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BIS-HOMOKETONIZATION OF SOME 4,5-DISUBSTITUTED HOMOCUBYL DERIVATIVES

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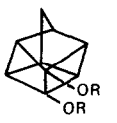
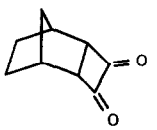
There are presently a number of examples of homoketonization reported in the literature.[1] Our current interest in strained, unenolizable α-diketones led to the investigation of the phenomenon of bis-homoketonization of certain vicinal diols, where the alcohol functionality is situated at strained ring junctures, as potential synthetic sources of interesting α-diketones. Our preliminary results on 4,5-dihydroxypentacyclo [4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$] nonane, 1b, are described in this communication.



1a R=$(CH_3)_3Si$
1b R=H



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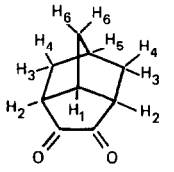
The diol, 1b, was prepared in high yield (>70%) by treatment of the bis-trimethylsiloxy derivative, 1a, with methanol at room temperature as described previously.[2] When 1b was treated at 25° with a 0.5M solution of sodium methoxide in methanol (2 mmoles NaOMe/mmole diol) the starting material rapidly disappeared. Acidification and subsequent workup yielded an isomeric yellow, crystalline carbonyl compound (mp 147-8°) in 50-60% yield.[3] The product was stable for extended periods in methylene chloride, but decomposed rapidly upon standing in ether at room temperature. The same product was generated in good yield and more conveniently by direct treatment of 1a with two equivalents of 0.1N sodium methoxide in methanol at 0°. The structure of the reaction product was secured by analytical and spectral data supported by an unambigious chemical synthesis.

The long wavelength visible spectrum of the product ($\lambda_{max}^{CH_2Cl_2}$ = 478 nm, ε = 34) was remenicient of non-enolizable diketones where the carbonyl functionality is restricted to cisoid coplanarity by a five membered ring.[4] The spectrum was, in fact, quite similar to

that of camphorquinone. The partial mass spectrum of the product showed a molecular ion at m/e 150 and strong fragments at 122, 94, 93, 80, 79, 78, 67, 66 and 55. The infrared spectrum ($CDCl_3$) showed strong absorptions at 2980, 2870, 1755, 1745, 1200, 1080 and 980 cm^{-1}. The NMR of the rearrangement product was particularly informative and exhibited absorptions at $\tau(CDCl_3)$ 6.95-7.27 (m, 3H), 7.52 (br m, 1H), 8.27 (m, 1/2 wd 4Hz, 2H) and 8.55 (d, J = 13Hz, 2H). The addition of small quantities of the shift reagent, $Eu(fod)_3$, to the solution caused the separation of the low field three proton multiplet into a component broad two proton doublet complicated by additional splitting and a broad one proton multiplet. The remaining resonances were shifted downfield to varying degrees. This NMR data is inconsistent with compounds 2 and 3 which could have resulted from a simple bis-homoketonization without attending rearrangement. In particular, the presence of two nonequivalent one proton multiplets in the spectrum of the isolated product is not reconcilable with either 2 or 3 which possess either a plane or an axis of symmetry, requiring that magnetically nonequivalent protons occur in pairs.[5] This inconsistancy necessitated consideration of alternative structures for the reaction product. The isomeric α-diketone, 4, seemed a reasonable candidate, since the two single proton multiplets might realistically be assigned to the nonequivalent bridgehead protons H_1 and H_5.



