

Unexpected Syntheses of *seco*-Cyclopropyltetrahydroquinolines From a Radical 5-*Exo-Trig* Cyclization Reaction: Analogs of CC-1065 and the Duocarmycins

Hari Pati, Tiffany Howard, Heather Townes, Brian Lingerfelt, LuAnne McNulty and Moses Lee*

Department of Chemistry, Furman University, Greenville, SC 29613, USA.

*Author to whom correspondence should be addressed: email: moses.lee@furman.edu

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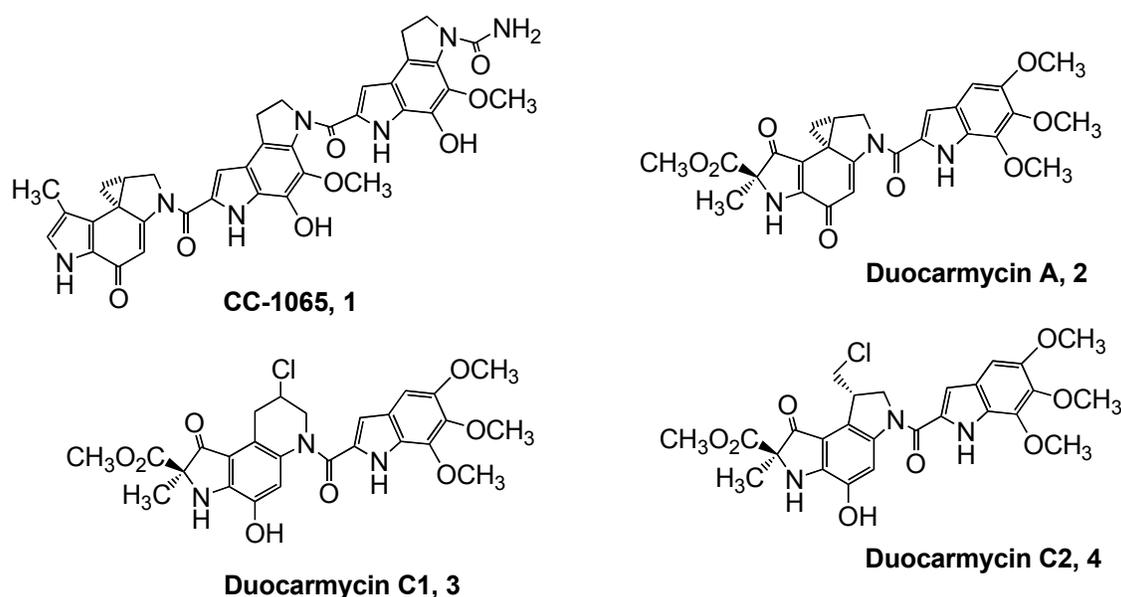
Abstract: Analogs of the *seco*-cyclopyrroloindoline (*seco*-CPI), the DNA alkylation pharmacophore of CC-1065 and the duocarmycins, can be prepared through a 5-*exo-trig* radical cyclization of a free radical and a 3-chloro-2-allylic moiety. This manuscript reports an unexpected discovery that, depending on the structure and stability of the free radical, the cyclization process leads to the production of an appreciable amount of *seco*-cyclopropyltetrahydroquinolines **7a-d** along with the *seco*-cyclopropyltetrahydroindoline products (**6a-e**). For instance, free radical reaction of the bromoallylic chloride **5a** produced an equal amount of 6-benzyloxy-*N-t*-butoxycarbonyl-3-(chloromethyl)furano[*e*]indoline (**6a**), and 7-benzyloxy-*N-t*-butoxycarbonyl-3-chloro-1,2,3,4-tetrahydrofurano[*f*]quinoline (**7a**). Three other examples that produced mixtures of indoline and quinoline products are provided. In only one of the examples reported in this manuscript, the 6-benzyloxy-*N-t*-butoxycarbonyl-3-(chloromethyl)benzo[*e*]indoline, was a *seco*-CBI precursor **6e** formed exclusively, consistent with literature precedents.

