ORGANIC LETTERS

2005
Vol. 7, No. 14
2841−2843

Synthesis of 1,10-Dimethylbicyclo[8.8.8]hexacosane and 1,10-Dihydroxybicyclo[8.8.8]hexacosane

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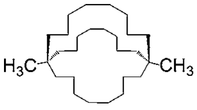
Received April 4, 2005

ABSTRACT



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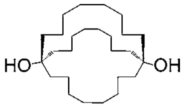

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1,10-Dimethylbicyclo[8.8.8]hexacosane (1) and 1,10-dihydroxybicyclo[8.8.8]hexacosane (2) were prepared in 4% yield over seven steps and in 18% yield over three steps, respectively, starting from 1,10-cyclooctadecanedione. The identities and *out,out* conformations of these compounds were established by single-crystal X-ray analysis.

In 1972, Park and Simmons synthesized the diastereomers of bicyclo[8.8.8]hexacosane (Figure 1).[1] Diastereomerism was due to different configurations at the bridgeheads. The *out,out* and *in,in* structures represent possible conformer subpopulations of the diastereomer of higher symmetry. The *in,in* conformers were thought to predominate on the basis of unpublished theoretical calculations and on the unreactivity of this diastereomer to attack by bromine. Synthetic work on other carbon bicycles capable of exhibiting *in/out* stereoisomerism has been somewhat limited,[2,3]

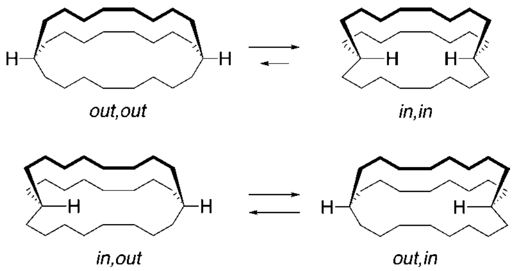

Figure 1. Representations of conformer subpopulations for the diastereomers of bicyclo[8.8.8]hexacosane.

In contrast with smaller *out,out* bicyclo[*n.n.n*]alkanes, which are relatively inflexible,[4] larger homologues should exhibit greater flexibility and conformational diversity.[5] Flexibility might be important, for example, in the stepwise

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(1) Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 7184−7186.

(2) (a) Gassman, P. G.; Thummel, R. P. *J. Am. Chem. Soc.* **1972**, *94*, 7183−7184. (b) Vinter, J. G.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1974**, *96*, 5466−5478. (c) Gassman, P. G.; Korn, S. R.; Bailey, T. F.; Johnson, T. H.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1979**, *20*, 3401−3404. (d) McMurry, J. E.; Hodge, C. N. *J. Am. Chem. Soc.* **1984**, *106*, 6450−6451. (e) McMurry, J. E.; Lectka, T.; Hodge, C. N. *J. Am. Chem. Soc.* **1989**, *111*, 8867−8872. (f) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387−400. (g) Saunders, M. Krause, N. *J. Am. Chem. Soc.* **1990**, *112*, 1791−1795. (h) McMurry, J. E.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 10167−10173. Considerable work on heteroatom-containing *in/out* bicyclic molecules has also appeared. See: (i) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097−2111.

(3) Recently a novel synthesis of bridgehead-substituted *out/out* bicyclo[10.10.10]dotriacontanes was described. See: Kurata, H.; Rikitake, N.; Okumura, A.; Oda, M. *Chem. Lett.* **2004**, *33*, 1018−1019.

(4) (a) Zimmerman, H. E.; Goldman, T. D.; Hirzel, T. K.; Schmidt, S. P. *J. Org. Chem.* **1980**, *45*, 3933−3951. (b) Kaszynski, P.; Michl, J. *J. Am. Chem. Soc.* **1988**, *110*, 5225−5226.

