# Stereoselective Synthesis of the Basic Skeleton of Aphidicolan-type Diterpenes *via* Intramolecular Diels–Alder Cyclisation. Synthetic Approach to Aphidicoline

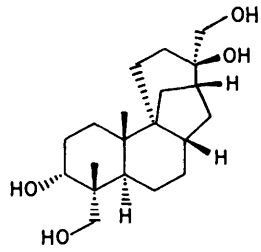
By **Tetsuji Kametani,* Toshio Honda, Yuichi Shiratori, Hiroo Matsumoto,** and **Keiichiro Fukumoto,**
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

The basic tetracyclic skeleton of aphidicolan-type diterpenes has been synthesised by an intramolecular Diels–Alder reaction of 1-(1-cyano-5-methoxy-3-methylbenzocyclobuten-1-yl)hept-6-en-3-one (9). The cyclised product (10) was converted into the tetracyclic compound (11) by treatment with base followed by acid hydrolysis. The stereochemistry of (11) was easily determined from the n.m.r. spectral data, in which one of the aromatic protons was observed to be deshielded by the five-membered ketone moiety. Thus benzocyclobutene thermolysis again proved to be a powerful method for the construction of a complex molecule.

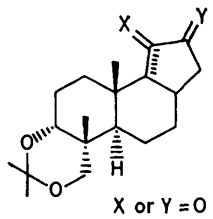
THE structure of aphidicoline (1), isolated from a culture of *Cephalosporium aphidicola* Petch by Hesp,[1] was determined by *X*-ray analysis.[2] Its unique carbon framework, the $C_9$ and $C_{12}$ epimer of the stemodan nucleus, results in aphidicolan being categorized as an 'unusual' diterpene.[3] Since aphidicoline is not only a complex molecule, but also displays very interesting biological activities, there have been a number of attempts at its synthesis.

Recently, three total syntheses of aphidicoline have been reported independently by Trost,[4] McMurry,[5] and Corey.[6] The tricyclic compound (2), the key intermediate in their syntheses, was used to construct the A, B, and D rings of aphidicoline (1).

We designed an alternative synthesis of aphidicoline, in which we planned to use the seven-membered ring of the tricyclic compound (10) as the source of the CD-ring system in (1).

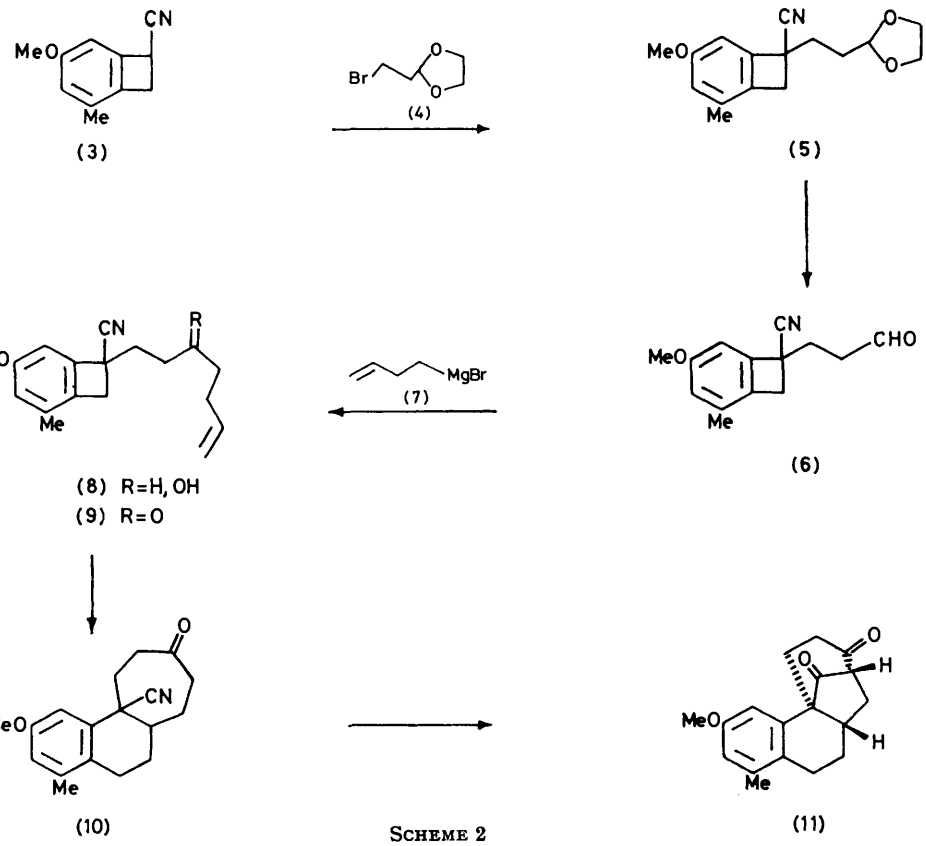



(1)



