Center on a Kratos MS 80RFA instrument. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. (±)-**3**, 38848-21-4; **4**, 6882-28-6; **5**, 1490-25-1; (±)-**6**, 124021-68-7; **7**, 124021-69-8; **8**, 124021-70-1; **9**, 124021-71-2; **10**, 124021-72-3; **11**, 124021-73-4; (±)-**12**, 124021-74-5; **13**, 124021-75-6; **14**, 35667-11-9; **15**, 1484-85-1; **16**, 124021-76-7; **17**, 124021-77-8; **18**, 4635-59-0; (±)-**19**, 124021-78-9; (±)-**20**, 124021-79-0; **21**, 124021-80-3; **22**, 124021-81-4; **23**, 124021-82-5; **24**, 124021-83-6; **25**, 124021-84-7; **26**, 124021-85-8; **27**, 124021-86-9; **28**, 124021-87-0; **29**, 124021-88-1; **30**, 124021-89-2; **31**, 124021-90-5; **32**, 124021-91-6; **33**, 124021-92-7; **34**, 124021-93-8; **35**, 33542-98-2; **36**, 65239-07-8; **37**, 124021-94-9; **38**, 927-58-2; (±)-**39**, 124021-95-0; **40**, 124021-96-1; **41**, 124021-97-2; **42**, 124021-98-3; **43**, 124021-99-4; I, 124021-66-5; II, 124021-67-6; (*E*)-III, 124022-00-0; (*Z*)-III, 124022-01-1; $(MeO_2C)_2$, 553-90-2.

Supplementary Material Available: Single-crystal X-ray analysis of compound **42**, including positional parameters, intramolecular distances, bond angles, torsional angles, and *U* values, and ^1H NMR spectra of compounds **7–11**, **13**, **16**, **17**, **19–22**, **24–28**, **33**, **36**, **37**, and **39–43** (32 pages). Ordering information is given on any current masthead page.

Glycosylcarborane Derivatives and the Determination of the Absolute Configuration of a Diastereomeric Triol from X-ray Diffraction

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Received November 17, 1988

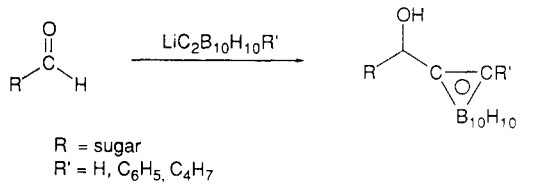
Lithiated 1,2-dicarba-*closo*-dodecaboranes (carboranes)[1] react with aldehydic sugars to give the corresponding hydroxyalkylated carboranes in good yields. In tetrahydrofuran solutions, high diastereoselectivity is observed. A single-crystal X-ray structure of a typical reaction product (**1e**) confirmed that the erythro isomer was the major diastereomer formed. Epimeric inversion was accomplished by a simple oxidation–reduction sequence, which can introduce a tritium label into the glycosylcarborane. A representative 1-(hydroxyalkyl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane was converted to a *m*-diazonium ion and coupled to β-naphthol.

Introduction

The application of the cytotoxic ^{10}B neutron-capture reaction [$^{10}B(n,\alpha)^7Li$] to the treatment of human tumors coupled with the use of antitumor antibodies as a vehicle for depositing boron-10 selectively in tumors has been discussed for many years.[2] The slow progress in this approach has been principally due to the difficulty in labeling antibodies with large quantities of boron while retaining immunoreactivity of the immunoglobulins and also to the lack of a truly specific tumor-localizing antibody for human studies. Mizusawa et al. have shown that it is possible to attach as many as 14 molecules of suitably functionalized carborane units to a single antibody molecule.[3] However, they also found that protein precipitation and loss of immunoreactivity are significant when as few as six carborane units are attached to each antibody.[3] The extremely hydrophobic nature of the carboranes used in these studies led us to conclude that the addition of polar, hydrophilic functional groups had the potential of drastically reducing antibody conjugate precipitation.

Attempts to increase the water solubility of carborane–antibody complexes have met with some success in the past. Soloway and co-workers examined the inclusion of a gluconamide moiety in a polyhedral borane prior to IgG coupling.[4] This resulted in placement of the water-soluble group between the polyhedral borane and the protein backbone. Gabel et al. have reported the preparation of dextran molecules boronated with decachlorocarboranes and subsequent conjugation of these hydrophilic compounds to antibodies.[5] We propose that the hydrophobic character of the carborane cage could be more effectively minimized if this unit were placed between the protein and the hydrophilic carbohydrate group. Our initial work in this area[6] focused on the extension of Ferrier-type chemistry[7] to include the addition of carboranyl alcohols to unsaturated sugars. Upon examining the reactivity of

Scheme I



(1) Throughout this paper, the terms carborane or 1,2-dicarba-*closo*-dodecaborane refer to an icosahedron with carbons at two adjacent vertices and boron at the remaining ten. Unsubstituted carborane has the formula $C_2B_{10}H_{12}$, with one hydrogen attached to each of the heavier atoms.

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(3) (a) Mizusawa, E.; Dahlman, H. L.; Bennett, S. J.; Goldenberg, D. M.; Hawthorne, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3011. (b) Goldenberg, D. M.; Sharkey, R. M.; Primus, F. J.; Mizusawa, E.; Hawthorne, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 560.

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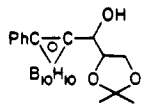
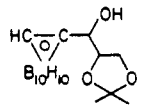
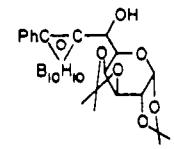
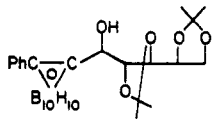
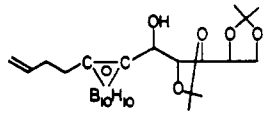
(7) (a) Ferrier, R. J. *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1967; Vol. VI, p 307. (b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *59*, 261. (c) Wulff, G.; Röhle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*(3), 157.

