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Report

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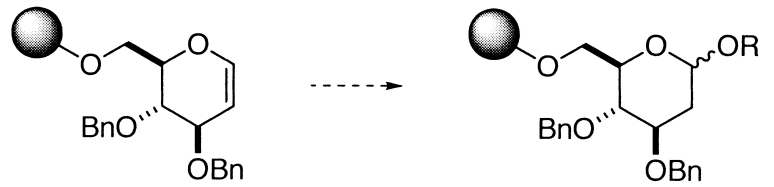

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Reports

Simple Glucal-Based Linker for the Immobilization of Alcohols on Solid Support

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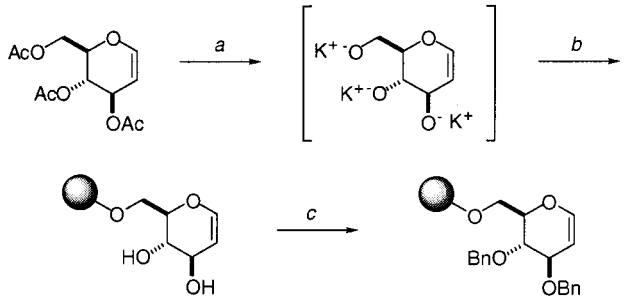
Introduction

Combinatorial synthesis is now accepted as a powerful tool for drug discovery.[1] Solid-phase organic synthesis in particular has taken a place alongside traditional medicinal chemistry in lead generation, as a result of increased throughput and minimization of time-consuming purification and isolation steps. As the interest in combinatorial synthesis has grown, it has been accompanied by increased demand for new, versatile linkers. Ideally, these linkers should be designed to withstand a variety of reaction conditions, should be introduced and loaded in a minimal number of steps, and should be readily available from commercial sources in large quantities. Existing methods for the attachment of alcohols to the solid phase involve multiple steps,[2] result in sensitive linkages,[3] or are only accessible through expensive precursors.[4] Herein, we report a convenient, inexpensive linker for the immobilization of alcohols that overcomes these limitations. The linker-derivatized resin can be synthesized in two steps from Merrifield resin and tri-*O*-acetyl-*d*-glucal (Scheme 1)[5,6] and allows single-step loading and release of substrate under very mild conditions.

Loading of Merrifield Resin with Linker

The synthesis of the linker is outlined in Scheme 1.[7] The inexpensive and commercially available tri-*O*-acetyl-*d*-glucal undergoes spontaneous deacylation in the presence of strong base, and the anion that is generated can be trapped with Merrifield's chloromethylpolystyrene resin in a one-pot procedure. This avoids the preparation or use of the very hygroscopic glucal alcohol, which is not as readily available as the peracylated derivative. The resin-bound glucal can then be reacted with excess potassium *t*-butoxide and benzyl bromide to yield resin bearing the fully protected linker, which appears to be indefinitely stable when stored at room temperature. It should also be noted that the linker can be utilized without passivation of the secondary hydroxy groups because these remain on the resin after cleavage and do not affect the cleaved product composition.[8] However, protection ensures that the resin is relatively inert to reaction with any reagents in solution. While we have focused on benzyl protecting groups, in principle other functionality could be employed.

Scheme 1. Synthesis of the Glucal Linker[a]



[a] (a) KO^{t}Bu, DMA, 50 °C, 1 h. (b) (i) Chloromethyl polystyrene, 50 °C, 36 h; (ii) wash consists of water, DMF, THF, hexanes; air-dry. (c) (i) KO^{t}Bu, BnBr, DMF, 60 °C; (ii) wash consists of DMF, THF, hexanes; air-dry.

In a representative preparation, KO^{t}Bu (0.973 g, 7 mmol) was added to tri-*O*-acetyl-*d*-glucal (0.637 g, 2.35 mmol) in THF (8 mL) at room temperature. After the mixture was stirred for 1 h, chloromethylpolystyrene (0.5 g, 0.94 mmol/g)[9] was added and the mixture was warmed to 50 °C. After it was stirred for 30 h, the resin was filtered and washed with DMF (2 × 10 mL), DMF/H_2O (2 × 10 mL), DCM (3 × 10 mL), and hexane (3 × 10 mL), then dried under reduced pressure to afford 0.561 g of light-yellow resin. The IR spectrum (KBr pellet) of a resin sample showed a strong O−H stretch and no carbonyl signal. The resin was resus-

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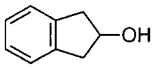
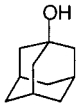
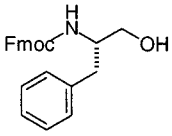
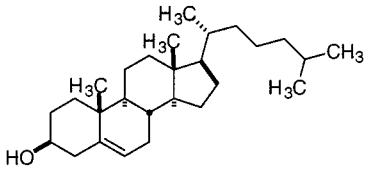
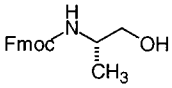
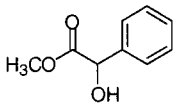
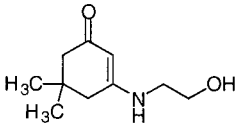
Table 1. Recovered Yields of Loaded and Cleaved Alcohols from the Glucal Linker[a]

