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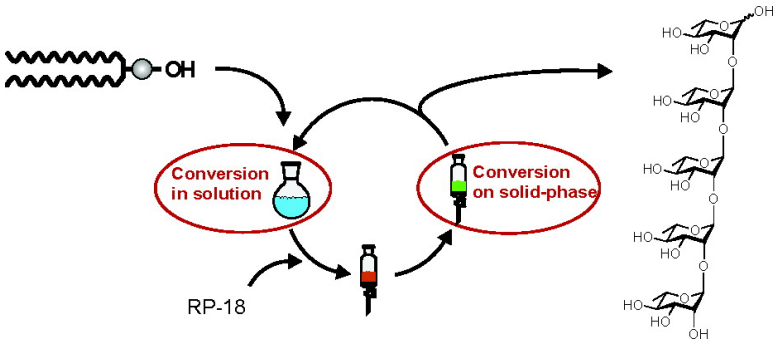

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Hydrophobically Assisted Switching Phase Synthesis: The Flexible Combination of Solid-Phase and Solution-Phase Reactions Employed for Oligosaccharide Preparation

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Polymer-supported oligosaccharide synthesis has been for more than three decades one of the most challenging fields for solid-phase chemistry.[1] Though progress has been made by the introduction of mildly activated carbohydrate donors[2] and rugged linker chemistries,[3] the reported yields for repetitive glycosylations are still unsatisfactory and the preparation of oligosaccharide-based libraries has hardly ever been realized.

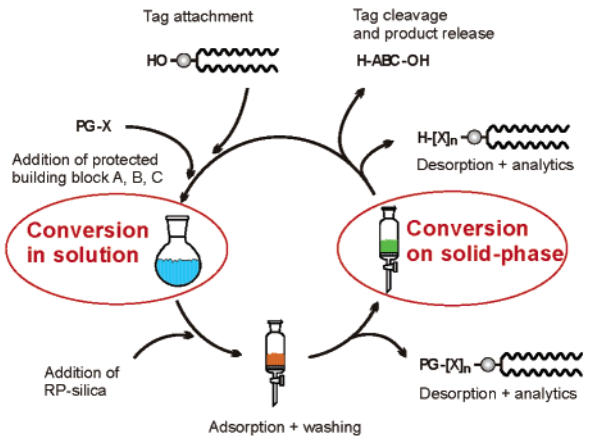
Recently, several protocols have been developed exploiting the ease of solution-phase reactions together with preserving the advantages of facilitated isolation procedures. Examples include the oligosaccharide assembly on soluble (PEG) polymers,[4] fluorous tags,[5] and thermoresponsive polymers.[6]

None of these methods has yet been satisfactory in respect to yields, costs, and above all flexibility. Hydrocarbon-coated silica supports are the inexpensive standard material in reversed-phase chromatography. Hindsgaul et al. have described a hydrocarbon tag for the preconcentration of samples by solid-phase extraction (SPE).[7] This system, however, required subsequent workup by column chromatography and thus was never used for repetitive reaction steps. We envisioned that a quantitative and fully reversible anchor molecule would enable the hydrophobically assisted switching of phases (HASP) between solution and the solid support in each single step (Scheme 1). Therefore, the completion and quantitative reversibility of the adsorption and desorption processes of various hydrophobic anchor molecules were investigated.

The retention of single hydrocarbon chains (C_8−C_{20}) depended strongly on the polarity and charge of the headgroup, rendering these molecules unsuitable as high-yielding and reversible tags. On the contrary, a sufficiently long, hydrophobic double chain anchor (C_{18}) was both adsorbed and desorbed quantitatively. This effect was independent of the size and polarity of the headgroup, at solvent compositions permitting the quantitative removal of nontagged byproducts without leaching the products.[8a] On the basis of these findings, the double chain HASP anchor **5** was designed, a benzyl-type linker for releasing the final product (Scheme 2).[8b] Compound **5** could be prepared from (±)-epichlorohydrin and 1-octadecanol as inexpensive starting materials. As an optimal sorbent combining high yields with high loading capacity, hydrophobically end-capped RP-18 silica with 120 Å pores and a grain size of 50 μm was selected.

