Notes

The First Optically Pure *nido*-Monothiocarborane Cluster

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Summary: One of the enantiomers of racemic [NMe_4][7-SPh-8-CH_2OH-7,8-$C_2B_9H_{10}$] is isolated in 68% yield. Resolution is achieved by means of differential crystallization of the diastereoisomeric camphanate ester derivatives.

Introduction

The preparation and properties of chiral ligands have attracted considerable attention from a wide range of chemists especially in the field of organic, biological, and medicinal chemistry. Their applications have been further widened to include some currently most focused areas such as chiral recognition and chiral catalysis.[1] One of the main principles in designing asymmetric reagents and catalysts is to allow the reaction center to be surrounded by a recognition site and a chiral moiety, as the former governs the substance selectivity and the latter the stereoselectivity.[2] In contrast, despite the great development of boron chemistry produced in the past decades, the chemistry of chiral compounds with borane framework remains relatively unexplored. A dreaded easy boron or carbon rearrangement in the cluster leading to rapid racemization of a pure enantiomer may account for it. Until 1991 only 10 papers dealing with optically active boron cage compounds had been published, concerning approximately 20 individual compounds,[3] of which only four were *nido*-C_2B_9 derivatives.[4] The resolution of derivatives of [7,8-$C_2B_9H_{12}$]$^-$ or [7,9-$C_2B_9H_{12}$]$^-$ was accomplished via differential crystallization of their diastereoisomeric l-*N*,*N*,*N*-trimethyl-α-phenylethylammonium salts.[4] For these C_2B_9 derivatives a high number of recrystallizations were required to achieve resolution, and low yields of pure enantiomers were obtained in all cases. The successful resolution of more than 35 racemic boron cage compounds into optically pure enantiomers using semipreparative HPLC on chiral stationary phases has been reported.[5] The species resolved were mainly zwitterionic 7,8-$C_2B_9H_{10}$ and 5,10-$C_2B_8H_{10}$ clusters and a variety of metallaboranes. Recently, this technique has been applied to the resolution of [6,6-μ-Me_2P−(1,7-($C_2B_9H_{10}$)$_2$)-2-Co], and their absolute configurations have been elucidated by X-ray diffraction.[6] Although HPLC is not so convenient for large-scale preparation, it provided a route for the resolution of racemic [7-SR-8-R′-7,8-$C_2B_9H_{10}$]$^-$ anionic compounds. The interest in these anions was motivated by the fact that *exo-nido*[7] and *closo*[8] derivatives of [7-SR-8-R′-7,8-$C_2B_9H_{10}$]$^-$ have been demonstrated to be efficient hydrogenation catalysts for terminal and internal alkenes, respectively, and we wanted to find a suitable procedure to get the *nido*-monothiocarborane ligands in pure enantiomeric form. However, continued efforts to resolve [7-SR-8-R′-$C_2B_9H_{10}$]$^-$ anions using several types of chiral stationary phases were unsuccessful.[9] At this point we turned to the idea of racemic resolution via diastereoisomeric derivatives. The classical methods of resolution seem to have been improved by the simultaneous addition of more than one member of a "family" of resolving agents to a solution of a racemate to produce the crystallization of one diastereomeric salt.[10,11] However, previous negative results attempting the crystallization with only one resolving cationic agent motivated us to form covalent diastereoisomers that could result in a more efficient resolution.

Results and Discussion

Diastereoisomeric esters have been used extensively in the resolution of organic compounds containing hydroxyl groups, in part due to the ease of formation of

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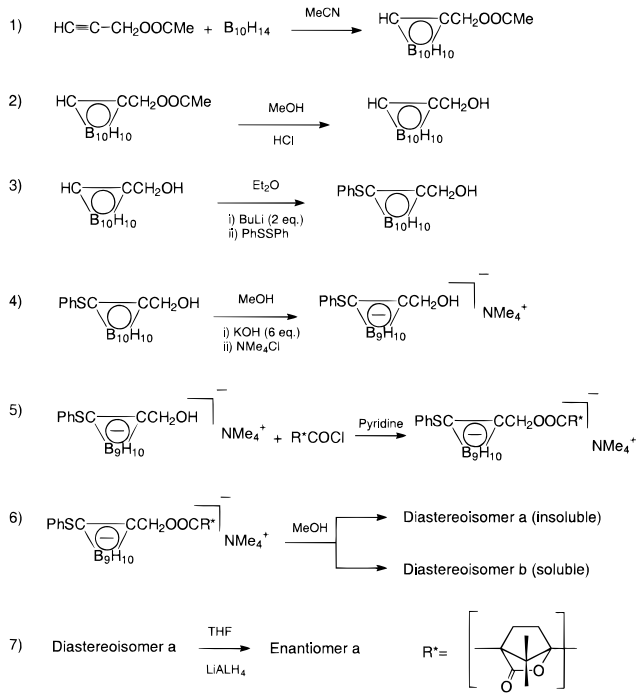
Scheme 1



