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A new synthesis of pyrrolo[3,2-*b*]quinolines by a tandem electrocyclization–oxidation process

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ABSTRACT

A new synthesis of pyrrolo[3,2-*b*]quinolines is described. Condensation of anilines with dimethyl 4-oxopyrrolidine-1,3-dicarboxylate yields enaminoesters, which upon reaction with Bredereck's reagent produce the title compounds. A possible reaction mechanism is briefly discussed.

1. Introduction

Heterocycles containing the azaindole ring system have been reported to show a wide range of biological activities[1] (Fig. 1). Among them, a few natural products have been found, such as harmine derivatives (MAO inhibitors),[2] the DNA intercalator cryptolepine,[3] or the antileukemic canthin-6-one.[4] In this context, we became interested in the less studied pyrrolo[3,2-*b*]quinolines **1**, which possess the 4-azaindole core. This scaffold affords a wide range of modulation allowing its chemical structure to fit with a variety of targets involved in tumor progression, such as kinases, growth factor receptors, or DNA itself.

To the best of our knowledge, a very few pyrrolo[3,2-*b*]quinolines have been prepared and only three synthetic routes leading to this family have been described (Scheme 1).[5] The main method involves the cyclocondensation of 3-amino-2-methylquinoline **2** with triethyl orthoformate,[5a] Vilsmeier reagent,[5b] or acylation followed by treatment with Cu/NaOEt.[5b] Pyrrolo[3,2-*b*]quinolines **1b** can be obtained by rearrangement of 2-amino-5-phenyl-3*H*-1,4-benzodiazepines **3** with 1,3-dicarbonyl compounds **4**.[5c] Moreover, the reduced 1*H*-pyrrolo[3,2-*b*]quinoline **5**, accompanied with isomer **6**, can be obtained by Friedländer reaction of cyclic ketone **7**.[6] A review describing the main accesses to 4-, 5- or 6-azaindoles has recently been published.[7]

Because of our interest in new chemical structures targeting tumor progression, we have been paying attention to the synthesis of highly functionalized pyrrolo[3,2-*b*]quinolines **1** allowing easy further dressing. We now wish to report a new practical general method for the synthesis of such a scaffold.

2. Results and discussion

2.1. Chemical context

A classical synthesis of quinolines is based on the Friedländer condensation. In the pyrroloquinoline series, this method has been extensively used for the preparation of precursors of the antitumoral alkaloid camptothecin and some of its derivatives (last synthesis of Scheme 1).[8] In order to introduce various substituents on the phenyl ring, substituted aminobenzaldehydes would be required. However, it is well established that these aldehydes are often unstable due to self-condensation,[9] and Friedländer condensation may require harsh conditions (high temperature, strong acidic medium).[10] We did not consider this method since it would hardly be applied to highly functionalized compounds.

Ring closure of azahexatrienes **8** via electrocyclization represents another alternative method leading to quinoline scaffold **9**.

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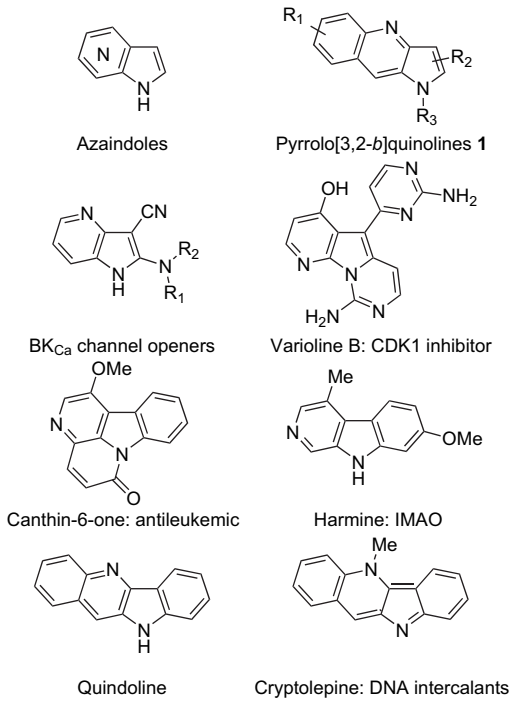
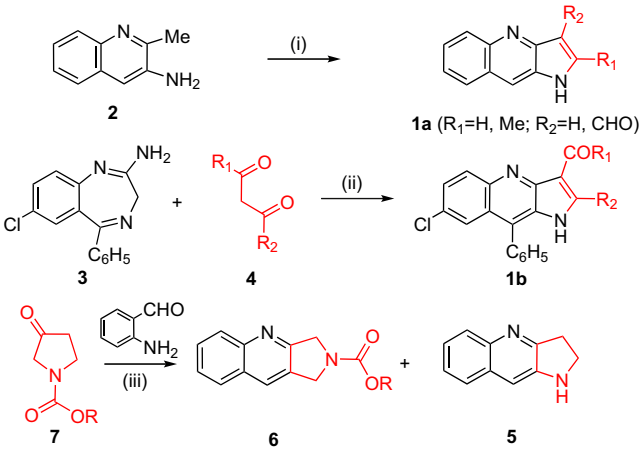


Figure 1. Targeted compounds and known active biological derivatives of azaindoles.