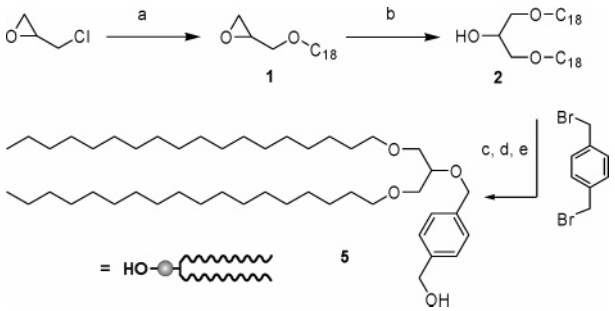
The α-1,2-*trans*-glycosidic linkage found in the oligorhamnanes has been a popular model linkage in polymer-supported glycosylations, allowing direct comparison with previous results.[2a,3a,4a] Glycolipids containing the L-rhamnopyranosyl-α-1,2 linkage[9] displayed a surprisingly strong cytotoxic effect, the mechanism of which has yet to be elucidated.[10] For efficient donor preparation,

Scheme 1[a]



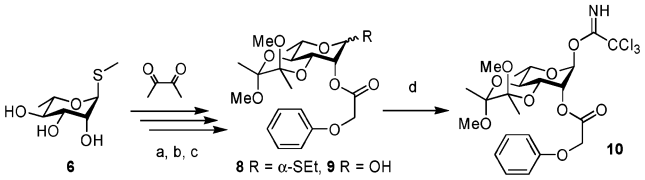
[a] In hydrophobically assisted synthesis by switching phases, a suitable hydrophobic anchor allows high-yielding reactions both in solution and attached to a solid support.

Scheme 2[a]



[a] Reagents and conditions: (a) 1-Octadecanol, Aliquat 336, 50% NaOH, cyclohexane, 98%; (b) 1-octadecanol, BF_3·OEt_2, DCM, 25 °C; (c) NaH, abs. THF/abs. toluene, 90 °C, 71%; (d) NaOAc, DMF, 100 °C, 99%; (e) NaOMe, DCM/MeOH, $KHSO_4$, 90%.

Scheme 3[a]



[a] Reagents and conditions: (a) TMOF, *p*-TosOH, MeOH, 95%; (b) phenoxyacetic anhydride, DMAP, pyridine, 96%; (c) NBS, acetone/water, 85%; (d) trichloroacetonitrile, DBU, DCM, 73%.

the 3,4-hydroxy groups of thiorhamnoside **6** were protected selectively employing the butane-2,3-diacetal (BDA) protecting group (Scheme 3).[11] This enabled protection of the 2-position with

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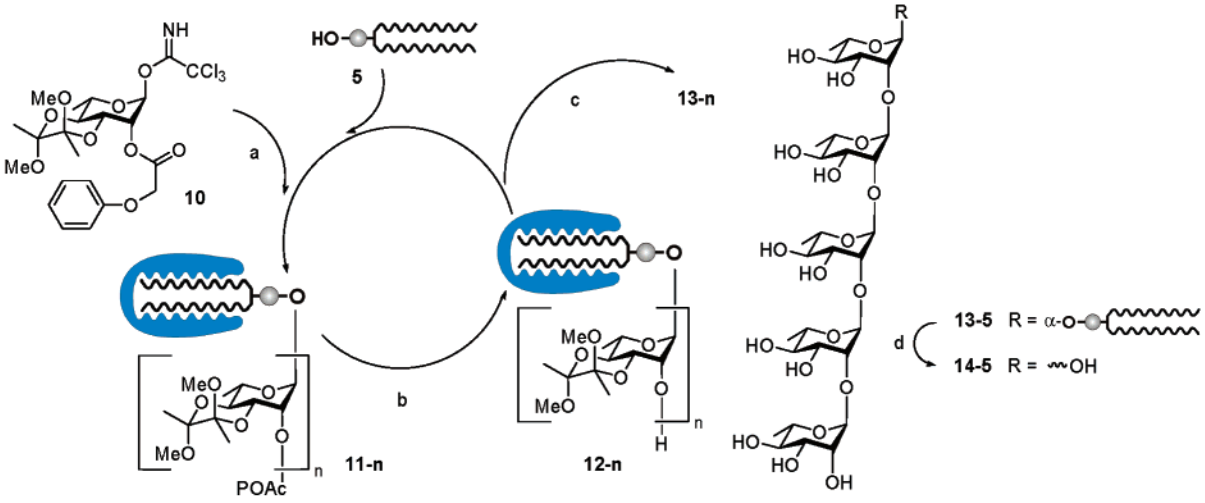
Scheme 4[a]



