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Synthesis and cytotoxic properties of a series of bicyclo[3.2.1]octane α-methylene ketones

J. A. Miller,[a,*] G. M. Ullah,[a] G. M. Welsh[a] and P. Mallon[b]

[a]*Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK*
[b]*Chemistry Department, University of St. Andrews, St. Andrews, Fife, Scotland KY16 9AL, UK*

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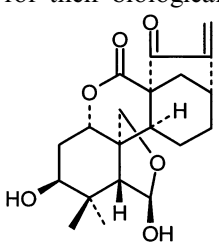
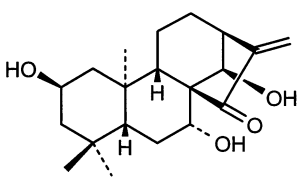
Abstract—The 8-chlorobicyclo[3.2.1]oct-6-ene **3** has been prepared by a [3+2] cycloaddition route, and converted to the bicyclic α-methylene ketones **6** and **8**–**12**, some of which showed cytotoxic properties.

Over the years, the literature has provided many examples of α,β-unsaturated ketones which possess interesting biological properties. These range in structure from simple monocyclics, like the antibiotic methylenomycin B[1] to more complex and usually more lipophilic substances, like the punaglandins[2] and the clavulones,[3] which have led to new approaches to anti-viral and anti-inflammatory drugs.[4] However, there is also a huge number of polycyclic terpenoid structures, e.g. the diterpenes of the *Rabdosia* family, such as enmein **1** and the *ent*-kaurane umbrosin A **2**, in which an α-methylene cyclopentanone is embedded in a bicyclo[3.2.1]octane framework.[5] Compounds such as **1** and **2** exhibit a range of anti-tumour and anti-microbial properties, and there is good evidence that the enone group is essential for their biological activity.[5]



1
enmein



2
umbrosin A

This background suggested that there would be potential interest in simpler lipophilic structures containing an α-methylene cyclopentanone sub-unit.[6] Arising from observations made in our [3+2] cycloaddition approach to the helminthosporanes,[7] it seemed reasonable to speculate that a bicyclo[3.2.1]oct-6-ene, such as **3**, would act as a one-pot precursor for an α-methylene ketone functionality, since the double bond in **3** is part of BOTH an allyl ether and a vinyl sulphide.[8] Moreover, **3** was likely to be accessible via a [3+2] cycloaddition of the allylic chloride **4** to the alkyne **5**—a particular example of a general reaction described some years ago.[9] It was also envisaged that this de novo synthetic approach would allow facile incorporation of different groups, including other rings, around the cyclohexane ring of the bicyclics, e.g. the 8-chloro group in **3** would, in principle, allow another functionality to be introduced at the site equivalent to where **2** has a hydroxyl group. In principle, this direct and flexible route[10] to α-methylene cyclopentanones could offer significant advantages over existing methodology, which is largely based on interconversions of natural products,[5] or on 1,2-rearrangements of synthetic bicyclo[4.2.0] systems.[6b] This report describes the synthesis of several of our targets via [3+2] cycloaddition chemistry, and briefly describes their anti-tumour properties.[11]

The synthesis of **5** and its [3+2] cycloaddition to the allylic chloride **4** (which contains about 15% of its allylic isomer 3-chloro-3-methylcyclohexene—both give the same allyl cation) are outlined in Scheme 1. The cycloaddition goes in reasonable yield, and is amenable to scale-up to the 50 g level. Thereafter, we established conditions for the selective hydrolyses of each of the functionalities of **3**—the ether/sulphide and the chlorine. The first of these, hydrolysis to the enone **6**, was

Keywords: [3+2] cycloaddition; Hg(II) mediated hydrolysis; alkynyl and vinyl sulphide; bicyclo[3.2.1]octane α-methylene ketones; cytotoxicity.

