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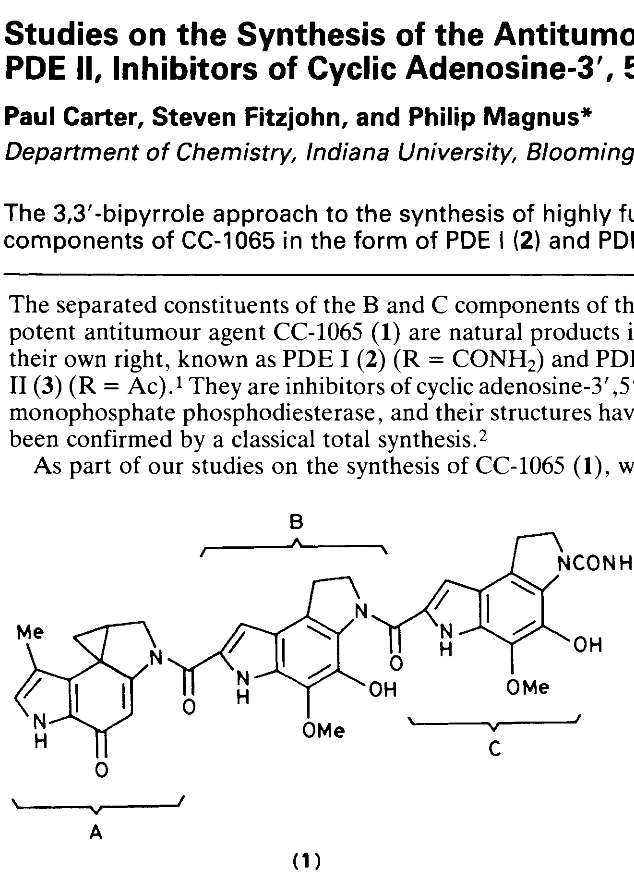
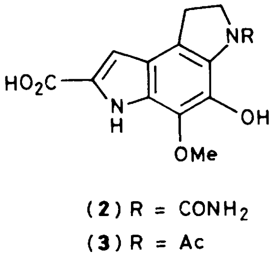
The 3,3′-bipyrrole approach to the synthesis of highly functionalized indoles has been used to construct the B and C components of CC-1065 in the form of PDE I (**2**) and PDE II (**3**) respectively.

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 = $CONH_2$) 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 cyclopropapyrroloindole 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]



(1)



(**2**) R = $CONH_2$
(**3**) R = Ac

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 $(EtO)_2P(O)CH_2CO_2Bn$–NaH–THF (Bn = benzyl, THF = tetrahydrofuran) gave the (*E*)-α,β-unsaturated ester (**6**) (80%), which on exposure to TOSMIC[6]–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.

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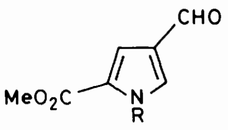
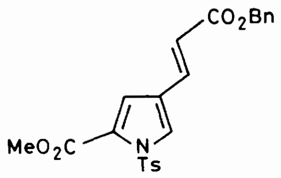
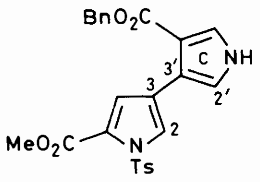
† The structures of all new compounds were confirmed by elemental analyses and spectroscopic data. (**7**): m.p. 152—154 °C (from EtOAc); i.r. (Nujol) 3480, 1720, 1687, 1455 cm^{-1}; n.m.r. (90 MHz, $CDCl_3$) δ 8.93 (1H, br s), 8.13 (1H, d, *J* 2 Hz), 7.90, 7.80 (2H, d, *J* 8 Hz), 7.60—7.13 (9H, m), 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, $CDCl_3$) 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 $dm^3\ mol^{-1}\ cm^{-1}$ respectively); n.m.r. (90 MHz, $CDCl_3$) 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).



