Carbohydrates as Multifunctional Chiral Scaffolds in Combinatorial Synthesis

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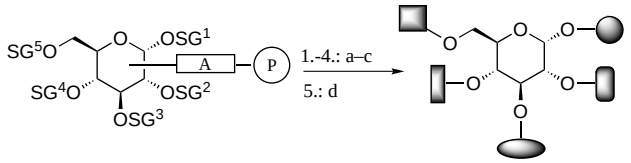
Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

Combinatorial chemistry has incisively changed the search for new biologically active substances in medicinal chemistry.[1] Owing to its roots in solid-phase peptide synthesis,[2] combinatorial reaction sequences were first carried out on solid phase to generate substance libraries (mixtures). Soon, these procedures were supplemented by one-pot reactions on nonprotected polyfunctional molecules[3] and by multicomponent reactions in solution[4] as well as on solid phase,[1f] likewise yielding mixtures of compounds. The parallel synthesis of numerous single compounds is considered most desirable nowadays and can be accomplished by sequential couplings of building blocks to solid-phase-linked substrates, if suitable combinations of protecting and anchoring groups are applied.[1] Alternatively, multiply functionalized scaffolds bound to solid phase are successively and regioselectively coupled with side chains, a procedure which also requires a tailor-made protecting and anchoring group technique.[5]

Besides peptides and amino acid derivatives,[1] functionalized aryl[6] and deoxycholic acid derivatives[7] have been applied in this sense. In comparison to these scaffolds and to the recently described squaric acid templates,[8] carbohydrates constitute templates which not only offer more utilizable functional groups but also numerous, alternatively addressable eligible stereogenic centers. On the basis of a glucose derivative protected as the benyzl ether in 2-, 3-, and 4-position, Hirschmann et al. reported the synthesis of a biologically efficient mimetic of somatostatin.[9]

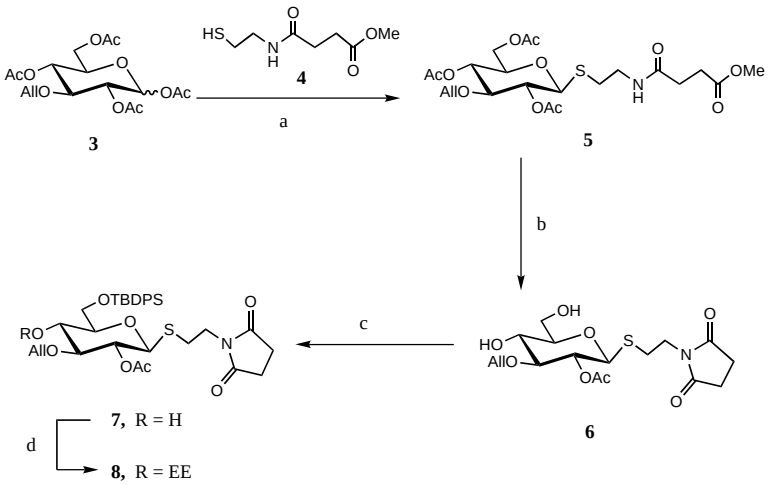
In order to apply carbohydrates as scaffolds in solid-phase combinatorial synthesis, a strategy based on orthogonally stable protecting groups must be developed which allows the selective deprotection at each hydroxylic group. Moreover, all other protecting groups must remain unaffected during the subsequent introduction of the potentially pharmacophoric side chains. Because side chains already linked to the scaffold must also be stable during these condensations, the coupling of the side chain through an ether-type linkage constitutes the most general solution. As a consequence, all protecting groups in **1** except for the one to be removed first must be unaffected under the basic conditions of an ether synthesis. The spectrum of protecting groups, thus limited, is further reduced because benzyl ether protecting and other protecting groups cleavable under heterogeneous conditions are not applicable to solid-phase syntheses. Last but not least, an anchoring group to the solid phase must be found which remains stable during all protecting group and side-chain-introducing manipulations, however, it must also allow the detachment of the undestroyed target compound **2** from the solid phase (Scheme 1).



