the same goal, phospholipidic probes carrying a photoactivable carbene precursor on the ω-position of the fatty-acid chain. However, most of the crosslinking involved Glu 70, which should be situated at the lipid–water interface in vesicles.[9] Their results might reflect the extensive disorder of the phospholipidic matrix and of the probe itself above the phase-transition temperature. In our case, the formation of an ordered bilayer structure due to the transmembrane "immobilization"[3, 12, 13] of the probe and to the concomitant use of cholesterol has led to an excellent selectivity for the photolabeling on the transmembrane domain of GPA in vesicles.

As judged by Engelman's three-dimensional model for the dimeric transmembrane domain of GPA, Ala 82 could also be potentially crosslinked by the probe. There could be two possible explanations for the lack of radioactivity associated with Ala 82. Either Phe 78 could generate a steric hindrance as neighbor residue on the preceding α-helical turn or, alternatively, a photochemical reaction had occurred on Ala 82 but a retro-aldol type degradation of the α-coupling product formed might have followed. Such a degradation of α-coupling products of amino acid derivatives, especially in the case of alanine, has been observed by us[14] and had already been noted by Schöllkoff et al.[15] In contrast, methionine is functionalized at positions (CH_3 and CH_2) located α to the sulfur atom.[14, 16] Valine should be attacked at the β-position ($(CH_3)_2CH$) in lipid bilayers. Since the radius of the reactive sphere for a benzophenone is estimated to be 3 Å around the carbonyl oxygen atom,[17] the α-position of valine could not be attacked. Therefore, no such degradation was observed in the case of the valine or methionine adducts.

For the first time, to our knowledge, the center of the transmembrane domain of a protein has been selectively functionalized. Although *photoaffinity-labeling* methods have been successfully employed to determine receptor–ligand binding sites,[18] there has been no success so far in the site-selective photolabeling of proteins *within* phospholipid bilayers. Despite the limitation cited above for the use of our probe, this method could be useful for the study of transmembrane domains of other proteins.

Experimental Section

Probe **1c** was synthesized from the diiodo precursor **1d**, according to the procedure employed for the synthesis of the dideuterated analogue **1b**[19] except for the use of $^3H_2$ in place of $^2H_2$. For the tritium-labeled compound **1c**, the radiochemical purity was checked by thin-layer chromatography on silica gel and $CHCl_3$/MeOH/H_2O (65/25/4) eluent and by HPLC using a Zorbax NH_2 column (eluent MeCN/MeOH/phosphate buffer pH 4.8 (50/40/10)). The former method showed the purity to be 100%; the latter 98.6%. **1c**: Specific radioactivity 40 Ci mmol^{-1}; ^{3}H NMR (320 MHz, $CDCl_3$/CD_3OD (9/1)): $\delta = 6.90$ (single sharp peak); UV/Vis (MeOH): λ_{max} (ε) = 200 (30000), 223 (14500), 295.5 nm (22500 M cm^{-1}). **1c** was stored as a stock methanolic solution at $-20\,^{\circ}C$.

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A Direct and Efficient α-Selective Glycosylation Protocol for the Kedarcidin Sugar, L-Mycarose: $AgPF_6$ as a Remarkable Activator of 2-Deoxythioglycosides**

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Without the stereodirecting ability of 2-substituents, strategies to prepare 2-deoxyglycosides selectively in high α- or β-anomeric forms rely heavily on indirect sequences from glycals or latent 2-deoxysugars.[1–3] As such, these require a subsequent reductive step that would be unsuitable for many

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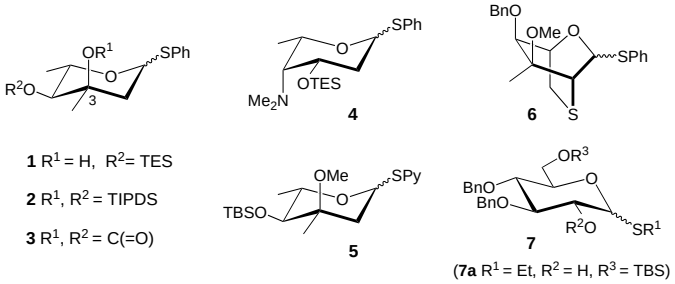
complex natural products and for any viable total synthesis program. A case in point is that of the kedarcidin chromophore and its α-linked 2,6-dideoxysugars, L-mycarose **1**–**3** and L-kedarosamine **4** (Scheme 1).[4–6] In particular, direct and