Keywords: *seco*-Cyclopropyltetrahydroquinoline, CC-1065, duocarmycins, (chloromethyl)furano[*e*]indoline, (chloromethyl)furano[*f*]tetrahydroquinoline.

Introduction

CC-1065 (**1**) and the duocarmycins [such as duocarmycin SA (**2**), duocarmycin C1 (**3**) and duocarmycin C2 (**4**)], whose structures are given in Figure 1, are members of an extremely potent group of anticancer agents that contain an interesting cyclopropylpyrroloindolone (CPI) DNA alkylating functionality. These compounds also consist of a non-covalently active portion, the phosphodiesterase inhibitor (PDE) moiety in CC-1065 and the 5,6,7-trimethoxyindole-2-carbonyl group in the duocarmycins [1,2]. Upon binding within the minor groove of AT-rich sequences of DNA, notably at 5'-TTA-3', the reactivity of the cyclopropane is enhanced by a million fold for reaction with the adenine-N3 atoms to form a covalent bond [3]. Two mechanisms have been proposed for the DNA-binding enhancement in reactivity of the cyclopropane with nucleophiles: the alkylation [4] and non-covalent driven model [5]. Covalent interaction of CC-1065 and the duocarmycins with DNA has been found to kill cancer cells by inducing the cells to undergo apoptosis [6].

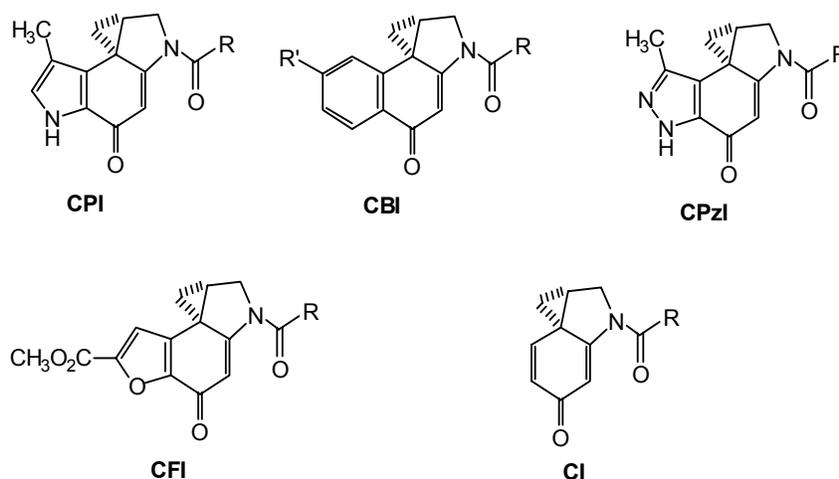
Figure 1. Structures of CC-1065 (**1**) and the duocarmycins, such as duocarmycin SA (**2**), duocarmycin C1 (**3**) and duocarmycin C2 (**4**).



Due to their potent anticancer properties, CC-1065 and the duocarmycins have enjoyed significant levels of attention. This attention has led to the development of several analogs that have superior activity over CC-1065 and the duocarmycins, and several analogs have been selected for clinical evaluation. Examples of such compounds include adozelesin [5], carzelesin [6], KW5189 [7], and bizelesin [8]. However, due to their severe toxicity to the bone marrow, currently only bizelesin remains in clinical evaluation. In an attempt to design novel analogs of the duocarmycins and CC-1065 with reduced toxicity to bone marrow cells, a wide range of analogs of the cyclopropylpyrrolo[e]indolone (CPI) subunit were synthesized and tested. Examples of such analogs,

