

A Total Synthesis of (\pm)-Coriolin

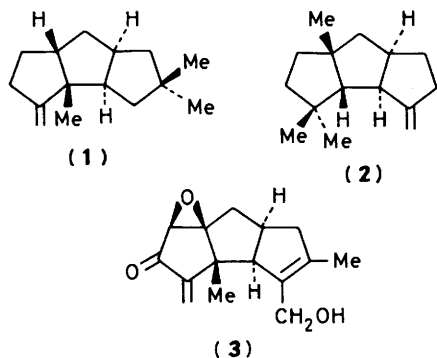
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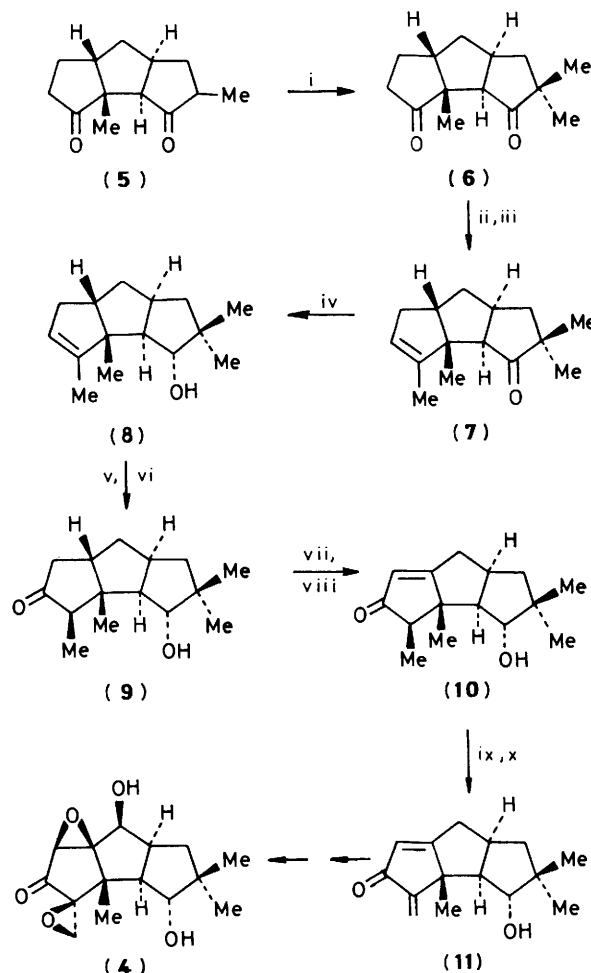
A simple synthesis of (\pm)-coriolin (**4**) from the readily available *cis,anti,cis*-tricyclic C₁₃-dione (**5**) is reported.

Linearly fused tricyclopentanoid natural products, *e.g.* hirsutene (**1**),¹ capnellene (**2**),² and pleurotellol (**3**),³ have attracted considerable attention recently because of their novel structures and the promising biological activity displayed by many members of this group. The antitumour sesquiterpenoid coriolin (**4**),⁴ isolated from the fermentation broth of a *Bacidomycetes*, *Coriulus consors*, and possessing the carbon framework of hirsutene, is of special interest to synthetic chemists because of its molecular and stereochemical complexity. We report here a synthesis⁵ of (\pm)-coriolin (**4**) starting from the easily available tricyclic C₁₃-dione precursor (**5**),⁶ by a method which can be extended readily to provide other oxygenated members of the hirsutanoid family.

