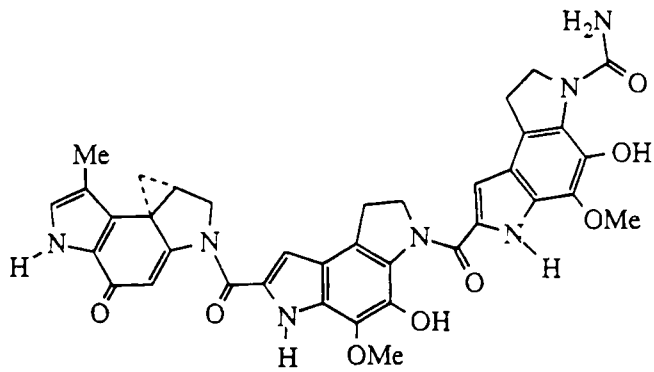
# A PRACTICAL ROUTE TO OPTICALLY ACTIVE CBI, A POTENT ANALOG OF THE CC-1065 ALKYLATION SUBUNIT

**Lei Ling, Yu Xie, and J. William Lown***

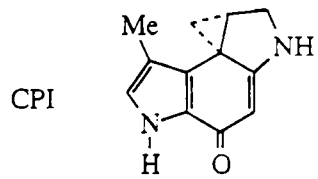
Department of Chemistry, University of Alberta, Edmonton, Canada T6G 2G2

**Abstract:** A 1,2,9,9a-tetrahydrocycloprop[*c*]benz[*e*]indol-4-one, CBI precursor, racemic **3** was resolved by Lipase PS catalyzed hydrolysis in water-saturated isopropyl ether. A practical route for the synthesis of optically active CBI, a potent analog of the CC-1065 pharmacophore, starting from the resolved material was thereby developed.

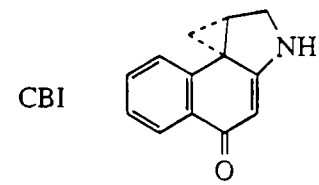
CC-1065, an antitumor antibiotic isolated from the culture of *Streptomyces zelensis* (1), is one of the most potent compounds discovered to date and has a wide spectrum of activities against tumor cells *in vitro* and *in vivo* as well as against microbial organisms (2). CC-1065 binds to double-stranded DNA within the minor groove at AT-rich sites and alkylates the N-3 position of the 3'-adenine by its warhead, the left hand subunit of cyclopropylindole (CPI) (3). Despite its high potency, CC-1065 can not be used in humans because of the delayed death it causes in experimental animals. In the search for compounds with better antitumor selectivity, many CC-1065 analogs have been synthesized in attempts to avoid its unwanted side effects but to retain its potency against tumor cells (4). This contains the modification of DNA binder, the right-hand segment of the molecule (4) and the modification of the DNA alkylating moiety, the left-hand segment (5,6).