cyclopropylbenzo[*e*]indolone (CBI) [9], cyclopropylpyrazolo[*e*]indolone (CPZI) [10], cyclopropylfurano[*e*]indolone (CFI) [11], and cyclopropylindolone (CI) [12], are given in Figure 2. We have contributed to this list of analogs by the design and synthesis of an iso-cyclopropylfurano[*e*]indolone (iso-CFI) pharmacophore, a highly cytotoxic pharmacophore that is significantly less toxic to murine bone marrow cells than the corresponding CBI analogs [13]. As depicted in Figure 3, synthesis of the iso-CFI intermediate relied on the free radical *5-exo-trig* cyclization in refluxing toluene of the bromoallylic chloride **5a** in the presence of 2,2'-azobisisobutyronitrile (AIBN) and tributyltin hydride. To our surprise, radical cyclization of compound **5a** gave not only the iso-CFI precursor, indoline **6a**, but it also afforded an equal amount of a CFQ precursor, quinoline **7a**. In order to further explore whether the unexpected ring closure process that led to the production of quinoline products is more common, or whether the formation of compound **7a** represented an exceptional behavior, the *5-exo-trig* radical cyclizations of five different bromoallylic chlorides **5a-e** were studied.

Figure 2. Structures of the cyclopropylpyrrolo[*e*]indolone (CPI), cyclopropylbenzo[*e*]indolone (CBI), cyclopropylpyrazolo[*e*]indolone (CPZI), cyclopropylfurano[*e*]indolone (CFI), and cyclopropylindolone (CI) analogs.



Results and Discussion

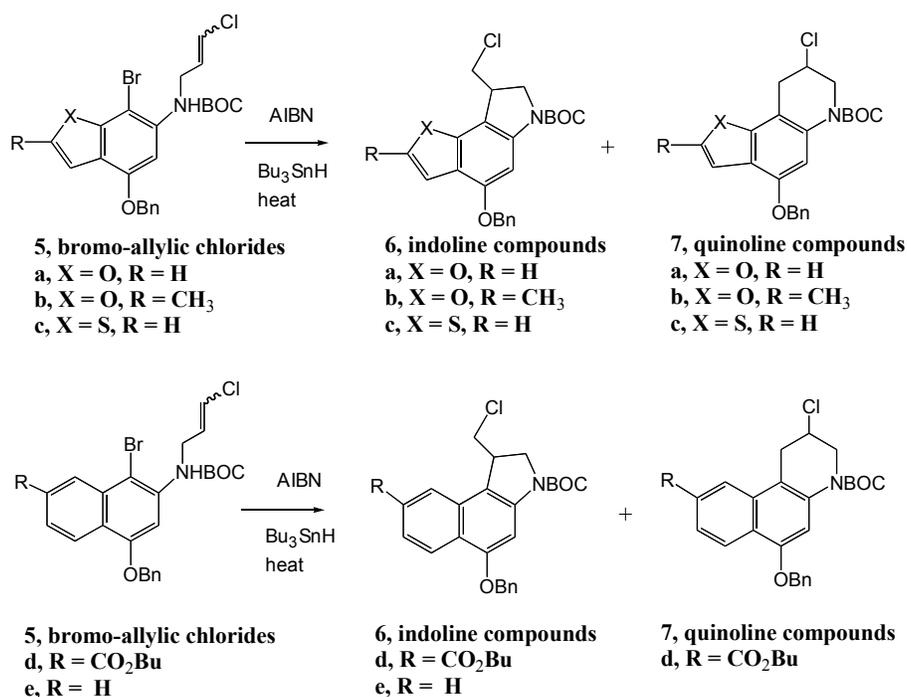
Syntheses of the benzofuran bromoallylic chlorides **5a** and **5b** were accomplished according to a procedure recently published from our laboratory [13]. Using a similar approach, and an appropriate starting material, such as thiophene-2-carboxaldehyde and 3-bromobenzaldehyde, the corresponding bromoallylic chlorides **5c** and **5d** were prepared. The naphthalene bromoallylic chloride **5e** was prepared according to a literature process [14]. With the five compounds **5a-e** at hand, their free radical promoted ring closure reactions were carried out as depicted in Figure 3. Each compound **5a-e** was treated with 0.33 mole-equivalents of AIBN and 2.5 mole-equivalents of tributyltin hydride. The mixture was dissolved in freshly distilled (over sodium) toluene or benzene and the solution was thoroughly deoxygenated by degassing the same under vacuum and opening the flask to nitrogen (three

