

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.

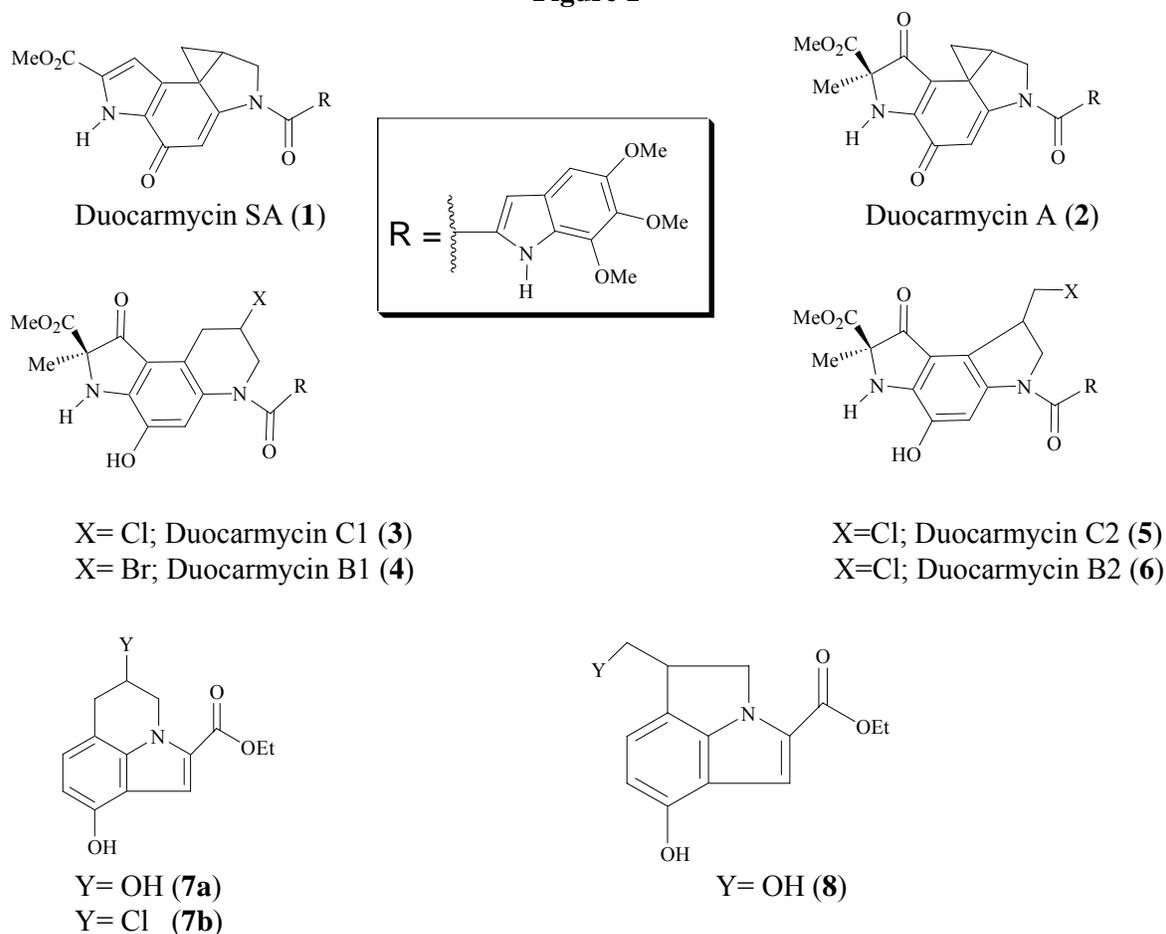
Keywords: Duocarmycin, free-radicals, intramolecular cyclization, indole, pyrroloquinoline

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 cyclopropyldienone formation and its stability versus vinylogous amide conjugation.