0022-3263/90/1955-0838$02.50/0

Table I. Diastereomeric Ratios of Hydroxyalkyl Carboranes

compd	struct	crude product comp (erythro:threo)[a]	isolated yield,%
1e/t		80:20	71
2e/t		70:30	76
3e		80:20	68
4e/t		80:20	69
5e/t		80:20	67

[a] Estimated by ^{1}H NMR (integration).

these compounds, particularly that of the glycosidic linkage, we realized that (hydroxyalkyl)carboranes in which a carbon–carbon bond attached the carborane to the remainder of the molecule were desirable synthetic targets. With this goal, we extended our investigation to the syntheses of the glycosylcarboranes described here.

Results and Discussion

Reactions of substituted acetylenes with $B_{10}H_{12}L_2$ derivatives (where L = MeCN, Et_2S) of decaborane are well documented and are reported to proceed smoothly to give high yields of carboranes.[8] We investigated the reactions of synthetically available acetylenic sugars[9] with $B_{10}H_{12}L_2$ derivatives. This reaction sequence involved the reaction of a protected galactose dialdehyde with the Grignard reagent of a (bromoalkyl)acetylene, followed by acetylation to give a carbohydrate-substituted alkyne that is suitable for reaction with $B_{10}H_{12}L_2$ species. In addition to galactose, several other carbohydrates were used as starting materials in this general reaction scheme. Yields of the reactions of acetylenic carbohydrates with $B_{10}H_{12}L_2$ derivatives were routinely poor (less than 20%). Although substituted alkynes are commonly converted to carboranes,[8,10] yields of these reactions are generally better when the substituent is an electron-withdrawing group, particularly an alkyl halide. Propargyl bromide is one example of such an alkyne. In the present case, lack of an electron-withdrawing group and the steric requirements of the $B_{10}H_{12}L_2$ precursor are both presumed to interfere with formation of the desired product.

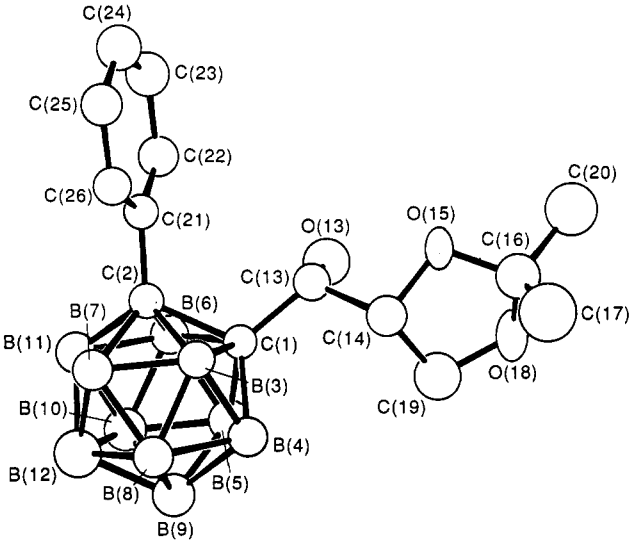


Figure 1. X-ray crystal structure of the major diastereomer of 1e (hydrogen atoms omitted for clarity).

After several unsuccessful attempts to prepare (hydroxyalkyl)carboranes by this general route, we turned to a more promising reaction sequence, shown in Scheme I. Aldehydic sugars used in this study were easily synthesized from the commercially available compounds mannose, galactose, xylose, and arabinose.[11] The isopropylidene ketal, a common protecting group for 1,2-diols, is present in each of these sugar aldehydes. This protecting group was chosen because it is unreactive when exposed to organometallic reagents (RLi, RMgBr, etc.) and it is easily removed under acidic conditions.[12]

Addition products from the reactions of several carborane anions with a number of sugar aldehydes were isolated in 60–85% yields, after purification (Table I). The majority of the crude reaction products were purified by silica gel chromatography, which often separated the erythro and threo products as well as removing other contaminants. Considering the relative amounts of the two diastereomers formed in these reactions (erythro:threo, ca. 4:1), this was essentially a purification of the erythro isomer. The crude product from the reaction of lithiated carborane with 2,3-*O*-isopropylidene-D-glyceraldehyde (2) was purified by sublimation. Under high vacuum, unreacted starting material sublimed at 70 °C, while the product sublimed between 85 and 90 °C virtually free of starting material or other contaminants. The erythro and threo epimers were subsequently separated by silica gel chromatography.

Upon examination of the ^{1}H NMR spectra of these crude reaction products, it was readily apparent in all cases that two diastereomers were present in a ratio of ca. 4:1. The configuration at the 2-position of the glyceraldehyde fragment, where present, was known to be *R*, but determination of the configuration of the other chiral center was not trivial. Thus, detailed studies to determine the configuration of the 1-position of 1 (Table I) were undertaken. A trans-ketalization reaction converted the 2,3-*O*-isopropylidene portion of compound 1 into a 1,2-*O*-iso-

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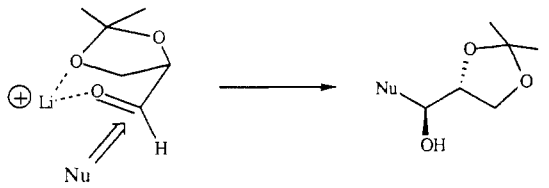
(9) (a) Horton, D.; Hughes, J. B.; Thomson, J. K. *J. Org. Chem.* **1968**, *33*, 728. (b) Horton, D.; Tronchet, J. M. *J. Carbohydr. Res.* **1966**, *2*, 315. (c) Godman, J. L.; Horton, D.; Tronchet, J. M. *J. Carbohydr. Res.* **1972**, *25*, 205.

