, 2 H, ArH), 4.49 (q, J = 8 Hz, 2 H, CO_2CH_2), 3.96 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.15 (s, 3 H, CH_3), 1.45 (t, J = 8 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.2 (C=O), 159.1 (C^{IV}), 151.8 (C^{IV}), 149.5 (C^{IV}), 140.6 (C^{IV}), 130.2 (C^{IV}), 121.9 (C^{IV}), 116.7 (ArCH), 108.6 (ArCH), 108.5 (ArCH), 61.8 (CO_2CH_2), 56.1 (OCH_3), 56.0 (OCH_3), 29.1 ($ArCH_3$), 14.6 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2936, 1718, 1259, 1045, 1030, 728 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.1236; found 276.1230.

Ethyl 6,7-Dimethoxy-1-methylisoquinoline-3-carboxylate (11b): Same procedure as for compound **11a** starting from **10b**. Yield: 64%. Yellow solid. M.p. 150 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.30 (s, 1 H, ArH), 7.31 (s, 1 H, ArH), 7.17 (s, 1 H, ArH), 4.48 (q, J = 8 Hz, 2 H, CO_2CH_2), 4.05 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 2.95 (s, 3 H, CH_3), 1.44 (t, J = 8 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.5 (C=O), 156.7 (C^{IV}), 153.1 (C^{IV}), 151.8 (C^{IV}), 140.0 (C^{IV}), 132.4 (C^{IV}), 125.3 (C^{IV}), 121.9 (ArCH), 106.8 (ArCH), 104.2 (ArCH), 61.8 (CO_2CH_2), 56.4 (OCH_3), 56.3 (OCH_3), 23.1 ($ArCH_3$), 14.7 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2971, 1701, 1509, 1426, 1249, 1217, 1160, 859 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.1236; found 276.1230.

Ethyl 1-Formyl-5,8-dimethoxyisoquinoline-3-carboxylate (12a): Same procedure of oxidation as for compound **5** starting from **11a**. Yield: 67%. Yellow powder. M.p. 113 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.78 (s, 1 H, CHO), 8.99 (s, 1 H, ArH), 7.03 (s, 2 H, ArH), 4.52 (q, J = 8 Hz, 2 H, CO_2CH_2), 4.02 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 1.47 (t, J = 8 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.7 (CHO), 165.5 (C=O), 154.6 (C^{IV}), 154.4 (C^{IV}), 149.7 (C^{IV}), 141.9 (C^{IV}), 130.5 (C^{IV}), 124.2 (C^{IV}), 120.4 (ArCH), 109.4 (ArCH), 109.3 (ArCH), 62.3 (CO_2CH_2), 56.5 (OCH_3), 56.3 (OCH_3), 14.6 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2931, 1736, 1695, 1259, 1026, 808 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}NO_5$ $[M + H]^+$ 290.1028; found 290.1024.

Ethyl 1-Formyl-6,7-dimethoxyisoquinoline-3-carboxylate (12b): Same procedure of oxidation as for compound **5** starting from **11b**. Yield: 87%. Yellow powder. M.p. 94 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.46 (s, 1 H, CHO), 8.81 (s, 1 H, ArH), 8.62 (s, 1 H, ArH), 7.27 (s, 1 H, ArH), 4.56 (q, J = 8 Hz, 2 H, CO_2CH_2), 4.18 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 1.51 (t, J = 8 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.3 (CHO), 165.4 (C=O), 154.7 (C^{IV}), 153.8 (C^{IV}), 147.2 (C^{IV}), 140.6 (C^{IV}), 134.6 (C^{IV}), 126.7 (ArCH), 124.7 (C^{IV}), 106.1 (ArCH), 104.1 (ArCH), 62.2 (CO_2CH_2), 56.7 (OCH_3), 56.4 (OCH_3), 14.6 ($CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 1726, 1694, 1504, 1263, 1135, 1111, 991, 881 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}NO_5Na$ $[M + Na]^+$ 312.0848; found 312.0844.

