problems. Even the use of the less symmetric MeCp anion as a ligand only yielded twinned crystals.[19]

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[6] Crystal structure analysis of $[(Cp_3Ba)(Bu_4P)(thf)]$: orthorhombic, $a = 9.6826(8)$, $b = 25.276(2)$, $c = 29.742(4)$ Å, $V = 7279.0(1)$ Å^3, space group *Pbca*, $[(C_{15}H_{15}Ba)(C_{16}H_{36}P)\cdot(C_4H_8O)]$, $M_r = 664.1$, $Z = 8$, $\rho_{calcd} = 1.212$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 1.158$ mm^{-1}, 7110 reflections were measured on a Enraf Nonius CAD4 diffractometer ($Mo_{K\alpha}$, graphite monochromator, $T = -105$°C), 7110 unique reflections, 4201 observed reflections with $F > 4.0\sigma(F)$, empirical absorption correction (ψ scans). Solution by direct methods with the DIRDIF program.[20] Refinement with the SHELXL-93 program[21] to $R1(F) = 0.041$ and $wR2(F) = 0.075$ (382 parameters; hydrogen atoms in calculated positions). The carbon atoms of the THF molecule were severely disordered and refined as a split model in a 0.55/0.45 ratio. Residual electron density around the THF molecule probably also arises from the presence of small amounts of pyridine instead of THF at this site. The compound was crystallized from THF/pyridine, and NMR analyses in CD_3OD shows that the crystals contain 5 – 10% pyridine. Geometry calculations and plots were made with the EUCLID package.[22] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100832.

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Solid-Phase Supported Synthesis of the Branched Pentasaccharide Moiety That Occurs in Most Complex Type *N*-Glycan Chains**

Jörg Rademann, Armin Geyer, and Richard R. Schmidt*

N-glycosylation is a well-known feature of many natural polypeptides in eukaryotic organisms that contributes to their structural as well as functional properties.[1] It determines among others the stability, folding, and intracellular transport of proteins, and is required for cellular adhesion in events such as inflammation, immunogenicity, and metastasis. Unfortunately, naturally occurring *N*-glycans display a high degree of structural diversity, and an array of different carbohydrate isoforms are synthesized even on one type of protein. Varied glycan patterns are expressed in different types of tissues and at different stages of embryonic development. Consequently, for the chemical synthesis of these compounds[2] an approach is needed that intrisically permits a high degree of variation and the application of combinatorial[3] as well as split-synthesis techniques to supply a broad array of natural and

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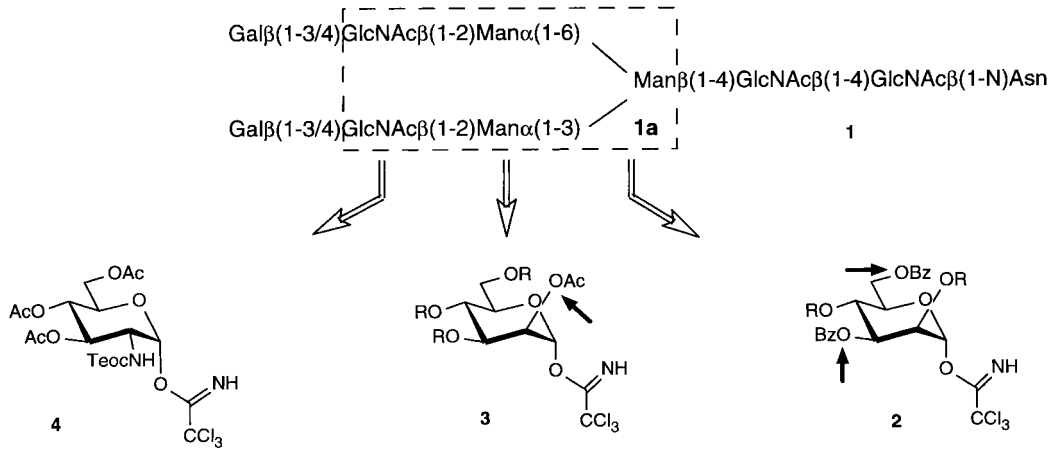


Scheme 1. Retrosynthesis of the building block **1a**.R = Bn; Teoc = trichloroethoxycarbonyl.