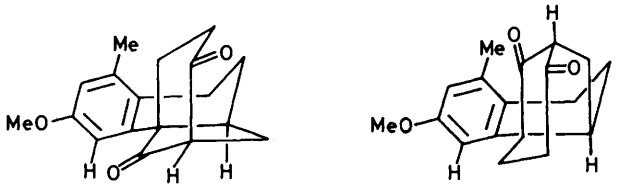

(2)

SCHEME 1




SCHEME 2

Here we report a stereoselective synthesis of the aromatic aphidicolan-type diterpene skeleton (11) with an aromatic A ring, *via* benzocyclobutene thermolysis. The benzocyclobutene (3) [7] was treated with the bromoacetal (4),[8] in the presence of sodium amide in liquid ammonia, to afford the acetal (5), *m/e* 273 ($M^+$), in 73% yield. The latter was converted into the aldehyde (6), *m/e* 229 ($M^+$), by treatment with concentrated hydrochloric acid in tetrahydrofuran. Grignard reaction of this aldehyde with but-3-enylmagnesium bromide in tetrahydrofuran gave the alcohol (8), *m/e* 285 ($M^+$), in 84% yield, which showed no carbonyl absorption in its i.r. spectrum; in its n.m.r. spectrum however it showed resonances for three olefinic protons. The alcohol (8) was oxidised with pyridinium chlorochromate (PCC),[9] in methylene chloride at room temperature, to furnish the ketone (9), *m/e* 283 ($M^+$), in 71% yield. Thermolysis of the benzocyclobutene (9), in *o*-dichlorobenzene at 180 °C for 6 h, afforded the cyclised product (10), *via* an *o*-quinodimethane intermediate, in 55% yield. The i.r. spectrum of this product showed cyano and carbonyl group absorptions at 2 225 and 1 705 $cm^{-1}$ respectively, while the characteristic benzocyclobutene methylene and olefin proton resonances were absent from the n.m.r. spectrum. These spectral data are thus consistent with structure (10). Although difficulties were initially encountered in the conversion of (10) into (11), *e.g.* attempted cyclisation by treatment with lithium diisopropylamide, sodium hydride, and sodium amide in appropriate solvents failed, treatment of (10) with sodium hexamethyldisilazide in benzene, followed by acid hydrolysis, afforded the desired tetracyclic compound (11), *m/e* 284 ($M^+$), the structure of which was determined on the basis of spectral data. Thus, while no cyano-group absorption was found in the i.r. spectrum of (11),




SCHEME 3

absorptions due to carbonyl groups were observed at 1 735 and 1 710 $cm^{-1}$; one low-field aromatic proton resonance at 7.63 p.p.m. was also observed in its n.m.r. spectrum.

From an examination of molecular models it could be seen that the aphidicolan-type stereoisomer (11) can be depicted as in (A) or (B) of Scheme 3.

A perspective drawing of the molecule (A) clearly showed that one aromatic proton is deshielded by a carbonyl group. Thus these results support structure (11). The same deshielding effect has been observed with the A-ring aromatic isodrimenin ring system.[10]

Thus, a stereoselective synthesis of the basic aphidicolan-type diterpene skeleton was achieved *via* the key-step of an intramolecular cycloaddition of an *o*-quinodimethane derived by thermolysis of a benzocyclobutene.

## EXPERIMENTAL

M.p.s were measured with a Yanagimoto microapparatus, i.r. spectra with a Hitachi 260-10 recording spectrophotometer, and mass spectra with a Hitachi M-52G spectrometer. N.m.r. spectra were taken with a JEOL JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference).

