

cis-endo-Bicyclo[1.1.1]pentane-1,2,3,4-tetracarboxylic Acid and Its Derivatives

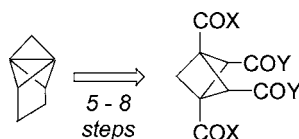
Ctibor Mazal,^{*,‡} Ondřej Škarka,[‡] Jiří Kaleta,[‡] and Josef Michl[†]

Department of Organic Chemistry, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic, and Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

mazal@chemi.muni.cz

Received December 14, 2005

ABSTRACT



X = Y = OH
 X = OH, Y = OMe
 X = NH₂, Y = OMe
 X = (*R*)-NHCHMePh, Y = OMe

We report the synthesis of *cis-endo*-bicyclo[1.1.1]pentane-1,2,3,4-tetracarboxylic acid and several of its derivatives with differentiated bridgehead and bridge positions, starting with tetracyclo[3.2.0.0^{1,6}.0^{2,6}]heptane.

We are interested in the possibility that close spatial proximity of multiple functional groups crowded on a small cage, such as bicyclo[1.1.1]pentane, might lead to unusual properties as a result of their mutual interactions. In addition to offering interesting substrates for reactivity studies, highly functionalized bicyclo[1.1.1]pentanes might also provide future access to bridge-functionalized [1.1.1]propellanes and thus to laterally substituted [*n*]staffane molecular rods.¹

Although numerous bicyclo[1.1.1]pentanes substituted only in the bridgehead positions are known,² those also functionalized on the bridges are extremely rare. 1,3-Disubstituted 2,2-dichloro and 2,2-dibromo derivatives were prepared by reaction of bicyclo[1.1.0]butane derivatives with dichloro^{3–6} and dibromo carbenes, respectively. Such tetra-substituted bicyclo[1.1.1]pentanes were also prepared by direct chlorination of bicyclo[1.1.1]pentane-1,3-dicarboxylic acid, its dichloride,⁷ and 1,3-dibromobicyclo[1.1.1]pentane.⁸

Interestingly, 2-monochloro derivatives did not accumulate and had to be obtained by subsequent partial dehalogenation. Direct fluorination of the 1,3-dicarboxylic acid provided almost all of the possible fluorinated diacids which were separated and used for an investigation of long-range NMR coupling constants.^{9,10} Some 2,2-difluoro derivatives have been patented as structural units for liquid crystals.¹¹ Carbon-linked bridge substitution is only represented by 2,4-ethano¹² and 2,4-propano^{13–16} bridged derivatives (tricyclo[3.2.0.0^{2,6}]heptanes and tricyclo[4.2.0.0^{2,7}]octanes, respectively) and by poly[1.1.1]propellanes, whose bicyclo[1.1.1]pentane cages carried an alkyl chain,¹⁷ including one with a remote hydroxyl function¹⁸ used to anchor a dendritic fragment.¹⁹

(8) Hamrock, S. J.; Michl, J. *J. Org. Chem.* **1992**, *57*, 5027.

(9) Levin, M. D.; Hamrock, S. J.; Kaszynski, P.; Shtarev, A. B.; Levina, G. A.; Noll, B. C.; Ashley, M. E.; Newmark, R.; Moore, G. G. I.; Michl, J. *J. Am. Chem. Soc.* **1997**, *119*, 12750.

(10) Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. *J. Am. Chem. Soc.* **2001**, *123*, 3484.

(11) Yano, H.; Takeuchi, H. *Jpn. Kokai Tokkyo Koho* 1998 JP 10168453 A2 19980623 Heisei. CAN 129:142670.

(12) Mazal, C.; Paraskos, A. J.; Michl, J. *J. Org. Chem.* **1998**, *63*, 2116.

(13) Stroeter, T.; Szeimies, G. *J. Am. Chem. Soc.* **1999**, *121*, 7476.

