Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 6487–6489

Tetrahedron Letters

A hydrogen atom sandwiched by cyclopropanes

Robert S. Walters, Douglas M. Ho and Robert A. Pascal, Jr.*

Department of Chemistry, Princeton University, Princeton, NJ 08544, USA

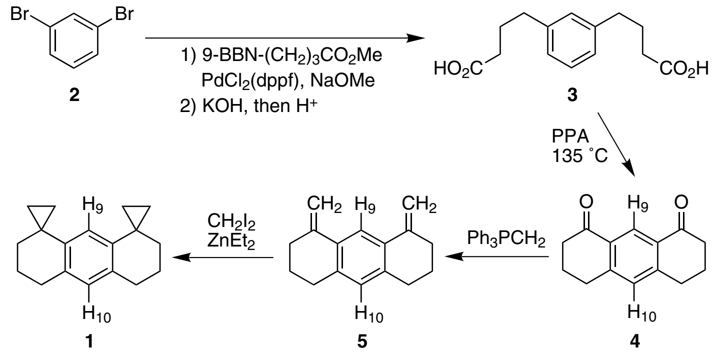
Received 16 June 2005; revised 14 July 2005; accepted 20 July 2005

Abstract—2′,3′,4′,5′,6′,7′-Hexahydrodispiro[cyclopropane-1,1′-anthracene-8′,1″-cyclopropane] (**1**) was prepared by double olefination (Wittig) and double methylenation (Furukawa) of 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroanthracene (**4**) that was in turn prepared in two steps from 1,3-dibromobenzene. The X-ray structure of **1** shows that the C–9-H of its anthracene core is located 2.6 Å from the centroids of each of the flanking cyclopropane rings. The ^{1}H NMR spectrum of **1** shows that the C–9-H resonance (δ 5.95) falls 0.84 ppm upfield from the C–10-H resonance (δ 6.79).

Cyclopropane rings display large magnetic anisotropic effects that are particularly evident in proton NMR spectra,[1–4] and numerous examples of the shielding or deshielding of protons near cyclopropane rings in a wide variety of molecules have been cataloged.[2–6] The vast majority of these cases involve the interaction of protons with a single cyclopropane ring, and even in those molecules containing more than one cyclopropane, the orientation of the cyclopropanes with respect to the affected hydrogens has not been 'ideal'. We wondered if a large cyclopropane-induced shielding would be observed in a molecule containing a proton sandwiched between the faces of two parallel cyclopropane rings.

Compound **1** is such a molecule. HDFT calculations at the B3LYP/6-31G(d) level[7] indicate that it may adopt either C_2- or C_s-symmetric conformations that differ in energy by only 0.02 kcal/mol, and thus the two conformations should be equally populated. GIAO calculations[7] indicated that the H_9 resonance should fall 1.09 ppm upfield of the H_{10} resonance in the C_2 conformation and 0.79 ppm upfield in the C_s conformation (see Table 1).

Given the diketone **4**, the synthesis of **1** should be simple, but the literature syntheses of **4**[8,9] proved challenging for us. Ultimately, we found that 1,3-bis(3-carboxypropyl)benzene (**3**) was most efficiently prepared (54% yield) by means of a double Suzuki coupling reaction of 1,3-dibromobenzene with the adduct of 9-BBN and methyl 3-butenoate using the method of Esteban et al.[10] With **3** in hand, a double intramolecular



Keywords: Cyclopropane; Magnetic anisotropy; NMR.

* Corresponding author. Tel.: +1 6092 585417; fax: +1 6092 586746; e-mail: snake@chemvax.princeton.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.097

Table 1. Experimental and calculated[a] chemical shifts of aromatic protons in compound **1**

	δ (H_9)	δ (H_{10})	$\Delta\delta$ (H_9–H_{10})
1 (calcd, C_2 conf.)	5.97	7.06	−1.09
1 (calcd, C_s conf.)	6.06	6.85	−0.79
1 (calcd, average)	6.01	6.96	−0.95
1 (exptl, $CDCl_3$)	5.95	6.79	−0.84

[a] GIAO calculations at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level.

Friedel–Crafts acylation proceeded exactly as described by Christopfel and Miller[8] to give diketone **4** in 28% yield.[11] The double Wittig olefination of **4** gave **5**,[12] and methylenation using the Furukawa modification[13] of the Simmons–Smith reaction gave the desired biscyclopropane **1**.[14] The last two steps suffered from low yields (14% and 24%, respectively), but sufficient material for NMR and crystallographic studies was obtained.

