0.71073 Å, graphite monochromator), empirical absorption correction using symmetry-equivalent reflections (SADABS), direct methods, difference Fourier syntheses. The initial structures were refined against F^2 (Bruker-SHELXTL, version 5.1, **1998**). The hydrogen atoms were calculated in geometrically idealized positions. The crystals were picked directly out of the mother liquor under a cold nitrogen stream. **1**: Crystal size: $0.33 \times 0.32 \times 0.31$ mm, $T = 193$ K, monoclinic $P2_1/n$, $a = 10.140(2)$, $b = 13.081(2)$, $c = 10.438(2)$ Å, $\beta = 97.050(2)$ Å, $V = 1373.9(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.910$ g cm^{-3}, $2\theta_{max} = 60.02°$, 16192 collected reflections, 4009 unique reflections, 176 parameters, $\mu = 2.034$ mm^{-1}, absorption correction, effective transmission max./min. = 0.64/0.53, R_1 $[I > 2\sigma(I)] = 0.0422$, wR_2 $[I > 2\sigma(I)] = 0.1243$, R_1 (all data) = 0.0541, wR_2 (all data) = 0.1331, largest difference peaks 0.837/−0.691 e Å^{-3}. Abridged versions of the crystallographic data of compounds **2a**–**5** are given in the Supporting Information. CCDC-186491 (**1**), CCDC-186494 (**2a**), CCDC-186495 (**2b**), CCDC-186493 (**3a**), CCDC-186492 (**3b**), CCDC-186496 (**4a**), CCDC-186497 (**4b**), CCDC-186498 (**4c**), CCDC-186499 (**4d**), and CCDC-186500 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[15] R. Damico, *J. Org. Chem.* **1964**, *29*, 1971–1976.
[16] C. H. Ng, C. W. Lim, S. G. Teoh, H.-K. Fun, A. Usman, S. W. Ng, *Inorg. Chem.* **2002**, *41*, 2–3.
[17] A. Müller, F. Peters, M. T. Pope, D. Gatteschi, *Chem. Rev.* **1998**, *98*, 239–271.
[18] N. E. Brese, M. O'Keeffe, *Acta Crystallogr. Sect. B* **1991**, *47*, 192–197. The oxidation state of atom i is given by $\sum_j v_{ij} = V$ with $v_{ij} = \exp[(R_{ij} - d_{ij})/b]$. Here b is taken to be a 'universal' constant equal to 0.37 Å, v_{ij} is the valence of a bond between two atoms i and j, R_{ij} is the empirical parameter, and d_{ij} is the observed bond length.

Synthesis of Glycoconjugates

Solid-Phase-Assisted Solution-Phase Synthesis with Minimum Purification—Preparation of 2-Deoxyglycoconjugates from Thioglycosides**

*Janis Jaunzems, Edgar Hofer, Martin Jesberger, Georgia Sourkouni-Argirusi, and Andreas Kirschning**

Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

High-throughput synthesis is one of the major challenges for organic chemistry today and solid supports have played a dominant role in this field.[1] However, disadvantages of solid-phase synthesis are a) the necessity for robust linkers that are stable under various reaction conditions, b) difficulties in the structural analysis of the supported species, as well as c) the requirement that every functional site on the support needs to react. These problems are also found in solid-phase synthesis of oligosaccharides and glycoconjugates. Therefore, various techniques that are capable for performing high-throughput solution-phase synthesis have seen a renaissance lately or have been developed recently. In the context of carbohydrates, important examples of solution-phase synthesis include the use of fluorous phases,[2] functionalized polymers,[3] scavenging protocols based on "capping and tagging" protecting groups,[4] multienzyme loaded beads for sugar nucleotide regeneration,[5] and computer-assisted planning of syntheses in solution.[6]