(14) Bunz, U.; Szeimies, G. *Tetrahedron Lett.* **1990**, *31*, 651.

(15) Schlueter, A. D.; Wegner, G.; Feast, W. J. *Angew. Chem.* **1988**, *100*, 283.

(16) Belzner, J.; Szeimies, G. *Tetrahedron Lett.* **1987**, *28*, 3099.

(17) Bothe, H.; Schlueter, A. D. *Adv. Mater.* **1991**, *3*, 440.

(18) (a) Freudenberger, R.; Lamer, W.; Schlueter, A. D. *J. Org. Chem.* **1993**, *58*, 6497–6498. (b) Lassale, I.; Schmidt, M.; Schlueter, A. D. *Acta Polym.* **1994**, *45*, 389.

[‡] Masaryk University.

[†] University of Colorado.

(1) Schwab, P. F. H.; Levin, M. D.; Michl, J. *Chem. Rev.* **1999**, *99*, 1863.

(2) Levin, M. D.; Kaszynski, P.; Michl, J. *Chem. Rev.* **2000**, *100*, 169.

(3) Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, 3411.

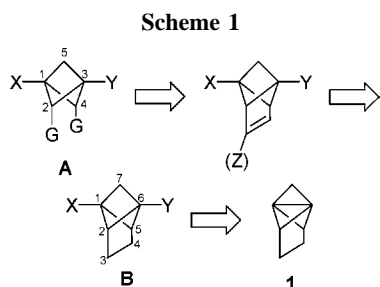
(4) Applequist, D. E.; Renken, T. L.; Wheeler, J. W. *J. Org. Chem.* **1982**, *47*, 4985.

(5) Hall, H. K., Jr.; Smith, C. D.; Blanchard, E. P., Jr.; Cherkofsky, S. C.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 121.

(6) Potekhin, K. A.; Maleev, A. V.; Struchkov, Yu. T.; Surmina, L. S.; Koz'min, A. S.; Zefirov, N. S. *Dokl. Akad. Nauk SSSR Ser. Khim.* **1988**, *298*, 123.

(7) Robinson, R. E.; Michl, J. *J. Org. Chem.* **1989**, *54*, 2051.

In this paper, we report the preparation of *cis-endo* 1,2,3,4-tetrafunctionalized bicyclo[1.1.1]pentanes (Scheme 1, struc-

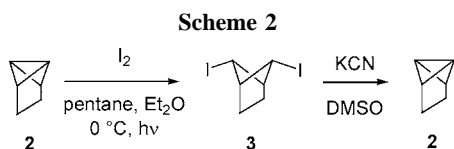


ture **A**); this type of structure has also been a target for others.²⁰

The retrosynthetic approach to structure **A** (Scheme 1) uses tetracyclo[3.2.0.0^{1,6}.0^{2,6}]heptane (**1**)²¹ as a starting point since [1.1.1]propellanes are known to undergo addition across the transannular bond to yield doubly bridgehead substituted bicyclo[1.1.1]pentanes. Subsequent derivatization by hydrogen atom abstraction should occur preferentially at the ethano bridge, and not the quite unreactive, bicyclopentane cage.

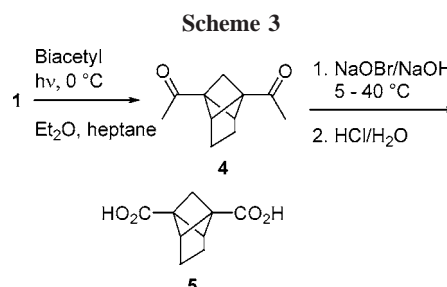
The tetracycloheptane **1** is accessible in 50% yield from tricyclo[3.1.0.0^{2,6}]hexane (**2**),²² obtained by the reduction of benzvalene.^{23,24} Inspired by the Szeimies²⁵ procedure for the preparation of solvent-free [1.1.1]propellane, we have improved the isolation of **2** from the reaction mixture by converting it into the less volatile diiodo derivative **3** and subsequently regenerating **2** by reaction with potassium cyanide.

