JOC Article

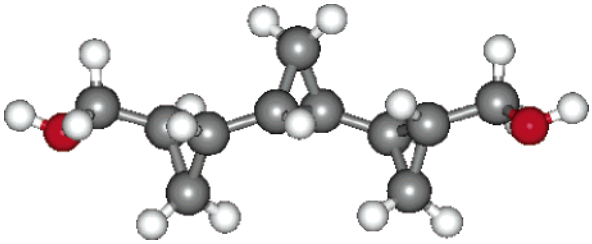
Helical Structure of Tercyclopropanedimethanol in Solution

Anthony G. M. Barrett,*,† Rachel A. James,† Gillian E. Morton,† Panayiotis A. Procopiou,‡
Christian Boehme,§ Armin de Meijere,‖ Christian Griesinger,*,⊥ and Uwe M. Reinscheid*,⊥

Department of Chemistry, Imperial College, South Kensington, London SW7 2AY, United Kingdom, GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, Herts SG1 2NY, United Kingdom, Gesellschaft für wissenschaftliche Datenverarbeitung Göttingen, Am Fassberg 11, 37077 Göttingen, Germany, Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany, and Max-Planck-Institute for Biophysical Chemistry, Department of NMR based Structural Biology, Am Fassberg 11, 37077 Göttingen, Germany

agmb@ic.ac.uk; cigr@nmr.mpibpc.mpg.de; urei@nmr.mpibpc.mpg.de

Received December 19, 2005



Oligocyclopropanes with repetitive stereochemistry occur in two unusual natural products with interesting bioactivity. X-ray crystal structures are available for these compounds but with partially contradicting results. Because the ^{1}H and ^{13}C NMR spectra of oligocyclopropanes are far from trivial to be assigned even at highest magnetic fields, we have prepared a specifically deuterated sample and have applied high field NMR spectroscopy and DFT calculations to determine its conformation. The helix with equal handedness shown in the stereopicture was found for tercyclopropanedimethanol. A dihedral angle of around +40° is the best representation of the experimental data and characterizes, therefore, the dominating helical conformation of tercyclopropanedimethanol with a single repetitive (+)-gauche interunit dihedral angle. This is in full agreement with the crystal structure of the all *syn*,*trans*-quinquecyclopropanedimethanol with an *R* configuration at the termini that also adopted an all (+)-gauche conformation. However, the crystal structure of the title compound and the solution structure are different.

Introduction

Oligocylopropane moieties have recently been shown to be important in nature as they appear in two natural products from different sources:[1] the antifungal nucleoside FR-900848[2] and the cholesteryl-transfer-protein inhibitor U-106305.[3] Some of us previously reported the total synthesis of both compounds, which relied upon a sequence of bidirectional double Simmons–Smith cyclopropanation reactions.[4] The fatty acid side chains of both compounds contain all-syn,trans disubstituted oligocyclopropanes that, as it is shown in this work, conformationally restrict these lipophilic domains to a single conformation. Compound **1** constitutes such an all-syn,trans disubstituted tercyclopropane. The nondeuterated analogue of the hydroxymethyl derivative **1** [(1*R*,3*S*,4*R*,6*R*,7*S*,9*R*)-1,9-bis(hydroxymethyl)tercyclopropane] in the solid state showed interunit dihedral angles (designated ϕ in the formula **1**) of +49.7° and

---

* Corresponding authors. Fax: (+44)207-594-5805 (A.G.M.B.); (+49)551-201-2202 (C.G. and U.M.R.).

† Imperial College.

‡ GlaxoSmithKline Research and Development.

§ Gesellschaft für wissenschaftliche Datenverarbeitung Göttingen.

‖ Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen.

⊥ Max-Planck-Institute for Biophysical Chemistry.

(1) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051.

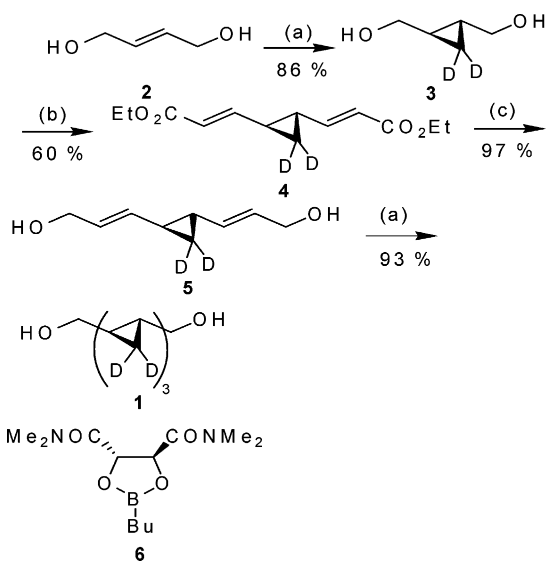
(2) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748. Yoshida, M.; Horikoshi, K. Eur. Pat. 286 330, 1988; U.S. Patent, 4 803 074, 1989; *Chem. Abstr.* **1989**, *110*, 210961.

