Cyclization of Free Radicals at the C-7 Position of Ethyl Indole–2-carboxylate Derivatives: an Entry to a New Class of Duocarmycin Analogues

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Abstract: Aryl free-radicals generated at the C-7 position of ethyl indole-2-carboxylates bearing N-allyl and propargylic groups triggered intramolecular cyclizations to furnish a new class of Duocarmycin analogues, formal ethyl pyrrolo[3,2,1-ij]quinoline-2-carboxylate derivatives, through the less favorable 6-endo-trig cyclization mode.

Keywords: Duocarmycin, free-radicals, intramolecular cyclization, indole, pyrroloquinoline

Introduction

In the course of our research aimed at the synthesis of biologically active simple pharmacophores of structurally complex natural products [1-2], we turned our attention to the duocarmycins (1-6, Figure 1) [3-7]. These compounds are natural potent antitumor antibiotics that have drawn a great deal of attention [8-10]. Their cytotoxicity is directly related to the chemical stability of these compounds in aqueous acidic solutions and it is believed that this stability is mainly due the vinylogous amide conjugation, which is disrupted after binding to the DNA. The non-covalent binding to the DNA induces a conformational change that twists the linking amide, disrupting the stabilization and activating the cyclopropane for nucleophilic attack by adenine [11-12]. Despite these observations, no attempt was made to maintain the stabilizing vinylogous amide conjugation and make it insensitive to
conformational changes after binding to DNA. We believed that fusing the nitrogen to pyrrole system would address the issues of the cyclopropylidienone formation and its stability versus vinylogous amide conjugation.

![Figure 1](image_url)

In order to investigate the importance of the carboxamido moiety to the biological activity of these natural products, pyrroloquinoline (seco-PQC, 7\textsubscript{a,b}) and pyrroloindoline (seco-PIC, 8) derivatives were designed. We planned to construct these systems based on the strategy of intramolecular cyclization of an aryl radical generated at the C-7 position of ethyl indole carboxylates bearing a radical acceptor attached onto the indole nitrogen. One such example of radicals being generated at the C-7 position of a simple indole system having a radical acceptor attached onto the indole nitrogen has been documented [13]. It was found that these reactions formed either the reduction product or a mixture of products comprising the reduction product as the major and the 6-endo-cyclization product as the minor one. Surprisingly, no studies were cited in the literature of radicals being generated at the C-7 position of a C-2 substituted indole tethered with a radical acceptor at the nitrogen. As a prelude to biological evaluation, we describe herein the cyclizations of aryl free radicals generated at the C-7 position of N-allylic and N-propargylic substituted ethyl 7-haloindole-2-carboxylates that provided pyrroloquinoline (seco-PQC, 7\textsubscript{a,b}) derivatives through an 6-endo cyclization mode.
Results and Discussion

Among the various documented methods for the synthesis of ethyl 7-haloindole carboxylates, we chose to employ the nitrene insertion methodology [14]. The use of degassed chlorobenzene as a solvent in this reaction instead of toluene improved the yields. Thus, aldehydes 9a and 9b were condensed with ethyl azidoacetate to give azides 10a and 10b, respectively. Azide 10a was then converted to ethyl 7-iodo-indole-2-carboxylate (11b) by thermolysis followed by iodination (with ICl). Similarly, azide 10b was thermolysed to furnish ethyl 7-bromoindole-2-carboxylate (11c) [14]. The radical acceptors were introduced by N-alkylation of 11b and 11c with suitable acceptors (Scheme 1) [16]. Three types of acceptors were attached to the indole nitrogen.

Scheme 1: Synthesis of Ethyl N-substituted haloindole-2-carboxylate

\[
\begin{align*}
\text{CHO} & \quad \text{OBn} \\
\text{X = H; 9a} & \quad \text{X = H; 10a} \\
\text{X = Br; 9b} & \quad \text{X = Br; 10b} \\
\end{align*}
\]

Reagents: a) \(\text{N}_3\text{CH}_2\text{CO}_2\text{Et}, \text{NaOMe}, \text{MeOH}, -15^\circ\text{C}\); b) chlorobenzene, reflux; c) ICl, AcOH, rt; d) RX, K_2\text{CO}_3, \text{DMF}, 50^\circ\text{C};

