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A Fluorinated Selenide Linker for Solid-Phase Synthesis of *n*-Pentenyl Glycosides

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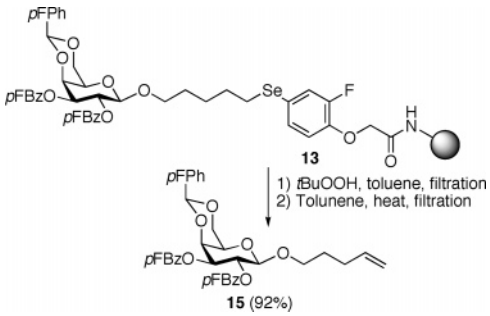
ABSTRACT



A fluorine-labeled selenide linker for installing terminal isolated olefins has been synthesized in high overall yield. The resin-bound linker could be glycosylated both with glycosyl trichloroacetimidates and glycosyl fluorides. The linker did not decompose after oxidation with *t*BuOOH but underwent *β*-elimination when it was subjected to heat. This allowed the released *n*-pentenyl glycoside 15 to be isolated in excellent yield and purity after filtration.

Development of novel linkers and protective group protocols, together with advances in automation and monitoring techniques for solid-phase oligosaccharide synthesis, is of major importance for the discovery of new biologically active glycoconjugates.[1] The choice of linker for tethering the first monosaccharide to the polymeric support is crucial in planning oligosaccharide synthesis, since the linker has to be orthogonal to the protective groups employed.[2] The linker should also be stable under the different conditions used during synthesis and permit a wide range of reagents. Finally, release from the support should proceed in high yield using mild conditions that do not damage the final product.

Use of organoselenium compounds for effective selenoxide elimination to install olefin functionalities is well-established in solution-phase synthesis.[3] Selenium-based linkers have previously been successfully applied with highly activated substrates for introduction of conjugated double bounds[4a−t] and for preparation of allyl esters[5a−c] on release from solid supports. However, use of this methodology for installing terminal isolated olefins is rare,[6] because primary alkyl phenyl selenoxides are rather stable and therefore less prone to undergo syn elimination.[7] We anticipated that the stability of the primary alkyl phenyl selenoxide would be advantageous in solid-phase synthesis, provided that the resin-bound selenoxide exhibited sufficient stability to permit removal of the oxidizing reagent prior to releasing the product from the solid support.

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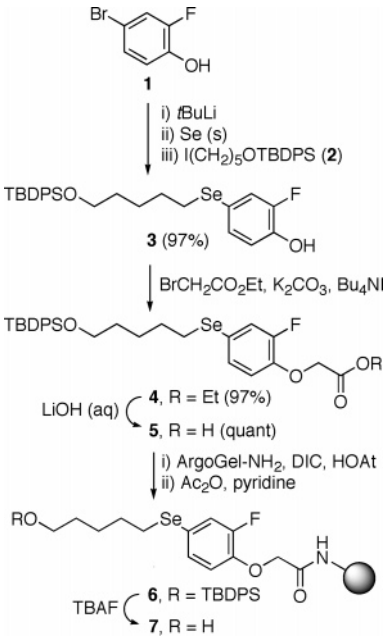
Selenoethers are essentially chemically inert toward a broad range of reagents, such as hard Lewis acids, alkylating agents, strong bases, nucleophiles, and reductive conditions, but they react readily with soft Lewis acids, radicals and peroxides.[3] Thus, the selenoether linkage is compatible with a wide range of reagents and protective group protocols commonly used in oligosaccharide synthesis. The present paper describes the preparation of a fluorine-labeled selenium-based linker (compound **5**, Scheme 1) and its use in solid-phase synthesis of *n*-pentenyl glycosides and analysis of resin-bound intermediates with gel-phase ^{19}F NMR spectroscopy. In recent years, gel-phase ^{19}F NMR spectroscopy has been established as a simple, effective, and nondestructive method for gaining both quantitative and qualitative information on reaction steps performed on solid phase.[8]

