A SIMPLE AND STEREOSPECIFIC SYNTHESIS OF DITERPENE ALKALOID INTERMEDIATE

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Thermolysis of 1-cyano-5-methoxy-1-(4-methoxycarbonyl-4-vinylpentyl)benzocyclobutene (7) gave (±)-4aα-cyano-6-methoxy-1α-methoxycarbonyl-1β-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (9), which on reduction afforded (±)-16,17-imino-16-oxo-12-methoxypodocarpane-8,11,13-triene (10).

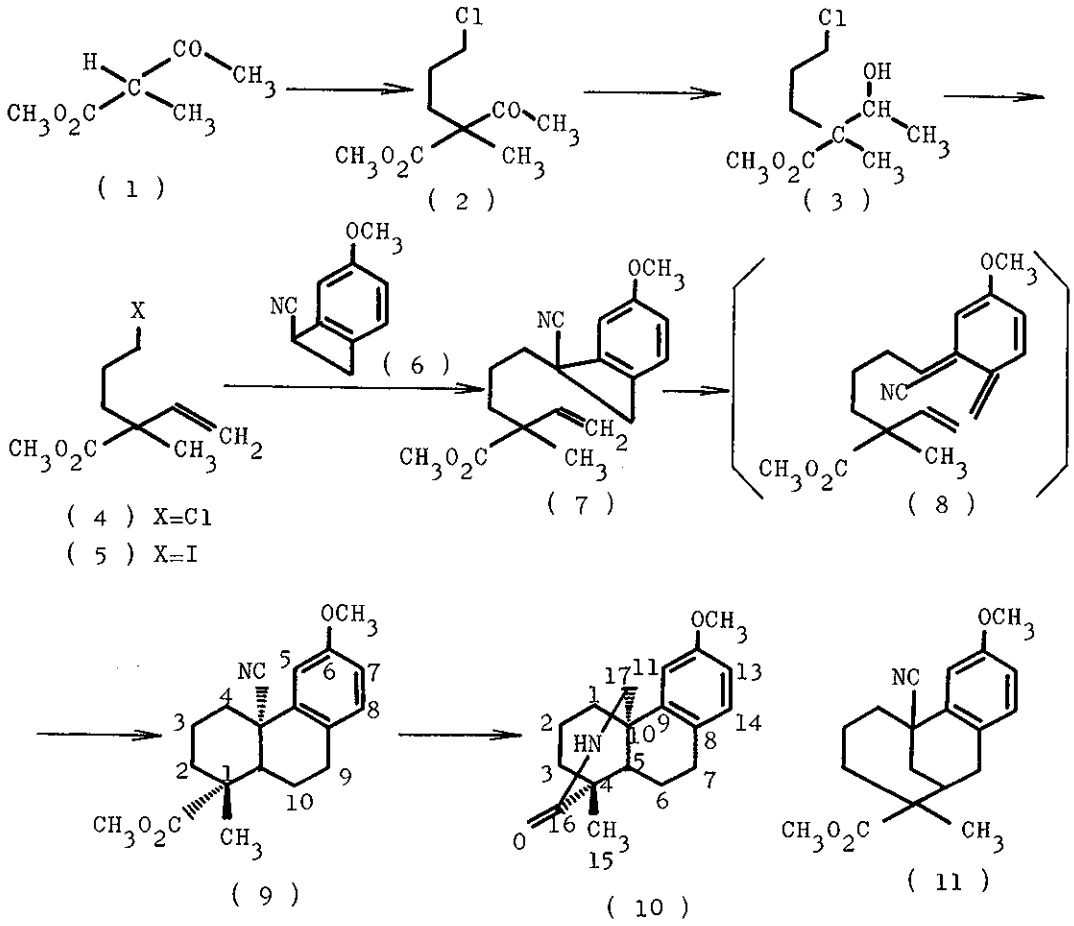
The synthetic challenge of diterpenes[1] and diterpene alkaloids has attracted much attention of many workers.[1-3] A crucial step in a synthesis of these natural products is the introduction of a functionalised carbon unit at C-10 angular position in combination with C-4 substituents under an appropriate stereochemical control in the hydrophenanthrene ring.

We have been investigating a simple synthesis of natural products by a cycloaddition and an electrocyclic reaction of the cyanated o-quinodimethane to imines and olefins,[4] and here wish to report an unusually simple and stereospecific synthesis of the 16,17-imino-

16-oxopodocarpane-8,11,13-triene (9) by an electrocyclic reaction of the o-quinodimethane (8).

