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Pseudotetrahedral Polyhaloadamantanes as Chirality Probes: Synthesis, Separation, and Absolute Configuration

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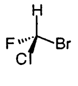
Pseudotetrahedral stereogenic centers such as carbon atoms with four different substituents are at the heart of organic stereochemistry. Perhaps the simplest, stable, and conformationally rigid compound of this kind is bromochlorofluoromethane (**1**),[1] which was first synthesized at the end of the 1800s.[2,3] Almost a century passed before the enantiomers would be even partially resolved[4−6] and the absolute configuration assigned.[7] This is due to the very small estimated value for the maximal optical rotation ($[\alpha]^{25}_{\mathrm{D}} \pm 1.6°$), the overall poor optical resolution ($ee = 4.3 \pm 1\%$;[5,6] $ee = 34 \pm 1\%$[7,8]), and facile epimerization during the elaborate separation of the enantiomers of **1**.[9] Enantiomerically pure **1** is therefore not an ideal compound for developing theories of optical activity further.[10]

The next higher pseudotetrahedral homologues of **1** are the unknown tetrahedrane, cubane, and adamantane derivatives **2**−**4**. Because parent tetrahedrane has not been realized, **2** is currently unrealistic. Although we were able to prepare mixed 1,3-dihalocubanes, the incorporation of a third halo substituent is rather challenging.[11] In contrast, adamantane derivatives such as **4** are expected to be quite stable. Hence, the present paper describes the synthesis, characterization, chromatographic enantioseparation, and stereochemical analysis of **4** and related analogues, including 1-bromo-3-chloro-5-fluoro-7-iodoadamantane (**5**), the first pseudotetrahedral compound[12] incorporating all stable (i.e., nonradioactive) halogens. These compounds may help in the development of more sophisticated models for the theory of chirality. For instance, the effect of having (**1**) or not having (**4**) a carbon atom in the stereogenic center of a conformationally rigid, near-tetrahedral,[13] chiral saturated hydrocarbon is unknown. Aspects of the parity violation (related to a fascinating electroweak, *P*-odd process in the low energy regime of atoms and molecules[14]) in, for instance, chiral internal vibrational energy relaxation may also be examined with these kinds of structures.[15−19]



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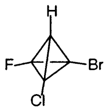

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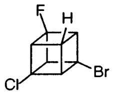

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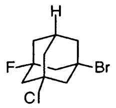

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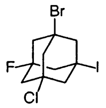

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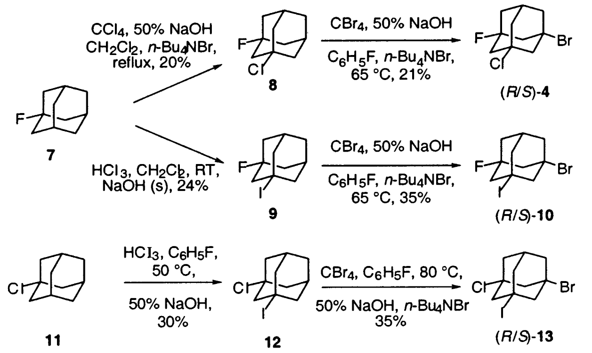
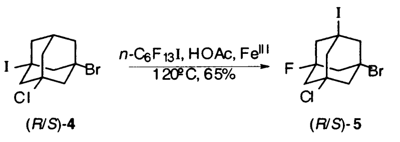
With current alkane halogenation methods, it would be quite difficult to prepare selectively isolable amounts of (*R*/*S*)-**4** or (*R*/*S*)-**5**.[20] A partial motivation for this study was therefore to examine the limits of our recently developed C−H-bond halogenation protocol, utilizing selective radical reactions under phase-transfer conditions (PTC).[21−23] Thus, 1-fluoroadamantane (**7**), available through fluorination of 1-hydroxyadamantane (**6**), could be chlorinated and then brominated under these conditions.[11] All products could be isolated by column chromatography. Analogously, (*R*/*S*)-1-bromo-3-fluoro-5-iodoadamantane (**10**) was prepared from **7** via subsequent iodination and bromination. The yields are uncharacteristically low because halogen incorporation is increasingly deactivating. The related 1-bromo-3-chloro-7-iodoadamantane (*R*/*S*)-**13** can be prepared similarly from 1-chloroadamantane (**11**).