1 **2**

Scheme 1. Strategy of combinatorial synthesis with carbohydrate scaffolds: SG = protecting group, A = anchor, P = polymer (carrier); a) selective deprotection; b) functionalization; c) washing; d) cleavage of the anchor.

For D-glucopyranose as an example of a carbohydrate template, we have converted the 1,2,4,6-tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranose[10] **3** with succinic acid methyl ester-monocysteamide **4** into the thioglucoside **5** (Scheme 2). Zemplén transesterification resulted in the selective deacetylation in the 4- and 6-position, whereas the 2-*O*-acetyl group in **6** remained unaffected because of the neighboring equatorial substituents.[11] Reaction with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) gave the 6-O-silyl ether **7**, which was treated with ethyl vinyl ether to form the 1-ethoxyethyl (EE) ether group of the completely selectively deprotectable building block **8**.



Scheme 2. Synthesis of carbohydrate scaffolds **8** equipped with orthogonally stable protecting groups: a) $BF_3 \cdot OEt_2$, CH_2Cl_2, 85%; b) NaOMe/MeOH, 90%; c) TBDPS-Cl, DMAP,[12] CH_2Cl_2, 90%; d) $EtOCH{=}CH_2$, pyridinium-*p*-toluenesulfonate, CH_2Cl_2, 98%. TBDPS = *tert*-butyldiphenylsilyl; DMAP = 4-dimethylaminopyridine.

In this concept, the thioglycoside anchor functionalized in the side chain is considered crucial. It must be stable during all

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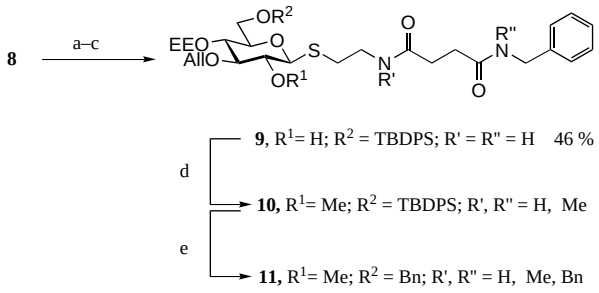
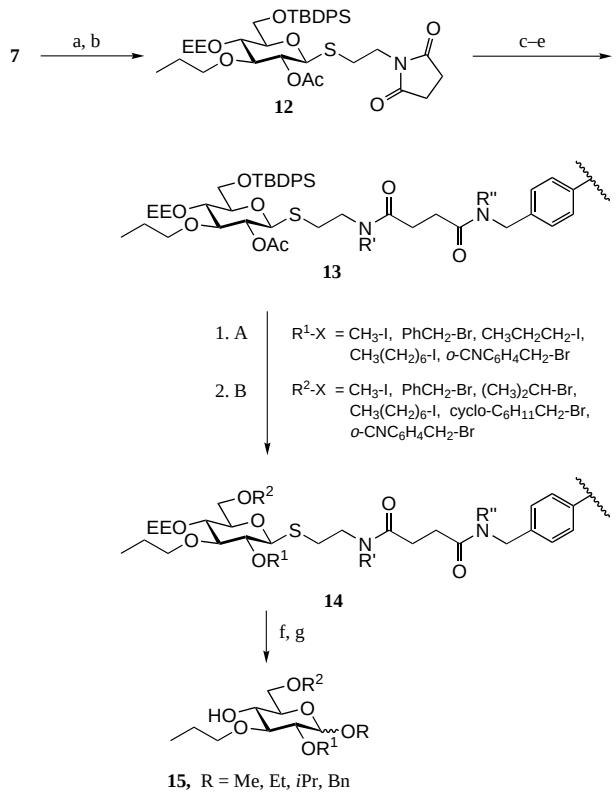
protecting group manipulations and alkylation reactions.[13] In order to prove these prerequisites, the imide **8** was opened and the product condensed with benzylamine.[14] Subsequent treatment with hydrazine hydrate yielded model compound **9** (Scheme 3).