times). The resulting clear solutions were heated to reflux under a nitrogen atmosphere for 5 hours, at which time the reactions were completed as monitored by TLC analyses. Because of their different structures, the indoline compounds (**6**) were separated readily from the more polar quinoline compounds (**7**) by chromatography. In all cases the unpurified products, as well as the silica gel column purified compounds (**6** and **7**) were analyzed by 500 MHz $^1\text{H-NMR}$. As indicated in the Experimental section, the indoline and quinoline compounds gave characteristic spectra, each bearing peaks in the 3.5-4.5 ppm region. As depicted in Figure 4A, the spectrum of indoline **6a** gave four sets of peaks in this region, with two distinct triplet-like patterns at 3.6 and 4.2 ppm. Quinoline **7a**, as shown in Figure 4B, gave a simpler spectrum in this region, with one distinct triplet in the 4.2 ppm position and a multiplet at 3.6 ppm. As illustrated in Figure 4C, the spectrum for the unpurified material indicated a mixture of **6a** and **7a**, at a ratio of 1:1.2. The products for reactions of compounds **5b-e** are summarized in Table 1.

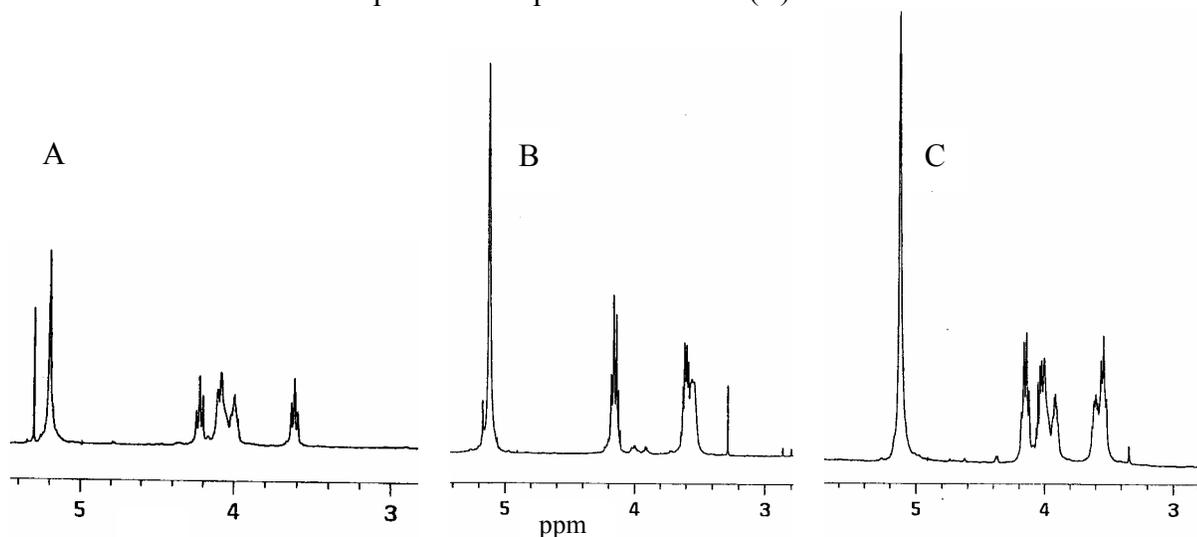
Table 1. Summary of the percent yields and product ratios resulting from the radical cyclizations of bromoallylic chlorides **5a-e**.

Reactant	Indoline (6)	Quinoline (7)	Ratio of 6:7
5a	40%	48%	1:1.2
5b	37	32	1.2:1
5c	35	32	1.1:1
5d	29	19	1.5:1
5e	86	none isolated	not calculated

Formation of substantial amounts of the *seco*-cyclopropyltetrahydroquinoline products **7a-d**, in addition to their *5-exo-trig* (*seco*-iso-CFI) counterparts **6a-d**, is noteworthy. This type of radical cyclization process on a diverse range of structures, including compound **5e**, has been widely reported [14]. In all of the reported cases, the indoline or *5-exo-trig* products were obtained exclusively [11b, 14], including the formation of a *seco*-CBI precursor (indoline **6e**) from bromoallylic chloride **5e**. We propose that formation of the quinolines **7a-d** is due to the generation of a stabilized radical intermediate, formed via a *5-exo-trig* ring closure reaction. Instead of immediately reacting with tributyltin hydride, the radical intermediate undergoes a ring expansion reaction to produce a more stable intermediate, which has a six-membered ring (quinoline) structure. The free radical is further stabilized by conjugation of the radical at the benzylic position. Subsequent reaction of the *seco*-CFQ radical with tributyltin hydride afforded products **7a-d**.