The propellane bridgehead positions of **1** were functionalized by addition of biacetyl across the transannular bond followed by an oxidation of the resulting diketone **4** to the dicarboxylic acid **5** in a haloform reaction (Scheme 3), a

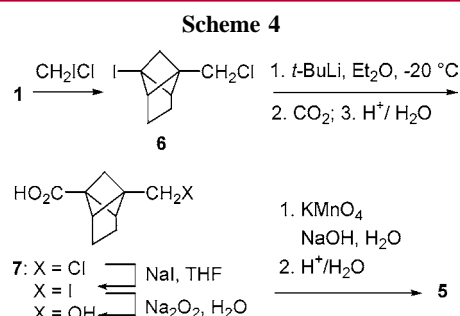


reaction sequence that gives excellent yields for the parent [1.1.1]propellane.²⁶ However, the oxidation of **4** proceeds in ~50% yield, perhaps due to a smaller stability of the

tricyclic ring system, making the overall yield of **5** from **2** less than ~25%.



The low yield of the oxidation of **4** has prompted us to look for alternatives. Since the conversion of **2** into **1** is always accompanied by the formation of about 10–15% of the byproduct **6**, we tried to maximize the yield of **6** and convert it to **5**. A reaction with *tert*-butyllithium and carbon dioxide produced the monoacid **7**. Since the hydrolysis of this chloromethyl derivative proved to be difficult, it was converted to an iodomethyl derivative by the Finkelstein reaction, hydrolyzed with sodium peroxide, and oxidized with potassium permanganate to yield **5** in an overall yield of 20% based on **2**, which is, however, no better than the first procedure described above.



As a crude guide to the regioselectivity of the halogenation of **5** to be expected in the next step, we estimated the *s* character of the carbon hybrid orbitals used to carry hydrogen atoms from ¹J_{CH} NMR coupling constants²⁷ and obtained an encouraging result. For positions 2 and 5, the value was 31.3%, for 7, 29.3%, and for 3 and 4, 26.7% (Scheme 1, structure **B**). After many unsuccessful bromination attempts, we turned to chlorination, which succeeded. Chlorination of the dichloride of **5** in a mixture of liquid chlorine and carbon tetrachloride at –20 °C under irradiation with an incandescent lamp yielded mainly the 3-chloro derivative **8**, and after extended reaction time, the 3,4-dichloro derivatives **9** and **10** (Scheme 5) in acceptable yields, plus rearranged and

(19) Freudenberger, R.; Claussen, W.; Schlueter, A.-D.; Wallmeier, H. *Polymer* **1994**, *35*, 4496.

(20) Stulgies, B.; Pigg, D. P.; Kaszynski, P.; Kudzin, Z. H. *Tetrahedron* **2005**, *61*, 89.

(21) Belzner, J.; Gareiss, B.; Polborn, K.; Schmid, W.; Semmler, K.; Szeimies, G. *Chem. Ber.* **1989**, *122*, 1509.

(22) Christl, M.; Bruentrup, G. *Chem. Ber.* **1974**, *107*, 3908.

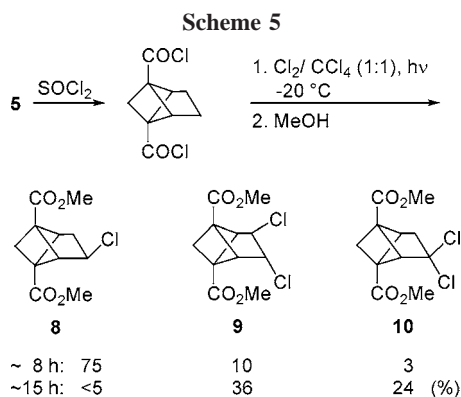
(23) Katz, T. J.; Roth, R. J.; Acton, N.; Carnahan, E. J. *J. Org. Chem.* **1999**, *64*, 7663.

