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Photocyclization of Tosylstilbenes as a Key Reaction in the Preparation of an Analogue of the Antitumor Agent CC-1065

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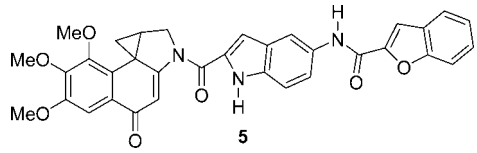
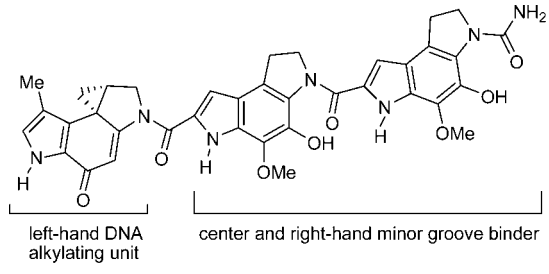


A photocyclization of tosylstilbenes in the presence of base is used as a key reaction in the synthesis of the CC-1065 analogue **5**.

CC-1065 (**1**) (Figure 1) is an extremely potent antitumor antibiotic isolated from a Streptomyces strain,[1] which, regrettably, possesses no clinical utility due to delayed hepatotoxicity.[2] Following the identification of the structural features leading to hepatotoxicity,[3] a substantial number of derivatives with antitumor activity have been prepared.[4]

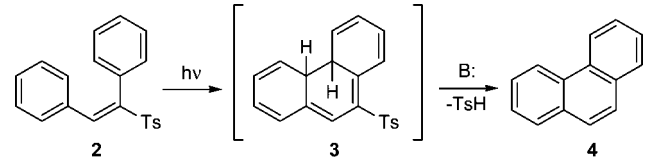


CC-1065 **(1)**

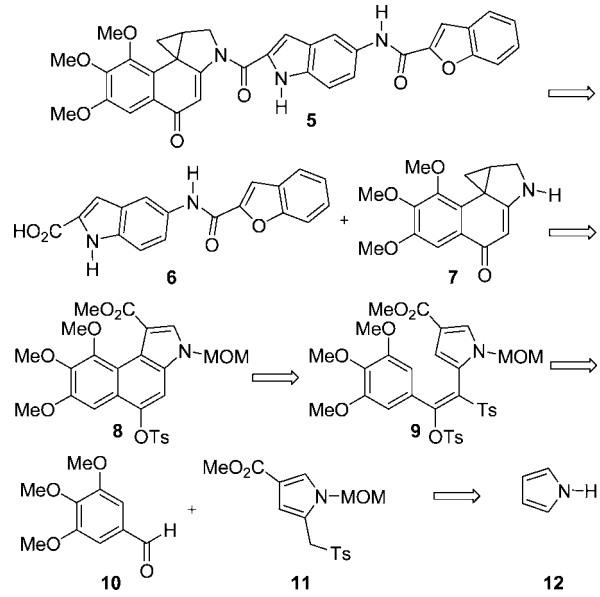
FIGURE 1. Structure of alkaloid CC-1065.

In a previous work,[5] we described a synthesis of phenanthrenes and phenanthrenoids involving irradiation with UV light, in the presence of base,[6] of stilbenes and stilbenoids containing a tosyl group on the central double bond. Thus, we showed that the irradiation of tosylstilbenes (**2**) causes a cyclization leading to a tosyldihydrophenantrene (**3**) that loses *p*-toluensulfinic acid in contact with base, resulting in aromatization to a phenanthrene (**4**) (Scheme 1).

SCHEME 1. Photochemical Preparation of Phenanthrenes from Tosylstilbenes



SCHEME 2. Retrosynthetic Analysis for the Preparation of 5



The synthesis of the CC-1065 analogue **5** is based in this phenanthrene synthesis (Scheme 2). Compound **5** presents a methoxy group closely positioned to the alkylating cyclopropane unit. Hopefully, the steric hindrance posed by this group would modulate in a biologically useful way the properties of compound **5**.

