

# An approach to the synthesis of polysaccharide analogues

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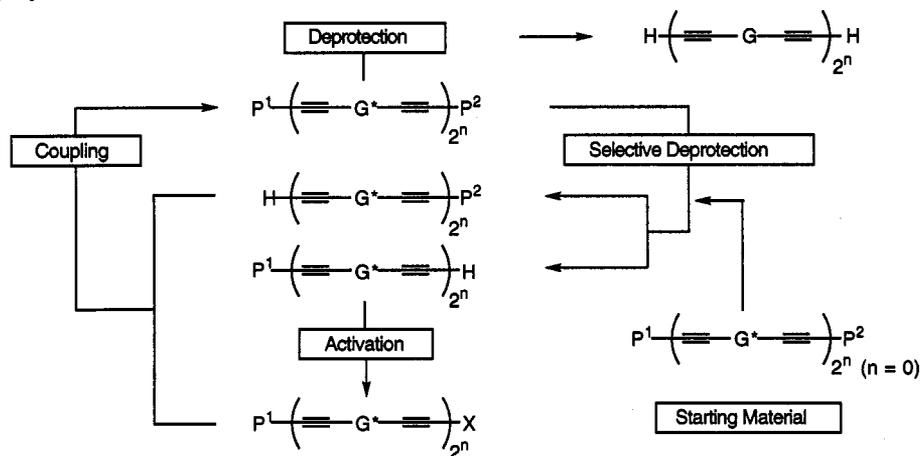
**Abstract:** A new approach towards polysaccharide analogues is described. The ratio of intra- to intermolecular hydrogen bonds is modified by replacing some or all of the glycosidic oxygens by butadiynediyl groups. The butadiynediyl groups allow a binomial synthesis, based upon the cross-coupling of orthogonally protected dialkynes. This report summarises methodical innovations that set the stage for the synthesis of higher oligomers of "acetylenosaccharides". We report the stereoselective introduction of alkynyl groups into glucose and the synthesis of monomers derived from glucose and cellobiose, the development of the two first orthogonal protecting group couples for dialkynes, optimisation of the cross-coupling of alkynes, and the preparation of oligomers derived from dialkynylated glucose up to a deprotected octamer and a protected hexadecamer. Also reported are the synthesis of novel cyclodextrin analogues, a *Bergman* cyclisation leading diastereoselectively to 2,3-di-*C*-glycosylated naphthalenes, and the synthesis of cellobiose-derived oligomers.

## INTRODUCTION

Polysaccharides possess very diverse properties and functions based on specific intra- and intermolecular interactions (ref. 1, 2, 3). Hydrogen bonds are the strongest single factor determining these interactions (ref. 4). We intend to study the role of hydrogen bonding by comparing the properties of analogues of polysaccharides with systematically modified hydrogen bonds to those of the native compounds. For this, we intend to substitute some or all glycosidic oxygens by a linker unit that is long enough to interrupt intramolecular (interresidue) hydrogen bonding without interfering with intermolecular hydrogen bonding, thereby modifying the ratio of intra- to intermolecular hydrogen bonds. Replacing the glycosidic oxygen by the slender and rather rigid butadiynediyl moiety allows a binomial synthesis of analogues, doubling the size of the oligomer with each binomial cycle. A binomial synthesis satisfies the requirement of the high efficiency that is required to make long, homogeneous oligomers and polymers.

*Scheme 1* illustrates the strategy and illustrates the methodical problems that must be solved *en route* to the oligomers.

**Scheme 1**



$G^*$  stands for any mono- or oligosaccharide carrying two orthogonally protected ethynyl substituents; partial deprotection leads to two building blocks of which one must be activated to allow for cross-coupling to a

dimer. In this dimer and in higher oligomers ( $n > 1$ )  $G^*$  possesses one or several internal butadiyne units. Orthogonal deprotection of the dimer again yields two building blocks, that, ideally, are cross coupled as before to lead to a tetramer; repetition of the binomial cycle should lead to the desired analogues.

To prepare the formally simplest analogue, where all glycosidic oxygens of the parent polysaccharide are replaced by butadiyne groups, one requires a dideoxy-diethynyl-monosaccharide, an orthogonal protection of the alkynyl groups, a reliable, high yielding procedure for the cross-coupling of two alkynes, a high yielding deprotection, and a meaningful comparison of the properties. The preparation of oligomers derived from diethynylated disaccharides or from higher oligosaccharides as monomers has to cope with similar problems. Considering these problems, we have elected to make analogues of cellulose and amylose, important and well studied homopolysaccharides.

