Oligocyclopropanols

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1,1′-Linked Cyclopropane Derivatives: The Helical Conformation of Quinquecyclopropanol**

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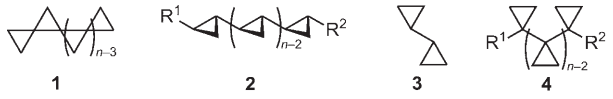
Dedicated to Professor Kenneth B. Wiberg on the occasion of his 80th birthday

Single-, double-, and even triple-helical structures play important roles for biological and synthetic macromolecules; however, for relatively small organic compounds helical arrangements are not common.[1] In most biological macromolecules such a helical structure is favored and maintained by hydrogen bonds. Helical conformations of saturated compounds without functional substituents is observed less frequently. Aliphatic perfluorocarbon chains are known to adopt a helical structure in the crystalline state and in solution as a result of electrostatic repulsion of the fluorine substituents in the 1- and 3-positions,[2] poly(ethyleneglycol) adopts a helical conformation in isobutyric acid solution,[3] and permethyldecasilane forms a helix in a helical schizophyllan matrix.[4] As formally saturated hydrocarbons have no driving forces to adopt helical conformations (apart from van der Waals interactions), their conformations range from "zig-zag" for linear hydrocarbons on one hand to helical for certain enantiomerically pure [*n*]triangulanes (**1**)[5,6] on the other. Helicity of the latter, however, is predetermined by their rigid helical shape.

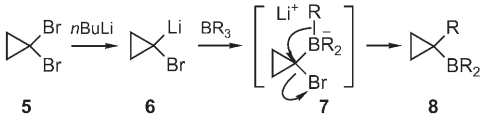


1 **2** **3** **4**

[1,1′;2′,1″;2″,1‴;…;2^{n-2},1^{n-1}]Oligocyclopropanes (**2**), which have been discovered as substructures in two natural products from different sources,[7] exhibit quite interesting conformational properties depending on their substituents. Thus, helical conformations were demonstrated for [1,1′;2′,1″]tercyclopropanedimethanol (**2**, $n=3$, $R^1=R^2=CH_2OH$) and for [1,1′;2′,1″;2″,1‴;2‴,1⁗]quinquecyclopropanedimethanol (**2**, $n=5$, $R^1=R^2=CH_2OH$) in solution as well as in the solid state, while other compounds of this type adopted different conformations, at least in the crystals.[8]

Based on an earlier observation that bicyclopropyl (**3**) in the gaseous and the liquid state preferentially adopts a synclinal (*gauche*) conformation,[9] one is intuitively led to conceive that the higher 1,1′-linked oligocyclopropanes **4** ($n\geq 3$) would prefer helical arrangements in which all bicyclopropyl subunits have either (+)- or (−)-*gauche* conformations. This notion is indeed supported by density functional theory (DFT) computations at the B3LYP/6-31G(d) level of theory. Since the only known higher 1,1′-linked oligocyclopropanes **4**, the 1,1-dicyclopropylcyclopropane **4a** ($n=3$, $R^1=R^2=H$),[10] its derivatives **4b–d** ($n=3$, $R^1=R^2=OH$,[11] $OSiMe_3$,[11c,d] and OMs[11d]), and 1,1‴-dimethyl-[1,1′;1′,1″;1″,1‴]quatercyclopropane **4e** ($n=4$, $R^1=R^2=Me$),[12] had not been structurally characterized at all, we set out to prepare such [1,1′;1′,1″;…;1^{n-2},1^{n-1}]oligocyclopropanes endowed with polar functionalities, in order to investigate their structural features.

The Matteson homologation methodology[13] was considered to be employable as the key step. In this, an organyl substituent migrates from the negatively charged boron to an adjacent carbon in a borate complex with inversion of configuration.[14] For example, intermediate **7**, which is formed upon treatment of a lithium halocarbenoid like **6** (prepared from dibromocyclopropane (**5**) and *n*-butyllithium)with a borane, is converted into the corresponding 1-organocyclopropylborane **8** (Scheme 1). The latter can then undergo the same transformation repeatedly upon treatment with the in situ generated carbenoid **6**, eventually leading to $1,1^n$-disubstituted oligocyclopropanes **4** ($n\geq 2$). Indeed, lithium halocyclopropylidenoids upon treatment with organoboronates have been found to produce cyclopropaneboronates in good yields.[13] Thus, when trimethylene methylboronate (**9**) was treated with a solution of dibromocyclopropane (**5**)[15] in tetrahydrofuran, to which *n*-butyllithium had been



5 **6** **7** **8**

Scheme 1. Example of a Matteson-type homologation.