(10) Hawthorne, M. F. *Endeavor* **1966**, *25*, 145.

(11) (a) Baer, E. *Biochem. Prep.* **1952**, *2*, 31. (b) Schmidt, O. Th. *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol. II, p 324. (c) Zinner, H.; Wittenberg, E.; Rembarz, G. *Chem. Ber.* **1959**, *92*, 1614. (d) Horton, D.; Hughes, J. B.; Thomson, J. K. *J. Org. Chem.* **1968**, *33*, 728.

(12) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1981; pp 76–78.

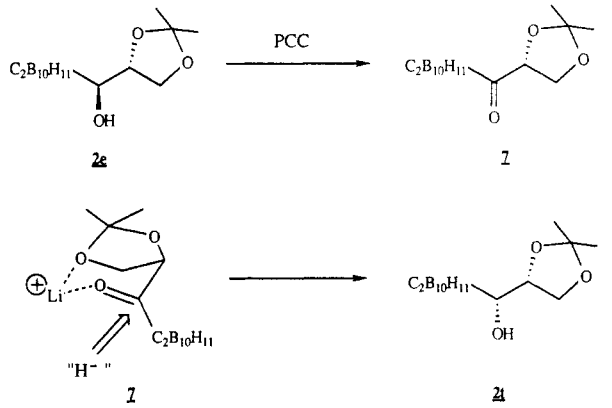
Scheme II



propylideneglycerol fragment, in which the two stereocenters were part of the 1,3-dioxolane ring. We attempted to use the coupling constant between the protons at the two chiral centers (extracted from the ^1H NMR spectra) to determine the configuration at the unassigned chiral center. This ring, like most five-membered rings, was not conformationally rigid, and the results of these experiments were ambiguous. Final determination of the stereochemistry at the 1-position was accomplished by X-ray crystallography. Figure 1 shows the structure of the predominant diastereomer of **1**, as deduced from the X-ray structure, to be the 1(*S*),2(*R*) (erythro) isomer, **1e**.[13] By analogy, we concluded that the erythro (e) isomer is the major product in compounds **2–5**. in each case, the diastereotopic proton at the chiral center formed in the reaction appeared further downfield in the ^1H NMR spectrum of the major, erythro isomer than it did in the similar spectrum of the minor, threo (t) isomer.

The stereochemistry of the addition of nucleophiles to (*R*)-2,3-*O*-isopropylideneglyceraldehyde has been investigated by many research groups[14] and was discussed at length in a recent review.[15] The stereoselectivity of this type of reaction varies with solvent, temperature, and nature of the nucleophile but generally favors the formation of erythro isomers. As mentioned previously, we observed preferential formation of erythro products when carboranyl anions were added to protected carbohydrate aldehydes. For the sake of illustration, consider the simplest reaction: that of a representative carborane carbanion (Nu) with (*R*)-2,3-*O*-isopropylideneglyceraldehyde. A transition-state analysis based on the model favored by Jurczak et al.[15] is shown in Scheme II. According to this model, the cation (Li^+) is presumed to coordinate with the oxygens at the 1- and 3-positions, forming a six-membered ring. This fixes the conformation of the 1,3-dioxolane unit and is responsible for the stereoselectivity of this reaction. Cram's rule[16] predicts that the nucleophile will attack from the less hindered face of the aldehyde to give the erythro isomer as the major product. The results we observed are in accord with these theoretical predictions. The carboranyl nucleophiles examined here react in a more stereoselective fashion than the majority of previously examined nucleophiles.[14] This stereoselectivity is consistent with the fact that the carborane is an extremely bulky group, with steric requirements considerably greater than those of even phenyl or *tert*-butyl groups. It is worthwhile to note that the stereoselectivity of these reactions is essentially independent of the nature of the substituent at the second carbon of the carborane cage (Table I). Replacement of the hydrogen at the 2-position of the carborane cage with 1-buten-4-yl or phenyl has little impact on the stereochemical course of the reaction.

Scheme III



A simple oxidation–reduction sequence achieved inversion at the epimeric center and was demonstrated with alcohols **1e** and **2e** (Scheme III). In both cases, the alcohol was oxidized with pyridinium chlorochromate (PCC) in refluxing benzene to give **6** and **7**, respectively. Reduction of these ketones was accomplished using sodium borohydride in ethanol (0–5 °C) or lithium aluminum hydride in diethyl ether (−78 °C). The stereochemical course of the reduction of **7** is identical with that of addition of a carboranyl nucleophile to (*R*)-isopropylidene-D-glyceraldehyde; namely, the nucleophile (hydride ion in the case of the reduction) adds to the less hindered face of the carbonyl group, to give the "Cram" product. Since the aldehyde proton of (*R*)-glyceraldehyde has been replaced by the bulky carborane moiety in **7**, this oxidation–reduction sequence effectively inverts the configuration of C-1 and produces the threo epimer **2t** from **2e** (Scheme III).

While strong preference for formation of the threo isomer was observed with both reducing agents, reaction with lithium aluminum hydride proved to be slightly more stereoselective. In the reduction of ketone **6**, integration of epimeric proton signals in the ^1H NMR spectrum indicated 95% formation of the threo isomer (**1t**) using this reagent, compared to 85% threo formation when sodium borohydride was used. Since lithium aluminum hydride is generally more reactive than sodium borohydride, we presume that this enhanced stereoselectivity is the result of the reaction having been conducted at low temperature. Both sodium borohydride and lithium aluminum hydride are commercially available in tritium-enriched forms. Use of these reducing agents allows the introduction of a tritium label into glycosylcarboranes, via the aforementioned oxidation–reduction sequence. A previous determination of the number of carborane units covalently bound to monoclonal *anti*-CEA based on [^3H] decay demonstrates the utility of this tritiation.[9]

The isopropylidene protecting group of **2e** was easily removed under strongly acidic conditions (90% aqueous trifluoroacetic acid) to give the triol **8**. While straightforward, this conversion was important, since it demonstrated the feasibility of converting protected glycosylcarboranes to hydrophilic compounds. Subsequent investigations confirmed that the isopropylidene groups were also cleaved during nitration of the glycosylated phenylcarborane derivative.