CC-1065



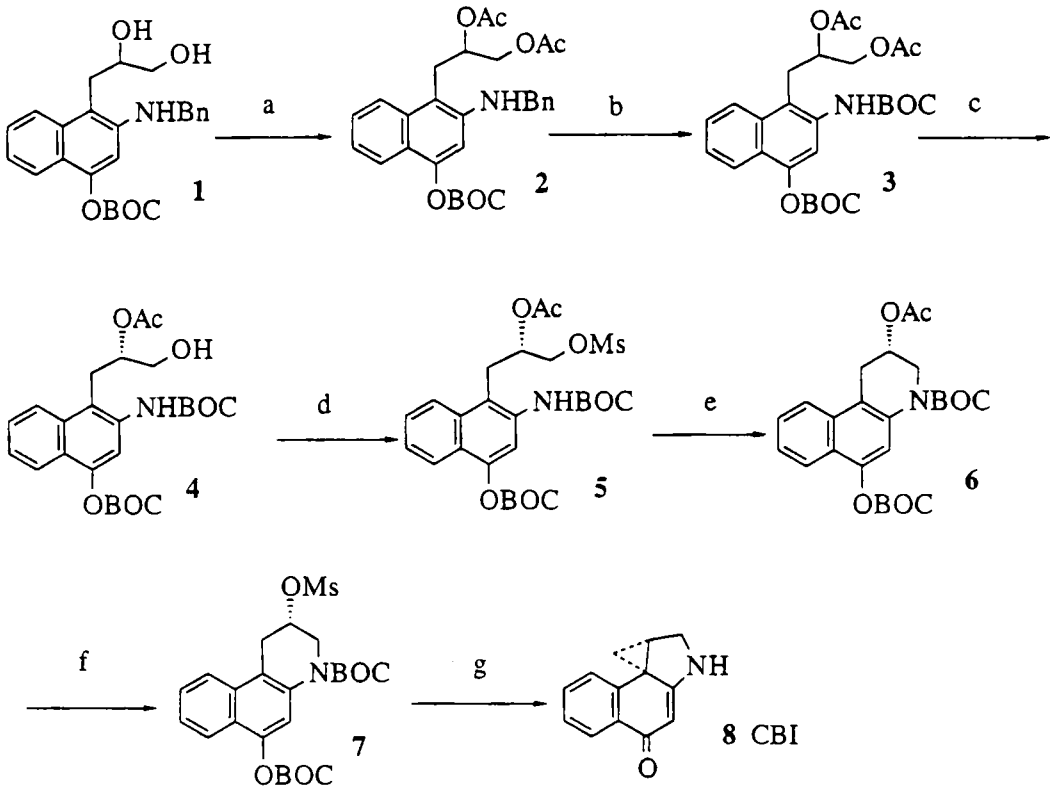

CPI




CBI

Figure 1

As a successful example, Boger first reported the synthesis of a simplified warhead, 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indole-4-one (CBI) (Figure 1) and its analogs (6). It was found that CBI analogs were more stable and more potent than the CPI counterparts. Subsequently, some additional routes to CBI were developed by other groups (7). The common drawback in the synthesis is the optical resolution of the precursor, which was performed by preparation of its diastereomers and HPLC separation or direct HPLC separation of the enantiomers by using a chiral column. This represents a severe limitation on the scale of the syntheses. Herein we report a practical route to optically active CBI based on lipase mediated optical resolution and selective deprotection.




**Scheme 1:** a) $Ac_2O$, pyridine; b) (i) $HCO_2H$, Pd/C, MeOH; (ii) $(t\text{-}BuO_2C)_2O$, dioxane; c) Lipase PS, $H_2O/{}^iPr_2O$; d) MsCl, pyridine; e) NaH, THF; f) (i) $Na_2CO_3$, MeOH; (ii) MsCl, pyridine; g) KOH, MeOH

Scheme 1 shows a modified method for synthesis of CBI (7a). Compound **1** was synthesized according to reported method (7a). Acetylation of both hydroxyl groups, removal of the benzyl group and reprotection of amino group by BOC gave **3** in the overall yield of 80% in three steps. The optical resolution of **3** was attempted by lipase catalyzed hydrolysis. Considering the low solubility of the material in aqueous media, the reaction was carried out in organic solvent, water-saturated isopropyl ether. In the presence of Lipase PS (Amano, a lipase from *Pseudomonas sp.*), the acetate of the primary hydroxyl group of S enantiomer, which corresponds to the natural enantiomer of CPI, was selectively hydrolyzed. The reaction was monitored by TLC. The reaction was quenched by removal of the enzyme when half of the material was hydrolyzed. Both enantiomers were obtained in the optical purity of 75-80% e.e. Each enantiomer was

then obtained in its optically pure form (>99% e.e.) by simply repeating the same reaction once more. Both optically pure enantiomers were obtained in about 80% yield in this way. The resolution was carried out in gram scale (8). Along with the resolution, selective deprotection of the primary hydroxyl group was accomplished. This afforded an important optically active intermediate for the synthesis of CBI. Mesylation of the primary hydroxyl group of **4** gave **5** in 89% yield. Cyclization of **5** in the presence of sodium hydride gave **6** in 79%. Removal of acetyl group of **6** and mesylation of hydroxyl group gave **7** in 94% yield. Finally removal of all of the protection group and formation of cyclopropane ring was performed in one step to give CBI (**8**) (9) almost quantitatively (98%).

The optical purity of the resolved material (**4**) was determined by preparing its MTPA ester and analyzing by $^{19}F$ NMR (10). The optical purity was confirmed once more by replacing the acetate of **6** with MTPA ester and analyzing by $^{19}F$ NMR. The absolute configuration of the resolved product was determined by comparing the specific rotation value of **8** derived from **4** with the reported data.[11]

In summary, a CBI precursor **3** was resolved by enzyme-catalyzed hydrolysis in an organic solvent. Optically pure (+)-CBI, which corresponds to natural enantiomer of CPI, was synthesized by a modified method (7a). Short steps in the procedure and the simplicity of the treatment in all of the steps provides a practical route to a potent analog of CC-1065 alkylation subunit. The preparation of CBI-lexitropsin conjugates and investigation of their properties is in progress.