Suitable reaction conditions to generate the aryl free radical at the C-7 position were first examined in detail using (Bu)_3SnH and the 7-bromo derivative 12b. Conducting the reactions in dry benzene at reflux temperature allowed the cyclization described in Scheme 2 to occur smoothly in good isolated yield (Table 1). Heating the N-allyl derivatives (12a or 12b) with Bu_4SnH (four equivalents) and AIBN as a radical initiator gave exclusively the cyclized product 13a through \textit{6-endo-trig} mode (Entries 1, 2). These encouraging results prompted us to trap the intermediate of the \textit{6-endo-trig} cyclization mode with TEMPO [17]. Thus, treatment of 7-iodo compound 12a with an equivalent amount of Bu_3SnH and excess TEMPO furnished, after immediate reduction (Zn, AcOH) of the reaction products, a mixture of two alcohols, the \textit{6-endo-trig} product 13b and the \textit{5-exo-trig} closure product 14 \((Y = \text{OH}, \text{Entry 3})\). The \(^1\text{H}-\text{NMR}\) spectrum of the crude mixture of products showed that 13b and 14 were formed in the ratio of 6:1. The \textit{6-endo-trig} cyclization product 13 was isolated in reasonable yield (60%), but the \textit{5-exo-trig} closure product 14 could not be fully characterized because it was contaminated with inseparable impurities. On the other hand, the 7-bromo 12b (Entry 4) was
recovered unchanged under wide range of reaction conditions (benzene, toluene and xylene, large excesses of TEMPO, slow addition of Bu$_3$SnH). This result is presumably a consequence of the competing reaction of the generated tributyltin radical with TEMPO.

Scheme 2

Table 1: Synthesis of Pyrroloquinoline (seco-PQC, 7) via Free Radical Cyclization

| Entry | Substrate | Reagents | Product(s) | Yield (%) |
|-------|-----------|----------|------------|-----------|
| 1     | 12a       | Bu$_3$SnH (4 eq), AIBN | 13a, H | 82 |
| 2     | 12b       | Bu$_3$SnH (4 eq), AIBN | 13a, H | 84 |
| 3     | 12a       | 1) Bu$_3$SnH (1 eq), TEMPO (4 eq) 2) Zn, AcOH:THF: H$_2$O (3:1:1) | 13b, OH | 60 |
| 4     | 12b       | Bu$_3$SnH, TEMPO | Starting material | |
| 5     | 12c       | 1) Bu$_3$SnH (4 eq), AIBN 2) BH$_3$-THF, then aq. NaOH- H$_2$O$_2$ | 13b, OH | 50 |
| 6     | 12d       | 1) Bu$_3$SnH (4 eq), AIBN 2) BH$_3$-THF, then aq. NaOH- H$_2$O$_2$ | 13b, OH | 35 |
| 7     | 12e       | Bu$_3$SnH (1 eq), AIBN | 13c, Cl | 94 |
| 8     | 12f       | Bu$_3$SnH (1 eq), AIBN | 13c, Cl | 92 |

The formation of the thermodynamically less favored 6-endo-trig cyclization product as a major component in the presence of large excess of TEMPO in the reaction mixture ruled out 5-exo-trig closure followed by rearrangement of the less stable primary radical 15a intermediate to the more stable secondary radical 15b. Since the primary radical 15a is expected to form the most stable benzylic radical 15c after rearrangement (Figure 2).
Therefore, in comparison with the previously reported results on aryl radical cyclization of C-2 unsubstituted indole 16, the most reasonable explanation for the formation of the 6-endo-trig cyclization product would be based on the free rotation of the vinylic group [13]. Three conformers 17a-c can be considered for the radical intermediate (Figure 3). The two conformers 17b and 17c are ruled out due to the long distance between the radical and the acceptor carbon required for the 5-endo-trig pathway. Conformer 17b in addition has steric repulsion between the N-alkenyl and ester groups.

Strain and distortion in the five-membered ring are also important factors favoring the 6-endo-trig product. In order to probe the effect of the geometry and size of the acceptor on the regiochemistry of cyclization, ethyl N-propargylic haloindoles 12c,d were prepared. Trapping the aryl free radical generated at the C-7 position with sp hybridized carbon employing excess Bu₃SnH furnished an inseparable mixture of products. Examination of the ¹H-NMR spectrum of the mixture produced from the 7-iodoindole compound 12c indicated that it was actually converted to a mixture of alkenes assumed to be the 6-endo-dig cyclization product 18 and the 5-exo-dig closure product 19 (Entry 5, Figure 4).

Fortunately, this analysis could be further confirmed after the crude mixture of products was treated with BH₃-THF, followed by oxidation (NaOH-H₂O₂). This furnished alcohol 13b in 50% isolated yield (Entry 5). The 5-exo-dig closure product 19 was isolated as an impure component in a
very low yield (<5%). Similar results were obtained from the cyclization of the 7-bromo derivative 12d but in lower yields (Entry 6). These results suggest that the strain and distortion in the five-membered ring are major factors favoring the 6-endo-trig product.

These results prompted us to study the closure of chloroallyl derivatives 12e-f. These derivatives incorporate the necessary functionality directly in the free radical substrate and would furnish the desired pyrroloquinoline (seco-PQC, 7, Y= Cl) in a single step. Therefore, standard cyclization conditions (Bu3SnH, AIBN, benzene, 80 °C) were employed to bring about the cyclization of 12e-f. Both compounds furnished the desired indoloquinoline 13c in excellent yields through 6-endo-trig cyclization mode (Entries 7 and 8). The optimum conditions for the formation of 13c required the use of stoichiometric amount of Bu3SnH. The implementation of chloroallyl derivatives solved the problem of postcyclization functionalization and reinforced the inherent regioselectivity of the free radical cyclization.