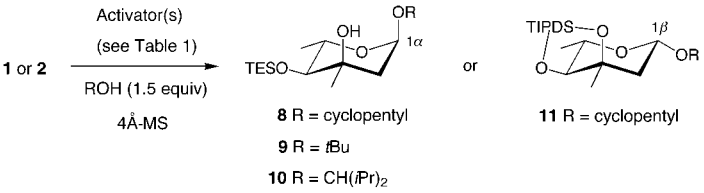


Scheme 1. TES = triethylsilyl, TIPDS = 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Py = 2-pyridyl.

efficient α-selective methods for *allo*-configured systems **1**–**3** and **5** are especially difficult to realize.[3] For example, to overcome the lack of success in the α-glycosylation of erythromycin A, Toshima, Tatsuta and co-workers developed the masked 2,6-anhydrothiopyranoside **6** of L-cladinose.[3c,d] As notable exceptions, the groups of Martin and Nicolaou have reported direct procedures that are partially α-selective in CH_3CN; namely, *N*-bromosuccinamide activation of **3** and $Cu(OTf)_2/CuO$ (Tf = triflate = OSO_2CF_3) activation of **5**.[3e,g] Herein we describe a direct, potent, and mild protocol to efficiently generate α-L-mycarosides from **1** or **2** by using $AgPF_6$, which is exemplified by the α-mycosylation of an advanced kedarcidin substructure **14**. Although the present method is applicable to other 2-deoxy systems, such as the synthesis of α-L-kedarosaminides from **4**, normal 2-oxythioglycosides **7** remain inert to $AgPF_6$ and can be used as acceptors armed with strategic anomeric linkages.

Based on previous work, stable α- and β-thioglycosides **1**, **2**, and **4** were readily prepared in anomerically pure form.[5b] Preliminary model studies on **2** and literature precedent revealed that any protection of a 3-hydroxy group in a 2-deoxy-*allo*-pyranoside apparently confers enough *A* strain to suppress the normally preferred kinetic mode of α-anomeric (axial) attack.[1–3] As a consequence, various activation methods that could tolerate the unprotected tertiary 3-OH in thioglycoside **1** were investigated.[7]

Although the thiophilic activators PhSOTf and PhSeOTf gave encouraging results in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),[7a,b] it was found that Me_2S^+-$SMe\cdot^-OTf$ (DMTST) and $Me_2S^+SMe\cdot^-BF_4$ (DMTSB) generated **8** from **1** in acceptable yields and α-selectivity (Scheme 2, Table 1).[7c] Although changes in solvent at various temperatures gave similar stereochemical results, there was a distinct difference in the α/β anomer ratio between the two reagent systems (Table 1, entries 1 and 2). Based on this observation and to make the reaction more amenable to low temperatures for DMTSB (Table 1, entry 2), the effect of adding thiophilic additives with different counteranions was investigated. Remarkably, the addition of silver salts not only gave acceptable reaction times even at $-80\,^\circ C$, but gave a stereochemical outcome for DMTSB similar to that found for



Scheme 2. Complementary and direct α- and β-glycosylation protocols for L-mycarose: Realization of α-selectivity by using the partially protected system **1**. 4 Å MS = molecular sieves (4 Å).

Table 1. Stereoselective glycosylation of cyclopentanol with phenyl thioglycosides **1** or **2** (Scheme 2).[a]