(5,8-Dimethoxyisoquinoline-1,3-diyl)dimethanol (13a): To a solution of aldehyde **12a** (1.5 g, 1 equiv.) in ethanol (100 mL) was added sodium borohydride (800 mg, 4 equiv.), and the mixture was heated at reflux for 3 h. After being cooled to room temperature, the solvent was evaporated, and the residue was dissolved in dichloromethane (50 mL). The organic phase was washed with water (20 mL), dried with $MgSO_4$, filtered, and concentrated to yield pure diol **13a** (950 mg, 72%) as a yellow powder. M.p. 124 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.95 (s, 1 H, ArH), 6.91 (d, J = 8 Hz, 1 H, ArH), 6.76 (d, J = 8 Hz, 1 H, ArH), 5.25 (s, 2 H, CH_2OH), 4.89 (s, 2 H, CH_2OH), 3.95 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.75 (br., 2 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.0 (C^{IV}), 151.6 (C^{IV}), 150.8 (C^{IV}), 148.7 (C^{IV}), 131.2 (C^{IV}), 118.0 (C^{IV}), 110.7 (ArCH), 108.5 (ArCH), 105.6 (ArCH), 65.6 (CH_2OH), 65.1 (CH_2OH), 56.1 (OCH_3), 55.9 (OCH_3) ppm. IR (ATR-D): $\tilde{\nu}$ = 3397, 3199, 2944, 1332, 1261, 1233, 1094, 1022, 804 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079; found 250.1071.

(6,7-Dimethoxyisoquinoline-1,3-diyl)dimethanol (13b): Same procedure of reduction as for compound **13a** starting from compound **12b**. Yield: 65%. White solid. M.p. 89 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.49 (s, 1 H, ArH), 7.09 (s, 1 H, ArH), 7.04 (s, 1 H, ArH), 5.13 (s, 2 H, CH_2OH), 4.88 (s, 2 H, CH_2OH), 4.03 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 154.9 (C^{IV}), 153.4 (C^{IV}), 150.5 (C^{IV}), 149.9 (C^{IV}), 133.8 (C^{IV}), 120.1 (C^{IV}), 115.8 (ArCH), 105.7 (ArCH), 101.5 (ArCH), 65.5 (CH_2OH), 61.7 (CH_2OH), 56.3 (2 OCH_3) ppm. IR (ATR-D): $\tilde{\nu}$ = 3389, 3133, 1462, 1246, 1077, 876 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079; found 250.1076.

1,3-Bis(bromomethyl)-5,8-dimethoxyisoquinoline (14a): To a solution of diol **13a** (840 mg, 1 equiv.) in chloroform (100 mL) was added phosphorus tribromide (1.9 mL, 6 equiv.), and the mixture was heated at reflux for 14 h. After being cooled to 0 °C, the medium was hydrolyzed with a saturated solution of sodium hydrogencarbonate (250 mL) to pH 8. The phases were separated, and the aqueous phase was extracted with dichloromethane (100 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to give compound **14a** (690 mg, 61%) as a yellow solid. M.p. 150 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.11 (s, 1 H, ArH), 6.94 (d, J = 8 Hz, 1 H, ArH), 6.89 (d, J = 8 Hz, 1 H, ArH), 5.28 (s, 2 H, CH_2Br), 4.70 (s, 2 H, CH_2Br), 4.02 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 155.7 (C^{IV}), 150.7 (C^{IV}), 149.4 (C^{IV}), 149.0 (C^{IV}), 131.9 (C^{IV}), 118.7 (C^{IV}), 115.3 (ArCH), 108.4 (ArCH), 107.6 (ArCH), 56.4 (OCH_3), 56.1 (OCH_3), 37.5 (CH_2Br), 34.7 (CH_2Br) ppm. IR (ATR-D): $\tilde{\nu}$ = 2927, 1251, 1089, 1036, 814, 724 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{14}NO_2Br_2$ $[M + H]^+$ 373.9391; found 373.9385.