With both pyrroloquinoline products 13b,c available, they were deprotected under mild hydrogenolysis conditions (H2/Pd on C) to furnish the corresponding phenol derivatives 7a and 7b, respectively, in good yields, thus forming analogs of the duocarmycins. It is worth noting here that the deprotection of the benzyl group in 13c under mild conditions (H2 balloon, Pd on C) gave the minor product 21 (<10%). This minor product was identified using 1H-NMR. The formation of the minor product 21 is unlikely to be due to overreduction of 7b under the very mild conditions used and presumably it was generated from the reduction of cyclopropylidenone system 21, formed in situ from 7b (Scheme 3). This promising result revealed that our designed system might form the alkylating subunits of the duocarmycins. The formation of 21 from 7b is under investigation and the results will be reported in due course.

Conclusions

In summary, a reliable synthetic route to functionalized pyrroloquinoline systems has been developed. The central step in this strategy is based on an 6-endo cyclization process involving aryl free-radicals. Ethyl 4-benzyloxyindole-2-carboxylate was manipulated in four steps to give the pyrroloquinoline derivatives. These derivatives are potential candidates to alkylate the DNA.

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Experimental

General

Melting points (mp) were determined on an Electrothermal digital melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Nicolet-Impact 410 spectrophotometer. Both $^1$H- and $^{13}$C-NMR spectra were recorded on Bruker Avance 250 and Bruker DPX-300 instruments. The chemical shifts (δ) are reported in ppm relative to TMS used as an internal standard.

Ethyl 4-(benzyl)oxy)-1H-indole-2-carboxylate (11a)

Sodium (1.39 g, 60 mmol) was dissolved in ethanol (50 mL) and the solution was cooled to -13°C. A mixture of aldehyde 9a (3.20 g, 15 mmol) and ethyl azidoacetate (7.79 g, 60 mmol) in ethanol (30 mL) was added dropwise over 30 minutes with continuous stirring while maintaining the temperature below -10°C. The reaction mixture was stirred below -10 °C for 3 h, warmed carefully to -5°C, and stirred for another 3h. The reaction mixture was directly poured into ice-water mixture and extracted with ether (2×100 mL). The combined ether extracts were washed with brine, dried over anhydrous sodium sulphate, and evaporated to give crude azide product 11a (62-70%), which was used immediately without further purification. The crude 11a was dissolved in chlorobenzene (650 mL), degassed with N₂ and then refluxed for 20 min. Evaporation of the solvent gave a solid, which was dissolved in ethyl acetate and passed over a layer of Florisil. The resulting solution was evaporated. The residual solid was recrystallized from ethyl acetate-hexane mixture to afford indole 11a as white crystals (1.80 g, 66%). An additional quantity was obtained from the mother liquors, and the combined yield of 11a was 2.35 g (overall 86%): mp. 170-172 °C, (Lit. mp. 169-171 °C [14]); IR (KBr, cm$^{-1}$) 3325 (N-H) and 1685 (C=O); $^1$H-NMR (300 MHz, CDCl$_3$) δ 9.23 (br s, 1H, N-H), 7.52-7.30 (br m, 6H, Ar-H), 7.20 (t, $J = 7.9$ Hz, 1H, Ar-H), 7.04 (d, $J = 8.3$ Hz, 1H, Ar-H), 6.6 (d, $J = 7.7$ Hz, 1H, Ar-H), 5.19 (s, 2H, -OC$_2$H$_5$Ph), 4.41 (q, $J = 7.1$ Hz, 2H, -OC$_2$H$_5$CH$_3$), and 1.40 (t, $J = 7.1$ Hz, 3H, -CH$_3$).

Ethyl 4-(benzyl)oxy)-7-iodo-1H-indole-2-carboxylate (11b).

