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Highly substituted cyclohexanes: strong proximity effects influence synthetic access to 1,3,5-tris(bromomethyl)-1,3,5-trialkylcyclohexanes (alkyl = methyl, *n*-propyl)

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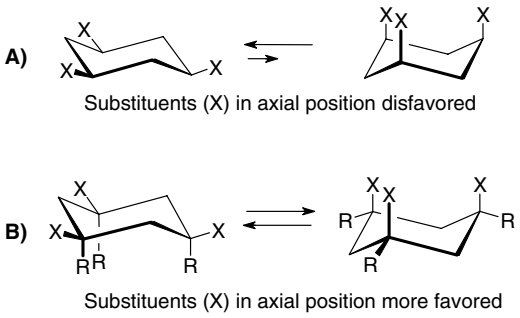
Abstract—1,3,5-Tris(bromomethyl)-1,3,5-trialkylcyclohexanes (alkyl = methyl, *n*-propyl) were prepared. These are the first examples of 1,3,5-tris(halomethyl)-1,3,5-trialkylcyclohexanes. One synthetic method directly converted the corresponding triols with PPh_3Br_2, where an excess of the bromination reagent and high temperature (175 °C) were required. Stoichiometric use of PPh_3Br_2 under mild conditions, successfully employed for the synthesis of the parent tris(bromomethyl)cyclohexane, did not lead to the desired tribromides but rather to cyclic ethers. Proximity effects triggered by the 1,3,5-alkyl groups strongly influence the reactivity of such highly substituted cyclohexanes. An alternative synthetic access to the tris(bromomethyl) compounds was also developed, using 1,3,5-tris(triflatomethyl)-1,3,5-trialkylcyclohexanes (triflato = F_3CSO_3) as synthetic intermediates. An X-ray crystal structure of 1,3,5-tris(bromomethyl)-1,3,5-trimethylcyclohexane was obtained.

1,3,5-Trisubstituted cyclohexanes have proven tremendously useful as scaffolds for the preparation of complex molecular architectures, such as clefts for molecular recognition,[1] dendrimers,[2] and polycyclic cages.[1a,3] The formation of cage-type structures typically involves that a linker bridges substituents in axial position of the cyclohexane ring. For this purpose, trifunctional cyclohexanes bearing additional alkyl substituents at the 1,3,5-carbons are particularly useful: *cis*,*cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid ('Kemp's triacid')[4] is probably the best-known example for such 1,3,5-trifunctional 1,3,5-trialkylcyclohexanes. These alkyl-substituted derivatives undergo reactions leading to cage-type structures generally more easily than the parent compounds,[3a,c,e] where the bonds leading to closure of the cage might be covalent bonds,[3c] metal–ligand interactions,[3e] or hydrogen bonds.[3a] This can reasonably be attributed to the effect the alkyls exert on conformational equilibria.[3a,c,e] Conformations involving axial functional groups, generally disfavored for an unsubstituted system (Scheme 1A), might become more favored with the help of 1,3,5-alkyls (Scheme 1B), such that the functional groups (X) are forced into closer proximity. While this effect is often desirable, it regularly makes synthetic procedures rather challenging. For example, *cis*,*cis*-1,3,5-triaminocyclohexane has been known since 1957, but the synthesis of *cis*,*cis*-1,3,5-trimethylcyclohexane-1,3,5-triamine was reported only in 2002, and complications due to an unusually stable intramolecular acid anhydride were encountered during its synthesis.[3a]



Scheme 1.

