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SYNTHESIS OF THE NON-ISOPRENOID SESQUITERPENE, β-GORGONENE

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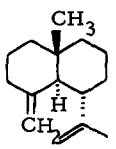
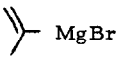
In 1968 Weinheimer and co-workers reported the isolation of β-Gorgonene, a unique non-isoprenoid member of the sesquiterpenes from Pseudopteragorgia americana, which was assigned structure 1 on the basis of spectroscopic and x-ray data.[1,2] The structure of β-Gorgonene seemed to provide a convenient test of the control which steric factors in an α, β unsaturated ketone have over the stereochemical outcome of conjugate addition as well as the synthetic utility of this approach.

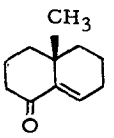
Presently, empirical evidence[3] and mechanistic rationalizations[4] suggest that the preferred mode of addition of organometallic reagents to α, β unsaturated ketones is antiparallel entry during which continuous overlap of the developing bond with the π system of the enone is possible through the transition state.[5] In most cases the stereochemical outcome of this process is axial substitution. However, steric factors play an important role in determining the nature of the transition state.[6] The conformational preferences of the enone system may be altered in order to accomodate stereoelectronically favored antiparallel approach and relieve the steric interactions in the transition state (Scheme 1).



(1)



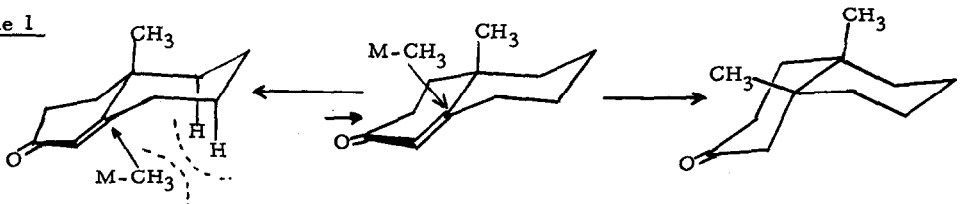
(2)



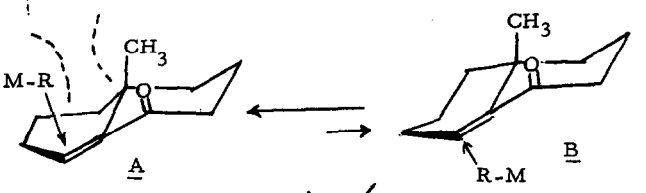
(3)

We wished to determine the stereochemical outcome of a case in which the reagent approaching the enone system in its preferred conformation from the antiparallel direction would encounter severe non-bonded interactions. Such a case is the addition of isopropenyl Grignard reagent (CuI catalyzed) (2) to octalone (3), since the incoming group should encounter a large isopropenyl-methyl interaction in the transition state.[7] Conformational interconversion similar to that shown in Scheme 1 should allow approach from the less hindered direction and retain the antiparallel approach of the reagent (Scheme 2). Reaction should then occur primarily through a transition state resembling conformer B and result overall in the desired equatorial substitution.