* Corresponding author. Present address: Protherics PLC, Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL, UK. Tel.: +44 (0)1625 500555; fax: +44 (0)1625 500666; e-mail: allen.miller@protherics.com

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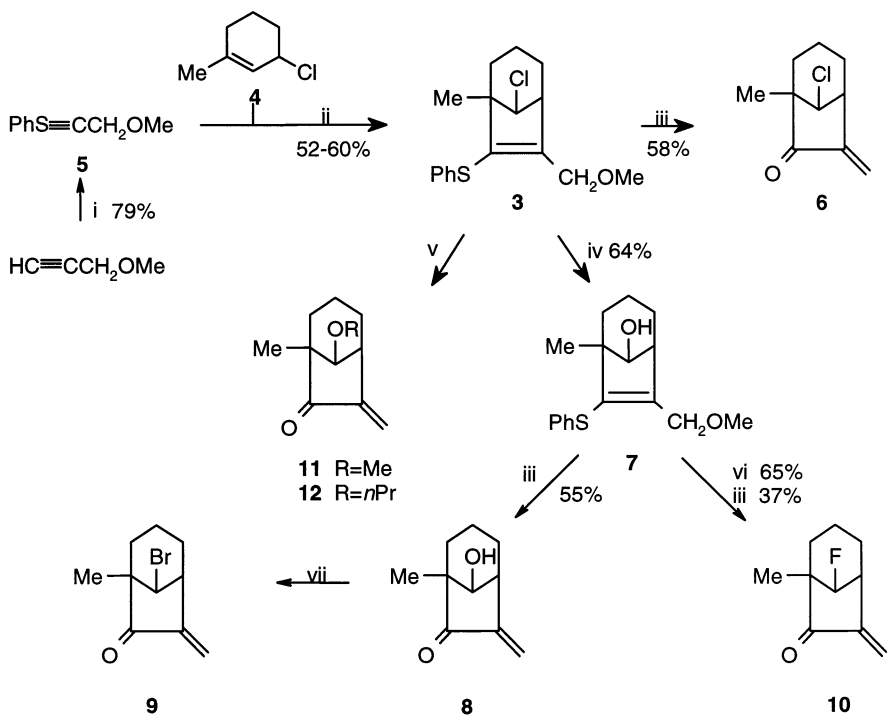
achieved with mercury(II) chloride in refluxing aqueous acetone, whereas the latter was accomplished with mercury(II) perchlorate at room temperature, and yielded the alcohol **7**—see Scheme 1. Availability of **7** then allowed entry to the analogues **8**–**10**. The similarity in these hydrolysis conditions[12] suggested that all of the functionalities in **3** might be altered in the same operation, and this was indeed the case, e.g. the preparation of **11** and **12** from **3**, as shown in Scheme 1.

Structural assignment of the enones in Scheme 1 is based on appropriate analytical data, but the enone functionality was easily recognised[13] from the consistent broadened singlets (J<0.5 Hz) that appeared at δ 5.2± 0.08 and 5.99±0.06 ppm in the proton NMR spectra, and from the strong infrared absorptions at 1720±5 and 1635±5 cm^{-1}. Similarly, the proton NMR spectra are diagnostic for the relative configuration at C-8 and all the compounds reported here show a doublet (J=5 Hz) for the C-8 proton. This is well established in the literature for the *endo* series (i.e. in which the functional group at C-8 is *anti* to the enone group), and is readily distinguished from the *exo* series, for which the vicinal coupling constant (<1 Hz) is considerably smaller.[14] The *endo* configuration of the starting chloride **3**, and the observed retention of configuration in its analogues, are expected[15] in bicyclo[3.2.1]oct-6-enes, on account of participation by the 6-ene in stabilisation of positive charge development at the 8-position, e.g. in solvolyses, or Lewis acid-mediated substitutions at C-8.

Having established a general route to 8-substituted bicyclo[3.2.1]octan-7-ones, the 'parent' compound **6** was found to be active against two tumour cell lines-P388 (IC_{50} 0.53 μM) and DLD-1 (IC_{50} 9.7 μM), both run as proliferative assays. The analogues **8** and **9** were considerably weaker (about 10% growth inhibition at 10 μM in each case). The chloride **6** was then found to kill mice after dosing at levels ranging from 65–225 mg/kg. Furthermore, when the 8-fluoro derivative **10** was subject to the in vitro assays, it was observed that it was so volatile that it killed cells in neighbouring wells. At this point work on this series of compounds ceased, and we would caution other investigators to bear in mind the potential for toxicity and volatility in these compounds and their analogues.

Details of key experimental procedures are given below.