Crystals of **1** were grown from ethanol, and the X-ray structure was determined. Compound **1** adopts the C_2 conformation in the crystal, and its molecular structure is illustrated in Figure 1.[15] H_9 is located almost exactly above the centroids, X(1) and X(2), of the two cyclopropane rings at distances of 2.57 and 2.64 Å, respectively, and thus H_9 is well positioned in the NMR shielding regions of the flanking cyclopropanes.

In the ^{1}H NMR spectrum of **1**, the H_9 resonance (δ 5.95) falls 0.84 ppm upfield from that of H_{10} (δ 6.79), a reasonable reference proton (Table 1). The observed difference is slightly less than the calculated value of 0.95 ppm, but the overall agreement of experiment and calculation is very good, given that two interconverting conformations of **1** must be considered. The observed difference in the H_9 and H_{10} chemical shifts probably represents the largest cyclopropane-induced shift of a proton resonance due purely to shielding (rather than deshielding) effects, and is due to the fact that H_9 is close to the centers of two cyclopropane rings, a very rare situation.

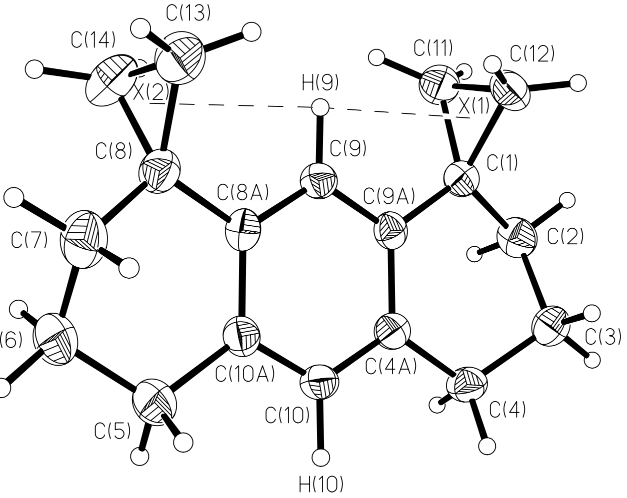
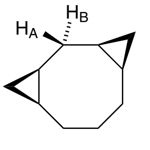
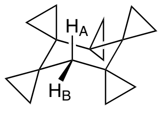


Figure 1. Molecular structure of compound **1**.

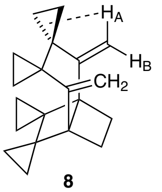
In the older literature, the largest differential shift for two chemically similar protons due to cyclopropanes seems to be 1.80 ppm for H_A and H_B in compound **6**,[5] and an extensive (but certainly not exhaustive) search of the modern literature found a difference of 2.46 ppm for H_A and H_B in compound **7** at low temperature.[18] However, these large differences are due to a combination of shielding *and* deshielding effects.



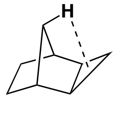
6



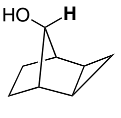
7



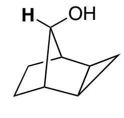
8



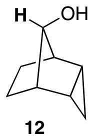
9



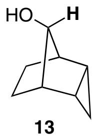
10



11



12



13

In an attempt to find the most extreme cases of pure shielding, we conducted a search of Cambridge Crystallographic Database[19] for protons lying very close to, *and* directly above, the centers of cyclopropane rings. Compound **1** seems to have claimed the record for the closest such approach of one proton to the centers of *two* different cyclopropanes (at 2.57 and 2.64 Å), but the closest *single* approach is found in compound **8**,[20] where H_A is only 2.36 Å from the center of the opposing ring. However, H_A is shielded by only 0.43 ppm with respect to H_B, likely due to a conformational exchange process. Quite a few molecules with the substructure **9** (or similar fragments) possess contacts on the order of 2.4–2.6 Å, but the magnitudes of the proton shielding in these molecules (where reasonable reference protons can be found) are smaller than observed in compound **1**. For example, the chemical shifts of the bold protons in compounds **10**, **11**, **12**, and **13** are δ 3.57, 3.60, 4.09, and 4.24, respectively.[5] Poulter et al.[5] analyzed this series and concluded that the protons in compounds **10–12** were shielded by the cyclopropane, but the proton in **13** was deshielded; however, the entire range of chemical shifts is only 0.67 ppm.

Acknowledgement

This work was supported by National Science Foundation Grant CHE-0314873, which is gratefully acknowledged.

References and notes

1. Lacher, J. R.; Pollock, J. W.; Park, J. D. *J. Chem. Phys.* **1952**, *20*, 1047–1048.
2. Forsen, S.; Norin, T. *Acta Chem. Scand.* **1961**, *15*, 592–598.

