A Facile Synthesis of 5-Mesyl-3-benzylbenz[*e*]indole: Implications for the Involvement of a *p*-Quinone Methide Intermediate

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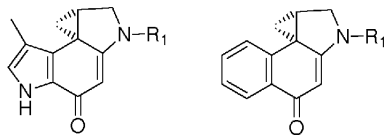
Introduction

The potent antitumor antibiotic (+)-CC-1065, isolated from *Streptomyces zelensis* in 1974,[1] has been shown to exhibit several interesting biological effects.[2] At the time of isolation, (+)-CC-1065 was the most potent cytotoxic low-molecular weight compound known.[3] (+)-CC-1065 interacts with AT-rich sequences of DNA in a sequence-specific manner, resulting in the N3 alkylation of adenine.[4] Due to its cytotoxic properties and efficacy against a variety of tumors in vitro, (+)-CC-1065 served as a new lead in anticancer drug design.[5] Unfortunately, the discovery that it exhibited delayed lethality in mice at subtherapeutic doses precluded its development as a clinical candidate.[6] To circumvent the delayed lethality associated with (+)-CC-1065, analogues that have increased efficacy and no delayed lethality have been synthesized and studied.[7] In addition to their potential as clinical agents, these analogues have aided in the understanding of the interaction of these DNA-alkylating agents with DNA.

(+)-CC-1065 analogues incorporating the (+)-CBI (1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one) **2** moiety, the benzannulated counterpart of the CPI [1,2,8,8a-tetrahydro-7-methylcyclopropa[*c*]pyrrolo[3,2-*e*]-indol-4(5*H*)-one] **1**, have been synthesized.[8] It has been



(+)-CPI **1** (+)-CBI **2**

established that the replacement of the (+)-CPI moiety with the (+)-CBI moiety in the natural product does not affect the sequence specificity or the structural, biochemical, or biological effects.[8] The CBI-based analogues are more stable than the corresponding CPI-based compounds and retain potent biological activity.[8] The synthesis of CBI was first described by Boger, in which the indoline component was constructed on a naphthalene core via a 5-*exo*-dig aryl radical cyclization.[9] Subsequently, several radical cyclization routes to the benzindoline have been described.[10] Recently, the synthesis of difluoro CBI has been reported where the five-membered ring was generated by an intramolecular rhodium metal-catalyzed carbene insertion into a 1,1-difluoro alkene.[11] Aristoff and Johnson have described a synthesis of (+)-CBI where the five-membered ring was synthesized by the transannular cyclization of a benzquinoline to produce the indoline fused to the cyclopropane ring.[12]

An interesting photochemical approach to the synthesis of CBI involves the photocyclization of a heterostilbene to produce benzindoles of the general structure **3**. These were then subjected to a regioselective Mannich alkylation at the 3 position of the indole to produce the cyclopropane ring system.[13] In this paper, we report the synthesis of 5-mesyl-3-benzylbenz[*e*]indole **7**, an intermediate in the synthesis of **2**. In addition to being a new route to the synthesis of the key intermediate, this method also provides a novel and facile entry into the benzindole ring system.

Results and Discussion

The formation of the N−C2 bond in the synthesis of the indole nucleus can take place by the routes shown in Scheme 1.[14] In the first instance, the cyclization is accomplished by addition−elimination at a carbonyl or an imine group, while in the second case, the activation of an acetylene bond by metal catalysts leads to the nucleophilic addition of the nitrogen to produce the indole. The addition of a styrene olefin to an electrophilic nitrogen species is also a versatile method for the generation of indoles.[14] The above synthetic routes generally require refluxing conditions to force the cyclization. In the synthesis described in this paper, we

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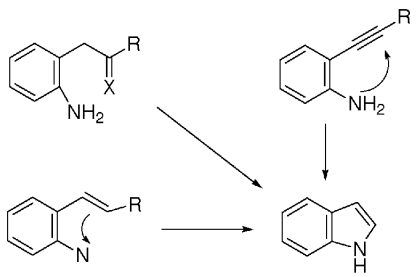
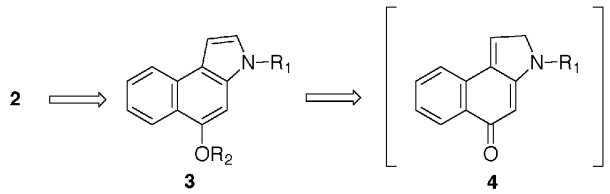
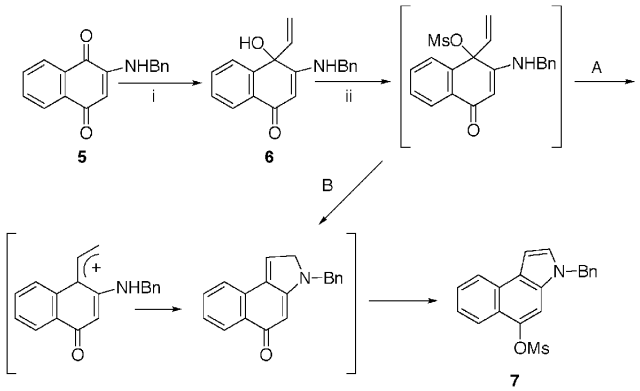
Scheme 1



Scheme 2



Scheme 3[a]



[a] Reagents: (i) vinylmagnesium bromide, THF; (ii) MsCl, Et_3N.

designed the cyclization to occur by the addition of a nitrogen nucleophile to an allylic carbocation (Scheme 2). Since this reaction was rapid and facile, the cyclization took place at low or modest temperatures.