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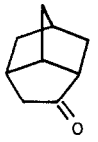

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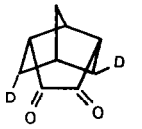

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Based on this structure, consideration of the NMR spectrum supported by decoupling experiments and results employing shift reagents led to the following tentative proton assignments. The composite three proton multiplet at 6.95-7.27 was attributed to the protons designated as H_1 and H_2 in, 4, while the one proton multiplet at 7.52 was ascribed to the remaining bridgehead proton H_5. The broadened triplet centered at 7.91 was assigned to the two exo protons, H_4. The protons, H_6, appear as a characteristic unresolved multiplet at 8.27, while the two proton doublet at 8.55 appears to be part of an AB quartet and is assigned to the protons designated as H_3. Further splitting of H_4 by H_2 and to a lesser

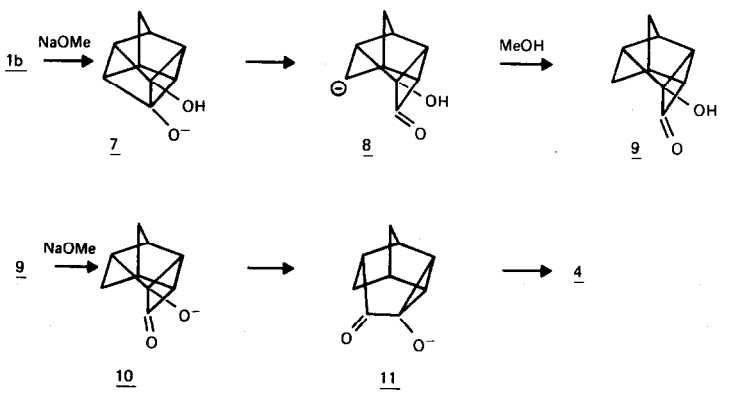
extent H_5 would be expected.[6] The endo protons, H_3, are predictably shifted to higher field due to shielding by the geometrically proximate α-dicarbonyl functionality.

The diketone, 4, should be predominately unenolized due to incipient strain development upon enolization caused by the generation of a bridgehead double bond. Consistently, no enol could be detected by IR and treatment of 4 at room temperature for 12 hr with 0.1N sodium methoxide in deuterated methanol led to essentially no deuterium incorporation.[7]

The assignment of structure, 4, to the product of bis-homoketonization is further supported by an unambigious synthesis. The tricyclic ketone, 5, was prepared as described by Nickon and coworkers[8] and cleanly oxidized by selenium dioxide to a yellow crystalline α-diketone whose spectral properties were identical in every respect with those of the rearrangement product. This example of bis-homoketonization offers therefore a synthetically simple, high yield entry into the functionalized brendane system.

When 1a was similarly treated with sodium methoxide in methanol-d_1, the isolated diketone was found to be ca. 93% d_2 by mass spectral analysis. The NMR spectrum of the deuterated material showed the following absorptions: τ($CDCl_3$) 6.95-7.28 (m, 3H), 7.52 (br, 1H), 7.91(d, J = 12Hz broadened by additional splitting, 1H) 8.28(m, 1/2 wd 3Hz, 2H) and 8.56(br s, 1/2 wd 6Hz, 1H). The original two proton triplet assigned to the exo protons, H_4, had thus collapsed to a broad doublet while the upfield doublet portion of the original AB quartet assigned to the endo protons, H_3, became a broad singlet. We believe this data is most consistent with a stereospecific incorporation of two deuterons one each into an exo and endo position as shown in 6.

An attractive albeit tentative mechanism which rationalizes the rearranged product and also predicts the curious stereospecificity of deuterium incorporation is presented below.



The direction of the initial homoketonization is predicted by the work of Zwanenburg and Klunder, who have also demonstrated specific endo deuteration of half cage homoenolates.[1d] The subsequent deprotonation and rearrangement finds a loose mechanistic analogy in the base catalyzed ring contraction of 1,2 cyclobutanediones to cyclopropyl derivatives.[9] Subsequent ketonization of the intermediate 11 would be expected to generate the least strained diketone. One could also hypothesize based on work of other authors[1a,10] that homoketonization of the cyclopropanol anion, 11, in base should take place predominately with inversion, placing the second deuterium atom in an exo position.

Further mechanistic studies together with a continued investigation of the chemistry of 4 and the general phenomenon of bis-homoketonization are in progress.

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5. This is not strictly true for 2 where the methylene protons of the one carbon bridge are nonequivalent. However, these protons would be expected to occur at considerably higher fields.
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