Compound **7** can be obtained from phenanthrenoid **8**, which, in turn, can be derived from stilbenoid **9**. This stilbenoid **9** can

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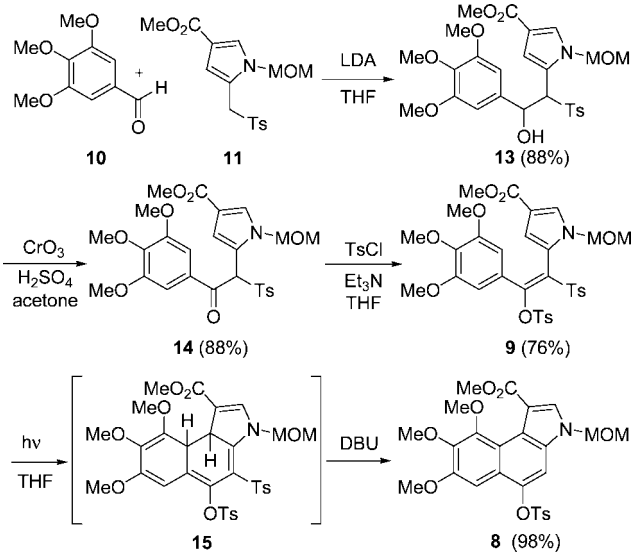
SCHEME 3. Preparation of Phenanthrenoid 8

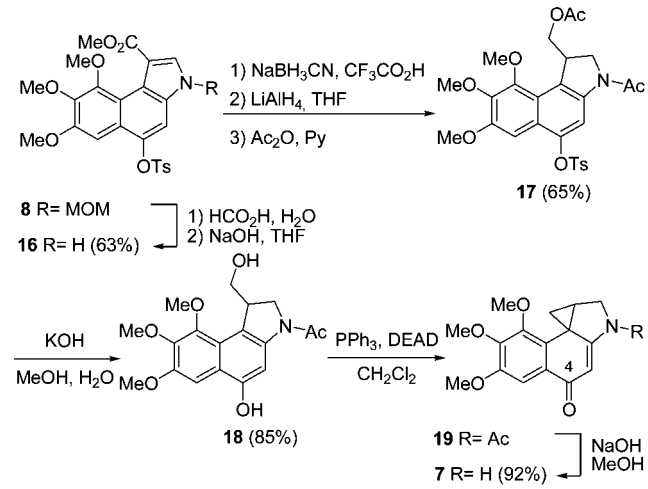


be accessed in a convergent way from pyrrole derivative **11** and 3,4,5-trimethoxybenzaldehyde (**10**).

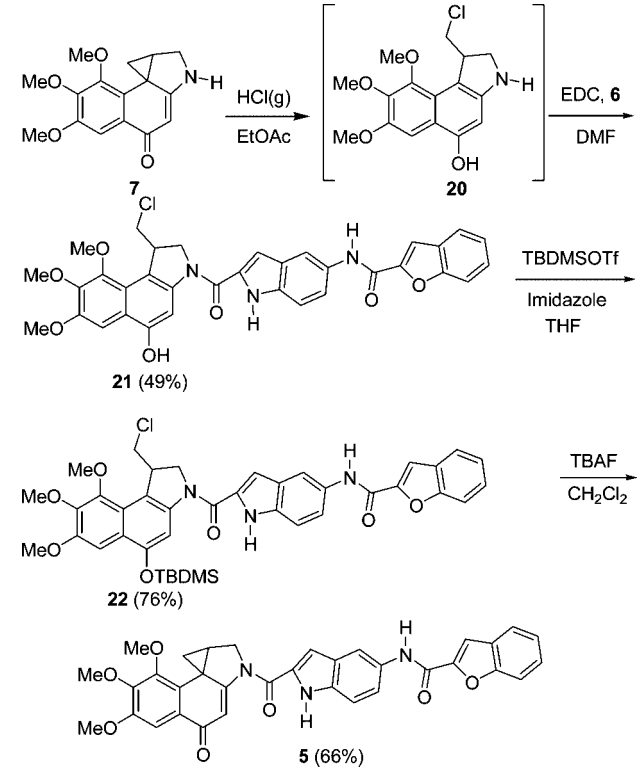
LDA-induced condensation of sulfone **11**[7] with aldehyde **10** led to alcohol **13** (Scheme 3). Oxidation of alcohol **13** under Jones conditions[8] followed by treatment with tosyl chloride yielded the key tosylstilbenoid **9**. Irradiation with a 450 W medium pressure mercury lamp of tosylstilbenoid **9** in the presence of DBU under strictly anhydrous conditions led to a 98% yield of the key phenanthrenoid **8**, in which the tosyl group was lost from the intermediate dihydrophenanthrenoid **15** by a base-induced elimination.

