

Studies on the Synthesis of the Antitumour Agent CC-1065. Synthesis of PDE I and PDE II, Inhibitors of Cyclic Adenosine-3', 5'-monophosphate Phosphodiesterase

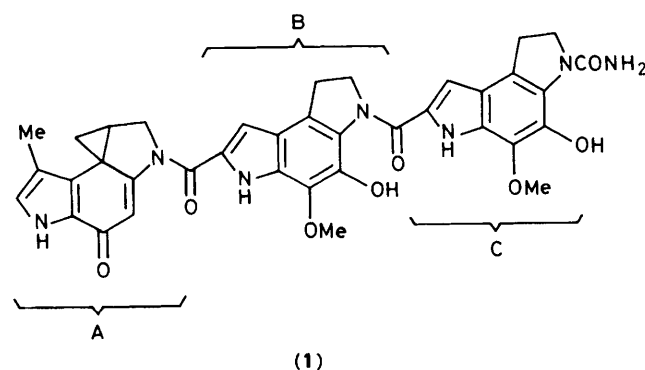
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The 3,3'-bipyrrole approach to the synthesis of highly functionalized indoles has been used to construct the B and C components of CC-1065 in the form of PDE I (**2**) and PDE II (**3**) respectively.

The separated constituents of the B and C components of the potent antitumour agent CC-1065 (**1**) are natural products in their own right, known as PDE I (**2**) (R = CONH₂) and PDE II (**3**) (R = Ac).¹ They are inhibitors of cyclic adenosine-3',5'-monophosphate phosphodiesterase, and their structures have been confirmed by a classical total synthesis.²

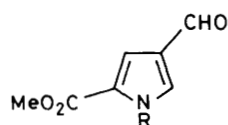
As part of our studies on the synthesis of CC-1065 (**1**), we



have developed a route to 3,3'-bipyrroles, which has been successfully applied to the construction of the cyclopropa-pyrroloindole A portion.³ Here we report the adaptation of this strategy for the synthesis of the separate B and C portions, in the form of the natural products PDE I and PDE II.⁴

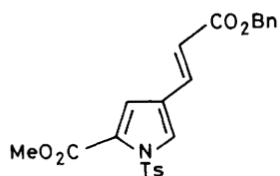
N-Tosylation of methyl 4-formylpyrrole-2-carboxylate (**4**)⁵ gave (**5**) (50%), thus providing the necessary activation of the 4-formyl group for the subsequent addition processes. Treatment of (**5**) with (EtO)₂P(O)CH₂CO₂Bn-NaH-THF (Bn = benzyl, THF = tetrahydrofuran) gave the (*E*)-α,β-unsaturated ester (**6**) (80%), which on exposure to TOSMIC⁶-LiHMDS-THF (TOSMIC = tosylmethyl isocyanide, HMDS = hexamethyldisilazane) at -78 °C provided the crucial 3,3'-bipyrrole (**7**) (30%).[†] Both pyrrole systems in (**7**) are deactivated towards electrophilic substitution, but the A-ring by virtue of the *N*-Ts (Ts = tosyl) group is more so.

