

# A concise total synthesis of (±)-antheclarin†

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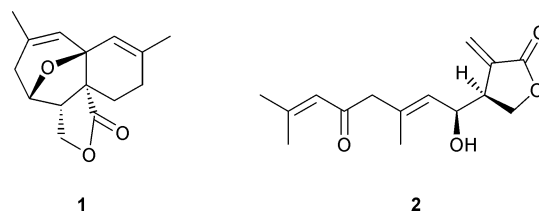
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A total synthesis of the novel sesquiterpene antheclarin **1**, isolated from Greek *Anthemis auriculata*, based on an intramolecular [5+2] (1,3-dipolar) cycloaddition involving the oxidopyrylium ion **12** derived from the furanmethanol **9**, is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

Antheclarin **1** is a new and unusual sesquiterpene which was recently isolated from *Anthemis auriculata*.<sup>1</sup> Interestingly, antheclarin originates from the same family of plants, *i.e.* *Asteraceae*, that produce the well-known anti-malarial compound artemisinin.<sup>2</sup> Indeed, antheclarin does exhibit anti-malarial activity, but the level is low in comparison with artemisinin. Antheclarin 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.<sup>1</sup>

The compact tetracyclic structure of antheclarin **1** accommodates a core oxabicyclo [3.2.1] octane ring system which is fused to a cyclohexene and to a butyrolactone *via* two contiguous

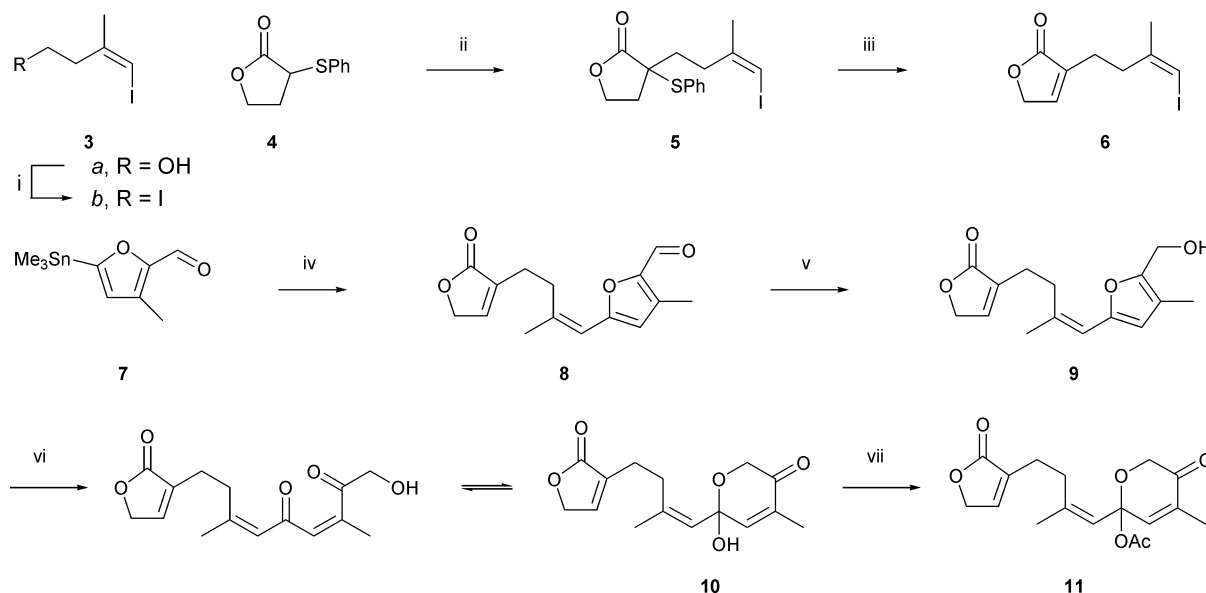
quaternary carbon centres. The origin of the “non-regular” C<sub>15</sub>-terpenoid carbon framework in antheclarin is not immediately obvious. However, the isolation of the substituted lactone **2** as a co-metabolite in *A. auriculata*<sup>3</sup> had led to the proposal that the cyclohexene ring in antheclarin 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.<sup>1</sup> In this paper we describe a conceptually distinct synthetic approach to antheclarin, 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<sup>4,5</sup> involving the oxidopyrylium ion **12**.<sup>6</sup>



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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>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**<sup>7</sup> containing a terminal Z-alkenyl iodide 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