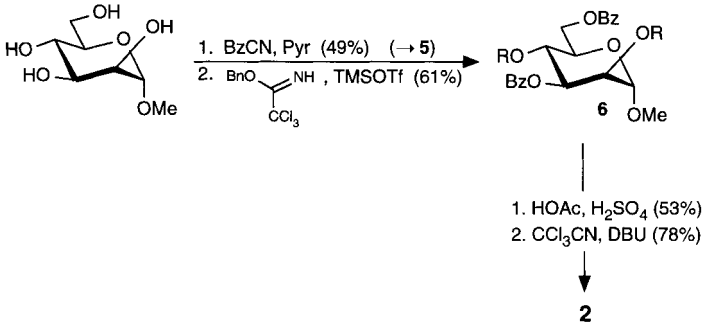
unnatural structures. We present here the first solid-phase synthesis of the branched pentasaccharide moiety **1a** (Scheme 1) that occurs in most complex type *N*-glycan chains **1**. The solid-phase methodology demonstrated should be applicable for the generation of molecular diversity of *N*-glycan structures with some generality.

Solid-phase synthesis of oligosaccharides on polystyrene resins has recently been investigated in several research groups.[3b, 4, 5] Preliminary studies with other polymers as the solid phase have also been performed.[6, 7] However, the yields often drop dramatically for a repeated glycosylation protocol.[5a]

Recently, we introduced a novel strategy for the synthesis of oligosaccharides on a solid support[8, 9] in which an alkylthiol linker is coupled to a chloromethylated Merrifield resin; then the first sugar is attached in a standard glycosylation procedure with an *O*-glycosyl trichloroacetimidate as glycosyl donor. In this way a thioglycoside linkage is generated, which is resistant to the standard glycosylation conditions for *O*-glycosyl trichloroacetimidates as donors and to removal of various protective groups. However, this linkage is rapidly cleaved with different thiophilic reagents; thus, all the reaction steps can be monitored readily on the solid phase: the supernatant of the cleavage reaction from a small resin sample can be analyzed spectroscopically after a few minutes either by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) or by chromatographic methods. So far, this concept has essentially been employed for the synthesis of glucose (1 →6) oligomers and of mannose $\alpha(1\rightarrow2)$ oligomers.[8, 9] The demanding pentasaccharide target chosen (**1a**)[10] should serve to demonstrate the general validity of this concept, since regio- and stereoselective α- and β-glycoside bond formation, respectively, is required. Additionally, the target molecule demands double glycosylation of a sugar substrate in one step, a feature that has to our knowledge not been demonstrated on solid phase so far.

Pentasaccharide **1a** consists of three differently linked sugar residues, which necessitates a corresponding protective group pattern for each of these building blocks. In solid-phase syntheses benzyl protective groups are best employed for permanent protection, and readily removable acyl groups are generally most appropriate for temporary protection; anomeric control is achieved by anchimeric assistance, and glycosyl donor properties are generated by trichloroacetimidate formation. This protocol leads to *O*-(3,6-di-*O*-benzoyl-2,4-di-*O*-benzyl-α-D-mannopyranosyl)trichloroacetimidate (**2**) as the mannosyl residue to be attached first to the resin linker; the demands for the two mannosyl residues should be accommodated by *O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)trichloroacetimidate (**3**); finally, attachment of the two *N*-acetylglucosamine residues should be possible with *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroethoxycarbonylamino-α-D-glucopyranosyl)trichloroacetimidate (**4**).

