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SYNTHESIS OF A DITERPENE ALKALOID INTERMEDIATE FROM BENZOCYCLOBUTENE

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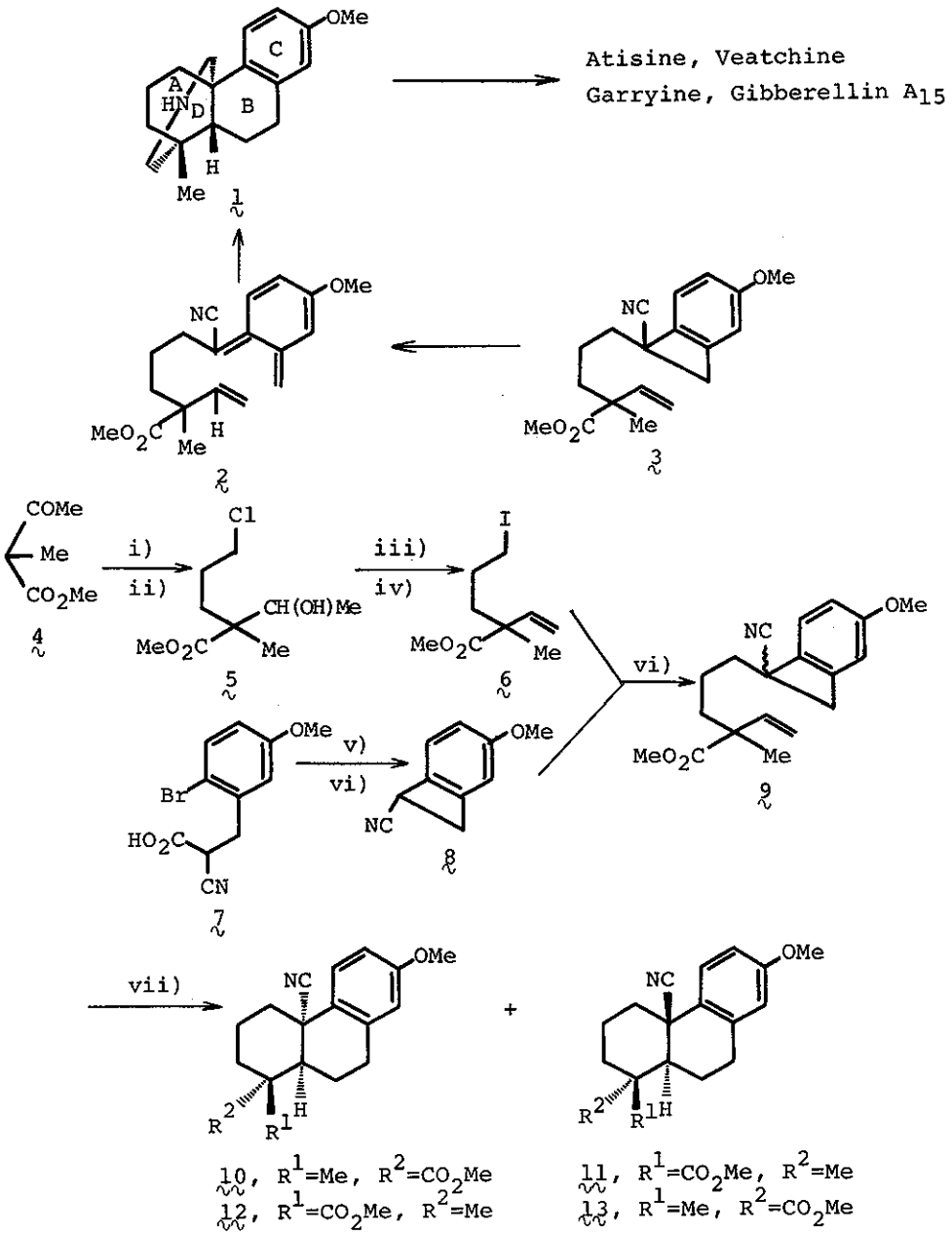
The synthetic challenge of diterpenes[1] and diterpene alkaloids[2,3] has attracted much attension by many investigators. A crucial step in the synthesis of these types of natural products is the introduction of a functionalised carbon unit at the C-4a angular position in combination with C-1 substituents with appropriate stereochemical control in the phenanthrene ring.[4~7] Here we describe a simple and stereocontrolled synthesis of (±)-16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (1),[3,4,6,8] which has already been correlated with atisine[5,7], veatchine,[9] garryine,[10] and gibberellin A_{15},[11] as an extension of our work on a simple total synthesis of the natural products by electrocyclic reaction or cycloaddition of o-quinodimethanes.