The removal of the MOM group in benzoindole **8** was effected in two steps, involving reaction with aqueous formic acid followed by reaction of the resulting aminal with sodium hydroxide in wet THF (Scheme 4), leading to compound **16**.[9] Reduction of benzoindole **16** with $NaBH_3CN$ in trifluoroacetic acid[10] led to the corresponding unstable indoline, whose ester was reduced to alcohol with $LiAlH_4$. Treatment of the alcohol with acetic anhydride allowed the isolation of the stable acetylated compound **17**. Deprotection of the tosylated phenol and the alcohol in compound **17** by treatment with KOH led to benzoindoline **18**, which was subjected to an intramolecular Mitsunobu reaction with DEAD and triphenylphosphine,[11] giving the acetylated compound **19**. The acetyl group in **19** could be removed under very mild conditions using sodium methoxide[12] because the nitrogen atom in the resulting compound **7** belongs to a vinylogous amide.

SCHEME 4. Synthesis of CC-1065 Derivative Alkylating Subunit



SCHEME 5. Synthesis of CC-1065 Analogue 5



It is not possible to couple **18** with the central and right parts because the nitrogen is protected as an amide. The amide could be hydrolyzed in **18**, but it would demand very harsh reaction conditions—either acidic or basic. The removal of the acetate was made under much milder conditions in the cyclized compound **19**, where the leaving group was a nitrogen in the form of a vinylogous amide. The conjugation of the nitrogen of amine **7** with the carbonyl group in position 4 impedes the condensation of amine **7** with the acid **6**. Therefore, the amine **7** was treated with gaseous hydrogen chloride (Scheme 5) leading to the phenol **20**, which was condensed in situ with the acid **6** using EDC[13] to give compound **21**. Compound **21** is very insoluble, making the formation of cyclopropane ring not possible. In variance, the TBDMS-protected compound **22**—whose preparation was possible regardless of the insolubility

(7) Sulfone **11** can be easily prepared using a procedure previously reported by our group: Castedo, L.; Delamano, J.; López, C.; López, M. B.; Tojo, G. *Heterocycles* **1994**, *38*, 495.

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(9) This two-step deprotection protocol resulted from extensive experimentation in which other methods failed due to the sensitivity of benzoindole **8** to acid.

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of **21**—reacts with TBAF[14] to leading to deprotection of the TBDMS group and simultaneous cyclization to the desired CC-1065 analogue **5**.

A versatile photochemical procedure was used as a key step in the preparation of a new and potentially enhanced CC-1065 analogue. This preparation of phenanthrenes is equally useful for the preparation of heterocyclic analogues thereof.

Experimental Section

3,4,5-Trimethoxybenzaldehyde (**10**) was purchased from commercial sources. Methyl 1-methoxymethyl-5-tosylmethyl-1*H*-pyrrole-3-carboxylate[15] (**11**), methyl *N*-methoxymethyl-5-tosyloxy-7,8,9-trimethoxybenzo[*e*]indolecarboxylate[16] (**8**), and 5-[(benzofuran-2-carbonyl)amino]-1*H*-indole-2-carboxylic acid[17] (**6**) were prepared according to published procedures.

Preparation of Key Compounds. N-Acetyl-1-acetoxymethyl-5-tosyloxy-7,8,9-trimethoxy-1,2-dihydro-3*H*-benzo[*e*]indole (17). A mixture of benzoindole **16** (97 mg, 0.20 mmol) and $NaBH_3CN$ (126 mg, 2.00 mmol) in 2.4 mL of trifluoroacetic acid was stirred at −5 °C under argon during 20 min. Aqueous sodium hydroxide (10%, 15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The solvent was removed in vacuo from the collected organic phases, and the residue was dissolved in 5 mL of dry THF. $LiAlH_4$ (70 mg, 1.84 mmol) was added, and the resulting mixture was stirred for 15 min at room temperature. EtOAc (10 mL) and 10% NaOH (15 mL) were added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The solvent was removed in vacuo from the collected organic phases, and the residue was treated with Ac_2O (23 mmol, 2.2 mL) and pyridine (27 mmol, 2.2 mL). After 5 h at room temperature, 10% HCl (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The solvent was removed in vacuo, and the crude was purified by column chromatography in silica (10 × 1 cm ∅), delivering 71 mg (65%) of acetate **17** as a white solid. Mp: 224 °C (CH_2Cl_2). R_f: 0.12 (EtOAc/hexane (1:1)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (s, 1H); 7.84 (d, J = 8.1 Hz, 2H); 7.34 (d, J = 8.1 Hz, 2H); 7.08 (s, 1H) 4.40 (dd, J = 10.5 and 3.2 Hz, 1H); 4.08 (m, 3H); 4.00 (s, 3H); 3.91 (s, 3H); 3.87 (s, 3H); 3.68 (m, 1H); 2.44 (s, 3H); 2.22 (d, J = 6,9 Hz, 3H); 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.4 (C); 168.9 (C); 152.8 (C); 148.7 (C); 145.9 (C); 145.8 (C); 140.1 (C); 130.4 (CH); 128.8 (CH); 122.9 (C); 122.6 (C); 121.0 (C); 110.7 (CH); 98.2 (CH); 66.9 (CH_2); 61.7 (CH); 61.4 (CH_3); 56.1 (CH_3); 53.3 (CH_2); 41.6 (CH_3); 24.6 (CH_3); 22.1 (CH_3); 21.3 (CH_3). MS (EI, 75 eV, *m*/*z*): 543 ($M^{+\bullet}$, 26.31); 470 ($M^{+\bullet}$ − CH_2, 7.20); 329 ($M^{+\bullet}$ − OTs − Ac, 21.07). Anal. Calcd for $C_{27}H_{29}O_9NS$: C, 59.65; H, 5.37; N, 2.57; S, 5.89. Found: C, 59.95; H, 5.71; N, 2.50; S, 5.53.