Earlier work in this laboratory quantitatively determined the average number of diazotized carborane moieties attached to monoclonal antibodies using visible absorption

(13) Throughout this discussion, the term "erythro" is used in reference to a diastereomer in which the configuration of two adjacent chiral centers differs (*R,S* or *S,R*). The term "threo" refers to a diastereomer in which two adjacent chiral centers have the same configuration (*R,R* or *S,S*).

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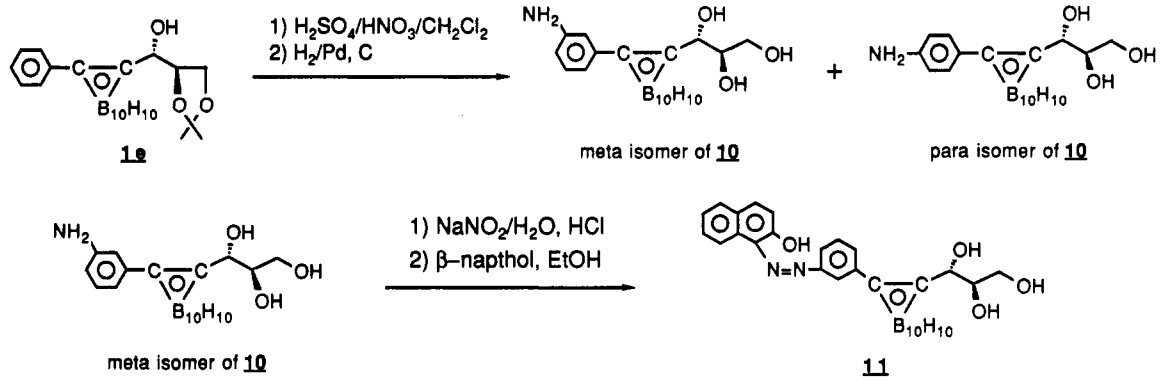
(16) Paddon-Row, M. N.; Randan, N.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 162.

Scheme IV



spectra.[3a] When a carborane derivative that contained a diazonium group was reacted with the antibody, tyrosine residues were substituted with the diazonium group to form an azo compound, which absorbed light at λ_{max} = 485 nm. In this vein, **1e** has been converted to a diazonium derivative suitable for conjugation with antibodies (Scheme IV). Under the conditions for aromatic nitration, the isopropylidene ketal is cleaved, and the resulting triol reacts to give a mixture of (*p*- and *m*-nitrophenyl)-carboranyl trinitrate esters (**9**). The meta isomer was the major product (meta:para ≃ 2:1) and was purified by flash chromatography and recrystallization from carbon tetrachloride. Reduction of *m*-**9** by dihydrogen over 10% palladium on carbon gave the (*m*-aminophenyl)carborane triol, **10**. This compound was diazotized and reacted with β-naphthol to give the diazo compound **11** (λ_{max} = 476 nm). The structure of **11** was assumed to be that shown in Scheme IV, on the basis of literature precedents of the tendency for β-naphthol to react with diazonium ions at the α-position.[18] Careful analysis of the ^{1}H NMR spectrum of **11** showed that only one proton in the aromatic region did not have ortho coupling interactions ($J \simeq 8$ Hz). Assignment of this signal to the proton ortho to the two substituents on the benzene ring excludes the possibility of substitution at other than the α-position of the naphthol skeleton and identifies the regiochemistry of this reaction.

Conclusions

The compounds described here represent a novel class of hydroxyalkyl compounds that were synthesized in high yields from readily available starting materials. Formation of these compounds proceeds in a stereoselective fashion, as does the reduction of the ketones **6** and **7**. Synthesis of a phenyldiazonium–(hydroxyalkyl)carborane demonstrates a simple method for the preparation of hydrophilic carboranes that can be covalently attached to proteins. Inclusion of a ^{3}H label and an azo group makes these compounds especially attractive candidates for use as boron neutron-capture therapy reagents.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Dry solvents were distilled shortly before use from an appropriate drying agent: benzene from calcium hydride, dichloromethane from phosphorus pentoxide, and tetrahydrofuran and diethyl ether from the sodium benzophenone ketyl. Melting points are uncorrected. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Infrared (IR) spectra were recorded on a Beckman 1100 FT-IR spectrometer and are reported in cm^{-1}. Proton (^{1}H NMR) spectra were recorded at 200, 360, and 500 MHz. Boron (^{11}B NMR) spectra were obtained at 126.7 MHz on an instrument designed and constructed by F. A. L. Anet of this department and at 160.4 MHz in the Southern California Regional NMR Facility at the California Institute of Technology, Pasadena, CA. Chemical shifts for ^{11}B NMR spectra are reported in ppm on the δ scale with external reference to boron trifluoride etherate (δ 0.00). Coupling constants (*J*) are given in hertz.

