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Synthesis and anti-fungal properties of some simple cyclopentenones and derivatives

J. Allen Miller,* Ashley W. Pugh, G. Mustafa Ullah and G. Malcolm Welsh

Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

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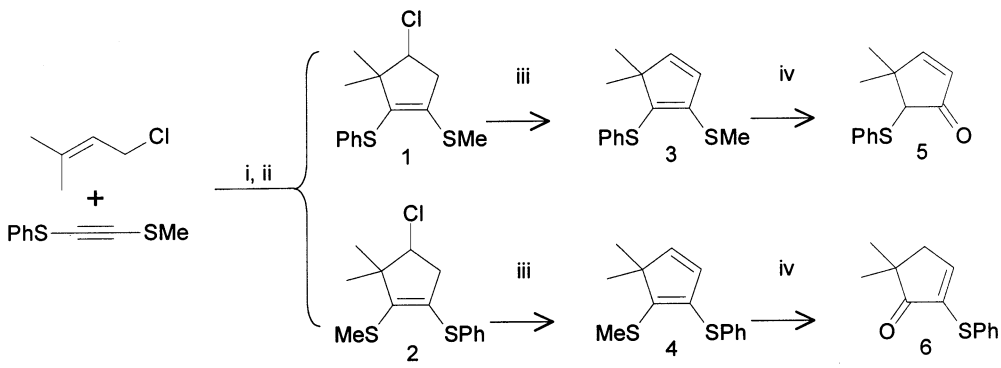
Abstract—1-Methylsulphenyl-2-phenylsulphenylethyne has been shown to be a precursor for either α-sulphenyl ketone or α-methylene ketone moieties in cyclopentenoids produced via [3+2] cycloaddition of an allyl cation. One of these ketones, the α-sulphenyl cyclopentenone **5**, has been found to display potency against a range of fungi in vitro but its close analogues are largely inactive.

More than a decade ago, one of us reported[1] the synthesis of 4-chlorocyclopentenes via the [3+2] cycloaddition of alkynes to allyl cations, generated from allylic chlorides under Lewis acidic conditions. Subsequently, this reaction was applied to 1-sulphenylalkynes bearing either an MeS- or PhS- group, and incorporation of these sulphenyl ligands was observed to result in regiochemical control and in higher yielding cycloadditions.[2,3] Given the facility with which these cycloadducts can be transformed into sulphenylated cyclopentadienes,[4] there was a good prospect that the use of bis-sulphenylethynes in the cycloaddition would allow entry to a range of simple sulphenylcyclopentenones via the cycloadducts **1** and **2**, followed by hydrolysis of the dienyl sulphide intermediates **3** and **4**, as outlined in Scheme 1. We report here that this projected chemistry has been achieved and represents a novel, short and flexible route to cyclopentenones, such as **5** and **6**, bearing organosulphur ligands.[5]

The reason for this structural focus lay in the range of biological and potentially medicinal properties exhibited by cyclopentenones and their analogues. Some of these are natural products like methylenomycin B, an anti-bacterial,[6] and a range of cyclopent-2-enone prostanoids such as the punaglandins and clavulones,[7] which were originally of interest for their anti-tumour properties, but which are now under scrutiny as potential anti-viral agents and cytoprotectives.[8] The patent literature[9] also describes natural cyclopentenones and



Scheme 1. *Reagents*: (i) $ZnCl_2$, CH_2Cl_2; (ii) chromatographic separation; (iii) KO^{t}Bu, THF; (iv) $HgCl_2$, aq. acetone, Δ.

Keywords: [3+2] cycloaddition; allyl cations; sulphenyl cyclopentenones; anti-fungal activity.