A solution of iodine monochloride (98%, 0.48 g, 2.90 mmol) in acetic acid (70 mL), was added dropwise to a stirred solution of indole 11a (0.89 g, 3.01 mmol) in acetic acid (150 mL) at room temperature, until no starting material was detected by TLC. The solvent was evaporated and the residue was dissolved in ethyl acetate (100 mL). The resulting solution was washed with saturated solution of sodium bicarbonate (150 mL) followed by water (100 mL). The organic layer was dried (MgSO$_4$) and concentrated. Purification by column chromatography on silica gel (1-2.5% ethyl acetate in hexane) furnished indole 11b as a white solid (1.08 g, 85%): mp. 114-115 °C; IR (KBr, cm$^{-1}$) 3425 (N-H), 1708 (C=O) and 1608 (C=C); $^1$H-NMR (250 MHz, CDCl$_3$) δ 8.81 (br s, 1H, N-H), 7.60-7.30 (br m, 7H, Ar-H), 6.40 (d, $J = 10$ Hz, 1H, Ar-H), 5.16 (s, 2H, -OCH$_2$Ph), 4.40 (q, $J = 7.5$ Hz, 2H, -OCH$_2$CH$_3$), and 1.40 (t, $J = 7.5$ Hz, 3H, -CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 161.66, 154.37, 139.70, 136.81, 134.57, 128.76, 128.21, 127.51, 126.53, 119.36, 107.89, 103.80, 70.25, 66.13, 61.35, and 14.57; EIMS (m/z rel intensity) calc for C$_{18}$H$_{16}$INO$_3$: 421; found 421 (M$^+$, 48).
Ethyl 4-(benzyloxy)-7-bromo-1H-indole-2-carboxylate (11c).

A solution of the vinyl azide 10b (2.10 g, 5.22 mmol) in chlorobenzene (700 mL) was refluxed for 1 h. Evaporation of the solvent gave a solid, which was recrystallized from ethyl acetate-hexane mixture to furnish the expected indole 11c as white crystals (1.35 g, 69%). A further quantity was obtained from the mother liquors and the combined yield of 11c was 1.85 g (95%): mp. 135-136 °C; IR (KBr, cm\(^{-1}\)) 3323 (N-H), and 1692 (C=O); 1H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.90 (br s, 1H, N-H), 7.40 (m, 7H, Ar-H), 6.49 (d, \(J = 8.3\) Hz, 1H, Ar-H), 5.19 (s, 2H, -OC\(_2\)H\(_2\)Ph), 4.41 (q, \(J = 7.1\) Hz, 2H, -OC\(_2\)H\(_2\)CH\(_3\)), and 1.39 (t, \(J = 7.1\) Hz, 3H, -CH\(_3\)).

General procedure for the preparation of ethyl N-substituted indole carboxylates 12a-f.

A mixture of indole 11b or 11c (4.0 mmol), potassium carbonate (8.0 mmol), sodium iodide (2.00 mmol) and the appropriate alkyl halide (16.0 mmol) in DMF (100 mL) was stirred at 50 °C for 24 h. The solvent was evaporated to dryness. The residue was washed with ethyl acetate (4x50 mL). The combined organic layers were washed with brine solution, dried (MgSO\(_4\)), and concentrated in vacuo. The resulting products were purified by column chromatography on silica gel (1-2.5% ethyl acetate in hexane) to give the desired ethyl N-substituted indole carboxylate.

Ethyl 1-allyl-4-(benzyloxy)-7-iodo-1H-indole-2-carboxylate (12a). Prepared from 11b and allyl chloride as a white solid (95%): mp. 85-86 °C; IR (KBr, cm\(^{-1}\)) 1716 (C=O), 1638 and 1599 (C=C); 1H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) 7.69 (d, \(J = 7.5\) Hz, 1H, Ar-H), 7.50-7.30 (br m, 6H, Ar-H), 6.34 (d, \(J = 7.5\) Hz, 1H, Ar-H), 6.03 (m, 1H, vinylic C\(_2\)H), 5.78 (m, 2H, -NC\(_2\)H\(_2\)), 5.17 (s, 2H, -OC\(_2\)H\(_2\)Ph), 5.08 (br d, \(J = 10\) Hz, 1H, vinylic C\(_2\)H), 4.63 (br d, \(J = 17.5\) Hz, 1H, vinylic C\(_2\)H), 4.33 (q, \(J = 7.5\) Hz, 2H, -OC\(_2\)H\(_2\)CH\(_3\)), and 1.38 (t, \(J = 7.5\) Hz, 3H, -CH\(_3\)); 13C-NMR (62.9 MHz, CDCl\(_3\)) 161.42, 153.06, 136.70, 136.00, 135.71, 131.23, 128.62, 128.09, 127.86, 127.47, 120.69, 115.15, 109.50, 103.74, 102.37, 95.37, 70.40, 60.69, 46.70, 14.33; EIMS (m/z rel intensity) calc for C\(_{21}\)H\(_{20}\)INO\(_3\): 461; found 461 (M\(^+\), 24).

