Model Studies towards Crinipellin Diterpenes and Paniculatine-type Lycopodium Alkaloids from a Common Triquinane Precursor

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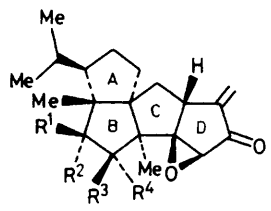
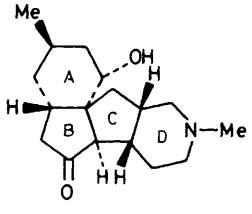
A short, stereo-controlled construction of tetracyclo[6.6.0.$0^{1,11}$.$0^{3,7}$]tetradecane derivative (**11**) and tetracyclo[7.6.0.$0^{1,6}$.$0^{10,14}$]-pentadecane derivative (**14**) from a common, readily available triquinane precursor is described.

In 1985, Anke, Steglich and co-workers reported the discovery of tetraquinanes in Nature from the strains of the basidiomycete *Crinipellis stipitaria* (Agaricales).[1] Three of these tetraquinane diterpenes crinipellin-A (**1a**), crinipellin-B (**1b**), and O-acetylcrinipellin-A (**1c**) were found to be antibiotically active. With a novel carbon skeleton, extensive functionalisation, eight stereogenic centres, and biological activity, crinipellins are an instant attraction to the synthetic chemist.

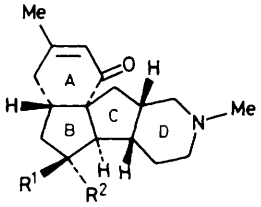
Several years ago, Castillo *et al.*[2a–c] encountered a new type of tetracyclic alkaloids from the lycopodium family and elucidated the structures of paniculatine (**2**) from *Lycopodis paniculatum*,[2b] and magellanine (**3a**)[2b] and magellaninone (**3b**)[2c] from *L. magellanicum*. These complex alkaloids, bearing a diquinane moiety, also pose a considerable synthetic challenge. Our interest in the synthesis of (**1**)—(**3**) was aroused through the recognition of common structural and stereochemical features present in these two different classes of natural products. It is reasonable to assume that the piperidine ring in (**2**) can be derived from a cyclopentanone equivalent, so (**1**)—(**3**) can be regarded as having a common BCD triquinane core (**4**). Three and four carbon ring annulation at the starred positions in (**4**) would then provide synthetic entry into the tetracyclic crinipellins and the lycopodium alkaloids, respectively. We describe here the synthesis of the carbocyclic framework of (**1**) and of a carbocyclic system suitable for the generation of the heterocyclic portion of (**2**) and (**3**).



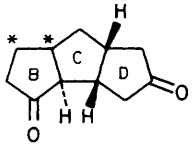
(**1**) **a**; R^1 = H, R^2 = OH, R^3 = R^4 = O
b; R^1 = R^2 = O, R^3 = OH, R^4 = H
c; R^1 = H, R^2 = OCOMe, R^3 = R^4 = O



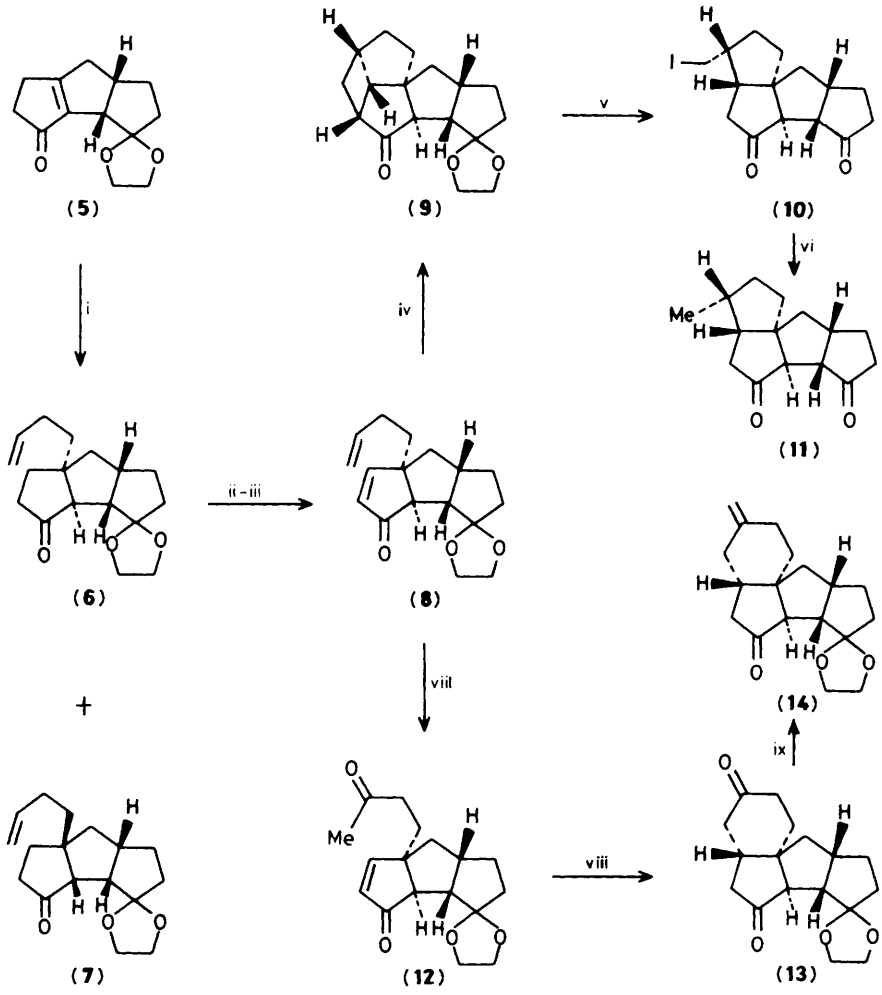
(**2**)



