AN EFFICIENT METHOD FOR THE SYNTHESIS OF SUBSTITUTED 4-ACETOXYNAPHTHALENE-2-CARBOXYLATE ESTERS, ETHYL 4-ACETOXYBENZOFURAN-6-CARBOXYLATE, AND ETHYL 4-ACETOXYBENZOTHIOPHENE-6-CARBOXYLATE

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Abstract: 4-Acetoxynaphthalene-2-carboxylate esters and their corresponding benzofuran and benzothiophene esters are important synthetic intermediates for the preparation of analogs of CC-1065 and the duocarmycins. In this communication, an efficient method for the synthesis of the titled compounds using an Emmons-Horner reaction strategy is reported. As an alternative to the Stobbe condensation reaction, coupling of *tert*-butyl 3-ethoxycarbonyl-3-(phosphonodiethyl)propionate with a series of aromatic aldehydes, followed by acid promoted removal of the *tert*-butyl group and Friedel-Crafts reaction, produced the target compounds in good overall yields and of excellent quality.

Introduction

Based on their interesting biological properties and unique structural features, CC-1065[1] and the duocarmycins, such as duocarmycin SA,[2] (see Figure 1) have been the subject of intense investigations in recent years.[3,4] A substantial portion of the studies were focused on the design, synthesis and testing of a wide range of analogs, with the goal of creating compounds with equal anticancer potency as the natural products, but lacking systemic toxicity.[3a] From the extensive structure-activity relationship (SAR) studies, a number of CPI analogs were discovered to have favorable preclinical biological properties and were subjected to clinical trials.[3a] Thus far, only one of the analogs, bizelesin,[5] is still undergoing phase II clinical trials. Also from the SAR studies, it became evident that the CPI moiety of the duocarmycins and CC-1065 could be replaced by other synthetically more accessible heterocycles, while still retaining potent DNA alkylation and cytotoxic properties. Example of CPI analogs include cyclopropylbenz[*e*]-indolone (CBI),[6] cyclopropylpyrazolo[e]indolone (CPzI),[7] cyclopropylfurano[*e*]indolone (CFI),[8] iso-cyclopropylfurano[2,3-*e*]indolone (iso-CFI).[9] The most common synthetic strategy that researchers have used to construct the indolone subunit of these analogs involves a novel 5-e*xo-trig*

