

CONFORMATIONAL CONSEQUENCES OF INTRAMOLECULAR CYCLOPROPANATION WITHIN SMALL BICYCLIC SYSTEMS.

SYNTHESIS AND DESYMMETRIZATION OF 1-METHYLTRICYCLO[2.2.2.0^{2,6}]OCTANE-3,5-DIONE

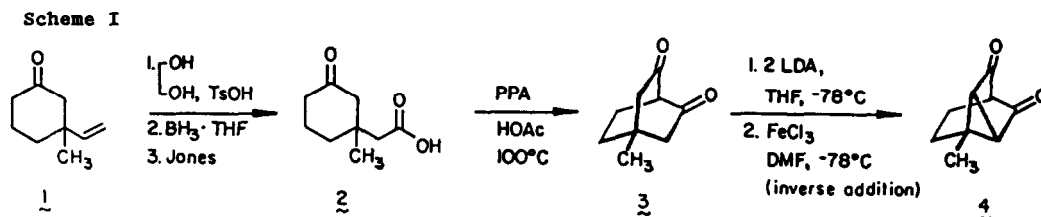
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Summary: Diketone 3, available by cyclization of keto acid 2 with PPA/HOAc, undergoes intramolecular oxidative cyclization to 4 by exposure of its dienolate to FeCl₃ in DMF at -78 °C. Convenient monomethylenation of 4 with optical resolution to give optically pure (+)- and (-)- 12 is described.

The unique structural features of cerorubenic acid-III have prompted us to undertake its synthesis.² The oxyanionic Cope strategy envisioned for its efficient elaboration necessitated access to the conformationally rigid β,γ -unsaturated ketone 12. Herein we disclose a route to diketone 4, discuss its geometry, and detail the crafting of 12 from 4 in a manner that allows the acquisition of either optically active antipode.

The most efficacious route (64% overall) from 1 to keto acid 2 involved hydroboration of the ethylene ketal followed directly by Jones oxidation (Scheme I). When heated with 36% (w/w) polyphosphoric acid in acetic acid at 100 °C for 7 h,³ 2 underwent smooth cyclization to 3 (80%). An interest in the prospect of intramolecular oxidative coupling^{4,5} within 3 led to generation of its dienolate in THF at -78 °C and *inverse addition* of this cold solution to one consisting of anhydrous ferric chloride in DMF at the same temperature during 30 min. This first example of cyclopropane construction via technology of this type proved highly serviceable (54% of 4, 11% of recovered 3 at the 1 g level), although somewhat scale-dependent.



Model calculations⁶ on 3 and 4 (Figure 1) clearly reveal the consequences brought on by insertion of the additional three-membered ring bond. The two carbonyl groups are *not* in fact brought closer together as their α -carbons, but become much more outwardly splayed in 4 than in 3. The propensity of nucleophiles to be captured by 4 from the right hand direction in Figure 1 should therefore be considerably enhanced relative to 3.⁷

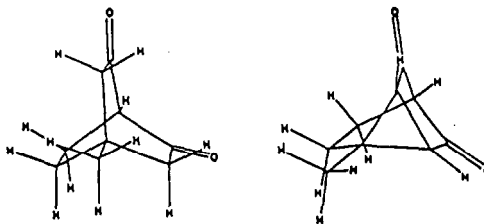
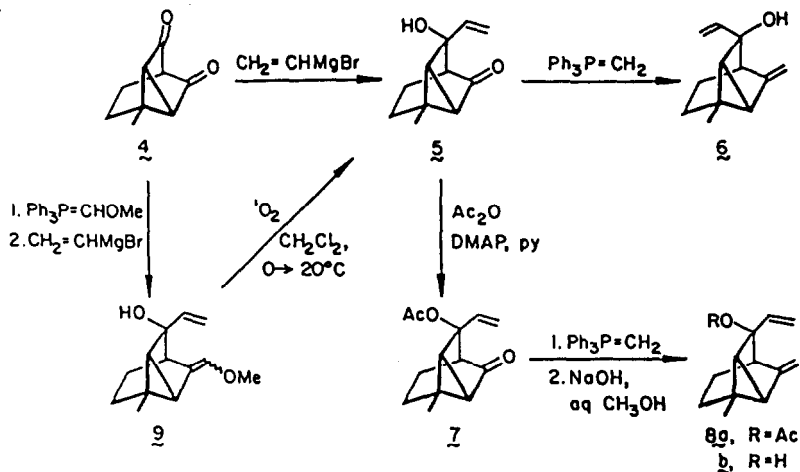