Figure 1

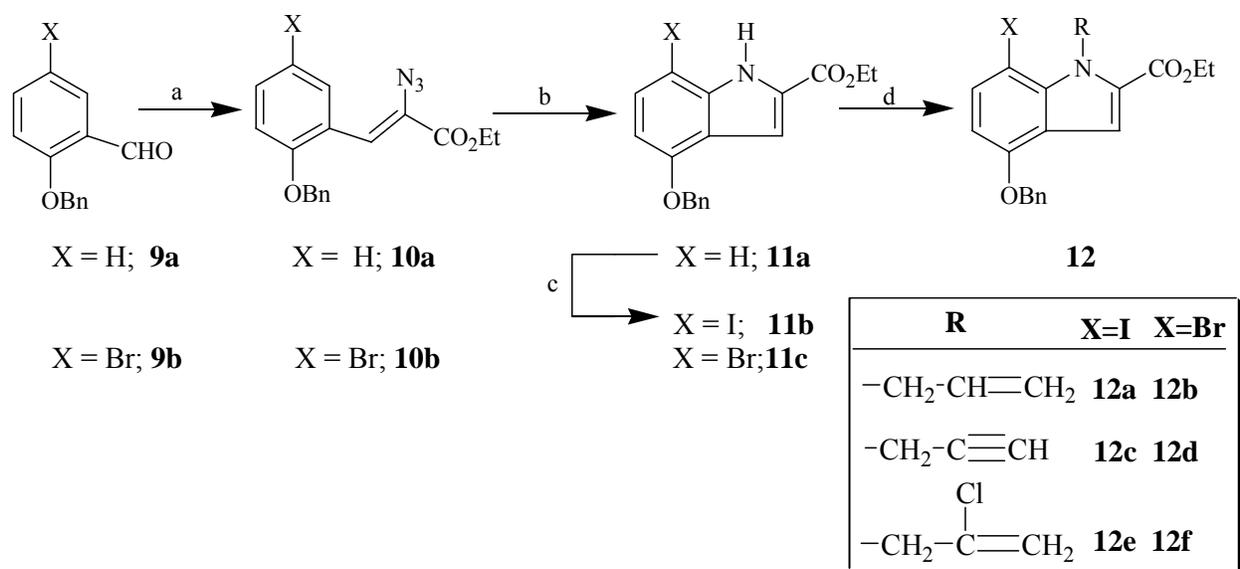


In order to investigate the importance of the carboxamido moiety to the biological activity of these natural products, pyrroloquinoline (*seco*-PQC, **7a,b**) and pyrroloindoline (*seco*-PIC, **8**) derivatives were designed. We planned to construct these systems based on the strategy of intramolecular 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, **7a,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

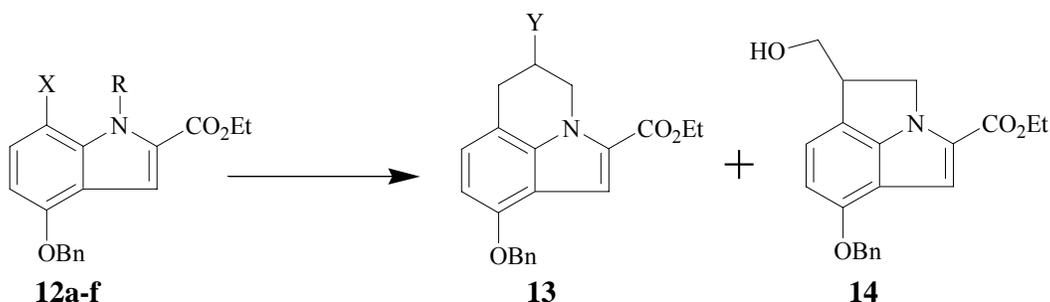


Reagents: a) N₃CH₂CO₂Et, NaOMe, MeOH, -15 °C; b) chlorobenzene, reflux; c) ICl, AcOH, rt; d) RX, K₂CO₃, DMF, 50 °C;