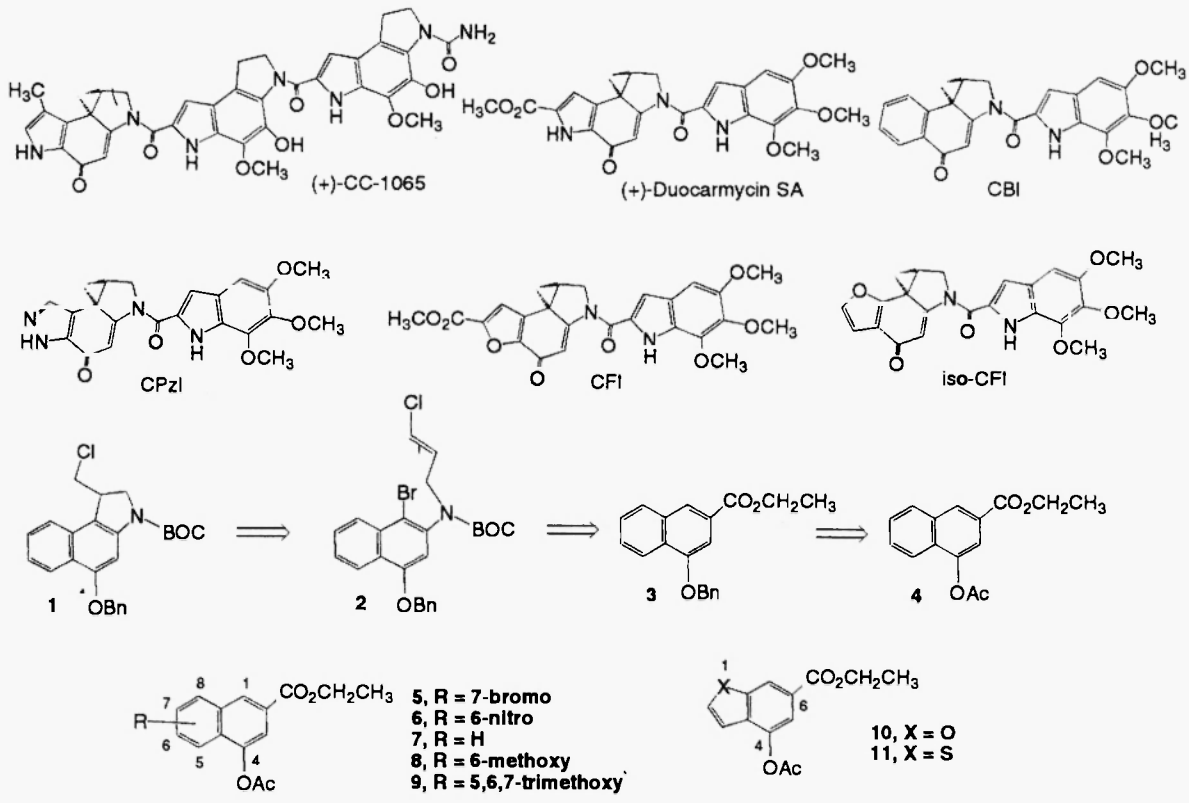


Figure 1. Structures of (+)-CC-1065, (+)-duocarmycin SA, CBI, CPzI, CFI, iso-CFI, retrosynthesis of indoline **1** from ester **4**, and structures of the target esters **5** – **11**.

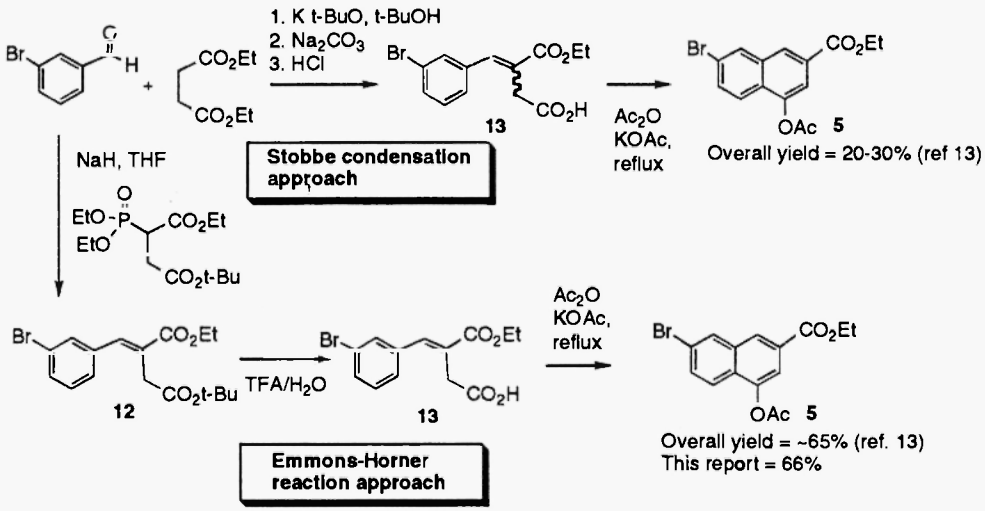
aryl radical-vinyl chloride cyclization reaction.[10] For instance, as depicted in Figure 1, indoline **1** was prepared from bromide **2** by reaction with AIBN and tributyltin hydride in refluxing toluene. Bromide **2** and related compounds for the preparation of the other analogs were, in turn, synthesized from their corresponding esters **3** and **4**.