* Corresponding author. Present address: Protherics plc, Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL, UK. Tel.: +0044 (0)1625 500555; fax: +0044 (0)1625 500666; e-mail: allen.miller@protherics.com

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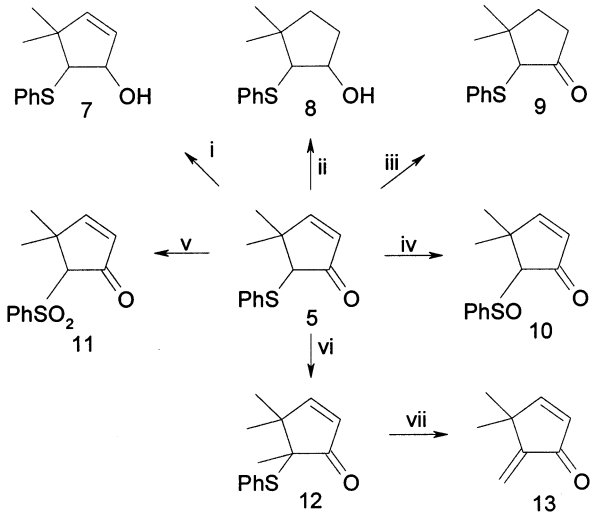
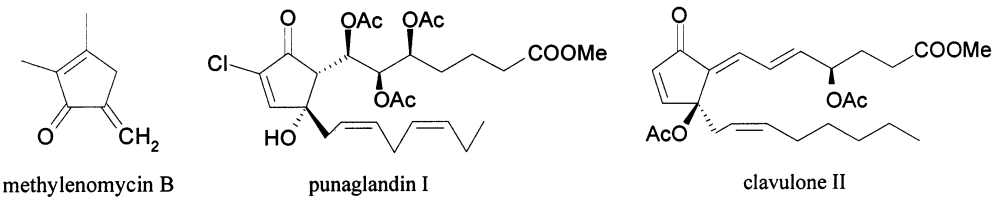


Scheme 2. *Reagents*: (i) LAH, Et_2O; (ii) $NaBH_4$, EtOH; (iii) $ZnCl_2$, Ph_2SiH_2, $Pd(PPh_3)_4$, $CHCl_3$; (iv) *m*-CPBA, CH_2Cl_2 (–40°C); (v) *m*-CPBA, CH_2Cl_2 (22°C); (vi) LDA, MeI; (vii) *m*-CPBA.

synthetic 2-substituted variants for which a range of claims are made with respect to anti-tumour activity and inhibition of osteoporosis. Here we also describe the in vitro anti-fungal properties of **5**, along with the subsequent synthesis and anti-fungal testing of a series of its simple analogues.



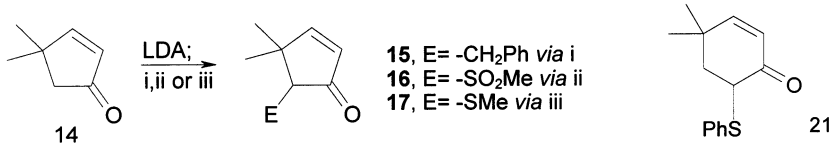
methylenomycin B punaglandin I clavulone II

1-Chloro-3-methylbut-2-ene was used as the allyl cation precursor in our cycloaddition experiments, which were run under the same conditions as those reported earlier.[1–3] Cycloaddition to 1-methylsulphenyl-2-phenylsulphenylethyne occurred in good yield, but, interestingly, the product was a 50:50 mixture of the regioisomeric adducts **1** and **2**. Fortunately, these adducts were readily separated by careful column chromatography, and each was then transformed individually into the corresponding dienes, **3** and **4**, respectively, using potassium *t*-butoxide.[4] Subsequent mercuric chloride catalysed hydrolyses of **3** and **4** (**1** and **2** were both inert to hydrolysis) each gave only the products resulting from hydrolysis of the methylsulphenyl group, i.e. enones **5** and **6**, respectively. The highly selective hydrolysis of the methyl vinyl sulphide function was no surprise,[10] although it contrasts sharply with the complete lack of regioselection in the previous [3+2] cycloaddition step. As shown in Scheme 2, ketone **5** was then elaborated into further derivatives **7**–**13** using methods that were standard, apart from the use of palladium mediated reduction of **5** with diphenylsilane,[11] to give **9**—conditions that were novel at the time. The dienone **13**, which is a structural isomer of methylenomycin B, and also contains the same dienone 'pharmacophore' as the clavulones, was formed spontaneously from the diastereomeric sulphoxides derived from **12**.

