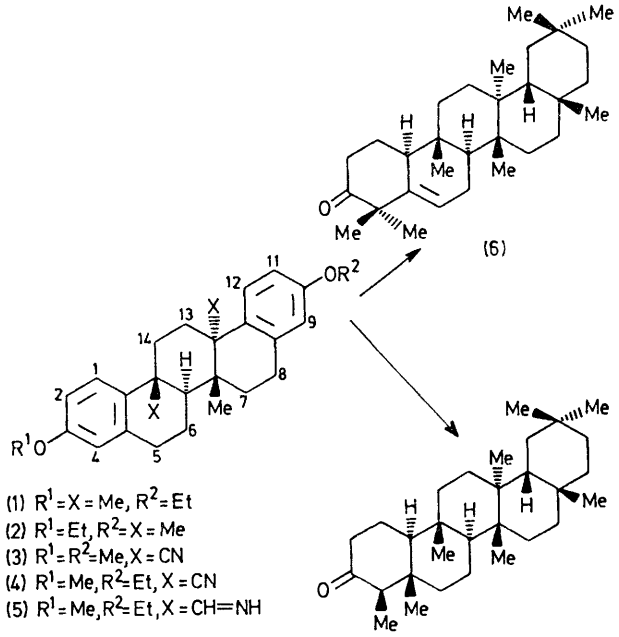
Short and Stereoselective Construction of a Key Intermediate for Synthesis of Unsymmetrical Pentacyclic Triterpenes

By TETSUJI KAMETANI,* YOSHIRO HIRAI, FUMIO SATOH, and KEIICHIRO FUKUMOTO

(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan*)

Summary A key intermediate, 10-ethoxy-3-methoxy-6bβ, 12bα, 14aβ-trimethyl-5,6,6aα, 6b,7,8,12b,13,14,14a-decahydropicene (**1**), for synthesis of pentacyclic triterpenoids has been stereoselectively synthesised; the key stage is an intramolecular cycloaddition of the *o*-quinodimethane (**19**) to give the corresponding cyclised compound (**4**).

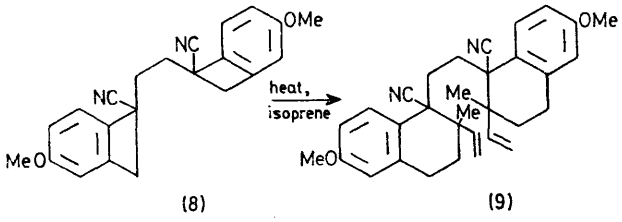
THE pentacyclic aromatic diethers (**1**) and (**2**), having the *trans,anti,trans*-BCD ring structure and the correct array of angular methyl groups, are important intermediates in the total synthesis of the pentacyclic triterpenes, alnusenone



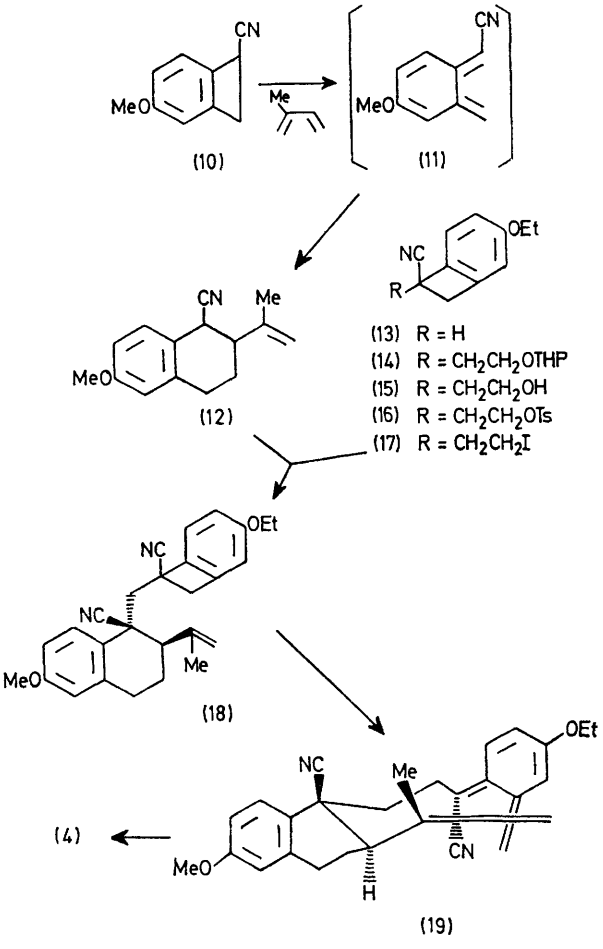
(**6**)[1] and friedelin (**7**)[2]. A crucial step in the synthesis of compounds (**1**) and (**2**) is the introduction of methyl groups at angular positions with the required stereochemistry.[1]

