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SYNTHESIS OF CARBOCYCLIC CLITOCINE

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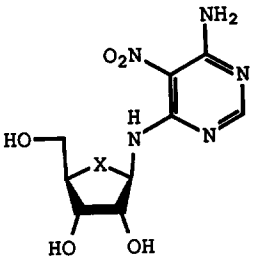
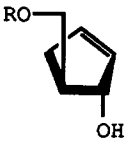
Abstract: Cyclopentadiene has been converted into carbocyclic clitocine (2) in eleven steps.

The nucleoside clitocine (1) was isolated by Kubo *et al.*[1] and shown to have strong insecticidal activity against the pink bollworm *Pectinophora gossypiella*. A synthesis of this unusual natural product has been reported[2] and the compound has been shown to be an inhibitor of the enzyme adenosine kinase.[3]



(1) X = O

(2) X = CH_2



(3) R = H

(4) R = $SiPh_2{}^tBu$

It is firmly established in some areas of medicinal chemistry that carbocyclic nucleosides can mimic, to a greater or less extent, the biological activity of the corresponding (deoxy)ribofuranose.[4] With this fact in mind it was of interest to prepare carbocyclic clitocine (2).

A Prins reaction on cyclopentadiene produces, as one of the major components, the diol (3),[5] a compound which was protected as the *tert*-butyldiphenylsilyl derivative (4).[6]

Treatment of the alkene (4) with *meta*-chloroperoxybenzoic acid gave the epoxide (5) in 56% yield (Scheme).[7] Physical data for the epoxide (5) were as follows:- δ ($CDCl_3$) 7.7-7.4 (10H, m, Ar), 4.18 (1H, dd, J 7, 6.5 Hz, H-2), 3.82 and 3.66 (2H, 2 x dd, J 10, 6 Hz, $-CH_2O$), 3.54 (1H, dd, J 3, 2 Hz, H-5), 3.46 (1H, d, J 3 Hz, H-1), 2.15 (2H, m, H-4 and OH), 1.82 (1H, m, H-3),

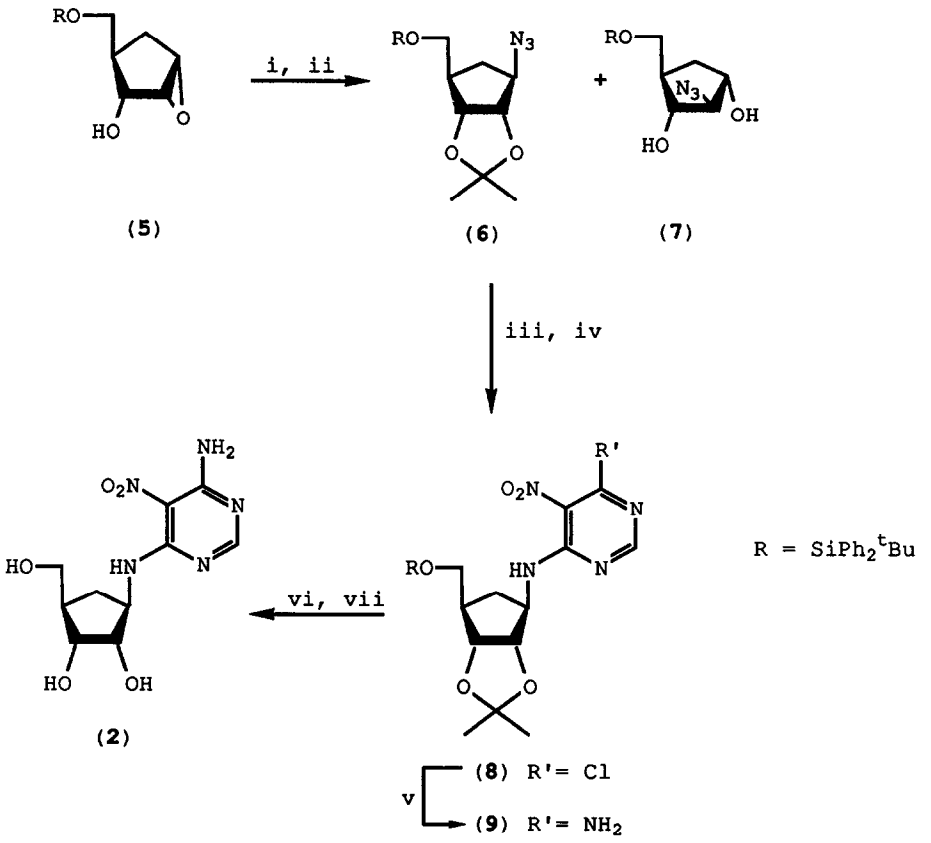
1.58 (1H, ddd, J 14, 10, 2 Hz, H-4): ν_{max} 3446 br, 1250: found $[M + H]^+$ 369.1886, $C_{22}H_{28}O_3Si$ requires M + H 369.1886. Opening of the epoxide ring in compound (5) with azide ion occurred in a highly regioselective manner: treatment of the crude product with 2,2-dimethoxypropane in the presence of acid gave the acetonide (6) (50%) which was readily separated from a small amount of the diol (7) by chromatography. Reduction of the azido group and reaction of the resultant amine with 4,6-dichloro-5-nitropyrimidine gave the required compound (8) (54% yield from (6)). Treatment of the chloro-compound (8) with methanolic ammonia gave the aminopyrimidine (9) (86%). The latter compound was deprotected in stepwise fashion to provide the target compound (2) in 81% yield. The structure of compound (2) was confirmed by physical methods. δ (DMSO-d_6) 9.3 (1H, d, NH), 8.5 (2H, s, NH_2), 8.0 (1H, s, H-2), 4.7 (2H, s br, 2 x OH), 4.42 (1H, ddd, J 6.5 Hz, H-1'), 3.41 (2H, d, J 8 Hz, CH_2O), 3.75 (2H, m, H-2' and H-3'), 2.24 (1H, ddd, J 13.5, 7 Hz, H-5'), 1.96 (1H, m, H-4'), 1.18 (1H, m, H-5'): ν_{max} 3311, 1595 and 1375 cm^{-1}: found $[M + H]^+$ 286.1161, $C_{10}H_{15}O_5N_5$ requires M + H 286.1151.