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 Bu₄SnH (four equivalents) and AIBN as a radical initiator gave exclusively the cyclized product **13a** through *6-endo-trig* mode (Entries 1, 2). These encouraging results prompted us to trap the intermediate of the *6-endo-trig* cyclization mode with TEMPO [17]. Thus, treatment of 7-iodo compound **12a** with an equivalent amount of Bu₃SnH and excess TEMPO furnished, after immediate reduction (Zn, AcOH) of the reaction products, a mixture of two alcohols, the *6-endo-trig* product **13b** and the *5-exo-trig* closure product **14** (Y = OH, Entry 3). The ¹H-NMR spectrum of the crude mixture of products showed that **13b** and **14** were formed in the ratio of 6:1. The *6-endo-trig* cyclization product **13** was isolated in reasonable yield (60%), but the *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 Bu₃SnH). This result is presumably a consequence of the competing reaction of the generated tributyltin radical with TEMPO.

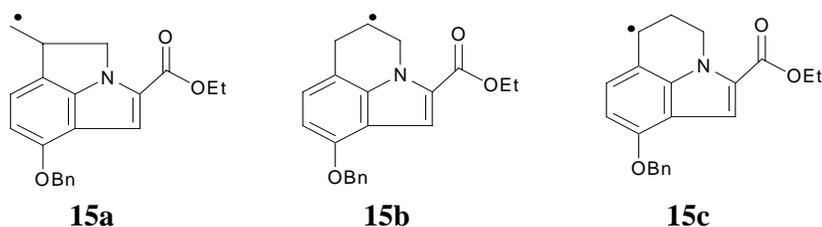
Scheme 2

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

Entry	Substrate	Reagents	Product(s)	
			Y	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

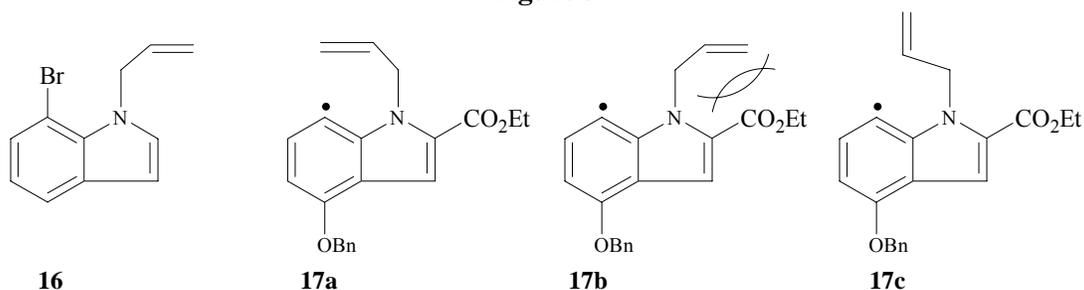
The formation of the thermodynamically less favored *6-endo-trig* cyclization product as a major component in the presence of large excess of TEMPO in the reaction mixture ruled out *5-exo-trig* closure followed by rearrangement of the less stable primary radical **15a** intermediate to the more stable secondary radical **15b**. Since the primary radical **15a** is expected to form the most stable benzylic radical **15c** after rearrangement (Figure 2).

Figure 2



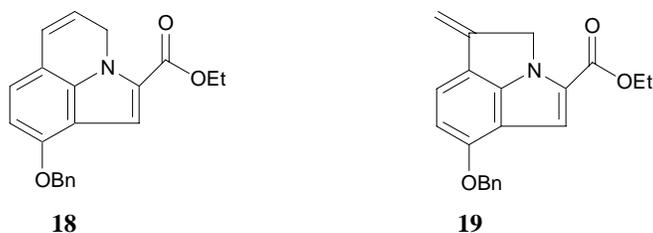
Therefore, in comparison with the previously reported results on aryl radical cyclization of C-2 unsubstituted indole **16**, the most reasonable explanation for the formation of the *6-endo-trig* cyclization product would be based on the free rotation of the vinylic group [13]. Three conformers **17a-c** 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.