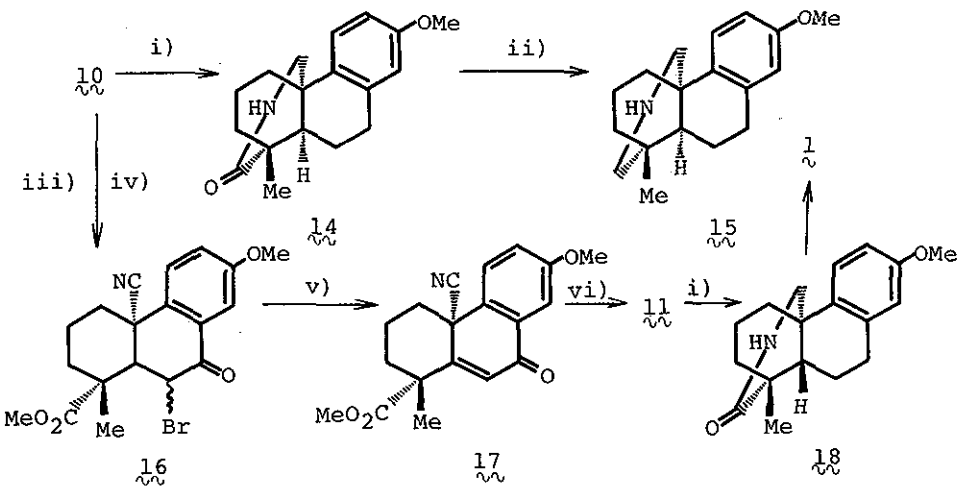
Reagents : i) $Br(CH_2)_3Cl$, NaH, Me_2NCHO ii) $NaBH_4$ iii) P_2O_5, celite iv) NaI, MeCOEt v) DMA, 170~180°C vi) $NaNH_2$, liq.NH_3 vii) 230°, toluene

Our synthesis was designed on the basis of the idea that a hydrophenanthrene derivative which has two functional groups would be most effective for construction of the D ring of 1, and that such an intermediate should be prepared in one step by an intermolecular cycloaddition reaction of an o-quinodimethane derivative. The benzocyclobutene 3 was chosen as a suitable starting material because the cyano and methoxycarbonyl groups are necessary for building up the D ring.

The benzocyclobutene 3 was synthesised as follows. Alkylation of methyl methylacetoacetate (4) with 1-bromo-3-chloropropane gave the chloropropyl derivative, which was reduced with $NaBH_4$ to afford the secondary alcohol 5. Dehydration[12] of 5 formed the olefin which was converted into the iodide 6. This iodide was condensed with 1-cyano-4-methoxybenzocyclobutene (8) to afford the 1-cyano-1-(4-vinylpentyl)benzocyclobutene 9.

Heating the benzocyclobutene 9 at 230°C for 8 h gave a separable stereoisomeric mixture of four octahydrophenanthrenes 10, 11, 12, and 13 in a ratio of 20:2.5:5:1.

Catalytic hydrogenation of the main product 10 followed by reduction of the resultant lactam 14 with $LiAlH_4$ afforded 16,17-imino-13-methoxy-5α,10α-podocarpane-8,11,13-triene (15), an epimer of the expected compound 1. These facts showed the structure of 10 should have the cis A/B ring junction. Oxidation of 10 gave the ketone, which on bromination afforded the α-bromoketone 16. Debromination of 16 using N-phenylbenzamidine gave the α,β-unsaturated ketone 17, which was subjected to catalytic hydrogenation to afford 4aα-cyano-1,2,3,4,4a,9,10,10aβ-octahydro-7-methoxy-1α-



Reagents; i) H_2, Raney Ni ii) $LiAlH_4$ iii) CrO_3, AcOH
iv) Br_2, AcOH v) N-phenylbenzamidine
vi) H_2, 10%Pd-C

methoxycarbonyl-1β-methylphenanthrene (11). This sample was identified with the compound 11 separated from the thermolysis products of the benzocyclobutene 9. High-pressure reduction of 11 under the same conditions as before gave the lactam 18, which was treated with $LiAlH_4$ as before to afford the objective triene 1, identical with the authentic sample[5] provided by Dr. Nagata, to whom we thank. The lactam 18 has been transformed into atisine by Wiesner[7] and the tetracyclic secondary amine 1 was also correlated to atisine[5], garryine[10], veatchine[9], and gibberellin A_{15}.[11] Thus, we have succeeded in synthesis of a key intermediate which has been used in the total synthesis of these materials.

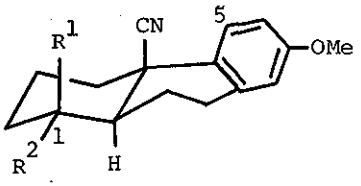
The stereochemistry of four octahydrophenanthrenes 10, 11, 12 and 13 was revealed by the following NMR and chemical studies.

Proton chemical shifts of C-1 methyl and C-5 proton of these hydrophenanthrenes are given in the following Table.