Figure 3. Free radical promoted cyclization of bromo-allylic chlorides **5a-e**

With both quinoline (**7**) and indoline (**6**) products available, they were conjugated to a 5,6,7-trimethoxyindole-2-carboxylic acid moiety, thereby forming analogs of the duocarmycins. Conjugates of compounds **6a,b** and **7a,b** to the trimethoxyindole moiety were found to have significant, yet similar, cytotoxicity against the growth of cancer cells grown in culture. The IC₅₀ values for these compounds derived from a three-day drug exposure against murine B16 melanoma are 0.04 – 0.09 μM [13].

Figure 4. Expanded 500 MHz ¹H-NMR spectra of indoline **6a** (A), quinoline **7a** (B) and an unpurified sample of **6a** and **7a** (C).

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Experimental

General

Instruments, etc

General Procedure for the Free Radical 5-Exo-Trig Cyclization

6-Benzyloxy-N-t-butoxycarbonyl-3-(chloromethyl)furano[e]indoline (6a) and *7-benzyloxy-N-t-butoxycarbonyl-3-chloro-1,2,3,4-tetrahydrofuranof[f]quinoline (7a)*. To a mixture of *cis* and *trans* bromo allylic-chloride **5a** (1.37 g, 2.59 mmol) was added 2,2'-azobisisobutyronitrile (AIBN) (250 mg, 1.52 mmol). The reagents were then dissolved in freshly distilled toluene (140 mL), and $n\text{Bu}_3\text{SnH}$ (1.87 mL, 6.95 mmol) was added. The solution was degassed with nitrogen and heated in an oil bath (90°C) for 2 hours. The toluene was removed *in vacuo* to produce a light yellow oil which was dissolved in CH_2Cl_2 and loaded on a hexane/silica gel column. The products were eluted with 1% EtOAc/hexane with the composition of EtOAc gradually increased to 5%. Fractions containing the products were concentrated *in vacuo*. The expected indoline product **6a** was obtained as a colorless clear oil (430 mg, 1.03 mmol, 40%); TLC (10% EtOAc/hexane) $R_f = 0.52$; IR (KBr, cm^{-1}) 3070, 3024, 2971, 2927, 1701, 1652, 1634, 1617, 1559, 1541, 1493, 1457, 1417, 1368, 1342, 1257, 1155, 1080, 1049, 1023, 978, 929, 903, 858, 823, 788, 739, 712; $^1\text{H-NMR}$ (CDCl_3) 7.57 (s br, 1H), 7.41 (d br, 8.0, 2H), 7.35 (d, 2.5, 1H), 7.33 (t, 8.0, 2H), 7.28 (t, 8.0, 1H), 6.77 (d, 2.5, 1H), 5.13 (s, 2H), 4.15 (dd, 9.5, 10.0, 1H), 4.02 (dd, 4.0, 11.0, 1H), 3.98 (m, 1H), 3.92 (dt, 4.0, 10.0, 1H), 3.54 (t, 10.5, 1H), 1.51 (s, 9H); EI-MS (m/z rel. intensity) 413 (M^+ , 14); Accurate mass for $\text{C}_{23}\text{H}_{24}\text{NO}_4^{35}\text{Cl}$: calcd. 413.1394, obsd. 413.1381.