(3) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629.

(4) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863. Barrett, A. G. M.; Kasdorf, K. *J. Am. Chem. Soc.* **1996**, *118*, 11030.

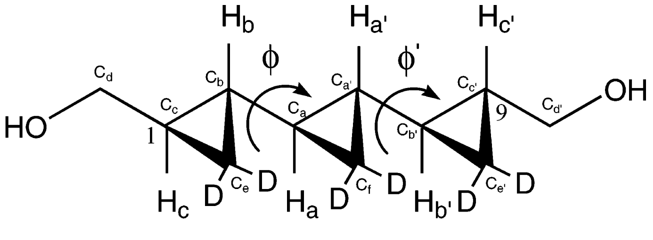
10.1021/jo0525985 CCC: $33.50 © 2006 American Chemical Society
Published on Web 03/03/2006

SCHEME 1[a]



[a] Reagents: (a) (i) **6**, (ii) $Zn(CD_2I)_2\cdot DME$, DCM, from −45 °C to rt; (b) (i) Dess−Martin periodine, DMSO/pyridine, 0 °C; (ii) PPh_3; (iii) $Ph_3P{=}CHCO_2Et$, Et_2O; (c) DIBALH, DCM, −78 °C

−58.6°, respectively, which breaks the symmetry in the conformation of a configurationally repetitive molecule.[5] In contrast, Charette and Lebel published a crystal structure of a configurationally repetitive all *syn*,*trans*-quinquecyclopropanedimethanol with all interunit dihedral angles as being (+)-gauche.[6] To shed some light on these partially contradicting observations, we closely examined the conformation of **1** as a model in acetone solution by NMR spectroscopy and by DFT calculations. The result of this study also clarifies whether configurationally repetitive oligocyclopropanes adopt repetitive conformations such as those of isotactic polymers.



1

Results and Discussion

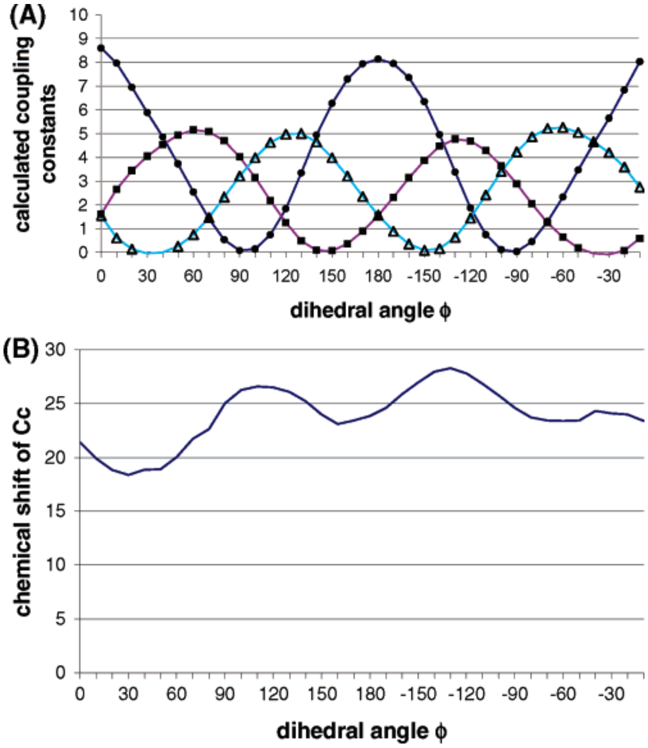


FIGURE 1. Relationship between (A) coupling constants and (B) chemical shift vs the interunit dihedral angle ϕ, as calculated by DFT.[12] (A) Filled circle: ${}^3J_{H_a,H_b}$ coupling constant. Filled square: ${}^3J_{H_a,C_c}$ coupling constant. Open triangle: ${}^3J_{H_a,C_e}$ coupling constant. (B) Chemical shift of C_c vs dihedral angle ϕ.