Table Chemical shifts (ppm) of octahydrophenanthrenes

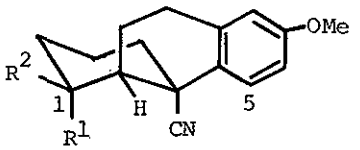
Compound	C_1-CH_3	C_5-H	
10	1.26	7.35	J=8Hz
11	1.35	7.26	J=8Hz
12	1.72	7.36	J=8Hz
13	1.51	7.25	J=8Hz

The resonances at abnormally lower chemical shifts (1.72 and 1.51 ppm) of 12 and 13 than 1.26 and 1.35 ppm of 10 and 11 are recognized as the result of the strong deshielding due to the cyano function[13]. Therefore the compound 12 and 13 should have 1,2-diaxial relationship between C-1 methyl and C-4a cyano functions, that is, the structure should be nonsteroidal form (C) and/or trans form (D). If either of 12 or 13 is the nonsteroidal form (C), the C-5 proton should appear at a lower field by the deshielding effect of C-4a cyano group at peri-position. In fact, the C-5 proton of



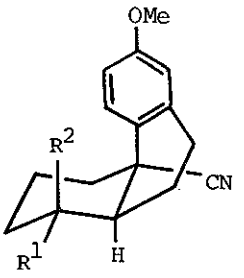
trans

B, R^1=CO_2Me, R^2=Me
D, R^1=Me, R^2=CO_2Me



cis ; nonsteroidal form

A, R^1=CO_2Me, R^2=Me
C, R^1=Me, R^2=CO_2Me



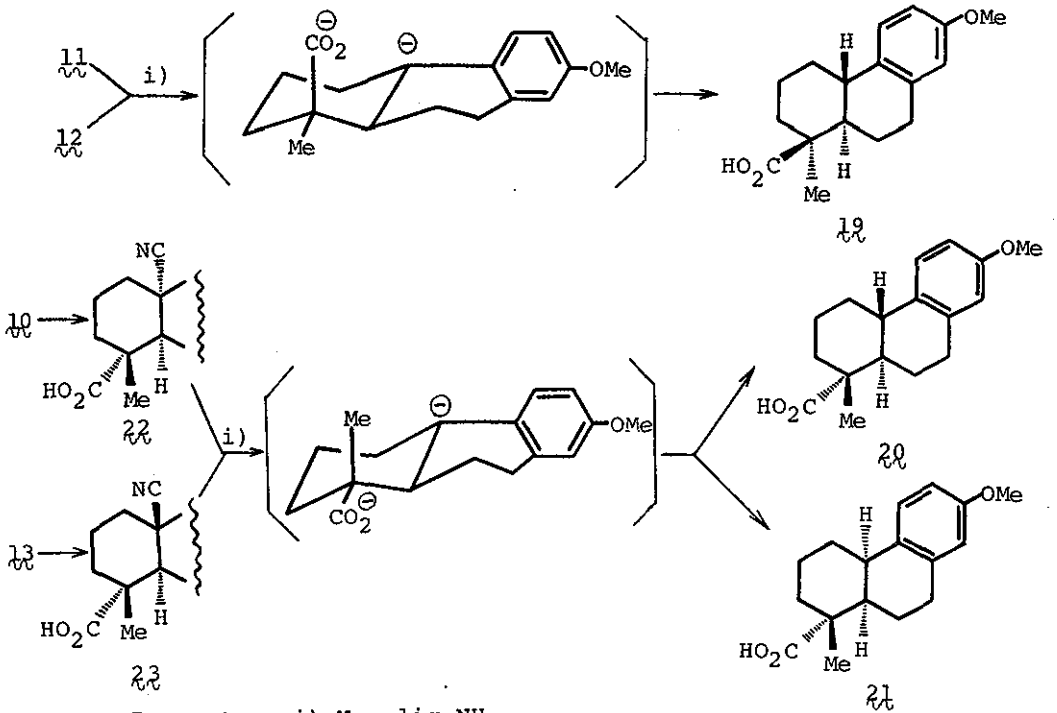
cis ; steroidal form

E

12 was observed at 7.36 ppm, whereas 13 appeared at 7.26 ppm as a normal chemical shift. The same phenomena that the C-5 protons of 10 and 11 appeared at 7.36 and 7.25 ppm, respectively, have been found.

As mentioned above, we have concluded that the structures 10 and 12 were conformers A and C and 11 and 13 were conformers B and D.

A relative configuration between C-4a cyano and C-1 carbomethoxy groups in the compounds 10 and 11 was found to be <u>cis</u> by catalytic hydrogenation of 10 and 11 giving the lactams 14 and 18, respectively as mentioned before. The chemical structure determination of 12 and 13 was carried out by transformations using a decyanation reaction into the known carboxylic acid 19, 20 and 21 which had already been reported by Ghatak.[14]



Reagents : i) Na, liq.NH_3

Decyanation[15] of 11 and 12 by Birch type reduction gave the known acid 19, 1β-carboxy-1,2,3,4,4aβ,9,10,19aα-octahydro-7-methoxy-1α-methylphenanthrene[14]. Also the acids 22 and 23 obtained from 10 and 13 by alkaline hydrolysis were treated under the same conditions as above to afford a separable mixture of two acids, 1α-carboxy-1,2,3,4,4aβ,9,10,10aα-octahydro-7-methoxy-1β-methylphenanthrene (20) and 1α-carboxy-1,2,3,4,4aα,9,10,10aα-octahydro-7-methoxy-1β-methylphenanthrene (21), both of which were also known compound.[14]

Thus we could reveal the structures of octahydrophenanthrenes 10, 11, 12 and 13 to be conformers A, B, C, and D, respectively.[16,17]

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