Synthesis and Structure of a New *cis*-1,3-Dihydroxycyclohexane Derivative having Four Convergent Hydroxy Groups

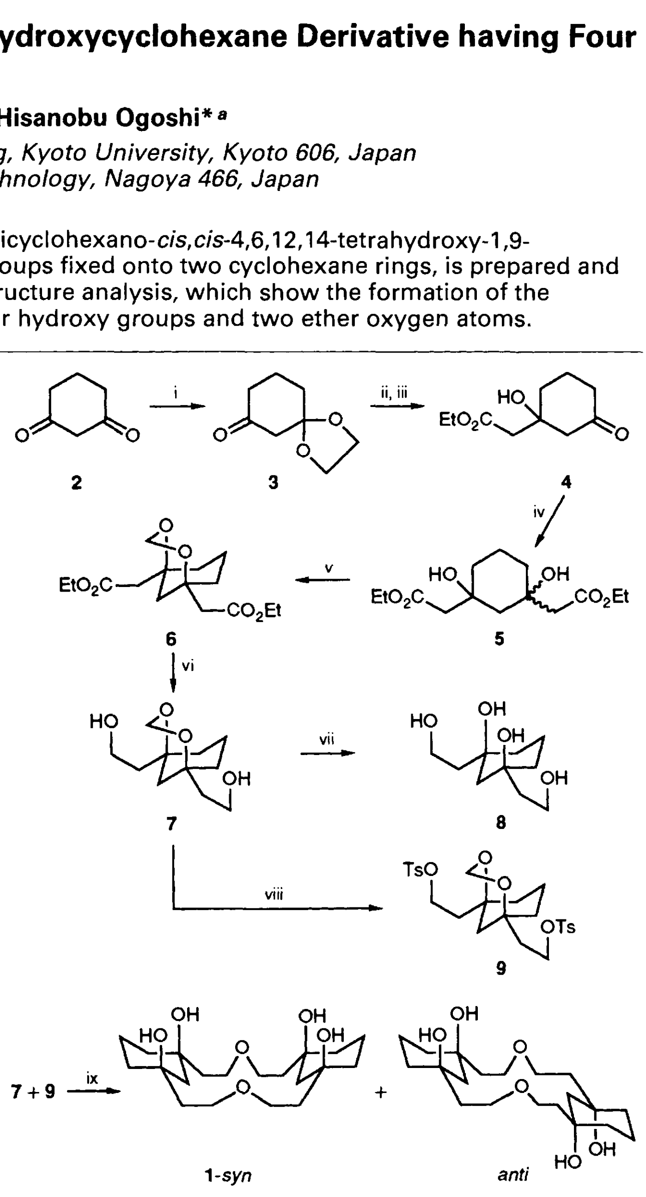
Takashi Hayashi,*[a] Hideki Takagi,[a] Hideki Masuda[b] and Hisanobu Ogoshi*[a]

[a] *Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan*
[b] *Department of Applied Chemistry, Nagoya Institute of Technology, Nagoya 466, Japan*

A novel macrocyclic compound, the *syn*-form of 4,6;12,14-dicyclohexano-*cis,cis*-4,6,12,14-tetrahydroxy-1,9-dioxacyclohexadecane **1** having four convergent hydroxy groups fixed onto two cyclohexane rings, is prepared and characterized by ^{1}H and ^{13}C NMR spectroscopy and X-ray structure analysis, which show the formation of the intramolecular hydrogen bonding network among these four hydroxy groups and two ether oxygen atoms.

Hydrogen bonding is one of the most important interactions to form the multicomponent aggregation or host–guest complex.[1] Convergent functional groups such as a hydroxy group especially provide efficient multiple interaction sites with the polar guest molecules. Here, we report the synthesis and peculiar structure of a new cyclic compound **1** having four tertiary convergent hydroxy groups.

Scheme 1 shows the preparation of **1** from cyclohexane-1,3-dione **2** in seven steps. Stepwise treatment of two carbonyl groups with the enolate anion generated by ethyl acetate and lithium diisopropylamide (LDA) gave a mixture of *cis* and *trans* isomers of the diester **5** in 50% yield from **3** (*cis–trans* = 1:1), although the addition of an excess of enolate anion to diketone **2** gave no diester **5**. Methylene acetal protection of two hydroxy groups of **5** facilitates separation of the two isomers by silica gel column chromatography to give only acetal **6** due to polymerization and/or lactonization of the *trans* isomer. After reduction and hydrolysis acetal **6** gave **8** (m.p. 101–104 °C). Coupling reaction between **7** and **9** in the presence of caesium hydroxide in Me$_2$SO followed by deprotection of acetal gave *syn* **1** and the *anti* isomer of **1** in 2.3% yield. These two isomers were separated carefully by silica gel column chromatography (eluent: CHCl$_3$–EtOAc = 1:4) and characterized by ^{1}H and ^{13}C NMR, MS and IR spectra, respectively.† Recrystallization of each isomer from EtOAc gave amphiphilic white crystalline solids.