Trichloroacetimidate **2** can be readily prepared (Scheme 2): regioselective 3,6-di-*O*-benzoylation of commercially available methyl α-D-mannopyranoside (→**5**) and then benzylation



Scheme 2. Synthesis of the trichloroacetimidate **2**.R = Bn.

with *O*-benzyl trichloroacetimidate[11] in the presence of TMSOTf as catalyst afforded fully protected methyl α-mannoside derivative **6**; the corresponding methyl β-mannoside was not detected. Acid-catalyzed cleavage of the glycosidic linkage and then treatment with trichloroacetonitrile in the presence of 1,8-diazabicylco[5.4.0]undec-7-ene (DBU) afforded **2** in good yield (Table 1). Trichloroacetimidates **3** and **4** were prepared as previously described.[12, 13]

Sulfanylpropyloxymethyl-functionalized Merrifield resin (**7**) was employed for the solid-phase synthesis; this has a loading of 0.15 mmol g^{-1} based on the dry resin.[9] Swelling of **7** in CH_2Cl_2 (Scheme 3) and then reaction with **2** (3 equiv) in the

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Table 1. Selected physical data of **2, 6, 11,** and **14**.

2: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.20-4.32$ (m, 2H, 2-H, 5-H), 4.39 (dd, $J_{3,4} = 8.9$, $J_{4,5} = 8.9$ Hz, 1H, 4-H), 4.55–4.82 (m, 6H, 2 6-H, 2CH_2-Ph), 5.64 (dd, $J_{2,3=}4.6$, $J_{3,4} = 8.9$ Hz, 1H, 3-H), 6.45 (d, $J_{1,2} = 2.3$ Hz, 1H, 1-H), 7.1–8.1 (m, 20H, 4 Ph), 8.67 (s, 1H, NH). $[\alpha]_D = +34.6$ ($c = 1.0$ in $CHCl_3$)

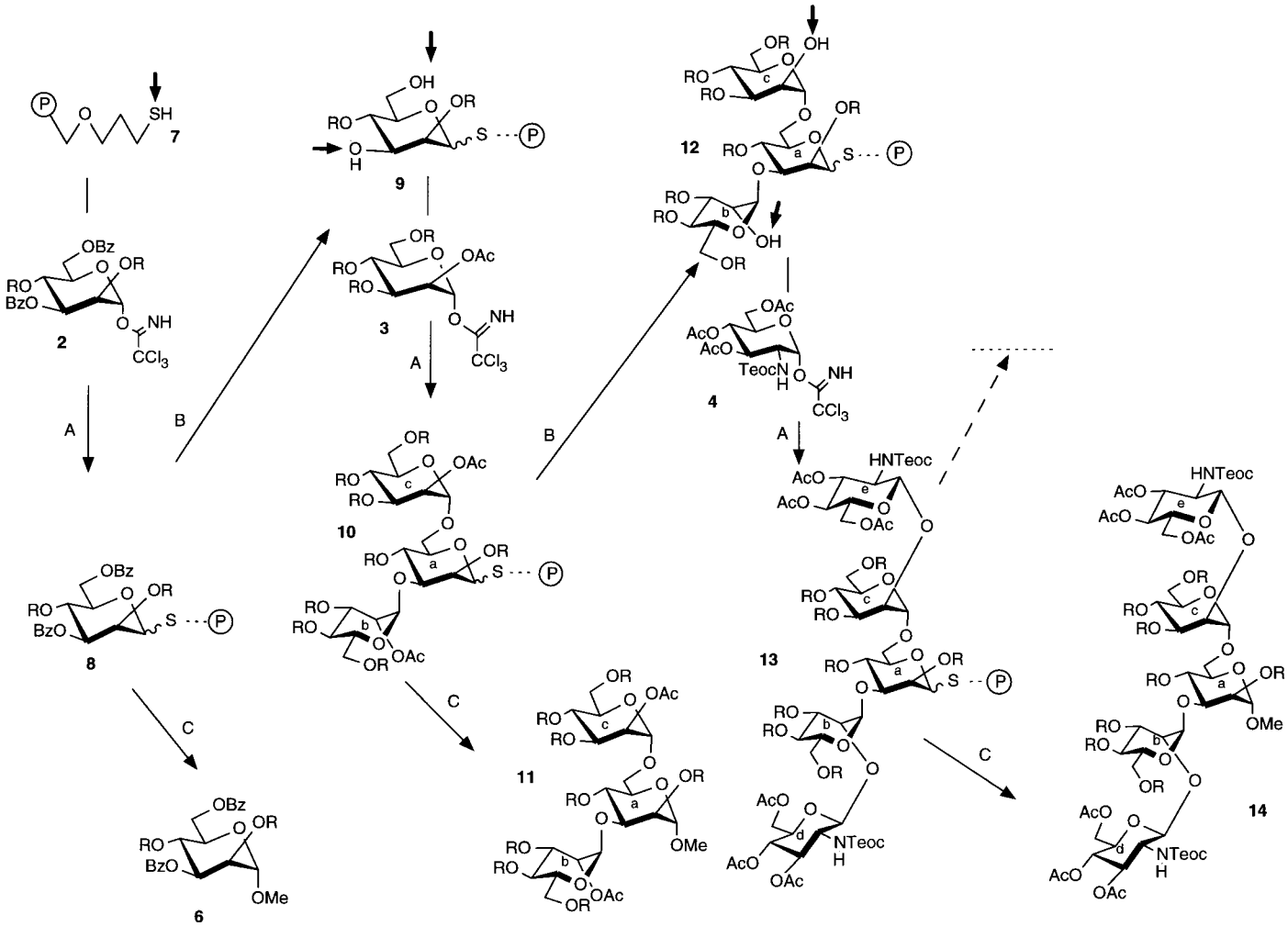
6: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.42$ (s, 3H, OCH_3), 4.03 (dd, $J_{1,2} = 2.0$, $J_{2,3} = 3.2$ Hz, 1H, 2-H), 4.0-4.1 (m, 1H, 5-H), 4.27 (dd, $J_{3,4} = 9.5$, $J_{4,5} = 9.5$ Hz, 1H, 4-H), 4.55-4.8 (m, 6H, 2 6-H, 2 CH_2-Ph), 4.84 (d, $J_{1,2} = 1.9$ Hz, 1H, 1-H), 5.59 (dd, $J_{2,3} = 3.2$, $J_{3,4} = 9.5$ Hz, 1H, 3-H), 7.0–8.2 (m, 20H, 4Ph). $[\alpha]_D = +22.4$ ($c = 1.0$ in $CHCl_3$)