Alkylation of methyl methylacetoacetate (1) with 1-bromo-3-chloropropane in the presence of sodium hydride in dimethylformamide gave, in 80 - 90 % yield, the chloropropyl derivative (2), b.p. 90° (3 mmHg), δ (CCl_4) 3.47 (2H, t, J 7.5 Hz, $CH_2\underline{CH_2}Cl$), which was reduced with sodium borohydride, followed by a dehydration of the resulting alcohol (3) [δ (CCl_4) 1.1 (3H, d, J 4.5 Hz, $-CH\underline{CH_3}$)] on phosphorus pentoxide and celite, afforded, in 60 % yield, the olefin (4), b.p. 100 - 103° (1 mmHg) [δ (CCl_4) 5.07 (1H, dd, J 2 and 16 Hz, $\underline{H}>C=C<_H$), 5.12 (1H, dd, J 2 and 11 Hz, $\underline{H}>C=C<_H$) and 5.98 (1H, dd, J 11 and 16 Hz, $C\underline{H}=CH_2$)]. Treatment of this product with sodium iodide in boiling ethyl methyl ketone furnished the iodide (5), which without purification was condensed with 1-cyano-5-methoxybenzocyclobutene (6)[5] in the presence of sodium amide in liquid ammonia to give in 75 % yield the 1-cyano-1-(4-vinylpentyl)benzocyclobutene (7) as an oil [ν max ($CHCl_3$) 2236 and 1720 cm^{-1}; δ ($CDCl_3$) 3.08 (1H, d, J 14 Hz, ArC$\underline{H}$H) and 3.58 (1H, d, J 14 Hz, ArCH$\underline{H}$)]. Heating the benzocyclobutene (7) in dry toluene in a sealed tube at 180 - 230° afforded 4aα-cyano-6-methoxy-1α-methoxycarbonyl-1β-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (9), m.p. 138 - 139°, in 40 - 50 % yield, in a regiospecific and stereospecific manner, which showed cyano and ester groups at 2235 and 1720 cm^{-1}, respectively, in the ir spectrum. The nmr spectrum lacked the resonances of cyclobutene and olefinic protons and revealed three methyl groups at 1.20, 3.69, and 3.76 as each singlet. In this stage, the stereochemistry could not be determined but was evidenced

Scheme 1

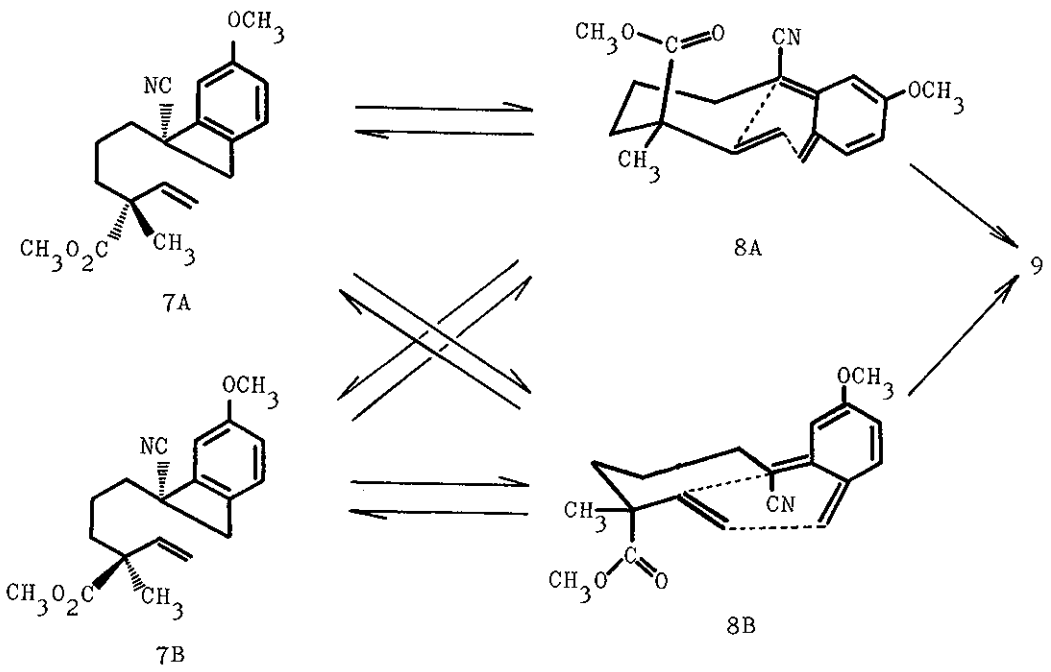


by a hydrogenation of this product to the lactam (10). Thus, catalytic hydrogenation of this product (9) was carried out on Raney nickel in ethanol under 115 atm of hydrogen at 80° to afford the lactam (10), m.p. 259 - 260° [ν max ($CHCl_3$) 3410 and 1645 cm^{-1}, δ ($CDCl_3$) 1.27 (3H, s, C-CH_3), 2.76 (2H, t, J 4 Hz, ArCH_2), 3.36 (1H, d, J 11 Hz, C_{17}-H), 3.73 (3H, s, OCH_3), 3.77 (1H, d, J 11 Hz, C_{17}-H), 6.53 (1H, d, J 2 Hz, C_{11}-H), 6.63 (1H, dd, J 2 and 8 Hz, C_{13}-H), and 6.98 (1H, d, J 8 Hz, C_{14}-H)] in quantitative yield, whose fact revealed a relative configuration between cyano group and ester group to be cis and also ruled out another possible structure (11) in a thermolysis of 7, because the compound (11) could not form a lactam from a stereochemical point of view.

The stereospecific conversion of the benzocyclobutene derivative (7) into the hydrophenanthrene (9) could be explained as shown in Scheme 2. The structure of 1-cyanobenzocyclobutene (7) would be possible as 7A and 7B, which on thermolysis forms the o-quinodimethane (8) by an electrocyclic reaction of the cyclobutene ring.[6] Since 7A and 7B are thermally equilibrated through 8A and 8B by a reversible interconversion between cyclobutene and butadiene, both 7A and 7B would afford the product (9).

Thus, we have accomplished a simple and stereospecific synthesis of 16,17-imino-16-oxo-podocarpane-8,11,13-triene, and the synthesis of the key intermediate in the total synthesis of atisine,[7] veatchine,[8] and gibberellin-A_{15}[9] by Nagata, is now under investigation.

Scheme 2



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Received, 8th December, 1975