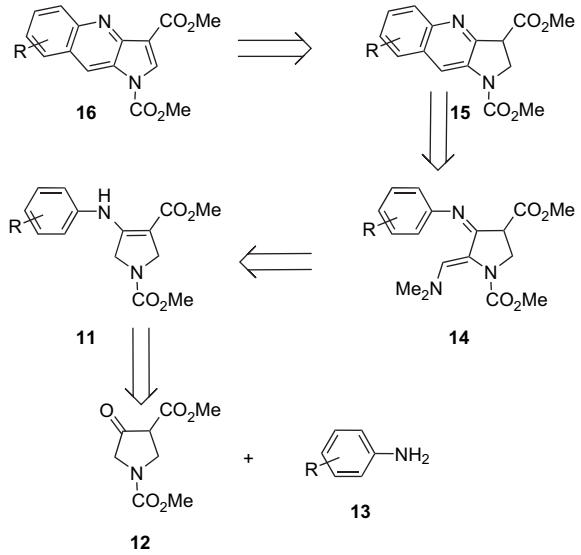


Scheme 1. Described syntheses of pyrrolo[3,2-*b*]quinolines. Reagents and conditions: (i) (a) $HC(OEt)_3$, HCl, 64% yield or (b) Ac_2O, then Cu/NaOEt, 22–42% yield or (c) $POCl_3$/DMF, 35% yield; (ii) 24% yield; (iii) NaOH, EtOH, 81% yield.

The vinamidines **10** are treated with sodium methoxide and then reacted with aniline to give **8**. Thermal cyclization of this key precursor followed by elimination of dimethylamine, then lead to aromaticity (Scheme 2).[11,12]

2.2. Retrosynthetic approach

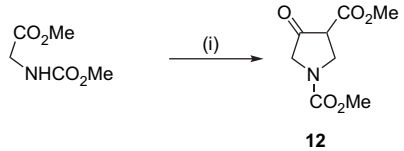
In our hands, these methods did not allow isolation of the targeted compounds, probably because of the use of highly sensitive intermediates. Thus, we have chosen a procedure involving stable precursors. This new approach was based on the retrosynthetic strategy depicted in Scheme 3, in which formation of vinamidine occurred lately. The first step requires the synthesis of β-enaminoesters **11** by condensation of β-ketoester **12** with anilines **13**. Then, formation of the dimethylaminomethylene adducts **14**, followed by electrocyclization of this vinamidine, could lead to the tricyclic core system **15**. In order to obtain the fully aromatic skeleton **16**, the last step involved oxidation of the pyrroline moiety. In comparison with the Friedländer condensation, introduction of substituents on the phenyl ring could be easily achieved with commercially available anilines.



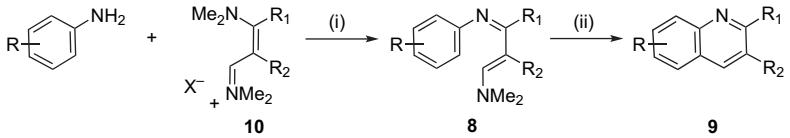
Scheme 3. Retrosynthetic approach to the substituted benzoazaindoles.

2.3. Synthesis of enamine compounds

By using an established procedure,[13,15a] β-ketoester **12** was obtained *one-pot* by Michael addition of glycine to methyl acrylate followed by Dieckmann cyclization; this synthesis has been recently optimized by our group (Scheme 4).[6] Such pyrrolidones have been involved in Friedländer synthesis of the ABC ring system of the naturally occurring alkaloid camptothecin.[14] Although synthesis of β-enaminoesters from β-ketoesters and amines was trivial, only few products have been reported from ethyl or *tert*-butyl analogs of ketoester **12**: for exemple,[15] unsubstituted or acylated analogs of enaminoesters **11** have been obtained by using ammonium formate, possibly in the presence of acetic anhydride.[16]

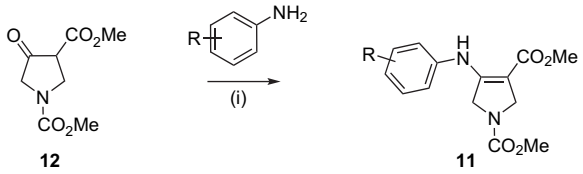


Scheme 4. Reagents and conditions: (i) (a) NaH (1 equiv), toluene, rt, 16 h; (b) $CH_2{=}CHCO_2Me$, rt, 24 h; (c) NaH (1.2 equiv), 5 h, then HCl (37%), 75% yield.



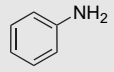
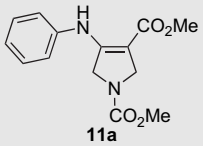
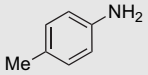
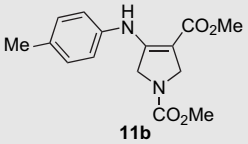
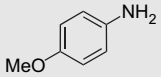
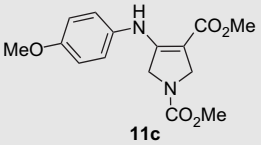
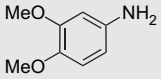
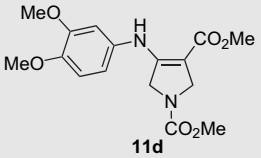
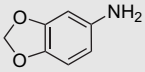
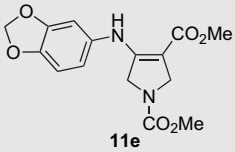
Scheme 2. Reported synthesis of quinolines via electrocyclization of vinamidines. Reagents and conditions: (i) NaOMe, 80 °C; (ii) quinoline, 130–180 °C.

Compound **12** easily reacted with anilines **13** in methanol at room temperature, giving moderate to good amounts of pyrrolidines **11**; no attempt was realized to increase yields (Scheme 5 and Table 1). The observed ^{1}H and ^{13}C NMR spectra of compounds **11a–e** were quite complex at room temperature. This complexity could be due to strong stacking interactions and/or the presence of few rotamers: the NMR spectra were strongly simplified by heating. For instance, in the case of β-enaminoester **11e** (Table 1), one of the two methoxycarbonyl groups appeared at room temperature in $CDCl_3$ as two singlets (3.71 and 3.74 ppm), which ended up as a single peak (3.71 ppm) by heating at 55 °C.