11: ^{1}H NMR (600 MHz, $CDCl_3$): mannosyl residue a: $\delta = 4.63$ (d, $J_{1,2} <$ 2 Hz, 1H, 1-H), 3.78 (2-H), 4.10 (3-H), 3.84 (4-H), 3.63 (5-H), 3.63, 3.82 (2 6-H); mannosyl residue b: $\delta = 5.16$ (d, $J_{1,2} = 1.7$ Hz, 1H, 1-H), 5.48 (2-H), 4.00 (3-H), 3.79 (4-H), 3.76 (5-H), 3.58, 3.70 (2 6H); mannosyl residue c: $\delta = 4.94$ (d, $J_{1,2} = 1.9$ Hz, 1H, 1-H), 5.44 (2-H), 3.93 (3-H), 3.87 (4-H), 3.92 (5-H), 3.66 (2 6-H)

14: ^{1}H NMR (600 MHz, $CDCl_3$): sugar residue a: $\delta = 5.17$ (d, $J_{1,2} < 2$ Hz, 1H, 1-H), 3.78 (2-H), 4.15 (3-H), 4.22 (4-H), 3.80 (5-H), 3.74, 4.29 (2 6-H); sugar residue b: = 5.06 (d, $J_{1,2} = 1.9$ Hz, 1H, 1-H), 3.93 (2-H), 3.79 (3-H), 3.72 (4-H), 3.62 (5-H), 3.52 (2 6-H); sugar residue c: $\delta = 4.89$ (d, $J_{1,2} =$ 6.5 Hz, 1H, 1-H), 4.02 (2-H), 3.95 (3-H), 3.59 (4-H), 3.82 (5-H), 3.39 (2 6-H); sugar residue d: $\delta = 3.90$ (d, $J_{1,2} = 8.5$ Hz, 1H, 1-H), 3.47 (2-H), 4.83 (3-H), 4.87 (4-H), 2.89 (5-H), 3.93, 4.05 (2 6-H); sugar residue e: $\delta = 4.92$ (d, $J_{1,2} = 8.6$ Hz), 3.84 (2-H), 5.04 (3-H), 5.04 (4-H), 3.17 (5-H), 3.79, 4.01 (2 6-H)