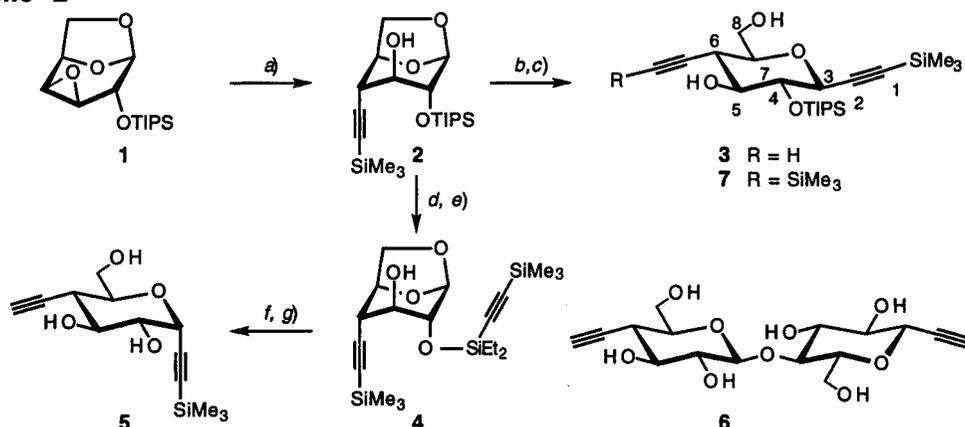
The first phase of the project is concerned with methodical problems; the most important results are summarised below.

## PREPARATION OF DIETHYLATED GLUCOSE AND CELLOBIOSE

The ethynyl group was conveniently introduced at C(4) of the dianhydroglucose **1** (Scheme 2), following a precedent by *Fraser-Reid* (ref. 5). Alternatively, C(4)-ethynylated glucosides were prepared by nucleophilic substitution of a C(4)-trifloxy group of an allyl  $\alpha$ -D-galactopyranoside by cyanide, transformation of the nitrile to an aldehyde, and application of the *Corey-Fuchs* procedure (ref. 6, 7). The OH group of the intermediate anhydroglucose **2** directs the coordination of an *in situ* generated aluminum acetylide, resulting in a retentive, alkynylating opening of the acetal, and a short, high yielding synthesis of the diequatorially ethynylated monomer **3**.

The preparation of the  $\alpha$ -C-glucoside **5**, required for the preparation of amylose and cyclodextrin analogues was also based on an intramolecular, alkynylating opening of the anhydro ring and resulted in an equally efficient synthesis (ref. 8).

**Scheme 2**



a) Me<sub>3</sub>Al, Me<sub>3</sub>SiC≡CLi; 85%. b) Bu<sub>4</sub>NF; 95%. c) 3 equiv. of Me<sub>3</sub>SiC≡CLi, 3 equiv. of AlCl<sub>3</sub>; 80% of **3**. d) Bu<sub>4</sub>NF. e) ClEt<sub>2</sub>SiC≡CSiMe<sub>3</sub>, lutidine; 85–90%. f) AlCl<sub>3</sub>/BuLi 1:1. g) HCl, AcOH; 85–90%.

Alternative procedures for the synthesis of **3** are based on the addition of trimethylsilyl acetylide to gluconolactones, obtained either from **2** or from the allyl  $\alpha$ -D-galactopyranoside mentioned above, followed by reductive dehydroxylation; these procedures are longer, but more flexible (ref. 7).