[†] The structures of all new compounds were confirmed by elemental analyses and spectroscopic data. (**7**): m.p. 152–154 °C (from EtOAc); i.r. (Nujol) 3480, 1720, 1687, 1455 cm⁻¹; n.m.r. (90 MHz, CDCl₃) δ 8.93 (1H, br s), 8.13 (1H, d, *J* 2 Hz), 7.90, 7.80 (2H, d, *J* 8 Hz), 7.60–7.13 (9H, m), 6.80 (1H, t, *J* 2 Hz), 5.23 (2H, s), 3.77 (3H, s), 2.77 (3H, s). (**11**): m.p. 152–153 °C (decomp.); i.r. (Nujol) 3400–2600, 1710, 1460, 1150 cm⁻¹; n.m.r. (360 MHz, CDCl₃) δ 10.63 (1H, br s), 8.75 (1H, br s), 8.42 (1H, s), 7.88 (1H, d, *J* 3 Hz), 7.68, 7.64 (2H, d, *J* 8 Hz), 7.5–7.3 (5H, m), 7.16, 7.14 (2H, d, *J* 8 Hz), 5.37 (2H, s), 4.32 (4H, m), 3.98 (3H, s), 2.34 (3H, s), 1.36 (6H, t, *J* 8 Hz). Satisfactory N analysis or high resolution mass spectrometric data could not be obtained. (**17**): m.p. 118–119 °C (from acetone-hexane); i.r. (Nujol) 3365, 3220, 1710, 1460, 1255 cm⁻¹; u.v. (MeOH) 208, 247, 316 nm (ε, 22200, 11400, and 17400 dm³ mol⁻¹ cm⁻¹ respectively); n.m.r. (90 MHz, CDCl₃) δ 10.13 (1H, br s), 9.33 (1H, br s), 7.40 (1H, d, *J* 2 Hz), 7.20 (1H, t, *J* 3 Hz), 6.70 (1H, t, *J* 3 Hz), 4.23 (4H, q, *J* 8 Hz), 4.00 (3H, s), 3.97 (3H, s), 1.27 (6H, t, *J* 8 Hz).

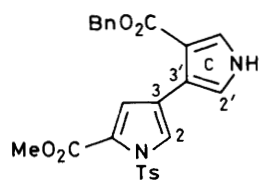


(4) R = H

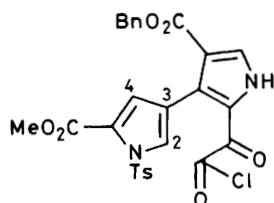
(5) R = Ts



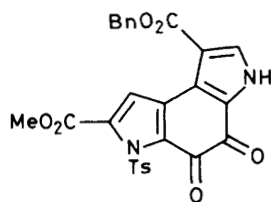
(6)



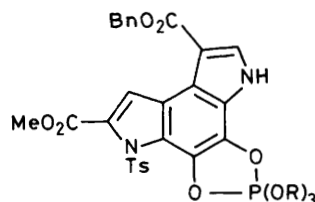
(7)



(8)



(9)



(10)

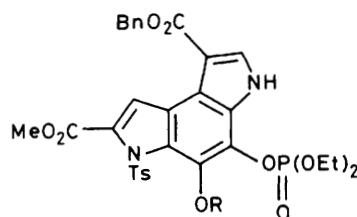
Bn = benzyl
Ts = tosyl

Consequently, initial electrophilic substitution of (7) should take place in the c-ring at the 2'-position. In the event, treatment of (7) with oxalyl chloride-CH₂Cl₂ at 0°C cleanly gave (8) [in the series where the Me and Bn esters are transposed, (8) was isolated as its derived Me ester]; further exposure of (8) to SnCl₄-CH₂Cl₂ at -78°C accomplished closure into the 2-position to provide the *o*-quinone (9) (72%). It is essential that the first electrophilic substitution is conducted without Lewis acid catalysis.⁷

In principle, the two quinoid oxygen atoms are chemically distinguishable because they are in vastly different steric environments. Reduction of (9) with triethylphosphite-CH₂Cl₂,⁸ followed immediately by aqueous hydrolysis of the cyclic oxyphosphorane (10) (R = Et), gave a single phenolic phosphate ester (11) (83%). The adduct (10) (R = Pr) is a reasonably stable compound.

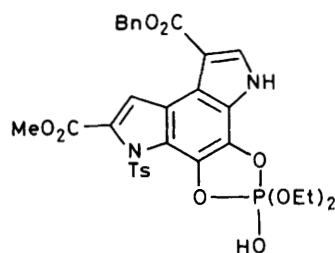
While the regioisomer depicted (11), is the least sterically encumbered adduct compared with (12), the phenolic hydroxy group is correspondingly the more hindered, especially towards methylation. In fact, treatment of (11) with a variety of *O*-methylating agents, including the adduct between P(OMe)₃ and methyl vinyl ketone (used successfully in a model series),⁴ gave the wrong regioisomer (14) as the major product. Presumably, equilibration of (11) via (11a) to (12) takes place, and the more exposed hydroxy group is more rapidly methylated. A solution to this problem was discovered when it was found that treatment of (11) in CH₂Cl₂ at -78°C with CH₂N₂ (for 48 h) gave the correct regioisomer (13) (50%) after crystallization from the crude reaction mixture, along with (14) (3:1 ratio). Removal of the *N*-Ts group with Al-Hg amalgam-THF gave (15) (90%), which was hydrogenolysed to give the carboxylic acid (16) (90%). Decarboxylation of (16) was best accomplished by heating in anisole at 130°C in the presence of Cu powder (8 equiv.) and Pr₂NEt (150 equiv.)-dimethylformamide (cat.) to give (17) (50–60%).

