Progress towards viridin: synthesis of the pentacyclic furanosteroid ring system *via o*-benzoquinonoid cycloadditions

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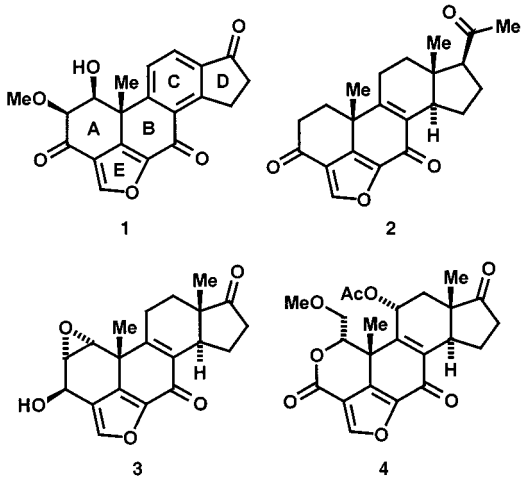
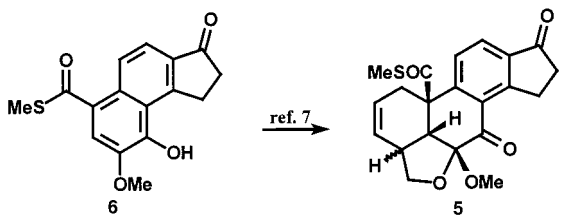
The pentacyclic ring system of viridin is synthesised in nine steps from 4-methylguaicol by means of successive cycloadditions involving *o*-benzoquinonoid intermediates generated *in situ*.

The viridin family of pentacyclic furanosteroidal antibiotics[1] isolated from various species of fungi possess several unusual structural features. Viridin **1** contains an aromatic ring C, a



highly oxygenated ring A and a furan ring in a 'triterpenoid' location, betraying its biogenetic origins from lanosterol. Virone **2**, wortmannolone **3**[2] and wortmannin **4**[3] have an additional 'angular' methyl group at C-13 and *trans* C/D ring fusion. Viridin has powerful species specific anti-fungal activity, and wortmannin has attracted some attention as an anti-inflammatory agent and, more recently, as a potent inhibitor of phosphatidylinositol 3-kinase in neutrophils of the guinea pig.[4]

Apart from a long and low yielding conversion[5] of hydrocortisone to wortmannin no synthesis of any of these compounds has been achieved, but two other studies in this area have been reported.[6] Our recent explorations in the use of *o*-benzoquinonoid intermediates for natural product synthesis had led to the preparation[7] of the pentacyclic system **5** of viridin from benzindanone **6** and penta-2,4-dienol in one step (Scheme 1). However, we were unable to selectively reduce the C-10 thiol ester of **5** to the desired methyl group and even worse, an attempt at prior installation of the methyl group as in the model