[a] Reagents and conditions: (a) 2 equiv of donor **10**, 0.05 equiv of TMSOTf, abs. DCM, Ar, > 95%; (b) NaOMe, MeOH/water, > 92%; (c) TFA/water > 72%; (d) 2 mol % Pd/C, H_2, MeOH, > 93%.Total yield (12 steps) 45%, i.e. an average of 94% per step.

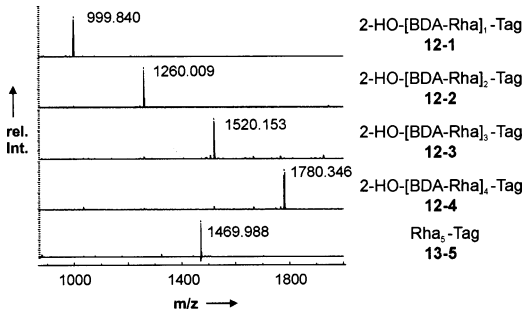


Figure 1. During HASP synthesis the full conversion of synthetic steps can be monitored by MALDI-TOF-MS. Raw products of **12-n (n = 1−4)** and **13**−**5**.

an α-directing and orthogonally cleavable phenoxyacetyl group.[12] The trichloroacetimidate donor **10** was furnished in multigram amounts and employed in repetitive glycosylations in HASP synthesis.

Glycosylations of HASP anchor **5** were conducted in DCM with an excess of the donor **10** (2 equiv) and TMSOTf (0.05 equiv) as Lewis acid. Direct monitoring of the glycosylations by TLC and MS indicated full conversion (Figure 1). The C-18 silica support was added to the reaction mixture, solvents were evaporated, and all unlabeled material was easily removed by washing with MeOH/water (80%). Subsequently, compounds **11-n** were deprotected while attached to the solid phase. Again completion of the reaction could be followed by TLC and MS. Finally, $MgSO_4$ was added to the solid support, and the clean products were released with DCM. Each reaction step was finished after 30 min with 94% average yield (Scheme 4).

BDA-protecting groups were removed on the solid support to obtain compounds **13-n**, and hydrogenolytic removal of the tag furnished the oligosaccharides **14-n**. Contrary to solid-phase glycosylations, the HASP system allowed high yields in repetitive glycosylation/deprotection cycles at the scale of 0.1 mmol with no obvious limitation for further up-scale. All steps were conducted on parallel synthesis equipment and thus can be automated.

Hydrophobically assisted glycosylation reactions open a new access to oligosaccharide and glycoconjugate libraries; a complex library of rhamnolipids has been prepared meanwhile and is currently under biological investigation. Evidently, the concept can be extended to general organic synthesis. In addition, the described hydrophobic anchor permits the direct immobilization of the synthesized molecules on compartmentalized hydrophobic surfaces and their incorporation in membrane models, liposomes, and cell membranes.

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Supporting Information Available: Detailed experimental procedures, yields, and fully assigned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) HASP-tag **5** remains quantitatively adsorbed to the hydrophobic support when rinsing the support with MeOH/water (95/5), whereas the highly lipophilic carbohydrate methyl-2,3,4,6-tetra-*O*-benzyl-glucoside was found to be completely rinsed out of the support by washing with MeOH/water (85/15). (b) A hasp is a device for fastening, like the fastening of tagged products to RP silica by means of the HASP method.
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