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Photochemistry of Tosylstilbenoids in the Preparation of Complex Heterocyclic Compounds. Synthesis of a Cyclopropafuroindolone Analogue of the DNA-Alkylating Section of the Antitumor Compound CC-1065

Juan Enjo, Luis Castedo, and Gabriel Tojo*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

qogatojo@uscmail. usc.es

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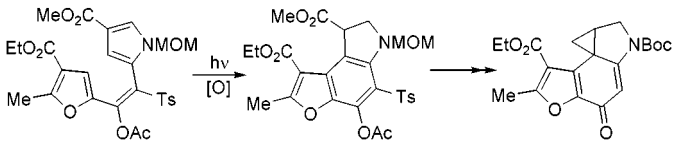
ABSTRACT



A novel photocyclization of tosylstilbenoids is used in the preparation of a cyclopropafuroindolone analogue of the DNA-alkylating unit of the antitumor compound CC-1065.

The agent CC-1065 (**1**, Figure 1)[1] and the duocarmycins[2] represent an exceptionally potent kind of antitumor natural compounds. They interact with the minor groove of DNA in a highly selective manner, producing the alkylation of the genetic material and the interference in the replication of cancer cells.[3]

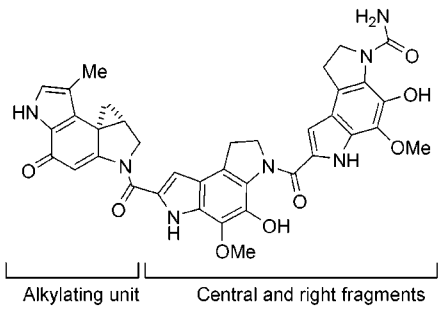


Figure 1. CC-1065 (**1**).

To find therapeutically useful compounds with maximum potency and minimum toxicity, a large collection of non-natural derivatives was prepared.[4] The central and right fragments interact in a noncovalent manner and increase the affinity for DNA, while the left fragment produces the alkylation of DNA by the attack of an adenine on the electrophilic cyclopropane ring.

While the action of the central and right parts may be mimicked by simple indole and benzofuran dimers, the

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(2) Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I.; Ogawa, T.; Takahashi, K.; Sano, H.; Saitoh, Y. *Chem. Pharm. Bull.* **1995**, *43*, 378−391.

(3) For a review on DNA alkylation properties of these compounds, see: Boger, D. L.; Johnson, D. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1438−1474.

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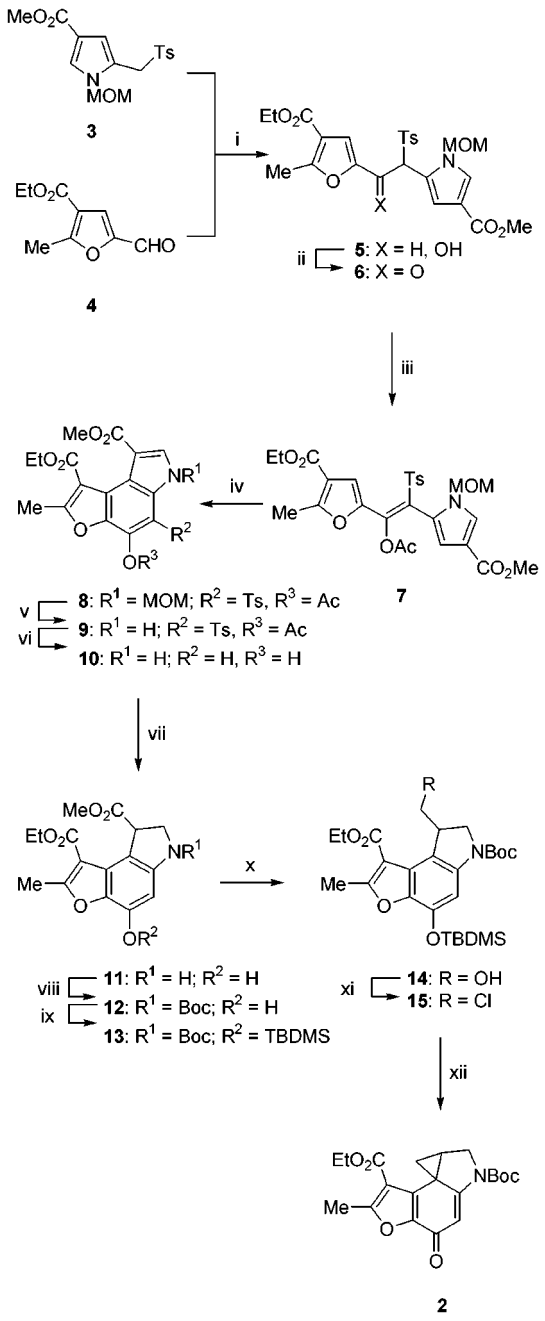
structure of the left part plays a key role in the selectivity and therapeutic efficacy of these drugs.[3]