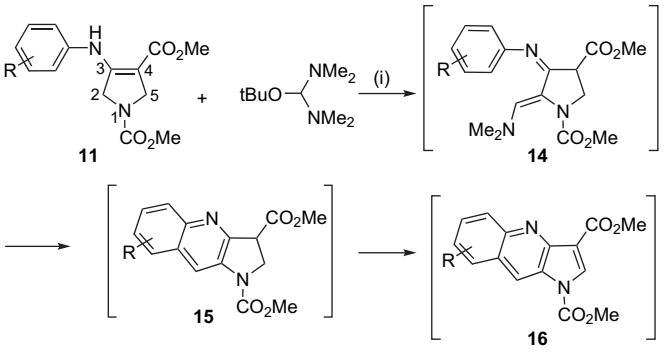
Scheme 5. Reagent and condition: (i) MeOH, 20 °C.

Table 1
Synthesis of β-enaminoesters **11a–e**

Entry	Aniline	Reaction time (h)	Product	Yield (%)
1		6	 **11a**	69
2		4	 **11b**	69
3		2	 **11c**	67
4		4	 **11d**	63
5		2	 **11e**	69

2.4. Cyclization of enamines 11a–e

In order to obtain an amino azahexatriene π system **14** (Scheme 3), which is able to be electrocyclized, we functionalized the previous β-enaminoesters **11** by reaction with Bredereck's reagent.[17] This compound is very efficient for α-methylation, α-methylenation or α-amination of activated methylene groups.[18] The use of Bredereck's reagent is a clean potent alternative to the Vilsmeier conditions. It allows a facile access to ketones[19] or various heterocycles, via dimethylaminomethylene intermediates.[17] Since position 2 of pyrrolinone **11** is vinylogous of a CH_2 in α position of a carbonyl group (Scheme 6),[20] compounds **11** were supposed to be able to react with Bredereck's reagent giving aminoazatrienes and, eventually, tricycles **15**.

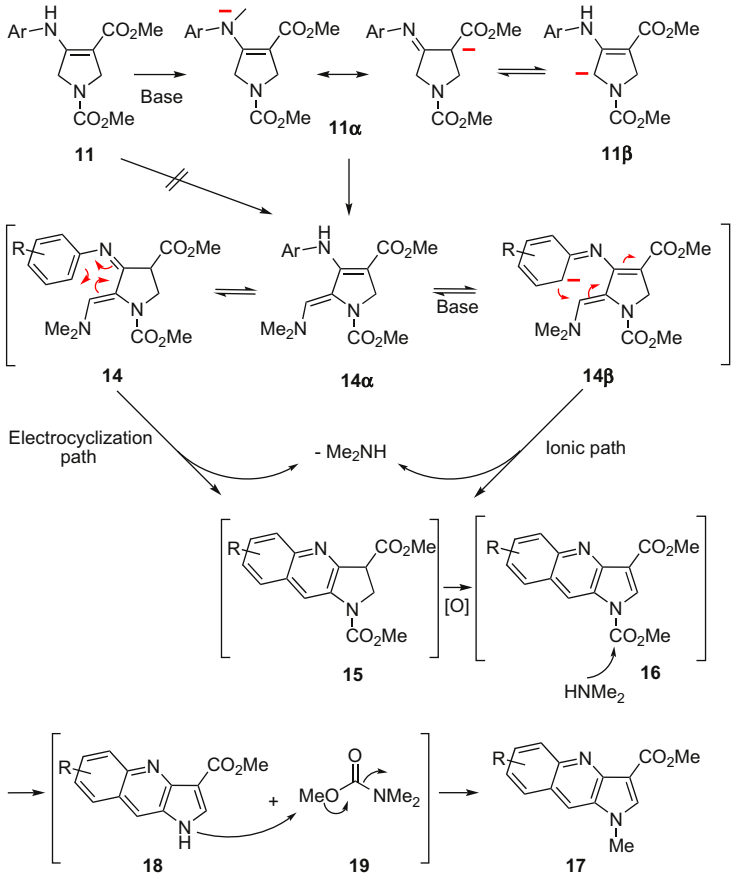


Scheme 6. Reagent and conditions: (i) ^{t}BuOK (1 equiv), 110 °C, 6 h.

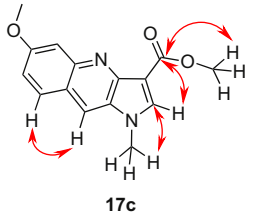
In order to examine this reaction sequence, Bredereck's reagent was heated with β-enaminoester **11c** (R=4-OMe) (Table 1). The reaction on the activated methylene group started very slowly, leading to dimethylenamine **14** (Scheme 6). Nonetheless, under these neutral conditions, very long reaction times were required. The addition of 1 equiv of a base dramatically increased reaction speeds and yields. Strong basic alkoxide was necessary, with better results observed with ^{t}BuOK than with sodium methoxide. The use of a base to catalyze the reaction could correspond to the formation of the different anions **11α** and **11β** in equilibrium (Scheme 7). The key intermediate **14α** was not isolated, but in situ led to condensed pyrrolidinoquinoline **15** and dimethylamine. In comparison with the electrocyclic ring closure of hexa π system **14** that was initially predicted, the mechanism may also involve ionic cyclization of **14β** promoted by basic media. Since some examples of rather similar electrocyclizations had been described in literature,[15] this mechanism was preferred. To our delight, compound **15** was not observed, but directly oxidized to an unisolated product that was supposed to be the corresponding pyrroloquinoline **16** (intermediate **15** was not detected even if the reaction was carried out under inert atmosphere). The ability of oxidation of these scaffolds has been already mentioned, either spontaneously, or with oxidant such as MnO_2 or DDQ.[21]

Surprisingly, only one carbonyl signal appeared on the ^{13}C NMR spectrum of the obtained product. Moreover, the methoxycarbonyl function of compounds **17** (Scheme 7) was detected at about 3.7 ppm whereas a second methyl group was observed at 4 ppm. That value was not compatible with a methyl carbamate function like **16** (Scheme 7). Elemental analysis and MS performed on the obtained product confirmed the loss of carbon dioxide; in addition, structure **17c** (Scheme 8) was deduced from 2D NMR. *N*-Methyl benzoazaindole **17c** could be formed by cleavage of the carbamate group followed by N-methylation. Indeed, since the enaminoester function was substituted by a methoxycarbonyl group, compound **16** was a vinylogous of a methoxycarbonyl carbamate, and thus sensitive toward nucleophilic attack of dimethylamine (leading to the release of **19**). It is well established that dimethyl carbonate can react as a methylation reagent.[22] So far, to the best of our knowledge, such a reactivity for trimethyl carbamate **19** has never been described. However, we postulate that nucleophilic attack of **18** on **19** yielded *N*-methylazaindole **17**, carbon dioxide, and dimethylamine (Scheme 7).