4-Oxo-1,2,9,9a-tetrahydro-6,7,8-trimethoxybenzo[*e*]cyclopropa[*c*]indole (7). To a suspension of phenol **18** (211 mg, 0.6 mmol) and Ph_3P (231 mg, 0.88 mmol) in CH_2Cl_2 (20 mL) was added 0.1 mL (0.79 mmol) of DEAD. After 17 h of stirring at rt under argon, the solvent was removed and the resulting crude was purified by column chromatography in silica (10 × 1.5 cm ∅), providing a mixture of cyclopropabenzindol **19** and triphenylphosphine oxide. This mixture was dissolved in methanol (20 mL). A solution of NaOMe in MeOH (1.5 M, 2 mL), was added and the resulting mixture was stirred at room temperature under argon during 8 min. The solvent was removed and the resulting crude material was purified by column chromatography in silica (10 × 1.5 cm ∅), delivering compound **7** (161 mg) in 92% overall yield from benzindol **18**. Mp: 185−189 °C (EtOAc/methanol). R_f: 0.08 (EtOAc). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.61 (s, 1H); 6.24 (s, 1H); 5.73 (s, 1H); 3.93 (s, 3H); 3.88 (s, 3H); 3.87 (s, 3H); 3.79 (dd, J = 10.8 and 5.1 Hz, 1H); 3.63 (d, J = 10.5 Hz, 1H); 3.25 (m, 1H); 1.92 (dd, J = 7.6 and 3.2 Hz); 1.10 (t, J = 3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.83 MHz) δ: 183.3 (C); 172.4 (C); 152.2 (C); 149.2 (C); 144.5 (C); 130.6 (C); 125.5 (C); 105.4 (CH); 95.7 (CH); 61.8 (OCH_3); 61.1 (OCH_3); 56.4 (OCH_3); 50.7 (CH_2); 31.7 (C); 26.8 (CH); 26.0 (CH_2). MS (EI, 75 eV, *m*/*z*): 287 ($M^{+\bullet}$, 100); 272 ($M^{+\bullet}$ − CH_3, 46.95); 273 ($M^{+\bullet}$ − CH_2, 7.28); 256 ($M^{+\bullet}$ − CH_3O, 19.53). HRMS: calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1157.

