

SYNTHESIS OF A DITERPENE ALKALOID INTERMEDIATE
FROM BENZOCYCLOBUTENE

Fumio Satoh*

The Sendai Institute of Heterocyclic Chemistry,

Kawauchi Sanjuninmachi, Sendai 980, Japan

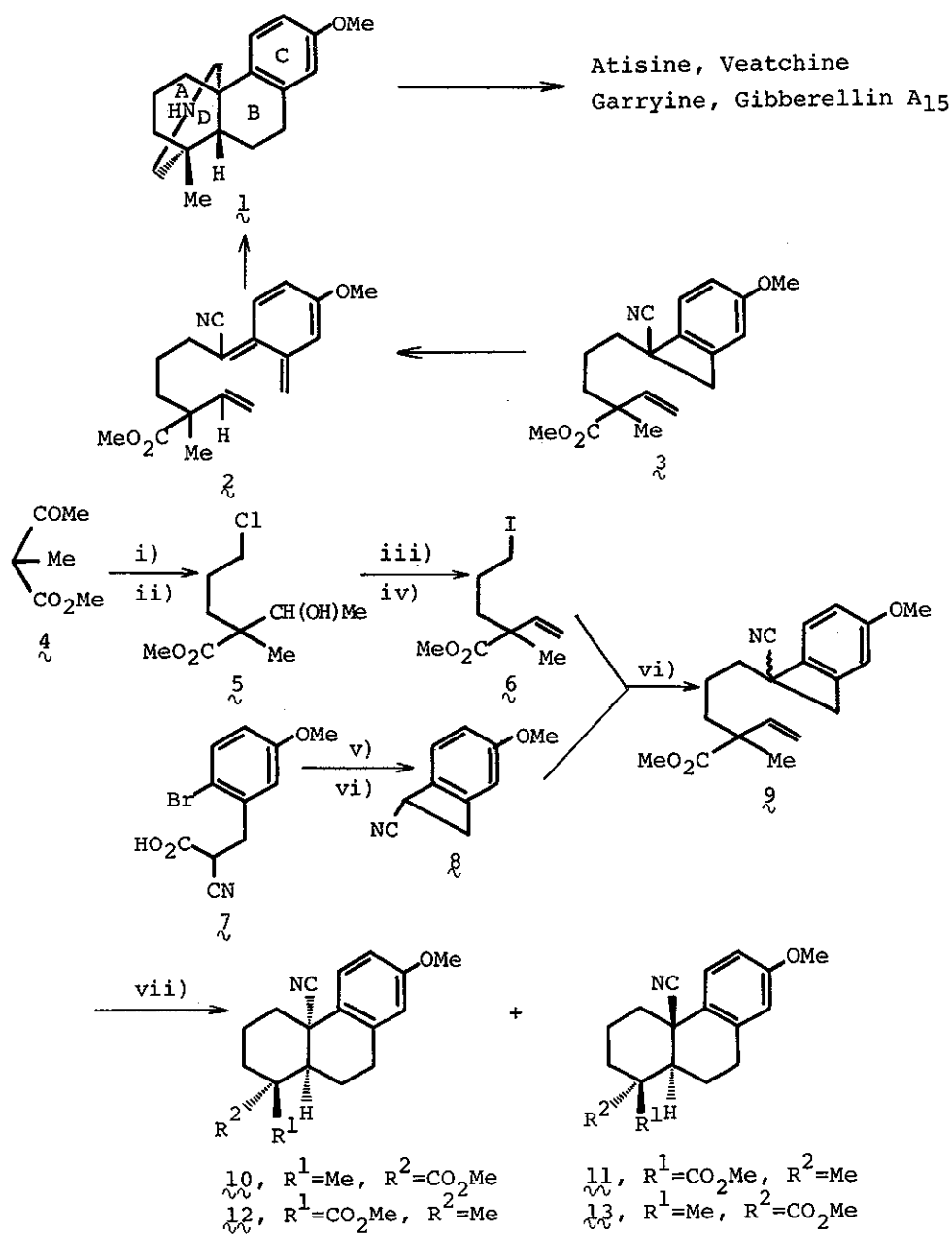
Tetsuji Kametani, Yasuyuki Kato, Toshio Honda,