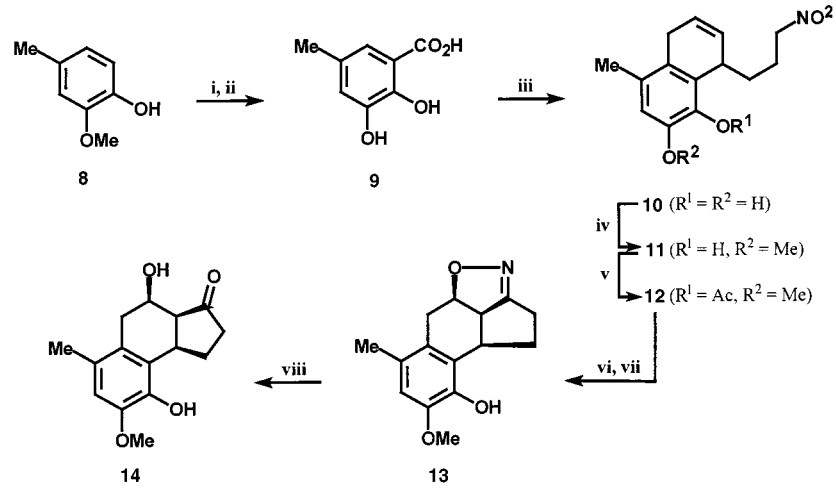


Scheme 1

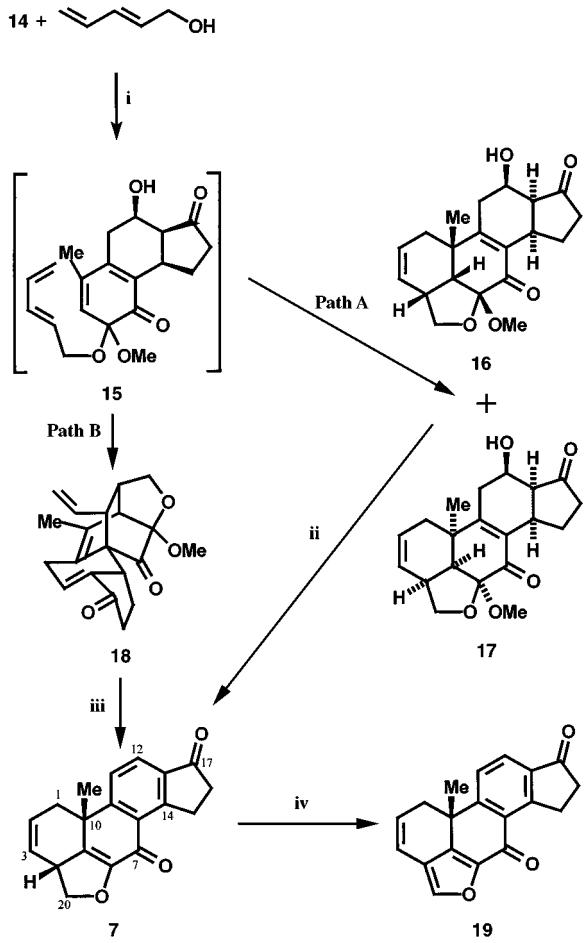
substrate 2-methoxy-4-methylnaphthol resulted in failure of the intramolecular Diels–Alder (IMDA) reaction with the pentadienol under the usual oxidative conditions. We now report that the problems associated with the incorporation of the C-10 methyl group have been overcome and the first synthesis of the desired pentacycle **7** has been achieved in nine steps from 4-methylguaicol **8**.

The acid **9** was conveniently prepared on a multi-gram scale from **8** by Kolbe–Schmitt carboxylation[8,9] followed by BBr_3 demethylation (72% overall). This methylcatechol containing the carbon skeleton of ring B will serve as a linchpin for the attachment of rings CD and AE in two separate annulations employing novel *o*-benzoquinonoid protocols recently developed in our laboratory. When treated with an excess of 1-nitrohepta-4,6-diene[10] in the presence of bis(trifluoroacetoxy)iodobenzene (BTIB) it underwent a sequence of reactions (oxidation to the *o*-quinone, regiospecific Diels–Alder cycloaddition, decarboxylation of the β-keto acid adduct and rearomatisation) to provide the dihydronaphthalene **10** in 86% yield. This remarkable 'one-pot' process, in which the evanescent carboxy group of **9** plays a key role,[11] is the equivalent of a regiospecific cycloaddition of the 5,6-benzyne derived from 4-methylcatechol. Methylation of **10** with Me_3OBF_4 is both selective and quantitative. The methyl ether **11** was acetylated and subjected to the intramolecular nitrile oxide cycloaddition[12] by treatment with *p*-chlorophenyl isocyanate and Et_3N to produce the isoxazoline **13** after hydrolytic work-up with aqueous base. Catalytic hydrogenolysis (10% Pd/C, boric acid) then generated the benzindanone **14**, representing the BCD rings of viridin, as a single diastereomer[13] (52% overall, Scheme 2).