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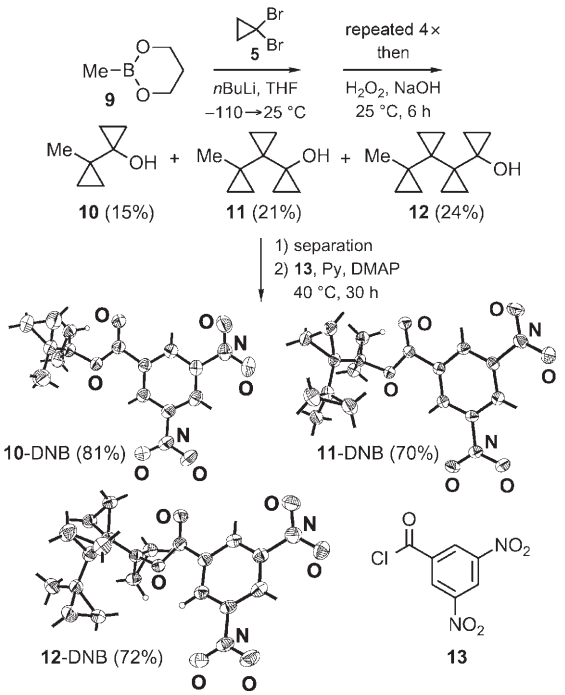
added at −110 °C, and this treatment was iterated four more times, a mixture of cyclopropylcyclopropaneboronates was formed. Subsequent oxidation with hydrogen peroxide in the presence of sodium hydroxide gave a mixture of the cyclopropylcyclopropanols **10**–**12** in good overall yield (Scheme 2).

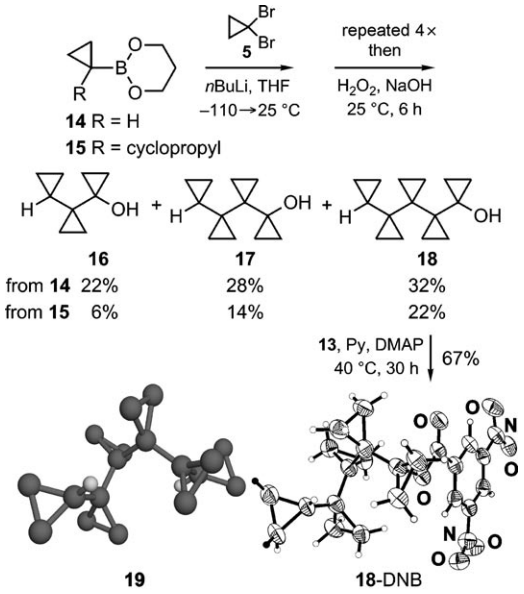


Scheme 2. Facile synthesis of bis-, ter-, and quatercyclopropane derivatives by a Matteson-type homologation of 1,1-dibromocyclopropane.

These products could be separated by column chromatography, and each cyclopropanol was individually transformed to the corresponding 3,5-dinitrobenzoate—**10**-DNB (81% yield), **11**-DNB (70%), and **12**-DNB (72%)—by reaction with 3,5-dinitrobenzoyl chloride (**13**). Crystals of all three dinitrobenzoates were grown and subjected to X-ray diffraction analysis.[16]

In order to obtain an even higher 1,1′-linked oligocyclopropanol than **12**, the same iterative homologation was performed with cyclopropaneboronates **14**[17] and **15** (Scheme 3).[18,19] Indeed, the [1,1′;1′,1″;1″,1‴;1‴,1⁗]quinquecyclopropan-1-ol (**18**) was isolated in 32% (from **14**) and 22% yield (from **15**) along with tercyclopropanol **16** (22% from **14**, 6% from **15**) and quatercyclopropanol **17** (28% from **14**, 14% from **15**). The quinquecyclopropanol **18** was also converted to its dinitrobenzoate **18**-DNB, and the latter was analyzed by X-ray diffraction.[16]

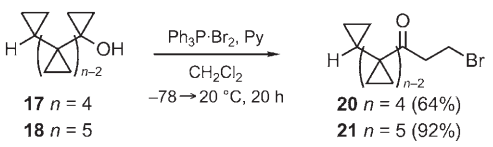
The DFT computations[20–25] for [1,1′;1′,1″;1″,1‴;1‴,1⁗;1⁗,1⁗⁗]sexicyclopropane (**19**) in the gas phase predicted dihedral angles of −55.0, +60.6, +62.5, +59.4, and −52.5° (see the Supporting Information) along the chain for the lowest energy conformer; in other words, the inner quatercyclopropane fragment in this molecule has an all-(+)-*gauche* conformation, while the two outer cyclopropyl groups are (−)-*gauche* oriented. In the crystal, the quinquecyclopropane moiety of **18**-DNB, on going from the cyclopropanol to the



Scheme 3. Synthesis of quinquecyclopropanol **18** and computed conformation of sexicyclopropane **19.**

terminal cyclopropane moiety, has dihedral angles between each two neighboring cyclopropanes of 52.9, 64.5, 60.3, and −68.6°, respectively (averages for the two independent molecules in the asymmetric unit); this orientation is completely analogous to that calculated for the inner section of the sexicyclopropane. In the crystals of the other three dinitrobenzoates **10**-DNB, **11**-DNB, and **12**-DNB the 1,1′-linked cyclopropane moieties adopt analogous helical all-*gauche* conformations.