The crucial selective reduction of the indole-2,3-double

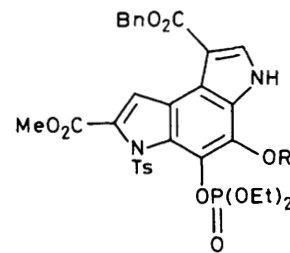


(11) R = H

(13) R = Me

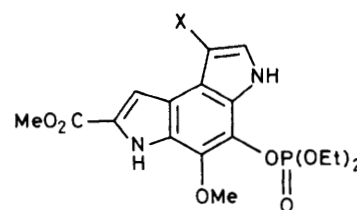


(11a)

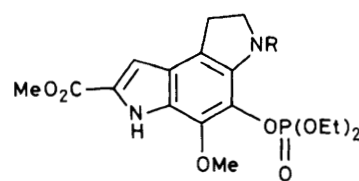


(12) R = H

(14) R = Me

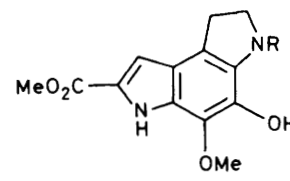
(15) X = CO₂Bn(16) X = CO₂H

(17) X = H



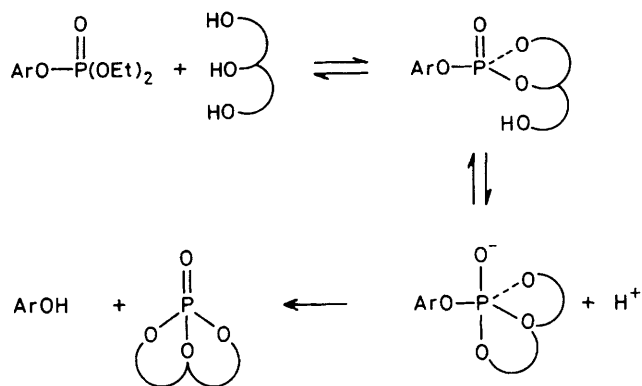
(18) R = H

(19) R = Ac

(20) R = CONH₂

(21) R = Ac

(22) R = CONH₂



Scheme 1

bond in (17)[†] was carried out using Et₃SiH-trifluoroacetic acid-CH₂Cl₂ at 0–20°C to give the dihydro-derivative (18), which was directly treated with Ac₂O providing (19) [60% overall from (17)]. Standard methods for the hydrolysis of phenolic phosphate esters did not give any of the required phenol (21), only extensive decomposition to intractable material. Since it is well known that the alkoxy substituents in phosphate esters are readily exchanged by alcoholysis,⁹ we reasoned that treatment of a dialkoxyposphate with a triol would result in exchange, followed by intramolecular attack of the third hydroxy group on phosphorus, to give a pentacoordinate species that can readily expel the phenolate leaving group, Scheme 1.

When (19) was treated with KOH-MeOH-MeC(CH₂OH)₃ the required phenol (21) (80%) was produced. If the triol MeC(CH₂OH)₃ is omitted, (21) is not formed. Finally, base hydrolysis (KOH-aq. EtOH) of (21) gave PDE II (3) (60%). Treatment of (18) with NaOCN-AcOH gave (20) [56% from (17)], which was converted into (22) (68%) by exposure to MeC(CH₂OH)₃-KOH-MeOH; and lastly, base hydrolysis of (22) using 0.01 M KOH in water gave PDE I (2) (75%).

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