To test the limits of this approach, we also ventured into the preparation of 1-bromo-3-chloro-5-fluoro-7-iodoadamantane (*R*/*S*)-**5**. As the PTC-iodination of deactivated (*R*/*S*)-**4** with $\cdot CI_3$ as the radical chain carrier is very slow,[21] we prepared (*R*/*S*)-**5** utilizing the more reactive n-C_6F_{13} radical as the abstracting species.[24]



The ^{13}C NMR spectra of (*R*/*S*)-**5** are in agreement with the substitution pattern (cf. Supporting Information); the crystal structure of (*R*/*S*)-**5** (Figure 1) confirms the NMR analysis.[25]

Owing to their near spherical shape, the enantioseparation of **4**, **5**, **10**, and **13** is quite challenging. GC separation proved unsuc-

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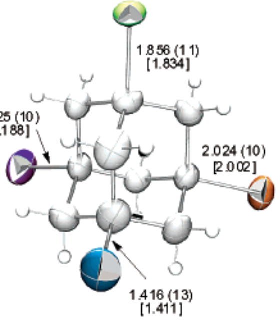

Figure 1. Molecular structure of 1-bromo-3-chloro-5-fluoro-7-iodoadamantane (**5**) (50% probability ellipsoids for Br (orange), Cl (green), F (blue), I (purple), and C). Selected experimental and computed bond lengths at B3LYP/6-31+G** (C, H, F, Cl, Br), MIDI! (I) [in brackets] in Å.

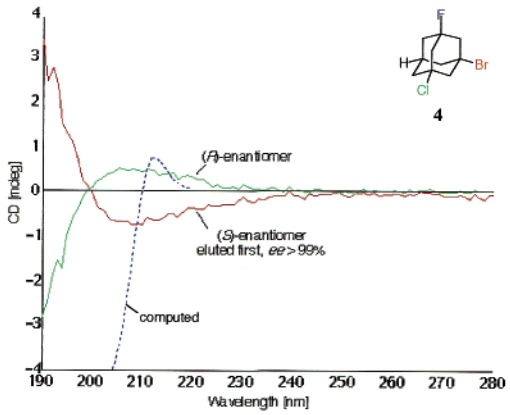

Figure 2. Measured and computed (DFT/CI-B3LYP/TZVP//B3LYP/6-31+G**, blue line) CD spectra for the assignment of the absolute configuration of **4**. Cell length 0.50 mm, concentration 1.2 × 10^{-3} M for the (*S*)-enantiomer and 7.8 × 10^{-4} M for the (*R*)-enantiomer.

cessful; HPLC using Chiralpak AD columns (25 cm × 0.46 cm, CH_3OH)[26] finally gave the enantiomers of **4** and **10** in ee's > 99% for the species eluted first (elution times (min) for first and second peaks: 14.3 and 15.3 for **4**, and 18.9 and 23.1 for **10**).

The absolute configuration of **4** was assigned by matching computed and experimental CD data.[27] As found for **1**,[7] the optical rotatory strengths of the enantiomers of **4** at the Na-*D*-line are very small ($[\alpha]_D \approx 1°$), so that matching this value computationally alone would be quite unreliable.

The CD spectra show appreciable intensities in the 190−240 nm range (Figure 2). Although the computed absorption spectrum[28] is red-shifted by about 10−12 nm due to the neglect of solvent and spin−orbit effects (currently not feasible), the resemblance and qualitative fit of the experimental line shape for the shown (*R*)-enantiomer of **4** are strikingly obvious. Hence, its absolute configuration is (*R*)-(+)-**4**. A comparable procedure for the assignment of **10** identifies the (*R*)-enantiomer as (*R*)-(−)-**10**.

The present work demonstrates the power of combining experiment and theory in assigning absolute configurations even for molecules *without* chromophors *and* with very small values for the optical rotation at a set wavelength. This, together with the exemplary work of others in this field,[29−31] emphasizes that the assignment of absolute stereochemistry of a structure by means of the tedious derivatization of a compound or by starting a synthesis from materials of known absolute configuration has come to age.

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Supporting Information Available: *xyz*-Coordinates and absolute energies for all computed species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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