This procedure was then successfully generalized to a series of compounds substituted on the phenyl ring (Table 2). The reaction sequence was realized *one-pot* from enaminoesters **11a–e** and led to compounds **17** in good yields, except for enamine **11c** whose *para* methoxy group disfavored cyclization in the *meta* position (Table 2, entry 3).



Scheme 7. Suggested mechanisms of formation of benzoazaindole **17**.



Scheme 8. ^{1}H NMR spectra of pyrrolo[3,2-*b*]quinoline **17c** and assignments determined by 2D NMR techniques: COSY, NOESY, HMBC, and HSQC.

2.5. Attempted generalization of the reaction

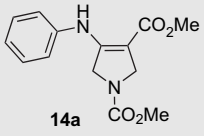
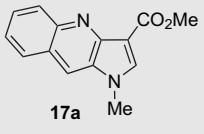
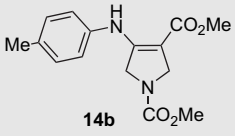
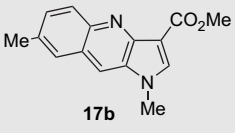
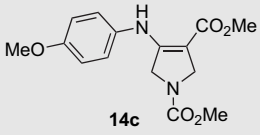
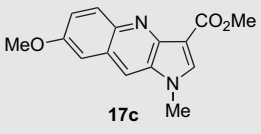
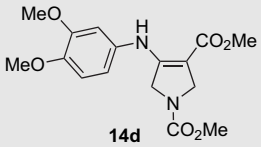
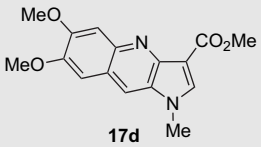
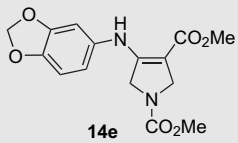
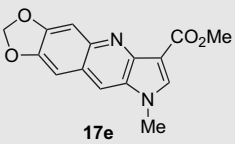
2.5.1. Case of benzaldehyde

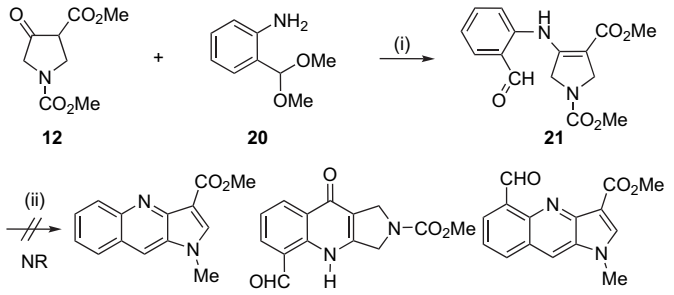
In spite of the disadvantage of using aminobenzaldehydes, we tried to perform a Friedländer cyclization between ketone **12** and aminoacetal **20**.[6] β-Enaminoester **21** was easily obtained (after deprotection of the acetal group) but, whatever the conditions, direct cyclization to pyrrolidinoquinoline as well as reaction with Bredereck's reagent did not succeed (Scheme 9).

2.5.2. Attempt of quinoline formation

Since quinoline moiety represents a privileged structure in drug chemistry,[23] it was interesting to examine if our electrocyclization method could give this heterocycle. We have already described that heating ethyl acetoacetate and fluoroaniline in PPA gave methyl quinolone **22** (without isolation of intermediate **23**).[24] Actually, enaminoester **23**, isolated in 75% yield from fluoroaniline and ethyl acetoacetate by refluxing in toluene, did not react with Bredereck's reagent in the presence of ^{t}BuOK (Scheme 10). Thus, our new electrocyclization reaction seemed to be limited to polycyclic compounds.

Table 2
Synthesis of pyrrolo[3,2-*b*]quinoline **17**

Entry	Enaminoester	Product	Yield (%)
1	 **14a**	 **17a**	68
2	 **14b**	 **17b**	82
3	 **14c**	 **17c**	58
4	 **14d**	 **17d**	95
5	 **14e**	 **17e**	87

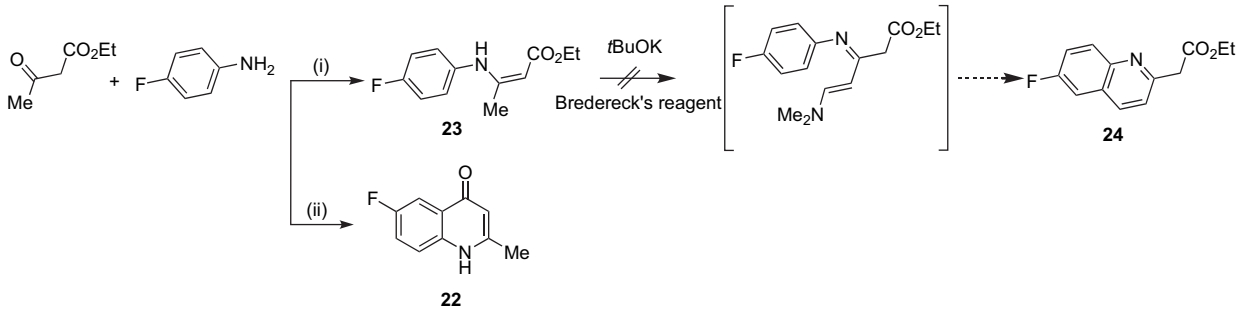


Scheme 9. Reagents and conditions: (i) MeOH, $CHCl_3$, pyrrolidine (1 equiv), 3 Å MS, MsOH (0.35 equiv), reflux, 24 h, 85% yield; (ii) Bredereck's agent (1 equiv), ^{t}BuOK (1 equiv), 110 °C, 6 h.

enaminoester, which was analyzed by NMR then utilized directly for the next reaction.