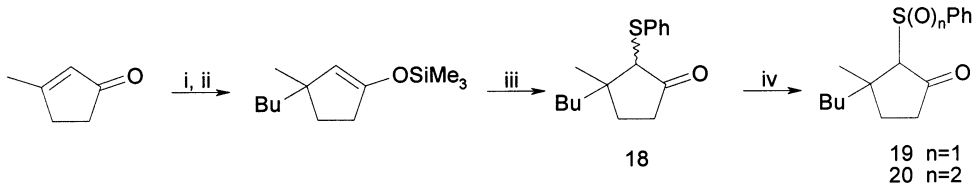
For some of our targets, **5** was not a sensible starting point. Thus we prepared[12] 4,4-dimethylcyclopent-2-enone **14** and from this the ketones **15**–**17** were made, as shown in Scheme 3. The benzylation and methanesulphonylation of the lithium dienolate of **14** proceeded normally, but sulphenylation was more problematic. Phenylsulphenylation, to provide **5** by a route different from [3+2] cycloaddition, worked well using diphenyldisulphide, but the corresponding reaction with dimethyldisulphide gave polysulphenylated products. This difficulty was overcome by using methyl methanthiol-sulphonate[13] as a sulphenylating agent.

It was also deemed desirable to have at least one lipophilic and relatively bulky group at the 4-position of analogues of **5**. This was achieved from 1-methylcyclopenten-3-one using the methodology of Horiguchi et al.[14] to add an *n*-butyl group in a copper mediated Michael addition. This chemistry is outlined in Scheme 4 and yielded compounds **18**–**20** as diastereomeric mixtures.

When the ketones and derivatives **5**–**21** were submitted to a range of microbiological screens, the anti-fungal properties of **5** stood out. Using miconazole as an internal standard, **5** was found to be more active against some strains, particularly the dermatophytes. The only other compound to display any significant activity was the methylated homologue **12**. From these data, it was clear that **5** had the makings of an anti-fungal lead, and that the structural features required for activity were rather tight, as shown by the data in the Table 1,[15] which records all compounds with any hint



Scheme 3. *Reagents*: (i) $PhCH_2Br$; (ii) $MeSO_2Cl$; (iii) $MeS\text{-}SO_2Me$.



Scheme 4. *Reagents*: (i) BuMgBr, THF, HMPA–CuBr·SMe_2; (ii) Me_3SiCl; (iii) PhSCl, CH_2Cl_2; (iv) *m*-CPBA, −78–20°C, CH_2Cl_2.

of activity. Compounds **7**–**9**, **14**, **16** and **18**–**21** were completely inactive. In particular, the data show that in **5** the double bond, the keto group, and the phenylsulphenyl group (especially striking is the lack of activity in the MeS, $PhCH_2$-, PhS(O)- and $PhS(O)_2$-analogues) are all critical to activity. Even the cyclohexenyl homologue **21** is inactive. We are not aware of any other reports of anti-fungal activity in sulphenyl cyclopentenones, although arylcyclopentanes, such as the herbertols[16] and arylated heterocyclics, such as the 2*H*,5*H*-furan-2-ones,[17] are known to have anti-fungal properties.

Given the interest in ketone **5**, it was subjected to a number of other bioassays. However, it showed little or no activity against a series of commercially important yeasts, and was not active in an in vivo model—*Candida albicans* nephritis in mouse. Moreover, it was not active against a range of Gram negative or Gram positive bacteria. Against flu-A and flu-B, **5** had IC_{50}s of 6 and 5 μM, respectively, but further studies suggested that these properties were the result of toxicity against the host MDCK cells in the culture. In contrast, no such indications of toxicity came from other cell culture media, or from studies of the effects of **5** on various measures of metabolic performance in isolated rat liver cells.