Scheme 3. a) LiOH, THF, H_2O; b) Bn-NH_2, DCC, *N*-hydroxysuccinimide; c) hydrazine hydrate, DMF; d) 1. KO*t*Bu, DMF; 2. CH_3I; 63 %; e) 1. TBAF, THF, 80 %; 2. KO*t*Bu, DMF; 3. BnBr, TBAI, 57 %. Bn = benzyl; DCC = dicyclohexylcarbodiimide.

Deprotonation of potassium *tert*-butylate (3 equiv) in dimethylformamide and reaction with methyl iodide (4 equiv) furnished the 2-*O*-methyl compound **10** without affecting the thioglycoside structure. In this reaction partial N-methylation of the amide grouping occurred. This effect as well as loss during purification are not relevant to the combinatorial synthesis on solid phase. The removal of the TBDPS group by using tetrabutylammonium fluoride (TBAF) and the subsequent formation of the 6-*O*-benzyl ether **11** were achieved again without affecting the thioglycoside. After these test reactions, the carbohydrate scaffold **8** was used for combinatorial multistep reactions. Because preliminary experiments had shown that the cleavage of allyl ethers on solid phase in contrast to the corresponding reactions in solution by treatment with $[(PPh_3)_3RhCl]$,[15] $PdCl_2$,[16] or the zirconocene reagent[17] were accompanied by side reactions, for example hydrogenation, the allyl ether **7** was converted into the propyl ether using diimine[18] prior to the introduction of the 1-ethoxyethyl group to give **12** (Scheme 4). The imide group was opened and coupled to aminomethyl polystyrene (AMPS, 1.3 mmol g^{-1}) to yield the solid-phase anchored carbohydrate scaffold **13** (0.6 mmol carbohydrate per gram resin).[19] In parallel syntheses, deprotonations were carried out using KO*t*Bu (10 equiv) while shaking at room temperature, and alkylations were performed by using alkyl halide (30 equiv) in dimethylformamide at room temperature within 2 h. The TBDPS group was removed by using TBAF (10 equiv) in tetrahydrofuran at room temperature within 16 h. After every reaction, the resin was washed several times with dimethylformamide, toluene, and the solvent of the subsequent conversion (Scheme 4).

After combinatorial substitution at the 2- and 6-position, the thioglycoside anchor was cleaved by using a 1M solution of bromine in dichloromethane (3 equiv) under addition of 2,6-di-*tert*-butyl-pyridine (7.5 equiv). To this mixture, a 25 % solution of the alcohol to be glycosylated (20 equiv) in dichloromethane containing tetraethylammonium bromide (1 equiv) and cyclohexene (6 equiv) were added. The products were isolated after filtration, elution from a short column of silica, and evaporation of the volatile components in high vacuum. They are obtained as mixtures of anomers (α:$\beta \approx$ 5:1) and are identified by analytical HPLC and FAB mass spectrometry. The anomeric configuration was determined for compounds **15** (R = R^1 = Me, R^2 = Bn), **16a**, and **17a** from ^{1}H NMR spectra (400 MHz). As a rule, the purity of the mixtures of anomers according to RP-HPLC ranges from 75 to 95 %; the remainder of di-*tert*-butyl-pyridine formed the major component of the impurities. Out of an array of 28 compounds **15** (Scheme 4), 25 mixtures of anomers **15** have been obtained after five reactions on solid phase and the subsequent glycosylation reaction in overall yields of 30 to 80 %.



Scheme 4. a) KOOCN=NCOOK, AcOH, MeCN; b) $EtOCH{=}CH_2$, TsOH; c) LiOH, THF/H_2O; d) *N*,*N*′-diisopropylcarbodiimide/*N*-hydroxysuccinimide/AMPS, CH_2Cl_2; e) hydrazine hydrate, DMF; A: 1. KO*t*Bu, DMF; 2. R^1-X; B: 1. TBAF, THF; 2. KO*t*Bu, DMF; 3. R^2-X; f) 1. pyridinium-*p*-toluenesulfonate; 2. Br_2, CH_2Cl_2, 2,6-di-*tert*-butylpyridine; g) R-OH, cyclohexene, Et_4NBr. AMPS = aminomethylpolystyrene; Ts = *p*-toluenesulfonyl.