In the context of general applicability, the development and use of solid-phase-attached reagents is particularly appealing[7] because workup is minimized and the reagent can be employed in excess. The activation of glycosyl bromides with silver ions that are immobilized on a solid phase was first studied by Paulsen and Lockhoff[8] and later by Capillon et al.[9] In conjunction with our research activities in this field, we recently initiated a program that is dedicated to the polymer-assisted solution-phase synthesis of deoxysugar-based glycoconjugates. We demonstrated that glycosyl acetates can be activated by polymer-bound Lewis acids.[3] Here, we describe the high-yielding preparation of oligodeoxysac-

[*] Prof. Dr. A. Kirschning, J. Jaunzems, Dr. E. Hofer
Institut für Organische Chemie
Universität Hannover
Schneiderberg 1b, 30167 Hannover (Germany)
Fax: (+49) 511-726-3011
E-mail: andreas.kirschning@oci.uni-hannover.de
Dr. M. Jesberger, Dr. G. Sourkouni-Argirusi
Institut für Organische Chemie
Technische Universität Clausthal
Leibnizstrasse 6, 38678 Clausthal (Germany)

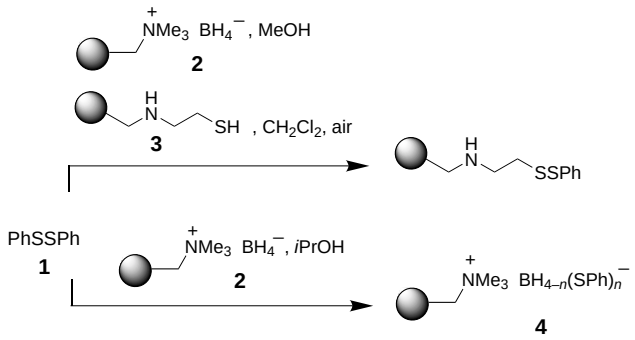
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie. This project is part of the joint initiative "Biologisch aktive Naturstoffe—Chemische Diversität" at the University of Hannover.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  1433-7851/03/4210-1166 $ 20.00+.50/0

charides and glycoconjugates derived therefrom by using thioglycosides as glycosyl donors.[10] Main features of this work are simple workup protocols that for the first time solely rely on the removal of by-products by simple filtration.

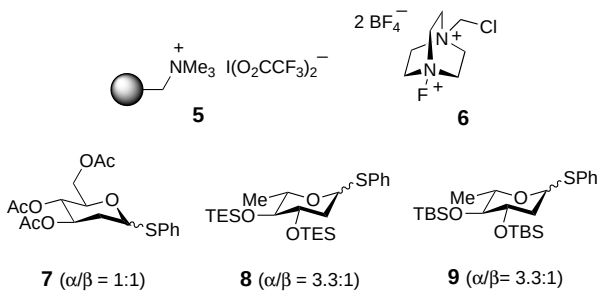
Problematic by-products that always result when employing phenylthioglycosides are thiophenol and diphenyl disulfide (**1**). Therefore, it first became necessary to develop scavenging protocols that allow quantitative removal of these two by-products from the reaction mixture (Scheme 1). Both



Scheme 1. Polymer-assisted removal of diphenyl disulfide (**1**) and thiophenol from solutions.

of our purification methods rely on borohydride exchange resin (BER) **2**.[11] Thus, treatment of **1** with **2** in methanol yields thiophenol (Scheme 1), which, after filtration, is quantitatively scavenged by adding polymer-bound thiol **3** to the reaction mixture under air. However, this reagent requires covalent attachment of 2-sulfanylethylamine to polystyrene.[12] Therefore, we searched for a simpler scavenging protocol. We found that 2-propanol is a solvent that reacts only very sluggishly with **2**. This observation allowed us to make double use of it: First, **2** acts as a reducing agent for **1** and second, it promotes the scavenging of the nucleophilic thiophenol in the presence of 2-propanol to furnish resin **4**. Both methods quantitatively remove thiophenol and **1** from reaction mixtures by simple filtration. Consequently, both protocols are truly of general importance.