Details of experimental procedures for the preparation of 1-methylsulphenyl-2-phenylsulphenyl-ethyne, for its [3+2] cycloaddition, and for the preparation of **5**, appear below.

Preparation of 1-methylsulphenyl-2-phenylsulphenyl-ethyne

Phenylsulphenylethyne (2.4 g, 17.9 mmol) was dissolved in dry THF (20 ml) in a flame-dried flask under dry nitrogen and the stirred solution was cooled to −78°C. *n*-Butyllithium (1.6 M in hexane, 12.2 ml, 19.6 mmol) was then added gradually by syringe and the mixture stirred at −78°C for a further hour. Dimethyldisulphide (1.61 ml, 17.9 mmol) in dry THF (5 ml) was added dropwise at −20°C and the mixture stirred for three hours at −20°C, before allowing the temperature to rise to 20°C. Then water (25 ml) was added and the shaken mixture separated into two phases. The aqueous phase was washed with ether (3×10 ml) and the ether washings combined with the original THF phase. The com-

Table 1. Anti-fungal activity[a] of cyclopentanoids and miconazole

Organism	Miconazole	Compound number in text						
		5	**6**	**10**	**11**	**12**	**15**	**17**
Candida albicans P712	6.2	25	>100	Nil	>100	100	>100	Nil
Candida tropicalis P501	6.2	25	>100	Nil	>100	>100	>100	Nil
Cryptococcuus neoformans S9027	1.6	>100	>100	Nil	>100	>100	>100	Nil
Saccharomyces cerevisiae S7449	6.2	25	>100	Nil	>100	100	>100	Nil
Aspergillus fumigatus S7448	6.2	25	>100	Nil	>100	100	>100	Nil
Fusarium solani P420	6.2	25	>100	Nil	>100	100	>100	Nil
Microsporum canis S8029	6.2	1.6	>100	100	>100	25	>100	Nil
Microsporum canis P351	6.2	1.6	>100	100	>100	25	>100	Nil
Microsporum gypseum P352	6.2	1.6	>100	100	>100	25	>100	Nil
Microsporum gypseum CN344	6.2	1.6	>100	100	>100	25	>100	Nil
Trichophyton equinum S6571	6.2	1.6	>100	100	>100	25	>100	Nil
Trichophyton mentagrophyt S8354	6.2	1.6	>100	100	>100	25	>100	Nil
Trichophyton mentagrophyt P354	6.2	1.6	>100	100	>100	25	>100	Nil
Trichophyton rubrum S6572	6.2	1.6	>100	100	>100	25	>100	Nil
Trichophyton rubrum P356	6.2	1.6	>100	100	>100	25	>100	Nil
Epidermophyton floccosum S8362	6.2	1.6	>100	100	>100	25	>100	Nil
Sporothrix schenckii S7445	6.2	6.2	>100	>100	>100	100	>100	Nil
Sporothrix schenckii S8380	6.2	6.2	>100	>100	>100	100	>100	Nil
Exophiala jeanselmei S8370	6.2	6.2	>100	>100	>100	100	>100	Nil
Exophiala werneckii S8366	6.2	6.2	>100	>100	>100	100	>100	Nil

[a] Data are reported as MIC (μg/ml), i.e. the minimum concentration of drug required to inhibit growth of the fungus on an appropriate in vitro medium.

bined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by fractioned distillation, and 1-methylsulphenyl-2-phenylsulphenylethyne (1.70 g, 53%) was obtained as a pure, colourless oil, bp 94–98°C/0.05 mmHg. The IR spectrum showed a weak C–C stretch at 2060 cm^{-1} and the ^1H NMR showed δ 2.40 (s, 3H, SMe) and 7.2 (bs, 5H, SPh) ppm.