4.2.1. Dimethyl 4-anilino-2,5-dihydro-1H-pyrrole-1,3-dicarboxylate **11a**

Yellow foam; 69% yield; mp 98–100 °C; TLC R_f (AcOEt)=0.7; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.73, 3.74 (2s, 3H, $COCH_3$), 3.76 (s, 3H, $COCH_3$), 4.27–4.37 (m, 2H, CH_2), 4.48–4.60 (m, 2H, CH_2), 6.98–7.39 (m, 5H, Ar*H*), 9.29 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 49.6 (CH_2), 50.8 (CH_3), 52.3 (CH_3), 52.6 (CH_2), 92.5 and 92.7 (C), 120.6 and 120.8 (CH), 120.9 and 121.1 (CH), 124.2 and 124.6 (CH), 129.4 (CH), 129.7 and 129.9 (CH), 139.2 and 139.3 (C), 153.0 and 153.1 (C), 155.2 (C), 166.5 and 166.7 (C); IR: ν cm^{-1} 1702, 1670, 1633, 1448, 1391, 1348, 1282. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C 60.86, H 5.84, N 10.14; found: C 60.48, H 5.97, N 10.07.



Scheme 10. Reagents and conditions: (i) toluene, 110 °C, 3 h, 75% yield; (ii) PPA, 130 °C, 100% yield.

3. Conclusion

In summary, starting from an easily obtained 3-pyrrolidone,[7] a general and rapid synthesis of pyrrolo[3,2-*b*]quinolines was described. The key-step consists in a reaction of Bredereck's reagent, leading in situ to a new electrocyclization followed by a spontaneous oxidation. Instead of isolating the targeted carbamate compounds, an in situ cleavage/methylation sequence led to the *N*-methylated products with good to excellent yields.

4. Experimental section

4.1. General

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were obtained in ATR mode on an FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel 60F_{254} plates. APCI$^+$ (Atmospheric Pressure Chemical Ionization) mass spectra were obtained on an LC–MS system Thermo Electron Surveyor MSQ. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France.

4.2. General procedure for the synthesis of enaminoesters 11a–e

A solution of substituted aniline (15 mmol) and pyrrolidin-3-one **7** (3.0 g, 15 mmol) in methanol (50 mL) was stirred at room temperature for the time indicated in Table 1. Solvent was evaporated and the residue was partitioned between CH_2Cl_2 (25 mL) and water (15 mL). The organic layer was washed once with a diluted solution of HCl (5%), twice with water, then dried over $MgSO_4$. The residue obtained upon evaporation was purified by HPLC on SiO_2 (heptane/EtOAc, 100/0%–0/100%) to give the corresponding

4.2.2. Dimethyl 4-[(4-methylphenyl)amino]-2,5-dihydro-1H-pyrrole-1,3-dicarboxylate **11b**

Yellow foam; 69% yield; mp 105–107 °C; TLC R_f (AcOEt)=0.6; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.32 (s, 3H, CCH_3), 3.71, 3.73 (2s, 3H, $COCH_3$), 3.75 (s, 3H, $COCH_3$), 4.27–4.53 (m, 4H, CH_2NCH_2), 6.89–6.98 (m, 2H, Ar*H*), 7.07–7.18 (m, 2H, Ar*H*), 9.14 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 20.8 (CH_3), 49.6, 50.0 (CH_2), 50.7 (CH_3), 51.5, 52.1 (CH_3), 52.5, 52.6 (CH_2), 91.6, 91.7 (C), 121.5 (2CH), 130.0 (2C), 134.5 (C), 136.7 (C), 153.4 and 153.5 (C), 154.8 and 155.2 (C), 166.4 and 166.6 (C); IR: ν cm^{-1} 1702, 1659, 1630, 1517, 1449, 1387, 1343, 1276. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C 62.06, H 6.25, N 9.65; found: C 61.81, H 6.09, N 9.53.

4.2.3. Dimethyl 4-[(4-methoxyphenyl)amino]-2,5-dihydro-1H-pyrrole-1,3-dicarboxylate **11c**

Yellow foam; 67% yield; mp 119–121 °C; TLC R_f (AcOEt)=0.7; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.70, 3.73 (2s, 3H, $COCH_3$), 3.75 (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 4.27–4.41 (m, 4H, CH_2NCH_2), 6.82–6.90 (m, 2H, Ar*H*), 6.96–7.06 (m, 2H, Ar*H*), 8.93 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 50 and 50.4 (CH_2), 50.7 and 50.8 (CH_3), 51.5 and 51.9 (CH_3), 52.5 and 52.7 (CH_3), 55.5 (CH_2), 91.1 and 91.2 (C), 114.6 (CH), 114.7 (CH), 124.3 (CH), 124.4 (CH), 132.1 (C), 154.5 (C), 154.9 and 155.3 (C), 157.4 (C), 166.6 and 166.7 (C); IR: ν cm^{-1} 1699, 1663, 1633, 1445, 1389, 1281, 1245. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C 58.82, H 5.92, N 9.15; found: C 58.46, H 5.98, N 9.22.