In addition to the inoline product **6a**, an unexpected quinoline substance **7a** was isolated as a colorless clear oil (513 mg, 1.24 mmol, 48%); TLC (10% EtOAc/hexane) $R_f = 0.51$; IR (KBr, cm^{-1}) 3122, 3069, 2971, 2927, 1701, 1639, 1612, 1493, 1457, 1417, 1368, 1342, 1258, 1222, 1160, 1138, 1084, 1071, 1049, 1023, 903, 858, 832, 756, 734, 694; $^1\text{H-NMR}$ (CDCl_3) 7.57 (s br, 1H), 7.41 (d br, 7.5, 2H), 7.36 (d, 2.0, 1H), 7.33 (t, 7.5, 2H), 7.27 (t, 7.5, 1H), 6.76 (d, 2.0, 1H), 5.13 (s, 2H), 4.17 (t, 9.5, 2H), 3.5-3.65 (m, 3H), 1.49 (s, 9H); EI-MS (m/z , rel. intensity) 413 (M^+ , 4), 379 ($\text{M}^+ + \text{H-Cl}$, 20); Accurate mass for $\text{C}_{23}\text{H}_{24}\text{NO}_4^{35}\text{Cl}$: calcd. 413.1394, obsd. 413.1384.

Note: The radical cyclization of pure *cis* or *trans* isomer of compound **5a** gave similar mixtures of products **6a** and **7a**.

6-Benzoyloxy-N-t-butoxycarbonyl-3-(chloromethyl)-5-methylfurano[e]indoline (6b), and *7-benzoyloxy-N-t-butoxycarbonyl-3-chloro-1,2,3,4-tetrahydro-5-methylfurano[f]quinoline (7b)*. The products were purified by silica gel column chromatography using 10% EtOAc/petroleum ether as eluent to give compounds **6b** and **7b** in 37% and 32% yield, respectively. Indoline **6b** was isolated as an off-white solid. Mp. 170-172°C; TLC (10% EtOAc/petroleum ether) $R_f = 0.44$; IR (KBr, cm^{-1}) 3045, 2965, 2927, 2856, 1701, 1638, 1621, 1493, 1457, 1417, 1368, 1342, 1258, 1213, 1164, 1146, 1058, 1027, 934, 898, 752; $^1\text{H-NMR}$ (CDCl_3) 7.58 (s br, 1H), 7.43 (d br, 2H), 7.38 (t, 8.0, 2H), 7.24 (t, 8.0, 1H), 6.45 (s, 1H), 5.23 (s, 2H), 4.20 (dd, 9.5, 10.0, 1H), 4.10 (dd, 4.0, 10.0, 1H), 4.06 (m, 1H), 3.97 (dt, 4.0, 10.0, 1H), 3.59 (t, 10.0, 1H), 2.41 (s, 3H), 1.61 (s, 9H); EIMS m/z (rel. intensity) 427 (M^+ , 15), 371 (67), 91 (100).

Quinoline product **7b**: Yellowish oil; TLC (10% EtOAc/petroleum ether) $R_f = 0.40$; IR (KBr, cm^{-1}) 3040, 2964, 2927, 1701, 1639, 1497, 1458, 1417, 1458, 1417, 1368, 1342, 1320, 1213, 1164, 1142, 1049, 974, 934, 898, 832, 761, 734, 694; $^1\text{H-NMR}$ (CDCl_3) 7.59 (s br, 1H), 7.47 (s br, 2H), 7.39 (t, 7.5, sH), 7.34 (d, 7.5, 1H), 6.44 (s, 1H), 5.17 (s, 2H), 4.22 (t, 9.5, 2H), 3.65 (m, 3H), 2.41 (s, 3H), 1.60 (s, 9H); EIMS m/z (rel. intensity) 427 (M^+ , 2), 393 (30), 337 (100).