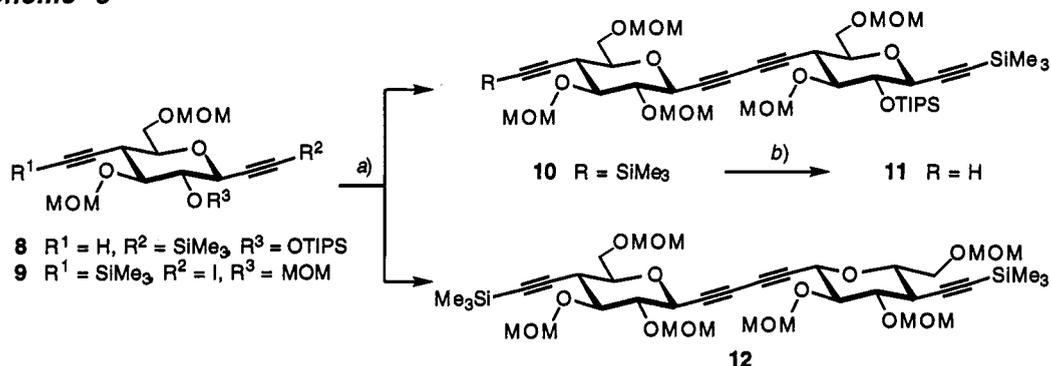
The cellobiose-derived monomer **6** has been prepared by glycoside synthesis of monoethynylated derivatives (ref. 9); it possesses the intramolecular H-bond between C(3)OH and C(5)O that is important for the conformation of cellulose. In agreement with this, molecular modelling of the octamer derived from **3**, and of the one derived from **6** predicts a linear, rigid shape for the former, and either a helical, or a corrugated shape for the latter; thus, the true homologues of the oligomers derived from **3** are those obtained from dialkynes derived from cellotriose rather than from cellobiose.

## ORTHOGONAL PROTECTING GROUPS FOR DIALKYNE CROSS-COUPLING

The minimum number of steps constituting a binomial cycle (*i.e.* doubling the size of the oligomer) requires an orthogonal deprotection of the alkynyl substituents. The trimethylsilylated ethynyl groups of the

monomer **7** (obtained directly from **3**, *Scheme 2*) differ sufficiently to allow a reagent-controlled, regioselective deprotection: the more highly nucleophilic group at C(6) is deprotected by  $\text{AgNO}_2/\text{KCN}$  in MeOH, and the more electrophilic propargylic ether moiety by BuLi (ref. 10). Deprotection by  $\text{AgNO}_2/\text{KCN}$  is compatible with a butadiyne moiety, transforming **10** (*Scheme 3*) into **11**, but BuLi destroyed **10**, demonstrating the need for orthogonal alkyne protecting groups. Cross-coupling of **8** and **9** catalysed by  $\text{Pd}(\text{PPh}_3)_4$ , CuI, and a base (ref. 11, 12) led to both the heterodimer **10** and the homodimer **12**; the unsatisfactory yields of **10** (56%) define a further problem to be solved (ref. 13). Although the combination, on the one hand, of a regioselective deprotection at "the left end" of **10** (and similarly of the corresponding tetramer) and, on the other hand, of the introduction of C-silyl groups of different bulk allowed to realise a sequence of three cycles and the preparation of the (deprotected) octamer, the restricted number of silyl groups of sufficiently different size and the low overall yields demonstrated the need to solve the above mentioned two problems.

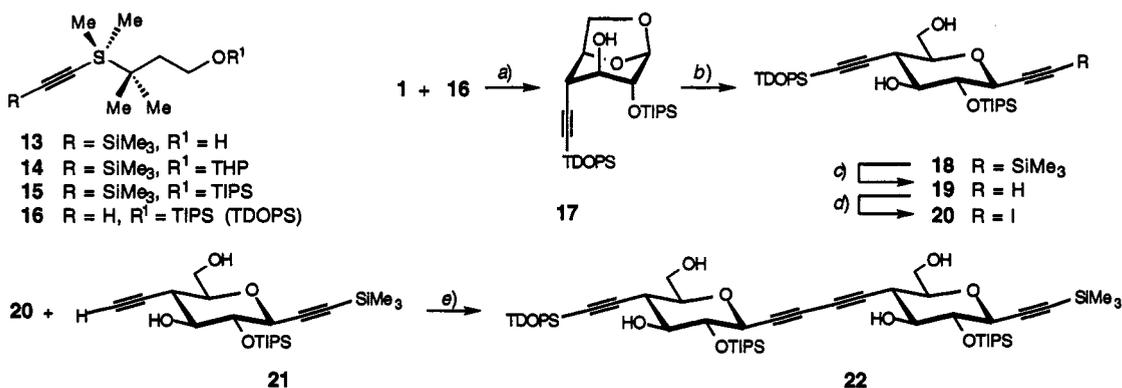
### Scheme 3



a) CuI,  $\text{Pd}(\text{PPh}_3)_4$ , pyridine; 56% of **10** and 21% of **12**. b)  $\text{AgNO}_2$ , KCN, MeOH; 70%.