and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University,

Aobayama, Sendai 980, Japan

The synthetic challenge of diterpenes¹ and diterpene alkaloids^{2,3} has attracted much attention 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-5 β ,10 α -podocarpene-8,11,13-triene (1),^{3,4,6,8} which has already been correlated with atisine^{5,7}, veatchine,⁹ garryine,¹⁰ and gibberellin A₁₅,¹¹ as an extension of our work on a simple total synthesis of the natural products by electrocyclic reaction or cycloaddition of o-quinodimethanes.

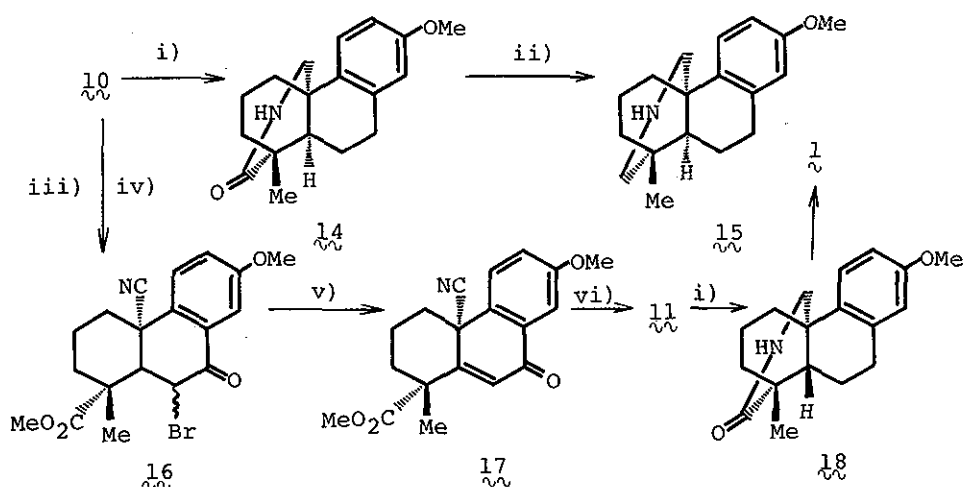


Our synthesis was designed on the basis of the idea that a hydrophenanthrene derivative which has two functional groups would be most effective for construction of the D ring of **1**, and that such an intermediate should be prepared in one step by an intermolecular cycloaddition reaction of an *o*-quinodimethane 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 NaBH₄ to afford the secondary alcohol **5**. Dehydration¹² 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 LiAlH₄ afforded 16,17-imino-13-methoxy-5 α ,10 α -podocarpene-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 4 α -cyano-1,2,3,4,4 α ,9,10,10 $\alpha\beta$ -octahydro-7-methoxy-1 α -



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-18-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 sample⁵ provided by Dr. Nagata, to whom we thank. The lactam 18 has been transformed into atisine by Wiesner⁷ and the tetracyclic secondary amine 1 was also correlated to atisine⁵, garryine¹⁰, veatchine⁹, and gibberellin A₁₅.¹¹ Thus, we have succeeded in synthesis of a key intermediate which has been used in the total synthesis of these materials.

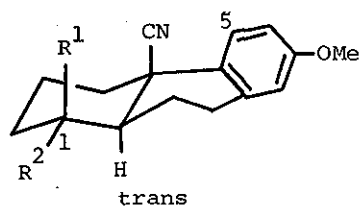
The stereochemistry of four octahydrophenanthrenes 10, 11, 12 and 13 was revealed by the following NMR and chemical studies.