In the next phase of the project a glycosidation protocol was envisaged that relies on our newly developed thiophilic polymer-bound reagent **5**[13,14] and alternatively on the fluorinating agent Selectfluor (**6**),[15] which also shows electrophilic and thiophilic properties. Advantageously, the resulting salt is insoluble in most organic solvents including acetonitrile and can be removed by simple filtration. Both reagents are able to activate the phenylthio group in glycosides **7**–**9** (Scheme 2).[16]



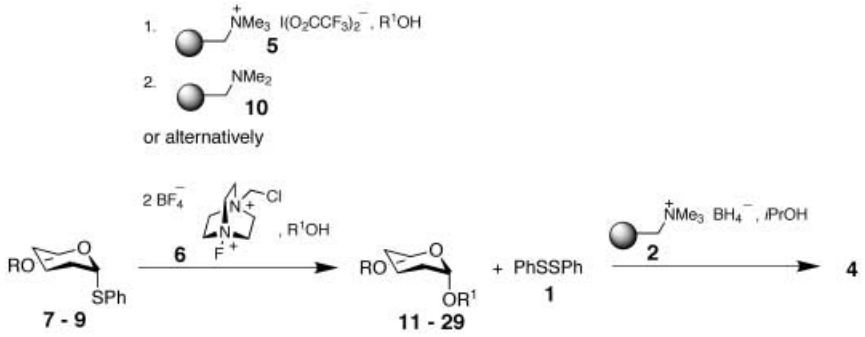
7 (α/β = 1:1) **8** (α/β = 3.3:1) **9** (α/β= 3.3:1)

The glycosidation commonly proceeds in high yields. Consumption of thioglycosides is observed for both reagents within 5 to 10 min. The best solvent for activation of thioglycosides promoted by reagent **5** is THF/CH_3CN in the ratio 1:2 at −50 °C. In CH_2Cl_2, the thioglycosides react at room temperature, but the glycosidation products are formed with reduced purity. The glycosidation is terminated after 2 to 3 h by addition of Amberlyst A-21 (**10**), which scavenges trifluoroacetic acid. In contrast to polymer-bound reagent **5**, acetonitrile is the solvent of choice when employing reagent **6**, and the reaction time is only 10 to 20 min. The workup is identical for both reagents. After filtration and concentration, **1** was sequestered as described in Scheme 1 so that the target glycosides **11**–**29** were isolated with preference for α anomers and free of thiophenol or **1** (Scheme 2). The stereoselectivities[17] observed are in accordance with those obtained for conventional solution-phase glycosidations of 2-deoxythioglycosides when no stereodirecting group is present at C2.[18] In general, the reaction conditions are very mild as is demonstrated for the preparation of highly reactive glycal **14**,[19] acid- and base-labile glycosylated digitoxigenin derivatives **18** and **29,** or the glycosylated decanolide decarestrictine D **19**.[20] Importantly, also the reductive removal of thiophenol and **1** kept the carbonyl groups in glycosides **16**–**19**, **23**, **24**, and **26**–**29** intact.[21]An important demonstration of the efficiency of the scavenging protocol is depicted in Scheme 3. Di-O-benzylated thioglycoside **30** was subjected to the usual glycosidation conditions, and after thorough removal of thio-containing impurities by using our scavenging protocol, the crude product was de-O-benzylated under catalytic hydrogenation conditions (RT, 2 h, 20 bar) to yield glycoside **31**. After one scavenging step the reaction mixture was basically free of any sulfur-containing impurities as judged from the crude ^{1}H NMR spectrum. As the catalytic hydrogenation proceeded only very sluggishly, we repeated the scavenging protocol. Based on the results described here we developed a multistep glycosidation strategy for the synthesis of oligodeoxysaccharides that is solely based on reagents that are removed by simple filtration after use (see Scheme 3).