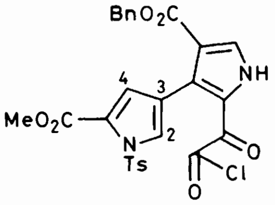
(4) R = H
(5) R = Ts



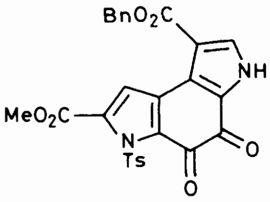
(6)



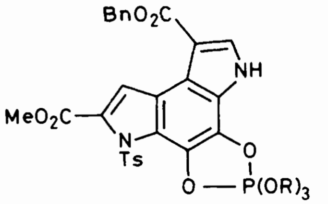
(7)



(8)



(9)



(10)

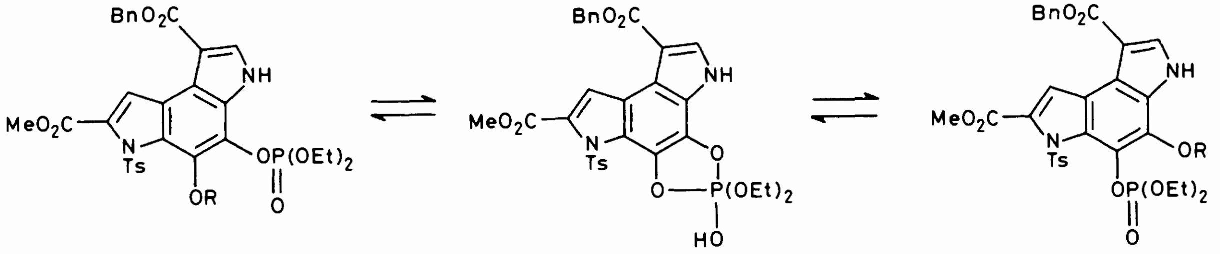
Bn = benzyl
Ts = tosyl

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–CH_2Cl_2 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 $SnCl_4$–CH_2Cl_2 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–CH_2Cl_2,[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^i) 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 CH_2Cl_2 at −78 °C with CH_2N_2 (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 Pr^i_2NEt (150 equiv.)–dimethylformamide (cat.) to give (**17**) (50—60%).

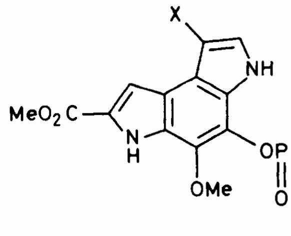
The crucial selective reduction of the indole-2,3-double



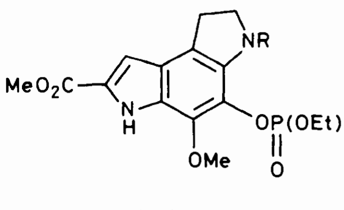
(11) R = H
(13) R = Me

(11a)

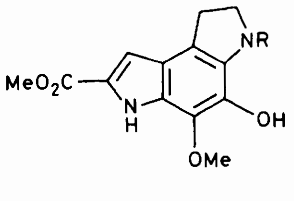
(12) R = H
(14) R = Me



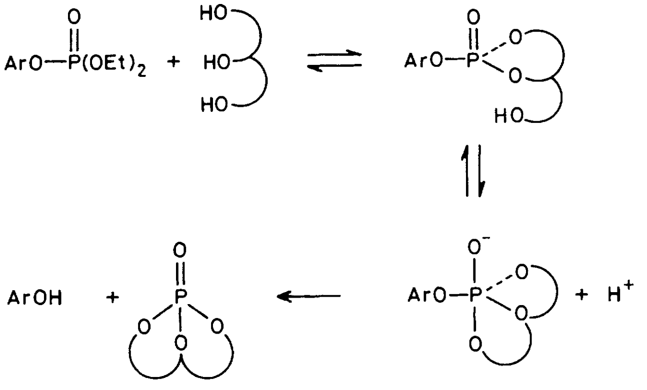
(15) X = CO_2Bn
(16) X = CO_2H
(17) X = H



(18) R = H
(19) R = Ac
(20) R = $CONH_2$



(21) R = Ac
(22) R = $CONH_2$



Scheme 1

bond in (**17**)† was carried out using Et_3SiH-trifluoroacetic acid–CH_2Cl_2 at 0—20 °C to give the dihydro-derivative (**18**), which was directly treated with Ac_2O 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 dialkoxyphosphate 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–$MeC(CH_2OH)_3$ the required phenol (**21**) (80%) was produced. If the triol $MeC(CH_2OH)_3$ 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 $MeC(CH_2OH)_3$–KOH–MeOH; and lastly, base hydrolysis of (**22**) using 0.01 M KOH in water gave PDE I (**2**) (75%).

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