Scheme 1

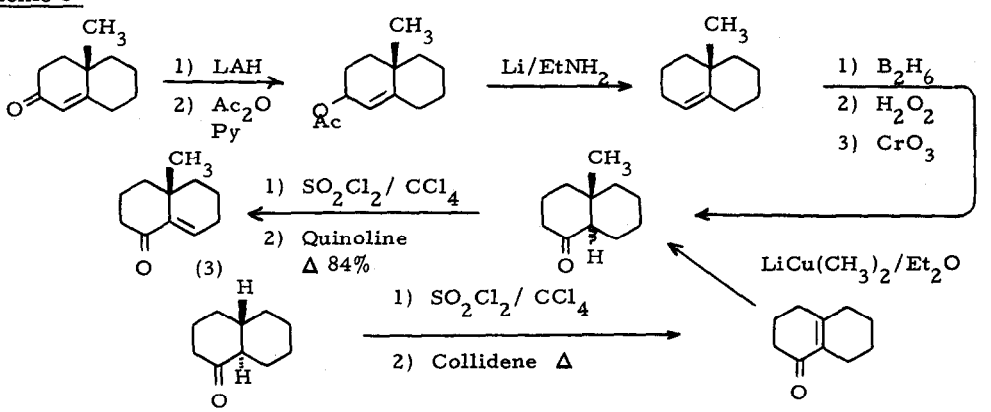


Scheme 2

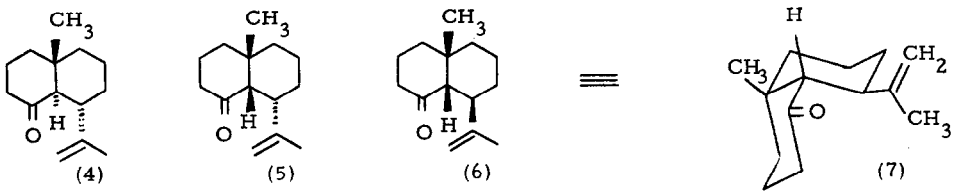


Octalone (3) (nmr: 6.50δ, t, J = 3.5 Hz $\rangle C=CH$, 1.08 δ, s, C-10 CH_3) was synthesized by two independent routes shown in Scheme 3.[8,9] Addition of 3 to a solution of isopropenyl Grignard[10] reagent in THF containing 5 mole % CuI, at -30°, then warming to 10° for 2 hrs, gave a mixture of three compounds 4 (nmr: 4.55 δ, m, 4.43 δ, s (br), $C=CH_2$, 0.81 δ, s, C-10 CH_3), 5 (nmr: 4.71 δ, s (br), $C=CH_2$, 1.20 δ, s, C-10 CH_3) and 6 (nmr: 4.71 δ, s (br), $C=CH_2$, 0.79 δ, s, C-10 CH_3) in a ratio of ~7:2:1 in 45% yield. Stereochemical assignments were made on the basis of the position of the angular methyl resonance which is characteristically high field in 10-methyl 1-decalones possessing the trans ring junction and lower field for the cis ring junction;[11] and equilibration studies ($NaOCH_3/CH_3OH$) which confirmed the epimeric relationship of 4 and 5. 6 was inert to these conditions. In 6, C-9β is the most stable epimer since only the cis compound has a conformation (7) available which relieves the steric interaction. The C-10 methyl in this conformation is axial with respect to the carbonyl containing ring and hence is found at high field.

Scheme 3

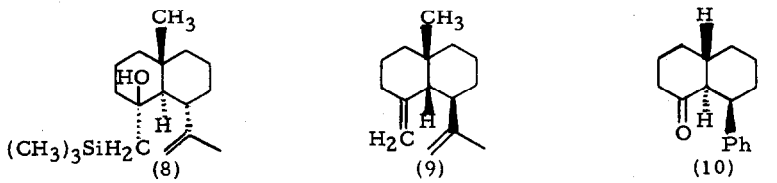


The final test of the stereochemical outcome, conversion of 4 to (±) β-Gorgonene, proved to be unexpectedly difficult. Ketones 4 and 6 were purified by preparative vpc.[12]



(4) (5) (6) (7)

4 was unreactive upon treatment with $CH_2=PO_3$ (DMSO/60°/48 hr); however, treatment with $(CH_3)_3SiCH_2MgCl$[13] (THF, Δ, 18 hr) gave carbinol 8. β-Elimination was then effected (HOAc/H_2O/3:1/r.t. 3 hr) to afford (±) β-Gorgonene which was purified by chromatography on 25% $AgNO_3$-SiO_2 (15%). The synthetic (±) β-Gorgonene obtained was identical in every respect (ir, nmr, vpc) with authentic (+) β-Gorgonene.[14]



(8) (9) (10)

The minor isomer 6 could be converted to isomeric olefin 9 [$(CH_3)_3SiCH_2MgCl$/THF followed by HOAc/H_2O] which was distinguishable from authentic (+) β-Gorgonene by nmr (olefinic region: a broad 4 proton singlet, 4.63 δ) and vpc.[15]

The result of the conjugate addition to octalone 3 produced a ratio of attack on conformers B:A of 9:1. In the absence of the angular methyl to the extent that conjugate addition occurs, the product (10) is derived solely from antiparallel attack on a conformer analogous to A in Scheme 2.[16] This implies an inherent 2-2.5 kcal preference for attack from the β side. The barrier to the conformational interconversion (A⇄B) is low (≤ 5.3 kcal).[17] Therefore, assuming antiparallel attack is the exclusive pathway, the magnitude of the steric interactions in the transition state is reflected in the change of the product partition (~3.5 kcal total) which is approximately that estimated for the ground state.

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12. 20' 3/8" 20% SE-30 at 188°.
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14. We wish to thank Professor Alfred Weinheimer for a generous gift of the Pseudopterogorgia americana extract from which authentic (+) β-Gorgonene was isolated and for providing spectral data for comparison.
15. 10' 1/4", 5% Carbowax-20-M at 140°.
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