1,3-Bis(bromomethyl)-6,7-dimethoxyisoquinoline (14b): Same procedure as for compound **14a** starting from **13b**. Yield: 70%. Yellow solid. M.p. 196 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.63 (s, 1 H, ArH), 7.42 (s, 1 H, ArH), 7.08 (s, 1 H, ArH), 4.97 (s, 2 H, CH_2Br), 4.69 (s, 2 H, CH_2Br), 4.08 (s, 2 H, OCH_3), 4.03 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 153.6 (C^{IV}), 153.5 (C^{IV}), 151.0 (C^{IV}), 148.3 (C^{IV}), 134.5 (C^{IV}), 122.1 (C^{IV}), 120.2 (ArCH), 105.7 (ArCH), 103.7 (ArCH), 56.4 (2 OCH_3), 34.9 (CH_2Br), 32.3 (CH_2Br) ppm. IR (ATR-D): $\tilde{\nu}$ = 1509, 1429, 1259, 842 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{14}NO_2Br_2$ $[M + H]^+$ 373.9391; found 373.9377.

Tetraethyl 2,2,2′′,2′′′-(5,8-dimethoxyisoquinoline-1,3-diyl)bis(methylene)bis(azanetriyl)tetraacetate (15a): To a solution of compound **14a** (650 mg, 1 equiv.) in acetonitrile (70 mL) was successively added diethyl iminodiacetate (720 mg, 2.2 equiv.), potassium carbonate (930 mg, 4 equiv.), and potassium iodide (570 mg, 2 equiv.). The mixture was heated at reflux for 14 h, and after being cooled to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), and the organic phase was washed with water (20 mL), dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (ethyl acetate) to give tetraester **15a** (1 g, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.06 (s, 1 H, ArH), 6.85 (d, J = 8 Hz, 1 H, ArH), 6.75 (d, J = 8 Hz, 1 H, ArH), 4.80 (s, 2 H, $ArCH_2$), 4.14 (m, 10 H, $ArCH_2$, CO_2CH_2), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.80 (s, 4 H, NCH_2), 3.67 (s, 4 H, NCH_2), 1.26 (t, J = 8 Hz, 6 H, $CO_2CH_2CH_3$), 1.22 (t, J = 8 Hz, 6 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (2 C=O), 171.4 (2 C=O), 157.0 (C^{IV}), 151.3 (C^{IV}), 148.9 (C^{IV}), 140.3 (C^{IV}), 131.8 (C^{IV}), 122.0 (C^{IV}), 112.4 (ArCH), 107.5 (ArCH), 107.1 (ArCH), 61.1–60.3 (4 CO_2CH_2, $ArCH_2$), 56.0–55.2 (2 OCH_3, $ArCH_2$, 8 NCH_2), 14.4 (4 $CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 2980, 1732, 1186, 1149, 1029, 808 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{42}N_3O_{10}$ $[M + H]^+$ 592.2870; found 592.2859.

Tetraethyl 2,2,2′′,2′′′-(6,7-dimethoxyisoquinoline-1,3-diyl)bis(methylene)bis(azanetriyl)tetraacetate (15b): Same procedure as for compound **15a** starting from **14b**. Yield: 77%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.37 (s, 1 H, ArH), 7.69 (s, 1 H, ArH), 7.05 (s, 1 H, ArH), 4.40 (s, 2 H, $ArCH_2$), 4.19–4.13 (m, 11 H, CO_2CH_2, OCH_3), 4.01 (s, 3 H, OCH_3), 3.65 (s, 4 H, NCH_2), 3.50 (s, 4 H, NCH_2), 3.46 (s, 2 H, $ArCH_2$), 1.26 (m, 12 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.0–171.2 (4 C=O), 154.5 (C^{IV}), 152.9 (C^{IV}), 150.0 (C^{IV}), 149.3 (C^{IV}), 134.2 (C^{IV}), 123.2 (C^{IV}), 118.4 (ArCH), 105.6 (ArCH), 104.9 (ArCH), 61.0–60.0 (4 CO_2CH_2), 59.1 ($ArCH_2$), 56.7 (OCH_3), 56.1 (OCH_3), 55.4 (2 NCH_2), 55.1 (2 NCH_2), 50.4 ($ArCH_2$), 14.4 (4 $CO_2CH_2CH_3$) ppm. IR (ATR-D): $\tilde{\nu}$ = 1735, 1186, 1149, 1027 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{42}N_3O_{10}$ $[M + H]^+$ 592.2870; found 592.2856.

