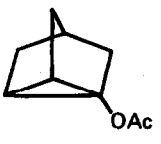
Tetrahedron Letters No. 12, pp 1023 - 1026, 1977. Pergamon Press. Printed in Great Britain.

The Stereochemistry of the Bis-Homoketonization of 4,5-Bis-Trimethylsilyl Homocubane and Homocuneane: Base Catalyzed Cleavage of a Cyclopropanol Derivative with Retention

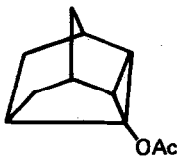
R. D. Miller* and D. L. Dolce
IBM Research Laboratory
San Jose, California 95193

(Received in USA 20 December 1977; received in UK for publication 9 February 1977)

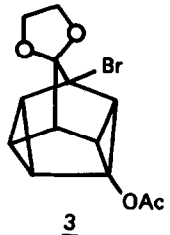
The phenomenon of homoketonization has attracted considerable experimental interest in recent years. The base catalyzed cleavage of strained four and five membered bridgehead alcohols has been demonstrated to produce the least strained ketone and to proceed with retention of configuration upon protonation[1-7]. In contrast, the cleavage of cyclopropanol derivatives proceeds predominately with inversion in polar media[8]. This stereospecificity has been dramatically demonstrated by Nickon and coworkers[9] for the polycyclic derivatives 1-acetoxynortricyclane 1 and 4-acetoxytriaxane 2 which result almost exclusively in exo deuterated material.



1



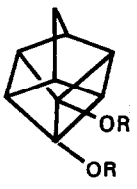
2



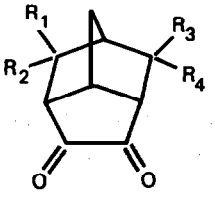
3

In this respect, the recent report by Zwanenburg and coworkers[12] on the base catalyzed homoketonization of the homocuneane derivative 3 which proceeded with >96% retention of configuration represents a striking deviation from precedent and prompts us to report our related findings.

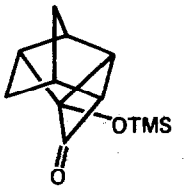
We have previously reported[5] that the bis-homoketonization of the homocubyl derivatives 4a,b by NaOMe-MeOH generated the rearranged α-diketone 5a. The use of methanol-d, as the solvent resulted in the specific incorporation of two deuterium atoms one each into an exo and endo position 5b. At that time, we proposed a complicated mechanistic scheme assuming retention of configuration in the initial homoketonization step and the intermediacy of a rearranged cyclopropyl ketone such as 7 (from 4b) to rationalize both the formation of 5 and the specific deuterium labeling pattern.[5]



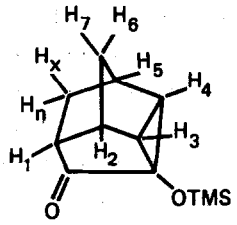
4a R = H
4b R = TMS



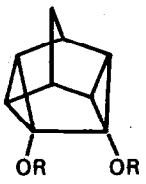
5a $R_1=R_2=R_3=R_4=H$
5b $R_1=R_4=D, R_2=R_3=H$
5c $R_1=R_2=R_4=H, R_3=D$



6



7



8a R=H
8b R=TMS

Since the ketone 7 is readily available by the treatment of 4b with excess methyl lithium (-10°) followed by the thermal rearrangement of the half cage ketone 6 produced initially, this mechanism is amenable to test by sequential deuterium incorporation. Consequently, when 4b, which had been treated with excess methyl lithium, was quenched with ammonium chloride-d_4-deuterium oxide and the crude product thermally rearranged,[13] the isolated ketone 7 was shown to be >88% d_1. The stereospecificity of the deuterium incorporation in this case, which presumably reflects that of the initial homoketonization of 4b, was determined by nmr to be >95% endo (7, H_n=D). The analysis was performed using Eu(fod)$_3$ shift reagent which allowed the observation of each individual resonance. Under these conditions, the endo proton (H_n) of 7 which is spatially close to the complexing carbonyl group rapidly shifted downfield away from H_x, H_6 and H_7 and appeared as a doublet (J=11Hz) due to the large geminal splitting by H_x. The exo proton (H_x) appeared upfield as a broadened doublet of doublets (J=11Hz, J=9Hz)[14] because of the additional strong splitting by the bridgehead proton H_1. When the monodeuterated derivative of 7 was analyzed in the same manner, the endo proton (H_n) was no longer detectible and the corresponding exo proton (H_x) now appeared as a slightly broadened doublet (J=9Hz) due to the loss of the strong geminal coupling. The production of 7 specifically labeled in the endo position with deuterium strongly suggests that the initial homoketonization of 4b proceeds as expected,[3,5,6] with retention.