Synthesis. The nondeuterated cyclopropanes have been synthesized previously via iterative double cyclopropanation using the Simmons−Smith reagent derived from di-iodomethane. However, in this instance, compounds were synthesized using the Simmons−Smith reagent derived from diiodomethane-d_2 (Scheme 1). Absolute stereochemical control was effected using the chiral dioxoborolane **6**, according to the protocol of Charette and co-workers.[7] Thus, Charette cyclopropanations of diol **2** gave the cyclopropane **3** (86% yield), which was homologated using a Dess−Martin oxidation with a Wittig homologation in situ[4] to directly provide diester **4**. A DIBALH reduction gave the diene **5**, which was subjected to a second double-Charette cyclopropanation to provide the tercyclopropanedimethanol **1**.

Conformational Analysis. For bicyclopropyl, the gauche conformer ($\phi \approx +50°$ or $-50°$) is stabilized in solution compared to the antiperiplanar conformer ($\phi = 180°$).[8] This was confirmed by Lüttke and co-workers, who established a Karplus relationship using the partially deuterated *cis*- and *trans*-tricyclo[5.1.0.0^{2,4}]octane as model compounds.[9] On the basis of the ${}^3J_{H,H}$ coupling constants, an interunit dihedral angle of 53 ± 7° was deduced for bicyclopropyl. Because analogous NMR studies of oligocyclopropanes encounter the difficulty that the cyclopropyl protons are in large part indistinguishable from one another, the partially deuterated compound **1** was synthesized to simplify spectral interpretation. Experimental NMR parameters, NOE, *J* couplings, and chemical shifts were used and compared to the predicted values for *J* couplings and chemical shifts from DFT calculations (Figure 1A,B).[10]

The one-dimensional (1D) ^1H and ^{13}C NMR spectra at 278 K in acetone-d_6 showed six signals each (Table 1), reflecting

---

(5) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608. Barrett, A. G. M.; Hamprecht, D.; James, R. A.; Ohkubo, M.; Procopiou, P. A.; Toledo, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2001**, *66*, 2187.

(6) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327.

(7) Charette, A. B.; Juteau, H. J. *J. Am. Chem. Soc.* **1994**, *116*, 2651. Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

(8) de Meijere, A.; Lüttke, W.; Heinrich, F. *Liebigs Ann. Chem.* **1974**, 306.

(9) Lüttke, W.; de Meijere, A.; Wolff, H.; Ludwig, H.; Schröter, W. *Angew. Chem.* **1966**, *78*, 141. Braun, H.; Lüttke, W. *J. Mol. Struct.* **1975**, *28*, 391.

(10) Bagno, A. *Chem.*−*Eur. J.* **2001**, *7*, 1652. Bagno, A.; Rastrelli, F.; Saielli, G. *J. Phys. Chem. A* **2003**, *107*, 9964. Bassarello, C.; Cimino, P.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. *Tetrahedron* **2003**, *59*, 9555. Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866.

TABLE 1. Chemical Shifts and J Coupling Constants of 1 in Acetone at 278 K[a]

δ C$_a$	δ C$_b$	δ C$_c$	δ C$_d$	δ C$_e$	δ H$_a$	δ H$_b$	δ H$_c$	δ H$_{d1}$	δ H$_{d2}$	δ OH	J_{H_a,H_b}	J_{H_a,C_c}	J_{H_a,C_e}
18.2	18.2	19.8	65.2	7.13	0.57	0.67	0.73	3.27	3.37	3.6	3.45	8.4	2.4

[a] Chemical shifts, δ, in ppm (solvent signal as reference) and coupling constants, J, in Hz.

either static symmetry, accidental degeneracy, or dynamic symmetry of the primed and unprimed nuclei. Thus, only the dihedral angle ϕ can be determined. Three situations are possible: In the first case, ϕ and ϕ' are identical and adopt a unique value (static symmetry). One would expect that this value is close to the ±50° previously found for the bicyclopropyl as well as the ter- and quinquecyclopropyl in the X-ray structure. In the second case, if ϕ and ϕ' each adopted one value and they were not identical (accidental degeneracy), the NMR data measured simultaneously for ϕ and ϕ' would reflect the 1:1 average of these nonidentical values. This would be the situation if the structure found in the crystal for compound **1** would also prevail in solution. In the third case (dynamic symmetry), the two angles would be identical and averaged between at least two conformations. This situation would be indistinguishable from the second case. In the following we show that all experimental data are in agreement with the first situation of static symmetry and that we do not have to assume the more complicated second and third cases. This procedure of taking the simplest structural model is justified when more NMR parameters (Table 1: chemical shifts; proton−proton and proton−carbon coupling constants; and NOE cross-peaks) are in agreement with a single value for ϕ and ϕ'.