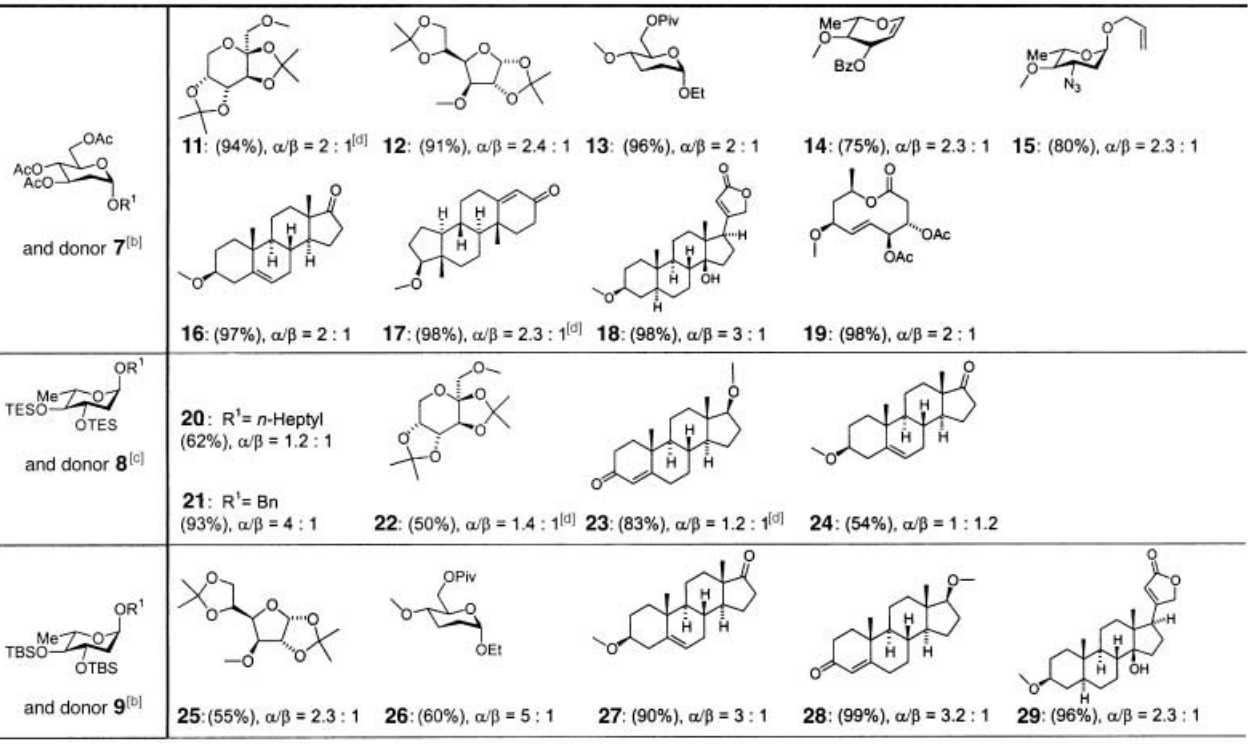
Under the glycosidation conditions and purification protocols 2,6-dideoxythioglycoside **32** and glycals **33** and **34** exclusively furnished α-linked disaccharides **35** and **36**, respectively, in high purity (see Scheme 4). After filtration and proton-induced activation of the enol ether double bond in **35** in the presence of testosterone using polymer-bound sulfonic acid **37**, we obtained glycoconjugate **38**. Likewise, polymer-assisted deprotection of disaccharide **36** followed by activation using β-configured thioglycoside **32** afforded trisaccharide **40** (α/β = 4.3:1), again after the polymer-assisted scavenging of **1**.

In conclusion, we developed a multistep solution-phase approach to 2-deoxyoligosaccharides and glycoconjugates in which workup of each transformation is achieved by simple

  1433-7851/03/4210-1167 $ 20.00+.50/0

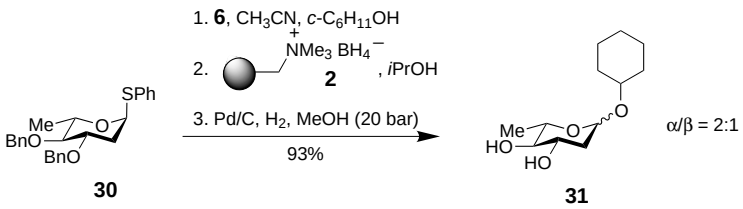


Glycosidation[a] products with R^1 (R^1 refers to glycosyl acceptor R^1OH)