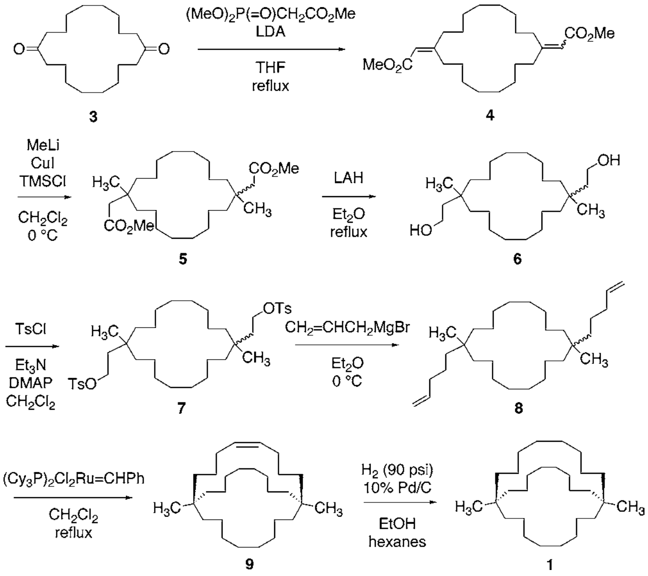
(5) Saunders has used computational methods to investigate the conformer populations of many unsubstituted bicyclic alkanes. See: Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203−208.

10.1021/ol050714k CCC: $30.25

binding to cell surface receptors of two or more bioactive ligands joined by *out,out* bicyclo[*n.n.n*]alkane linkers.[6] Development of such linkers depends on the availability of large *out,out* bicyclo[*n.n.n*]alkane derivatives. We report herein syntheses of 1,10-dimethylbicyclo[8.8.8]hexacosane (**1**) and 1,10-dihydroxybicyclo[8.8.8]hexacosane (**2**), the first examples of *out,out* bicyclo[8.8.8]hexacosanes.

The syntheses of **1** and **2** follow a pathway similar to that established by Park and Simmons but employ modern synthetic methodology. 1,10-Cyclooctadecanedione (compound **3**, Scheme 1) was prepared from sebacoyl chloride by the method of Blomquist.[7] Reaction of **3** with the lithium enolate derived from trimethyl phosphonoacetate gave an inseparable 1:1 mixture of diene-diesters **4** in 75% yield. Copper-mediated conjugate addition of methyllithium proceeded in methylene chloride[8] to give an inseparable 1:1 mixture of diesters **5** in 82% yield. Reduction of **5** to the corresponding diols **6** (62%), conversion of **6** to the ditosylates **7** (67%), and coupling of **7** with allylmagnesium bromide gave the dienes **8** (60%). Dienes **8** were inseparable and were carried forward as a mixture.

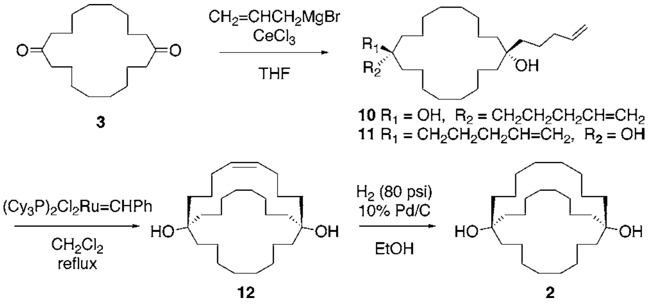
Scheme 1. Synthesis of 1,10-Dimethylbicyclo[8.8.8]hexacosane (**1**)



Ring-closing olefin metathesis using the Grubbs first generation catalyst, $(Cy_3P)_2Cl_2Ru{=}CHPh$,[9] produced bicyclic alkene **9** (double bond geometry unknown) in 30% yield.[10] The ^{13}C NMR spectrum of **9** showed nine peaks for sp^3 carbons and one peak for sp^2 carbon consistent with either an *in,in* or an *out,out* isomer.[11] Hydrogenation of **9** was sluggish but proceeded using 10% Pd/C under 90 psi of H_2 and, after 6 days, produced alkane **1** in 97% yield. The structure of **1** was supported by NMR data, and the *out,out* conformation was established by X-ray crystallography (*vide infra*).

For the synthesis of **2**, dione **3** was treated with pentenylmagnesium bromide[12] in the presence of $CeCl_3$ [13] to give a 1:1 mixture of diols **10** and **11** in 80% yield (Scheme 2). These diols were separated by flash chromatography and were independently subjected to olefin metathesis using the Grubbs first generation catalyst. Although the less polar diol **10** afforded no bicyclic products, the more polar diol **11** gave bicyclic alkene **12** (double bond geometry unknown) in 42% yield.[14] The ^{13}C NMR spectrum of **12** showed eight peaks for sp^3 carbons and one peak for sp^2 carbon consistent with either an *in,in* or an *out,out* isomer.[15] Hydrogenation of **12** was again sluggish but proceeded under forcing conditions to give alkanediol **2** in quantitative yield. The structure of **2** was supported by NMR data, and the *out,out* conformation was established by X-ray crystallography (*vide infra*).