2,2,2′′,2′′′-(5,8-Dimethoxyisoquinoline-1,3-diyl)bis(methylene)bis(azanetriyl)tetraacetic Acid (16a): To a solution of tetraester **15a** (1 g, 1 equiv.) in THF/H_2O (1:1, 50 mL) was added lithium hydroxide (850 mg, 12 equiv.), and the solution was stirred for 4 h at room temperature. The solvent was then evaporated, and the crude product was purified on Dowex 1X2 100(Cl) ion-exchange resin. The resin was activated with a solution of sodium hydroxide (1 M, 20 mL) to pH 14 and with water (30 mL) to pH 7. After deposition of the crude, the impurities were washed with H_2O/MeOH (1:1, 100 mL) before elution of the product with pure formic acid. Evaporation afforded product **16a** (810 mg, 99%) as a yellow powder. M.p. 140 °C. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.32 (s, 1 H, ArH), 7.50 (d, J = 8 Hz, 1 H, ArH), 7.29 (d, J = 8 Hz, 1 H, ArH), 5.07 (s, 2 H, $ArCH_2$), 4.43 (s, 2 H, $ArCH_2$), 4.06 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 3.91 (s, 4 H, NCH_2), 3.77 (s, 4 H, NCH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 174.0 (2 C=O), 173.9 (2 C=O), 158.8 (C^{IV}), 154.3 (C^{IV}), 149.8 (C^{IV}), 142.4 (C^{IV}), 132.9 (C^{IV}), 119.0 (C^{IV}), 117.7 (ArCH), 115.9 (ArCH), 110.7 (ArCH), 60.7 ($ArCH_2$), 57.2–56.0 ($ArCH_2$, 4 CH_2N, 2 OCH_3) ppm. IR (ATR-D): $\tilde{\nu}$ = 3000, 2935, 1729, 1368, 1198, 1093, 819 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{24}N_3O_{10}$ $[M - H]^-$ 478.1462; found 478.1478.

2,2,2′′,2′′′-(6,7-Dimethoxyisoquinoline-1,3-diyl)bis(methylene)bis(azanetriyl)tetraacetic Acid (16b): Same procedure as for compound **16a** starting from **15b**. Yield: 98%. Pale yellow solid. M.p. 140 °C. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.86 (s, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.44 (s, 1 H, ArH), 4.38 (s, 2 H, $ArCH_2$), 4.03 (s, 6 H, OCH_3), 3.80 (s, 4 H, NCH_2), 3.73 (s, 4 H, NCH_2), 3.65 (s, 2 H, $ArCH_2$) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 174.2–174.0 (4 C=O), 170.4 (C^{IV}), 158.1 (C^{IV}), 153.8 (C^{IV}), 142.2 (C^{IV}), 137.7 (C^{IV}), 121.8 (C^{IV}), 112.5 (ArCH), 107.1 (ArCH), 106.7 (ArCH), 57.7–56.8 (2 $ArCH_2$, 4 CH_2N, 2 OCH_3) ppm. IR (ATR-D): $\tilde{\nu}$ = 3000, 1715, 1613, 1506, 1258, 1162, 991, 866 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{24}N_3O_{10}$ $[M - H]^-$ 478.1462; found 478.1465.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for all isolated compounds.

Acknowledgments

The authors thank the financial support of the Institut National du Cancer, the Ligue contre le Cancer, and the French Research Ministry (FC).