4.2.4. Dimethyl 4-[(3,4-dimethoxyphenyl)amino]-2,5-dihydro-1H-pyrrole-1,3-dicarboxylate **11d**

Yellow foam; 63% yield; mp 82–85 °C; TLC R_f (AcOEt)=0.6; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.71, 3.73 (2s, 3H, $COCH_3$), 3.76 (s, 3H, $COCH_3$), 3.86, 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.27–4.45 (m, 4H, CH_2NCH_2), 6.57–6.66 (m, 2H, Ar*H*), 6.77–6.85 (m, 1H, Ar*H*), 8.98 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 49.8 and 50.3 (CH_2),

50.7 (CH_3), 51.4 and 52 (CH_3), 52.5 and 52.6 (CH_3), 55.9 (CH_3), 56 (CH_2), 91.4 (CH_2), 107.1 and 107.4 (C), 111.4 and 111.5 (CH), 114.4 and 114.6 (CH), 132.4 (CH), 146.8 (C), 149.4 (C), 154.2 (C), 155.2 (C), 166.6 (C); IR: ν cm^{-1} 1697, 1666, 1544, 1518, 1446, 1388, 1281, 1258, 1237, 1190. Anal. Calcd for $C_{16}H_{20}N_2O_6$: C 57.14, H 5.99, N 8.33; found: C 57.34, H 6.34, N 8.42.

4.2.5. Dimethyl 4-(1,3-benzodioxol-5-ylamino)-2,5-dihydro-1H-pyrrole-1,3-dicarboxylate **11e**

Yellow foam; 69% yield; mp 156–158 °C; TLC R_f (AcOEt)=0.7; ^1H NMR 20 °C ($CDCl_3$, 200 MHz) δ 3.71, 3.73 (2s, 3H, $COCH_3$), 3.75 (s, 3H, $COCH_3$), 4.27–4.41 (m, 4H, CH_2NCH_2), 5.98, 5.99 (2s, 2H, OCH_2O), 6.49–6.59 (m, 2H, ArH), 6.71–6.79 (m, 1H, ArH), 8.91 (br s, 1H, NH); ^1H NMR 55 °C ($CDCl_3$, 200 MHz) δ 3.71 (s, 3H, $COCH_3$), 3.74 (s, 3H, $COCH_3$), 4.04–4.41 (m, 4H, CH_2NCH_2), 5.96 (2s, 2H, OCH_2O), 6.52 (dd, J=8.2, 2.5 Hz, 1H, NHCCHCH), 6.57 (d, J=2.5 Hz, 1H, NHCCHCO), 6.73 (d, J=8.2 Hz, 1H, NHCCHCH), 8.89 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 48.9 and 49.3 (CH_2), 49.7 and 49.8 (CH_3), 50.4 and 51 (CH_3), 51.5 and 51.6 (CH_2), 90.5 and 90.7 (C), 100.6 (CH), 103.7 (CH_2), 107.4 (CH), 115.1 (CH), 132.2 and 132.3 (C), 144.4 (C), 147.2 (C), 153 and 153.1 (C), 153.8 and 154.2 (C), 165.5 and 165.6 (C); IR: ν cm^{-1} 1729, 1710, 1658, 1442, 1279, 1241, 1194. Anal. Calcd for $C_{15}H_{16}N_2O_6$: C 56.25, H 5.04, N 8.75; found: C 56.29, H 5.26, N 8.39.

4.3. General procedure for the synthesis of pyrrolo[3,2-b]quinolines 17a–e

A stirred mixture of enaminoester **11** (0.5 mmol), ^{t}BuOK (145 mg, 0.5 mmol), and Bredereck's reagent (632 mg, 3 mmol) was heated at 110 °C for 6 h (N_2). Dichloromethane (20 mL) and HCl 5% solution (10 mL) were added to the residue obtained upon evaporation, and then aqueous $NaHCO_3$ was added until neutralization. The aqueous phase was extracted with dichloromethane (2×100 mL). The organic phase was dried ($MgSO_4$). The residue obtained upon evaporation was purified by HPLC on SiO_2 (heptane/EtOAc, 100/0%–0/100%) to give the corresponding pyrroloquinoline.

4.3.1. Dimethyl 1H-pyrrolo[3,2-b]quinoline-1,3-dicarboxylate **17a**

Yellow oil; 68% yield; TLC R_f (AcOEt)=0.3; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.94 (s, 3H, CO_2CH_3), 4.01 (s, 3H NCH_3), 7.5 (t, J=7.5 Hz, 1H, ArH), 7.68 (t, J=7.5 Hz, 1H, ArH), 7.93 (d, J=8.4, 1H, ArH), 8.07 (s, 1H, ArH), 8.34 (d, J=9.2 Hz, 1H, ArH); IR: ν cm^{-1} 1752, 1685, 1647, 1528, 1306, 1257, 1201. Anal. Calcd for $C_{14}H_{12}N_2O_2\cdot H_2O$: C 65.11, H 5.46, N 10.85; found: C 65.17, H 5.69, N 11.02.

4.3.2. Dimethyl 7-methyl-1H-pyrrolo[3,2-b]quinoline-1,3-dicarboxylate **17b**

Yellow oil; 82% yield; TLC R_f (AcOEt)=0.3; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H, CH_3), 3.9 (s, 3H, CO_2CH_3), 3.99 (s, 3H, NCH_3), 7.5 (dd, J=8.7, 2.2 Hz, 1H, ArH), 7.65 (br s, 1H, ArH), 7.93 (s, 1H, ArH), 8.21 (d, J=2.2 Hz, 1H, ArH), 8.23 (s, 1H, ArH); IR: ν cm^{-1} 1710, 1680, 1543, 1377, 1335, 1236; LC–MS (APCI$^+$) m/z 255 (MH^+). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C 70.85, H 5.55, N 11.02; found: C 70.76, H 5.59, N 11.19.