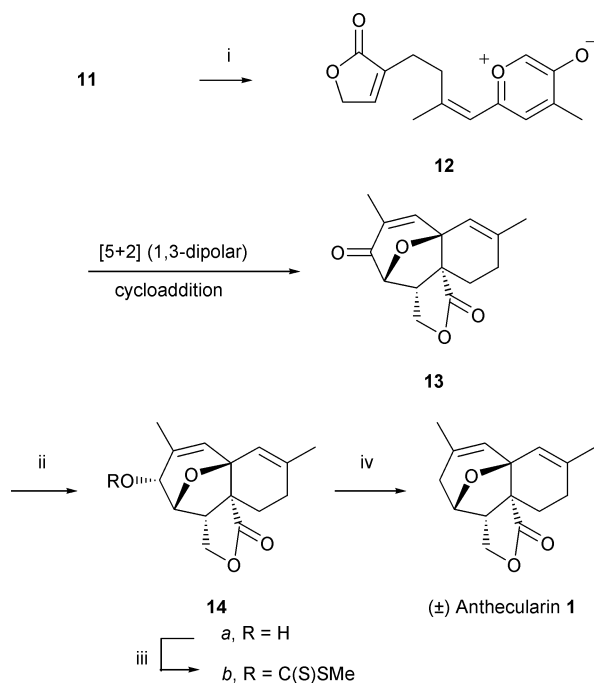


**Scheme 1** Reagents and conditions: (i) Ph<sub>3</sub>P, I<sub>2</sub>, THF/CH<sub>3</sub>CN, rt, 85%; (ii) LDA, HMPA, THF, 0 °C to rt, 23%; (iii) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min, then toluene, reflux, 2 h, 91%; (iv) Pd(OAc)<sub>2</sub>, CuI, AsPh<sub>3</sub>, DMF, rt, 2 h, 85%; (v) NaBH<sub>4</sub>, MeOH, –10 °C, 30 min, 99%; (vi) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, –20 °C, 1 h; (vii) Ac<sub>2</sub>O, pyridine, DMAP(cat.), CH<sub>2</sub>Cl<sub>2</sub>, 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.

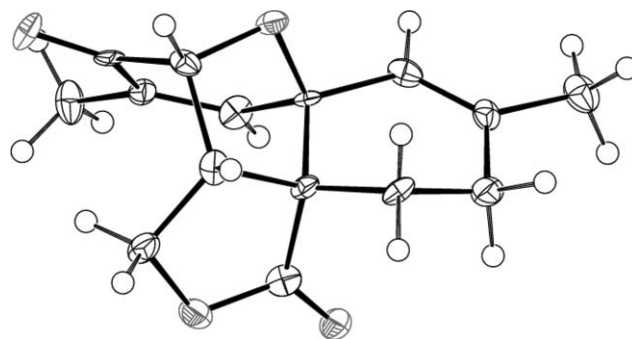
A Stille coupling reaction between the *Z*-alkenyliodide **6** and 3-methyl-5-trimethylstannylfurfural **7**,<sup>8</sup> using Pd(OAc)<sub>2</sub>, CuI, and Ph<sub>3</sub>As in DMF at room temperature, gave the substituted *Z*-vinylfuran **8** in 85% yield. Reduction of the furfural **8**, using NaBH<sub>4</sub> in MeOH at –10 °C, next led to the corresponding furanmethanol **9** (99%). Treatment of the furanmethanol **9** with *m*-CPBA in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>O–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).<sup>9</sup> The tetracycle displayed <sup>1</sup>H and <sup>13</sup>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).<sup>†10</sup>



**Scheme 2** Reagents and conditions: (i) DBU, toluene, reflux, 1 h, 15–20%; (ii) NaBH<sub>4</sub>–CeCl<sub>3</sub>, MeOH, rt, 20 min, 95%; (iii), NaH, CS<sub>2</sub>, MeI, THF, rt, 85%; (iv) Bu<sub>3</sub>SnH, AIBN, toluene, reflux, 20 min, 65%.

Treatment of the tetracyclic enone **13** with NaBH<sub>4</sub>–CeCl<sub>3</sub> 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<sub>3</sub>SnH–



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

AIBN followed by chromatography gave (±)-anthecularin **1** in 65% yield.<sup>11</sup> The synthetic anthecularin showed <sup>1</sup>H and <sup>13</sup>C NMR spectra which were superimposable on those recorded for the natural product isolated from *Anthemis auriculata*.

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

- 1 A. Karioti, H. Skaltsa, A. Linden, R. Perozzo, R. Brun and D. Tasdemir, *J. Org. Chem.*, 2007, **72**, 8103–8106.
- 2 For a recent overview, see: M. Schlitzer, *Arch. Pharm. Chem. Life Sci.*, 2008, **341**, 149–163.
- 3 R. Theodori, A. Karioti, A. Rančić and H. Skaltsa, *J. Nat. Prod.*, 2006, **69**, 662–664.
- 4 (a) For some earlier examples of the use of intramolecular oxidopyrylium–alkene cycloaddition reactions in the synthesis of natural products, see: S. M. Bromidge, P. G. Sammes and L. J. Street, *J. Chem. Soc., Perkin Trans. I*, 1985, 1725–1730; (b) P. Wender, K. D. Rice and M. E. Schnute, *J. Am. Chem. Soc.*, 1997, **119**, 7897–7898, and references therein; (c) P. Magnus and L. Shen, *Tetrahedron*, 1999, **55**, 3553–3560.
- 5 For a recent review of cycloaddition reactions involving oxidopyrylium species in synthesis, see: V. Singh, U. M. Krishna Vikrant and G. K. Trivedi, *Tetrahedron*, 2008, **64**, 3405–3428.
- 6 For some of our contemporaneous studies and those of others, see: B. Tang, C. D. Bray and G. Pattenden, *Tetrahedron Lett.*, 2006, **47**, 6401–6404; P. A. Roethle, P. T. Hernandez and D. Trauner, *Org. Lett.*, 2006, **8**, 5901–5904.
- 7 S. Ma and E.-i. Negishi, *J. Org. Chem.*, 1997, **62**, 784–785.
- 8 P. A. Roethle and D. Trauner, *Org. Lett.*, 2006, **8**, 345–347, see also: F. Roschangar, J. C. Brown, B. E. Cooley, M. J. Sharp and R. T. Matsuoka, *Tetrahedron*, 2002, **58**, 1657–1666.
- 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.