[1] K. W. Bentley in *The Isoquinoline Alkaloids*, Hardwood Academic, Amsterdam **1998**, vol. 1.
[2] L. Marion in *The Alkaloids* (Eds.: R. H. F. Manske, H. L. Holmes), Academic Press, New York, **1975**, p. 209.
[3] J. W. Wilson III, N. D. Dawson, W. Brooks, G. E. Ullyot, *J. Am. Chem. Soc.* **1949**, *71*, 937–938.
[4] *NIOSH, Registry of Toxic Effect of Chemical Substances (RTECS)*, Dialog Information Service, Inc., **1985–86**, File #45130.
[5] H. W. Gibson, F. C. Bailey, *Macromolecules* **1976**, *9*, 688–690.
[6] J. R. Parrish, R. Stevenson, *Anal. Chim. Acta* **1974**, *70*, 189–198.
[7] M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370 and references cited therein.
[8] E. L. Larghi, M. Amongero, A. B. J. Bracca, T. S. Kaufman, *Arkivoc* **2005**, *xii*, 98–153 and references cited therein.
[9] A. R. Katritsky, C. W. Rees, E. F. Scriven in *Comprehensive Heterocyclic Chemistry III: A Review of Literature 1982–1995*, Elsevier, Tarrytown, NY, **1996**, pp. 282–283.
[10] For example, see: a) K. C. Agrawal, R. J. Cushley, S. R. Lipsky, J. R. Wheaton, A. C. Sartorelli, *J. Med. Chem.* **1972**, *15*, 192–195; b) S. J. Martinez, L. Larsen, J. D. Street, J. A. Joule, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1705–1710; c) J. Feng, S. Dastgir, C.-J. Li, *Tetrahedron Lett.* **2007**, *49*, 668–671.
[11] a) W. J. Gensler, *Org. React.* **1951**, 191; b) J. M. Bobbitt, A. J. Bourque, *Heterocycles* **1987**, *25*, 601–616.
[12] a) W. M. Whaley, T. R. Govindachari, *Org. React.* **1951**, 74; b) M. D. Rozwadowska, *Heterocycles* **1994**, *39*, 903–931.
[13] a) T. Sato, K. Tamura, K. Nagayoshi, *Chem. Lett.* **1983**, *12*, 791–794; b) X.-H. Yin, M.-Y. Tan, *Synth. Commun.* **2003**, *33*, 1113–1119.
[14] For example, see: a) D. M. B. Hickey, A. R. MacKenzie, C. J. Moody, C. W. Rees, *J. Chem. Soc. Perkin Trans. 1* **1987**, 921–926; b) P. Molina, A. Vidal, F. Tovar, *Synthesis* **1997**, 963–966; c) P. Molina, S. Garcia-Zafra, P. M. Fresneda, *Synlett* **1995**, 43–44.
[15] For example, see: a) K. Hibino, E. Sugino, Y. Adachi, K. Nomi, K. Sato, *Heterocycles* **1989**, *28*, 275–282; b) W. Zielinski, *Synthesis* **1979**, 70–72.
[16] For example, see: a) Y. Kitahara, T. Nakai, S. Nakahara, M. Akazawa, M. Shimizu, A. Kubo, *Chem. Pharm. Bull.* **1991**, *39*, 2256–2263; b) F. Lauërat, Y. Fort, V. Mamane, *Tetrahedron Lett.* **2009**, *50*, 5716–5718 and references cited therein.
[17] For example, see: a) M. Chaumontet, R. Piccardi, O. Baudoin, *Angew. Chem. Int. Ed.* **2009**, *121*, 185–188; b) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359–9364; c) N. T. Patil,

A. K. Mutyala, P. G. V. V. Lakshimi, P. V. K. Raja, B. Sridhar, *Eur. J. Org. Chem.* **2010**, 1999–2007.

[18] L. Pellegatti, J. Zhang, B. Drahos, S. Villette, F. Suzenet, G. Guillaumet, S. Petoud, É. Tóth, *Chem. Commun.* **2008**, 6591–6593.

