Stereoselective Synthesis of the Pentacyclic System as a Model for Bruceantin

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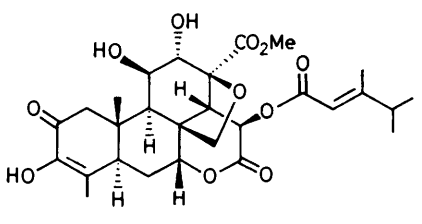
A stereoselective synthesis of compound (**2**), a model of bruceantin (**1**), is described that employs an efficient approach to the construction of the pentacyclic skeleton *via* an intramolecular Diels–Alder reaction.

In connection with a possible synthetic approach to the antitumour quassinoid bruceantin (**1**)[1] isolated from *Brucea antidysenterica*, we became interested in the stereoselective construction of the pentacyclic model system (**2**) since efficient routes to this pentacyclic skeleton are lacking.[2] We now describe an efficient and stereoselective route to the model compound (**2**) employing the intramolecular Diels–Alder reaction of the *o*-quinodimethane (**7**)[3] as the key step (Scheme 1).

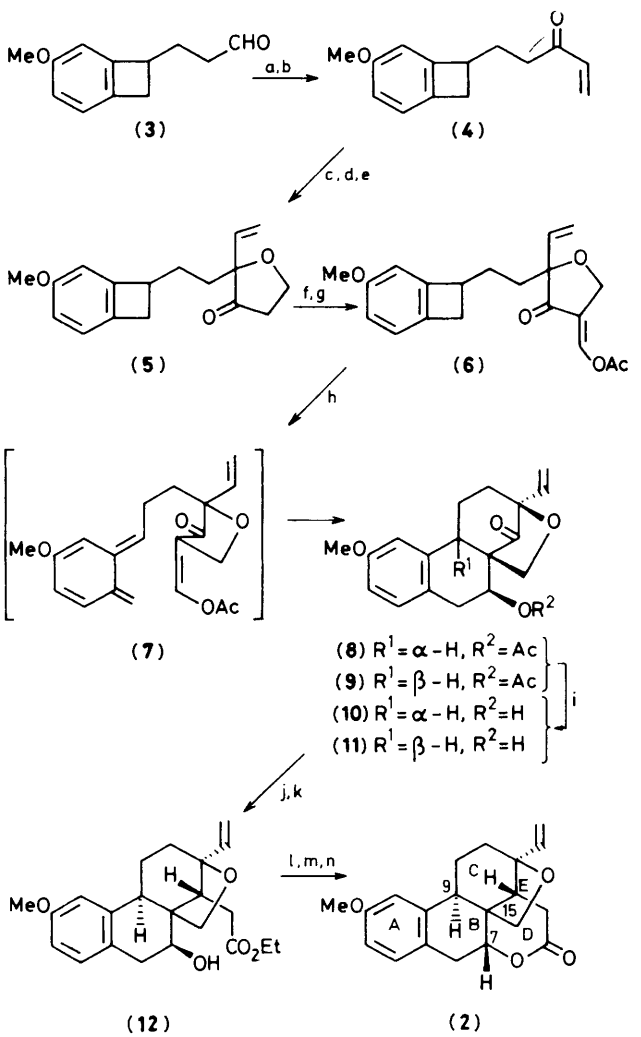
The enone (**4**) was prepared from the aldehyde (**3**), readily available from 1-cyano-5-methoxybenzocyclobutene,[4] with vinylmagnesium bromide followed by oxidation with pyridinium chlorochromate. Subsequent construction of the dihydrofuranone ring, the future *E* ring of (**2**), was accomplished by the method due to Magnus.[5] Thus, the enone (**4**) was converted into the dihydrofuranone (**5**) in 61% overall yield by sequential 1,2-addition of α-lithio-α-methoxyallene, base-induced cyclization, and acid hydrolysis of the resulting enol ether. Introduction of the acetoxymethylene unit with *E* geometry, which would be a dienophilic moiety, into the dihydrofuranone ring of (**5**) was conducted in 78% yield by a standard method to give the acetate (**6**) [i.r. ($CHCl_3$) 1780 and 1733 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 8.11 (1H, t, *J* 2.5 Hz)]. On heating the benzocyclobutene (**6**) in *o*-dichlorobenzene at 180 °C for 11 h, the tetracyclic acetates (**8**, **9**) were obtained in 74.5% yield as a pair of inseparable diastereoisomers at C-9. Subsequent hydrolysis of the mixture (**8**, **9**) gave two alcohols (**10**) and (**11**), which could easily be separated by silica gel column chromatography, in 61 and 10% yield respectively. The thermal cyclization of (**6**) thus proceeds stereoselectively.