Keywords: Proximity effect; Cyclohexane; Axial; Equatorial; Alkyl halide.
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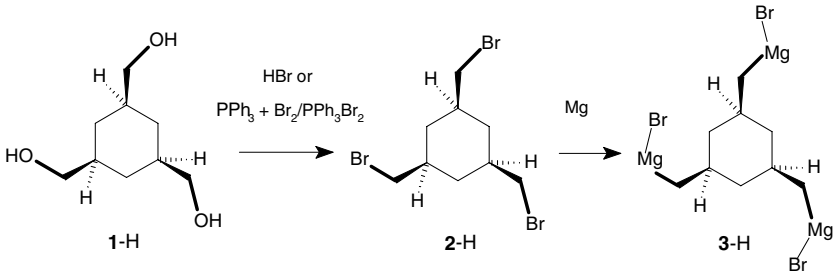
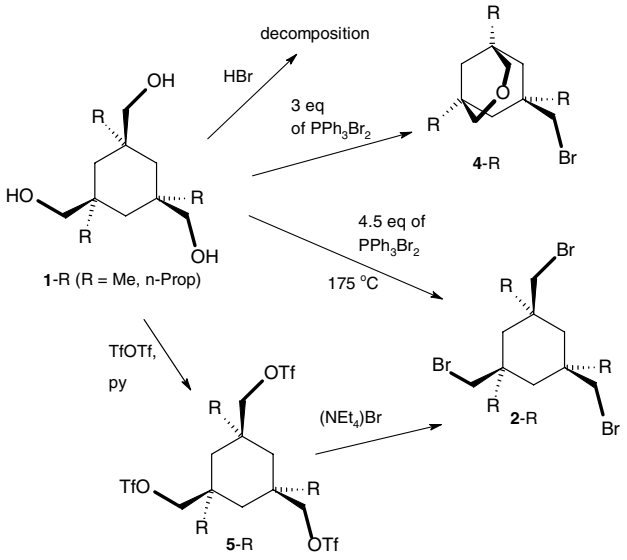


Scheme 2.

We are interested in cyclohexane-based alkyl trihalides. 1,3,5-tris(halomethyl)cyclohexanes are important intermediates for the synthesis of cage-type compounds. For example, 1,3,5-tris(bromomethyl)cyclohexane was recently used to prepare a rare example of a tris-Grignard reagent (compound **3**-H in Scheme 2), useful for the synthesis of silaadamantane cages.[3f,g] Given the usefulness of alkyl halides as synthetic intermediates, it is notable that this chemistry has not yet been extended to the 1,3,5-trialkyl-substituted systems. In fact, we were surprised to find that no 1,3,5-tris(halomethyl)-1,3,5-trialkylcyclohexanes (Scheme 1B, X = –CH_2-halogen, R = alkyl) have been reported so far. In this contribution, we report on the preparation of the first examples of such compounds, using two different strategies.

Transformations on the unsubstituted 1,3,5-tris(hydroxymethyl)cyclohexane (**1**-H) are straightforward and proceed as shown in Scheme 2. The conversion of **1**-H into the 1,3,5-tris(bromomethyl)cyclohexane (**2**-H) has been classically performed using PPh_3 and Br_2 (an equivalent reagent is Ph_3PBr_2) but significant difficulties in removing the triphenylphosphine oxide by-product have been noted.[3g] We found that **2**-H is easily made by refluxing **1**-H in 48% HBr overnight.[5] A remarkable transformation on the tribromide **2**-H has been reported recently, namely, the conversion into a tris-Grignard compound **3**-H, a very rare compound of a triply metalated aliphatic framework.[3f,g] We found that the reported formation of a tris-Grignard compound is easily reproduced.

We tried to perform similar transformations on the 1,3,5-trialkyl derivatives **1**-Me and **1**-Prop (Scheme 3, compounds **1**-R).[6] However, we found that the latter compounds exhibit reactivity very different from that of **1**-H. Reacting compounds **1**-R (R = Me, *n*-Prop) with HBr did not form the desired tribromides **2**-R, but led to complete decomposition instead. The reaction with Ph_3PBr_2, however, led to the following observations: room temperature reactions where **1**-R were reacted with a slight excess of PPh_3Br_2 (1:3.2 molar ratio), yielded a mixture of compounds, which contained no **2**-R. We were able to isolate the bicyclic esters **4**-R (Scheme 3) as the main products, unambiguously characterized by NMR spectroscopy.[7] Clearly, the alkyl groups in the 1,3,5-positions exert a profound effect on the reactivity of the hydroxyls, by facilitating intramolecular ring-closure reactions.[8] Apparently, the ester is formed when one CH_2–O functionality, activated by



Scheme 3.

phosphorus, is being attacked, in a nucleophilic fashion, by an adjacent CH_2OH. This intramolecular attack seems to be much faster than attack by external bromide. This behavior contrasts with the reactivity of **1**-H, and we propose that the difference lies in the position of the conformational equilibrium between structures having CH_2OH in either equatorial or axial position. Such effects would not necessarily be visible in solid state structures, and in the X-ray structure of compound **1**-Me, the CH_2OH groups are still in equatorial positions.[3e] When we varied the reaction conditions, we found that the desired tribromides **2**-R are formed in 34–35% yield during 4 h if 50% excess of Ph_3PBr_2 (molar ratio 4.5:1) and high temperature conditions (175 °C) are used.[9] These reaction conditions are optimized, and while low temperatures lead to incomplete bromination, higher temperatures lead to decomposition.