Entry	Activator(s)	Solvent	T [°C]	t [h]	Yield [%]	α/β ratio[b]
1[c]	DMTST	Et_2O	0	2	71	1.3
2[c]	DMTSB	Et_2O	0[d]	4	84	2.5
3	DMTST/AgOTf	Et_2O	−80	15	61	1.5
4	DMTSB/AgOTf	Et_2O	−80	15	64	1.5
5	AgOTf	Et_2O	−28	7	81	2.0
6	$AgBF_4$	Et_2O	−40	7.5	85	2.1
7	$AgPF_6$	Et_2O	0[e]	1.5	85	4.5
8	$AgSbF_6$	Et_2O[f]	0	2.5	71	4.8
9	$AgPF_6$	CH_2Cl_2	0	0.5	88	7.7
10	$AgPF_6$	CH_2Cl_2	−60	13	79	7.7
11	β-**1**/$AgPF_6$	CH_2Cl_2	0	2	88	14.0
12	α-**2**/$AgPF_6$	CH_2Cl_2	0	0.5	87	**11** (3.9)
13	β-**2**/$AgPF_6$	CH_2Cl_2	0	2	83	**11** (6.7)
14[g]	**2**/Cp_2HfX_2	CH_2Cl_2[h]	−50	1	82	**11** (β-only)

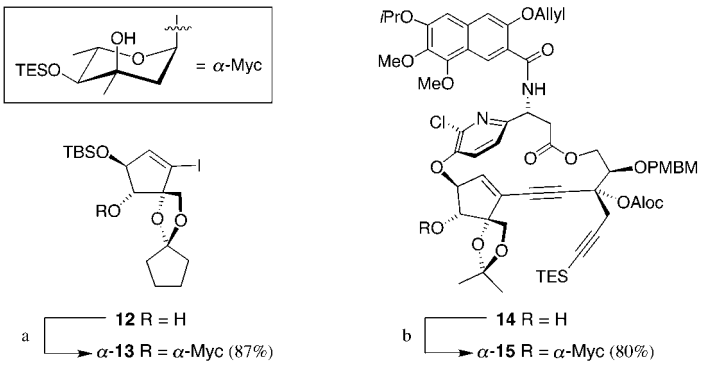
[a] Except for entries 11–14, reactions were performed using α-**1** with the activating system (3–4 equiv) and DTBMP (4.0 equiv); yields are reported relative to **8**; see text for abbreviations. [b] Determined on the crude mixture by 500 MHz ^1H NMR integration of anomeric signals. [c] At $-28\,^\circ C$: Et_2O, CH_2Cl_2, and mixtures with CH_3CN, gave $\alpha/\beta \approx 1.4$ (for DMTST) and $\alpha/\beta \approx 2.5$ (for DMTSB). [d] Poor conversion below $0\,^\circ C$. [e] 90% complete at $-60\,^\circ C$ after 13 h, $\alpha/\beta = 4.8$. [f] In CH_2Cl_2, $\alpha/\beta = 5.6$. [g] Glycosyl fluoride ($\alpha/\beta = 1{:}1.9$) derived from **2** ($\alpha/\beta = 1{:}5.4$) and $Cp_2HfCl_2/AgClO_4$ (1:2) used.[2c, 8] [h] Best in THF, $\alpha/\beta = 1{:}1.7$.

DMTST (Table 1, entries 3 and 4). Indeed, the sole use of a silver salt was sufficient for a rapid reaction, and $AgPF_6$ gave α/β ratios approaching 8:1 in favor of the α-anomer (Table 1, entries 9 and 10). Although the temperature did not greatly influence the stereochemical outcome, a change of solvent from Et_2O to CH_2Cl_2 with $AgPF_6$ gave an improvement in both the reaction rate and the α/β ratio (Table 1, cf. entries 7 to 10).

Additional experiments revealed that a superior α-selectivity resulted when the β-thioglycoside of **1** was used (Table 1, cf. entries 9 and 11) and, remarkably, both anomeric forms of the bulky thioglycoside **2** with cyclopentanol gave an α-rich mixture of **11** when treated with $AgPF_6$ (Table 1, entries 12 and 13). These latter results were surprising since extensive studies with fluorophilic complexes and a glycosyl fluoride derived from **2** only ever gave β-selectivity, for example $[Cp_2HfCl_2]/AgClO_4$ gave β-**11** exclusively and complements the α-selective $AgPF_6$ method for this sugar-type (Table 1, cf. entries 11 and 14).[2c, 8] Control experiments further revealed that α-**1** and α-**2** reacted more quickly with $AgPF_6$ than their β-counterparts. Also, in the absence of alcohol, pure α-**2** rapidly epimerized to form a β-rich mixture ($\alpha/\beta = 1{:}10$, $0\,^\circ C$, 2 h), whereas β-**2** retained its anomeric integrity. Collectively, these findings suggest that the activa-

tion of α-**1** and α-**2** involves the intermediacy of an oxocarbenium salt and that the α-stereoselectivity conceivably results from an anionic species adopting a pseudo-equatorial position. For β-forms, the reversible formation of a less reactive $AgPF_6$–thiosugar complex that directly undergoes S_N2 displacement can be envisaged.