6-Benzoyloxy-N-t-butoxycarbonyl-3-(chloromethyl)thiopheno[e]indoline (6c) and *7-benzoyloxy-N-t-butoxycarbonyl-3-chloro-1,2,3,4-tetrahydrothiopheno[f]quinoline (7c)*. The products were purified by column chromatography using 5% ethyl acetate/petroleum ether as eluent. Both products were viscous and colorless oils. Indoline **6c**: TLC (5% EtOAc/petroleum ether) $R_f = 0.62$; IR (KBr, cm^{-1}) 3010, 2963, 1705, 1697, 1438, 1461, 1394, 1368, 1337, 1293, 1257, 1223, 1164, 1142, 1116; $^1\text{H-NMR}$ (CDCl_3) 7.45 (m, 6H), 7.32 (t, 7.5, 1H), 7.17 (d, 5.0, 1H), 5.21 (s, 2H), 4.21 (m, 2H), 4.05 (dd, 2.0, 9.9, 1H), 3.87 (m, 1H), 3.62 (t, 10.5, 1H), 1.59 (s, 9H); EIMS m/z (rel. intensity) 430 [M^+ , 10].

Quinoline **7c**: TLC (5% EtOAc/petroleum ether) $R_f = 0.55$; IR (KBr, cm^{-1}) 3007, 1953, 1700, 1607, 1483, 1461, 1394, 1368, 1332, 1292, 1142 and 1120; $^1\text{H-NMR}$ (CDCl_3) 7.54 (s, 7.0, 2H), 7.53 (d, 5.0, 1H), 7.44 (t, 7.0, 1H), 7.36 (t, 7.0, 1H), 7.16 (d, 5.0, 1H), 5.23 (s, 2H), 4.28 (t, 6.0, 2H), 3.68 (m, 1H), 3.61 (m, 2H), 1.59 (s, 9H); EIMS m/z (rel. intensity) 430 [M^+ , 6].

Butyl 5-[6-benzoyloxy-N-t-butoxycarbonyl-3-(chloromethyl)benzo[e]indoline]carboxylate (6d) and *butyl 5-[7-benzoyloxy-N-t-butoxycarbonyl-3-chloro-1,2,3,4-tetrahydrobenzo[f]quinoline]carboxylate (7d)*. Silica gel column chromatography purification of the crude product using 5% EtOAc/hexane as eluent afforded compounds **6d** and **7d** in 29% and 19%, respectively. Compound **6d** was isolated as a white solid. Mp 146-149°C; TLC (10% EtOAc/hexane) $R_f = 0.55$; IR (KBr, cm^{-1}) 2961, 1701, 1409, 1363, 1329, and 1141; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) 8.38 (d, 2.0, 1H), 8.33 (d, 8.0, 1H), 7.90 (dd, 2.0, 8.0, 1H), 7.54 (d, 8.0, 1H), 7.42 (m, 5H), 5.30 (s, 2H), 4.40 (t, 6.0, 2H), 4.30 (m, 1H), 4.18 (m, 1H), 4.08 (m, 1H), 3.93 (dd, 2.5, 11.1, 1H), 3.50 (t, 11.0, 1H), 1.81 (quintet, 6.0, 2H), 1.61 (s, 9H), 1.53 (quintet, 6.0, 2H), 1.02 (t, 6.0, 3H); EIMS m/z (rel. intensity) 523 [M^+ , 10]; Accurate mass calcd. for $\text{C}_{30}\text{H}_{34}\text{NO}_5^{35}\text{C}1$ 525.2126, obsd. 525.2137.

Quinoline **7d**: Colorless oily residue; TLC (10% EtOAc-Hexane) $R_f = 0.51$; IR (KBr, cm^{-1}) 2991, 1704, 14062, 1368, 1328, and 1147; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) 8.56 (d, 2.0, 1H), 8.36 (d, 8.0, 1H), 8.03 (s br, 1H), 7.94 (dd, 2.0, 8.0, 1H), 7.54 (d, 8.0, 7H), 7.48 (t, 8.0, 2H), 7.39 (t, 8.0, 1H), 5.30 (s, 2H), 4.40 (t, 6.0, 2H), 4.21 (t, 6.0, 2H), 3.80 (m, 3H), 1.82 (quintet, 6.0, 2H), 1.60 (s, 9H), 1.50 (quintet, 6.0, 2H), 0.98 (t, 6.0, 3H); EIMS m/z (rel. intensity) 523 [M^+ , 7].

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Sample Availability: Available from authors