The experimental detail of one of the key reactions, namely the conversion of the epoxide (5) into the azide (6) is detailed below:

Preparation of the Azide (6):

A solution of the epoxide (5) (206.6 mg, 0.56 mmol), sodium azide (172.4 mg, 2.65 mmol, 5 eq) and ammonium chloride (173.7 mg, 3.25 mmol, 6 eq) in dry dimethylformamide (5 ml) was stirred at 100 °C under an argon atmosphere for four days. The solution was partitioned between ethyl acetate (50 ml) and saturated ammonium chloride (10 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 25 ml). The combined organic layers were washed with brine (2 x 5 ml) and dried over $MgSO_4$. The solution was concentrated under reduced pressure and partially purified by passing through a short silica column (3:1 petroleum ether 60/80 ethyl acetate). To the crude residue was added *para*-toluenesulphonic acid (5 mg) and 2,2-dimethoxypropane (5 ml) and the solution stirred at room temperature under argon for 24 hrs. Sodium bicarbonate was added, the solution filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluant, 13:1 petrol/ethyl acetate) to give the azide (6) (125 mg, 50%) and the 1,3-diol (7) 9.9 mg (4.3%). The physical characteristics of compound (6) were as follows:- δ ($CDCl_3$) 7.7-7.4 (10H, m, Ar), 4.48 (1H, dd, J 6, 2.5 Hz, H-3), 4.34 (1H, dd, J 6, 3 Hz, H-2), 3.93 (1H, ddd, J 6, 3.3 Hz, H-1), 3.68 (2H, m, CH_2O), 2.38 (1H, m, H-4), 1.75 (1H, m, H-5), 1.48 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.10, (9H, s, $(CH_3)_3C$): ν_{max} 2108, 1633, 1580 cm^{-1}.

The above sequence represents an efficient preparation of clitocine clitocine [12% overall yield from the epoxide (5)]. The biological properties of this molecule will be detailed elsewhere.



Scheme

Reagents (i) NaN_3, NH_4Cl, DMF, 100 °F, 4 days; (ii) 2,2-Dimethoxy propane, *p*-toluenesulphonic acid, r.t. 18h; (iii) H_2, MeOH Lindlar cat.; (iv) 4,6-dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2; (v) NH_3, MeOH, r.t. 18h; (vi) tetrabutylammonium fluoride/THF; (vii) H^+.

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