(α*S*)-α-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl-1,2-dicarbadodecaborane(12)-1-methanol (1e/t). A 2.5 M solution of *n*-BuLi (2.1 mL) was added dropwise to a solution of phenylcarborane (1.12 g) in dry THF (13 mL) at 0 °C under argon. After 1 h at 0 °C, the reaction mixture was cooled to −50 °C, and a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (668 mmol) in dry THF (2 mL) was added dropwise. The reaction was then cooled to −78 °C. After 1 h at this temperature a few drops of 5% $NaHCO_3$ were added, and the reaction was allowed to warm to ambient temperature. $MgSO_4$ was added, and filtration was followed by the evaporation of the solvent. Flash column chromatography of the crude product (erythro:threo, 80:20) in 20% EtOAc/hexane gave 71% of the substituted phenylcarborane (65% erythro:32% threo): IR ($CHCl_3$) 3500, 2980, 2860, 2590, 1520, 1490, 1470, 1420, 1220, 1150, 1060, 940, 865, 810; ^{1}H NMR ($CDCl_3$) δ 7.69–7.64 and 7.51–7.34 (5 H, m), 4.27 (1 H, ddd, *J* = 6.7, 5.5, 2.8), 4.09 and 4.04 (2 H, overlapping peaks), 3.50 (1 H, dd, *J* = 2.8, 3.8), 2.30 (1 H, d, *J* = 3.8), 1.33 (3 H, s), 1.30 (3 H, s). Anal. Calcd for $B_{10}C_{14}H_{26}O_3$: C, 47.98; H, 7.48; B, 30.84. Found: C, 47.74; H, 7.40; B, 30.95. Further column chromatography (20% EtOAc/hexanes) and recrystallization from hexane/methylene chloride gave crystals of the major diastereomer. A single-crystal X-ray structure of this material confirmed its identity as **1e**.

Collection and Reduction of X-ray Data for 1e. A colorless crystal, obtained from a CH_2Cl_2/hexane solution, was mounted on a thin glass fiber on a Syntex P$\bar{1}$ diffractometer modified by Professor C. E. Strouse of this department. Systematic absences were found for *hkl* reflections for which $k + l \neq 2n$. Unit-cell parameters were determined from a least-squares fit of 16 accurately centered reflections ($18.6 < 2\theta < 47.6°$). These dimensions and other parameters, including conditions of data collection, are summarized in the supplementary material (see the paragraph at the end of the paper). Data were collected at 25 °C in the θ–2θ scan mode. Three intense reflections (2 0 −4, 3 0 4, 1 3 −3) were monitored every 97 reflections to check stability. Intensities of these reflections decayed less than 3% during the course of the experiment (42.0 h). Of the 1100 unique reflections measured, 1064 were considered observed ($I > 3\sigma(I)$) and were used in the subsequent structure analysis. Data were corrected for Lorentz, polarization, and absorption effects. Programs used in this work include locally modified versions of the following programs: CARESS (Broach, Coppens, Becker, and Blessing), peak profile analysis, Lorentz and polarization corrections; ORFLS (Busing, Martin, and Levy), structure factor calculation and full-matrix least-squares refinement, SHELX76 and SHELX86 (Sheldrick); ORTEP (Johnson).

Solution and Refinement of the Structure of 1e. Atoms were located by use of statistical methods (SHELX86). All calcu-

(17) Deleted in proof.
(18) (a) Bradley, W.; Thompson, J. D. *Nature* **1956**, *178*, 1069. (b) Zollinger, H. I. *Azo and Diazo Chemistry*; Interscience: New York, 1961; p 232.

lations were performed on the VAX 11/750 crystallographic computer. Anisotropic thermal parameters were refined for oxygen. Phenyl, methyl, and methylene groups were constrained to be rigid, C–C (phenyl) 1.395 Å, C–H 1.0 Å, angles of phenyl group 120°, H–C–H angles for other groups 109.5°. Phenyl, methyl, and methylene H were included in calculated positions in structure factor calculations with an assigned μ value of 0.10 or 0.06 Å^2 for phenyl and all other H, respectively. For the other H, positional parameters were refined. Scattering factors for H were obtained from Stewart et al.[19] and for other atoms were taken from The International Tables for X-ray Crystallography.[20] Anomalous dispersion terms were applied to the scattering of Cl. Peak maxima and minima on a final difference electron density map were 0.25 e Å^{-3}.

(αS)-α-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,2-dicarbadodecaborane(12)-1-methanol (2e). To a solution of 1,2-dicarba-*closo*-dodecaborane (11.5 g, 79.6 mmol) in dry THF (200 mL, 0.4 M) at 0 °C was added a 2.5 M solution of *n*-BuLi in hexane (33.5 mL, 83.6 mmol) dropwise with stirring. The mixture was allowed to stir 30 min at 0 °C and then cooled to −10 °C, and a cold solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (10.9 g, 83.6 mmol) in THF (27 mL, 3.0 M) added dropwise but rapidly. After 10 min the mixture was quenched with saturated aqueous $NaHCO_3$ (200 mL) and transferred to a separatory funnel with dilution by diethyl ether (200 mL). The layers were separated, and the aqueous layer was extracted with additional Et_2O (2 × 100 mL). The combined ethereal extracts were then dried over anhydrous Na_2SO_4 and concentrated in vacuo. Sublimation at 70 °C (1 × 10^{-3} mmHg) removed unreacted 1,2-dicarbadodecaborane (0.6 g), and at 85–90 °C the product sublimed as a white solid (15.76 g, 76%), erythreo:threo 70:30. Chromatography on silica (20% EtOAc/hexane) then allowed for the separation of diastereomers and isolation of **2e** (48%): mp 86–87 °C; $[\alpha]_D$ +5.9° (*c* 5.0, EtOH); IR ($CHCl_3$) 2980, 2860, 2590, 1520, 1480, 1220, 1060, 940, 865, 810; ^{1}H NMR ($CDCl_3$) δ 4.22–4.08 (2 H, m), 3.95 (1 H, dd, *J* = 6.4, 4.4), 3.85 (1 H, dd, *J* = 7.8, 4.4), 3.55 (1 H, br s, whh = 10 Hz), 3.07 (1 H, d, *J* = 6.4), 1.46 (3 H, s), 1.38 (3 H, s). Anal. Calcd for $B_{10}C_8H_{22}O_3$: C, 35.02; H, 8.08. Found: C, 34.78; H, 8.30.