Scheme 2. Glycosidations with minimum purification using thioglycosides **7**–**9**. [a] Only α isomers are depicted; product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated pure products. If not otherwise stated, thioglycosides are employed as anomeric mixtures. [b] Typical reaction conditions for Selectfluor (**6**)-mediated glycosidations: CH_3CN, 0 °C, 10–20 min. [c] Typical reaction conditions when reagent **5** is employed: THF/CH_3CN (1:2), −50 °C, 2–3 h (TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl). [d] The scavenging protocol using reagent **3** was employed (see Scheme 1).

filtration. These steps include removal of thiophenol and diphenyl disulfide (**1**) from solution and activation of thioglycosides and a glycal. Studies towards automated solution-phase glycosidation are in progress in our laboratories.

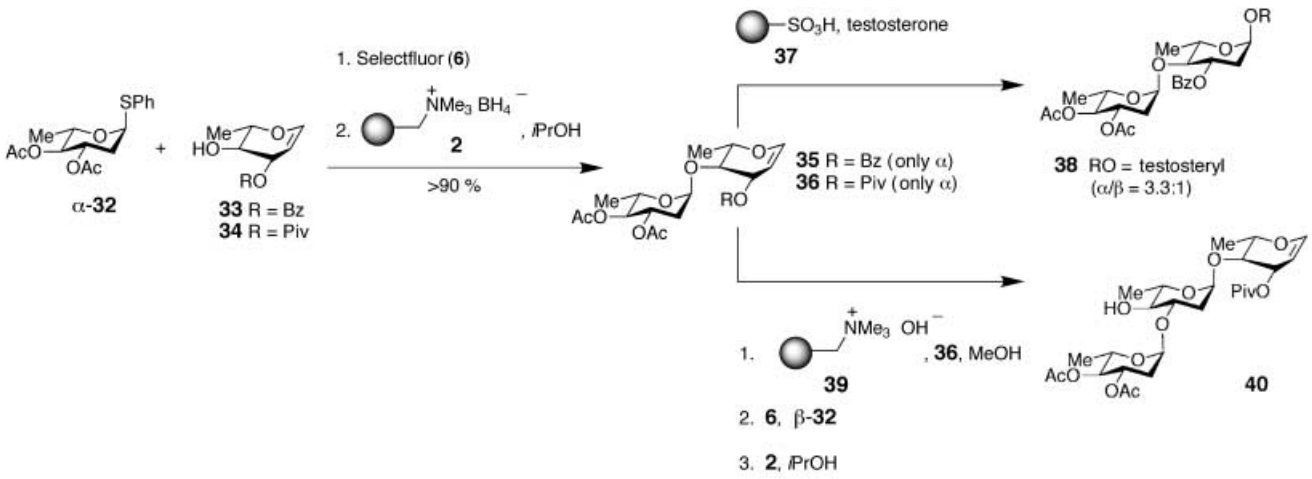


Scheme 3. Multistep polymer-assisted glycosidations. Bn = benzyl.

Experimental Section

Activation of thioglycosides with **5** followed by sequestration of **1**: To a solution of thioglycoside (1 equiv) in absolute THF/CH_3CN (1:2; 50 mL mmol^{-1}) at −50 °C were added the glycosyl acceptor (1.0 equiv) and resin **5** (1 equiv; 2.5 mmol g^{-1} based on the original loading of the commercial resin). The reaction mixture was shaken at −50 °C for 2–3 h at 300 rpm under exclusion of light. The reaction was monitored by TLC and was terminated by addition of Amberlyst A-21 (3 equiv; 0.11 equiv g^{-1} for the

