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REARRANGEMENTS IN 4,5-DISUBSTITUTED HOMOCUBYL SYSTEMS

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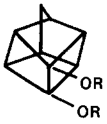
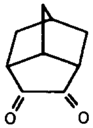
We have recently reported the transformation of 1 into 2 by treatment with NaOMe/MeOH.[1] The mechanism which was implied by the extensive structural rearrangement and supported by the stereospecific exo-endo deuterium labeling, 3, observed in MeOD, suggested a number of interesting rearrangements for the highly functionalized homocubyl skeleton 1. Additional mechanistic evidence based on the isolation of a number of key intermediates and their subsequent transformation into 2 under basic conditions is described.



1 R = $(CH_3)_3Si$



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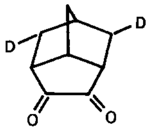

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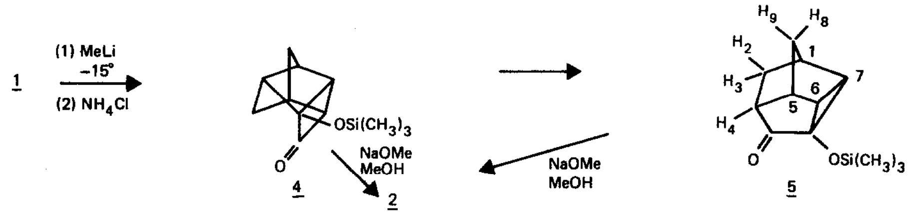
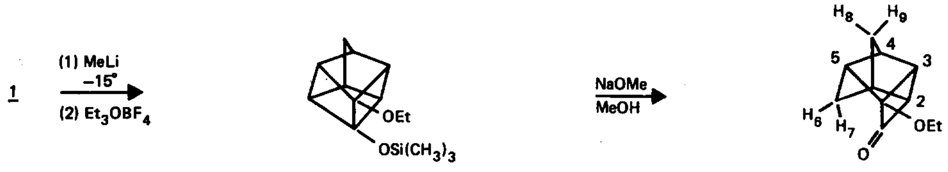
Treatment of 1 with 3-4 equivalents of methyl lithium at -15° for 5-6 hr. and subsequent quenching with a cold saturated NH_4Cl solution resulted in the production of an unstable transformation product, 4, in nearly quantitative yield. When the work-up was conducted at -15°, the material was produced in 80-90% purity.[2] This product showed a strong molecular ion at m/e 222 and the IR spectrum showed no absorption above 3000 cm^{-1} with strong bands at 2960, 1782 (CO of cyclobutanone), 1330, 1250, 1120, 935, 885 and 840 cm^{-1}. The NMR spectrum of this material was recorded immediately after work-up: τ (CCl_4) 7.34 - 8.17 (complex m), 8.37 - 8.97 (complex m) and 9.90 (s). The integrated ratios could not be assigned with confidence due to overlapping resonances of small amounts of starting material (*ca.* 5-10%) and the presence of *ca.* 10% of another secondary rearrangement product. Treatment of the crude reaction mixture with a NaOMe/MeOH solution resulted in a high yield transformation to the dione 2. This data is consistent with structure 4 for the initial product of the transformation. The isolation of a stable half cage ketone, 9, upon treatment of the corresponding 4-hydroxyhomocubyl derivative with NaOMe/MeOH has been reported previously.[3]



Attempts to purify, 4, by preparative GLPC at 150° led to complete transformation into a rearranged product as evidenced by the disappearance of the cyclobutanone carbonyl absorption at 1782 cm^{-1}, and its replacement by a strong band at 1735 cm^{-1}. Neat material left standing several hours at room temperature showed a dramatic increase in the 1735 cm^{-1} absorption. Complete rearrangement on a preparative scale could be effected by heating neat material to 75° for 40 min. or by refluxing a solution of 4 in carbon tetrachloride for 1-1.5 hr. The rearrangement in CCl_4 was unaffected by the addition of a few drops of diisopropylethylamine. The structure of the rearranged product was assigned as 5 on the basis of its spectral data: mass spectrum parent m/e 222; IR (neat) 3050, 2960, 2880, 1735, 1380, 1250, 1195, 1140, 990, 890, 860, 840 and 750 cm^{-1}; NMR τ (CCl_4) 7.20 - 7.68 (m, 3H), 7.72 - 7.96 (m, 2H), 8.17 - 8.45 (m, 3H), 8.62 (d, J=9 Hz, 1H) and 9.83 (s, 9H). The use of $Eu(fod)_3$ and concurrent decoupling was extremely useful in identifying 5 as the rearrangement product. This was particularly true in the assignment of the upfield resonances. Using this technique, it was determined that the doublet at τ 8.62 was due to one of the bridge methylene protons H_8 or H_9. The complex three proton multiplet τ 8.17 - 8.45 was created by the overlapping resonances H_2, H_3 and the remaining bridge proton H_8 or H_9, which appeared as a broad doublet (J=9 Hz) upon treatment with the shift reagent. The endo proton H_3 occurred as a broad doublet (J=12 Hz) comprising one portion of an AB pattern. The exo proton H_2 was split into a d,d (J=12 Hz, J=9 Hz) which took the appearance of a much broadened triplet in the undecoupled spectrum. The additional large splitting (J=9 Hz) is due to H_4 in a manner previously observed in the spectrum of 2. Consistently, 5, was readily transformed into 2 upon treatment with NaOMe/MeOH.