1,2:3,4-Di-*O*-isopropylidene-6-[2-phenyl-1,2-dicarbadodecaboran(12)-1-yl]-α-D-*galacto*-1,5-pyranose (3e). Following the procedure for the preparation of **2**, a 0.3 M solution of 1-phenyl-1,2-dicarbadodecaborane (5.2 g, 23.6 mmol) in THF was metalated with *n*-BuLi (9.5 mL, 2.6 M in hexane) and reacted with 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (6.1 g, 23.6 mmol) at −70 °C. Chromatography (solvent A) of the crude product (erythro:threo 80:20) afforded **3e** as a syrup which solidified in vacuo (3.7 g, 68% based on recovered 1-phenyl-1,2-dicarbadodecaborane); mp 72–73 °C; $[\alpha]_D$ −63.3° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, erythro isomer) δ 7.70–7.66 (2 H, m), 7.46–7.33 (3 H, m), 5.57 (1 H, d, *J* = 5.0), 4.57 (1 H, dd, *J* = 2.4), 4.30 (1 H, dd, *J* = 5.0, 2.4), 4.17 (1 H, dd, *J* = 8.0, 1.8), 3.90–3.87 (1 H, m), 3.54–3.51 (2 H, m). Anal. Calcd for $B_{10}C_{20}H_{34}O_6$: C, 50.19; H, 7.16; B, 22.59. Found: C, 50.49; H, 7.37; B, 22.85.

2,3:4,5-Di-*O*-isopropylidene-1-[2-phenyl-1,2-dicarbadodecaboran(12)-1-yl]arabinitol (4). Following the procedure for the preparation of **1**, a 0.3 M solution of 1-phenyl-1,2-dicarbadodecaborane (1.1 g, 5 mmol) in THF was metalated with *n*-BuLi (2.1 mL, 2.5 M in hexane) and reacted with 2,3:4,5-di-*O*-isopropylidene-L-arabinose (1.15 g, 5 mmol) at −70 °C. Chromatography (20% EtOAc/hexanes) of the crude product (erythro:threo 80:20) afforded a syrup only slightly enriched in the erythro isomer (1.55 g, 69% based on recovered phenylcarborane): IR (film) 3440, 2850, 2620, 1570, 1550, 1520, 1485, 1450, 1410, 1250, 1180, 1070, 1050, 930, 855, 805; ^{1}H NMR ($CDCl_3$) δ 7.70–7.32 (5 H, m), 4.33–3.00 (6 H, m), 1.38 (3 H, s), 1.35 (3 H, s), 1.34 (3 H, s), 1.16 (3 H, s). Anal. Calcd for $B_{10}C_{19}H_{34}O_5$: C, 50.65; H, 7.61. Found: C, 50.27; H, 7.56.

2,3:4,5-Di-*O*-isopropylidene-1-[2-(but-3-enyl)-1,2-dicarbadodecaboran(12)-1-yl]arabinitol (5). Following the general procedure of **1**, a 0.3 M solution of 1-(but-3-enyl)-1,2-dicarbadodecaborane (2 g, 10.1 mmol) in THF was metallated with *n*-BuLi (4.1 mL, 2.6 M in hexane) and reacted with 2,3:4,5-di-*O*-isopropylidene-L-arabinose (2.32 g, 10.1 mmol) at −70 °C. Chromatography (20% EtOAc/hexanes) of the crude product (erythro:threo 80:20) afforded a syrup only slightly enriched in the erythro isomer (2.89 g, 67% based on recovered carborane): IR ($CHCl_3$) 3020, 2580, 1520, 1470, 1420, 1380, 1240, 1200, 1155, 1120, 1075, 1050, 935, 890, 860, 800; ^{1}H NMR ($CDCl_3$) δ 5.84–5.60 and 5.13–5.01 (3 H, m), 4.50–3.15 (16 H, m), 2.32–2.26 (4 H, m), 1.54–1.32 (12 H, m). Anal. Calcd for $B_{10}C_{17}H_{36}O_5$: C, 47.64; H, 8.47. Found: C, 47.18; H, 8.55.

α-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-phenyl-1,2-dicarbadodecaboran(12)-1-ylformaldehyde (6) and Reduction by $NaBH_4$. A solution of **1e** (0.375 g, 1.07 mmol) in benzene (12 mL) was oxidized by pyridinium chlorochromate (0.385 g, 1.79 mmol) to afford a white solid which was recrystallized from *n*-heptane (231 mg, 62%); IR (film) 2940, 2900, 2550, 1740, 1370, 1225, 1150, 1110, 1070, 845; ^{1}H NMR ($CDCl_3$) δ 7.61–7.56 and 7.42–7.33 (5 H, m), 4.85 (1 H, dd, *J* = 7.3, 5.2), 4.13 (1 H, dd, *J* = 8.8, 7.3), 3.76 (1 H, dd, *J* = 8.8, 5.2), 1.32 (3 H, s), 1.30 (3 H, s). This ketone (**6**, 40 mg, 0.115 mmol) was dissolved in absolute EtOH (0.5 mL, 0.4 M), and to this solution was added $NaBH_4$ (2.2 mg, 0.58 mmol) with stirring. After stirring for 2 h at ambient temperature, the reaction mixture was acidified to pH 4–6 by the addition of 1 N HCl and then concentrated to a residue which was extracted with Et_2O (3 × 10 mL). The combined extracts were dried over $MgSO_4$, then concentrated in vacuo to a syrup of the diastereomers **1e** and **1t** (erythro: threo 15:85), and chromatographed (20% ETOAc/hexane) to provide the alcohol **1t** (17.5 mg, 44%): $[\alpha]_D$ + 23.7° (*c* 1.75, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.69–7.64 and 7.64–7.35 (5 H, m), 4.26 (1 H, ddd, *J* = 6.6, 6.6, 2.5),3.95 (1 H, dd, *J* = 8.3, 6.6), 3.61 (1 H, dd, *J* = 8.3, 6.6), 3.16 (1 H, dd, *J* = 9.3, 2.5), 2.93 (1 H, d, *J* = 9.3), 1.36 (3 H, s), 1.35 (3 H, s).