the ester and regeneration of the starting alcohol.[12] On this basis we designed a synthetic procedure to incorporate the hydroxyl group to *nido*-monothiocarborane ligands, which is depicted in Scheme 1.

Compound *closo*-1-CH_2OH-1,2-$C_2B_{10}H_{11}$ was chosen as starting material. This 1,2-C_2B_{10} cluster incorporates the desired hydroxyl group and can be prepared from decaborane in good yield (steps 1 and 2 in Scheme 1). The reaction of *closo*-1-CH_2OH-1,2-$C_2B_{10}H_{11}$ with 2 equiv of BuLi followed by reaction with diphenyl disulfide led to the isolation of *closo*-1-SPh-2-CH_2OH-1,2-$C_2B_{10}H_{11}$ (**1**) (step 3). Subsequent partial degradation of **1** in KOH/methanol afforded the *nido* derivative [NMe_4][7-SPh-8-CH_2OH-7,8-$C_2B_9H_{10}$] ([NMe_4][**2**], step 4). (−)-Camphanic acid chloride, which has been successfully used in the resolution of alcohols,[13] was chosen as resolving agent. The camphanate derivative [NMe_4][7-SPh-8-$CH_2OOC(C_9H_{13}O_2)$-7,8-$C_2B_9H_{10}$] ([NMe_4][**3**]) was obtained by reaction of [NMe_4][**2**] with (−)-camphanic acid chloride in dry pyridine (step 5), and ^1H and $^{13}C\{^1H\}$ NMR spectra confirmed the formation of two diastereomers. TLC in silica gel using different solvent mixtures was performed to investigate whether chromatographic separation could be convenient for resolution, but no sign of separation was observed probably due to the long tails inherent to the ionic nature of the diastereoisomers. Also ionic chromatographic separation was attempted, but we found no success. Nevertheless, the diastereoisomeric esters displayed quite distinct solubility properties. A single recrystallization of the diastereoisomeric mixture in methanol yielded one of the diastereoisomers in ca. 95% purity according to ^1H NMR spectroscopy. A second recrystallization in the same solvent afforded virtually 100% pure diastereoisomer [NMe_4][**3a**] in 68% yield (step 6). Attempts to isolate the more soluble diastereoisomer [NMe_4][**3b**] from the mother liquor were unsuccessful. Diastereoisomeric salt [NMe_4][**3a**] is stable both in the solid state and in acetone solutions, showing no sign of decomposition or conversion to its diastereoisomer [NMe_4][**3b**] after several months.

To regenerate [**2**]$^-$, several procedures were attempted. Saponification of [NMe_4][**3a**] in H_2O/ethanol yielded a mixture of the alcohol [**2**]$^-$ and the ether derivative [NMe_4][7-SPh-8-CH_2OEt-7,8-$C_2B_9H_{10}$] according to ^1H, ^{13}C, and ^{11}B NMR spectroscopy. Also, transesterification in KOH/methanol yielded a mixture of [**2**]$^-$ and the methyl ether derivative [NMe_4][7-SPh-8-CH_2OMe-7,8-$C_2B_9H_{10}$]. These results suggest that nucleophilic attack to the alkyl carbon of the $C_{cage}-CH_2-O-CO$ group is a competitive reaction in saponification conditions. Nevertheless, reduction of the ester derivative [NMe_4][**3a**] with $LiAlH_4$ in THF yielded pure enantiomer (+)-[NMe_4][**2**] in 90% yield (step 7). To check whether racemization had occurred during the reduction step, (+)-[NMe_4][**2**] was reacted again with (−)-camphanic acid chloride to regenerate the ester derivative. ^1H and $^{13}C\{^1H\}$ NMR spectroscopy showed no signals belonging to [NMe_4][**3b**], thus confirming that the reduction step had proceeded without racemization. In summary, the first chiral *nido*-monothiocarborane cluster has been isolated in good yield. The method can be extended to other *nido*-carboranes provided that the hydroxyl functionality not be an obstacle in the future application for which the molecule has been conceived.