An alternative access to **2**-R was also developed. We reasoned that care should be taken since once a good leaving group is formed at one position, nucleophilic attack by an adjacent group should be prevented. This might be achievable by efficient functionalization of the OH groups at low temperature, and the triflate species **5**-R are promising synthetic intermediates. We prepared the known[3e] compound **5**-Me, along with the new compound **5**-Prop.[10] The tris-triflates **5**-R were reacted with three equivalents of $(NEt_4)Br$ in $CHCl_3$

to obtain **2**-R.[11] These reactions are less straightforward than envisioned, since the tris-triflates **5**-R are temperature-sensitive, decomposing within days at room temperature (even under inert atmosphere). Unfortunately, elevated temperature is needed to facilitate the nucleophilic attack by bromide, and the reaction is essentially a competition between decomposition and S_N2 substitution. Thus, it seems unlikely that this method can be optimized to give high yields of **2**-R. However, a small amount of very pure **2**-Me was obtained by means of slow recrystallization from crude **2**-Me, prepared by this method. This crystalline material was suitable for X-ray crystallography.

In order to gain insight into the structural features of the 1,3,5-tris(bromomethyl)-1,3,5-trialkylcyclohexanes, a single-crystal X-ray structure determination of **2**-Me was undertaken (Fig. 1).[12] The compound adopts a chair conformation in the solid state, where the methyl groups occupy the axial positions and the bromomethyl groups occupy the equatorial positions. This can reasonably be expected from the relative size of these groups. The C–Br vectors are parallel to C–C bonds in the cyclohexane framework, and anti-geometry is observed for those bonds. While this might be an indication of hyperconjugation, packing effects cannot be excluded, of course. Compared to unsubstituted cyclohexane, the cyclohexane ring in this heavily substituted compound undergoes flattening. Steric repulsion enforces widening of the endocyclic bond angles around CH_2, leading to a value of 117.3(6) (average of three values, see legend to Fig. 1) for these angles, compared to the literature value[13] of 111.5° for cyclohexane. The flattening becomes manifested in the six endocyclic torsion angles, where the average of the absolute values is 49(1)° compared to the cyclohexane value of 55°. The values we observe seem typical for 1,1-3,3-5,5-hexasubstituted cyclohexanes: endocyclic bond angles to methylene of 117.4 and 119.9, as well as endocyclic torsions of 48.5 and 47.3 were previously observed for compounds **1**-Me and for *cis*,*cis*-1,3,5-tris[(diphenylphosphanyl)-methyl]-1,3,5-trimethylcyclohexane, respectively.[3e]