The diversity of the single compound libraries is expanded by involving the 4-position. The EE-protecting group was removed by a transacetalization reaction (Scheme 5). The fourth variable substituent can be introduced into these compound libraries not only by alkylations to give compounds of type **16**, but also by reactions with isocyanates to form **17**. The developed strategy thus provides the generation of libraries of large diversity already on the basis of the four functional groups used so far. By means of carbamate formations, branched and heterocyclic substituents can be introduced, in particular, if not only commercially available reagents are applied. The inclusion of the fifth function and

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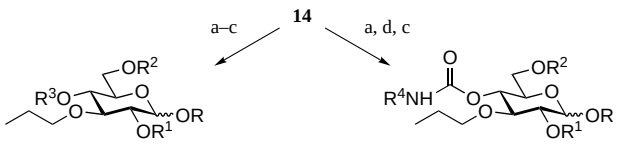

16a, $R^1 = R^3 = Bn$; $R^2 = R = Me$

16b, $R^1 = Bn$; $R^2 = Me$, $R^3 = CH_2COOtBu$, $R = Me$

17a, $R^1 = R^2 = Bn$; $R^4 = 2\text{-}CF_3C_6H_4$; $R = Me$

17b, $R^1 = R^2 = Bn$; $R^4 = 4\text{-}CNC_6H_4$; $R = Me$

Scheme 5. a) MeOH, dioxane, pyridinium-*p*-toluenesulfonate; b) KO*t*Bu, DMF, R^3-X; c) Br_2, CH_2Cl_2, 2,6-di-*tert*-butylpyridine, ROH, Et_4NBr, CH_2Cl_2, cyclohexene; d) R^4-NCO, DMAP, dioxane.

translation of the combinatorial synthesis to stereoisomers of the glucose scaffold (galactose, mannose) are presently under investigation.

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[1] Reviews: a) L. A. Thomson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17; c) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; d) A. Netzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev.* **1997**, *97*, 449.

[2] a) "Highlight of Modern Biochemistry": A. Furka, F. Sebesteyn, M. Asgedom, G. Dibo, *Proc. 14th Int. Congress Biochem.*, Utrecht (Netherlands), **1988**, *5*, 47; b) H. M. Geysen, R. H. Meloen, S. J. Barteling, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998; c) R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.

[3] a) T. Carell, E. A. Winter, A. Bashir-Hashemi, J. Rebek, Jr., *Angew. Chem.* **1994**, *106*, 2159; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2161; b) H. An, L. L. Cummins, R. H. Griffey, R. Bharadwaj, B. D. Haly, A. S. Fraser, L. Wilson-Lingardo, L. M. Risen, J. R. Wyatt, P. D. Cook, *J. Am. Chem. Soc.* **1997**, *119*, 3696.

[4] M. Goebel, I. Ugi, *Tetrahedron Lett.* **1995**, *36*, 6043.

[5] Siehe z.B.: M. Patek, B. Drake, M. Lebl, *Tetrahedron Lett.* **1994**, *35*, 9169.

[6] See for example: J. Green, *J. Org. Chem.* **1995**, *60*, 4287.

[7] a) G. Wess, K. Bock, H. Kleine, M. Kurz, W. Guba, H. Hemmerle, E. Lopez-Calle, K.-H. Baringhaus, H. Glombik, A. Ehnsen, W. Kramer, *Angew. Chem.* **1996**, *108*, 2363; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2222; b) R. Boyce, G. Li, H. P. Nestler, T. Suenaga, W. C. Still, *J. Am. Chem. Soc.* **1994**, *116*, 7955.

[8] P. A. Tempest, R. W. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 7607.