Several synthetic strategies exist for the preparation of esters related to compound **4**, such as Stobbe condensation of aryl aldehydes with diethyl succinate,[9,11] and Emmons-Horner condensation of *tert*-butyl 3-ethoxycarbonyl-3-(phosphonodiethyl)propionate with aromatic aldehydes.[11,12] For example, reaction of 3-bromobenzaldehyde by the Stobbe method gave ester **5** in an overall 20-30% yield. But, a similar reaction by the Emmons-Horner route gave ester **5** in an overall yield of 65%.[13] In this communication, we report studies on the synthesis of seven aromatic esters using the Emmons-Horner reaction approach. In addition to the preparation of naphthalene derivatives, two

novel heterocylic esters, benzofuran and benzothiophene esters, were also synthesized, thereby demonstrating the versatility of this methodology.

Results and Discussion

A general synthetic strategy for preparing the substituted naphthalene esters (**5** – **9**) and the heterocyclic (benzofuran and benzothiophene) esters (**10** and **11**, respectively) is given in Scheme 1. In a typical reaction, the phosphonate ylide of *tert*-butyl 3-ethoxycarbonyl-3-(phosphonodiethyl)propionate was prepared by treatment of the phosphonate with sodium hydride at 0 °C, under an atmosphere of nitrogen. The respective aromatic aldehyde was then added dropwise into the solution of ylide.



Scheme 1. A general synthetic strategy for the preparation of ester **5**, by either the Stobbe condensation or Emmons-Horner reaction approach.

After the mixture was allowed to gradually warm to room temperature overnight, alkene **12** was isolated in essentially quantitative yield. Analysis by 500 MHz ^{1}H-NMR indicated that the alkenes were homogeneous and were essentially one stereoisomer. The *tert*-butyl group in alkene **12** was readily removed by treatment with aqueous trifluoroacetic acid at room temperature. Loss of the *tert*-butyl group was confirmed by ^{1}H-NMR analysis, which indicated the elimination of a singlet at about 1.4 ppm. Acid **13** was used directly in the Friedel-Crafts reaction without purification. The Friedel-Crafts and subsequent O-acetylation reactions were accomplished by heating to reflux a

solution of acid **13** and potassium acetate in acetic anhydride for 1.5 hours. The target esters (**5** - **11**) were isolated and purified by silica gel column chromatography. The structures of these compounds were ascertained by ^{1}H-NMR, FT-IR and mass spectrometry, and in the case of ester **5**,[13] and **10**,[9] the data were compared to reported values.

The overall percent yields for the three-step synthesis, Emmons-Horner - Freidel-Crafts - acetylation, of the seven target esters are given in Table 1. For comparison, the overall percent yields for esters **5** and **10**, synthesized previously using the Stobbe condensation, are also listed in Table 1. The results provide supporting evidence that the Emmons-Horner approach is significantly more efficient than the Stobbe approach for the synthesis of esters **5** – **11**.

Table 1. Overall three-steps percent yields of substituted acetoxy-naphthalene, benzofuran, and benzothiophene carboxylate esters, derived from the Emmons-Horner and Stobbe condensation approaches.

Esters	Emmons-Horner Method	Stobbe method	Melting points of esters	MS (EI)
5	66 (65)[13]	(20-30)[13]	109 °C (113)[13]	337, M^+
6	41 (42)[14]	-	145	303, M^+
7	60	-	70	258, M^+
8	52	-	84	288, M^+
9	74	-	110	348, M^+
10	53	(25)[9]	61	248, M^+
11	50	-	56	264, M^+

Experimental

A representative synthesis of ester **7** is described.

Alkene 12 (R = H). NaH (207 mg, 60%, 5.18 mmol) was suspended in dry THF (15 mL) and stirred under N_2 at -5°C for 20 minutes. A solution of *tert*-butyl 3-ethoxycarbonyl-3-(phosphonodiethyl)propionate (1.65 g, 4.87 mmol) in dry THF (5 mL) was added dropwise to the NaH suspension. The reaction mixture was stirred under N_2 at 0 °C for 2.5 hours, followed by a dropwise addition of benzaldehyde (500 mg, 1.72 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to room temperature while stirring under N_2 over 12 hours. The mixture was concentrated under vacuum to give a brown oil, which was separated between water and methylene chloride. The organic layer was collected, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give alkene **12** (R = H) (1.11 g, 81 %) as a light yellow oil. IR (neat) 3020, 2970, 1734, 1366, 1263, 1200, 1156, 1096; ^{1}H-NMR ($CDCl_3$, 500 MHz) 7.85 (s, 1H), 7.37 (m, 5H), 4.29 (q, 6.0, 2H), 3.46 (s, 2H), 1.47 (s, 9H), 1.34 (t, 6.0, 3H).