A first pair of orthogonal protecting groups (illustrated by **13–15**) was designed, based upon size differences of the trialkylsilyl groups and inter- vs. intramolecular reactions (ref. 14). The small  $\text{SiMe}_3$  group is selectively removed under mild conditions, as long as the OH group of the dimethyl-(oxypropyl) silyl (DOPS) moiety is protected. Treating the *O*-deprotected DOPS moiety with a catalytic amount of base induces an intramolecular attack at silicon and a regioselective deprotection, not affecting the  $\text{Me}_3\text{Si}$ -ethynyl group. The distillable, DOPS- and  $\text{SiMe}_3$ -protected acetylene synthon **13** was prepared from senecioaldehyde in five steps (30–35% overall), and further protected to afford **14–16**. The synthon **16** is conveniently introduced into aromatic, heteroaromatic, and aliphatic compounds, and into monosaccharides; either *via* glyconolactones, or *via* oxiranes. Thus, epoxide opening of **1** with the acetylide derived from **16** ( $\rightarrow$ **17**), followed by alkynylating opening of the dioxolane ring yielded the orthogonally protected dialkyne **18** (ref. 15). This dialkyne was deprotected either by base to yield **19**, or by dilute HCl to de-*O*-silylate the TDOPS group followed by mild base to afford **21** in high yields.

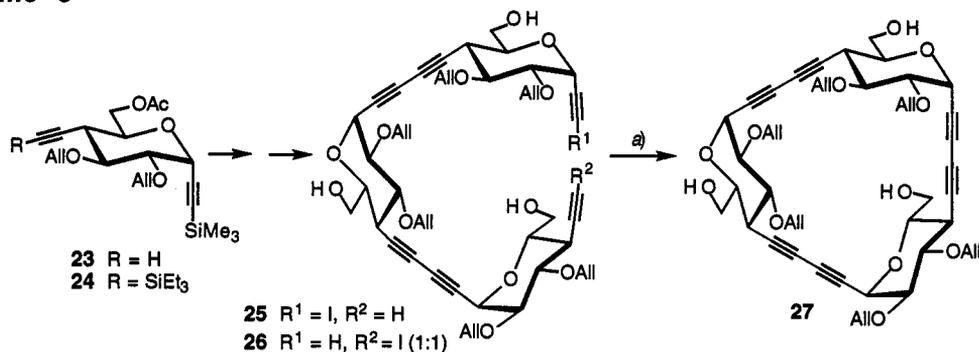
### Scheme 4



a) BuLi,  $\text{AlMe}_3$ , toluene; 87%. b)  $\text{Me}_3\text{SiC}\equiv\text{CLi}$ ,  $\text{AlCl}_3$ , toluene; 72%. c) NaOMe, MeOH; 94%. d) NIS,  $\text{CF}_3\text{CO}_2\text{Ag}$ ; 94%. e)  $\text{Pd}_2(\text{dba})_3$ , CuI, (furyl) $_3\text{P}$ ,  $\text{Et}_3\text{N}$ , DMSO; 81%.

Parallel to this work, we studied the cross coupling, proposed a mechanism explaining the formation of the hetero- and homocoupling products, and improved the conditions (ref. 16). It originally appeared advantageous to use bromoalkynes rather than iodoalkynes, however, this depends upon the number and nature of protecting groups, presumably reflecting the initial formation of a  $\eta^2$ -Pd complex. Optimisation of the coupling conditions (ref. 17) improved the yield of the heterodimer **22** to 81% (ref. 15). Similar conditions allowed the preparation of cyclodextrin analogues, such as the cyclotrimer **27**, obtained by cyclisation of the iodides **25** and **26** (ref. 18), *Scheme 5*).

### Scheme 5



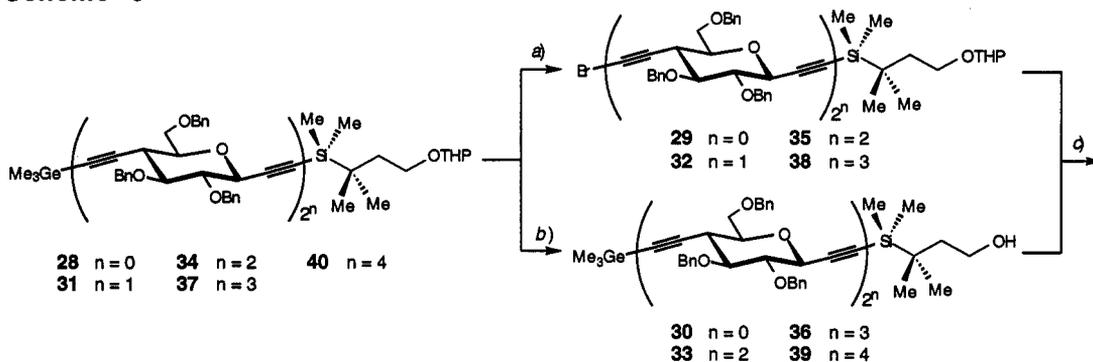
a) Pd<sub>2</sub>(dba)<sub>3</sub>, (furyl)<sub>3</sub>P, CuI, Et<sub>3</sub>N, C<sub>6</sub>H<sub>6</sub>, (1.4 mM); 65%.