presence of TMSOTf as catalyst (0.15 equiv; Procedure A, see Experimental Section) afforded mannosylated resin **8**, as indicated after cleavage with *N*-bromosuccinimide (NBS) and di-*tert*-butylperoxide (DTBP) in CH_2Cl_2/MeOH (Procedure C) by MALDI-TOF analysis and NMR spectroscopy, yielding known methyl mannoside **6** (see Scheme 2). The temporary *O*-benzoyl protective groups in **8** could be readily removed by treatment with NaOMe/MeOH in MeOH/CH_2Cl_2 (Procedure B). Washing with THF and CH_2Cl_2 led to 3,6-*O*-unprotected **9**, as indicated after cleavage from a small resin sample with AgOTf/MeOH (Procedure D).

Repetition of this sequence of reactions could be successfully carried out. Thus, reaction of **9** with **3** (Procedure A) gave trisaccharide **10.** MALDI-TOF-MS analysis of a small resin sample (Procedure D) showed a signal corresponding to the MAg^+ ion of **11** as the only detectable peak above m/z 380. Trisaccharide **10** was cleaved from the resin (Procedure C) to afford trisaccharide **11** in 38% overall yield; the corresponding β-derivative was not detected. Compound **11** could be fully characterized by ^{1}H NMR spectroscopy (Table 1). De-*O*-acetylation of **10** (Procedure B) furnished 2b,2c-*O*-unprotected trisaccharide **12** (Procedure D), which on treatment with donor **4** (Procedure A) led to resin-bound pentasaccharide **13**.



Scheme 3. Synthesis of the pentasaccharide **14**, R = Bn. A) TMSOTf (0.15 equiv), CH_2Cl_2, room temperature; B) NaOMe, MeOH/THF or CH_2Cl_2; C) NBS, DTBP, CH_2Cl_2/MeOH; washing with CH_2Cl_2 and THF.

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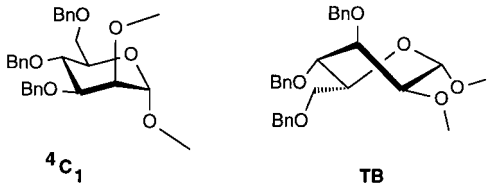
Cleavage from the resin (Procedure C) gave the desired methyl-α pentasaccharide **14** in 20% overall yield starting from **7**; this yield encompasses formation of five glycosidic linkages, removal of four acyl groups, and product cleavage from the resin under formation of a methyl α-glycoside (i.e. ca. 85% yield per reaction event). The pentasaccharide **14** could be fully characterized by ^{1}H NMR data (Table 1); the data for the mannosyl residue c exhibit an unusual twist boat (TB) conformation (Scheme 4). The structural assignments derived from NMR data indicate that the $\alpha(1\rightarrow2)$ linkage between mannosyl residues e and c is retained. Evidently, voluminous axial substituents in ring positions 1 and 2 destabilize the $^4C_1$ conformation of mannosyl residue c in **14** (but not in **11**!). The conformational equilibrium is shifted to a



Scheme 4.

twist boat. The coupling constants supporting this assignment are summarized in Table 2; they are taken from a Lorentz-to-Gauss transformed ^{1}H NMR spectrum and from selective TOCSY spectra (600 MHz).

Table 2. Expected and detected $^3J_{H,H}$ coupling constants [Hz] for the α-linked mannosyl residue c in **14**.

Expected ($^4C_1$ conformation)	Detected	
1-H/2-H	1.9	6.5
2-H/3-H	3.3	ca. 2 (not resolved)
3-H/4-H	9.3	2.4
4-H/5-H	9.7	7.1

In conclusion, the synthetic protocol for the solid-phase synthesis of oligosaccharides described in this paper enables repetitive stereoselective glycosylations, controlled partial deprotection, and resin cleavage in high yields, thus permitting the synthesis of oligosaccharides possessing quite complex and demanding structures. Oligosaccharide residues, for instance, found in mammalian systems, contain a limited number of different sugars, also their linkage site and stereochemistry, though manifold, is not unlimited. Therefore, the design of proper building blocks is now an important goal in order to establish a versatile methodology for fast and efficient solid-phase supported syntheses of a great variety of oligosaccharides.