Experimental Section

Instrumentation. Elemental analyses were performed using a Carlo Erba EA1108 microanalyzer. IR spectra were recorded with KBr pellets on a Nicolet 710 FT spectrophotometer. The ^1H NMR (300.13 MHz), $^{13}C\{^1H\}$ NMR (75.47 MHz), and ^{11}B NMR (96.29 MHz) spectra were recorded at room temperature using a Bruker ARX 300 instrument equipped with the appropriate decoupling accessories. Chemical shift values for ^{11}B NMR spectra were referenced to external $BF_3{\cdot}OEt_2$, and those for ^1H and $^{13}C\{^1H\}$ NMR spectra were referenced to $SiMe_4$. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in hertz. The specific rotation was measured using a Dr. Kernchen Optik+Electronik Propol polarimeter.

Materials. Unless otherwise noted, all manipulations were carried out under a dinitrogen atmosphere using standard vacuum line techniques. Diethyl ether was distilled from sodium benzophenone prior to use. The rest of the solvents were of reagent grade quality and were used without further purification. Decaborane (KATCHEM) and (1*S*)-(−)-camphanic acid chloride (Aldrich) were purchased from commercial sources and used as received. Propargyl acetate[14] was prepared according to the literature methods. *closo*-1-CH_2OH-1,2-$C_2B_{10}H_{11}$[15] was prepared from *closo*-1-CH_2OOCMe-1,2-$C_2B_{10}H_{11}$, which in turn was prepared from decaborane and propargyl acetate according to the literature.

Synthesis of 1-SPh-2-CH_2OH-1,2-$C_2B_{10}H_{10}$ (1). A solution of 1-CH_2OH-1,2-$C_2B_{10}H_{11}$ (1.00 g, 5.74 mmol) in 40 mL of ether

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was cooled to −78 °C, and 7.4 mL of BuLi (1.55 M, 11.5 mmol) was added dropwise with vigorous stirring. After half of the BuLi solution had been added, the cooling bath was removed and the addition continued, precipitating a white solid. The suspension was vigorously stirred for 1 h at room temperature, after which time Ph-S−S−Ph (1.26 g, 5.77 mmol) was added as a solid, and the suspension was stirred for 2 h. Next, water (40 mL) and additional ether (40 mL) were added, and the organic phase was decanted, washed with water (3 × 40 mL), and dried with $MgSO_4$. The ether was removed on a rotary evaporator, obtaining a pale yellow oil which contains the desired product and a small amount of hexylphenylsulfide. The oil was chromatographed on silica gel (eluent: CH_2Cl_2) to afford a colorless viscous oil which slowly crystallizes on cooling. Yield: 1.4 g (86%). IR (KBr): ν [cm^{-1}] = 2593, 2568 (B−H). ^1H NMR ($CDCl_3$): 7.6−7.5 (m, 5, H_{aryl}), 5.32 (t, ^3J(H−H) = 6.6 Hz, 1, CH_2OH), 4.48 (d, ^3J(H−H) = 6.6 Hz, 2, CH_2-OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 138.4, 132.5, 130.4 (C_{aryl}), 87.2, 83.9 (C_{cage}), 63.5 (CH_2OH). $^{11}B\{^1H\}$ NMR ($CDCl_3$): −3.7 (2B), −8.9 (2B), −10.2 (4B), −12.0 (2B). Anal. Calcd for $C_9H_{18}B_{10}S$: C, 38.28; H, 6.42; S, 11.35. Found: C, 38.33; H, 6.07; S, 11.15.

