

# Structure and total synthesis of benzylthiocrellidone, a novel dimedone-based vinyl sulfide from the sponge *Crella spinulata*

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A concise synthesis of the yellow pigment benzylthiocrellidone **1**, based on a Michael addition–elimination of dimedone **2** to the ketene thioacetal **7** derived from dimedone, benzyl bromide and carbon disulfide, is described. The synthetic pigment had an X-ray crystal structure identical to that measured for the natural product.

Benzylthiocrellidone is the name given to a novel and unprecedented sulfur-containing yellow pigment isolated from the brightly red coloured sponge *Crella spinulata* found on the Great Barrier Reef in Australia.<sup>1</sup> The molecule has a structure, viz. **1**, based on two dimedone (5,5-dimethylcyclohexane-1,3-

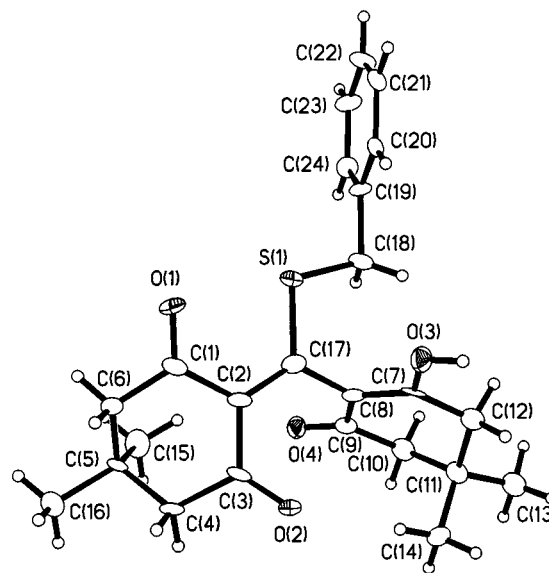
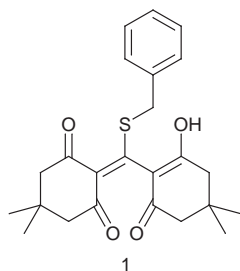
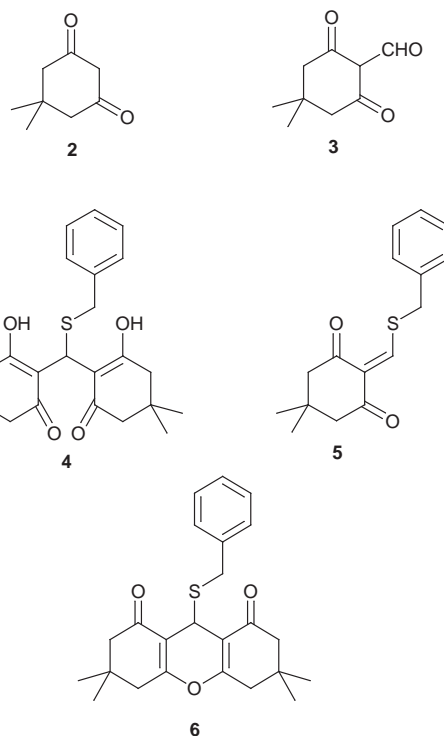


Fig. 1

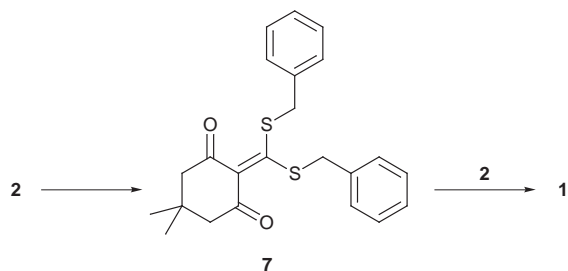
dione) rings linked *via* a benzylthio methyldene bridge at their C-2 positions. Benzylthiocrellidone is the first recorded example of a natural product containing a dimedone (or dimedone methane) unit.<sup>2</sup> The natural product exhibits strong absorption in both the ultraviolet A ( $\lambda_{\max}$  345 nm;  $\epsilon$  18 500 dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>) and ultraviolet B ( $\lambda_{\max}$  295 nm;  $\epsilon$  16 000 dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>) regions which may indicate a biological role in providing protection for the sponge from the deleterious effects of ultraviolet radiation. The structure of benzylthiocrellidone followed from extensive analysis of its spectroscopic properties in conjunction with an X-ray crystal structure determination (Fig. 1).<sup>1</sup> In pursuance of our interests in the synthesis of novel heteroatom containing natural products of biological significance from marine organisms, we now describe a short and concise total synthesis of benzylthiocrellidone.

We examined two conceptually similar synthetic approaches to the structure **1**, both using dimedone **2** and benzyl derivatives as starting materials, but differing in the source of the one carbon unit making up the methyldene residue joining the two dimedone rings to the benzylthio moiety. Thus, formylation of dimedone **2**, using ethyl orthoformate in the presence of acetic anhydride, first led to the known 2-formyl derivative **3**<sup>3</sup> which was next reacted with a second equivalent of dimedone under acid catalysis<sup>4</sup> in the presence of phenylmethanethiol producing the symmetrical adduct **4** in 43% yield; the by-product from this reaction was the vinyl sulfide **5** (34% yield). In spite of several attempts however, using a range of reagents (*e.g.* DDQ, MnO<sub>2</sub>, NBS), we were unable to selectively oxidise the adduct **4** to the target molecule **1**. The only interesting product to emerge from this particular study was the formation of the pyran **6**



(37% yield) following treatment of **4** with DDQ in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 12 h.