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

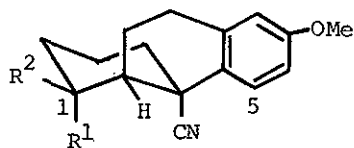
Compound	C ₁ -CH ₃	C ₅ -H
10	1.26	7.35 J=8Hz
11	1.35	7.26 J=8Hz
12	1.72	7.36 J=8Hz
13	1.51	7.25 J=8Hz

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 function¹³. 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



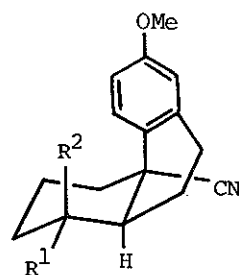
B, R¹=CO₂Me, R²=Me

D, R¹=Me, R²=CO₂Me



A, R¹=CO₂Me, R²=Me

C, R¹=Me, R²=CO₂Me

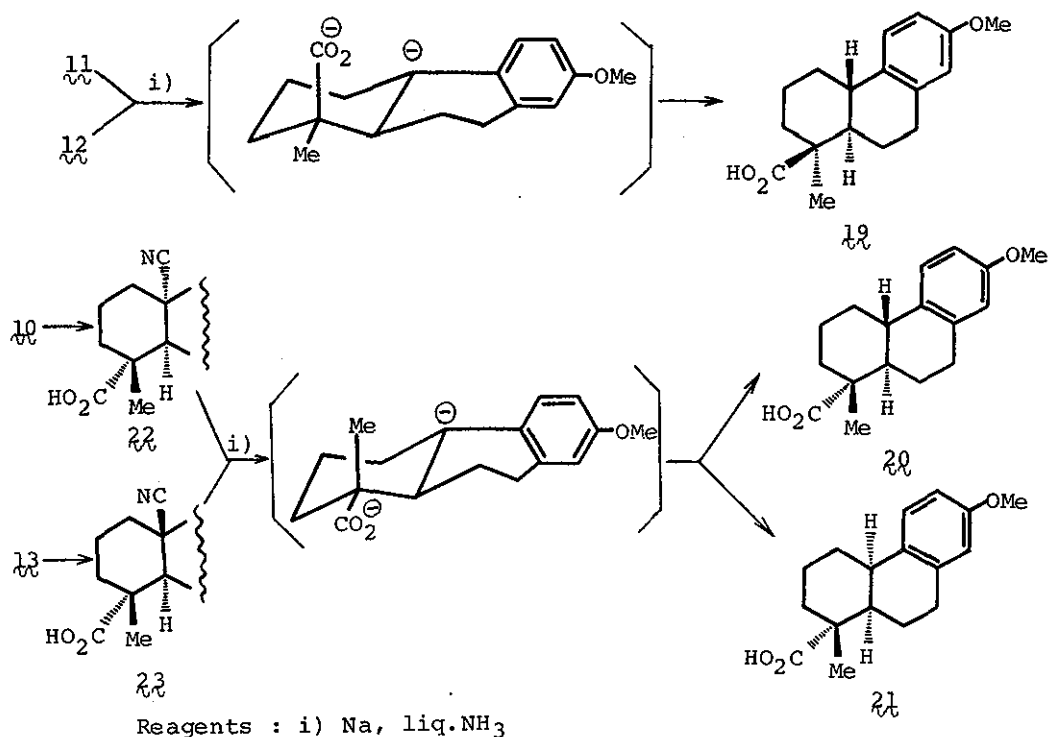


cis ; steroidal form

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

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

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



Decyanation¹⁵ of **11** and **12** by Birch type reduction gave the known acid **19**, 1 β -carboxy-1,2,3,4,4a β ,9,10,19 α -octahydro-7-methoxy-1 α -methylphenanthrene¹⁴. 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, 1 α -carboxy-1,2,3,4,4a β ,9,10,10 α -octahydro-7-methoxy-1 β -methylphenanthrene (**20**) and 1 α -carboxy-1,2,3,4,4a α ,9,10,10 α -octahydro-7-methoxy-1 β -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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