  1433-7851/03/4210-1168 $ 20.00+.50/0



Scheme 4. Preparation of α-linked disaccharides **35** and **36** and their subsequent conversion to glycoconjugate **38** and trisaccharide **40**, respectively. Bz = benzoyl, Piv = pivaloyl.

dry resin). Shaking was continued for 30 min. After filtration, the resin was washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure to yield the desired glycoside along with impurities of **1**. The crude material was taken up in *i*PrOH (50 mL mmol^{-1}) and **2** (100 mg mmol^{-1}; 3 mmol g^{-1} loading) was added. The reaction mixture was shaken overnight at room temperature, filtered, and concentrated under reduced pressure to yield the desired glycoside. Isolation of each anomeric isomer required column chromatography on silica gel.

Activation of thioglycosides with **6** and hydrogenolytic deprotection of benzyl ethers: To an icecold suspension of thioglycoside (1 equiv), glycosyl acceptor (1 equiv), and powdered molecular sieves (1 g mmol^{-1}; 4 Å) in absolute acetonitrile (100 mL mmol^{-1}) was added **6** (1.05 equiv) and stirring was continued for 10–20 min. The reaction was terminated by addition of dry Amberlyst A-21. After filtration through a pad of basic Al_2O_3 the solid material was washed with acetonitrile and the combined filtrates were concentrated under reduced pressure. Again, sequestration of **1** was achieved as described above. In the case of 3,4-di-*O*-benzyl-2,6-dideoxy-1-phenylthio-*arabino*-pyranoside (**30**) sequestration of sulfur-containing impurities was achieved by repeating the scavenging procedure a second time (12 h) followed by filtration and removal of the solvent in vacuo. To the resulting material in methanol (20 mL 0.1 mmol^{-1}) was added a catalytic amount (5 mol %) of Pd/C (10 %). Deprotection was achieved within 2 h under a hydrogen atmosphere at 20 bar. After filtration and removal of the solvent under reduced pressure the deprotected glycoside **31** was isolated as pure material (α/β = 2:1; 93 %).

Received: August 26, 2002
Revised: November 12, 2002 [Z50042]

Keywords: functionalized polymers · glycosidation · separation techniques · solid-phase synthesis · thioglycosides

[1] a) D. E. Bergbreiter, *Med. Res. Rev.* **1999**, *19*, 439–450; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19–46; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17–42; c) F. Balkenhohl, C. von Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2488; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337.

[2] D. P. Curran, R. Ferritto, Y. Hua, *Tetrahedron Lett.* **1998**, *39*, 4937–4940.

[3] A. Kirschning, M. Jesberger, A. Schönberger, *Org. Lett.* **2001**, *3*, 3623–3626.

[4] a) E. R. Palmacci, M. C. Hewitt, P. H. Seeberger, *Angew. Chem.* **2001**, *113*, 4565–4568; *Angew. Chem. Int. Ed.* **2001**, *40*, 4433–4437; b) V. Pozgay, *Org. Lett.* **1999**, *1*, 477–479.

[5] X. Chen, J. Fang, J. Zhang, Z. Liu, J. Shao, P. Kowal, P. Andreana, P. G. Wang, *J. Am. Chem. Soc.* **2001**, *123*, 2081–2082.

[6] a) Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753; b) F. Burkhart, Z. Zhang, S. Wacowich-Sgarbi, C.-H. Wong, *Angew. Chem.* **2001**, *113*, 1314–1317; *Angew. Chem. Int. Ed.* **2001**, *40*, 1274–1277.

[7] Recent reviews on polymer-supported reagents: a) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670–701; *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679; b) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195; c) D. H. Drewry, D. M. Coe, S. Poon, *Med. Res. Rev.* **1999**, *19*, 97–148.

[8] H. Paulsen, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3102–3114.

[9] J. Capillon, A. Richard, R. Audebert, C. Quivoron, *Polym. Bull.* **1985**, *13*, 185–192.

[10] Thioglycosides have proven to be excellent glycosyl donors for the synthesis of deoxyglycoconjugates such as cyclamycin 0: S. Rhagavan, D. Khane, *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581.