The deuteration facilitated the extraction of the homonuclear coupling $^3J_{H_a,H_b} = 3.45$ Hz. According to the calculated Karplus relationship, this value would fit to dihedral angles of $+50 \pm 10°$, $+140 \pm 10°$, $-50 \pm 10°$, and $-140 \pm 10°$. The coupling constants predicted for the crystal structure (second case), previously reported by some of us with alternating dihedral angles ϕ and ϕ' ($-57.6°$ and $+49.7°$), would be approximately 2.9 Hz $= [J_{H_a,H_b(\phi\,=\,-57.58°)} + J_{H_a,H_b(\phi\,=\,+49.74°)}]/2$, which does not agree with this newly measured value of 3.45 (± 0.15) Hz.[5]

Heteronuclear couplings are indispensable to further define the structure of **1**, because the deuteration removed all relevant homonuclear couplings except for the interunit $^3J_{H_a,H_b}$ coupling.[11] Applying the robust HMBC of Verdier et al.,[11] the $^3J_{H_a,C_c}$ and $^3J_{H_a,C_e}$ couplings were determined to be 8.4 and 2.4 Hz, respectively (Table 1). Two regions, $\phi = -50$ and $+140°$, are excluded by these experimental values for which $^3J_{H_a,C_c}$ is smaller than $^3J_{H_a,C_e}$. Only $\phi = +50$ or $-140°$ are compatible with the homonuclear and the heteronuclear couplings. By contrast, the values predicted for the conformation found in the crystal structure[5] would be 2.8 Hz $= [J_{H_a,C_c(\phi\,=\,-57.58°)} + J_{H_a,C_c(\phi\,=\,+49.74°)}]/2$ and 2.9 Hz $= [J_{H_a,C_e(\phi\,=\,-57.58°)} + J_{H_a,C_e(\phi\,=\,+49.74°)}]/2$, respectively, which is clearly incompatible with the experimental data. It should be stated that for the heteronuclear couplings, we relied on the difference of the $^3J_{H_a,C_c}$ and $^3J_{H_a,C_e}$ couplings and not their absolute values. It is well-established that the absolute values of the $^3J_{H,C}$ couplings calculated with DFT methods may deviate from experimental ones by approximately 2 Hz while retaining faithfully the differences.[10]

Information about the dihedral angle ϕ independent of J couplings was obtained from NOEs. Due to the identities of the chemical shifts of primed and unprimed nuclei, the H$_a$−H$_c$ NOE integral reflects the distances between the protons H$_a$−H$_c$, H$_{a'}$−H$_c$, H$_{a'}$−H$_{c'}$, and H$_a$−H$_{c'}$. This integral is compared to the H$_a$−H$_b$ NOE integral that reflects the H$_a$−H$_b$ and H$_{a'}$−H$_b$ distances. We found similar values for the two integrals. This is in agreement with the dihedral angle ϕ being $+50$ or $-140°$, but is inconsistent with ϕ being -50 and $+140°$ because the distances between the H$_a$ and H$_c$ protons would be too long.

DFT calculations of the chemical shifts of all carbon atoms of **1** and their dependence on the dihedral angle ϕ have been performed. The chemical shift of C$_c$ shows the largest variation of 10 ppm when ϕ varies between 0 and 360° (Figure 1B).

When the calculated chemical shift of the methyl carbon of acetone is used as a reference, the δ value is 19.5 ppm on the tetramethylsilane scale for the $+50°$ conformer, and 24.2 ppm for the $-140°$ conformer. The experimental value is 19.8 ppm, which clearly fits that of the $+50°$ conformer. It should be noted that the observation of the very high-field shift of C$_c$ further corroborates the predominant existence of a single conformation in solution, because only the ϕ values ranging between $+20$ and $+60°$ exhibit these high-field chemical shifts and exclude the presence of other conformations. The calculated chemical shifts for C$_a$ and C$_b$ show only small variations which, therefore, cannot deliver further information about the conformation (maximal differences for C$_a$ = 5.8 ppm and C$_b$ = 5.1 ppm).