Synthesis of [NMe_4][7-SPh-8-CH_2OH-7,8-$C_2B_9H_{10}$]-([NMe_4][2]). A solution of **1** (0.990 g, 3.51 mmol) in methanol (25 mL) containing KOH (1.40 g, 21.2 mmol) was refluxed for 6 h. After this time, the solution was cooled to room temperature and the solvent was evaporated. Water was added (10 mL), and the solution was acidified to pH = 7 with HCl 35% and was filtered through Celite. To the resulting clear solution was added slowly with stirring [NMe_4]Cl (1.15 g, 10.5 mmol) dissolved in water (2 mL), producing a white precipitate, which was filtered, washed with cold water (3 × 5 mL), and dried in vacuo. Yield: 1.25 g (93%). IR (KBr): ν [cm^{-1}] = 3563(m), 2534-(s) (B−H). ^1H NMR ($(CD_3)_2CO$): 7.3−7.0 (m, 5, H_{aryl}), 3.90 (m, 1, CH_2OH), 3.71 (m, 1, CH_2OH), 2.48 (m, 1, CH_2OH), −2.42 (b s, 1, B−H−B). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$): 143.2, 128.9, 127.8, 124.9 (C_{aryl}), 66.9 (CH_2OH), 55.9 ($N(CH_3)_4$). ^{11}B NMR ($(CD_3)_2$-CO): −6.5 (d, ^1J(B,H) = 143 Hz, 1B), −9.8 (d, ^1J(B,H) = 139 Hz, 1B), −13.4 (d, ^1J(B,H)= 165 Hz, 1B), −15.0 (d, ^1J(B,H) = 145 Hz, 1B), −17.8 (d, ^1J(B,H) = 132 Hz, 3B), −33.3 (d, ^1J(B,H) = 130 Hz, 1B), −36.3 (d, ^1J(B,H) = 139 Hz, 1B). Anal. Calcd for $C_{13}H_{30}B_9NOS$: C, 45.16; H, 8.75; N, 4.05; S, 9.27. Found: C, 45.06; H, 8.51; N, 4.02; S, 9.16.

Synthesis of [NMe_4][7-SPh-8-$CH_2OOC(C_9H_{13}O_2)$-7,8-$C_2B_9H_{10}$] ([NMe_4][3]). A 25 mL Schlenk flask was charged with **2** (1.437 g, 4.156 mmol), (−)-camphanic acid chloride (0.970 g, 4.48 mmol), a magnetic stirring bar, and 6 mL of pyridine. Upon stirring, the solids dissolved, precipitating a white solid within minutes. The suspension was stirred at room temperature for 12 h, after which time the pyridine was removed in vacuo, affording a syrup, which was taken up with THF (10 mL), followed by the addition of a solution of [NMe_4]-Cl (1.37 g, 12.5 mmol) in water (6 mL). The THF was removed in vacuo until a solid appeared, and methanol (2 mL) was added with stirring, precipitating a white solid. The methanol and the rest of the THF were evaporated to complete precipitation, and the resulting solid was filtered, washed with water (3 × 5 mL), and dried in vacuo. Yield: 2.0 g (91%). The isolation of diastereoisomer [NMe_4][**3a**] is described below.