[9] R. Hirschmann, K. C. Nicolaou, S. Pietramico, J. Salvino, E. M. Lealy, W. C. Shakespeare, P. S. Spengler, P. Hamley, A. B. Smith, T. Reisine, K. Raynor, C. Donaldson, W. Vale, L. Maechler, R. M. Freidinger, C. D. Strader, *J. Am. Chem. Soc.* **1993**, *115*, 12550; siehe auch: K. C. Nicolaou, J. I. Trujillo, K. Chibale, *Tetrahedron* **1997**, *53*, 8751.

[10] K. Takeo, T. Nakaji, K. Shinmitsu, *Carbohydr. Res.* **1984**, *133*, 275.

[11] Z. Szurmai, A. Liptak, G. Snatzke, *Carbohydr. Res.* **1990**, *200*, 201; M. Kaltenbach, Dissertation, Universität Mainz, **1994**.

[12] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

[13] This is a crucial point, because thioglycosides can be activated by electrophiles, in particular, alkylating reagents: a) H. Lönn, *Carbohydr. Res.* **1985**, *139*, 115; b) H. B. Meregata, V. R. Kulkarni, D. Ravi, G. V. Sharma, B. V. Rao, G. B. Reddy, *Tetrahedron* **1992**, *48*, 545; c) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503.

[14] F. Weygand, D. Hoffmann, E. Wünsch, *Z. Naturforsch. B* **1966**, *21*, 426.

[15] E. J. Corey, J. W. Suggs, *J. Org. Chem.* **1973**, *38*, 3224.

[16] T. Ogawa, S. Nakabayashi, T. Kitajima, *Carbohydr. Res.* **1983**, *114*, 225.

[17] Y. Hanzawa, H. Ito, T. Taguchi, *Synlett* **1995**, 299.

[18] S. Hünig, H. R. Müller, W. Thier, *Angew. Chem.* **1965**, *77*, 368; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 271.

[19] The loading was determined by elemental analysis (sulfur) and gravimetrically.

[20] For a thioglycoside anchor in oligosaccharide synthesis and an alternative cleavage: J. Rademann, R. R. Schmidt, *Tetrahedron Lett.* **1996**, *37*, 3989.

Evidence for Selective Association of Tetrahedral BO_4 Units with Na^+ and of Trigonal BO_3 Units with H^+ in Dehydrated Zeolite B-ZSM-5 from Solid-State NMR Spectroscopy**

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The study of local structure and bonding in zeolites is of fundamental interest for a better mechanistic understanding of their catalytic function. One of the unresolved questions regards the stabilization of boron in different coordination states in the zeolite framework. Typically, only boron centers tetrahedrally coordinated by O atoms (B[4]) are present in hydrothermally synthesized zeolites, some of which are transformed into trigonally coordinated centers (B[3]) when the organic structure directing agent is removed by calcination.[1–4] The negative charge of the $BO^-_{4/2}$ groups in as-synthesized zeolites is balanced by sodium and quaternary ammonium cations, while the counterions in the calcined zeolite are Na^+ and H^+. Quantum-chemical calculations suggest that the bond between boron and protonated framework oxygen atoms is much weaker than the Al–O bond in Al-O(H)-Si groups; hence, the existence of three-coordinate boron centers in calcined zeolites is plausible.[5]

Here we show that in calcined B-ZSM-5 the B[3] units selectively associate with H^+, and the B[4] units with Na^+ counterions. The zeolites were prepared hydrothermally with tetrapropylammonium (TPA) cations as structure-directing agent. The content of sodium cations in the zeolites was varied by changing the gel composition in the syntheses. The TPA was subsequently removed from the zeolite channels by calcination, and the samples were dehydrated in vacuum at elevated temperature. The ^{11}B MAS NMR spectra of the calcined and dehydrated samples show that the B[4]/B[3] ratio increases with increasing sodium content, and this suggests that sodium cations are associated with B[4] units (MAS = magic angle spinning; rotation of the probe in a magnetic field).

More direct evidence for this association can be obtained on the basis of the heteronuclear dipole interaction between

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