The chemical behavior of the 1,1′-oligocyclopropylcyclopropanols **16**–**18** is also noteworthy as it differs from that commonly observed for 1-cyclopropyl-substituted cyclopropanols. Thus, an attempted conversion of the alcohols **17** and **18** to the corresponding bromides—which were desired for reduction to the unsubstituted quatercyclopropane **4f** ($n=4$, $R^1=R^2=H$) and quinquecyclopropane **4g** ($n=5$, $R^1=R^2=H$)—did neither occur with complete retention of their cyclopropane moieties (cf. Ref. [26]) nor with iterative ring enlargement by way of cascade rearrangements involving all their cyclopropane moieties.[11c,d,27] Instead, in each case only the cyclopropanol moiety itself underwent ring opening to a β-bromoketone fragment (cf. Ref. [28]) to give the 3-bromopropionyl-1,1′-oligocyclopropanes **20** and **21** in 64 and 92% yield, respectively, with retention of the other three-membered rings (Scheme 4).



Scheme 4. Ring opening of [1,1′;1′,1″;1″,1‴]quatercyclopropan-1-ol (**17**) and [1,1′;1′,1″;1″,1‴;1‴,1⁗;1⁗,1⁗⁗]quinquecyclopropan-1-ol (**18**) upon attempted conversion into the corresponding bromides.

Thus, both the 1,1-linkage and the 1,2-linkage of oligocyclopropanes lead to helical structures of relatively small molecules. The consequences of this preferred arrangement of [1,1′;1′,1″;…;1^{n-2},1^{n-1}]oligocyclopropane units are currently being studied.

Experimental Section

Representative procedure: Synthesis of **18**: *n*-Butyllithium in hexane (2.2 mmol, 0.91 mL of a 2.42 M solution in hexane) was added dropwise under argon to a solution of 1,1-dibromocyclopropane (**5**)[15] (440 mg, 2.2 mmol) in anhydrous THF (20 mL) at −110 °C, and the mixture was stirred at −110 °C for 5 min. The mixture was then treated with trimethylene cyclopropaneboronate (**14**) (252 mg, 2.0 mmol), and the resulting mixture was gradually warmed to room temperature within approximately 12 h. After that, dibromide **5** (440 mg, 2.2 mmol) was added at 25 °C, and the mixture was cooled to −110 °C again. *n*-Butyllithium (2.2 mmol, 0.91 mL of a 2.42 M solution in hexane) was added at −110 °C, and the mixture was gradually warmed to room temperature again. This procedure was repeated another three times. Finally, hydrogen peroxide (8 mmol, 908 mg, 820 μL of 30 % aq. solution) and sodium hydroxide (5 mmol, 5 mL of 1 N aq. solution) were added at 0 °C, and the reaction mixture was stirred at 25 °C for 6 h. The resulting mixture was extracted thoroughly with diethyl ether (6 × 50 mL), and the combined organic extracts were dried ($MgSO_4$). The solution was concentrated under reduced pressure, and the residue was separated and purified by column chromatography (80 g of flash silica gel, 2 × 60 cm column, hexane/ether 10:1→4:1, $R_f = 0.25$ in hexane/ether 4:1) to yield quinquecyclopropan-1-ol **18** (139 mg, 32 %) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.55$ (br s, 1H; OH), 1.66–1.57 (m, 1H; CH), 0.71–0.66 (m, 2H; CH_2), 0.56–0.51 (m, 2H; CH_2), 0.49–0.44 (m, 2H; CH_2), 0.39–0.31 (m, 2H; CH_2), 0.29–0.21 (m, 6H; CH_2), 0.12–0.06 (m, 4H; CH_2), −0.02 to −0.09 ppm (m, 2H; CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 59.9$ (C-OH), 25.7 (C), 25.2 (C), 23.6 (C), 14.8 (CH), 12.4 (2CH_2), 9.7 (2CH_2), 8.0 (2CH_2), 7.5 (2CH_2), 1.9 ppm (2CH_2). The structure of **18** was proved by X-ray crystal structure analysis of its 3,5-dinitrobenzoate **18**-DNB.[16]

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[16] CCDC 642257 (**10**-DNB), CCDC 642256 (**11**-DNB), CCDC 642258 (**12**-DNB), and CCDC 642255 (**18**-DNB) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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