Subsequent treatment of the rearranged ketone 7 (d_o) under the same conditions with NaOMe-MeOD resulted in the isolation of 5c which was 87%d_1. NMR analysis of the monodeuterated material

assured that the deuterium incorporation was specifically into the exo position as evidenced by the appearance of the two endo protons (R_2=R_4=H) as a broad singlet superimposed on the normal doublet (J=13Hz) at τ8.55. The single exo proton remained a doublet of doublets at τ7.85 as in the undeuterated material. The base catalyzed homoketonization of 7 thus proceeds with inversion upon protonation as predicted from previous studies.[9]

This result suggested that the bis-homoketonization in deuterated media of the homocuneane derivatives 8a,b should produce 5 with two deuteriums each in the exo positions (R_1=R_3=D). The desired material 8a was conveniently prepared (89%) by the treatment of 4b with silver perchlorate (0.05M)[15] in chloroform (12 hr, 25°). The corresponding diol 8a was generated by reaction of 8b with methanol for 4 hr at 25° (80%). As expected, both 8a,b yielded the dione 5a upon treatment with 0.2M MeOH-NaOMe (2 hr, 25°). The use of methanol-d under the same conditions, however, produced a rather unexpected result. The nmr spectrum of the dione isolated in this case (88% d_2) was identical to 5b produced previously from 4b. This unusual result indicates that the two homoketonizations occurring presumably in a sequential fashion within the same molecule are each proceeding with high but apparently opposite stereospecificity. Since the ketone 7 is a logical intermediate in the transformation of 8b→5 and we have previously demonstrated that the homoketonization of 7 proceeds with inversion, it seems that the initial ring cleavage of 8b occurs with retention. While this cleavage of a cyclopropanol derivative in base with retention is contrary to most literature precedent[8,9], it is however completely consistent with the report by Zwanenburg and coworkers[10] on the stereospecificity of the ring cleavage of the homocuneane 3. At the same time, the example of 8b demonstrates unequivocially that the endo stereochemistry observed in the cleavage of 3 in MeOD is not a result of any steric or electronic effect of the ethylene ketal moiety. These results clearly show that the stereochemistry of homoketonization of cyclopropanol derivatives is a complicated function of structure, particularly in polycyclic systems.

Further work is continuing in this area.

References

1. R. Howe and S. Winstein, J. Am. Chem. Soc., 87, 916 (1965).

2. T. Fukunaga, J. Am. Chem. Soc., 84, 916 (1965).

3. A. J. H. Klunder and B. Zwanenburg, Tet. Lett., 1721 (1971).

4. W. T. Borden, V. Varma, M. Cabell, and T. Ravendranthan, J. Am. Chem. Soc., 93, 3880 (1971).

5. R. D. Miller and D. L. Dolce, Tet. Lett., 1151 (1973).

6. A. Padwa and W. Eisenberg, J. Am. Chem. Soc., 94, 5882 (1972).

7. A. B. Crow and W. T. Borden, Tet. Lett. 1976 (1976).

8. D. H. Gibson and C. H. DePuy, Chem. Rev., 74, 605 (1974) and references cited therein.

9. a. A. Nickon, J. L. Lambert, R. O. Williams and N. H. Werstiuk, J. Am. Chem. Soc., 88, 3354 (1966); b. A. Nickon, D. F. Covey, G. D. Pandit and J. J. Frank, Tet. Lett., 3681 (1975).

10. While it is generally true that cyclopropanols cleave with inversion in basic media the stereochemical coarse of this reaction can apparently be altered by appropriate substituents. For example, Wharton and Fritzberg[11] found almost complete retention during the basic cleavage of trans-2,3-di-t-butylcyclopropanone hemiketals in either polar or nonpolar solvents.

11. P. S. Wharton and A. R. Fritzberg, J. Org. Chem., 37, 1899 (1972).

12. A. B. A. Arts, A. J. H. Klunder and B. Zwanenberg, Tet. Lett., 2359 (1976).

13. Due to the instability of 6, the crude reaction mixture was heated to 65° for 1 hr to insure complete rearrangement of 6 to 7 to facilitate the subsequent spectral analysis.

14. The actual peak shape was that of a broadened triplet, due to the similiarity in the magnitude of the primary couplings and the presence of additional small splittings.

15. The use of silver perchlorate rather than silver tetrafluoroborate as originally described[16] greatly improved the yield and reproducibility of this reaction.

16. R. D. Miller and D. L. Dolce, Tet. Let., 4541 (1972).