*1-(1-Cyano-5-methoxy-3-methylbenzocyclobutenyl)propanal Ethylene Acetal* (5).—To a stirred solution of the benzocyclobutene (3) (5.25 g) and sodium amide (prepared from 776 mg of sodium) in liquid ammonia at −33 °C was added the bromoacetal (4) (8.76 g) during 5 min. After the mixture had been stirred at −33 °C for 2 h, the solvent was removed to give a reddish residue which was treated with an excess of solid ammonium chloride and diluted with saturated aqueous ammonium chloride. The resulting mixture was extracted with ether, and the ethereal layer washed with saturated aqueous sodium chloride and dried ($Na_2SO_4$). Removal of the solvent gave a reddish gum which was purified by column chromatography on silica gel (150 g), using benzene as eluant, to afford the *benzocyclobutene* (5) (5.0 g, 73%) as needles, m.p. 74—76 °C (methanol) (Found: C, 70.0; H, 7.0; N, 4.85. $C_{16}H_{19}NO_3$ requires C, 70.30; H, 7.00; N, 5.15%); $\nu_{max.}$ ($CHCl_3$) 2 225 $cm^{-1}$ (CN); δ($CDCl_3$) 2.17br (4 H, s, $CH_2CH_2$), 2.30 (3 H, s, $ArCH_3$), 3.18 (1 H, d, *J* 14 Hz, ArC*H*), 3.67 (1 H, d, *J* 14 Hz, ArC*H*), 3.88 (3 H, s, $OCH_3$), 3.97—4.07 (4 H, m, $OCH_2CH_2O$), 5.00 (1 H, t, *J* 3 Hz, OCHO), and 6.77br (2 H, s, aromatic protons); *m/e* 273 ($M^+$).

*1-(1-Cyano-5-methoxy-3-methylbenzocyclobutenyl)propanal* (6).—A mixture of the acetal (5) (1 g), 35% hydrochloric acid (10 ml), and tetrahydrofuran (20 ml) was stirred at 0 °C for 15 min. The mixture was basified with saturated aqueous sodium hydrogencarbonate at 0 °C, and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried ($Na_2SO_4$). Evaporation of the solvent gave the aldehyde (6) (772 mg, 92%) as an oil: $\nu_{max.}$ ($CHCl_3$) 2 220 (CN) and 1 720 $cm^{-1}$ (CO); δ($CDCl_3$) 2.20 (3 H, s, $ArCH_3$), 3.17 (1 H, d, *J* 14 Hz, ArC*H*), 3.65 (1 H, d, *J* 14 Hz, ArC*H*), 3.80 (3 H, s, $OCH_3$), 6.70 (1 H, s, ArH), 6.75 (1 H, s, ArH), and 9.93 (1 H, s, CHO); *m/e* 229 ($M^+$).

*1-(1-Cyano-5-methoxy-3-methylbenzocyclobutenyl)hept-6-en-3-ol* (8).—To a stirred solution of but-3-enylmagnesium bromide (7) [prepared from 4-bromobut-1-ene (269 mg) and magnesium turnings (49 mg)] in dry tetrahydrofuran (10 ml) at 0 °C under a stream of nitrogen was added the aldehyde (6) (380 mg) in tetrahydrofuran (3 ml) during 5 min. After being stirred for 1 h at 0 °C, the reaction mixture was quenched by addition of water, and the resulting mixture was extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride and dried ($Na_2SO_4$). Removal of the solvent gave an oil which was chromatographed on silica gel (10 g), using benzene as eluant, to afford the *alcohol* (8) (397 mg, 84%) as needles, m.p. 89—92 °C (ether–n-hexane) (Found: C, 72.1; H, 7.5; N, 4.55. $C_{18}H_{23}NO_2 \cdot 0.75H_2O$ requires C, 72.35; H, 7.85; N, 4.7%), $\nu_{max.}$ ($CHCl_3$) 2 225 $cm^{-1}$ (CN); δ($CDCl_3$) 2.33 (3 H, s, $ArCH_3$), 3.20 (1 H, d, *J* 14 Hz, ArC*H*), 3.70 (1 H, d, *J* 14 Hz, ArC*H*), 3.83 (3 H, s, $OCH_3$),

5.00—5.50 (2 H, m, CH=C$H_2$), 5.66—6.35 (1 H, m, C$H$=C$H_2$), 6.77 (1 H, s, ArH), and 6.80 (1 H, s, ArH) (Found: $M^+$ 285.1734. $C_{18}H_{23}NO_2$ requires $M^+$ 285.1729).