[19] M. F. Anton, W. R. Moomaw, *J. Chem. Phys.* **1977**, *66*, 1808–1818 and references cited therein.

[20] S. Sivakumar, M. L. P. Reddy, A. H. Cowley, K. V. Vasudevan, *Dalton Trans.* **2010**, *39*, 776–786.

[21] V.-M. Mukkala, C. Sund, M. Kwiatkowski, P. Pasanen, M. Hoegberg, J. Kantare, H. Takalo, *Helv. Chim. Acta* **1992**, *75*, 1621–1632.

[22] A. Pictet, A. Grams, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

[23] J. A. Weeden, J. D. Chilsholm, *Tetrahedron Lett.* **2006**, *47*, 9313–9316.

[24] Y. L. Janin, E. Roulland, A. Beurdeley-Thomas, D. Decaudin, C. Monneret, M.-F. Poupon, *J. Chem. Soc. Perkin Trans. 1* **2002**, 529–532.

[25] Y. L. Janin, D. Decaudin, C. Monneret, M.-F. Poupon, *Tetrahedron* **2004**, *60*, 5481–5485.

[26] a) C. Fontenas, E. Bejan, H. A. Haddou, G. G. A. Balavoine, *Synth. Commun.* **1995**, *25*, 629–633; b) T. Koenig, *J. Am. Chem. Soc.* **1966**, *88*, 4045–4049 and references cited therein.

[27] T. Lakhlifi, A. Sedqui, B. Laude, N. Dinh An, J. Vebrel, *Can. J. Chem.* **1991**, *69*, 1156–1160.

[28] D. G. Hartzfeld, S. D. Rose, *J. Am. Chem. Soc.* **1993**, *115*, 850–854.

[29] A. Van Oeveren, J. F. G. A. Jansen, B. L. Feringa, *J. Org. Chem.* **1994**, *59*, 5999–6007.

[30] Y.-F. Zhu, K. Wilcoxen, T. Gross, P. Connors, N. Strack, R. Gross, C. Q. Huang, J. R. McCarthy, Q. Xie, N. Ling, C. Chen, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1927–1930.

[31] For example, see: a) J. Van der Eycken, J.-P. Bosmans, D. van Haver, M. Vandewalle, A. Hulkenberg, W. Veerman, R. Nieuwenhuizen, *Tetrahedron Lett.* **1989**, *30*, 3873–3876; b) Z. Z. Liu, Y. F. Tang, S. Z. Chen, *Chin. Chem. Lett.* **2001**, *12*, 947–950.

[32] A. P. Krapcho, *Synthesis* **1982**, 893–914.

[33] For example, see: a) C. B. Schapira, M. I. Abasolo, I. A. Perillo, *J. Heterocycl. Chem.* **1985**, *22*, 577–581; b) D. Chemyak, C. Skontos, V. Gevorgyan, *Org. Lett.* **2010**, *12*, 3242–3245; c) M. Pascu, G. L. Clarkson, M. Kariuki, M. J. Hannon, *Dalton Trans.* **2006**, *22*, 2635–2642; d) G. Guanti, R. Riva, *Tetrahedron: Asymmetry* **2001**, *12*, 1185–1200.

[34] For example, see: a) L. J. Street, F. Sternfield, R. A. Jelley, A. J. Reeve, R. W. Carling, K. W. Moore, R. M. McKernan, B. Sohal, S. Cook, A. Pike, G. R. Dawson, F. A. Bromidge, K. A. Wafford, G. R. Seabrook, S. A. Thompson, G. Marshall, G. V. Pillai, J. L. Castro, J. R. Atack, A. M. MacLeod, *J. Med. Chem.* **2004**, *47*, 3642–3657; b) R. C. Young, R. C. Mitchell, T. H. Brown, C. R. Ganellin, R. Griffiths, M. Jones, K. K. Rana, D. Saunders, I. R. Smith, N. E. Sore, T. J. Wilks, *J. Med. Chem.* **1988**, *31*, 656–671.

Received: December 16, 2010
Published Online: March 2, 2011