***N*-{5-[(Benzofuran-2-carboxyl)amino]-1*H*-indol-2-carboxyl}-1-chloromethyl-1,2-dihydro-5-hydroxy-7,8,9-trimethoxybenzo[*e*]indole (21).** A current of gaseous HCl was passed during 30 min through a solution of cyclopropabenzindole **7** (72 mg, 0.25 mmol) in 20 mL of dry EtOAc. The solvent was removed in vacuo, and the crude chlorophenol **20** was dissolved in 20 mL of dry DMF. The acid **6** (214 mg, 0.67 mmol) and EDC·HCl (173 mg, 0.90 mmol) were added, and the resulting mixture was stirred at room temperature during 21 h. Water was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The collected organic phases were dried (Na_2SO_4) and concentrated. The resulting oil was purified by column chromatography in silica (10 × 1 cm ∅), delivering compound **21** as a white solid possessing very low solubility, which could be purified further by washing with EtOAc. This results in 76 mg of **21**, obtained in 50% overall yield from **7**. R_f: 0.63 (toluene/acetone/acetic acid (50:50:1)). ^{1}H NMR (DMSO, 250 MHz) δ: 11.7 (s, 1H); 10.52 (s, 1H); 8.26 (s, 1H); 7.97 (d, J = 6.9 Hz, 1H); 7.79 (m, 3H); 7.65 (d, J = 8.9 Hz, 1H); 7.52 (d, J = 8.4 Hz, 2H); 7.39 (d, J = 7.7 Hz, 1H); 7.35 (s, 1H); 7.22 (s, 1H); 4.73 (t, J = 10.2 Hz, 1H); 4.57 (d, J = 10.5 Hz, 1H); 4.13 (m, 1H); 3.98 (s, 3H); 3.91 (s, 3H); 3.88 (s, 3H); 3.6 (t, J = 10.0 Hz, 1H). ^{13}C NMR (DMSO, 62.8 MHz) δ: 160.7 (C); 157.2 (C); 155.1 (C); 153.6 (C); 151.5 (C); 149.9 (C); 148.0 (C); 143.0 (C); 141.8 (C); 134.2 (C); 132.4 (C); 131.7 (C); 127.9 (C); 127.7 (C); 127.6 (CH); 124.4 (CH); 123.4 (CH); 121.7 (C); 120.4 (C); 120.1 (CH); 114.1 (CH); 113.9 (C); 112.8 (CH); 112.5 (CH); 110.7 (CH); 106.1 (CH); 101.0 (CH); 99.4 (CH); 62.1 (CH_3); 61.3 (CH_3); 56.3 (CH_3); 55.3 (CH_2); 49.1 (CH_2); 44.5 (CH). MS (FAB+, *m*/*z*): 625 ($M^{+\bullet}$, 19.73); 323 (left fragment, 12.42); 145 (right fragment, 22.96); 131 (central fragment, 6.14); HRMS: calcd for $C_{34}H_{28}ClN_3O_7$ 625.1616, found 625.1595. UV (nm, λ_{max}, CH_3CN): 303.

***N*-{5-[(Benzofuran-2-carbonyl)amino]-1*H*-indole-2-carboxyl}-1,2,9,9a-tetrahydro-4-oxo-6,7,8-trimethoxybenzo[*e*]cyclopropa[*c*]indole (5).** A 1 M solution of TBAF (63 μL, 0.06 mmol) in THF was added over a solution of silyl ether **22** (20 mg, 0.03 mmol) in dry CH_2Cl_2 (2 mL). The resulting solution was stirred at room temperature under argon during 20 min. The solvent was removed at the rotatory evaporator and the resulting crude was purified by column chromatography in silica (5 × 1.5 cm ∅) delivering 10 mg (66%) of compund **5** as a white solid. M.p: >250 °C (EtOAc/hexane). R_f: 0.39 (EtOAc). ^{1}H NMR (DMSO, 500 MHz) δ: 11.83 (s, 1H); 10.47 (s, 1H); 8.21 (s, 1H); 7.82 (d, J = 7.8 Hz, 1H); 7.75 (s, 1H); 7.72 (d, J = 8.3 Hz, 1H); 7.62 (d, J = 8.9 Hz, 1H); 7.48 (m, 2H); 7.44 (s, 1H); 7.36 (t, J = 8.5 Hz, 1H); 7.24 (s, 1H); 6.97 (s, 1H); 4.60 (dd, J = 10.2 and 5 Hz, 1H); 4.45 (d, J = 10 Hz, 1H); 3.88 (s, 3H); 3.87 (s, 3H); 3.82 (s, 3H); 1.96 (m, 2H). ^{13}C NMR (DMSO, 125 MHz) δ: 183.5 (C); 162.2 (C); 161.6 (C); 156.5 (C); 154.4 (C); 152.1 (C); 149.1 (C); 145.1 (C); 134.0 (C); 131.3 (C); 130.2 (C); 128.5 (C); 127.2 (C); 127.0 (CH); 126.8 (C); 126.0 (C); 123.8 (CH); 122.8 (CH); 120.1 (CH); 113.5 (CH); 112.4 (CH); 111.9 (CH); 110.2 (CH); 109.5 (CH); 107.2 (CH); 104.2 (CH); 102.5 (C); 61.6 (CH_3); 60.5 (CH_3); 55.8 (CH_3); 54.2 (CH_2); 30.7

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(15) See ref 7.

(16) See ref 5.

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(C); 24.3 (CH); 23.8 (CH_2). MS (FAB+, *m/z*): 588 ($M^{+\bullet}$ − H, 1.11). HRMS: calcd for $C_{34}H_{27}N_3O_7$ 589.1849, found 589.1858. UV (nm, λ_{max}, CH_3CN): 324, 259.

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Supporting Information Available: General procedure to obtain compounds **16**, **18**, and **22**, characterization for new products, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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