α-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,2-dicarbadodecaboran(12)-1-ylformaldehyde (7). A diastereomeric mixture of the alcohol **2e** (0.73 g, 2.66 mmol) was dissolved in dry benzene (30 mL, 0.09 M) and heated to 60 °C with stirring. Freshly prepared pyridinium chlorochromate (0.98 g, 4.5 mmol) was then added, and the mixture stirred for 3 h at reflux temperature. The hot solution was then filtered through a bed of Celite, and the dark, gummy precipitate rinsed repeatedly with additional warm benzene. The combined filtrates were then concentrated in vacuo and extracted with warm *n*-heptane (3 × 25 mL) with filtration through a bed of florisil to remove insoluble chromium compounds. The combined filtrates were again concentrated in vacuo to a white solid which was recrystallized from *n*-heptane (384 mg, 53%): mp 98–99 °C, $[\alpha]_D$ +3.4° (*c* 5.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 5.03 (1 H, dd, *J* = 7.3, 4.9), 4.31 (1 H, dd, *J* = 9.3, 7.3), 4.05 (dd, *J* = 9.3, 4.9), 4.23 (1 H, br s, whh = 10 Hz), 1.49 (3 H, s). Anal. Calcd for $B_{10}C_8H_{20}O_3$: C, 35.28; H, 7.40; B, 39.70. Found: C, 35.44; H, 7.35; B, 40.05.

(1*S*,2*R*)-1-[1,2-Dicarbadodecaboran(12)-1-yl]-1,2,3-propanetriol (8). To the acetonitrile solution of **2e** (350 mg, 1 mmol) was added 90% aqueous CF_3CO_2H (5 mL) with stirring. After 10 min at ambient temperature, the mixture was concentrated in vacuo and extracted into ethyl ether (3 × 10 mL). The combined extracts were washed with water (1 × 30 mL), then dried over Na_2SO_4, and concentrated to a solid which was purified by chromatography (185 mg, 60%); mp 170 °C, $[\alpha]_D$ −4.7° (*c* 1.7, EtOH); IR ($CHCl_3$) 2980, 2860, 2580, 1740, 865. Anal. Calcd for $B_{10}C_5H_{18}O_3$: C, 42.57; H, 7.14; B, 34.83. Found: C, 42.78; H, 7.19; B, 34.70.

(1*S*,2*R*)-1-[2-(*m*-Nitrophenyl)-1,2-dicarbadodecaboran(12)-1-yl]-1,2,3-propanetriol Trinitrate Ester (9). Concentrated H_2SO_4 (3 mL) was added to a solution of the acetonide **1e** (544 mg) in CH_2Cl_2 (20 mL), and this mixture was added dropwise to concentrated H_2SO_4 (13 mL) and 70% HNO_3 (3 mL) at 0 °C. The reaction was stirred for 1 h at 0 °C and overnight at ambient temperature. The CH_2Cl_2 (upper layer) was decanted, and the acid layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with water and then dried ($MgSO_4$). Flash chromatography (10% EtOAc/hexane) gave the para isomer (28%) and the meta isomer (57%) with an overall yield of 85%. Upon removal of solvent, the meta isomer solidified and was recrystallized from CCl_4: mp 95 °C; $[\alpha]_D$ +99.8° (*c* 4.0, $CHCl_3$);

(19) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

(20) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.

IR ($CHCl_3$) 3040, 2930, 1660, 1540, 1350, 1270, 1075, 1020, 920, 845; ^1H NMR ($CDCl_3$) δ 8.49–8.40, 8.0–7.98 and 7.75–7.67 (4 H, m), 5.50–5.46 (1 H, ddd, J = 8.0, 2.2, 1.9). Anal. Calcd for $B_{10}C_{11}H_{18}N_4O_{11}$: C, 26.94; H, 3.70; N, 11.43; B, 22.04. Found: C, 26.59; H, 3.69; N, 11.24; B, 22.24.

(1*S*,2*R*)-1-[2-(*m*-Aminophenyl)-1,2-dicarbadodecaboran-(12)-1-yl]-1,2,3-propanetriol (10). A mixture of **9** (234 mg) in dioxane (3.5 mL), 95% EtOH (11 mL), water (1.1 mL), and 10% Pd/C (39 mg) was stirred under 4 atm of H_2 at 23 °C for 6 h. The catalyst was filtered off, and the filtrate evaporated. Flash column chromatography (MeOH:hexane:CH_2Cl_2 1:3:6) gave 112 mg (72%) of a white solid. Recrystallization in CH_2Cl_2 gave a white solid: mp 178 °C; $[\alpha]_D$ = +5.0 (c 10, EtOH); ^1H NMR ($CDCl_3$, meta isomer) δ 7.19–7.04 (2 H, m), 6.87–6.73 (2 H, m), 3.70–3.29 (4 H, br m); ^1H NMR ($CDCl_3$ + acetone-d_6, para isomer) δ 7.35 (2 H, d, J = 8.6), 6.57 (2 H, d, J = 8.6), 3.72 (2 H, br s), 3.40 (2 H, br s). Anal. Calcd for $B_{10}C_{11}H_{23}NO_3$ (meta isomer): C, 40.60; H, 7.12; N, 4.30; B, 33.22. Found: C, 40.63; H, 7.03; N, 4.11; B, 33.34.