2-(Benzylamino)-1,4-naphthalenedione **5**[12] was treated with vinylmagnesium bromide to produce the vinyl alcohol **6** in 60% yield (Scheme 3). Our initial attempts to generate the allylic carbocation from compound **6** involved the use of an acid catalyst. Compound **6** was dissolved in polar aprotic, polar protic, and nonpolar solvents and stirred in the presence of a catalytic amount of *p*-toluenesulfonic acid or concentrated sulfuric acid at various temperatures (0 °C reflux).[15] These conditions did not initiate the formation of the carbocation, and the starting material was recovered. Similar results were obtained when **6** was refluxed in 85% formic acid, indicating that the elimination of the hydroxy group under acid-catalyzed conditions was not facile. Since the sulfonate esters of tertiary alcohols are highly reactive and unstable, the conversion of the tertiary allylic alcohol to the corresponding mesylate was expected to produce the allylic carbocation.[16] When the allylic alcohol **6** was reacted with mesyl chloride in the presence of triethylamine, the indole **7** was obtained in 58% yield. Two pathways can be proposed to explain this facile cyclization (Scheme 3). The first pathway (A) involves the generation of a tertiary carbocation due to the loss of the mesylate followed by its rearrangement to extend the conjugated system.[15] Addition of the lone pair from the amine to the carbocation results in the formation of the five-membered ring and the *p*-quinone methide. Subsequent aromatization produced the indole product **7**. On the other hand, the formation of the *p*-quinone methide could also be explained by the initial formation of the tertiary mesylate, attack of the nitrogen lone pair on the terminal carbon of the olefin, rearrangement of the double bond, and elimination of the mesylate (pathway B). Although the mesylate is a good leaving group, this route seems less likely because the nitrogen lone pair forms a conjugate with the α,β-unsaturated ketone. In addition, since this route is a 5-*endo*-trig cyclization, it would be thermodynamically unfavorable on the basis of Baldwin's rules.[17] Irrespective of which of the above two mechanisms is actually involved, both result in the formation of the *p*-quinone methide intermediate. The *p*-quinone methide undergoes rearrangement to produce the more stable indole **7**.[18]

In conclusion, a new route to a key intermediate **7** in the synthesis of (+)-CBI has been developed. The synthesis involves the formation of the heterocyclic ring of the indole by a nucleophilic addition of the amine to an allylic carbocation and differs from other reported procedures for forming the N−C2 bond of indoles. The cyclization is facile and takes place at low temperatures. Aromatization of the resultant unstable *p*-quinone methide occurred rapidly to produce the indole **7**. Several reports in the literature discuss the versatility of *p*-quinone methides in organic synthesis,[19] and this method expands the use of *p*-quinone methides to the synthesis of indoles.[20]

Experimental Section

All reagents and solvents employed were reagent grade and were used without further purification. Column chromatography was performed with silica gel (200−400 mesh, Aldrich Chemicals). The chromatographic solvent system is reported as volume per volume. NMR spectra were recorded on a Varian 500 MHz NMR instrument at room temperature (18−20 °C). The mass spectra were recorded by the Mass Spectrometry Laboratory of The Department of Chemistry, The University of Texas at Austin. Microanalyses were performed by QTI Inc.

1-Hydroxyl-2-(benzylamino)-1,4-dihydro-1-vinylnaphthalen-4-one (6). To a cooled solution of 2-(benzylamino)-1,4-naphthalenedione **5**[12] (1.052 g, 4 mmol) in dry THF (50 mL) at 0 °C was added dropwise vinylmagnesium bromide (1.0 M in THF, 10 mL, 10 mmol) and the mixture stirred. The reaction mixture was stirred in an inert atmosphere at 0 °C for 2 h. After 2 h, the reaction was quenched carefully with water and the compound extracted with CH_2Cl_2 (2 × 150 mL). The organic layers were combined and washed with brine and saturated aqueous $NaHCO_3$. The organic layer was dried and filtered, and

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the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (0−5% CH_3OH in $CHCl_3$) to yield **6** (756 mg, 65%), which decomposes when heated above 60 °C: ^{1}H NMR (500 MHz, $CDCl_3$, free base) δ 7.82 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.38 (m, 1H), 7.29 (m, 6H), 5.89 (bs, 1H), 5.70 (dd, J = 10.5 Hz, J = 17.0 Hz, 1H), 5.48 (d, J = 16.5 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 5.07 (s, 1H), 4.08 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 182, 165, 143, 141, 136, 131, 130, 128, 127.7, 127.6, 127.3, 126, 125, 113, 95, 72, 46; HRCIMS m/z 292.1336 (M + 1). Anal. Calcd for $C_{19}H_{17}NO_2 \cdot 0.5H_2O$: C, 75.98; H, 6.04; N, 4.66. Found: C, 76.19; H, 6.13; N, 4.31.

5-Mesyl-3-benzylbenz[*e*]indole (7). To a cooled solution of **6** (145 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triethylamine (1 mL, 7.17 mmol) and the mixture stirred. After 5 min, mesyl chloride (0.5 mL, 6.5 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to room temperature and stirred under an inert atmosphere for 1 h. The reaction was then quenched with water and the compound extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with brine and saturated aqueous $NaHCO_3$. The organic layer was dried and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$) to yield **7** (101 mg, 58%): mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$, free base) δ 8.25 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.60 (dd, 1H), 7.57 (s, 1H), 7.49 (dd, 1H), 7.30 (m, 4H), 7.15 (m, 2H), 7.06, (m, 1H), 5.39 (s, 2H), 3.06 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 141, 136, 130, 128.8, 128.6, 127.8, 127.7, 126, 124, 123, 122.8, 122.5, 122.1, 105, 101, 50, 37; HRCIMS m/z 352.1004 (M + 1). Anal. Calcd for $C_{20}H_{17}NO_3 \cdot 1H_2O$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.75; H, 5.21; N, 3.43.

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