Ethyl 1-allyl-4-(benzyloxy)-7-bromo-1H-indole-2-carboxylate (12b). Prepared from 11c and allyl chloride as a white solid (90%): mp. 74-76 °C; IR (KBr, cm\(^{-1}\)) 1715 (C=O, ester), 1646 and 1606 (C=C); 1H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50-7.25 (br m, 7H, Ar-H), 6.49 (d, \(J = 8.4\) Hz, 1H, Ar-H), 5.97 (m, 1H, vinylic CH), 5.68 (m, 2H, -NCH\(_2\)), 5.10 (s, 2H, -OC\(_2\)H\(_2\)Ph), 4.99 (br d, \(J = 10.5\) Hz, 1H, vinylic CH\(_2\)), 4.64 (br d, \(J = 17.2\) Hz, 1H, vinylic CH\(_2\)), 4.26 (q, \(J = 7.1\) Hz, 2H, -OC\(_2\)H\(_2\)CH\(_3\)), and 1.39 (t, \(J = 7.2\) Hz, 3H, -CH\(_3\)); 13C-NMR (62.9 MHz, CDCl\(_3\)) 161.42, 153.06, 136.70, 136.00, 135.71, 131.23, 128.62, 128.09, 127.86, 127.47, 120.69, 115.15, 109.50, 102.37, 95.37, 70.40, 60.69, 46.70, 14.33; EIMS (m/z rel intensity) calc for C\(_{21}\)H\(_{20}\)NO\(_3\)\(_{79}\)Br: 413; found 413 (M\(^+\), 24).

Ethyl 4-(benzyloxy)-7-iodo-1-prop-2-ynyl-1H-indole-2-carboxylate (12c). Prepared from 11b and propargylic chloride as a white solid (94%): mp. 132-133 °C; IR (KBr, cm\(^{-1}\)) 3274 (C\(_{sp}\)-H), 2114 (C\(_{sp}\)-C\(_{sp}\)), 1712 (C=O), and 1597 (C=C); 1H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) 7.7 (d, 1H, Ar-H) 7.5-7.3 (br m, 6H, Ar-H), 6.4 (d, 1H, Ar-H), 5.9 (br d, 2H, -NCH\(_2\)), 5.2 (s, 2H, -OC\(_2\)H\(_2\)Ph), 4.4 (q, 2H, OCH\(_2\)CH\(_3\)), 2.3
(t, 1H, acetylinic CH); and 1.4 (t, 3H, -CH3); 13C-NMR (75.5 MHz, CDCl3) 161.47, 154.08, 139.09, 138.37, 136.60, 128.64, 128.12, 127.57, 127.45, 120.98, 110.23, 104.13, 80.14, 73.10, 70.11, 60.92, 34.83, 14.32; Anal. Calcd for C21H18INO3: C, 54.92; H 3.95; N, 3.05; found C, 55.6; H, 4.05; N, 3.25; EIMS (m/z rel intensity) calc for C21H18INO3: 459; found 459 (M+, 35).

**Ethyl 4-(benzoyloxy)-7-bromo-1-prop-2-ynyl-1H-indole-2-carboxylate (12d).** Prepared from 11c and propargyl chloride as a white solid (100%); mp. 100-101°C; IR (KBr, cm⁻¹) 3275 (C sp-H), 2114 (C sp-C sp), 1713 (C=O) and 1606 (C=C); 1H-NMR (300 MHz, CDCl3) δ 7.52-7.30 (br m, 7H, Ar-H), 6.44 (d, J = 8.4 Hz, 1H, Ar-H), 5.92 (br d, J = 2.4 Hz, 2H, -NC2H), 5.16 (s, 2H, -OCH2Ph), 4.39 (q, J = 7.2 Hz, 2H, -OC2H2CH3), 2.30 (t, J = 2.4 Hz, 1H, acetylinic CH), and 1.39 (t, J = 7.1 Hz, 3H, -CH3); 13C-NMR (75.5 MHz, CDCl3) 161.43, 153.08, 136.61, 136.07, 131.50, 128.64, 128.12, 127.49, 127.45, 120.96, 110.35, 102.96, 95.35, 80.12, 72.57, 70.17, 60.93, 35.28, 14.32; Anal. Calcd for C21H18BrNO3: C, 61.18; H, 4.40; N, 3.40; found C, 61.40; H, 4.60; N, 3.42; EIMS (m/z rel intensity) calc for C21H18BrNO3: 411; found 411 (M+, 18).

**Ethyl 4-(benzoyloxy)-1-(2-chloro-allyl)-7-iodo-1H-indole-2-carboxylate (12e).** Prepared from 11b and 2,3-dichloropropene as a white solid (92%): mp. 114-116°C; IR (KBr, cm⁻¹) 1712 (C=O), 1646 and 1598 (C=C); 1H-NMR (200 MHz, CDCl3) δ 7.7 (d, 1H, Ar-H), 7.5-7.3 (br m, 6H, Ar-H), 6.4 (d, J = 8.7 Hz, 1H, Ar-H), 5.86 (s, 2H, -NC2H), 5.23 (d, J = 1.2 Hz, 1H, vinylic CH2), 5.19 (s, 2H, -OCH2Ph), 4.51 (d, J = 2.1 Hz, 1H, vinylic CH2), 4.35 (q, J = 7.2 Hz, 2H, -OCH2CH3), and 1.39 (t, J = 7.2 Hz, 3H, -CH3); 13C-NMR (75.5 MHz, CDCl3) 161.18, 154.08, 139.29, 138.71, 137.99, 136.54, 128.66, 128.17, 127.70, 127.50, 120.62, 111.62, 109.92, 104.06, 70.16, 60.91, 49.36, 14.31; EIMS (m/z rel intensity) calc for C21H18INO3: 495, 13Cl: 495; found 495 (M+, 2).