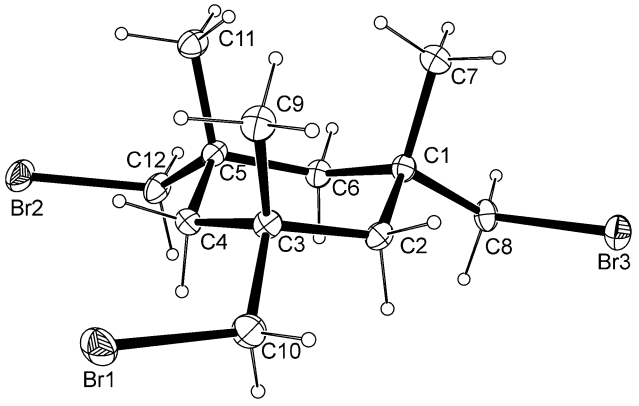


Figure 1. Thermal ellipsoid plot (30% probability) for **2**-Me. Selected distances (Å) and angles (°): C–Br: C10–Br1, 1.946(5); C12–Br2, 1.957(6); C8–Br3, 1.979(5); exocyclic angles: C7–C1–C8, 107.4(4); C10–C3–C9, 108.2(4); C11–C5–C12, 108.8(4); endocyclic angles to quaternary carbons: C2–C1–C6, 109.0(4); C2–C3–C4, 110.5(4); C4–C5–C6, 108.9(4); endocyclic angles to methylenes: C1–C2–C3, 117.8(4); C5–C4–C3, 116.7(4); C5–C6–C1, 117.3(4); torsion angles: Br3–C8–C1–C6, −175.8(6); Br1–C10–C3–C2, 179.6(6); Br2–C12–C5–C6, 179.1(6); average of the absolute values of the six endocyclic torsions: 49(1).

In conclusion, we have synthesized and characterized 1,3,5-tris(bromomethyl)-1,3,5-trialkylcyclohexanes (alkyl = methyl, *n*-propyl), the first examples of the class of 1,3,5-tris(halomethyl)-1,3,5-trialkylcyclohexanes. The target compounds were obtained, despite the fact that the alkyl groups in 1,3,5-positions render bromination reactions of the triols unusually challenging. We anticipate that the new compounds described here are very useful precursors for the synthesis of novel hydrocarbon-based cages.

Acknowledgments

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5. Compound **1**-H (500 mg) in 60 mL of 48% aqueous HBr. The product mixture was extracted with 3×25 mL of hexane, and the organic phase dried over $MgSO_4$. Removal of solvent under vacuum yeilded crystallize crude product. After recrystallization from MeOH, 331 mg (32%, yield not optimized) of pure **2**-H were obtained; ^{1}H NMR identical to literature data.[3g]
6. Compound **1**-Prop was synthesized using $LiAlH_4$ reduction of the commercially available (Aldrich) trimethyl-*cis*,*cis*-1,3,5-tripropyl-1,3,5-cyclohexane-tricarboxylate, analogously to the reported synthesis[3g] of **1**-H. Compound **1**-Me was similarly obtained from the trimethyl ester of

cis,*cis*-1,3,5-trimethyl-1,3,5-cyclohexanetricarboxylic acid, prepared by esterification of Kemp's triacid, using the two-step esterification procedure ($SOCl_2$, followed by ROH) described in: Weygand, F.; Klinke, P.; Eigen, I. *Chem. Ber.* **1957**, *90*, 1896.