(**3**) **a**; R^1 = OH, R^2 = H
b; R^1 = R^2 = O



(**4**)



Scheme 1. *Reagents and conditions:* i, CH_2=$CHCH_2CH_2MgBr$, Me_2SCuBr, Me_2S, tetrahydrofuran (THF), −78 °C, 2 h, 90%; ii, $(Me_3Si)_2NH$–Bu^nLi, PhSeCl, THF, −78 °C—25 °C, 16 h; iii, H_2O_2, THF, room temp., 30 min, 85%; iv, Quartz, *hv*, 450 W Hanovia lamp, hexane, 30 min, 70%; v, NaI, Me_3SiCl, MeCN, 80 °C, 18 h, 65%; vi, Bu^n_3SnH, C_6H_6, 80 °C, 20 min, 95%; vii, $PdCl_2$, CuCl, O_2, *N,N*-dimethylformamide, room temp., 30 min, 80%; viii, NaH, THF, 1 h, 75%; ix, $Ph_3P^+MeBr^-EtCMe_2O^-Na^+$, PhMe, room temp., 20 min, 80%.

Readily available enone acetal (**5**)[3] was quaternised through conjugate addition of the butenyl side chain to give a *ca.* 3 : 2 mixture of *cis, transoid, cis*- (**6**) and the *cis, cisoid, cis*- (**7**) in high yield.† The required triquinane (**6**) was transformed into the enone (**8**)‡ *via* a phenylselenylation–selenoxide elimination sequence and so the branching point for the formation of the crinipellins and the paniculatine-type precursors was reached, Scheme 1. Irradiation of (**8**) by a 450 W medium pressure lamp through quartz led to a smooth [2 + 2]-cycloaddition and the highly crystalline, pentacyclic ketone (**9**)‡ with secured stereochemistry at seven stereogenic centres was realised. Regioselective cyclobutane cleavage in (**9**) with Me_3SiI proceeded in the expected manner[4] with simultaneous acetal deprotection to give the iodo-tetraquinane derivative (**10**).‡ Reductive deiodination of (**10**) with tri-n-butylstannane gave the tetraquinanedione (**11**), m.p. 77—78 °C, ^{1}H n.m.r.: δ 0.92 (3H, d, *J* 7 Hz); ^{13}C n.m.r.: δ 220.3 (2C), 62.3, 59.3, 58.0, 49.7, 47.0, 40.9, 40.1, 39.8, 36.9, 34.4, 32.3, 23.1, 15.8, having ring junction stereochemistry corresponding to crinipellins.

Wacker oxidation of the butenyl side chain in (**8**) was accomplished using Tsuji reaction conditions[5] to give (**12**). Exposure of (**12**) to base led to the anticipated intramolecular Michael addition and tetracyclic dione (**13**), i.r.(KBr): $\nu_{max.}$ (C=O) 1740, 1720 cm^{-1}, ^{13}C n.m.r.: δ 218.4, 211.0, 117.3, 64.6, 64.0, 61.7, 54.8, 52.8, 44.3, 43.5, 42.2, 40.9, 39.7, 38.6, 34.5, 33.2, 28.0, was realised, Scheme 1. The two carbonyl

† The stereochemical assignments of (**6**) and (**7**) were made on the basis of unambiguous chemical transformations (unpublished results).

‡ *Selected spectroscopic data:* (**8**): i.r. (neat): 3100, 1720 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 7.25 (1H, d, *J* 6 Hz), 5.86 (1H, d, *J* 6 Hz), 5.82—5.44 (1H, m), 5.0—4.64 (2H, m), 4.0—3.7 (4H, m), 2.42—2.06 (2H, m), 2.0—1.2 (11H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 213.1, 171.0, 138.6, 132.3, 117.7, 114.7, 64.8, 64.2, 60.0, 57.0, 56.1, 41.7, 41.0, 37.6, 35.4, 30.1, 26.5; (**9**) m.p. 78—79 °C; i.r. (KBr): 1720 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 4.1—3.8 (4H, m) 3.0—1.2 (18H, series of m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 224.2, 117.7, 64.6, 63.8, 63.0, 60.6, 56.1, 50.3, 45.3, 43.2, 43.0, 38.3, 37.1, 34.4, 33.1, 28.3, 27.7; (**10**) m.p. 84—85 °C; i.r. (KBr): 1740 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 3.3—2.8, (2H, m), 2.8—1.0 (17H, series of m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 219.8, 218.5, 62.2, 58.8, 57.8, 49.8, 46.7, 46.2, 40.8, 39.7, 39.1, 34.1, 30.7, 22.8, 6.4; (**14**) i.r. (neat): 3050, 1735 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 4.8—4.5 (2H, d) 4.2—3.7 (4H, m), 3.0—2.8 (1H, m), 2.8—1.0 (17H, series of m).

groups in (**13**) were chemo-differentiated through the Wittig olefination which exclusively furnished (**14**).‡ The exocyclic methylene group in (**14**) is a necessary handle for generating the methyl group and functionality in ring A of (**2**) and (**3**).

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