Figure 1

Despite these considerations, the alcohol formed by sequential reaction of 4 with 1.5 equiv of vinylmagnesium bromide (THF solvent, $-78\text{ }^{\circ}\text{C}$, 15 min) and Wittig olefination (THF:HMPA (9:1), $-78 \rightarrow 0\text{ }^{\circ}\text{C}$, 1 h) showed no tendency to undergo oxy-anionic Cope rearrangement and was clearly 6 (Scheme II). It was soon recognized, however, that *exo* vinylation had not materialized during the conversion of 4 to 5, but *resulted instead as a direct consequence of rapid retro-aldol cleavage within 5 and reclosure exclusively in the opposite stereochemical sense following exposure to the "salt-free" methylenetriphenylphosphorane reagent.*⁸ Proof that this structural isomerization is kinetically favored was derived from two directions. In the first, 5 was instead acetylated initially to provide 7. The subsequent olefination of 7 cannot be comparably rerouted and in fact delivers 8a exclusively. The latter undergoes saponification to provide 8b, the double bonds in which are now proximal. Relevantly, the heating of 8b in basic solution does not give 6!²

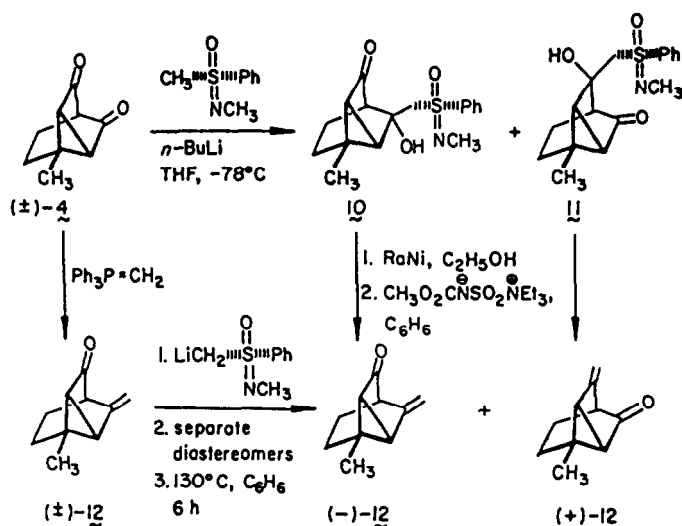
Scheme II



The sequence of steps may also be reversed to avoid the earlier complication. For example, conversion of 4 to 9 was accomplished by reaction of 4 with 1 equiv of methoxymethylenetriphenylphosphorane (THF, $-100\text{ }^{\circ}\text{C}$)⁸ and then vinylmagnesium bromide. Cleavage of the vinyl ether functionality in this tertiary allylic alcohol by photooxygenation⁹ again afforded 5.

The absolute stereochemistry of cerorubenic acid-III is presently unknown.¹⁰ Consequently, convenient acquisition of *both* antipodes of a key intermediate becomes desirable, since access to either enantiomer of the target is thereby made possible. Because diketone 4 possesses a plane of symmetry and is therefore achiral, resolution can usefully be effected only subsequent to arrival at this tricyclic compound. Actually, the symmetry of 4 proved to be a simplifying factor.¹¹ Thus, the lithium salt of (+)-(*S*)-*N*-methyl-*S*-phenylsulfoximine¹² adds to 4 exclusively from the same face as before to give diastereomers 10 and 11 (67%, Scheme III). Following their facile chromatographic separation on silica gel, 10 and 11 were separately reduced with Raney nickel and dehydrated with the Burgess reagent¹³ to give (-)-12, $[\alpha]_{\text{D}} -105.4^{\circ}$ (c 2.55, CHCl_3) and (+)-12, $[\alpha]_{\text{D}} +110.9^{\circ}$ (c 2.10, CHCl_3), respectively. Assignment of absolute configuration to these ketones was made possible by an X-ray crystallographic analysis of 10.¹⁴

Scheme III



At the preparative level, it proved more expedient and efficient to effect ketone methylenation with optical resolution by preliminary conversion of (\pm)-4 to (\pm)-12 (85%), condensation with the nucleophilic (+)-sulfoximine reagent (75%), and pyrolysis of the pure diastereomers at 130 °C (80%).¹⁵

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