A concise total synthesis of (±)-anthecularin†

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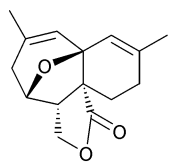
A total synthesis of the novel sesquiterpene anthecularin 1, isolated from Greek *Anthemis auriculata*, based on an intramolecular [5+2] (1,3-dipolar) cycloaddition involving the oxidopyrylium ion 12 derived from the furanmethanol 9, is described.

Anthecularin **1** is a new and unusual sesquiterpene which was recently isolated from *Anthemis auriculata*.[1] Interestingly, anthecularin originates from the same family of plants, *i.e. Asteraceae*, that produce the well-known anti-malarial compound artimisinin.[2] Indeed, anthecularin does exhibit anti-malarial activity, but the level is low in comparison with artimisinin. Anthecularin inhibits two of the key enzymes of the plasmodium fatty acid synthase enzyme complex, which has suggested that the natural product could be a valuable lead compound for the design of new antimalarial drugs.[1]

The compact tetracyclic structure of anthecularin **1** accommodates a core oxabicyclo [3.2.1] octane ring system which is fused to a cyclohexene and to a butyrolactone *via* two contiguous quaternary carbon centres. The origin of the "non-regular" C_{15}–terpenoid carbon framework in anthecularin is not immediately obvious. However, the isolation of the substituted lactone **2** as a co-metabolite in *A. auriculata*[3] had led to the proposal that the cyclohexene ring in anthecularin is derived from **2** *in vivo* by way of an intramolecular Diels–Alder reaction involving the methylene lactone unit in **2** as a key step.[1] In this paper we describe a conceptually distinct synthetic approach to anthecularin, whereby the entire carbon framework is elaborated in one step, from the acetoxypyranone-substituted butenolide **11** using an intramolecular [5+2] (or 1,3-dipolar) cycloaddition process[4,5] involving the oxidopyrylium ion **12**.[6]



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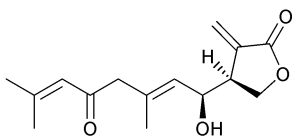

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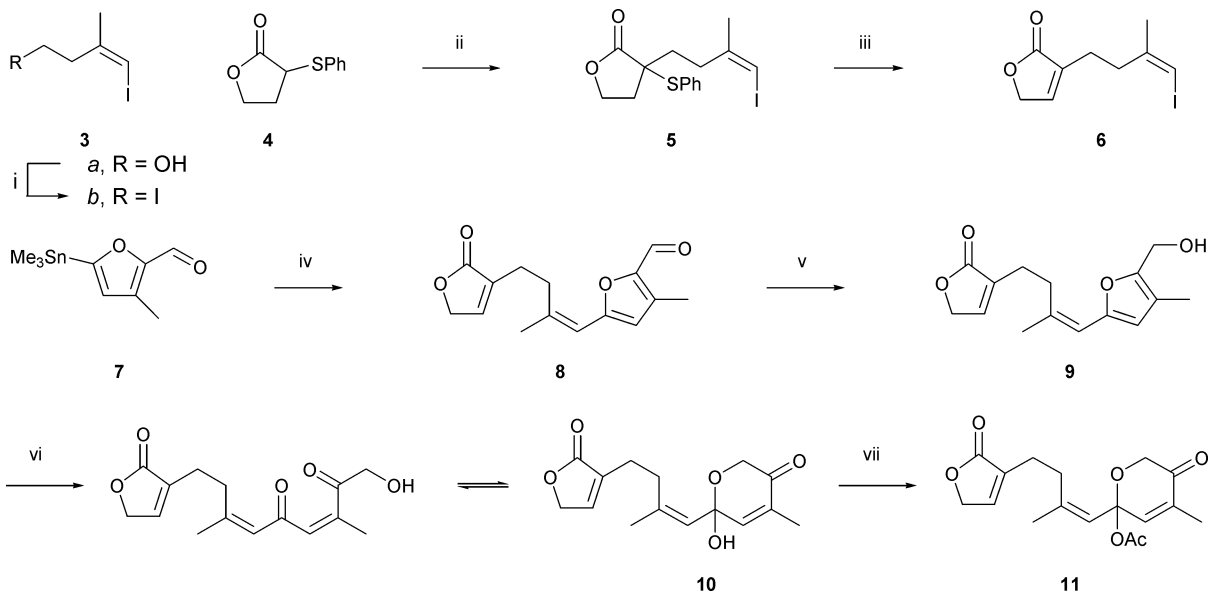
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **8** and **13**. CCDC reference number 707835. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b819454h

Thus, treatment of the known alcohol **3a**[7] containing a terminal *Z*-alkenyliodide with iodine–triphenylphosphine first gave the corresponding di-iodide **3b** in 85% yield (Scheme 1). Deprotonation of 2-phenylthiobutyrolactone **4**, using LDA–HMPA at 0 °C, followed by alkylation of the resulting enolate with the di-iodide **3b** next gave the adduct **5**, whose formation was accompanied by the

