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Sigmatropic Rearrangements as Tools for Amino Acid and Peptide Modification: Application of the Allylic Sulfur Ylide Rearrangement to the Preparation of Neoglycoconjugates and Other Conjugates

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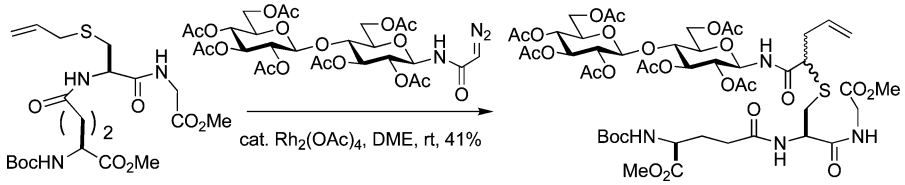


Reaction of *S*-allyl cysteine derivatives, generated by the selenocysteine ligation, with rhodium carbenoids, stabilized and unstabilized, enables the attachment of diverse functionality onto cysteine residues. The reaction is successfully applied to the introduction of lipid-like residues, a fluorous alkyl chain, and mono- and disaccharides.

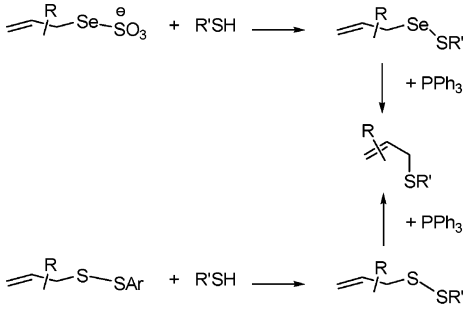
Introduction

Recently, we have described methods for the permanent ligation of thiols involving the coupling of either *Se*-allyl Bunte salts (*Se*-allyl selenosulfonates) or *S*-allyl *S*′-heteroaryl disulfides with thiols to give *Se*-allyl selenosulfides or *S*-allyl disulfides, respectively, followed by a dechalcogenative 2,3-sigmatropic rearrangement to give the ligated products (Scheme 1).[1] These complementary reactions, for which all steps take place at room temperature in protic media, were illustrated by the introduction of a range of allyl and prenyl groups to cysteine and other thiols.

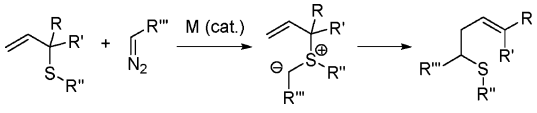
By virtue of the reaction mechanism these reactions afford allylic sulfides as products, thereby opening up avenues for further functionalization, one of which is the 2,3-sigmatropic rearrangement of allylic sulfur ylides as we describe here.

The 2,3-sigmatropic rearrangement of allylic sulfur ylides has been known for many years and has found widespread application in organic synthesis.[2] With an eye to eventual applications in the modification of peptides, proteins, and other bioconjugates, for our investigation we selected the modification of this reaction popularized by Kirmse and Doyle, in which the sulfur ylide is generated by transition-metal-catalyzed addition of a

SCHEME 1. Dechalcogenative Allylic Selenosulfide and Disulfide Ligations



SCHEME 2. Reaction of Metal Carbenoids with Allyl Thio Ethers



diazoalkane to an allylic sulfide (Scheme 2).[3] Our choice of the Kirmse−Doyle reaction was further guided by current interest in the deployment of transition-metal-catalyzed reactions in peptide chemistry[4] and more particularly by the recent publication of Francis on the reaction of a stabilized vinyl diazo

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(2) (a) Trost, B. M.; Melvin, S. M. *Sulfur Ylides*; Academic Press: New York **1975**. (b) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.

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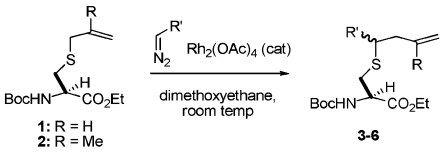
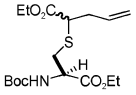
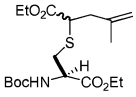
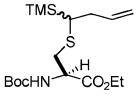
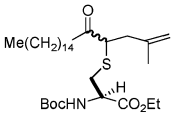
TABLE 1. Reaction of Carbenoids with Cysteine Derivatives



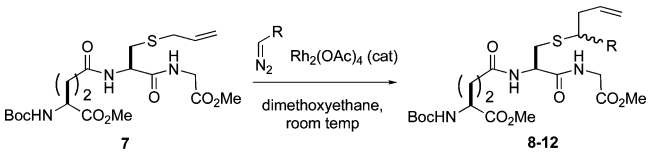
	Cmpd	Diazo Deriv	Product (% yield)
1	**1**	ethyl diazoacetate	 **3** (53)
2	**2**	ethyl diazoacetate	 **4** (42)
3	**1**	TMSdiazomethane	 **5** (57)
4	**2**	$Me(CH_2)_{14}COCHN_2$	 **6** (52)

acetate, catalyzed by dirhodium tetracetate, with tryptophan residues in horse heart myoglobin and subtilisin Carlsberg in aqueous ethylene glycol.[5]

