

# Synthesis and X-ray Analysis of an Unprecedented and Stable 2-Aza-4,4-spirocyclopropacyclohexadienone

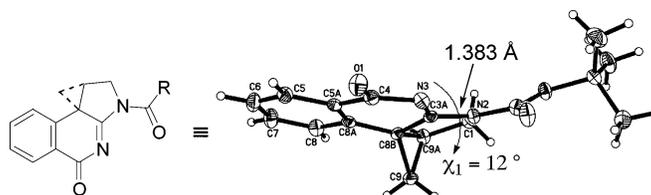
Jay P. Parrish, David B. Kastrinsky, and Dale L. Boger\*

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

boger@scripps.edu

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## ABSTRACT



An efficient eight-step synthesis (54% overall) and the subsequent X-ray characterization of 1,2,9a-tetrahydrocyclopropa[*c*]benz[*e*]-3-azindol-4-one (CBA) containing an aza variant of the CC-1065/duocarmycin alkylation subunit are detailed. Despite the unique deep-seated aza modification providing an unprecedented and stable 2-aza-4,4-spirocyclopropacyclohexadienone, CBA proved to be structurally identical with CBI, the carbon analogue, in terms of the stereoelectronic alignment of the key cyclopropane, its bond lengths, and the length of the diagnostic C3a–N2 bond reflecting the extent of vinylogous amide conjugation.

CC-1065 (**1**)<sup>1</sup> and the duocarmycins (**2** and **3**)<sup>2,3</sup> are the parent members of a class of potent antitumor antibiotics<sup>4</sup> that derive their properties through a sequence-selective alkylation of duplex DNA (Figure 1).<sup>5,6</sup> Since their disclosure, an extensive series of studies have characterized the structural features responsible for or important to the DNA alkylation reaction and established fundamental relationships between structure and reactivity or structure and activity.<sup>5–10</sup> Aside from the

structural complexity inherent in the alkylation subunit, they possess an uncharacteristic stability that defies intuition. This is due principally to the vinylogous amide conjugation with and stabilization of the cyclohexadienone structure, which is dominant over that activating the cross-conjugated cyclopropane.<sup>11–13</sup> Accordingly, disruption of this vinylogous amide conjugation leads to remarkable increases in reactivity as large as 10<sup>4</sup>-fold,<sup>13</sup> which we have suggested is the source of catalysis for the DNA alkylation reaction.<sup>7–11</sup>

The synthesis of analogues containing deep-seated structural changes, including those within the intricate alkylation subunit, have been central to these studies, providing insight not accessible through examination of the natural products.<sup>14</sup> Among those introduced, the 1,2,9a-tetrahydrocyclopropa-

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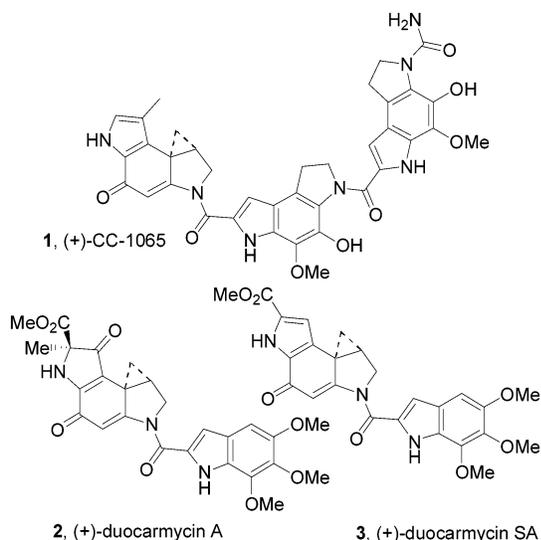


Figure 1.