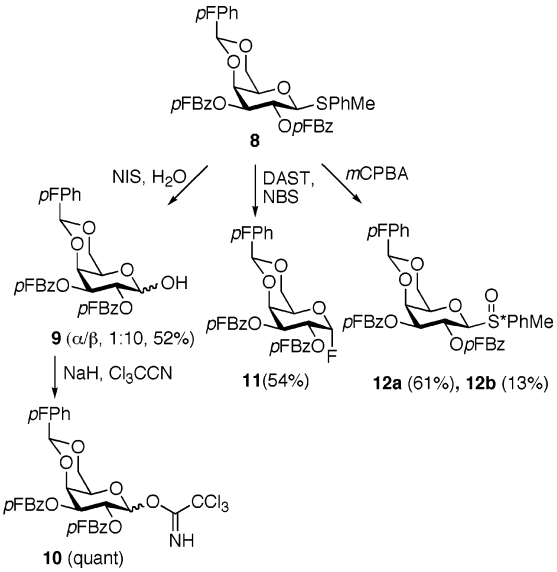
Synthesis of linker **5** started with lithiation of compound **1**, followed by addition of elemental selenium to access the corresponding selenide anion. This was used directly to substitute *iodo*-alkyl derivative **2**[6] to afford the selenoether **3** in excellent yield (97%) in a one-pot reaction (Scheme 1). The phenol functionality of **3** was then alkylated with ethyl bromoacetate using potassium carbonate as a base in the presence of tetrabutylammonium iodide, which gave compound **4** in 97% yield. Saponification of **4** with aqueous LiOH provided the desired linker building block **5** in 94% overall yield starting from **1**. The carboxy functionality of **5** was subsequently attached to amino-functionalized ArgoGel resin using standard peptide coupling conditions to give resin **6**. Since the commercial resin also had some hydroxy functionalities, the resin was capped with acetic anhydride after completing the amide bond formation. Subsequent

Scheme 1. Synthesis of Selenide Linker Resin **7**



cleavage of the silyl protective group with TBAF gave the hydroxy-functionalized resin **7**. To establish conditions for glycosylations it was decided to investigate the glycosylation of selenide linker **7** with three powerful and commonly employed types of glycosyl donors that are activated by hard Lewis acids: glycosyl trichloroacetimidates, glycosyl fluorides and glycosyl sulfoxides (Scheme 2).[9] The glycosyl

Scheme 2. Synthesis of Galactosyl Donors **10**−**12**



donors were prepared from the previously described thiogalactoside donor **8**,[10a] which is protected with fluorine-labeled protective groups to allow analysis with gel-phase ^{19}F NMR spectroscopy.[8,10a−c] Hydrolysis of the thiocresyl

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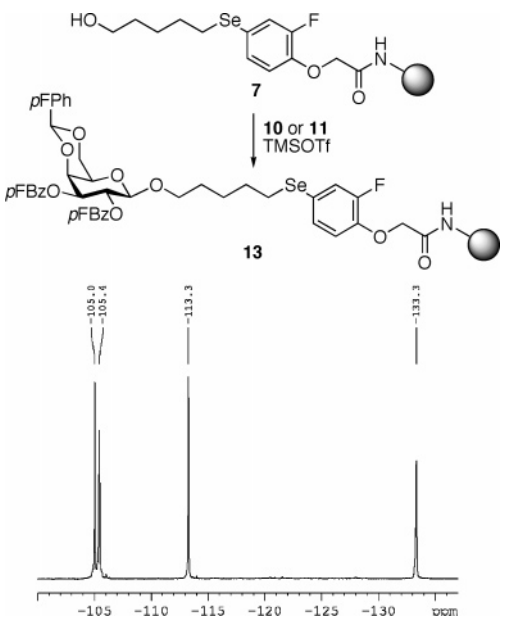
group of **8** was carried out by treatment with NIS in aqueous acetonitrile to give the reducing galactosyl derivative **9** in 52% yield. Subsequent treatment of **9** with sodium hydride in trichloroacetonitrile and dichloromethane furnished the glycosyl trichloroacetimidate **10** as a crude product, which was used directly for glycosylation. Treatment of **8** with DAST and NBS at −10 °C gave galactosyl fluoride derivative **11** (54%). The corresponding sulfoxide diastereomers **12a** and **12b** were obtained in 61 and 13% yields, respectively, by treatment of **8** with *m*CPBA in dichloromethane at −78 °C.