Scheme 1 *Reagents and conditions*: i, ethyleneglycol, *p*-TsOH (Ts = *p*-MeC$_6$H$_4$SO$_2$), 53%; ii, MeCO$_2$Et, LDA, H$^+$; iii, H$^+$, 74%; iv, MeCO$_2$Et, LDA, H$^+$; 94% (*cis–trans* = 1:1 mixture); v, (CH$_2$O)$_n$, *p*-TsOH, EtOH, 48%; vi, LiAlH$_4$, H$^+$, quant.; vii H$^+$, 84%; viii, *p*-TsOH, quant.; ix, CsOH, H$^+$, 2.3%

---

† *^{1}H NMR* spectrum of **1** (400 MHz, CDCl$_3$) δ 1.130 (ddd, J_{gem} 13.5, J_{vic} 13.5, J_{vic} 4.3 Hz, 4H), 1.201 (d, J_{gem} 13.2 Hz, 2H), 1.336 (dt, J_{gem} 14.8, J_{vic} 2.2 Hz, 4H), 1.358–1.435 (m, 4H), 1.690–1.755 (m, 4H), 1.967 (dtt, J_{gem} 13.8, J_{vic} 13.8, J_{vic} 3.7 Hz, 2H), 2.074 (ddd, J_{gem} 14.8, J_{vic} 12.9, J_{vic} 4.6 Hz, 4H), 2.174 (dt, J_{gem} 13.2, ^4J 2.4 Hz, 2H), 3.546 (ddd, J_{gem} 9.3, J_{vic} 4.5, J_{vic} 2.3 Hz, 4H), 3.708 (ddd, J_{gem} 9.3, J_{vic} 12.8, J_{vic} 2.3 Hz, 4H), 5.348 (s, 4H). ^{13}C NMR spectrum of **1** (recorded at 22.5 MHz in CDCl$_3$): 6 peaks, δ 16.67, 39.64, 39.88, 41.55, 67.31 and 71.75. MS: *m/z* 372 (M$^+$).

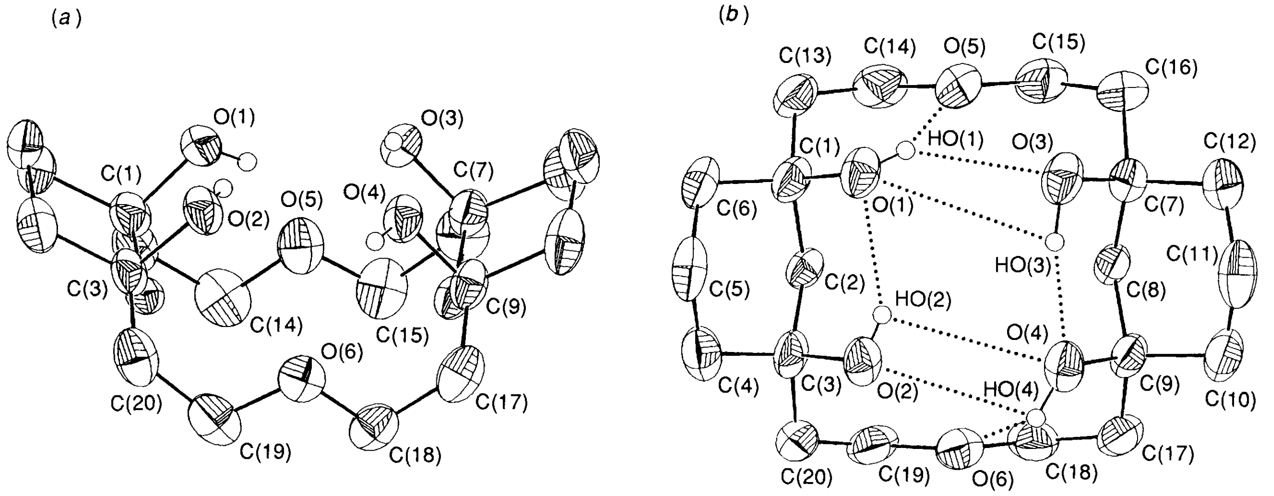


Fig. 1 ORTEP drawing of the structure of **1**: (*a*) side view, and (*b*) top view. Hydrogen atoms of hydroxy groups are shown as spheres of arbitrary size, and other atoms are represented by ellipsoids corresponding to 30% probability. The dotted lines denote hydrogen bonding. Important interatomic distances (Å) are as follows: O(1)–O(2), 2.760(4); O(1)–O(3), 2.943(4); O(1)–O(5), 2.780(5); O(2)–O(4), 2.945(4); O(2)–O(6), 2.893(4); O(3)–O(4), 2.749(4); O(3)–O(5), 2.866(4); O(4)–O(6), 2.817(3).