[c]benz[e]indol-4-one (CBI) alkylation subunit has emerged as the most extensively examined, extended, and modified series (Figure 2).<sup>15</sup> Not only is CBI the most synthetically

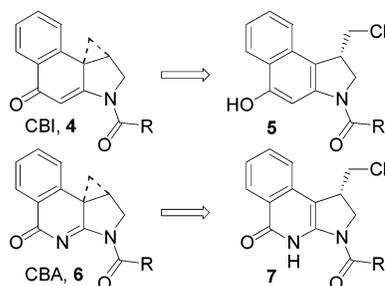


Figure 2.

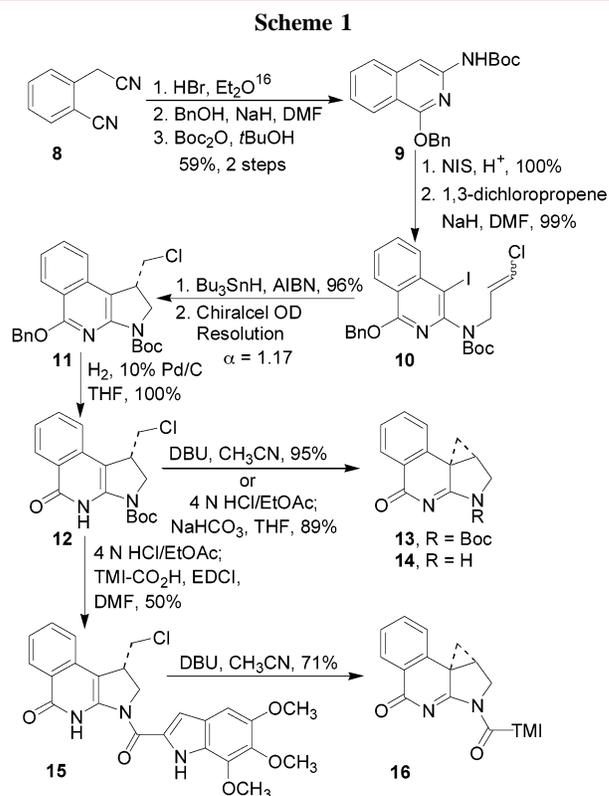
accessible alkylation subunit in a rich series, but its derivatives exhibit a potency and efficacy that surpass those of 1 and 2 and approach those of 3, and it exhibits a stability and inherent reaction regioselectivity that are near optimal.<sup>15</sup>

An unusual characteristic of this class of compounds is that the cyclopropane precursors such as 5 readily close in vitro and in vivo, displaying biological properties that are not distinguishable from the final cyclopropane-containing compounds, yet stand up to prolonged storage more effectively. In our examination of modified alkylation subunits, we targeted the pyridone 7 as an especially storage stable precursor to the unique 1,2,9,9a-tetrahydrocyclopropa[c]benz-

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[e]-3-azaindol-4-one (CBA, 6) alkylation subunit. Although 7 was anticipated to be even more stable than the CBI derivative 5, the properties of 6, incorporating an unprecedented 2-aza-4,4-spirocyclopropacyclohexadienone, were unknown. Herein, we report the first synthesis and structural characterization of this unique, and surprisingly stable, system.

The synthesis of the CBA subunit began by treatment of 8 under conditions disclosed to effect formation of 1-bromo-3-aminoisoquinoline (Scheme 1).<sup>16</sup> Nucleophilic introduction



of the C1 benzyloxy group and subsequent Boc protection of the resulting amine provided 9 in 59% over two steps. Regioselective C4 iodination and N-alkylation with 1,3-dichloropropene to give 10 set the stage for a key 5-exo-trig aryl radical-alkene cyclization to form 11.<sup>17</sup> Resolution of 11 by chromatographic separation on a semiprep Chiralcel OD column cleanly provided both enantiomers, which were then subjected to hydrogenolysis to provide 12 ((R)-enantiomer not shown).<sup>18,19</sup> Spirocyclization of 12 was effected by treatment with DBU in anhydrous CH<sub>3</sub>CN to give N-Boc-CBA (13) in superb yield (95%) in eight steps and 54% overall yield. Additionally, treatment of 12 with HCl and subsequent spirocyclization afforded CBA (14). Likewise,