1-(1-*Cyano*-5-*methoxy*-3-*methylbenzocyclobutenyl*)*hept*-6-*en*-3-*one* (9).—To a stirred solution of the alcohol (8) (3.98 g) in dry methylene chloride (20 ml) in the presence of sodium acetate (340 mg) was added pyridinium chlorochromate (4.5 g) in methylene chloride (20 ml). The resulting mixture was stirred for a further 1.5 h at ambient temperature. After addition of ether to the mixture, the ethereal layer was separated and washed successively with water, saturated aqueous sodium hydrogencarbonate, and water, and then dried ($Na_2SO_4$). Removal of the solvent gave a reddish gum which was chromatographed on silica gel (120 g), using benzene as eluant, to afford the *ketone* (9) (2.81 g, 71%) as needles, m.p. 63—64 °C (ether–n-hexane) (Found: C, 74.75; H, 7.4; N, 4.8. $C_{18}H_{21}NO_2 \cdot 0.33H_2O$ requires C, 74.80; H, 7.25; N, 4.65%), $\nu_{max.}$ ($CHCl_3$) 2 235 (CN), and 1 715 $cm^{-1}$ (C=O); $\delta$($CDCl_3$) 2.22 (3 H, s, ArC$H_3$), 3.17 (1 H, d, $J$ 14 Hz, ArC$H$), 3.67 (1 H, d, $J$ 14 Hz, ArC$H$), 3.83 (3 H, s, $OCH_3$), 5.00—5.30 (2 H, m, CH=C$H_2$), 5.68—6.28 (1 H, m, C$H$=$CH_2$), 6.85 (1 H, s, ArH), and 6.91 (1 H, s, ArH) (Found: $M^+$ 283.1612. $C_{18}H_{21}NO_2$ requires $M^+$ 283.1571).

*Thermolysis of the Benzocyclobutene* (9).—A solution of the ketone (9) (1 g) in *o*-dichlorobenzene (50 ml) was refluxed under a nitrogen atmosphere for 6 h. Evaporation of the solvent gave a reddish gum which was chromatographed on silica gel (30 g), using methylene chloride as eluant, to furnish the cyclised *ketone* (10) (550 mg, 55%) as needles, m.p. 79—81 °C (ether–n-hexane) (Found: C, 74.75; H, 7.4; N, 4.8. $C_{18}H_{21}NO_2 \cdot 0.33H_2O$ requires C, 74.4; H, 7.45; N, 4.75%); $\nu_{max.}$ ($CHCl_3$) 2 225 (CN) and 1 705 $cm^{-1}$ (C=O); $\delta$($CDCl_3$) 2.40 (3 H, s, ArC$H_3$), 3.82 (3 H, s, $OCH_3$), 6.80br (1 H, s, ArH), and 6.95 (1 H, d, $J$ 2 Hz, ArH) (Found: $M^+$ 283.1570. $C_{18}H_{21}NO_2$ requires $M^+$ 283.1571).

*Tetracyclic Compound* (11).—A stirred solution of the tricyclic ketone (10) (250 mg) and sodium hexamethyldisilazide [prepared from sodium amide (80 mg) and hexamethyldisilazane (330 mg)] in dry benzene (10 ml) under a nitrogen atmosphere was heated at 60 °C for 4 h. The mixture was then stirred overnight at ambient temperature under a nitrogen atmosphere. After addition of solid ammonium chloride, the solvent was evaporated to give a reddish gum which was treated with 3% hydrochloric acid solution and extracted with methylene chloride. The organic extract was washed with water and dried ($Na_2SO_4$). Evaporation of the solvent afforded a reddish gum which was chromatographed on silica gel (10 g), using methylene chloride as eluant, to give the tetracyclic compound (11) (77.8 mg, 31%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 1 735 (CO) and 1 710 $cm^{-1}$ (CO); $\delta$($CDCl_3$) 2.20 (3 H, s, ArC$H_3$), 3.87 (3 H, s, $OCH_3$), 6.70 (1 H, d, $J$ 2 Hz, ArH) and 7.63 (1 H, d, $J$ 2 Hz, ArH) (Found: $M^+$ 284.1428. $C_{18}H_{20}O_3$ requires $M^+$ 284.1413).

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