**Ethyl 4-(benzoyloxy)-7-bromo-1-(2-chloro-allyl)-1H-indole-2-carboxylate (12f).** Prepared from 11c and 2,3-dichloropropene as a white solid (100%); mp. 102-103°C; IR (KBr, cm⁻¹) 1704 (C=O), 1643 and 1604 (C=C); 1H-NMR (300 MHz, CDCl3) δ 7.56-7.36 (br m, 7H, Ar-H), 6.47 (d, J = 8.7 Hz, 1H, Ar-H), 5.86 (s, 2H, -NC2H), 5.23 (d, J = 1.2 Hz, 1H, vinylic CH2), 5.19 (s, 2H, -OCH2Ph), 4.51 (d, J = 2.1 Hz, 1H, vinylic CH2), 4.35 (q, J = 7.2 Hz, 2H, -OCH2CH3), and 1.39 (t, J = 7.2 Hz, 3H, -CH3); 13C-NMR (75.5 MHz, CDCl3) δ 161.39, 153.07, 138.54, 127.70, 127.50, 120.62, 111.62, 109.92, 104.06, 70.16, 60.91, 49.36, 14.31; EIMS (m/z rel intensity) calc for C21H19BrClNO3: C, 56.21; H, 4.27; N, 3.12; found C, 56.27; H, 4.23; N, 3.09.

**Ethyl 9-(benzoyloxy)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (13a).** A solution of allyl compound 12a or 12b (0.72 mmol), AIBN (0.02 g) and Bu3SnH (1.45 mmol) in benzene (50 mL) was degassed with N2 gas and the solution was heated at reflux for 1.3 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue obtained was purified by chromatography, to give the six-membered ring compound 13a as a colorless oil (82-84%); IR (CCl4, cm⁻¹) 1708 (C=O) and 1604 (C=C); 1H-NMR (300 MHz, CDCl3) δ 7.56-7.36 (br m, 7H, Ar-H), 6.88 (d, J = 7.7 Hz, 1H, Ar-H), 6.43 (d, J = 7.7 Hz, 1H, Ar-H), 5.17 (s, 2H, -OCH2Ph), 4.50 (t, J = 5.8 Hz, 2H, -NC2H), 4.33 (q, J = 7.7 Hz, 2H, -OCH2CH3), 2.87 (t, J = 5.9 Hz, 2H, benzylic CH2), 2.17 (m, J = 6.0 Hz, 2H, -CH2), and 1.38 (t, J = 7.1 Hz, 3H, -CH3); 13C-NMR (75.5 MHz, CDCl3) δ 162.21, 151.77, 137.88, 137.37, 128.47, 127.76, 127.33, 126.05, 121.90, 115.98, 115.92, 107.09, 100.89.
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69.89, 60.31, 44.11, 24.19, 23.22, and 14.39; Anal. Caled for C_{21}H_{21}NO_3: C, 72.20; H, 6.31; N, 4.18; found C, 72.8; H, 6.54; N, 4.22; EIMS (m/z rel intensity) cale for C_{21}H_{21}NO_3: 335; found 335 (M^+, 21).

Ethyl 9-(benzyloxy)-5-hydroxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (13b).