7. Compound **4**-Me_3: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (s, 2H, CH_2Br), 3.35 (d, br, 2H, $^2J = 11$ Hz, C*H*H′–O), 2.89 (d, br, 2H, $^2J = 11$ Hz, CH*H*′–O), 1.71 (d, apparent $J_{HH} = 14$ Hz, 3H, CH_aH_e, CH_2 of cyclohexane ring) 1.07 (d, apparent $J_{HH} = 16$ Hz, 3H, CH_aH_e, CH_2 of cyclohexane ring), 0.95 (s, 3H, CH_3), 0.613 (s, 6H, CH_3). Compound **4**-Prop: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.06 (s, 2H, CH_2Br), 3.54 (dd, 2H, $^2J = 11$ Hz, apparent $^4J = 1.6$ Hz, C*H*H′–O), 3.10 (dd, 2H, $^2J = 11$ Hz, apparent $^4J = 1.9$ Hz, CH*H*′–O), 1.0–1.8 (m, 18H, CH_2 of cyclohexane ring+CH_2 of isopropyls), 0.86 (t, 9H, $^2J = 7$ Hz, CH_3 of isopropyls).
8. A somewhat similar proximity effect was recently observed when an undesired intramolecular ester was obtained in a system having methyl groups in 1,3,5-positions.[3c]
9. Compound **2**-R from **1**-R and Ph_3PBr_2: The reactions were performed using dry solvents and air-free conditions, using glove-box and high-vacuum line techniques. *Synthesis of* **2**-*Me*: 83 mg (0.384 mmol) of **1**-Me and 728.8 mg (1.727 mmol) of PPh_3Br_2 were suspended in 3 mL of dry CH_3CN and sonicated for 30 min at room temperature. The mixture was stirred at 175 °C for 4 h under nitrogen (closed pyrex reaction vessel), after which the solvent was removed under vacuum to yield brown oil. The mixture was dissolved in hexane (30 mL) and stirred for 30 min. Removal of triphenylphosphine oxide by filtration, followed by evaporation of hexane, yielded 53.1 mg (34.2%) of product, pure by NMR, in the form of an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26 (s, 6H, CH_2Br), 1.41 ('AB' multiplet, 6H, CH_2), 1.24 (s, 9H, CH_3). ^{13}C NMR (125.9 MHz, $CDCl_3$): $\delta = 27.0$, 35.3, 43.4, 50.1 ppm. MS (EI), *m*/*e* 387, 323, 308, 244, 229. *Synthesis of* **2**-*Prop*: 140.7 mg (0.468 mmol) of **1**-Prop and 982.9 mg (2.33 mmol) of PPh_3Br_2 were subjected to an analogous procedure as described for **2**-Me above, to yield 80.7 mg (35.2%) of product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 6H, CH_2Br), 1.1–1.7 (m, 18H, CH_2 of cyclohexane ring+CH_2 of isopropyls), 0.91 (t, 9H, $^2J = 7.2$ Hz, CH_3 of isopropyls) ^{13}C NMR (125.9 MHz, $CDCl_3$): $\delta = 14.53$, 16.21, 37.2, 39.9, 43.3, 45.4 ppm. MS: *m*/*e* 486, 443, 407, 393, 363, 328. HRMS calcd for $C_{18}H_{33}Br_3$ 486.013, found 486.013.
10. Compounds **5**-Me and **5**-Prop: **5**-Me: all reactions were performed under inert conditions (Ref. 9). Compound **1**-Me (500 mg, 2.31 mmol) was suspended in 25 mL of $CHCl_3$, and 0.563 mL (6.97 mmol) of pyridine were added. The solution was cooled to −35 °C, and 1.165 mL (6.90 mmol) of trifluoromethanesulfonic anhydride were slowly added to this cold solution. The solution was stirred for 2 h at room temperature, and a precipitate formed. The precipitate was removed by filtration, and the brown solution passed through a column of silica gel. The resulting yellow solution was used for the next step. In order to establish purity, the solvent was removed from a sample of this solution under vacuum, and $CDCl_3$ was added by vacuum transfer. The ^{1}H NMR spectrum proved identical to that previously reported for **5**-Me.[3e] Compound **5**-Prop: this compound was synthesized in a completely analogous fashion, and characterized by ^{1}H NMR spectroscopy: ^{1}H NMR (200 MHz, THF-d^8) δ 4.35 (s, 6H, CH_2OTf), 1.1–1.9 (m, 18H, CH_2 of cyclohexane ring+CH_2 of isopropyls), 0.93 (t, 9H, $^2J = 7$ Hz, CH_3 of isopropyls).
11. Compounds **2**-Me and **2**-Prop from **5**-Me and **5**-Prop: all reactions were performed under inert conditions (Ref. 9). Compound **2**-Me: 1.457 g (6.93 mmol) of tetraethylammonium bromide were added to a $CHCl_3$ solution of tris-triflate **5**-Me (2.31 mmol). The solution was heated to 75 °C overnight, under stirring, in a closed pyrex reaction vessel. The $CHCl_3$ was removed under vacuum, and 25 mL of dry hexane were added via vacuum transfer. The organic salts were removed by filtration, and the solution was concentrated under vacuum. Yellow oil was obtained, which partly crystallized. After 10 days at −35 °C, a small amount (62 mg, 6.6%) of very pure crystalline material, suitable for X-ray crystallography, was obtained. This procedure was analogously applied to synthesize **2**-Prop. Both products were identified by NMR spectroscopy (full characterization given above (Ref. 9)). Compound **2**-Me was additionally characterized by single-crystal X-ray crystallography. Compound **2**-Prop did not crystallize.
12. Crystals were obtained as described above (Ref. 11). $C_{12}H_{21}Br_3$, MW = 405.0, clear cube, monoclinic, space group = $P2_1$, $T = 150(1)$ K, $a = 7.8052(4)$ Å, $b = 11.8722(6)$ Å, $c = 8.0925(4)$ Å, $\beta = 106.853(3)°$, $Z = 2$, R_1 ($I > 2\sigma(I)$) = 0.0323, wR_2 (all data) = 0.0784, GOF(F^2) = 1.04. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 293253. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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