Scheme 2. Synthesis of 1,10-Dihydroxybicyclo[8.8.8]hexacosane (**2**)



Crystals of compounds **1** and **2** were obtained from pentane and methanol, respectively, and were subjected to single-crystal X-ray analysis.[16,17] Whereas a single chiral conformer **1A** and its enantiomer were observed in the crystal of **1**, four chiral conformers **2A**−**D**, each possessing C_2

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[6] Maison, W.; Frangioni, J. V.; Pannier, N. *Org. Lett.* **2004**, *6*, 4567−4569.

[7] Blomquist, A. T.; Prager, J.; Wolinsky, J. *J. Am. Chem. Soc.* **1955**, *77*, 1804−1806.

[8] Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4265−4266.

[9] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452.

[10] A minor byproduct believed to be 1,10,19,28-tetramethyltricyclo-[26.8.8.8^{10,19}]dopentaconta-5,23-diene from cyclodimerization of **8** was also produced and was carried forward along with **9**.

[11] An *in,out* bicyclic alkene would be distinguished in the ^{13}C NMR by its lower symmetry.

[12] Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545−3556.

[13] Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236.

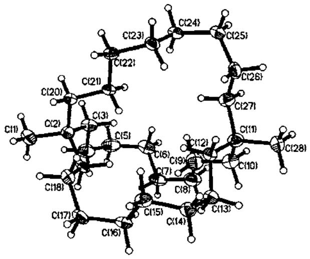
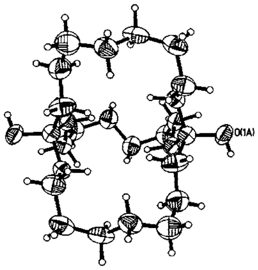
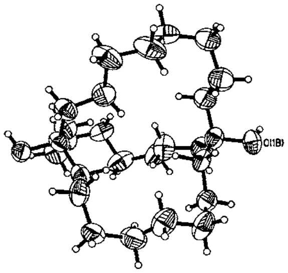
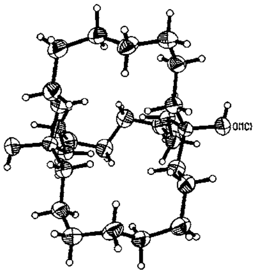
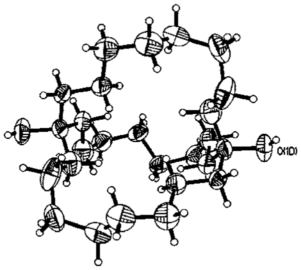
[14] The byproduct 1,10,19,28-tetrahydroxytricyclo[26.8.8.8^{10,19}]dopentaconta-5,23-diene from cyclodimerization of **11** may have been produced but, being a tetrol, would have been lost during chromatographic purification of **12**.

[15] Cyclization of trans isomer **10** might have afforded an *in,out* bicyclic alkene diol distinguished in the ^{13}C NMR by its lower symmetry, but did not.

[16] Crystal data for **1**: $C_{28}H_{54}$; $M = 390.71$ g mol^{-1}, monoclinic, $P2_1/c$, colorless prism measuring 0.34 mm × 0.21 mm × 0.07 mm, $T = 173(2)$ K, $a = 10.639(3)$, $b = 27.103(8)$, $c = 10.096(3)$ Å, $\beta = 116.417(5)°$, $V = 2607.3(14)$ Å^3, $Z = 4$, $D_c = 0.995$ Mg m^{-3}, $\mu = 0.055$ mm^{-1}, $T_{max} = 0.996$, $T_{min} = 0.943$, GOF on $F^2 = 1.007$, $R_1 = 0.0688$ and $wR_2 = 0.1433$ ([$I > 2\sigma(I)$]), $R_1 = 0.1754$ and $wR_2 = 0.1856$ (all data).