(1*S*,2*R*)-1-[2-[3-(2-Hydroxy-1-napthyl)azo]phenyl]-1,2-dicarbadodecaboran(12)-1-yl]-1,2,3-propanetriol (11). An aqueous solution (7.7 M) of $NaNO_2$ (44.7 μL) was added to a solution of the amine **10** (193 mg) in 4.2 M HCl (490 μL) at 0 °C. The reaction was stirred at 0 C for 0.5 h and then added to a solution of β-naphthol (47.7 mg) in EtOH (33.5 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and warmed to ambient temperature. The solvent was evaporated, and the mixture purified by flash column chromatography (MeOH:CH_2Cl_2:hexane 1:4:5) to give 32 mg (21%) of a red solid: mp (dec) 216–218 °C; IR (KBr) 3501, 3376, 2649, 1599, 1245, 1211, 838, 762; λ_{max} 476 nm; ^1H NMR (acetone-d_6) δ 8.49 (1 H, d, J = 8.2), 8.15 (1 H, br s), 7.94 (1 H, dd, J = 1.2, 7.9), 7.83 (1 H, d, J = 9.4), 7.70 (1 H, dd, J = 1.1, 8.0), 7.66 (1 H, d, J = 7.9), 7.58–7.53 (2 H, apparent t, $J \simeq$ 8.0), 7.41 (1 H, apparent d of t, J = 1.1, 8.1), 6.81 (1 H, d, J = 9.4), 5.49 (1 H, d, J = 7.0), 4.25 (1 H, d, J = 5.9), 3.92–3.69 (3 H, m), 3.57 (1 H, m), 3.06 (1 H, br s). Anal. Calcd for $B_{10}C_{21}H_{28}N_2O_4$: C, 52.48; H, 5.87; B, 22.49. Found: C, 52.81; H, 5.86; B, 22.11.

Acknowledgment. Generous support from the National Institutes of Health (CA-31753) is gratefully acknowledged.

Registry No. **1e**, 123052-37-9; **1t**, 123074-11-3; **2e**, 123052-38-0; **2t**, 123052-39-1; **3e** isomer 1, 123052-40-4; **3e** isomer 2, 123052-53-9; **4e**, 123052-41-5; **4t**, 123052-42-6; **5e**, 123052-43-7; **5t**, 123052-44-8; **6**, 123052-45-9; **7**, 123052-46-0; **8**, 123052-47-1; *meta*-**9**, 123052-48-2; *para*-**9**, 123052-49-3; *meta*-**10**, 123052-50-6; *para*-**10**, 123052-51-7; **11**, 123052-52-8; phenylcarborane, 16390-61-7; 2,3-*O*-isopropylidene-D-glyceraldehyde, 15186-48-8; 1,2-dicarba-*closo*-dodecaborane, 16872-09-6; 1,2:3,4-di-*O*-isopropylidene-α-D-galactohexodialdo-1,5-pyranoside, 4933-77-1; 2,3:4,5-di-*O*-isopropylidene-L-arabinose, 23568-31-2; 1-(but-3-enyl)-1,2-dicarbadodecaborane, 17522-80-4; β-naphthol, 135-19-3.

Supplementary Material Available: Listings of crystallographic data collection, position and thermal parameters, interatomic distances, and angles, anisotropic thermal parameters for compound **1e** (14 pages). Ordering information is given on any current masthead page.

Rearrangement of Bicyclo[2.2.1]heptane Ring Systems by Titanocene Alkylidene Complexes to Bicyclo[3.2.0]heptane Enol Ethers. Total Synthesis of (±)-$\Delta^{9(12)}$-Capnellene†,‡

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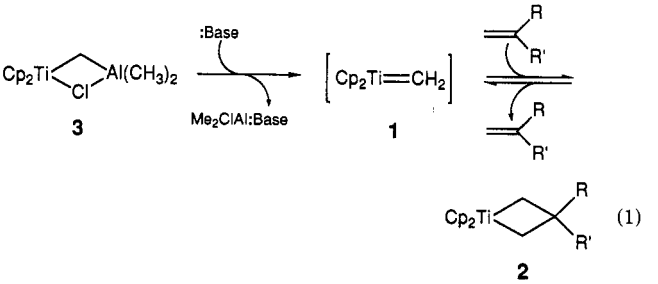
Received September 20, 1988

A variety of ester-substituted norbornenes react with titanamethylene complex (Tebbe's reagent) to yield stable titanacyclobutanes. Endo esters do not react with the reagent in competition with the norbornene double bond. The X-ray structure of the metallacycle formed from titanacene methylene complex and 1-methylbicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid diisopropyl ester was determined. On heating, the metallacycle rearranged to a carbene–olefin complex. The ratio of productive opening, cleavage of the bicycloheptane ring system, to nonproductive opening, regeneration of the starting materials, is controlled by a variety of steric factors that were studied and analyzed. The productive opening was detected by the formation of the product resulting from the intramolecular trapping of the intermediate titanium alkylidene by the endo ester functionality in a Wittig-like reaction to yield substituted bicyclo[3.2.0]heptenes. Rearrangement of the titanacycle formed from 4,4-dimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid *tert*-butyl ester yielded 10,10-dimethyl-3-methoxy-7-vinyltricyclo[5.3.0.0^{2,5}]dec-2-ene, which was transformed into $\Delta^{9((12)}$-capnellene in good yield.

Introduction

In recent years, titanium-catalyzed olefin metathesis has become a very well understood process. Titanium complexes capable of generating the titanocene methylidene species (1, eq 1) have been shown to display catalytic metathesis activity. Initially, the dimethylaluminum chloride adduct **3** was isolated by Tebbe and co-workers and found to slowly catalyze the selective exchange of terminal methylene groups of isobutene and methylene cyclohexane.[1] Addition of a strong Lewis base cocatalyst



(1)

† Contribution no. 7849.

‡ Dedicated to the memory of John K. Stille, Distinguished Professor of Chemistry (Colorado State University). Deceased July 19, 1989.

0022-3263/90/1955-0843$02.50/0