(24) Katz, T. J.; Roth, R. J.; Acton, N.; Carnahan, E. J. *Org. Synth.* **1973**, *53*, 1824.

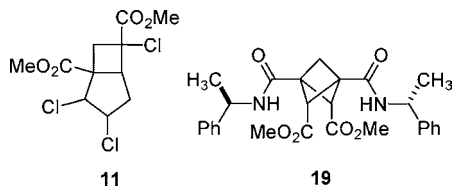
(25) Alber, F.; Szeimies, G. *Chem. Ber.* **1992**, *125*, 757.

(26) Levin, M. D.; Kaszynski, P.; Michl, J. *Org. Synth.* **2000**, *77*, 249.

(27) The *s* character of carbon hybrid orbitals was calculated from ¹J_{C–H} coupling constants measured in dimethyl ester of **5** (¹J_{C(2)–H} = 156.4 Hz, ¹J_{C(3)–H} = 133.3 Hz, ¹J_{C(7)–H} = 146.7 Hz) using the equation ¹J_{C–H} = 5 × %*s* (cf. Muller, N.; Pritchard, D. E. *J. Chem. Phys.* **1959**, *31*, 1471).

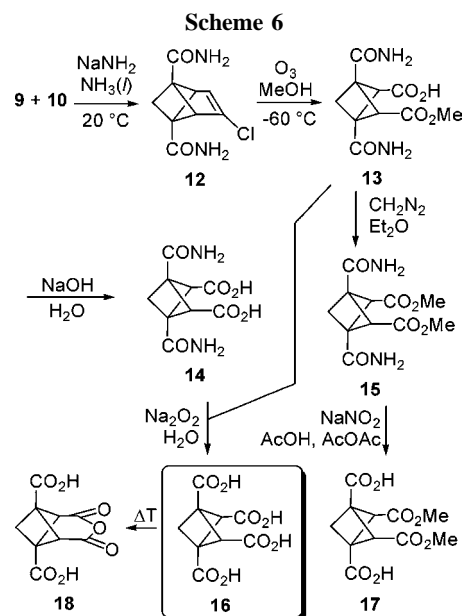


overchlorinated products. At lower chlorine concentrations or at higher reaction temperatures, the formation of the desired products was too slow relative to a rearrangement of the tricyclic ring system, probably to structure **11** suggested by GC–MS.



Following the retrosynthetic Scheme 1, hydrogen chloride elimination from the chloro derivatives was attempted. Surprisingly, none of the reagents tried succeeded with the monochloro derivative **8** or its various bridgehead protected derivatives, from alkaline hydroxide through sodium amide to Schlosser's superbase.²⁸ Fortunately, elimination with sodium amide in liquid ammonia succeeded with a mixture of dichloro derivatives **9** and **10** at room temperature and afforded the chloro olefin **12** in excellent yield. The vicinal isomer **9** reacted already at low temperature ($-25\text{ }^{\circ}\text{C}$), but room temperature and longer reaction time (hours) were necessary for complete reaction of **10**. The chloro olefin **12** is rather unstable and decomposes slowly in acetone, methanol, or chloroform solution, but solid samples can be stored in a refrigerator for weeks. Its ozonolysis in methanol at $-60\text{ }^{\circ}\text{C}$ gave the expected²⁹ monomethyl ester **13** in good yield, and this was either hydrolyzed to the diacid **14** or methylated with diazomethane to the diester **15** (Scheme 6).