Rings A and E were now attached to the benzene ring of **14** by our *o*-benzoquinone monoketal procedure.[7] Treatment of **14** with BTIB in the presence of excess penta-2,4-dienol produced the monoketal **15** which reacted *in situ* by both possible IMDA pathways to produce a 1:1 mixture of two inseparable *endo*-adducts, pentacycles **16** and **17** (path A, quinonoid double bond as dienophile), and bridged adduct **18** (path B, quinonoid ring as diene). The assignments of relative stereochemistry to **16** and **17** are based on our previous experience[7,14] with the IMDA reactions of *o*-quinone monoketals, and the *endo* stereochemistry of the adducts is confirmed by the fact that both lose MeOH very readily to form the dienone unit of ring B. *Exo* adducts of this type do not eliminate MeOH.[14] The stereochemical issue with **18** was decided on the assumption that one face of **15** is more crowded than the other because of the *cis* CD ring fusion of this compound; the reaction is therefore presumed to occur at the less congested face of the diene unit of **15**. We are endeavouring to confirm this assignment by an X-ray crystal structure. Bridged adduct **18** was easily separated from the mixture of two diastereomeric pentacycles and when subjected to the Cope rearrangement in refluxing tetrachloroethane provided the target **7** in 65% yield. The diastereomers **16** and **17** when treated with TsOH in benzene with exposure to air provided the same compound (**7**) by dehydration and spontaneous aromatisation of ring C.



Scheme 2 *Reagents and conditions:* i, K_2CO_3, CO_2 (800 psi), 200 °C, 4 h; ii, BBr_3, CH_2Cl_2, −78 °C to room temp. (72%, two steps); iii, 1-nitrohepta-4,6-diene (5 equiv.), BTIB, THF (86%); iv, K_2CO_3, Me_3OBF_4, CH_2Cl_2 (100%); v, Ac_2O, pyridine; vi, *p*-ClC_6H_4NCO, Et_3N, C_6H_6, room temp., 36 h; vii, NaOH, H_2O–THF (84%, three steps); viii, H_2, Pd/C, H_3BO_3, MeOH–THF–H_2O (100%).



Scheme 3 *Reactions and conditions:* i, BTIB, THF (path A: 33%, path B: 31%); ii, TsOH, C_6H_6, 45 °C, 4 h (50%); iii, $Cl_2CHCHCl_2$, reflux, 48 h (65%); iv, *p*-chloranil, xylenes, reflux, 36 h (60%).

The nine-step sequence described above is not only the first synthesis of the ring system of viridin, but it also makes **7** available in sufficient quantity (19% overall, Scheme 3) to enable a comprehensive investigation for installation of the oxygen substituents in ring A, by derivatisation of the C_2–C_3 alkene, to be undertaken. Dehydrogenation of the dihydrofuran is facile and can be effected at any convenient stage; in fact, the conversion **7** → **19** has already been achieved in 60% yield. The benzindanone **14** offers possibilities for modification into the C/D non-aromatic analogues (*e.g.* **2**, **3** and **4**). Many obvious problems remain before any of these antibiotics can be synthesised, but we regard this short and flexible route to the pentacyclic system[15] as an important first step on the way to members of the viridin family.

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15 *Selected data* for **7:** δ_H(500 MHz, $CDCl_3$) 1.51 (s, Me), 2.18 (dd, *J* 17.8, 3.1, H-1α), 2.67 (m, H-15), 2.74 (dd, *J* 17.8, 2.3, H-1β), 3.67 (m, H-16), 4.00 (app dt, *J* 10.3, 2.6, H-4), 4.06 (dd, *J* 10.7, 8.1, H-20α), 4.87 (dd, *J* 9.8, 8.1, H-20β), 5.74 (app s, H-2, H-3), 7.55 (d, *J* 8.1, H-11), 7.89 (d, *J* 8.1, H-12). Full details will be published later.

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