The facile transformation of 4 to 5 is unusual since it involves not only skeletal rearrangement but also an oxygen-to-oxygen migration of the trimethylsilyl group. Base catalyzed ring contractions of cyclobutanones substituted with good leaving groups alpha to the carbonyl group are well established processes.[4] Equally well known are the facile interconversions within cyclobutyl and cyclopropyl carbinyl cation systems.[5] For example, Conia and coworkers[6] have recently reported the thermal and acid catalyzed contraction of 2-methylene cyclobutanol to

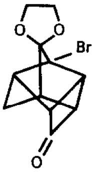
1-methylcyclopropanecarboxaldehyde. However, the transformation of 4 to 5 has been observed to proceed even at room temperature even in the absence of an acid catalyst. The role of the trimethylsilyl group in this rearrangement has been probed by substitution of a simple alkyl group. When the clear solution resulting from the treatment of 1 with MeLi at -15° was treated with a freshly prepared solution of triethyloxonium tetrafluoroborate in methylene chloride, a modest yield of the mixed ether, 7, (MW 246) was produced in addition to other products. The structure of 7 was secured by its characteristic spectral data: IR (neat) 2900, 1370, 1340, 1300, 1250, 930, 910, 890, 870 and 840 cm^{-1}; NMR (CCl_4) τ 6.5 (q, J=7.0 Hz, 2H), 6.90 (s superimposed upon a broad base, 6H), 8.34 (br s, 2H), 8.83 (t, J=7.0 Hz, 3H) and 9.83 (s, 9H). The NMR spectrum of the basic skeletal protons was extremely similar to 1. When, 7, was treated with 2 equivalents of 0.2N NaOMe/MeOH at 0° and the strongly basic solution extracted, a product was isolated which was identified as, 8, by its spectral data: IR (neat) 2900, 2880, 1780, 1320, 1290, 1130, 1100, 1080, 1050 and 1020 cm^{-1}; NMR (CCl_4) τ 6.56 (complex m. 2H), 7.20 - 8.07 (m, 6H), 8.31 - 8.73 (m, 3H) and 8.91 (t, J=6.5, 3H). As before, the complexity of the spectrum was greatly simplified by the use of $Eu(fod)_3$ and subsequent decoupling. The three proton multiplet (8.31 - 8.73) was composed of an AB quartet centered at 8.50 (J=10 Hz, 2H) for H_8 and H_9, and a doublet of doublets at 8.42 (J=10 Hz, J=2 Hz, 1H) assigned to the endo proton H_7. The chemical shift and splitting pattern is consistent with the values reported by Zwanenburg and coworkers for the half cage ketone 9.[3] The exo proton, H_6, appears downfield at τ 7.90 as a doublet (J=10 Hz) broadened by further splitting. The general upfield shift of H_7 relative to H_6 is anticipated due to shielding by the carbonyl group.



7 8

Another spectral feature requiring comment is the ABX_3 pattern of the methylene protons of the ethyl group which is quite complex and symmetrical about the midpoint at 6.38 τ. These protons are coupled only to each other and to the methyl group. It seems unlikely that magnetic non-equivalence is due solely to restricted rotation in light of the simple quartet observed for the similar protons in 7. Consistently, heating 8 to 110° in tetrachloroethylene caused only minor changes in the spectrum. Return to room temperature reproduced the original spectrum leading to the conclusion that the spectral complexity was not due primarily to restricted rotation.[7] It seems probably that the magnetic non-equivalence is due to the basic symmetry of the tricyclic skeleton even though the methylene protons are insulated from the chiral center by the ethereal oxygen. Long range transmission of chiral effects have been reported previously.[9] Consistently, a similarly complex ABX_3 pattern was observed for the isobornyl ether 10 prepared from isoborneol and triethyloxonium tetrafluoroborate.

9



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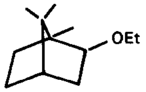

It is obvious that the thermal stability of 8, far exceeds that of the trimethylsilyl derivative, 4. The ethoxy derivative, 8, was stable to 110° in tetrachloroethylene and survived GLPC collection at 160°. Under these conditions complete rearrangement of 4 to 5 was observed. While the origin of this destabilization of 2 is not known with certainty, an attractive, albeit tenative explanation, is that interaction of the non-bonding electrons of the carbonyl group with the adjacent silicon atom could increase the electrophilicity of the carbonyl carbon atom and hence promote ring contraction in this strained system.

Further investigation of the chemistry of other α-trimethylsiloxy cyclobutanones and additional highly functionalized caged compounds is proceeding.

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