Figure 3



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 Bu_3SnH furnished an inseparable mixture of products. Examination of the $^1\text{H-NMR}$ 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).

Figure 4

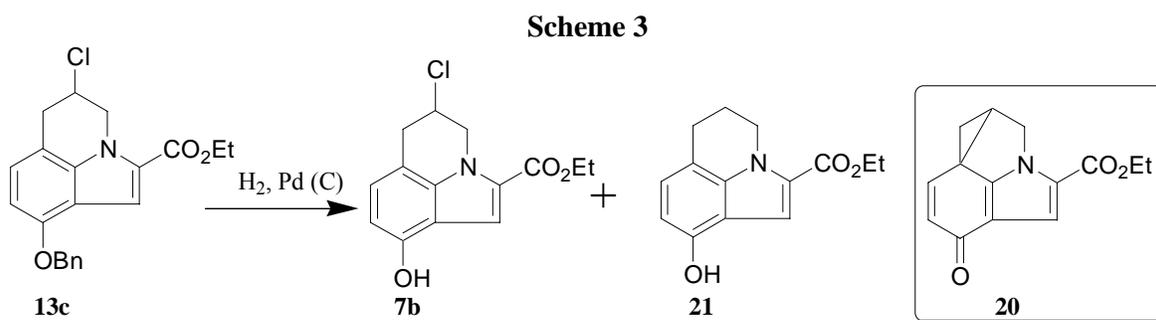


Fortunately, this analysis could be further confirmed after the crude mixture of products was treated with $\text{BH}_3\text{-THF}$, followed by oxidation ($\text{NaOH-H}_2\text{O}_2$). This furnished alcohol **13b** in 50% isolated yield (Entry 5). The *5-exo-dig* closure product **19** was isolated 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 cyclopropyldienone 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.

Acknowledgments

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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 ^1H - 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-(benzyloxy)-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 N_2 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. $170\text{--}172^\circ\text{C}$, (Lit. mp. $169\text{--}171^\circ\text{C}$ [14]); IR (KBr, cm^{-1}) 3325 (N-H) and 1685 (C=O); ^1H -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, $-\text{OCH}_2\text{Ph}$), 4.41 (q, $J = 7.1$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), and 1.40 (t, $J = 7.1$ Hz, 3H, $-\text{CH}_3$).

Ethyl 4-(benzyloxy)-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. $114\text{--}115^\circ\text{C}$; IR (KBr, cm^{-1}) 3425 (N-H), 1708 (C=O) and 1608 (C=C); ^1H -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, $-\text{OCH}_2\text{Ph}$), 4.40 (q, $J = 7.5$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), and 1.40 (t, $J = 7.5$ Hz, 3H, $-\text{CH}_3$); ^{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 $\text{C}_{18}\text{H}_{16}\text{INO}_3$: 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 1.85g (95%): mp. 135-136 °C [15]; IR (KBr, cm⁻¹) 3323 (N-H), and 1692 (C=O); ¹H-NMR (300 MHz, CDCl₃) δ 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, -OCH₂Ph), 4.41 (q, *J* = 7.1 Hz, 2H, -OCH₂CH₃), and 1.39 (t, *J* = 7.1 Hz, 3H, -CH₃).

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 (4x50mL). The combined organic layers were washed with brine solution, dried (MgSO₄), 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, CDCl₃) δ 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 CH), 5.78 (m, 2H, -NCH₂), 5.17 (s, 2H, -OCH₂Ph), 5.08 (br d, *J* = 10 Hz, 1H, vinylic CH₂), 4.63 (br d, *J* = 17.5 Hz, 1H, vinylic CH₂), 4.33 (q, *J* = 7.5 Hz, 2H, -OCH₂CH₃), and 1.38 (t, *J* = 7.5 Hz, 3H, -CH₃); ¹³C-NMR (62.9 MHz, CDCl₃) δ 161.63, 154.26, 139.12, 138.20, 136.87, 135.89, 128.81, 128.29, 127.99, 127.66, 120.82, 115.33, 109.50, 103.74, 70.25, 62.72, 60.88, 46.04, and 14.53. Anal. Calcd for C₂₁H₂₀INO₃: C, 54.68; H, 4.37; N, 3.04; found C, 54.60; H, 4.29; N, 2.99; EIMS (m/z rel intensity) calc for C₂₁H₂₀INO₃: 461; found 461 (M⁺, 40).

