Stereocontrolled Construction of the Guaiane Framework based on *trans*-3-Isopropenyl-2-(2′-methoxycarbonylethyl)cyclopentan-1-one

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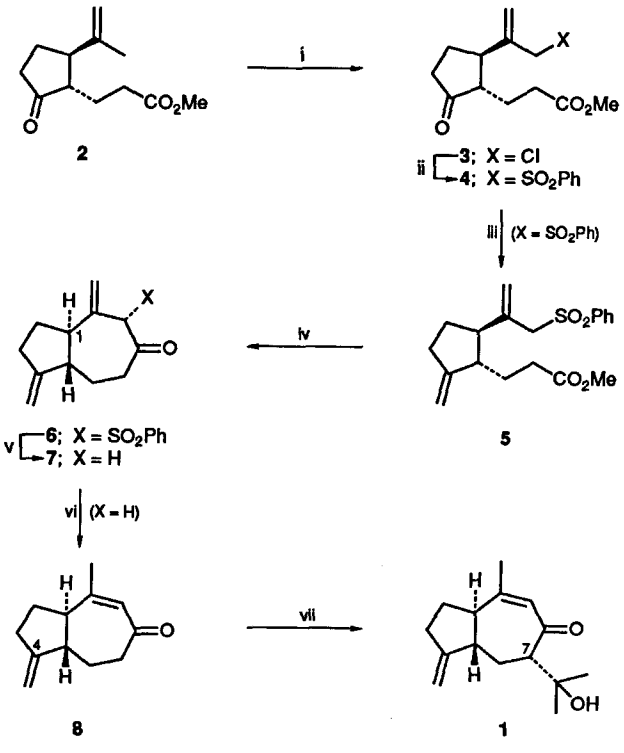
Starting from the readily available title cyclopentanone derivative, the *trans*-fused hydroazulenoid **1** has been prepared in seven steps by intramolecular heptaannulation of the key sulfonecarboxylate **5**.



Scheme 1 *Reagents and conditions*: i, SO_2Cl_2, Py, CCl_4, −10 to 0°C, 15 min; ii, $PhSO_2Na$, DMF, 50°C, 2 h; iii, CH_2Br_2, $TiCl_4$–Zn, THF–CH_2Cl_2, 25°C, 30 min; iv, $NaN(SiMe_3)_2$, C_6H_6, 25°C, 15 h; v, Al(Hg), EtOH–H_2O, 25°C, 1.5 h; vi, (*a*) LDA, THF–hexane, −10°C, 10 min, (*b*) Me_3SiCl, NEt_3 (cat.), THF, −10 to 25°C, 15 min, (*c*) 50% aq. H_2SO_4, 25°C; vii, (*a*) LDA, THF–hexane, −78 to −45°C, 15 min, (*b*) $ZnCl_2$–THF, −45°C, 10 min, (*c*) acetone, −45 to 0°C, 30 min

Of the few basic strategies for the construction of the hydroazulenoid ring system of guaiane sesquiterpenes, elaboration of a cycloheptane moiety onto an appropriately functionalized cyclopentane unit remains the most frequently employed approach.[1,2] Within this framework, we discuss here a stereocontrolled synthesis of the guaiane-type *trans*-fused hydroazulenoid **1** starting from the unsaturated cyclopentane derivative **2**,[3] which is readily available from methylheptenone (Scheme 1).

In our approach, chlorination of the alkene **2** with sulfuryl chloride in the presence of pyridine (Py) under the conditions we found earlier for related compounds[4] gave the allylic chloride **3**. Treatment of **3** with sodium benzenesulfinate in *N*,*N*′-dimethylformamide (DMF) furnished the corresponding sulfone **4**. Alkenation of the latter with Oshima–Lombardo reagent[5] led to the diene **5** in 40% overall yield.

The crucial step of the whole sequence is the intramolecular heptaannulation of the cyclopentene derivative **5**. The best result for this was achieved by treatment of **5** with a dispersion of sodium bis(trimethylsilyl)amide (2 mol equiv.) in benzene at ambient temperature. The β-keto sulfone **6** thus obtained in 60% isolated yield was then reductively desulfonylated following the Corey–Chaykovsky procedure[6] to give ketone **7** almost quantitatively.

Hydroazulenone **7** belongs to a series of *trans*-fused tris-norguaianes and possesses a suitable functionality to secure the introduction into its molecule of the missing isopropyl substituent at C-7. In order to exclude the potential formation at this stage of the unwanted α′-regioisomer the starting β,γ-ketone **7** was initially converted into the conjugated ketone **8**. The latter was readily prepared in a one-pot procedure by treatment of **7** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) solution, followed by thermodynamically controlled *O*-silylation of the resultant lithium enolate with trimethylsilyl chloride and triethylamine as a catalyst and then by acid catalysed hydrolysis of the intermediate 1,3-siloxydiene.

Finally, a zinc chloride-promoted aldol condensation[7] of the conjugated ketone **8** with acetone gave the target guaiane-type ketol **1** in 60% isolated yield from **7** as a single stereoisomer.

The new compounds **1**, **3**–**8** were identified comprehensively by elemental and spectroscopic† analyses. In addition, the structure of crystalline β-keto sulfone **6** was confirmed by X-ray analysis.[8]

This synthetic scheme opens new routes to the construction of natural *trans*-fused guaiane sesquiterpenes.

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Received: Moscow, 8th June 1992
Cambridge, 1st July 1992; Com. 2/03110H

† ^1H NMR spectrum (250 MHz, $CDCl_3$, rel. $SiMe_4$) of **1**: δ 1.10 and 1.21 (s, 6H, CH_3), 1.3–2.5 (m, 8H, CH, CH_2), 1.89 (br s, 3H, CH_3), 2.68 (dd, 1H, *J* 7 and 11 Hz, HC-7), 4.82 and 4.90 (br s, 2H, H_2C=C), 5.89 (br s, 1H, HC-9).