Cycloaddition of 1-chloro-3-methylbut-2-ene to 1-methylsulphenyl-2-phenylsulphenylethyne

Compounds **1** and **2**: 1-Methylsulphenyl-2-phenylsulphenylethyne (2.20 g, 12.20 mmol) and reagent grade zinc chloride (3.00 g, 22.05 mmol) were added sequentially to stirred, dry, dichloromethane (25 ml) under dry nitrogen in a flame-dried, three-necked flask. 1-Chloro-3-methylbut-2-ene (1.50 g, 14.66 mmol) in dry dichloromethane (10 ml) was then added dropwise over 10 min, and the mixture stirred at room temperature for a further 4 h. The reaction was then quenched by the cautious addition of a 33% ammonia solution and the dichloromethane phase was separated. The aqueous ammonia phase was then washed with chloroform (2×20 ml) and the combined dichloromethane and chloroform phases were dried over anhydrous magnesium sulphate. Filtration of the solution and evaporation of the solvents yielded 3.80 g of a slightly yellow oil, the TLC (1% ether in 40–60°C petrol) of which revealed two major close running, high R_f spots. These were then separated by careful dry column chromatography on silica using 40–60°C petrol to give compounds **2** (1.31 g, 38%) and **1** (1.28 g, 37%)[18] in sequence, as colourless oils.

Hydrolysis of 1-phenylsulphenyl-2-methylsulphenyl-5,5-dimethylcyclopenta-1,3-diene (3)

Compound **5**: Cyclopentadiene **3** (496 mg, 2.0 mmol) and mercuric chloride (2.7 g, 10 mmol) were dissolved in 20% aqueous acetone (20 ml) and the stirred mixture was refluxed for 6 days. The mixture was then filtered and the residue washed with acetone, and the original filtrate and the washings were then combined and the solvent evaporated to yield a yellowish oil (495 mg). Dry column chromatography with ether:40–60°C petrol (1:1) then gave pure 4,4-dimethyl-5-phenylsulphenylcyclopent-2-enone (**5**)[20] as a thick, colourless syrup (401 mg, 92%).

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18. Compound **2**: ^1H NMR ($CDCl_3$) δ 1.08 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.33 (s, 3H, SCH_3), 2.48 (m, 2H, CH_2), 3.93 (dd, $J=9$ Hz and 7.5 Hz, 1H, $CHCl$) and 7.27 (bs, 5H, PhS) ppm. IR (neat) 2940, 2900, 2840, 1570, 1540,

1465, 1450, 1425, 1270, 1250, 1010, 847 (str),[19] 730, 690 and 675 cm^{-1}. MS (m/z) 284.0459 ($C_{14}H_{17}S_2Cl$ requires: 284.0462). Compound **1**: ^1H NMR ($CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.25 (s, 3H, SCH_3), 2.90 (m, 2H, CH_2), 4.10 (dd, appears as t, $J=7$ Hz, 1H, $CHCl$), 7.13 (bs, 5H, Ph) ppm, MS (m/z) 284.0460 ($C_{14}H_{17}S_2Cl$ requires: 284.0462).

19. This absorption is consistent in the 4-chlorocyclopent-1-enes produced in this and other [3+2] cycloadditions to allyl cations, as described in References 1–3.
20. Compound **5**: ^1H NMR ($CDCl_3$) δ 1.23 (s, 6H, 2×CH_3), 3.57 (s, 1H, $CHSPh$), 6.1 (d, $J=6$ Hz, 1H, =CH–C=O), 7.2–7.5 (m, 6H, Ph and HC=C–C=O). IR (neat) 1670(s), 1470, 1450, 1425, 1350, 1325, 1240, 1130, 830, 800, 730 and 680 cm^{-1}. MS (m/z) 218.0773 ($C_{13}H_{14}OS$ requires: 218.0765).