All experimental information (chemical shift of C$_c$, homo- and heteronuclear coupling constants, ^3J, and NOE integrals of H$_a$−H$_b$ (H$_{a'}$−H$_b$) and H$_a$−H$_c$ (H$_{a'}$−H$_c$)) was cast into an equation of variance with the dihedral angle ϕ as the independent variable (Figure 2).

The dihedral angle with the lowest value of variance around $+40°$ is the best representation of the experimental data and characterizes, therefore, the dominating helical conformation of tercyclopropanedimethanol **1** with a single repetitive (+)-gauche interunit dihedral angle (Figure 3), in full agreement with the crystal structure of the all *syn,trans*-quinquecyclopropanedimethanol with *R* configuration at the termini that also adopted an all-(+)-gauche conformation. Thus, the second and third cases discussed above can be excluded and, consequently, one of the crystal structures of tercyclopropanedimethanol differs from the solution structure.

Additionally, the free energies calculated by DFT exhibited an asymmetric minimum at a dihedral angle ϕ of $+40°$, without an imaginary frequency, indicating a thermodynamically stable conformation.

The temperature dependence of the NMR parameters is quite interesting and further corroborates a unique conformation. The $^3J_{H_a,H_b}$ coupling constant increased (Figure 1A) with increasing temperature (298 K, 3.80 Hz), which normally would be interpreted as a higher population of a conformation in which the two protons are antiperiplanar or eclipsed. However, the chemical shift of C$_c$ (Figure 1B) should also increase, which is not the case (C$_a$ = 18.1 ppm, C$_b$ = 18.2 ppm, C$_c$ = 19.8 ppm, H$_a$ = 0.58 ppm, H$_b$ = 0.68 ppm, and H$_c$ = 0.73 ppm). However,

---

(11) Verdier, L.; Sakhaii, P.; Zweckstetter, M.; Griesinger, C. *J. Magn. Res.* **2003**, *163*, 353. Sheng, S.; van Halbeek, H. *J. Magn. Reson.* **1998**, *130*, 296. Cicero, D. O.; Barbato, G.; Bazzo, R. *J. Magn. Reson.* **2001**, *148*, 209. Marquez, B. L.; Gerwick, W. H.; Williamson, R. T. *Magn. Reson. Chem.* **2001**, *39*, 499.

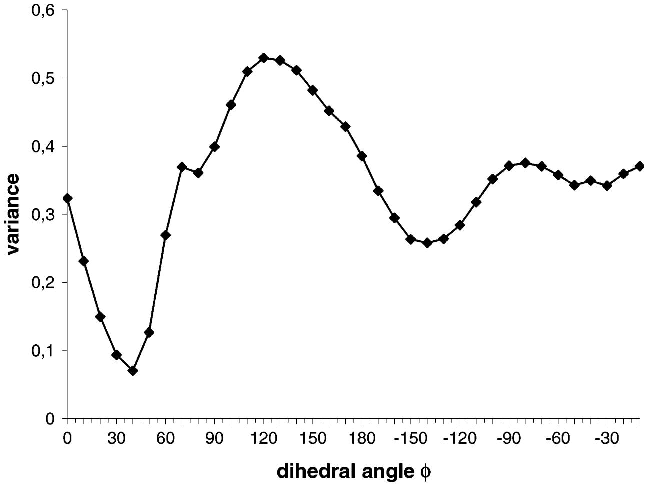


FIGURE 2. Variance with the interunit dihedral as an independent variable. The variance is defined as the following: variance $= ((\delta C_{c,exp} - \delta C_{c,calc})^2/(10\ \text{ppm})^2 + ({}^3J_{H_a,H_b,exp} - {}^3J_{H_a,H_b,calc})^2/(8.6\ \text{Hz})^2 + (({}^3J_{H_a,C_c,exp} - {}^3J_{H_a,C_e,exp}) - ({}^3J_{H_a,C_c,calc} - {}^3J_{H_a,C_e,calc}))^2/(10.86\ \text{Hz})^2) + (\sigma_{H_a,H_b,exp} - \sigma_{H_a,H_b,calc})^2/64^2 + (\sigma_{H_a,H_c,exp} - \sigma_{H_a,H_c,calc})^2/191.44^2)/5$. An almost identical curve was obtained when using the ratios of the heteronuclear *J* couplings instead of the differences.