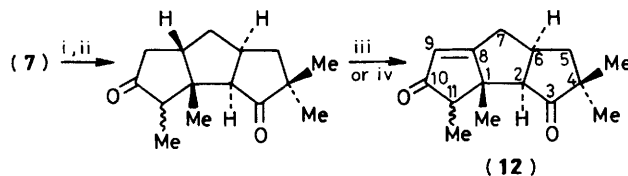
Retro-synthetic analysis of the coriolin molecule readily identified the C₁₅-hydroxy-ketone (**9**) and the cross-conjugated dienone (**11**) as the two key intermediates leading to (**4**) from the C₁₃-dione (**5**). We therefore adopted the (**5**) \rightarrow (**9**) \rightarrow (**11**) \rightarrow (**4**) approach to coriolin; our method involved several chemo- and stereo-selective reactions, and did not require protecting groups (Scheme 1). The dione (**5**) was efficiently alkylated regioselectively with NaH-MeI in refluxing tetrahydrofuran (THF) to yield the *gem*-dimethylated dione (**6**). Chemoselective Grignard addition of methylmagnesium iodide to the less hindered carbonyl group of the C₁₄-dione (**6**) and dehydration gave the C₁₅-olefinic ketone (**7**), ν_{\max} (neat): 1740 and 1650 cm⁻¹; ¹H n.m.r.: δ 5.02 br. (1H, s) and 1.68 (3H, s). The carbonyl group in (**7**) was reduced stereoselectively with lithium in liquid ammonia and the thermodynamically more stable, convex oriented, hydroxy-compound (**8**), m.p. 57–58 °C, ν_{\max} (KBr): 3350 cm⁻¹; ¹H n.m.r.: δ 3.52 (1H, d, *J* 8 Hz), was obtained. The conversion of (**8**) into the C₁₅-hydroxy-ketone (**9**), m.p. 162 °C, ν_{\max} (KBr): 1725, 3475, and 3510 cm⁻¹; ¹H n.m.r.: δ 0.97 (3H, d, *J* 6 Hz) and 3.5 (1H, d, *J* 1 Hz), was most conveniently accomplished through epoxidation and BF₃-catalysed isomerisation. The hydroxy-ketone (**9**) was then elaborated into the hydroxy-enone (**10**), ν_{\max} (neat): 1690 and 1640 cm⁻¹; ¹H n.m.r.: δ 5.7 (1H, d, *J* 1 Hz), in exceptionally good yield *via* conversion into the corresponding trimethylsilyl enol ether and palladium(II)-catalysed dehydrosilylation.⁷ The syrupy hydroxy-enone (**10**) was then transformed into the cross-conjugated dienone (**11**) through phenylselenenylation-selenoxide elimination.⁸ Since the dienone (**11**) has already been converted into (**4**) in a four-step sequence by Ikegami *et al.*,^{5c} our preparation of (**11**) constitutes a formal total synthesis of coriolin (**4**).



In another series of reactions, the olefinic ketone (**7**) was transformed into the enone (**12**) as outlined in Scheme 2. The enone (**12**) (mixture of C-11-epimers that were readily



Scheme 1. i, NaH-THF, MeI, reflux, 65%; ii, MeMgI-Et₂O, 30 °C, 30 min, aq. NH₄Cl, 90%; iii, POCl₃-pyridine, 30 °C, 14 h, 75%; iv, Li-liq. NH₃-MeOH, 63%; v, *m*-chloroperbenzoic acid-CH₂Cl₂-Na₂CO₃, 30 °C, 30 min, 100%; vi, BF₃-Et₂O-CH₂Cl₂, 0–5 °C, 5 min, 80%; vii, LiPr₂N-THF-Me₃SiCl, -78 °C; viii, Pd(OAc)₂-MeCN, 30 °C, 4 h and aq. THF-AcOH, >90% from (**9**); ix, LiPr₂N-THF, -78 °C, 30 min, PhSeBr; x, 30%, H₂O₂-THF-AcOH (trace), 0 °C, 30 min, 35% from (**10**).



Scheme 2. i, *m*-chloroperbenzoic acid-CH₂Cl₂-Na₂CO₃, 30 °C, 30 min; ii, BF₃-Et₂O-CH₂Cl₂, 30 °C, 5 min, 65% from (**7**); iii, LiPr₂N-THF-PhSeCl, -78 °C and 15% H₂O₂, CH₂Cl₂-pyridine, 30 °C, 2 h (15%); iv, LiPr₂N-THF-Me₃SiCl, -78 °C and Pd(OAc)₂-MeCN, 30 °C, 2 h (60%).

separable) was identical with one of the advanced intermediates in Danishefsky's coriolin synthesis.^{5b} Thus, Scheme 2 provides an alternative, short approach to coriolin (**4**).

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