The DOPS/SiMe<sub>3</sub> couple reduced the number of steps for a "binomial cycle" to five – the minimum number is three. *Isobe's* brominating desilylation (ref. 19) further reduced the number of steps to four. However, the brominating removal of the SiMe<sub>3</sub> group was slow and yields were fickle (ref. 20). For this reason, we introduced the more highly electropositive GeMe<sub>3</sub> group, either by trimethylgermylation of an alkyne, or by introduction of the (trimethylgermyl)ethynyl group. Bromodegermylation with NBS and CF<sub>3</sub>CO<sub>2</sub>Ag was rapid and high yielding; it did not affect the THP-protected DOPS group, but cleaved the SiMe<sub>3</sub> group to an extent of about 3%. Considering the resulting separation problem, we used a combination of the THP-DOPS and the GeMe<sub>3</sub> group.

This procedure reduced the number of steps per binomial cycle to four; the minimum number of three steps per cycle was reached by directly using the hydroxypropylsilyl intermediates **30**, **33**, **36** and **39** (*Scheme 6*) in the cross-coupling of alkynes. The products are also best purified at the stage of the hydroxypropylsilylated intermediates; the different number of OH groups of hetero- and homodimers facilitating the separation (ref. 20).

Yields of cross-coupling were high, up to the octamer, but the hexadecamer was only isolated in low yields; the severe losses during chromatography are presumably due to slow aggregation. The dependence of this behaviour upon the nature of the protecting groups is under scrutiny.

### Scheme 6

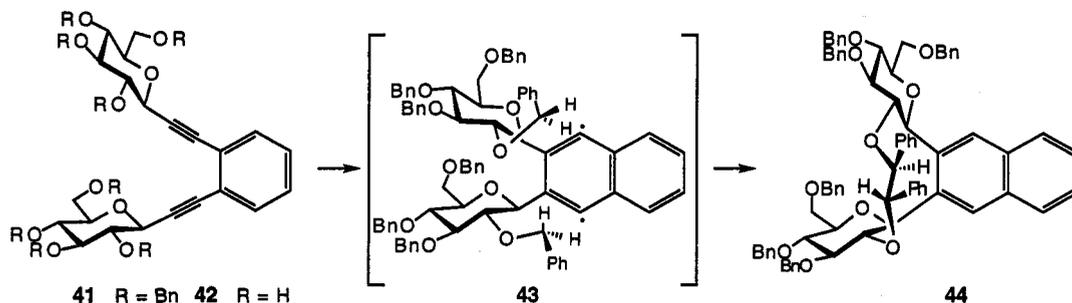


a) BuLi, AlMe<sub>3</sub>, toluene; 87%. b) Me<sub>3</sub>SiC≡CLi, AlCl<sub>3</sub>, toluene; 72%. c) NaOMe, MeOH; 94%. d) NBS, AgNO<sub>3</sub>; 85%. e) Pd<sub>2</sub>(dba)<sub>3</sub>, CuI, (furyl)<sub>3</sub>P, DMSO; 70%.

## ATTACHMENT TO A TEMPLATE: BERGMAN REARRANGEMENT AND SYNTHESIS OF NOVEL C-GLYCOSIDES

Attachment of two saccharide chains to a template will favour their interaction provided that the proximity of the chains is enforced. Aromatic compounds are convenient templates, as alkynylated saccharides are easily coupled to aryl groups, but the bond angle between two ethynylated saccharide chains in *ortho*-position may be large. To check this, we compared the *Bergman* cyclisation (ref. 21, 22, 23) of the protected and unprotected dialkynes **41** and **42** (ref. 24). Calculations (gas phase) indicated that weak interchain hydrogen bonding is possible; such hydrogen bonding may stabilise the transition state and lower the temperature of the rearrangement. Thermolysis of **41** at 230° in PhCl led to 55% of the naphthalene **44**, possessing a new, 10-membered ring formed by diastereoselective coupling of an intermediate dibenzyl diradical. Thermolysis of **41** in EtOH started around 160°, leading to 6% of **44** within 24 h, while **42** did not react at this temperature and decomposed between 180 and 220°; hence, hydrogen bonding of **42** increases the activation energy. Improved templates are currently evaluated. Thermolysis of *C*-glycosides of type **41** followed by hydrogenolysis constitutes a unique access to 2,3-di-*C*-glycosylated naphthalenes; the diastereoselective formation of **44** via regioselective H-abstraction of **43** has been rationalised.