This work reports a new synthesis of alkylating left-part derivatives, involving a key photochemical cyclization of stilbenoids developed by our group.[5] It is exemplified by the preparation of the furan-containing derivative **2**.

Condensation of the LDA-generated anion of sulfone **3**[6] with furaldehyde **4**,[7] leads to alcohol **5**,[8] which is obtained as a single diastereomer of unknown but irrelevant stereochemistry (Scheme 1). Oxidation with DDQ in hot chlorobenzene yields ketone **6**. Treatment with acetyl chloride and triethylamine produces stilbenoid **7**. Only one isomer on the central double bond is obtained. As the ensuing photochemical irradiation produces a photostationary equilibrium of the (*E*) and (*Z*) isomers, no effort was made to assign the stereochemistry to stilbenoid **7**. Irradiation with a medium-pressure mercury lamp of this stilbenoid in a benzene solution, with 1 equiv of iodine and excess propylene oxide leads to 91% furoindol **8**.[9] Propylene oxide is used to destroy the generated HI. The tosyl substituent on stilbenoid **7** imparts an electron deficiency that protects stilbenoid **7** against unwanted oxidations during this photochemical reaction. We wish to note the high yield obtained in this key photochemical reaction of a molecule with a dense functionality.

Deprotection of the MOM group with formic acid, followed by treatment with magnesium in methanol, produces the removal of the tosyl group and deacetylation of the phenol. The resulting furoindol **10** was reduced to the corresponding furoindoline **11** by ionic hydrogenation with Et_3SiH in trifluoroacetic acid. The unstable furoindoline **11** was immediately protected on the nitrogen with Boc anhydride. Silylation of the phenol with TBDMSCl, followed by regioselective reduction of the aliphatic ester with $LiAlH_4$ at −78 °C, led to the alcohol **14**. This alcohol was treated with triphenylphosphine in CCl_4, yielding the key substrate **15**, which contains a silicon-protected phenol and a chloride. Treatment of compound **15** with TBAF in chloroform led to the desilylation and simultaneous formation of the cyclopropane ring.[10] We believe that the nascent phenoxide, produced after the fluoride attack on the silicon, cyclizes to compound **2**, before it completely detaches from the silicon, as the treatment of the corresponding phenol with TBAF or with other bases does not produce compound **2**.

Scheme 1[a]



[a] (i) LDA, THF, −78 to −50 °C, 90%; (ii) DDQ, chlorobenzene, reflux, 82%; (iii) ClAc, Et_3N, CH_2Cl_2, −40 °C; 97%; (iv) hν, I_2, PO, benzene, 91%; (v) HCOOH, 96%; (vi) Mg, MeOH, 70%; (vii) Et_3SiH, F_3CCO_2H, 82%; (viii) Boc_2O, DMAP, CH_2Cl_2, 81%; (ix) TBDMSCl, imidazole, DMF, 98%; (x) $LiAlH_4$, THF, −78 °C, 79%; (xi) Ph_3P, CCl_4, CH_2Cl_2, 98%; (xii) *n*-Bu_4NF, $CHCl_3$, 100%.

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(8) New compounds are characterized at least by ^1H and ^{13}C NMR, EI or FAB mass spectra, and combustion analysis or HRMS.

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This work describes the use of the photocyclization of tosyl stilbenoids in the preparation of analogues of the alkylating unit of the antitumor compound CC-1065. This reaction may find use in the preparation of analogues of CC-1065 and other complex heterocyclic compounds.

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Supporting Information Available: Characterization data and experimental procedures for preparation of analogue **2** (Scheme 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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