Entry	Alcohol	Yield (%)	Entry	Alcohol	Yield (%)
1		71	5		70
2		77	6		32 (69)[b]
3		75	7		92
4		80			

[a] All products were found to be >95% pure by ^{1}H NMR. Conditions are as described in the text. [b] The parenthetical yield was obtained using THF as solvent.

pended in THF (8 mL) and treated with KO^{t}Bu (5 equiv) and stirred for 1 h at room temperature. Benzyl bromide (5.5 equiv) was added, and the resin was stirred for 20 h at 60 °C. The resin was filtered and washed with DMF (3 × 10 mL) and hexane (3 × 10 mL), then dried under reduced pressure to yield 0.596 g of yellow resin, which exhibited no O−H stretch by IR. On the basis of mass gain, this represents a loading of 0.73 mmol/g based on the initial loading of 0.94 mmol/g for the commercial chloromethylpolystyrene.

Loading of Alcohols on the Glucal Linker

All alcohols were loaded under identical conditions (Table 1). The alcohol was introduced as a 0.4 M solution in DCE, with half an equivalent of PPTS in relation to the alcohol. The molar quantity of alcohol in relation to resin active sites was varied from 3 to 7 equiv with no apparent changes in the yields; however, the 0.4 M alcohol concentration was found to be optimal. Although anhydrous dichloroethane is not necessary to effect loading, it was found to increase the yield in most cases.

Primary, secondary, and tertiary alcohols were all successfully loaded onto the glucal linker, with varying yields based on cleavage. To determine if the lower yield for entry 6 (31%) reflected poor loading or cleavage, all resins were weighed after loading and cleavage. Loading yields based on weight were virtually identical to recovered yields, indicating that low yields result from poor loading. Cholesterol, the alcohol employed in entry 6, has limited solubility in DCE, and the use of THF as an alternative solvent led to increased loading and recovery (69%).

Cleavage of Alcohols from the Glucal Linker

A variety of cleavage conditions were explored to obtain the highest yields purities of the cleaved products. Although cleavage with 95% TFA/H_2O has been reported for similar linker systems,[4] this led to partial cleavage of the linker and concomitant reduction in product purity. After exploration of a range of TFA/CH_2Cl_2 admixtures, 10% TFA in CH_2Cl_2/CH_3OH (9:1) was found to provide good recovery in 30−60 min. While cleavage is more rapid with higher concentrations of TFA, cleavage of the linker itself from the resin becomes problematic with >10% v/v TFA, requiring subsequent purification of the released alcohol.

In all procedures, the resin was combined in a dry screw-cap vial with a DCE solution containing alcohol (0.4 M, 5.0 equiv) and PPTS (0.2 M, 2.5 equiv) and shaken for 1 h. The reaction was then heated to 65 °C for 20 h. After the mixture was cooled to room temperature, the resin was filtered, washed with DMF (3×), CH_2Cl_2 (3×), and hexanes (3×), and dried in air. Cleavage is effected by suspending the resin in 10% TFA/CH_2Cl_2−CH_3OH (9:1) and shaking at room temperature for 30 min. The cleavage solution is then isolated by filtration and evaporated. The residue is extracted into AcOH/CH_3CN (1:1), frozen, and lyophilized to yield the alcohol.

Conclusions

We have successfully demonstrated the use of a glucal-based linker for the immobilization of alcohols for solid-phase organic synthesis. The linker is prepared from an inexpensive, commercially available glucose derivative, and the linker-derivatized resin can be synthesized in two steps from chloromethylpolystyrene. The alcohols are introduced in one step and subsequently cleaved under mild acidic conditions. Thus, this linker compares favorably to the analogous dihydropyranmethanol linker, which is both expensive and irregularly available.[4] The extensive literature associated with glycal chemistry suggests that it should also be possible to immobilize amines, carboxamides, and carboxylic amides using this linker.[4,6] In addition, the linker has the potential to be recycled, a characteristic that we are currently exploring.

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productive discussions and DuPont Pharmaceuticals for a graduate fellowship to R.S.D.

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(5) Glycals are well-established intermediates in the solution- and solid-phase synthesis of carbohydrate derivatives. However, with the exception of dihydropyranmethanol (ref 4), they have not been previously exploited for the transient immobilization of alcohols.

(6) For reviews of the extensive history of glycals in carbohydrate synthesis, see the following. (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (b) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685−695.

(7) Abbreviations: DCE, dichloroethane; DCM, dichloromethane; DMF, dimethyl formamide; PPTS, pyridinium *p*-toluenesulfonate; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

(8) Dahl, R. S.; Finney, N. S. Unpublished results.

(9) Merrifield resin with a nominal loading of 0.94 mmol/g was used in this procedure (Aldrich, 1% cross-linked). Other sources of resin have performed equally well in other preparations.

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