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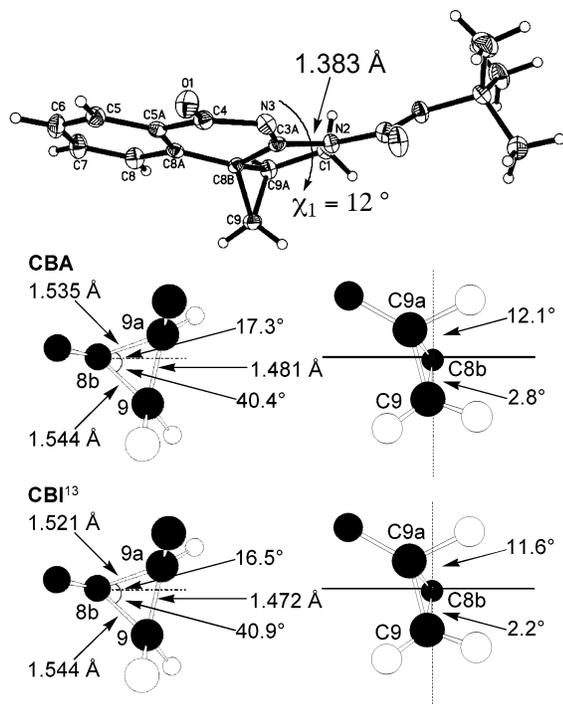
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acid treatment of **12** and subsequent coupling of the amine hydrochloride salt with 5,6,7-trimethoxyindole-2-carboxylic acid<sup>19</sup> (TMI) provided **15**, which could be spirocyclized to **16** using DBU.

With crystalline **13** in hand, its single-crystal X-ray structure determination<sup>20</sup> was conducted on needles obtained by recrystallization from 9:1 hexanes–CH<sub>2</sub>Cl<sub>2</sub>. Not only are its overall structural characteristics identical to those of *N*-CO<sub>2</sub>Me-CBI,<sup>13</sup> including the stereoelectronic alignment of the key cyclopropane (Figure 3), but the two structures are



**Figure 3.** X-ray analysis

nearly superimposable. Remarkably, essentially all bond lengths of *N*-Boc-CBA were within  $\pm 0.02$  Å of those of *N*-CO<sub>2</sub>Me-CBI, including not only all three cyclopropane bonds, of which the reacting C8b–C9 bonds are identical (1.544 vs 1.544 Å), but also the C3a–N2 bond (1.383 vs 1.390 Å, respectively), whose length is diagnostic of the extent of vinylogous amide conjugation.<sup>7,8</sup> The only exceptions are the slightly more perturbed C3a–N3 vs C3a–C3 bond (1.30 vs 1.35 Å) and the adjacent N3–C4 vs C3–C4 bond (1.40 vs 1.44 Å) reflecting the intrinsically shorter C=N vs C=C bond lengths. The unusual stability of **13** and its 2-aza-4,4-spirocyclopropacyclohexadienone may be attributed to the geometrical constraints of the fused five-membered ring that prevents the ideal, bisected conjugation of the cyclopropane with the  $\pi$ -system<sup>13</sup> and, most importantly, the N2 amidine cross-conjugation.

Thus, the structural characteristics and intrinsic chemical stability of CBA suggest that it may serve as an additional stable alternative to CBI and the related naturally occurring DNA alkylation subunits. The full characterization of the chemical and biological properties of the CBA-based compounds is in progress and will be reported in due course.

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**Supporting Information Available:** Full experimental details for the preparation of **9–16** and X-ray bond length comparisons of **13** with *N*-CO<sub>2</sub>Me-CBI. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) Atomic coordinates for **13** have been deposited with the Cambridge Crystallographic Data Centre under deposition number CDCC 209699.  
(21) Comparison figure is provided in Supporting Information.