Synthesis of (±)-Clavularin B: Unambiguous Structure Determination

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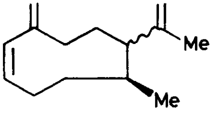
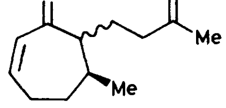
The structures of the clavularins have been established unambiguously through synthesis of (±)-clavularin B from cyclohepta-2,6-dienone.

The cytotoxic and anticarcinogenic clavularins A and B have recently been isolated from two different soft corals by a Japanese group.[1,2] On the basis of extensive ^{1}H n.m.r. studies they proposed cyclononenone structures (**1a**) and (**1b**) for the two epimeric clavularins A and B respectively.[1] However, in a subsequent Corrigendum, they revised their original proposals and assigned to clavularins A and B the seven-membered ring structures (**2a**) and (**2b**), a conclusion reached through interpretation of additional ^{1}H n.m.r. data.[3]

Encouraged by the interesting biological activity of the clavularins, we have synthesised the most readily accessible of the proposed compounds, cycloheptenone (**2b**).



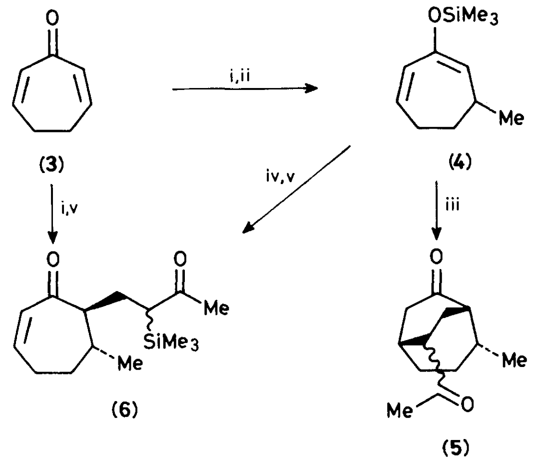
(**1**)



(**2**)

a *cis*
b *trans*

The logical starting material for a synthesis of (**2b**) is cyclohepta-2,6-dienone (**3**) which is readily available from cycloheptanone.[4] A conjugate addition of a methyl group to dienone (**3**) followed by a regioselective trapping of the intermediate enolate anion with methyl vinyl ketone (or a synthetic equivalent thereof) should provide a short and efficient preparation of enone (**2b**). Treatment of dienone (**3**) with lithium dimethyl cuprate followed by chlorotrimethylsilane gave the silyl dienol ether (**4**) in 93% yield (Scheme 1).



Scheme 1. *Reagents and conditions:* i, Me_2CuLi, tetrahydrofuran (THF), −20 °C; ii, Me_3SiCl, hexamethylphosphoramide (HMPA), Et_3N, −78 to 20 °C; iii, methyl vinyl ketone, $TiCl_4$, dichloromethane, −78 °C, 2 min; K_2CO_3; iv, MeLi, THF, 25 °C; v, 3-trimethylsilylbut-3-en-2-one (1.5 equiv.), HMPA (2.5 equiv.), −78 to −20 °C.

It has been found that Michael additions of kinetically generated enolate anions to methyl vinyl ketone proceed with extremely low yields.[5] Among the many ingenious solutions which have been put forward to overcome this problem, Mukaiyama's Lewis acid induced Michael reaction of silyl enol ethers with α,β-unsaturated ketones[6] seemed especially suitable for this case. When silyl dienol ether (**4**) was treated with methyl vinyl ketone in the presence of titanium tetrachloride the expected Michael reaction took place but was followed immediately by a second, intramolecular conjugate addition[7] of the intermediate titanium enolate to the resulting enone to produce the bicyclic compound (**5**) (one diastereoisomer only). Stork and coworkers[8] proposed the use of a trimethylsilyl substituted methyl vinyl ketone to circumvent the problems associated with the Michael reaction of methyl vinyl ketone under basic, aprotic conditions. Thus, the enolate anion generated from silyl dienol ether (**4**) was allowed to react with 3-trimethylsilylbut-3-en-2-one[9] in the presence of HMPA to produce a mixture of diastereoisomeric Michael adducts (**6**).† Ethanolysis of the silicon moiety[11] and preparative t.l.c. (silica gel) afforded the cycloheptenone (**2b**) in 62% yield from (**4**).

Alternatively, (**2b**) could be obtained directly by an analogous trapping of the enolate anion which was generated by the addition of lithium dimethyl cuprate to the cyclohepta-2,6-dienone (**3**) [(**3**) → (**2b**): 28%].

The spectral data for the synthetic cycloheptenone (**2b**) (^1H and ^{13}C n.m.r., i.r., and u.v.) are in complete agreement with the ones published for clavularin B.[1] Therefore, it can be concluded that clavularin B possesses the seven-membered ring structure (**2b**) and that the epimeric clavularin A corresponds to the *cis*-compound (**2a**).

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† Preferential formation of the *trans*-adduct was expected from analogy with smaller ring systems (ref. 10).