Glycosylation of resin **7** with 5 equiv of glycosyl trichloroacetimidate **10** was carried out at room temperature using dichloromethane as a solvent in the presence of TMSOTf (0.6 equiv) as a promoter to give the resin-bound galactoside **13** (Scheme 3). Integration of the ^{19}F NMR resonances from

Scheme 3. Solid-Phase Glycosylations of Resin **7** with **10** and **11**[a]



[a] The Gel-phase ^{19}F NMR spectrum was recorded in $CDCl_3$ with $CFCl_3$ (δ 0.00 ppm) as an internal standard after glycosylation of **7** with **10**.

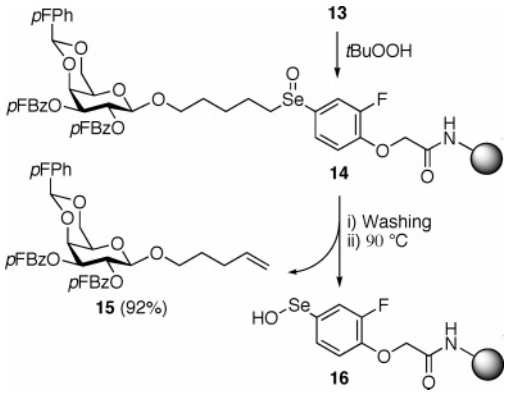
the two *p*-fluorobenzoyl groups (−105.0 and −105.4 ppm, respectively), the 4,6-*O*-*p*-fluorobenzylidene group (−113.3 ppm), and the linker signal (−133.3 ppm) revealed that the glycosidic linkage was installed in quantitative yield.

Glycosyl fluoride **11** was significantly less reactive than the corresponding trichloroacetimidate, and a variety of reaction conditions were evaluated in an attempt to optimize the glycosylation. An initial effort to glycosylate resin **7** with **11** under activation with $BF_3{\cdot}Et_2O$ was unsuccessful and did not produce any glycosylation product. Glycosylation of **7** with **11** using TMSOTf (0.6 equiv) resulted in only ∼20% conversion of resin **7**, and it was found that an excess (4 equiv) of the promoter TMSOTf was required for the reaction to proceed. Unexpectedly, these conditions resulted in partial cleavage of one of the benzoyl groups when the reaction was carried out in dichloromethane. However, a mixture of dichloromethane and ether as the solvent prevented the cleavage of the benzoyl group. Thus, glycosylation of resin **7** with **11** (4 equiv) in a mixture of dichloromethane and ether at room temperature gave resin **13** in quantitative yield as determined by integration of the resonances in the ^{19}F NMR spectrum.

An attempt to glycosylate resin **7** with glycosyl sulfoxide **12a** at room temperature was also carried out. Sulfoxide **12a** was activated at −78 °C with triflic anhydride in the presence of collidine in dichloromethane, and the mixture was subsequently transferred to resin **7**, which was allowed to react at ambient temperature. However, analysis with ^{19}F NMR spectroscopy revealed that no glycosylation product had been formed. Instead, degradation of the linker was observed and further glycosylations with **12a** were not performed.