Experimental Section

A) Protocol for the solid-phase glycosylation: A glass tube (8 × 80 mm) was used as reaction vessel; this vessel was tightly sealed with Teflon stoppers, fitted with a glass filter inlet to allow reactands to be added to the mixture under inert gas conditions. Dry functionalized resin (containing 0.033 mmol of **7**, **9**, or **12**) was placed unter argon in the described tube. Trichloroacetimidate donor (0.1 mmol per free hydroxy group) is dissolved in CH_2Cl_2 (2 mL) and added under argon to the resin. After shaking the mixture for 15 min trimethylsilyl trifluoromethanesulfonate (TMSOTf) (30 µL of a 0.5 M solution in CH_2Cl_2) was injected and the stoppered glass tube was shaken in a horizontal position for 1 h with a mechanical shaker. Then the resin was filtered off and washed by switching between CH_2Cl_2 and THF several times and finally dried with a stream of dry argon and then in vacuo. For the glycosylation leading to the resin-bound pentasaccharide **13**, the described glycosylation procedure was repeated to ensure complete glycosylation of all hydroxy groups.

B) Protocol for the solid-phase deacylation: Glycosylated resin (ca. 0.03 mmol) was placed in the reaction vessel and suspended in CH_2Cl_2 (2.5 mL), and 0.5 M NaOMe in MeOH was added (0.25 mL). The glass tube was shaken in a horizontal position for 2 h; a prolonged reaction time of 6 h was required for the removal of benzoyl protective groups. Then the resin was filtered off and washed in a batchwise procedure first with a 0.05 M solution of [15]crown-5 in THF/acetic acid (20/1), followed by several alternating washing steps with THF and CH_2Cl_2. The resin was dried first with a stream of dry argon and then in vacuo. Analysis was performed as described under Section D.

C) Protocol for product cleavage and isolation: Fully protected, glycosylated resin (ca. 0.015 mmol) was placed in the reaction vessel. A solution of *N*-bromosuccinimide (15 mg, 0.084 mmol), 1,6-di-*tert*-butylpyridine (20 µL) in CH_2Cl_2/MeOH (9/1) (2 mL) was added. After 2 h of vigorous shaking, the product mixture was washed off the resin by switching between CH_2Cl_2 and THF. It was concentrated in vacuo; the crude product was analyzed by MALDI-TOF-MS (see Section D) and HPLC (Europshere 100, 5 µm C-18 material, 4 × 160 mm column, gradient: acetonitrile in water, 5% to 60% in 5 min then 60% to 100% in 15 min). It was separated over silica (toluene/acetone) and final purification was carried out with preparative RP-18 HPLC. Yields; 7.5 mg (38%) in case of compound **11**; 6.5 mg (20%) in case of compound **14**.

D) Protocol for the MALDI-TOF-MS of products: A sample of dry resin (1–2 mg) was mixed in an Eppendorf cup with a solution of dry AgOTf (4 mg) in THF/MeOH (9/1) (50 µL). After 15 min 10 µL of the supernatant was mixed with a matrix solution (10 µL of a solution of 2,4-dihydroxybenzoic acid (10 mg) in THF (1 mL)). Of this solution 1 µL was applied on the sample slide of the MALDI-TOF-MS (Kratos, Maldi Kompakt). Under the described conditions exclusively signals corresponding to the silver ions (MAg^+) were observed in the mass spectrum. The same cleavage reaction was used for RP-HPLC analysis of the products as described under Section C.