It seemed reasonable to us that the *o*-quinodimethane (**7**) should cyclize *via* transition states (**7a**) and (**7b**). Transition state (**7a**) would lead to the stereochemistry observed in the cycloadduct (**8**). On the other hand, transition state (**7b**) would produce the undesired stereochemistry (**9**), the minor product in our experiment. Inspection of molecular models indicates that the transition state (**7b**) has an unfavourable nonbonded interaction between hydrogen atoms of the *o*-quinodimethane ring and of the connecting chain. The stereochemistry of the cycloadducts (**8**, **9**)† was assigned primarily on the basis of their 100 MHz ^1H n.m.r. spectra [(**8**): δ ($CDCl_3$) 4.28 (1H, dd, *J* 8, 1 Hz, H-15) and 4.08 (1H, d, *J* 8 Hz, H-15); (**9**): δ ($CDCl_3$) 4.37 (1H, d, *J* 8 Hz, H-15) and 4.14 (1H, d, *J* 8 Hz, H-15)] and decoupling experiments.

The keto alcohol (**10**) was then treated with triethyl phosphonoacetate in the presence of NaH. Reduction of the resulting *E*,*Z*-mixture of the conjugate ester with NaHTe,[6]

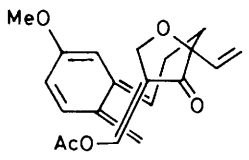


(**1**)

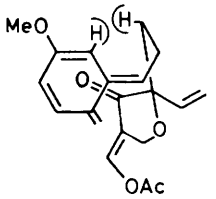


Scheme 1. *Reagents*: a, CH_2=CHMgBr, 83.8%; b, pyridinium chlorochromate, 62%; c, CH_2=C=CHOMe, Bu^nLi; d, Bu^tOK, Bu^tOH, 18-crown-6; e, 6 M-HCl, 61% from (**4**); f, HCO_2Et, NaH; g, Ac_2O, pyridine, 78% from (**5**); h, 180 °C in *o*-dichlorobenzene, 74.5%; i, NaOH, MeOH, CH_2Cl_2, 61% for (**10**), 10% for (**11**); j, $(EtO)_2P(:O)CH_2CO_2Et$, NaH, 91%; k, $NaBH_4$, Te, 84%; l, KOH, EtOH, 100%; m, $MeSO_2Cl$, NEt_3, *N*,*N*-dimethylaminopyridine; n, $NaHCO_3$, H_2O, CH_2Cl_2, 70% from (**12**).

† The acetates (**8**) and (**9**) were individually prepared for structure determination from the corresponding alcohols (**10**) and (**11**) by a standard method.



(7a)



(7b)

generated *in situ* by treating Te powder with $NaBH_4$ in EtOH, gave the ester (**12**) as a single product. The stereoselectivity for the hydride reduction of the conjugate ester is viewed as proceeding by selective attack of hydride at the less hindered β-face.[7]

Finally, the desired pentacyclic model compound (**2**) (m.p. 167—168 °C, colourless needles) was obtained in 70% yield on sequential hydrolysis, methanesulphonation, and treatment with $NaHCO_3$ of the ester (**12**). The structure of (**2**) was confirmed on the basis of its ^{13}C and ^1H (400 MHz) n.m.r. [δ ($CDCl_3$) 4.63 (1H, d, *J* 4 Hz, H-7), 3.84 (1H, d, *J* 8 Hz, H-15), and 3.59 (1H, dd, *J* 8, 1 Hz, H-15)], i.r. [($CHCl_3$) 1725 cm^{-1}], and high-resolution mass spectra, and *X*-ray crystallographic analysis.

This methodology should provide a basis for the total synthesis of the antitumour quassinoid bruceantin (**1**).

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