Acid 13 (R = H). A solution of alkene **12** (R = H) (1.10 g, 3.79 mmol) in TFA/water (5.5 mL, 9:1) was allowed to stir for 1.5 hours at room temperature. TFA was removed under reduced pressure to give a dark brown oil. The oil was co-evaporated with methylene chloride (2 x 25 mL) to remove any excess H_2O and TFA. The acidic product was cooled to 0 °C and treated with a saturated $NaHCO_3$ solution. The mixture was filtered, and to the filtrate was added 30% HCl to give a pH of 1. Ethyl acetate (50 mL) was added and the mixture was allowed to stir for 10 minutes. The organic layer was collected, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting yellow oil was dried under high vacuum to give acid **13** (R = H) (816 mg, 92%). IR (neat) 3431, 2980, 1709, 1638, 1204; ^{1}H-NMR ($CDCl_3$, 300 MHz) 11.05 (s br, 1H), 7.92 (s, 1H), 7.38 (m, 5H), 4.30 (q, 5.9, 2H), 3.57 (s, 2H), 1.31 (t, 5.9, 3H).

Ester 7. Acid **12** (R = H) (800 mg, 3.42 mmol) was dissolved in Ac_2O (10 mL) and kept under an atmosphere of N_2. KOAc (520 mg, 5.30 mmol) was added to the mixture, and the reaction was stirred and refluxed for 1.5 hours. The hot reaction mixture was poured into H_2O (30 mL) and stirred vigorously while it was allowed to cool to room temperature, some solid formed. Ethyl acetate was added to the mixture to partition the product. The organic layer was collected, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a brown oil. The oil was purified by column chromatography with 3% ethyl acetate in petroleum ether solvent to afford ester **7** (706 mg, 80%). The product was washed with hexanes to give beige solid. Mp 70 °C. IR (neat) 3067, 2979, 1768, 1714, 1366, 1292, 1199, 1062, 772; ^{1}H-NMR ($CDCl_3$, 500 MHz) 8.53 (s, 1H), 8.00 (d, 8.0, 1H), 7.89 (d, 8.0, 1H), 7.84 (s, 1H), 7.63 (m, 2H), 4.45 (q, 6.0, 2H), 2.48 (s, 3H), 1.44 (t, 6.0, 3H); EI-MS 258 (M^+, 15), 216 (100).

Ester **8**. IR (neat) 3068, 2959, 1768, 1720, 1469, 1337, 1260, 1209, 1118; ^{1}H-NMR ($CDCl_3$, 500 MHz) 8.44 (s, 1H), 7.88 (d, 8.0, 1H), 7.81 (s, 1H), 7.22 (d, 8.0 1H), 7.10 (s, 1H), 4.42 (q, 6.0, 2H), 3.95 (s, 3H), 2.49 (s, 3H), 1.43 (t, 6.0, 3H).

Ester **9**. IR (neat) 3068, 2959, 1768, 1720, 1469, 1337, 1260, 1209, 1118; ^{1}H-NMR ($CDCl_3$, 500 MHz) 8.33 (s, 1H), 7.55 (s, 1H), 7.10 (s, 1H), 4.41 (q, 6.0, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 2.39 (s, 3H), 1.42 (t, 6.0, 3H).

Ester **11**. IR (neat) 3097, 2979, 1763, 1715, 1400, 1366, 1278, 1195, 1086, 1023, 768; ^{1}H-NMR ($CDCl_3$, 500 MHz) 8.50 (s, 1H), 7.78 (s, 1H), 7.64 (d, 5.5, 1H), 7.29 (d, 5.5, 1H), 4.42 (q, 6.0, 2H), 2.43 (s, 3H), 1.42 (t, 6.0, 3H).

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