Chemoselective transformations of either bridgehead or bridge-located functionalities (Scheme 6) provided access to several bicyclo[1.1.1]pentane-1,2,3,4-tetracarboxylic acid (**16**) derivatives with differentiated bridgehead and bridge substituents. Both carboxamide groups in the diester diamide **15** were hydrolyzed to carboxyls by sodium nitrite in a mixture of acetic acid and acetic anhydride,³⁰ yielding the diester **17** with free carboxyls at the bridgeheads. The parent



tetraacid **16** was obtained by hydrolysis of the dicarboxamide diacid **14** or its monoester **13** with sodium peroxide³¹ and was characterized as its tetramethyl ester. An easy formation of the anhydride diacid **18** that was observed already during the isolation of **16** was completed upon heating above $80\text{ }^{\circ}\text{C}$ for several hours.

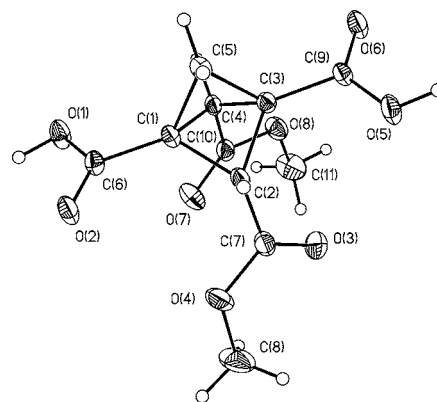


Figure 1. An ORTEP representation of the diester **17**.

The easy formation of **18** was not the only manifestation of an effect of close proximity of the bridge substituents on their reactivity. The diester **17** could not be reduced with LiAlH_4 , most probably for the same reason. This is reminiscent of a similar situation in 1,8- or 1,2-disubstituted naphthalenes,^{32,33} where crowded substituents not only

(28) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627.

(29) (a) Keul, H.; Griesbaum, K. *Can. J. Chem.* **1980**, *58*, 2049. (b) Griesbaum, K.; Keul, H. *Angew. Chem.* **1975**, *87*, 748.

(30) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069.

(31) Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187.

(32) Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161.

(33) Clayden, J.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1379.

showed altered reactivity but also led to atropisomerism. According to the X-ray structure of **17** (Figure 1), the distance of the two bridge methoxycarbonyls (2.83 Å) is comparable with that in 1,8-disubstituted naphthalenes

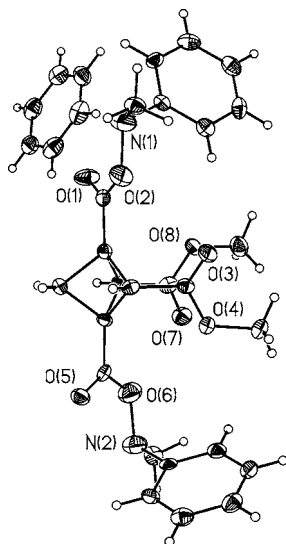


Figure 2. An ORTEP representation of the chiral diamide **19**, which crystallizes with benzene.

(2.60–2.90 Å),³⁴ and the ester groups prefer an antiparallel orientation, making the molecule chiral. Both enantiomers were found in the centrosymmetric crystals of **17** (space group $P\bar{1}$). The energy barrier to racemization in solution is probably low since no diastereomers of the chiral diamide **19** (Figure 2) were detected by low-temperature NMR measurements at -100 °C.

In conclusion, we have developed a synthetic procedure for *cis-endo*-1,2,3,4-tetrasubstituted bicyclo[1.1.1]pentanes carrying different substituents in bridgehead and bridge positions. The proximity of the bridge substituents in the *cis-endo* configuration clearly affects their reactivity. It also opens an opportunity for a so far unobserved atropisomerism.

Acknowledgment. We gratefully acknowledge financial support from the National Science Foundation, USA (Grant Nos. CHE-0446688 and OISE-0532040) and Ministry of Education, Youth and Sports, Czech Republic (Grant Nos. ME 571 and MSM0021622410).

Supporting Information Available: Experimental procedures, full characterization for compounds, ^1H and ^{13}C NMR spectra, and CIF files for compounds **17** and **19**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL053039N

(34) Clayden, J.; McCarthy, C.; Helliwell, M. *Chem. Commun.* **1999**, 2059.