At this juncture it was imperative to determine if this method could be applied to more demanding glycosyl acceptors (Scheme 2, 3). As such, **12** and **14** were assembled through

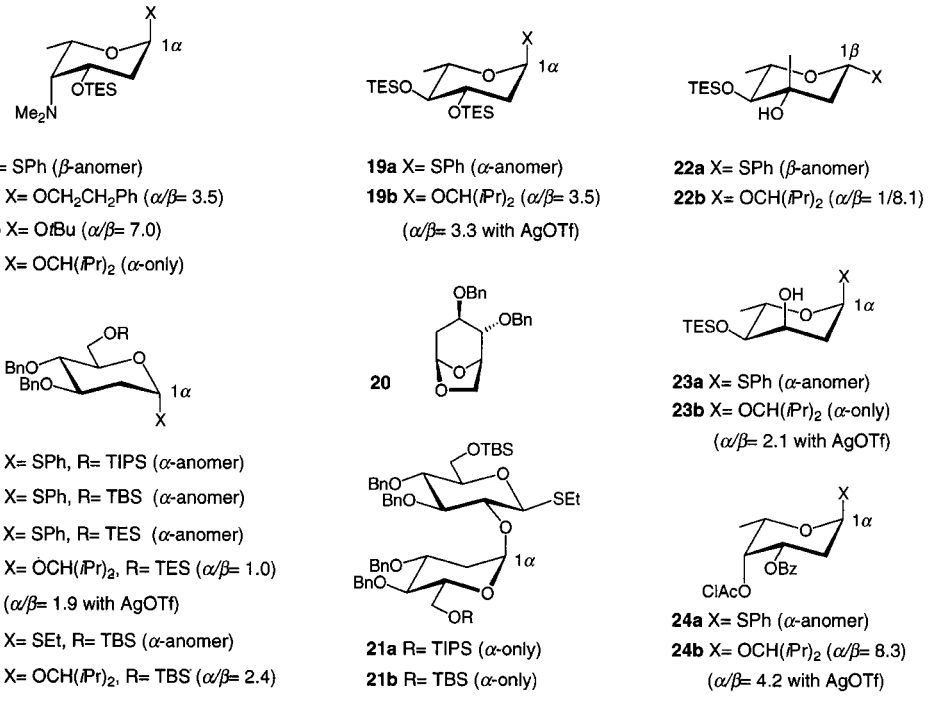


Scheme 3. Direct and efficient α-mycosylation of hindered kedarcidin subunits by using $AgPF_6$/DTBMP in CH_2Cl_2 at 0 °C. a) α-**1** (1.8 equiv), 1.5 h; b) β-**1**, (6.0 equiv), 6 h (97% based on recovered **14**). PMBM = *p*-methoxybenzyloxymethyl, Alloc = allyloxycarbonyl.

the elaboration of recent synthetic work on the kedarcidin chromophore.[5a] Gratifyingly, the application of α-**1**/$AgPF_6$/DTBMP to *t*BuOH, iPr_2CHOH, and **12**, generated the respective α-mycarosides **9**, **10**, and **13** exclusively in excellent yields (87–99%). To further confirm the α-selectivity induced by $AgPF_6$, the reactions that gave **9** and **10** were repeated with AgOTf, and significant amounts of β-products resulted ($\alpha/\beta \approx 2.5$). Most importantly, the efficiency of $AgPF_6$/DTBMP was clearly demonstrated in the construction of the formidable chromophoric subunit α-**15** from **14** (Scheme 3).[9] In this case, it was vital to use the less reactive β-anomer of **1**, since with complex systems similar to **14**, a large excess of α-**1** and $AgPF_6$ tended to give products with two sugar units attached in 10–15% yield. In addition, as long as the terminal acetylene in **14** was protected with a TES group, the possibility of undesired side reactions due to silver complexation was not a problem.[10]