**Method A:** A solution of 12a (0.47 g, 1.02 mmol), TEMPO (98%, 0.65 g, 4.08 mmol) and Bu$_3$SnH (97%, 0.32 g, 1.07 mmol) in 50 mL of freshly distilled benzene was degassed with N$_2$ for 5 min, and then heated at reflux. After 15 min of reflux, an additional 3 equiv of TEMPO (3×0.16 g) in 9 mL of benzene and 3 equiv of Bu$_3$SnH (3×0.30 g) in 9 mL of benzene were added successively over the next 40 min. After 15 min, another 1.5 equiv of TEMPO (0.24 g) in 5 mL of benzene was added, followed by the addition of another 1.0 equiv of Bu$_3$SnH (0.32 g) in 5 mL of benzene. The mixture was kept at reflux temperature for additional 80 min, cooled to room temperature, and concentrated in vacuo. The crude product was passed over short column of silica gel to remove excess Bu$_3$SnH and polar impurities. The crude product was then dissolved in 60 mL of a 3:1:1 mixture of HOAc: THF: H$_2$O and treated with Zn powder (0.88 g, 13.46 mmol). The resulting suspension was kept at 70 °C with continuous stirring. After 90 min, another amount of Zn powder (0.26 g, 4.00 mmol) was added as one portion followed by stirring for another 90 min. The solution was allowed to cool to room temperature, filtered off, and evaporated under reduced pressure. Water (80 mL) was added to the residue and the resulting aqueous solution was extracted with ethyl acetate (3×20 mL). The combined organic layers was washed with brine, dried, and concentrated in vacuo. The product was purified by column chromatography on silica gel (10-25% ethyl acetate in hexane) to give the alcohol derivative 13b as a white solid (0.23 g, 60%): mp. 143-144 °C; IR (KBr, cm$^{-1}$) 3447 (OH), 1685 (C=O), and 1604 (C=C); $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 7.50-7.20 (br m, 6H, Ar-$\text{H}$), 6.87 (d, $J = 7.7$ Hz, 1H, Ar-$\text{H}$), 6.40 (d, $J = 7.7$ Hz, 1H, Ar-$\text{H}$), 5.10 (s, 2H, -OC$_2$H$_2$Ph), 4.62-4.35 (br m, 3H, -NC$_2$H$_2$ and –C$_2$H$_4$OH), 4.29 (q, $J = 7.12$ Hz, 2H, -OC$_2$H$_2$CH$_3$), 3.10 (dd, $J = 15.8$ Hz and $J' = 2.5$ Hz, 1H, benzylic C$_2$H$_2$), 2.90 (dd, $J = 15.9$ Hz and $J' = 5.1$ Hz, 1H, benzylic CH$_2$), 1.93 (s, 1H, OH, D$_2$O exchangeable), and 1.31 (t, $J = 7.1$ Hz, 3H, -CH$_3$); $^{13}$C-NMR (62.9 MHz, CDCl$_3$) $\delta$ 162.04, 152.25, 137.21, 136.98, 128.49, 127.83, 127.33, 126.41, 123.80, 115.80, 111.76, 107.78, 101.60, 69.98, 64.79, 60.84, 50.43, 32.71, and 14.35; Anal. Caled for C$_{21}$H$_{21}$NO$_4$: C, 71.78; H, 6.02; N, 3.99; found C, 71.49; H, 5.91; N, 3.91; EIMS (m/z rel intensity) cale for C$_{21}$H$_{21}$NO$_4$: 351; found 351 (M$^+$, 7).

**Method B:** A solution of 12c (0.37 g, 0.90 mmol), Bu$_3$SnH (97%, 1.00 g, 3.33 mmol) and AIBN (40 mg) in freshly distilled benzene (75 mL) was bubbled with N$_2$ gas for 5 min and then heated at reflux for 2.5 h. The reaction mixture was cooled, and the solvent was removed in vacuo to afford the crude product as yellow oil. The oily product was dissolved in THF (7.5 mL), cooled to 0 °C. Then 1M BH$_3$-THF solution (2.7 mL) was added in one portion. The reaction mixture was allowed to warm to room temperature, and stirred for 3.0 h. The reaction mixture was cooled to 0°C and treated sequentially with water (2.7 mL), 2N aqueous sodium hydroxide (1.35 mL, 2.7 mmol), and 30% aqueous hydrogen peroxide (0.81 mL, 8.1 mmol). The reaction mixture was allowed to warm to room temperature, and stirred for 3.0 h. The reaction mixture was poured to ethyl acetate (50 mL). The organic layer was washed with brine (2×15 mL), dried, and concentrated in vacuo. The residue was purified by column
chromatography on silica gel (10-25% ethyl acetate in hexane) to give the alcohol derivative 13b as a white solid (0.16 g, overall 50%). This compound was also obtained in 35% yield from 12d.

Ethyl 9-(benzyloxy)-5-chloro-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (13c).

A solution of 12e or 12f (0.70 mmol), Bu3SnH (97%, 0.21 g, 0.700 mmol) and AIBN (30 mg) in benzene (50 mL) was degassed with nitrogen for 5 min, and then heated at reflux. After 30 min, an additional drop of Bu3SnH was added and refluxed for another 10 min. The reaction mixture was cooled to room temperature, and concentrated in vacuo. The resulting product was subjected into silica gel column chromatography to afford 13c as a colorless solid (0.21-0.24 g, 92-94%): mp. 122-123 °C; IR (KBr, cm⁻¹) 1706 (C=O) and 1608 (C=C); ¹H-NMR (250 MHz, DMSO-d₆) δ 7.60-7.30 (br m, 6H, Ar-H), 7.04 (d, J = 7.5 Hz, 1H, Ar-H), 6.65 (d, J = 7.5 Hz, 1H, Ar-H), 5.24 (s, 2H, -OCH₂Ph), 5.09 (m, 1H, –C-HCl), 4.85 (dd, J = 14.5 Hz and J’ = 3.8 Hz, 1H, benzylic C-H₂), 4.68 (dd, J = 14.3 Hz and J’ = 2.5 Hz, 1H, benzylic C-H₂), 4.33 (q, J = 7.3 Hz, 2H, -OCH₂CH₃), 3.50 (1H, benzylic C-H₂, buried under a signal from the solvent), 3.14 (dd, J = 16.3 Hz and J’ = 4.5 Hz, 1H, benzylic C-H₂), and 1.36 (t, J = 7.3 Hz, 3H, -CH₃); ¹³C-NMR (62.9 MHz, DMSO-d₆) δ 161.42, 151.80, 137.55, 136.40, 128.80, 128.12, 127.81, 126.19, 123.86, 115.38, 112.31, 106.89, 102.22, 69.60, 60.79, 53.83, 50.97, 33.37, and 14.50; Anal. Calcd for C₂₁H₂₀ClNO₃: C, 68.20; H, 5.45; N, 3.79; found C, 67.97; H, 5.31; N, 3.73.