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, CDCl₃) δ 7.50-7.25 (br m, 7H, Ar-H), 6.36 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.97 (m, 1H, vinylic CH), 5.68 (m, 2H, -NCH₂), 5.10 (s, 2H, -OCH₂Ph), 4.99 (br d, *J* = 10.5 Hz, 1H, vinylic CH₂), 4.64 (br d, *J* = 17.2 Hz, 1H, vinylic CH₂), 4.26 (q, *J* = 7.1 Hz, 2H, -OCH₂CH₃), and 1.39 (t, *J* = 7.2 Hz, 3H, -CH₃); ¹³C-NMR (62.9 MHz, CDCl₃) 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 C₂₁H₂₀NO₃⁷⁹Br: 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, CDCl₃) δ 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, -NCH₂), 5.2 (s, 2H, -OCH₂Ph), 4.4 (q, 2H, OCH₂CH₃), 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, 60.922, 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-(benzyloxy)-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, -NCH₂), 5.16 (s, 2H, -OCH₂Ph), 4.39 (q, J = 7.2 Hz, 2H, -OCH₂CH₃), 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 C₂₁H₁₈NO₃⁷⁹Br: 411; found 411 (M⁺, 18).

Ethyl 4-(benzyloxy)-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, 1H, Ar-H), 5.9 (s, 2H, -NCH₂), 5.2 (d, 1H, vinylic CH₂) 5.2 (s, 2H, -OCH₂Ph), 4.4 (d, 1H, vinylic CH₂), 4.3 (q, 2H, -OCH₂CH₃), and 1.4 (t, 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 C₂₁H₁₈INO₃³⁵Cl: 495; found 495 (M⁺, 2).

Ethyl 4-(benzyloxy)-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, -NCH₂), 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, 153.27, 138.90, 136.75, 131.88, 128.89, 128.40, 127.88, 127.75, 120.83, 111.46, 110.29, 103.09, 95.61, 70.40, 61.16, 50.17, and 14.54. Anal. Calcd for C₂₁H₁₉BrClNO₃: C, 56.21; H, 4.27; N, 3.12; found C, 56.27; H, 4.23; N, 3.09.

Ethyl 9-(benzyloxy)-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 7.50-7.30 (br m, 6H, 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, -NCH₂), 4.33 (q, J = 7.1 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,

69.89, 60.31, 44.11, 24.19, 23.22, and 14.39; Anal. Calcd for C₂₁H₂₁NO₃: C, 72.20; H, 6.31; N, 4.18; found C, 72.8; H, 6.54; N, 4.22; EIMS (m/z rel intensity) calc for C₂₁H₂₁NO₃: 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 Bu₃SnH (97%, 0.32 g, 1.07 mmol) in 50 mL of freshly distilled benzene was degassed with N₂ 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 Bu₃SnH (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 Bu₃SnH (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 Bu₃SnH and polar impurities. The crude product was then dissolved in 60 mL of a 3:1:1 mixture of HOAc: THF: H₂O 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); ¹H-NMR (250 MHz, CDCl₃) δ 7.50-7.20 (br m, 6H, Ar-H), 6.87 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.40 (d, *J* = 7.7 Hz, 1H, Ar-H), 5.10 (s, 2H, -OCH₂Ph), 4.62-4.35 (br m, 3H, -NCH₂ and -CHOH), 4.29 (q, *J* = 7.12 Hz, 2H, -OCH₂CH₃), 3.10 (dd, *J* = 15.8 Hz and *J'* = 2.5 Hz, 1H, benzylic CH₂), 2.90 (dd, *J* = 15.9 Hz and *J'* = 5.1 Hz, 1H, benzylic CH₂), 1.93 (s, 1H, OH, D₂O exchangeable), and 1.31 (t, *J* = 7.1 Hz, 3H, -CH₃); ¹³C-NMR (62.9 MHz, CDCl₃) δ 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. Calcd for C₂₁H₂₁NO₄: C, 71.78; H, 6.02; N, 3.99; found C, 71.49; H, 5.91; N, 3.91; EIMS (m/z rel intensity) calc for C₂₁H₂₁NO₄: 351; found 351 (M⁺, 7).