Cleavage of **13** was initially examined using aqueous hydrogen peroxide or *m*CPBA as oxidizing agents. As detected by ^{19}F NMR spectroscopy, these conditions only resulted in formation of byproducts that were unable to undergo syn elimination.[11] However, treatment of selenide resin **13** with anhydrous *t*BuOOH in toluene for 4 h resulted in complete conversion of the selenide to the corresponding selenoxide derivative **14** (Scheme 4). As determined by ^{19}F

Scheme 4. Oxidation of Resin **13** and Thermal *syn*-Elimination of Selenoxide Resin **14**



NMR spectroscopy, no ^{19}F NMR resonance originating from resin **13** (−133.3 ppm, Figure 1, spectrum a) remained and a new resonance derived from selenoxide resin **14** appeared at −130.2 ppm (Figure 1, spectrum b). Interestingly, the resonance from one of the *p*-fluorobenzoyl groups, presumably the protective group at the C-2 position, was split into

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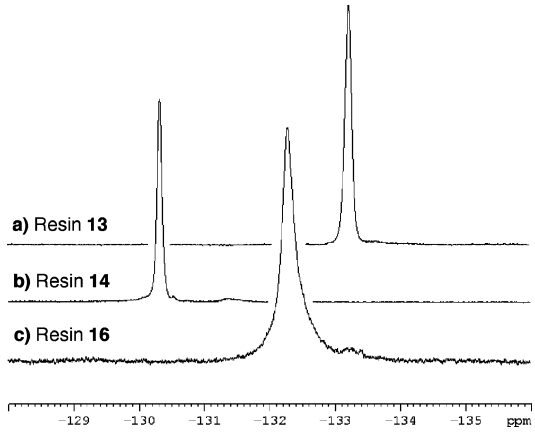

Figure 1. Linker region in ^{19}F NMR spectra of **13**, **14**, and **16**. Gel-phase ^{19}F NMR spectra were recorded in $CDCl_3$ with $CFCl_3$ (δ 0.00 ppm) as an internal standard.

a doublet most likely due to the proximity to the stereochemical center of the selenoxide. Importantly, no decomposition of selenoxide resin **14** was detected when the resin was subjected to oxidation at room temperature overnight. Since no spontaneous syn elimination had occurred, the reagent could be removed by washing the resin prior to cleavage, which is an advantage since the oxidizing agent could potentially harm the double bound of the released alkene. Subsequently, selenoxide resin **14** underwent syn elimination when it was heated in toluene at 90 °C for 4 h to provide pure *n*-pentenyl glycoside **15** in 92% yield based on the initial loading capacity of the resin. The β-galactosidic linkage of **15** was assured by ^1H NMR spectroscopy ($^3J_{1,2}$ = 8.0 Hz). Inspection of the ^{19}F NMR spectrum of resin **16** revealed a complete cleavage, since the resonance from the selenoxide resin **14** at −130.2 ppm had disappeared and only a resonance derived from what is assumed to be resin-bound selenic acid **16** at −132.4 ppm was detected (Figure 1, spectrum c). *n*-Pentenyl glycosides are well known as glycosylation reagents and have been extensively used in construction of complex oligosaccharide structures.[12] In addition, the *n*-pentenyl functionality can be further oxidized to the corresponding aldehyde or carboxylic acid to provide a handle for bioconjugation to carrier proteins,[13] or microchips used in high-throughput screening.[14a,b]

In conclusion, an efficient route for preparation of a hydroxylated selenide linker **5** in three steps and 94% overall yield from commercially available starting materials has been developed. The versatility of the linker for installing terminal isolated olefins was demonstrated by solid-phase synthesis of a pentenyl glycoside. It was found that the primary hydroxyl group of the linker could be glycosylated with glycosyl trichloroacetimidates or glycosyl fluorides, both of which were activated with TMSOTf. Furthermore, the linker carries a fluorine atom that served as an internal analytical marker throughout the synthesis. Thus, employing glycosyl donors that carry fluorine-labeled protective groups allowed both the yield and the stereochemical outcome to be conveniently determined directly on the resin with gel-phase ^{19}F NMR spectroscopy. After oxidation with *t*BuOOH, the selenoxide resin **14** was stable at room temperature, but it decomposed when it was subjected to heat. Since no reagents were required in the mild cleavage step, potential side-reactions and impurities from the reagent could be avoided, and the released *n*-pentenyl glycoside **15** was isolated in excellent yield and purity without purification.

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Supporting Information Available: Spectral data and experimental procedures for compounds **3**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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