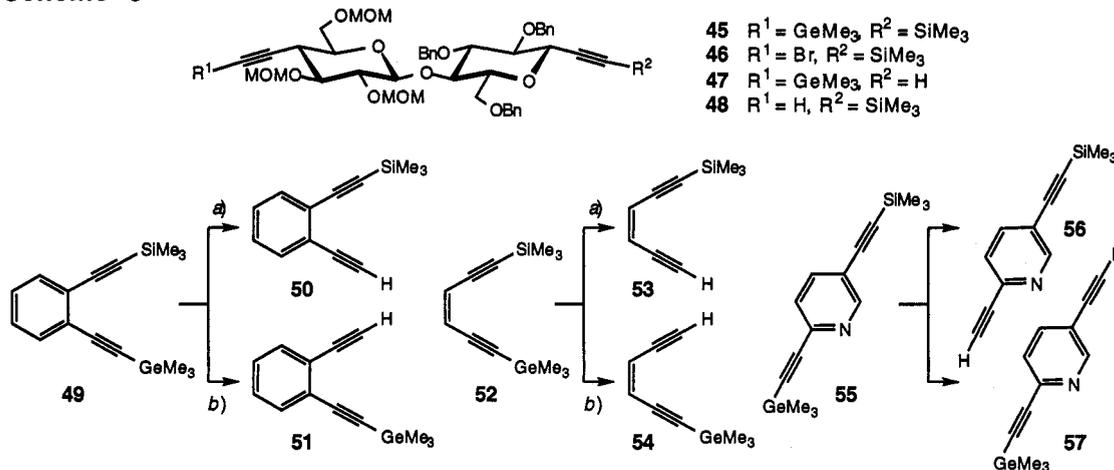
### Scheme 7



## OLIGOMERS DERIVED FROM CELLOBIOSE A CONVENIENT ORTHOGONAL PROTECTION OF DIALKYNES

The preparation of the DOPS protected ethyne requires five steps; hence, we studied the conveniently prepared SiMe<sub>3</sub>/GeMe<sub>3</sub> diprotected dialkynes for the preparation of the cellobiose-derived oligomers (ref. 9).

### Scheme 8



a) CuBr (10 mol%), acetone/H<sub>2</sub>O 5:1; 90% of **50**, 62% of **53**, 90% of **56**.

b) KF, 18-crown-6, THF/H<sub>2</sub>O 98:2; 88% of **51**, 59% of **54**, 91% of **57**.

The GeMe<sub>3</sub> group proved compatible with the conditions of cross-coupling which proceeded in 67% to the dimer and in 60% to the tetramer; yields depending upon the protection of the OH groups and the nature of

the protecting groups. At first, however, **45** (Scheme 8) and a related, partially deprotected dimer were bromodegermylated in a yield of only about 80% (protodesilylation proceeded in *ca.* 90%). Bromodegermylation was greatly improved by performing it with NBS in the presence of *ca.* 5–10 molpercent of CuBr; **45** yielding 92% of **46**, without concomitant desilylation. These conditions of bromodegermylation/protodesilylation are compatible with butadiyne moieties. We also found conditions for the orthogonal protodegermylation/protodesilylation (ref. 25). Protodegermylation is effected with CuBr in aqueous acetone (condition *a*) in Scheme 8); yields are about 90%, except in the case of the volatile **53**. Protodesilylation of **45** is possible with K<sub>2</sub>CO<sub>3</sub> in MeOH; in the general case, KF is preferred (condition *b*) in Scheme 8). These conditions will certainly prove useful in the synthesis of nanostructures.

The dependence of the cross-coupling on protecting groups, and the solution properties of higher oligomers are still matter of some concern, but most fundamental problems appear to be solved; the stage is set for the synthesis of long, homogeneous analogues of oligo- and of polysaccharides.

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