Method B: A solution of **12c** (0.37 g, 0.90 mmol), Bu₃SnH (97%, 1.00 g, 3.33 mmol) and AIBN (40 mg) in freshly distilled benzene (75 mL) was bubbled with N₂ 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 BH₃-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 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, -CHCl), 4.85 (dd, *J* = 14.5 Hz and *J'* = 3.8 Hz, 1H, benzylic CH₂), 4.68 (dd, *J* = 14.3 Hz and *J'* = 2.5 Hz, 1H, benzylic CH₂), 4.33 (q, *J* = 7.3 Hz, 2H, -OCH₂CH₃), 3.50 (1H, benzylic CH₂, buried under a signal from the solvent), 3.14 (dd, *J* = 16.3 Hz and *J'* = 4.5 Hz, 1H, benzylic CH₂), 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 CH₂), 2.77 (dd, *J* = 15.5 Hz and *J'* = 6.3 Hz, 1H, benzylic CH₂), 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 C₁₄H₁₅NO₄: 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

(0.125 g, 75%): (mp. 244-245°C, dec); IR (KBr disc, cm^{-1}) 3275 (OH), 1671 (C=O), and 1606 (C=C); $^1\text{H-NMR}$ (250 MHz, DMSO-d_6) 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 CH_2), 4.68 (dd, $J = 14.0$ Hz and $J' = 3.0$ Hz, 1H, benzylic CH_2), 4.31 (q, $J = 7.3$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 3.50 (1H, benzylic CH_2 , buried under a signal from the solvent), 3.10 (dd, $J = 16.3$ Hz and $J' = 4.5$ Hz, 1H, benzylic CH_2), and 1.34 (t, $J = 7.3$ Hz, 3H, $-\text{CH}_3$); $^{13}\text{C-NMR}$ (62.9 MHz, DMSO-d_6) 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 $\text{C}_{14}\text{H}_{14}\text{ClNO}_3$: C, 60.11; H, 5.04; N, 5.01; found C, 59.98; H, 4.93; N, 5.11.

References and Notes

1. Shawakfeh, K. Q.; Al-Said, N. H. *Asian J. Chem.* **2005**, *17*, 91.
2. Al-Said, N. H.; Ishttaiwi Z. N. *Acta Chim. Slov.* **2005**, *52*, 328.
3. Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I.; Saitoh, Y. *Chem. Pharm. Bull.* **1995**, *43*, 378.
4. Takahashi, I.; Takahashi, K.; Ichimura, M.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1915.
5. Ichimura, M.; Ogawa, T.; Katsumata, S.; Nakano, H. *J. Antibiot.* **1991**, *44*, 1045.
6. Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I. *Chem. Pharm. Bull.* **1988**, *36*, 3728.
7. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Kitos, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8961.
8. Boger, D. L.; Johnson, D. S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1439.
9. Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.
10. Pati, H.; Howard, T.; Townes, H.; Lingerfelt, B.; McNulty, L.; Lee, M. *Molecules* **2004**, *9*, 125.
11. Boger, D. L.; Robert, M. G. *Acc. Chem. Res.* **1999**, *32*, 1043.
12. Boger, D. L.; Schmidt, H. W.; Fink, B. E.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 6654.
13. Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5379.
14. Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc. Perkin Trans 1* **1984**, 2189.
15. Fresenda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355.
16. Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1995**, *36*, 4857.
17. Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.

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