Ethyl 5,9-dihydroxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (7a).

A solution of 13b (0.18 g, 0.512 mmol) and 10% Pd-C (0.12 g) in distilled ethyl acetate (40 mL) was degassed with N₂. The resulting mixture was placed under an atmosphere of H₂ in a balloon and stirred at 40 °C for 2.5 h. The reaction mixture was filtered through Celite and washed with ethyl acetate (3 x 50mL). The combined organic solvents were evaporated in vacuo, and the resulting crude product was purified by chromatography (25-35% ethyl acetate in hexane) to afford phenol 7a (0.122 g, 87%): IR (CCl₄, cm⁻¹) 3335 (OH), 1690 (C=O), and 1604 (C=C); ¹H-NMR (250 MHz, DMSO-d₆) δ 9.54 (s, 1H, phenolic-OH), 7.22 (s, 1H, Ar-H), 6.81 (d, J = 7.50 Hz, 1H, Ar-H), 6.33 (d, J = 7.5 Hz, 1H, Ar-H), 5.19 (d, J = 3.5 Hz, 1H, –CHOH), 4.47 (d, J = 9.75 Hz, 1H, benzylic N-CH₂), 4.28 (m, 3H, benzylic N-CH₂ and –OCH₂CH₃), 2.99 (dd, J = 15.5 Hz and J’ = 2.50 Hz, 1H, benzylic C-H₂), 2.77 (dd, J = 15.5 Hz and J’ = 6.3 Hz, 1H, benzylic C-H₂), and 1.33 (t, J = 7.0 Hz, 3H, -CH₃); ¹³C-NMR (62.9 MHz, DMSO-d₆) δ 161.29, 149.84, 137.27, 125.19, 123.45, 114.51, 111.34, 106.86, 103.86, 63.36, 60.15, 50.07, 32.30, and 14.27; Anal. Calcd for C₂₁H₂₀ClNO₃: C, 64.06; H, 5.29; N, 5.76; found C, 63.92; H, 5.14; N, 5.91.

Ethyl 5-chloro-9-hydroxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (7b).

A solution 13c (0.22 g, 0.595 mmol) and 10% Pd-C (50 mg) in distilled ethyl acetate (50 mL) was degassed with N₂. The resulting mixture was placed under an atmosphere of H₂ and stirred at 35 °C for 30 min. The reaction mixture was filtered through Celite and washed with ethyl acetate (3x50 mL). The combined organic solvents were removed in vacuo and the resulting crude product was purified by chromatography (5-15% ethyl acetate in hexane) to afford the expected phenol 7b as a white solid.

Ethyl 5,9-dihydroxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2-carboxylate (7a).
(0.125 g, 75%): (mp. 244-245 °C, dec); IR (KBr disc, cm−1) 3275 (OH), 1671 (C=O), and 1606 (C=C); 

1H-NMR (250 MHz, DMSO-d6) δ 9.75 (s, 1H, phenolic-OH), 7.28 (s, 1H, Ar-H), 6.89 (d, J = 7.5 Hz, 1H, Ar-H), 6.40 (d, J = 7.5 Hz, 1H, Ar-H), 5.05 (m, 1H, –CHCl), 4.83 (dd, J = 14.3 Hz and J′ = 3.5 Hz, 1H, benzylic CH2), 4.68 (dd, J = 14.0 Hz and J′ = 3.0 Hz, 1H, benzylic CH2), 4.31 (q, J = 7.3 Hz, 2H, -OCH2CH3), 3.50 (1H, benzylic CH2, buried under a signal from the solvent), 3.10 (dd, J = 16.3 Hz and J′ = 4.5 Hz, 1H, benzylic CH2), and 1.34 (t, J = 7.3 Hz, 3H, -CH3); 13C-NMR (62.9 MHz, DMSO-d6) δ 161.54, 150.70, 136.75, 125.70, 124.25, 114.96, 109.93, 107.54, 104.59, 60.70, 53.92, 50.93, 33.45, and 14.55; Anal. Calcd for C14H14ClNO3: C, 60.11; H, 5.04; N, 5.01; found C, 59.98; H, 4.93; N, 5.11.

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Sample Availability: Available from the authors.

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