Synthesis of [NMe_4][7-SPh-8-$CH_2OOC(C_9H_{13}O_2)$-7,8-$C_2B_9H_{10}$] ([NMe_4][3a]). A 250 mL flask equipped with a sidearm was charged with [NMe_4][**3**] (2.0 g, mmol), methanol (10 mL), and a magnetic stirring bar. The suspension was brought to reflux, and methanol was added until total dissolution of the solid (50 mL overall). The heating and stirring was stopped, and the clear solution was left aside for 5 h. Compound [NMe_4][**3a**] slowly crystallized during this time and was isolated by filtration, washed with cold methanol (2 × 3 mL), and dried in vacuo, yielding 0.78 g. The purity was 95% according to ^1H NMR spectroscopy. The solid was again suspended in methanol (7 mL) and refluxed for 15 min, and the suspension was left aside for 2 h. The solid was isolated by filtration and washed with methanol (2 × 2 mL). Yield: 0.68 g (68%). $[\alpha]_D^{22}$ = +37.6 (*c* = 2.33, acetone). IR (KBr): ν [cm^{-1}] = 2540 (B−H). ^1H NMR ($(CD_3)_2CO$): 7.3−7.0 (m, 5, H_{aryl}), 4.58 (d, ^2J(H,H) = 11.8 Hz, 1, $C_{cage}-CH_2O-$), 4.52 (d, ^2J(H,H) = 11.8 Hz, 1, $C_{cage}-CH_2O-$), 2.34 (ddd, $^2J(H_a,H_c)$ = 13.2 Hz, $^3J(H_a,H_b)$ = 10.8 Hz, $^3J(H_a,H_d)$ = 4.1 Hz, 1, H_a), 1.93 (ddd, $^2J(H_b,H_d)$ = 12.7 Hz, $^3J(H_b,H_a)$ = 10.8 Hz, $^3J(H_b,H_c)$ = 4.4 Hz, 1, H_b), 1.69 (ddd, $^2J(H_c,H_a)$ = 13.2 Hz, $^3J(H_c,H_d)$ = 9.3 Hz, $^3J(H_c,H_b)$ = 4.4 Hz, 1, H_c), 1.51 (ddd, $^2J(H_d,H_b)$ = 12.7 Hz, $^3J(H_d,H_c)$ = 9.3 Hz, $^3J(H_d,H_a)$ = 4.1 Hz, 1, H_d), 1.02 (s, 3, CH_3), 0.92 (s, 3, CH_3), 0.90 (s, 3, CH_3). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$): 178.6, 167.5, 142.7, 129.1, 128.1, 125.1 (C_{aryl}), 91.8, 69.9 ($-CH_2O-$), 56.0 ($N(CH_3)_4$), 55.3, 54.4, 31.0, 29.4, 17.0, 16.8, 9.9. ^{11}B NMR ($(CD_3)_2CO$): −6.2 (d, ^1J(B,H) = 143 Hz, 1B), −9.1 (d, ^1J(B,H) = 139 Hz, 1B), −13.5 (d, ^1J(B,H) = 165 Hz, 1B), −14.4 (d, ^1J(B,H) = 145 Hz, 1B), −17.7 (d, ^1J(B,H) = 132 Hz, 3B), −33.0 (d, ^1J(B,H) = 130 Hz, 1B), −36.0 (d, ^1J(B,H) = 139 Hz, 1B). Anal. Calcd for $C_{23}H_{42}B_9NO_4S$: C, 52.52; H, 8.05; N, 2.66; S, 6.10. Found: C, 52.14; H, 7.90; N, 2.63; S, 6.02.

Synthesis of [NMe_4][7-SPh-8-$CH_2OOC(C_9H_{13}O_2)$-7,8-$C_2B_9H_{10}$] ([NMe_4][3b]). The filtrate from de recrystallization of [NMe_4][**3**] (see above) contains diastereoisomer [NMe_4][**3b**] in ca. 75% purity. ^1H NMR (300.2 MHz, $(CD_3)_2CO$, 25 °C, TMS): 1.18 (s, 3, CH_3), 1.02 (s, 3, CH_3), 0.79 (s, 3, CH_3). The rest of resonances were overlapped with those of the diastereoisomer [NMe_4][**3a**]. $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$): 178.4, 167.5, 142.7, 129.0, 127.8, 125.1 (C_{aryl}), 91.9, 70.4 ($-CH_2O-$), 56.0 ($N(CH_3)_4$), 55.2, 54.5, 30.9, 17.3, 16.7, 9.9.

Synthesis of (+)-[NMe_4][7-SPh-8-CH_2OH-7,8-$C_2B_9H_{10}$] ((+)-[NMe_4][2]). To a suspension of $LiAlH_4$ (63 mg, 1.7 mmol) in THF (6 mL) was added a solution of [NMe_4][**3a**] (0.651 g, 1.24 mmol) in THF (10 mL), and the suspension was stirred at room temperature for 1 h. After this time the reaction was quenched with water (0.5 mL) and the suspension was filtered through Celite. The solvent was removed, methanol (1 mL) was added to dissolve the residue, and a solution of [NMe_4]Cl (0.420 g, 3.83 mmol) in water was added with stirring, precipitating a white solid. The methanol was evaporated to complete precipitation, and the solid was isolated by filtration, washed with cold water (3 × 5 mL), and dried in vacuo. The product was dissolved in acetone and filtered through Celite to remove a solid impurity. The acetone was evaporated, and the product was treated with ether (3 mL). The solvent was removed in vacuo to yield 0.40 g (93%) of product. The IR and NMR spectra were identical to those of racemic product [NMe_4]-[**2**]. $[\alpha]_D^{22}$ = +34.1 (*c* = 2.11, acetone). To check whether the reaction had proceeded with racemization, (+)-[NMe_4][**2**] and (−)-camphanic acid chloride were allowed to react as for [NMe_4]-[**3**], and ^1H and $^{13}C\{^1H\}$ NMR showed no traces of [NMe_4][**3b**].

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