We next turned to an examination of the synthesis of the



ketene thioacetal **7** and the substitution of one of the benzylthio units in **7** with dimedone *via* a Michael addition–elimination sequence. The ketene thioacetal **7** is actually a known compound<sup>5a</sup> that can be produced when dimedone is treated with carbon disulfide and benzyl bromide using fluoride ion as base on an inorganic support of alumina.<sup>5b</sup> When we added this ketene thioacetal **7** to the potassium enolate of dimedone in THF at 25 °C, work up and crystallisation gave the product **1** in 60% yield, as bright yellow crystals, mp 202–204 °C, which showed identical chromatographic behaviour and spectroscopic data to those of naturally derived benzylthiocrellidone, mp 211 °C.<sup>6,7</sup> Further studies are now in progress to synthesise structures similar to natural **1**, with modified chromophores, and to evaluate their ultraviolet absorbing properties for potential applications in skin care products.

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### Notes and references

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- 2 For the dimedone–formaldehyde reaction see: (a) E. C. Horning and M. G. Horning, *J. Org. Chem.*, 1946, **11**, 95. For an example of a naturally occurring prenylated cyclohexane-1,3-dione see: (b) H. Obara, J. Onodera, Y. Machida and S. Yada, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3034; (c) M. R. Cann, A. Davis and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1982, 375.
- 3 B. D. Akehurst and J. R. Bartels-Keith, *J. Chem. Soc.*, 1957, 4798.
- 4 K. Fuchs and L. A. Paquette, *J. Org. Chem.*, 1994, **59**, 528.
- 5 (a) A. Z.-Q. Khan and J. Sandström, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2085; (b) D. Villemain and A. B. Alloum, *Synthesis*, 1991, 301. We produced **7** from dimedone using the literature procedure in an unoptimised 20% yield.
- 6 Synthetic benzylthiocrellidone was prepared from dimedone and the ketene dithioacetal **7** as follows: potassium *tert*-butoxide (42 mg, 0.36 mmol) was added in one portion to a solution of dimedone (51 mg, 0.36 mmol) in THF (5 ml) and the mixture was then stirred at room temperature for 30 min. A solution of the ketene dithioacetal **7** (140 mg, 0.35 mmol) in THF (2 ml) was added dropwise over 10 min and the mixture was then left to stir overnight. Ether (10 ml) was added, and the mixture was extracted with water (2 × 10 ml). The combined aqueous extracts were acidified with 1 M HCl and the precipitated yellow solid was collected by filtration. Recrystallisation from methanol gave *benzylthiocrellidone* (87 mg, 60%) as yellow crystals, mp 202–204 °C;  $\nu_{\max}$ (Nujol<sup>®</sup>)/cm<sup>-1</sup> 2921, 2853, 1687, 1640, 1604, 1461, 1375, 1328;  $\delta_{\text{H}}$ (360 MHz, CDCl<sub>3</sub>), 1.13 (12H, s, 4 × Me), 2.47 (8H, s, 4 × CH<sub>2</sub>), 3.81 (2H, s, SCH<sub>2</sub>Ph), 7.25–7.34 (5H, m, C<sub>6</sub>H<sub>5</sub>);  $\delta_{\text{C}}$ (90 MHz, *d*<sub>6</sub>-DMSO), 28.4 (q), 39.0 (t), 127.7 (d), 128.9 (d), 129.5 (d), 136.6 (s), 171.8 (s) (some peaks not evident due to tautomeric exchange); *m/z* (Electrospray) 413.1754, C<sub>24</sub>H<sub>29</sub>O<sub>4</sub>S (MH<sup>+</sup>) requires 413.1787.
- 7 The X-ray structure for synthetic benzylthiocrellidone, shown in Fig. 1, was identical to the X-ray crystal structure measured for the natural product isolated from *Crella spinulata*.<sup>1</sup> A crystal of **1** was encapsulated in a film of RS3000 perfluoropolyether oil and mounted on a glass fibre before transfer to the diffractometer.
- Crystal data.** C<sub>24</sub>H<sub>28</sub>O<sub>4</sub>S, *M* = 412.52, monoclinic, *a* = 5.939(4), *b* = 14.950(7), *c* = 11.748(7) Å,  $\beta$  = 91.14(6)°, *U* = 1042.9(11) Å<sup>3</sup>, *T* = 150(2) K, space group *P*2<sub>1</sub> (No. 4), *Z* = 2, *D*<sub>c</sub> = 1.314 g cm<sup>-3</sup>,  $\mu$ (Mo-K $\alpha$ ) = 0.183 mm<sup>-1</sup>, 3195 unique reflections measured and used in all calculations. Final *R*<sub>1</sub>[2171 *F* ≥ 4 $\sigma$ (*F*)] = 0.0988 and *wR* (all *F*<sup>2</sup>) was 0.244. CCDC reference number 207/312. See <http://www.rsc.org/suppdata/p1/1999/847> for crystallographic files in .cif format.

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