One isomer obtained as a second fraction by column chromatography proved to be the *syn* form conformation of **1** having four convergent hydroxy groups as shown by X-ray crystal structure analysis (Fig. 1).‡ This result confirms the chair conformation of the cyclohexane ring and the 1,3-diaxial configuration of each hydroxy group.§ The interatomic distances between two adjacent oxygens are determined to be in the range of 2.750 to 2.945 Å and four hydroxy protons are directed to neighbouring oxygen atoms to form the intramolecular hydrogen bonding; *e.g.* H–O(1) forms hydrogen bonds with O(3) and O(5) at distances of approximately 2.35 and 2.05 Å, respectively. Thus, the polar functional groups assemble together owing to a series of mutual intramolecular hydrogen bonding networks.

^{1}H and ^{13}C NMR spectra of **1** in $CDCl_3$ at ambient temperature show C_2-symmetry. All proton resonances were assigned unambiguously by the coupling patterns, relative intensities and NOE (nuclear Overhauser effect) spectra. (*i*) Each methylene proton splits into AB patterns of geminal coupling. (*ii*) Long-range spin–spin coupling of cyclohexane ring protons was also detected to be ^4J 2.4 Hz. (*iii*) All of the coupling patterns were similar to those of unit molecule **8**. (*iv*) Significant changes of proton resonances of the cyclohexane ring were not observed at elevated temperature (135 °C). Thus, the cyclohexane ring maintains the chair form as the most favourable conformation ranging from ambient temperature to 135 °C and the framework of **1** seems to be relatively rigid, since four hydroxy groups are fixed as the axial positions on the cyclohexane ring by the strong hydrogen bonding.[5] Compound **1** is favourable to the formation of *intramolecular* hydrogen bonding in a similar manner as in the solid state.

Current efforts are being devoted to exploring further the binding properties of **1** with various guest molecules by use of convergent hydroxy groups.

This work was supported by a Grant-in-Aid for Specially Promoted Research (No. 04101003) from the Ministry of Education, Science, and Culture, Japan. T. H. acknowledges support of this work by Kaneka Corporation Award in Synthetic Organic Chemistry, Japan. We thank Mr Haruo Fujita of our Department for the measurement of the 400 MHz ^{1}H NMR spectra.

Received, 23rd November 1992; Com. 2/06205D

References

1 Recent book; G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer-Verlag, Berlin, 1991; recent reviews; J. Rebek, Jr., *Chem. Ind.*, 1992, **2**, 171; J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1304.

2 M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna and D. Viterbo, *J. Appl. Cryst.*, 1989, **22**, 389.

3 *International Tables for X-Ray Crystallography*, ed. J. A. Ibers and W. C. Hamilton, Kynoch, Birmingham, 1974, vol. IV.

4 B. A. Frenz, *Enraf-Nonius structure determination package. SDP user's guide*, Enraf-Nonius, Delft, The Netherlands, 1985, version 4.

5 According to the conformational study of cyclohexane-1,3-diols by OH stretching vibration in CCl_4 solution, the diequatorial form is more favoured than the diaxial and axial–equatorial forms. J. F. Bacon, J. H. van der Maas, J. R. Dixon, W. O. George and P. S. McIntyre, *Spectrochim. Acta, Part A*, 1989, **45**, 1313.

---

‡ *Crystallographic data* for compound **1**: $C_{20}H_{36}O_6$, M_r = 372.51, hexagonal, space group $P6_1$, a = 11.075(1), c = 29.515(1) Å, V = 3135.2 Å^3, Z = 6, D_c = 1.184 g cm^{-3}, μ = 15.30 cm^{-1}; Cu-Kα radiation (λ = 1.54178 Å). The structure was solved by use of the program SIR88[2] and refined by the full-matrix least-squares method to minimize the function $\Sigma w(|F_o| - |F_c|)^2$ with $w^{-1} = \{\sigma^2(|F_o|) + (0.02 \times |F_o|)^2\}$. The final R and R_w values were 0.0580 and 0.0854, respectively.[3,4] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ The X-ray structure of unit molecule **8** confirms also the chair conformation of the cyclohexane ring and the 1,3-diaxial configuration of the two tertiary hydroxy groups.