symmetry, were observed in the crystal of **2**. Conformers **2A** and **2C** are very nearly enantiomeric except for differences in the orientations of the hydroxyl groups. ORTEP drawings of these conformers are shown in Table 1 along with their relative energies after geometry optimization[18] determined using MMFF in Spartan '02 v1.0.4e.[19] Also listed are the measured values for κ, the bridgehead-to-bridgehead distance, and γ, the angles formed by the atom attached to a bridgehead and the two bridgehead atoms. Differences in κ provide a measure of the flexibility of the bicyclo[8.8.8]-hexacosane ring. Comparisons of the values of γ provide a measure of the colinearity of the methyl and bridgehead carbon atoms of **1** or the oxygen and bridgehead carbon atoms of **2** (when $\gamma_1 = \gamma_2 = 180°$ the four atoms are colinear). For compound **2** the largest difference in inter-bridgehead distance, $\Delta\kappa$, is 0.8 Å (a difference of 15%) observed for **2A** or **2C** and **2D**. A Monte Carlo search[5,20] for conformations of **2** within 25 kJ of the global minimum gave a maximum $\Delta\kappa$ of 1.8 Å (a difference of 30%). Close matches to conformers **2A** or **2C** and **2D** were found within 2.6 and 2.8 kJ of the global energy minimum conformer, **2B**, respectively. A similar search[5,20] for conformations of **1** within 25 kJ of the global minimum gave a maximum $\Delta\kappa$ of 1.8 Å (a difference of 29%). The global minimum located in this search was a close match to **1A**.[21]

Table 1. Conformers of **1** and **2** Observed in the Crystals

	conformer[a]	relative energy[b] (kJ/mol)	κ[c] (Å)	γ[d] (deg)
1A		na	6.35	170 171
2A		2.6	5.25	176
2B		0	5.88	166
2C		2.6	5.19	176
2D		5.6	6.02	167

[a] ORTEP structures showing 50% thermal elipsoids. [b] Determined using MMFF in Spartan '02 v1.0.4e. na = not applicable. [c] κ is the bridgehead-to-bridgehead distance observed in the crystal structure. [d] γ is the angle formed by the atom attached to a bridgehead and the two bridgehead atoms observed in the crystal structure.

Conformer **1A** very nearly possesses C_2 symmetry, and γ_1 and γ_2 are both close to 180°, indicating near linearity of the methyl and bridgehead carbon atoms. Conformers **2A**−**D** possess C_2 symmetry, so $\gamma_1 = \gamma_2$ for each. The values of γ for **2A**−**D** range from 166° to 176°, indicating near linearity of the oxygen and bridgehead carbon atoms.

In summary, a workable synthesis of bridgehead-substituted bicyclo[8.8.8]hexacosanes has been demonstrated by the preparation of compounds **1** and **2**. X-ray crystallographic analyses have confirmed the *out,out* conformations of these compounds. Although **1** and **2** resemble smaller homologues in the near linearity of their bridgehead substituents, they differ in that they possess considerable flexibility. This feature is expected to afford utility to bicyclo[8.8.8]hexacosane derivatives as linkers in biomedical and other applications.

Acknowledgment. This work was supported by grants R33 CA 95944 and RO1 CA 97360 from the National Cancer Institute, by grant CHE9610374 from the NSF, and by the University of Arizona. We thank Matthew A. Lynn for assistance with computational studies.

Supporting Information Available: Experimental procedures, spectral characterizations of new compounds, copies of the ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic information files in CIF format for compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Crystal data for **2**: $C_{26}H_{50}O_2$; $M = 394.66$ g mol^{-1}, tetragonal, $P4_122$, colorless block measuring 0.21 mm × 0.23 mm × 0.28 mm, $T = 170(2)$ K, $a = 19.4695(10)$, $b = 19.4695(10)$, $c = 26.580(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 10075.5(12)$ Å^3, $Z = 16$, $D_c = 1.041$ Mg m^{-3}, $\mu = 0.063$ mm^{-1}, $T_{max} = 0.987$, $T_{min} = 0.855$, GOF on F^2 = 1.028, $R_1 = 0.0945$, $wR_2 = 0.2439([I > 2\sigma(I)])$, $R_1 = 0.1470$ and $wR_2 = 0.3052$ (all data).

(18) The authors thank a reviewer for pointing out the proper way to perform these calculations.

(19) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490 and following papers in this issue.

(20) The details of this search will appear in a full paper to follow.

(21) The lowest energy *in,in* conformer of **1** was found 208.4 kJ above the *out,out* global minimum. The lowest energy *in,out* conformer was 72.3 kJ above the *out,out* global minimum.