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A New Carborane Cage: Hexacarba-*arachno*-dodecaborane(12)

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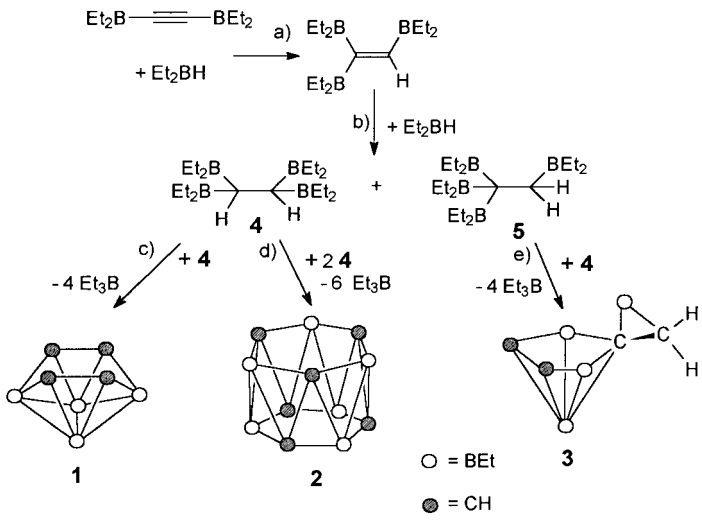
Dedicated to Professor Heinrich Nöth on the occasion of his 70th birthday

The multifaceted structural and synthetic chemistry of carboranes continues to diversify after more than thirty years.[1, 2] The reactions of various polyboranes with alkynes provides an access to a variety of carboranes;[1, 3, 4] however, with few exceptions, complex mixtures are obtained which may be difficult to separate. Transformations of simple organoboranes,[5, 6] mainly to B-alkylated derivatives, promise more specific entries into carborane chemistry. Thus, the hydroboration of 1-alkynyldiethylboranes under "hydride-bath" conditions (i.e., with a large excess of diethylborane Et_2BH[7]) gives access to new types of carboranes such as 1-carba-*arachno*-pentaborane(10),[8, 9] 2-carba-*nido*-pentaborane(8), or 2,4-dicarba-*nido*-hexaborane(8),[10, 11] and provides carboranes such as tetracarba-*nido*-octaborane(8)[12] (**1**) which were not readily accessible or well characterized before. Carborane **1** is a member of the family of carbon-rich carboranes on the borderline between classical and nonclassical structures. The known neutral carbon-rich carborane cages are all *nido* systems with a maximum of four skeleton carbon atoms: for example $C_4B_2R_6$,[13] $C_4B_4R_8$,[12] $C_4B_6R_{10}$,[4c, 14] and $C_4B_8R_{12}$.[15] There also are cationic *nido* carboranes with five carbon atoms: $[C_5BR_6]^+$.[16] We now report a carborane with six carbon and six boron atoms in the skeleton.

The reactions a – c shown in Scheme 1 provided the first straightforward route to the stable *nido*-C_4B_4 carborane **1**.[12] While all our attempts to improve the yield of **1** over 20% failed, these experiments revealed the nature of important



Scheme 1. Synthesis of **1** – **5**.

side products. The formation of **1** is accompanied by that of isomer **3**, which normally is destroyed (e.g. by oxidation) during the purification of **1**. As shown in Scheme 1 (reactions b and e), **3** results from Et_2BH-catalyzed condensation of **4** and **5**.[17] The spiro-carborane **3** is a new member of the still small family of 2,3,5-tricarba-*nido*-boranes(7).[18]

Other Et_2BH-catalyzed condensations are conceivable. Thus, the condensation of three molecules of 1,1,2,2-tetraborylethane (**4**) affords carborane **2** (Scheme 1, reaction e), which was isolated as a crystalline colorless solid. The simple NMR spectra of **2** (there are no appreciable changes between $-80\,^{\circ}C$ and ambient temperature) indicate either high symmetry or a highly fluxional structure. The one-dimensional $^1H-^{13}C$ heteronuclear shift correlation detected by ^1H NMR spectroscopy proves the presence of isolated H-C-C-H units by the splitting of the ^{13}C satellites ($^1J(^{13}C,^1H) = 152$ Hz) into doublets ($^3J(^1H,^1H) = 8.0$ Hz), and this suggests a rigid

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