Preparation of 1-methyl-6-methoxymethyl-7-phenylsulphenyl-8-chlorobicyclo[3.2.1]oct-6-ene ***3***. The cycloadduct was prepared by addition at −30°C of 1-methyl-3-chlorocyclohexene **4** (containing about 15% of its allylic isomer, 3-chloro-3-methylcyclohexene) (1.40 g, 10.7 mmol) to a stirred mixture of 1-phenylsulphenyl-2-methoxymethylethyne **5** (1.78 g, 10.0 mmol) and reagent grade zinc chloride (3.0 g, 22.0 mmol) suspended in dichloromethane (20 ml). Thereafter the sequence followed the published procedure,[9] and, after chromatographic purification, **3** (52–60%) was isolated as a very pale yellowish oil. Key ^{1}H NMR data include δ 0.85 (s, 3H, 1-CH_3), 3.32 (s, 3H, CH_2OCH_3), 4.12 (d, J=5 Hz, 1H, 8-CHCl) and 4.35 (d, ^2J=12 Hz, 1H, one of CH_2OCH_3) and 4.15 (d, ^2J=12 Hz, 1H, one of CH_2OCH_3) ppm.



Scheme 1. *Reagents*: (i) *n*BuLi, PhSCl, THF, −78°C; (ii) $ZnCl_2$, CH_2Cl_2; (iii) $HgCl_2$, aq. acetone, Δ; (iv) $Hg(ClO_4)_2$, aq. DME, 20°C; (v) $Hg(ClO_4)_2$, ROH, 20°C; (vi) DAST, CH_2Cl_2, −50 to 20°C; (vii) Ph_3P, CBr_4, MeCN, reflux.

General procedure for the preparation of 6-methylene bicyclo[3.2.1]oct-6-enes. Compound **6**: The 8-chlorobicyclo[3.2.1]oct-6-ene **3** (3.08 g, 10 mmol) and mercury(II) chloride (4.70 g, 17.3 mmol) were dissolved in 20% aqueous acetone (50 ml) and the mixture refluxed for 5 days. Solvents were then evaporated and the residue shaken with water (25 ml) and chloroform (25 ml). The aqueous layer was rewashed with chloroform (2×20 ml) and the combined chloroform extracts were washed with water (20 ml). The chloroform solution was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography and enone **6** (1.78 g, 58%) was isolated as a very pale yellow oil following elution with ether: 40–60°C petrol (1:10). Key ^{1}H NMR data include δ 1.04 (s, 3H, 1-CH_3), 3.97 (d, $J=5$ Hz, 1H, 8-CHCl), 5.20 (bs, 1H, one of =CH_2) and 5.93 (bs, 1H, one of =CH_2) ppm. Strong infrared absorptions for the α-methylene cyclopentanone appeared at 1725 and 1640 cm^{-1}.

Mercury(II) perchlorate mediated hydrolysis-preparation of 8-hydroxybicyclo[3.2.1]oct-6-ene **7**. Mercury(II) perchlorate was freshly prepared by addition of mercuric oxide (7.60 g) to 70% perchloric acid (8 ml) in dimethoxyethane (DME) (90 ml). Gentle heating was required to dissolve all the solid. After allowing to cool, water (6.8 ml) was added, followed by a solution of cycloadduct **3** (10 g, 32.4 mmol) in DME (20 ml). The reaction mixture was stirred at room temperature for 3.5 hours, then water (200 ml) was added and the reaction mixture extracted with ether (3×50 ml). The combined organic extracts were washed with dilute hydrochloric acid (100 ml) and then with a saturated sodium chloride solution and dried ($MgSO_4$). After removing the solvent, the crude product was purified by flash column chromatography, eluting with ether: 40–60°C petrol (1:2) and the pure bicyclic alcohol **7** (6.02 g, 64%) was isolated as a clear, thick syrup. Key ^{1}H NMR data include δ 0.82 (s, 3H, 1-CH_3), 2.47 (bs, 1H, OH), 3.27 (s, 3H, CH_2OCH_3), 3.69 (d, $J=5$ Hz, 1H, 8-CH-OH), 4.17 (d, $^2J=12$ Hz, 1H, one of CH_2OCH$_3$) and 4.37 (d, $^2J=12$ Hz, 1H, one of CH_2OCH$_3$) ppm. In the infrared spectrum a strong broad absorption appeared for the hydroxy group at 3430 cm^{-1}.

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