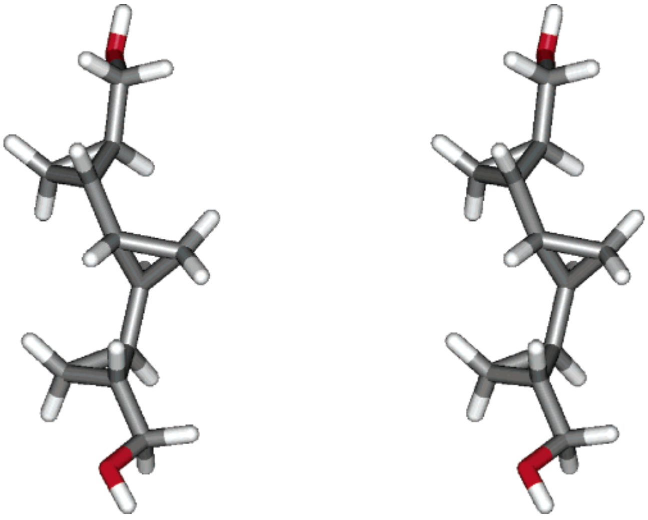


FIGURE 3. Stereoview of tercyclopropanedimethanol **1** in acetone-d_6 at 278 K.

the coupling constants and chemical shifts can be explained by a highly asymmetric potential around the $\phi = +40°$ value. Relative DFT calculated energies are 1.11, 0.98, 0, 11.12, and 14.76 kcal/mol for the angles $\phi = +20°, +30°, +40°, +50°$, and $+60°$. This suggests that the chemical shift of C_c stays the same while the ${}^3J_{H_a,H_b}$ increases upon temperature increase because of the strong asymmetry of the potential toward values of ϕ smaller than $+40°$.

Summary

In the present study we find for the configurationally repetitive all *syn,trans*-tercyclopropanedimethanol **1** a unique repetitive conformation with two (+)-gauche dihedral angles of +40°. It is induced by the *R* configuration of carbons C_c and $C_{c'}$, in complete agreement with the crystal structure of the all *syn,trans*-quinquecyclopropanedimethanol with an *R* configuration at the termini. This finding suggests conformational control of the oligocyclopropane by the configuration. The solution structure of the tercyclopropanedimethanol **1** differs from the crystal structure,[5] indicating that crystal-packing forces can supersede the intrinsic preference for the (+)-gauche, (+)-gauche conformation at least for three cyclopropane units. Our method of combining DFT with experimental restraints solves a long-standing and difficult question of conformational analysis of highly repetitive molecules and should, therefore, be applicable for other similar problems.

Experimental Section

NMR. NMR measurements were generally performed at 278 K on a 600-MHz spectrometer equipped with a cryoprobe and a 400-MHz spectrometer. The sample consisted of 3 mg of **1** in acetone-d_6. A total of 8 scans per t_1 increment were acquired for COSY and 28 scans per t_1 increment were acquired for NOESY spectra. A mixing time of 800 ms was used. The ^{13}C-HSQC and ^{13}C-HMBC experiments were performed according to Verdier and co-workers.[11] A delay of 50 ms was chosen. From these spectra, the heteronuclear ${}^3J$ coupling constants and ^{13}C chemical shifts were extracted. ${}^3J_{H,H}$ values were extracted from 1D-proton spectra and confirmed by selective versions. Measured chemical shifts are referenced with respect to the solvent signal relative to tetramethylsilane.

DFT. Structures were optimized using the hybrid B3LYP functional and the 6-31G(d,p) basis set.[12] The vibrational analysis provided $\Delta G_{calc}°$ values for the different conformations. With the obtained geometries, the calculations of the chemical shifts and the ${}^3J$ coupling constants were run using the same functional and basis set. Spin−spin coupling constants were calculated taking into account the contributions of the following interactions: Fermi contact, paramagnetic spin−orbit, diamagnetic spin−orbit, and spin−dipole. The calculated chemical shift values were referenced to the calculated acetone values computed at the same level of theory. The experimental and the calculated shifts were obtained with deuterated compound and computer models. Nondeuterated models exhibited similar chemical shifts, supporting the conformational analysis. However, it is not possible to obtain the same amount of experimental data of the nondeuterated compound, rendering a comparison impossible.

Acknowledgment. This work was supported by the EPSRC, GlaxoSmithKline, Max-Planck Society, the DFG (SFB 416), and the Fonds der Chemischen Industrie.

Supporting Information Available: Syntheses of **1**, **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0525985

---

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2003.