[11] A. Kirschning, *J. Prakt. Chem.* **2000**, *342*, 508–511.

[12] S. E. Ault-Justus, J. C. Hodges, M. W. Wilson, *Biotechnol. Bioeng.* **1998**, *61*, 17–22.

[13] In analogy to our earlier work we prepared reagent **5** by oxidative ligand transfer of the mobile ligands in [bis(trifluoroacetoxy)iodo]benzene onto polymer-bound iodide. After washing with dry dichloromethane, this new functionalized polymer is obtained, which can be stored at −20 °C for weeks: a) G. Sourkouni-Argirusi, A. Kirschning, *Org. Lett.* **2000**, *2*, 3781–3784; b) H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare, A. Kirschning, *Org. Lett.* **1999**, *1*, 2101–2104; c) A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem.* **1999**, *111*, 2720–2722; *Angew. Chem. Int. Ed.* **1999**, *38*, 2594–2596.

[14] Proposed structure is depicted based on observations described in ref. [13].

[15] V. Gouverneur, B. Greedy, *Chem. Eur. J.* **2002**, *8*, 766–771.

[16] We screened for thiophilicity among a wide range of polymer-bound halogenate(I) complexes such as $I(OAc)_2^-$, $Br(OAc)_2^-$, $Br(O_2CCF_3)_2^-$, as well reagent mixtures like $Br(OAc)_2^-$/

  1433-7851/03/4210-1169 $ 20.00+.50/0

TMSOTf, $I(OAc)_2^-$/TMSOTf which all failed to efficiently promote glycosidation.
[17] Pure α-configured thioglycoside **31** was glycosidated with testosterone in the presence of reagent **6**. It gave an α/β mixture of anomers in a 2.3:1 ratio, which was exactly the same ratio found when the β-configured thioglycoside **31** was employed.
[18] a) K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434; b) W. R. Roush, X. Lin, J. A. Straub, *J. Org. Chem.* **1991**, *56*, 1649–1655; c) K. Fukase, A. Hasuoka, S. Kusumoto, *Tetrahedron Lett.* **1993**, *34*, 2187–2190.
[19] Selectfluor (**6**) is capable of performing facile nucleophilic addition reactions to glycals: a) M. D. Burkhart, Z. Zhang, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746; b) S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang, C.-H. Wong, *J. Org. Chem.* **1999**, *64*, 5264–5279; c) M. Albert, K. Dax, J. Ortner, *Tetrahedron* **1998**, *54*, 4839–4848; d) M. Albert, B. J. Paul, K. Dax, *Synlett* **1999**, 1483–1485; e) J. Ortner, M. Albert, H. Weber, K. Dax, *J. Carbohydr. Chem.* **1999**, *18*, 297–316.
[20] a) S. Grabley, E. Granzer, K. Hütter, D. Ludwig, M. Mayer, R. Thiericke, G. Till, J. Wink, S. Phillips, A. Zeeck, *J. Antibiot.* **1992**, *45*, 56–65; b) A. Göhrt, A. Zeeck, K. Hütter, R. Hirsch, H. Kluge, R. Thiericke, *J. Antibiot.* **1992**, *45*, 66–73.

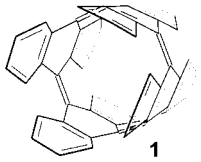
Chiral Picotube Derivatives

Synthesis of a Chiral Tube**

Rainer Herges, Markus Deichmann, Tsuneki Wakita, and Yoshio Okamoto**

The conventional synthesis of belt- and tubelike conjugated compounds[1] and the derivatization of carbon nanotubes[2] at either the sidewalls[3] or at the tip[4] are subjects of recent research because of their potential in supramolecular chemistry[5] and applications in nanotechnology.[4b,d,e] Covalently modified nanotube tips, for example, enable the mapping of chemical and biological functions in atomic probe microscopes. Herein, we report on a combination of both fields, in which the exhaustive alkylation of the rim of a synthetic tubelike structure leads to the formation of a chiral tube.