4.3.3. Dimethyl 7-methoxy-1H-pyrrolo[3,2-b]quinoline-1,3-dicarboxylate **17c**

Yellow powder; 58% yield; TLC R_f (AcOEt)=0.3; mp 175–177 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.87 (s, 3H, CO_2CH_3), 3.92 (s, 3H, OCH_3), 3.99 (s, 3H, NCH_3), 7.49 (dd, J=9, 2.7 Hz, 1H, ArH), 7.51 (s, 1H, ArH), 8.21 (d, J=9 Hz, 1H, ArH), 8.7 (s, 1H, ArH), 8.79 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.2 (CH_3), 51.5 (CH_3), 56 (CH_3), 103.3 (C), 106 (CH), 114.6 (CH), 123.2 (CH), 125.7 (CH), 127.7 (C), 131.6 (C), 138 (C), 142 (C), 146.2 (CH), 156.8 (C), 163.3 (C); IR: ν cm^{-1} 1710, 1380, 1368, 1332, 1235, 1206, 1112; LC–MS (APCI$^+$) m/z 271 (MH^+). Anal. Calcd for $C_{15}H_{14}N_2O_3\cdot 3/2H_2O$: C 60.60, H 5.76, N 9.42; found: C 61.00, H 5.39, N 9.35.

4.3.4. Dimethyl 6,7-dimethoxy-1H-pyrrolo[3,2-b]quinoline-1,3-dicarboxylate **17d**

Yellow oil; 95% yield; TLC R_f (AcOEt)=0.3; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 4.03 (s, 3H, CH_3), 7.12 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.93 (s, 1H, ArH), 8.36 (s, 1H, ArH). Anal. Calcd for $C_{16}H_{16}N_2O_4\cdot 3/2H_2O$: C 58.71, H 5.85, N 8.56; found: C 58.90, H 6.03, N 8.44.

4.3.5. Dimethyl 8H-[1,3]dioxolo[4,5-g]pyrrolo[3,2-b]quinoline-6,8-dicarboxylate **17e**

Yellow oil; 87% yield; TLC R_f (AcOEt)=0.3; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.11 (s, 2H, OCH_2O), 7.14 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.9 (s, 1H, ArH), 8.17 (s, 1H, ArH); IR: ν cm^{-1} 1729, 1710, 1658, 1442, 1279, 1241, 1194. Anal. Calcd for $C_{15}H_{12}N_2O_4$: C 63.38, H 4.25, N 9.85; found: C 63.05, H 4.14, N 9.52.

4.4. Dimethyl 4-[(2-formylphenyl)amino]-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate 21

A stirred mixture of ketone **12** (3 g, 15 mM), aniline **20** (2.5 g, 15 mM), pyrrolidine (1 g, 15 mM), and methanesulfonic acid (0.5 g, 5.2 mM) in chloroform (120 mL) and methanol (120 mL) was refluxed for 24 h while drying the solvent by condensing it in a Soxhlet-type apparatus containing 3 Å molecular sieves (150 g). Solvents were evaporated, then dichloromethane (300 mL) and water (300 mL) were added. The organic phase was extracted with slightly (HCl) acidified water (100 mL), then twice with water (100 mL), and the combined aqueous phases were extracted with dichloromethane (50 mL). The residue obtained upon evaporation was analyzed by NMR then utilized directly for the next reaction. Yellow powder; 85% yield; TLC R_f (AcOEt)=0.7; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.76, 3.77 (2s, 3H, $COCH_3$), 3.80 (s, 3H, $COCH_3$), 4.04–4.30 (m, 4H, CH_2NCH_2), 6.57–6.89 (m, 1H, ArH), 7.16–7.65 (m, 3H, ArH), 9.87, 9.96 (2s, 1H, CHO).

4.5. Ethyl 2,3-[(4-fluorophenyl)amino]but-2-enoate 23

A solution of fluoroaniline (11.1 g, 100 mmol) and ethyl acetoacetate (13 g, 100 mmol) in toluene (80 mL) was refluxed for 3 h while drying the solvent by Dean–Stark device. Solvent was evaporated and the residue was dissolved in 40 mL of dichloromethane/heptane mixture (50/50) then was taken to −40 °C. The precipitate was removed by filtration and the product **23** was obtained upon evaporation; Yellow oil; 75% yield; TLC R_f (ether/heptane 50/50)=0.4; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.92 (s, 3H, CH_3), 2.24 (br s, 1H, NH), 4.15 (q, J=7.1 Hz, 2H, CH_2CH_3), 4.69 (s, 1H, COCH), 6.95–7.12 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.4 and 14.5 (CH_3), 20.1 and 20.9 (CH_3), 58.7 (CH_2), 85.5 and 86.0 (CH), 115.1–116.47 (m, 2CH), 126.2–127.2 (m, 2CH), 135.1 and 135.2 (C), 159.1 (C), 160.2 (d, J=244.1 Hz, C), 170.4; IR: ν cm^{-1} 1649, 1613, 1509, 1271, 1230, 1154. Anal. Calcd for $C_{12}H_{14}FNO_2$: C 64.56, H 6.32, N 6.27; found: C 64.46, H 6.58, N 6.33.

References and notes

1. Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Meanwell, N.; Kadow, J.; Wang, T. *Tetrahedron Lett.* **2006**, *47*, 5653.
2. Moureau, F.; Wouters, J.; Depas, M.; Vercauteren, D.; Durant, F.; Ducrey, F.; Koenig, J.; Jarreau, F. *Eur. J. Med. Chem.* **1995**, *30*, 823.
3. Mardenborough, L.; Zhu, X.; Fan, P.; Jacob, M.; Khan, S.; Walkerb, L.; Ablordeppey, S. *Bioorg. Med. Chem.* **2005**, *13*, 3955.
4. Snyder, S.; Vosburg, D.; Jarvis, M.; Markgraf, J. *Tetrahedron* **2000**, *56*, 5329.
5. (a) Parrick, J.; Wilcox, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2121; (b) Khan, H.; Rocha, J. *Heterocycles* **1977**, *6*, 1927; (c) Szmuszkovicz, J.; Baczynskyj, L.; Chidester, C.; Duchamp, D. *J. Org. Chem.* **1976**, *41*, 1743.