The present glycosylation conditions (Table 1, entry 9) were then applied to other 2-deoxy systems, especially to the L-kedarosamine derivative **4** and to the *ribo*-configured (*allo*-like) L-digitoxose derivative **23** (Scheme 4).[3b] In brief, all phenyl and ethyl 2-deoxythioglycosides tested so far with $AgPF_6$/DTBMP (3–6 equiv) and an alcohol acceptor (2–3 equiv) afforded their corresponding 2-deoxyglycoside **16**–**24** in 75–99% yields, with low to high α-selectivity (except for olivomycarose derivative **22**) at 0 °C in CH_2Cl_2 over 0.5–2 h. In comparison, reactions performed with AgOTf remained 15–60% incomplete, even with excess reagents (8–20 equiv) at room temperature over 5 h, and typically gave lower α-selectivity. Furthermore, free amino and hydroxy groups in the donor system are well tolerated (cf. **4**, **22**, and **23**, Scheme 4) and the relatively labile OTES and chloroacetate (ClAc) groups are stable to these conditions (cf. **17c**, **d**, **19**, **22**–**24**, Scheme 4). However, in an attempt to conjugate **17c** with β-**7a** (Scheme 1) using $AgPF_6$, the cyclized product **20** (Scheme 4) was formed (73%). Notably, β-**7a** was fully recovered in this case and normal 2-oxythioglycosides **7** (R^1 = Ph or Et; R^2, R^3 = Bn, Ac, TBS) in general are unreactive to these conditions, even with a large excess of $AgPF_6$/DTBMP (50 equiv) at room temperature over 48 h. As such, interesting disaccharides that bear dormant sulfur weaponry for future glycosylation steps can be readily accessed, for example, the reaction of β-**7a** with α-**17a**, **b** exclusively gave α-**21a**, **b** (84–86%).[11]

In conclusion, while making significant headway towards assembling the kedarcidin chromophore,[5] we have established that $AgPF_6$/DTBMP is an exceptionally mild activating system for simple 2-deoxythioglycosides that are stable to storage and more readily prepared than their customized *S*-heteroaryl counterparts or *S*-carbodithioates.[3g, 7d, 12] Within the complex realms of natural product and carbohydrate synthesis, the potential of this and related Ag^I-based systems to sensitive and sterically hindered acceptors should thus help inspire new strategies with which to construct advanced 2-deoxyglycosides in a straightforward, direct, and stereoselective manner.[1, 3b,f]



Scheme 4. Expedient formation of 2-deoxyglycosides **16**–**24** of $PhCH_2CH_2OH$, *t*BuOH, iPr_2CHOH, or **7a**, by using $AgPF_6$/DTBMP (see text). ClAc = chloroacetyl, Bz = Benzoyl.

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Experimental Section

General protocol: The 2-deoxythioglycoside (0.1 mmol), alcohol (1.5 equiv), and DTBMP (4.5 equiv) were dissolved in CH_2Cl_2 (1.0 mL) under argon, using light-protected glassware. After the mixture had been stirred for 1.5 h at 23 °C over molecular sieves (4 Å, <5 microns, freshly activated), powdered $AgPF_6$ (3–4 equiv) was added at O °C. When the reaction was complete (0.5–2 h), pyridine (50 equiv) was added, and the mixture was stirred for a further 0.5 h. Filtration (celite pad, diethyl ether/*n*-hexane (1:4)), concentration, and chromatographic purification provided the 2-deoxyglycoside.

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[12] Schene and Waldmann have also reported the direct formation of 2-deoxyglycosides under extremely mild conditions, but through the prolonged exposure of glycosyl fluorides, trichloroacetimidates, or phosphites to $LiClO_4/Et_2O$; interestingly, they too observed the apparent superior α-selective effect of the PF_6 counteranion, see ref. [2f].

H_2O_2-Dependent Fe-Catalyzed Oxidations: Control of the Active Species**

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In memory of Olivier Kahn

The reaction of ferrous ion with hydroperoxides has been investigated for more than a century (Fenton chemistry), and yet the mechanism has still not been satisfactorily rationalized. The nature of the reactive species has always been a matter of debate, oscillating between hydroxyl or alkoxyl

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