Compound **1** [Eq. (1)] was synthesized by the dimerizing metathesis of tetradehydrodianthracene.[1c] Since **1** is a small substructure of an armchair carbon nanotube, we named it "picotube". The fully conjugated structure is 8.2 Å in length and 5.4 Å in diameter, and it is the first conventionally synthesized compound that exhibits tubular aromaticity.



(1)

Although unreactive towards oxidation (stable in air up to 450 °C; no reaction with peracids at room temperature) it smoothly reacts under Friedel–Crafts conditions. Alkylation with $CH_3Cl/AlCl_3$ leads to a number of isomers. Treatment with a large excess of *t*BuCl and catalytic amounts of $AlCl_3$, however, only gives two major products (**2** and **3**), in 15 and 14 % yield, which could be separated and isolated by HPLC [Eq. (1)].

The ^{13}C NMR spectra of the two products, which display seven and eight signals, respectively, point to a high symmetry in both isomers. X-ray structural analysis confirms this assumption, with **2** shown to be an octasubstituted picotube with D_4 symmetry (Figure 1).[6] Despite its high symmetry, **2** is chiral because it does not contain any symmetry element other than C_4 and C_2 symmetry axes. The structure of **3** has C_{4h} symmetry and is not chiral. The space-filling model based on an optimized structure derived from density functional theory (DFT) calculations (B3LYP/3-21G, Figure 2) reveals

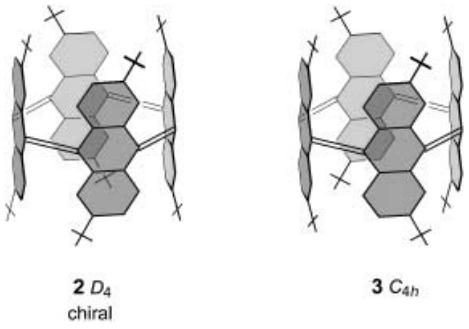


Figure 1. Structures of picotubes **2** and **3**.

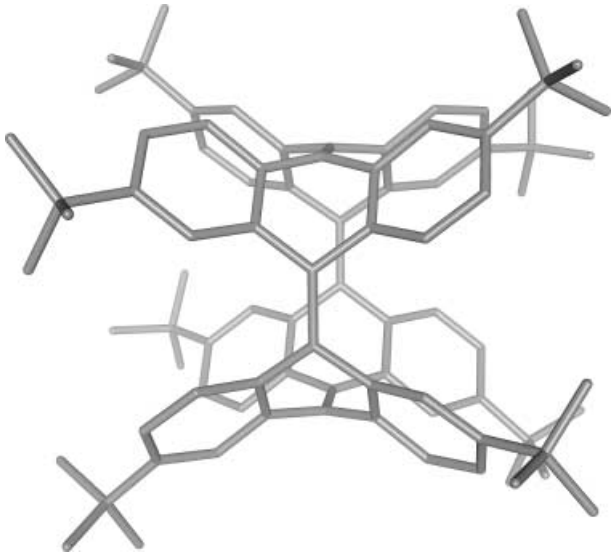


Figure 2. Structure of the chiral tube **2,** as derived by DFT calculations (H atoms are omitted).

[*] Prof. Dr. R. Herges, M. Deichmann
Institut für Organische Chemie
Universität Kiel
Otto-Hahn-Platz 4, 24098 Kiel (Germany)
Fax: (+49) 431-880-1558
E-mail: rherges@uni-kiel.de
Prof. Dr. Y. Okamoto, T. Wakita
Department of Applied Chemistry
Graduate School of Engineering, Nagoya University
Furo-Cho, Chikusa-Ku, Nagoya 464-01 (Japan)
Fax: (+81) 52-789-3188
E-mail: okamoto@apchem.nagoya-u.ac.jp

[**] This work was funded by the Deutsche Forschungsgemeinschaft. We thank Dr. C. Näther for the X-ray analysis.

  1433-7851/03/4210-1170 $ 20.00+.50/0