Since we found previously that intramolecular cycloaddition of an *o*-quinodimethane[3] in the synthesis of oestrone[4] could proceed stereoselectively, we have investigated a novel synthesis of triterpenoids by this method. We report now a simple and stereoselective synthesis of the key intermediate (**1**) for triterpenoid synthesis.

Attempted preparation of compound (**3**) by heating (**8**),† m.p. 210—211 °C with a 10 molar excess of isoprene in an autoclave at 180 °C for 2 h gave instead the 1 : 2 adduct (**9**), m.p. 175—178 °C, so our attention turned to a stepwise synthesis of (**1**).



The benzocyclobutene (**13**), m.p. 55·5—56 °C, prepared from *m*-ethoxybenzaldehyde by standard methods,[4,5]† was converted into the corresponding iodide (**17**), m.p. 82—83 °C, by alkylation with 2-bromoethyl tetrahydropyranyl ether ($NaNH_2$, liq. NH_3), followed by hydrolysis (HCl, MeOH, room temp.), tosylation (*p*-$MeC_6H_4SO_2Cl$, pyridine, room temp.), and iodination (NaI, Me_2CO, reflux) (**13** → **14** → **15** → **16** → **17**). Condensation of the 1-cyanotetralin (**12**) [prepared by heating (**10**) with isoprene in an autoclave at 180 °C for 2 h] with (**17**) in the presence of $NaNH_2$ in liquid NH_3 proceeded from the less hindered side of the C-1 position to give the key starting material (**18**) in 88% yield, with the 1-cyano and 2-vinyl groups *cis* to each other.



Heating compound (**18**) in dry toluene in a sealed tube at 210—215 °C for 3 h provided stereoselectively, in 58% yield, the pentacyclic compound (**4**), m.p. 97—98 °C [*m/e* 426 (M^+), δ (CCl_4) 0·88 (3H, s, Me), 1·37 (3H, t, *J* 7 Hz, CH_2Me), 3·73 (3H, s, OMe), 3·80 (2H, q, *J* 7 Hz, CH_2Me), and 6·33—6·80 (6H, m, ArH)], which was reduced with di-isobutylaluminium hydride in benzene at room temperature to give the di-imine (**5**), m.p. 134—136 °C [ν_{max} ($CHCl_3$) 1630 cm^{-1}], in 90% yield. Wolff–Kishner reduction of (**5**) with hydrazine hydrate and hydrazine dihydrochloride in triethylene glycol in the presence of potassium hydroxide at 160—165 °C gave the 6bβ,12bα,14aβ-trimethylated pentacyclic compound (**1**), m.p. 152—153 °C in 44% yield; i.r. and n.m.r. spectral data were identical with those obtained by Ireland.[1]

The stereoselective formation of (**4**) on the thermolysis of (**18**) can be explained as follows. Conrotatory ring opening

† Experimental details of the preparation of (**8**) and (**13**) will be published elsewhere.

of the cyclobutene unit in (**18**) would form the sterically favoured *o*-quinodimethane (**19**). Synchronous intramolecular cycloaddition of (**19**) would most favourably proceed through the *exo*-chair conformation shown to give (**4**) with the required stereochemical arrangement, rather than through the less stable '*endo*-chair' or 'boat' forms which would produce the *trans,anti,cis*-BCD and *trans,syn,trans*-BCD ring stereoisomers of (**4**).

Thus, we obtained the key compound (**1**), which has been correlated with the triterpenoid, alnusenone (**6**)[1] in a simple stereoselective way, providing an effective method for synthesis of pentacyclic diethers such as (**1**) and (**2**).

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