6. (a) Zalkow, L.; Nabors, J.; French, K.; Bisarya, S. *J. Chem. Soc. C* **1971**, 3552; (b) Akue-Gedu, R.; Gautret, P.; Lelieur, J.-P.; Rigo, B. *Synthesis* **2007**, *21*, 3319 and references cited therein.
7. Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689.
8. (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. I.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888; (b) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 365; (c) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047; (d) *Chinese Drugs of Plant Origin*; Tang, W., Eisenbrand, G., Eds.; Springer: New York, NY, 1992; p 239; (e) Ciufolini, M. A.; Roschangar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 25; (f) Kim, D.-K.; Lee, N. *Mini Rev. Med. Chem.* **2002**, *2*, 611; (g) Lerchen, H. G. *Drugs Future* **2002**, *27*, 869; (h) Ulukan, H.; Swan, P. W. *Drugs* **2002**, *62*, 2039; (i) Du, W. *Tetrahedron* **2003**, *59*, 8649; (j) Lee, K. H. *J. Nat. Prod.* **2004**, *67*, 273; (k) Craig, J. T.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585; (l) Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049.
9. Smith, L. I.; Opie, J. W. *Org. Synth.* **1955**, *28*, 11.
10. (a) Friedlander, P. *Chem. Ber.* **1882**, *15*, 2572; (b) Cheng, C. C.; Yan, S. J. *Org. React.* **1982**, *28*, 37; (c) Wu, J.; Zhang, L.; Diao, T.-N. *Synlett* **2005**, 2653; (d) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1647 and references cited therein; (e) Zalkow, L. H.; Nabors, J. B.; French, K.; Bisarya, S. C. *J. Chem. Soc. C* **1971**, 3551; (f) Desbois, N.; Chezal, J.-M.; Fauvelle, F.; Debouzy, J.-C.; Lartigue, C.; Gueiffier, A.; Blache, Y.; Moreau, E.; Madelmont, J.-C.; Chavignon, O.; Teulade, J.-C. *Heterocycles* **2005**, *65*, 1121; (g) Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 7249.
11. Jutz, C. *Top. Curr. Chem.* **1978**, *73*, 125.
12. (a) McNab, H.; Murray, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 333; (b) Selvi, S.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6263; (c) Gupton, J. T.; Miller, R. B.; Krumpe, K. E.; Clough, S. C.; Banner, E. J.; Kanters, R. P. F.; Du, K. X.; Keertikar, K. M.; Lauerman, N. E.; Solano, J. M.; Adams, B. R.; Callahan, D. W.; Little, B. A.; Scharf, A. B.; Sikorski, J. A. *Tetrahedron* **2005**, *61*, 1845; (d) Clough, S.; Gupton, J.; Ligali, A.; Roberts, M.; Driscoll, D.; Annett, S.; Hewitt, A.; Hudson, M.; Jackson, E.; Miller, R.; Norwood, B.; Kanters, R.; Wyre, H.; Petruzzi, H. *Tetrahedron* **2005**, *61*, 7554.
13. Yadav, J. S.; Sarkar, S.; Chandrasekhar, S. *Tetrahedron* **1999**, *55*, 5449.
14. (a) Shamma, M.; Novak, L. *Tetrahedron* **1969**, *25*, 2275; (b) Tanaka, T.; Mashimo, K.; Wagatsuma, M. *Tetrahedron Lett.* **1971**, *12*, 2803.
15. (a) Blake, J.; Willson, C.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293; (b) Sheradsky, T.; Southwick, P. *J. Heterocycl. Chem.* **1967**, *4*, 1; (c) Shamma, M.; Novak, L. *Collect. Czech. Chem. Commun.* **1970**, *35*, 3286.
16. Wormser, H. C.; Abramson, H. N. *J. Heterocycl. Chem.* **1976**, *13*, 113.
17. Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.
18. Giovanni, B. *Synlett* **2006**, 809.
19. (a) Brunin, T.; Hénichart, J.-P.; Rigo, B. *Tetrahedron* **2005**, *61*, 7916; (b) Brunin, T.; Legentil, L.; Hénichart, J.-P.; Rigo, B. *Tetrahedron* **2006**, *62*, 3959.
20. Lyubchanskaya, V.; Mukhanova, T.; Alekseeva, L.; Granik, V. *Khim. Farm. Zh.* **1995**, *29*, 40; *Chem. Abstr.* **1995**, *124*, 145843.
21. (a) Cocco, M.; Congiu, C.; Onnis, V. *Chem. Pharm. Bull.* **2001**, *49*, 703; (b) Congiu, C.; Cocco, M.; Liliu, V.; Onnis, V. *J. Med. Chem.* **2005**, *48*, 8245; (c) Cocco, M.; Congiu, C.; Onnis, V.; Bernard, A.; Piras, P. *J. Heterocycl. Chem.* **1997**, *34*, 1347; (d) White, D.; Cain, G.; Upjohn, C. *Tetrahedron Lett.* **1989**, *30*, 1469; (e) Kasum, B.; Prager, R. *Aust. J. Chem.* **1990**, *43*, 63.
22. (a) Shaik, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951; (b) Shieh, W.-C.; Dell, S.; Bach, A.; Repic, O.; Balcklock, T. J. *J. Org. Chem.* **2003**, *68*, 1954.
23. Horton, D.; Bourne, G.; Smythe, M. *Chem. Rev.* **2003**, *103*, 893.
24. Becker, B.; Antoine, M.-H.; Nguyen, Q.-A.; Rigo, B.; Cosgrove, K. E.; Barnes, P. D.; Dunne, M. J.; Pirotte, B.; Lebrun, P. *Br. J. Pharmacol.* **2001**, *134*, 375.