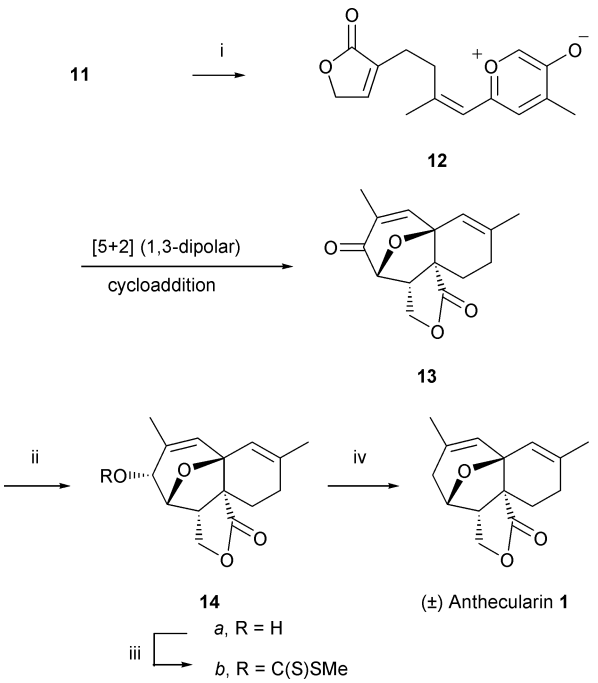


Scheme 1 *Reagents and conditions*: (i) Ph_3P, I_2, THF/CH_3CN, rt, 85%; (ii) LDA, HMPA, THF, 0 °C to rt, 23%; (iii) *m*-CPBA, CH_2Cl_2, 0 °C, 30 min, then toluene, reflux, 2 h, 91%; (iv) $Pd(OAc)_2$, CuI, $AsPh_3$, DMF, rt, 2 h, 85%; (v) $NaBH_4$, MeOH, –10 °C, 30 min, 99%; (vi) *m*-CPBA, CH_2Cl_2, –20 °C, 1 h; (vii) Ac_2O, pyridine, DMAP(cat.), CH_2Cl_2, 0 °C to rt, 51% over two steps.

product of dehydroiodination of **3b**. Oxidation of the phenylsulfide **5**, using *m*-CPBA at 0 °C, followed by dehydrosulfinylation of the resulting sulfoxide in refluxing toluene then produced the substituted butenolide **6** in 91% yield over the two steps.

A Stille coupling reaction between the *Z*-alkenyliodide **6** and 3-methyl-5-trimethylstannylfurfural **7**,[8] using $Pd(OAc)_2$, CuI, and Ph_3As in DMF at room temperature, gave the substituted *Z*-vinylfuran **8** in 85% yield. Reduction of the furfural **8**, using $NaBH_4$ in MeOH at −10 °C, next led to the corresponding furanmethanol **9** (99%). Treatment of the furanmethanol **9** with *m*-CPBA in CH_2Cl_2 at −20 °C resulted in oxidative cleavage of the furan ring and simultaneous tautomerisation, producing the hydroxypyranone **10**. The hydroxypyranone **10** was then treated with Ac_2O–DMAP leading to the corresponding stable acetate **11** in 51% yield over the two steps.

When a solution of the acetoxypyranone **11** in toluene containing DBU was heated under reflux for 1 h, the anticipated intramolecular [5+2] (1,3-dipolar) cycloaddition involving the oxidopyrylium ion intermediate **12** took place, leading to the crystalline tetracyclic product **13** in 15–20% yield (Scheme 2).[9] The tetracycle displayed ^1H and ^{13}C NMR data which were consistent with the structural assignment, *i.e.* **13**, and its relative stereochemistry was confirmed by X-ray crystallography (Fig. 1).†[10]



Scheme 2 *Reagents and conditions*: (i) DBU, toluene, reflux, 1 h, 15–20%; (ii) $NaBH_4$–$CeCl_3$, MeOH, rt, 20 min, 95%; (iii), NaH, CS_2, MeI, THF, rt, 85%; (iv) Bu_3SnH, AIBN, toluene, reflux, 20 min, 65%.

Treatment of the tetracyclic enone **13** with $NaBH_4$–$CeCl_3$ in MeOH at room temperature next gave the allylic alcohol **14a**, as a single diastereoisomer, which was then smoothly converted into the corresponding methyl xanthate **14b**. Finally, treatment of a solution of the xanthate **14b** in refluxing toluene with Bu_3SnH–AIBN followed by chromatography gave (±)-anthecularin **1** in 65% yield.[11] The synthetic anthecularin showed ^1H and ^{13}C NMR spectra which were superimposable on those recorded for the natural product isolated from *Anthemis auriculata.*

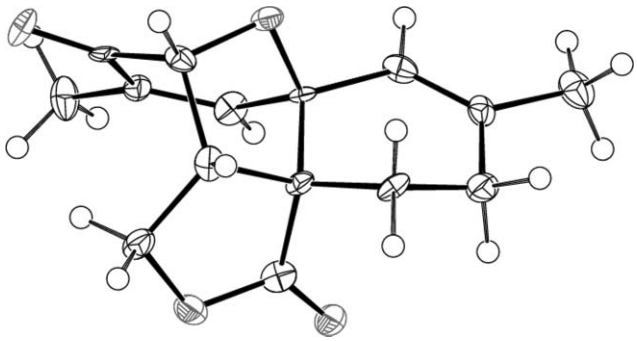


Fig. 1 X-ray structure of **13**.

In summary, a concise and convergent 10 step synthesis of anthecularin **1**, from readily available starting materials, has been achieved using an intramolecular oxidopyrylium ion–alkene cycloaddition involving the species **12** as a key step.

Acknowledgements

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Notes and references

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9 The yield of 15–20% is not optimised, and is consistent with the yields recorded for similar cycloaddition reactions involving oxidopyrylium ions and but-2-enolides; see reference 6.
10 We thank Dr. William Lewis of The School of Chemistry at Nottingham for this X-ray crystal structure determination.
11 A small amount (10–15%) of the dihydropyran positional isomer, corresponding to anthecularin, was produced concurrently; it was easily separated by chromatography.