3. Wiberg, K. B.; Nist, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 1226–1230.
4. Forsen, S.; Norin, T. *Tetrahedron Lett.* **1964**, *5*, 2845–2849.
5. Poulter, C. D.; Boikess, R. S.; Brauman, J. I.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2291–2296.
6. Hahn, R. C.; Howard, P. H. *J. Am. Chem. Soc.* **1972**, *94*, 3143–3148.
7. Frisch, M. J. et al. *All molecular orbital calculations were performed with* GAUSSIAN 98; Gaussian, Inc.: Pittsburgh, PA, 1998. B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) wave functions were employed in the GIAO calculations to give the absolute ^{1}H chemical shifts for **1**, and these were converted to ordinary chemical shifts by comparison to the ^{1}H chemical shift for tetramethylsilane computed at the same level.
8. Christopfel, W. C.; Miller, L. L. *J. Org. Chem.* **1984**, *49*, 5198–5202.
9. Caluwe, P.; Pepper, T. *J. Org. Chem.* **1988**, *53*, 1786–1790.
10. Esteban, G.; Lopez-Sanchez, M. A.; Martinez, M. E.; Plumet, J. *Tetrahedron* **1998**, *54*, 197–212.
11. Compound **4**: mp 177–179 °C (lit.[8] 198–199.5 °C); ^{1}H NMR ($CDCl_3$) δ 2.12 (quintet, $J = 6$ Hz, 4H), 2.65 (t, $J = 6$ Hz, 4H), 2.96 (t, $J = 6$ Hz, 4H), 7.13 (s, 1H, 10-H), 8.68 (s, 1H, 9-H).
12. Compound **5**: ^{1}H NMR ($CDCl_3$) δ 1.84 (m, 4H), 2.50 (m, 4H), 2.77 (m, 4H), 4.90 (d, $J = 1$ Hz, 2H), 5.46 (d, $J = 1$ Hz, 2H), 6.84 (s, 1H, 10-H), 7.92 (s, 1H, 9-H); ^{13}C NMR ($CDCl_3$) δ 24.1, 30.4, 33.6, 107.4, 119.9, 129.7, 132.8, 137.2, 143.7; MS (EI) *m*/*z* 210 (M^+, 100), 195 ($M{-}CH_3$, 53); exact mass 210.1408, calcd for $C_{16}H_{18}$ 210.1409.
13. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353–3354.
14. Compound **1**: ^{1}H NMR ($CDCl_3$) δ 0.73 and 0.86 ($AA'BB'$ system, 8H), 1.61 (m, 4H), 1.86 (m, 4H), 2.80 (t, $J = 6$ Hz), 5.95 (s, 1H, H_9), 6.79 (s, 1H, H_{10}); ^{13}C NMR (benzene-d_6) δ 18.6, 19.2, 23.0, 30.6, 35.9, 114.7, 129.2, 133.8, 139.2; MS (EI) *m*/*z* 238 (M^+, 54), 223 ($M{-}CH_3$, 53), 209 ($M{-}C_2H_5$, 100); exact mass 238.1716, calcd for $C_{18}H_{22}$ 238.1722.
15. Crystal data for **1**: $C_{18}H_{22}$; orthorhombic, space group $P2_12_12_1$ (No. 19); $a = 7.4834(4)$ Å, $b = 10.0592(5)$ Å, $c = 17.7749(7)$ Å, $V = 1338.0(1)$ Å^3, $Z = 4$. Data were collected at 200 K with $\lambda = 0.71073$ Å; a total of 7758 reflections ($\theta_{\max} = 27.47°$) were processed to give 3058 unique reflections ($R = 0.045$) by using the program DENZO-SMN.[16] The structure was solved and refined using Siemens SHELXTL.[17] All atomic coordinates were refined; carbon atoms were refined anisotropically and hydrogen atoms isotropically. The refinement converged to $R(F) = 0.0503$, $wR(F^2) = 0.0986$, and $S = 1.119$ for 2664 reflections with $I > 2\sigma(I)$, and $R(F) = 0.0623$, $wR(F^2) = 0.1092$, and $S = 1.149$ for 3057 unique reflections and 251 parameters (one reflection was suppressed). Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 275196. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.
17. Sheldrick, G. M. SHELXTL Version 5.04. Siemens Analytical X-ray Instruments, Madison, WI, USA, 1996.
18. Fitjer, L.; Klages, U.; Wehle, D.; Giersig, M.; Schormann, N.; Clegg, W.; Stephenson, D. S.; Binsch, G. *Tetrahedron* **1988**, *44*, 405–416.
19. Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146–153.
20. de Meijere, A.; Wenck, H.; Kopf, J. *Tetrahedron* **1988**, *44*, 2427–2438.