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**References and Notes**

1. L. J. Hanka; A. Dietz; S. A. Gerpheide; S. L. Kuentzel; D. G. Martin *J. Antibiot.*, *31*, 1211-1217 (1978).
2. a) B. K. Bhuyan; K. A. Newell; S. L. Crampton; D. D. Van Hoff *Cancer Res.*, *42*, 3532-3546 (1982). b) V. L. Reynolds; J. P. McGovern, L. H. Hurley *J. Antibiot.*, *39*, 319-329 (1986).
3. L. H. Hurley; V. L. Reynolds; D. H. Swenson; G. L. Petzold; T. A. Scahill *Science*, *226*, 843-844 (1984).
4. a) D. L. Boger; R. S. Coleman *J. Am. Chem. Soc.*, *110*, 4796-4807 (1988). b) R. C. Kelly; I. Gebhard; N. Wicnienski; P. A. Aristoff; P. D. Johnson; D. G. Martin *J. Am. Chem. Soc.*, *109*, 6837-6838 (1987). c) C. H. Lin; D. Sun; L. H. Hurley *Chem. Res. Toxicol.*, *4*, 21-29 (1991). d) M. A. Mitchell; R. C. Kelly; N. A. Wicnienski; N. T. Matzenbuhler; M. G. Williams; G. L. Petzold; J. L. Slighton; D. R. Siemeniak *J. Am. Chem. Soc.*, *113*, 8995-8996 (1991). e) J. H. Tidwell; S. L. Buchwald *Org. Chem.*, *57*, 6380-382 (1992).
5. a) Y. Wang; J. W. Lown *Heterocycles 36*, 1399-1410 (1993). b) Y. Wang; R. Gupta; L. Huang; J. W. Lown *J. Med. Chem.*, *36*, 4172-4182 (1993).
6. a) D. L. Boger; J. A. McKie *J. Org. Chem.*, *60*, 1271-1275 (1995). b) D. L. Boger; P. Mesini; C. M. Tarby *J. Am. Chem. Soc.*, *116*, 6461-6462 (1994). c) D. L. Boger; S. A. Munk *J. Am. Chem. Soc.*, *114*, 5487-5496 (1992). d) D. L. Boger; W. Yun; B. R. Teegarden *J. Org. Chem.*, *57*,

2873-2876 (1992). e) D. L. Boger; T. Ishizaki *J. Org. Chem.*, *55*, 5823-5832 (1990). f) D. L. Boger; T. Ishizaki *J. Am. Chem. Soc.*, *111*, 6461-6463 (1989).

7. a) P. A. Aristoff; P. D. Johnson *J. Org. Chem.*, *57*, 6234-6239 (1992). b) K. J. Drost; M. P. Cava *J. Org. Chem.*, *56*, 2240-2244 (1991).
8. General procedure for enzymatic resolution of **3**: To a solution of **3** (4.12 g, 7.97 mmol) in water-saturated isopropyl ether (300 ml) was added Lipase PS (13.0 g). The suspension was stirred at room temperature for 18 h. The enzyme was filtered out. The solvent was removed. The residue was chromatographed (AcOEt/Hexane = 1/2) to give R-**3** (1.99 g, 48%, 74% e.e.) (12) and S-**4** (1.96 g, 51%, 80% e.e.). After subject to the same reaction once more, R-**3** was obtained in the yield of 85% (96% e.e.). Optically pure S-**4** was obtained from second resolution in the yield of 78% (>99%e.e.) (12).
9. $^1$H NMR of CBI ($CD_2Cl_2$), δ= 8.11 (m, 1H, aromatic), 7.42 (m, 1H, aromatic), 7.35 (m, 1H, aromatic), 6.88 (m, 1H, aromatic), 5.85 (brs, 1H, NH), 5.70 (s, 1H, aromatic), 3.80 (dd, 1H, $J_1$=10.5 Hz, $J_2$=5.0 Hz), 3.65 (d, 1H, J=10.5 Hz), 2.88 (ddd, 1H, $J_1$=7.8 Hz, $J_2$=5.0 Hz, $J_3$=4.0 Hz), 1.59 (dd, 1H, $J_1$=7.8 Hz, $J_2$=4.0 Hz), 1.40 (dd, 1H, $J_1$=$J_2$=4.0 Hz).
10. $^{19}$F NMR of MTPA ester of racemic **4** showed two peaks: δ= -71.78 and -71.86 and were referenced to trichlorofluoromethane.
11. The specific rotation of compound **8** derived from optically pure **4** is: $[\alpha]_D^{24}$= +325° (C 0.08, MeOH), lit. (7a) $[\alpha]_D^{23}$ = +335° (c 0.20 g/mL, MeOH).
12. The specific rotation of optically pure S-**4** is: $[\alpha]_D^{24}$= -12.8° (c 0.36, $CHCl_3$). The specific rotation of compound S-**4** obtained from first resolution is: $[\alpha]_D^{24}$ = -9.5° (c 0.78, $CHCl_3$), 74% e.e.. The specific rotation of compound S-**4** obtained from second resolution is: $[\alpha]_D^{24}$ = -12.3° (c 0.48 g/mL, $CHCl_3$), 96% e.e.

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