Results and Discussion

We began with a feasibility study in which a series of diazoalkanes were allowed to react with *S*-allyl or *S*-methylallyl cysteine derivatives, obtained by the selenosulfide ligation method, in the presence of catalytic $Rh_2(OAc)_4$ in dimethoxyethane at room temperature. From the results of these experiments (Table 1) it is clear that a variety of simple alkyl groups may be introduced into cysteine in this manner, with moderate yields consistent with earlier studies on simple allylic sulfides.[3a−d,6]

TABLE 2. Reaction of Carbenoids with *S*-Allyl Glutathione



	R	Product (% Yield)
1	CO_2Et	**8** (45)
2	C_6H_5	**9** (45)
3	$CO(CH_2)_{14}Me$	**10** (38)
4	$(CH_2)_9Me$[a]	**11** (35)
5	$(CH_2)_2(CF_2)_5CF_3$[a]	**12** (32)

[a] Diazo precursors to **11** and **12** were prepared from the hydrazones with $Pb(OAc)_4$ and were used immediately.

In each case the new stereogenic center formed as a result of the sigmatropic rearrangement was obtained as an approximately 1:1 mixture of isomers.

Attention was turned to the functionalization of the tripeptide **7** (Table 2). Given the importance of the introduction of lipids onto cysteine in peptide and protein chemistry and biochemistry,[7] entries 3 and 4 of Table 2 are especially noteworthy. In view of the recent interest in the fluorous tagging of peptides and proteins, attention is also called to entry 5 of Table 2.[8]

With the exception of the tryptophan case discussed below, the main byproducts from the chemistry presented here are those of dimerization of the intermediate metal carbenoids, as is typical of this type of reaction. Analysis of crude reaction mixtures by NMR spectroscopy indicates that the mass balance of the amino acid or peptide derivatives is made up largely by the unreacted substrate; insertion into the peptide or carbamate NH bond is not a major problem, as anticipated from the work of Francis.[5]

Interest in the glycosylation of cysteine residues as a means of peptide and protein glycosylation[7a,9] led us to investigate carbohydrate-based diazoalkanes. To this end, peracetyl β-D-glucosyl and β-D-chitobiosyl diazo amides **13** and **14** were obtained from the glycosylamines, via the tosyl hydrazones. An important feature in the design of **13** and **14** was the use of the diazoamide function rather than the much more common diazo esters. This choice was made based on the trans-nature of the amide bond, with its high barrier to inversion relative to the ester bond, which it was anticipated would prevent the metal carbenoid intermediate from "biting back" on the carbohydrate moiety. This supposition was borne out in practice, as the only carbohydrate-based byproducts observed upon activation with $Rh_2(OAc)_4$ were those resulting from dimerization of the carbenoid, which is typical for this type of reaction. Glucosyl diazoamide **13** was attached to allyl hexadecyl sulfide (**15**) to establish the validity of the method (Table 3) before couplings to amino acid and peptide-based sulfides were undertaken (Table

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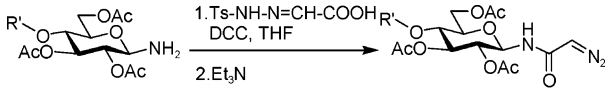
(8) Brittain, S. M.; Ficarro, S. B.; Brock, A.; Peters, E. C. *Nat. Biotechnol.* **2005**, *23*, 463.

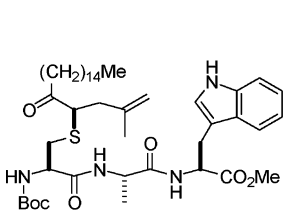
SCHEME 3. Preparation of Diazo Amides 13 and 14



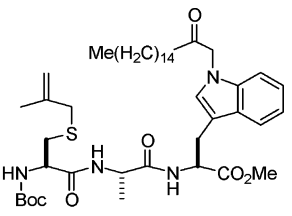
13: R' = Ac (46%)
14: R' = tetraacetyl-β-D-glucosyl (59%)

3, entries 2−5), providing access to a new class of neoglycoconjugates.[10] It is especially noteworthy that, although glycoamino acids and peptides **16**−**20** are cysteine derivatives, the amide linkage employed opens up the possibility of the application of this chemistry, coupled with native peptide ligation[11] and our dechalcogenative allylation protocols,[1] as mimics of the *N*-linked glycoproteins,[12] for which new methods are constantly being sought.[9d,e,13]

Finally, in view of the work of Francis,[5] we briefly investigated chemoselectivity with *S*-methallyl Boc-L-Cys-L-Ala-L-Trp-OMe[1] with a diazo ketone. Literature work on the addition of Rh carbenoids to sulfides in the presence of indoles provided grounds for optimism that our chemistry would be applicable in the presence of tryptophan;[14] however, complex reaction mixtures were obtained from which only two products, **21** and **22**, were obtained pure in low yield (18 and 9%, respectively). The insertion of stabilized rhodium carbenoids into the indole N−H bond, as in the formation of **22**, is a known reaction pathway[15] and is consistent with the structures proposed by Francis for reaction with protein-based tryptophan residues.[5] At least for the present, it appears that the application of the Doyle−Kirmse reaction to *S*-allylated peptides and proteins is not compatible with the presence of tryptophan.[16]



21



22

Experimental Section

Phenyldiazomethane was prepared following the procedure reported by Creary.[17]

1-Diazo-2-heptadecanone was prepared following the procedure reported by Scott and Sumpter.[18] A freshly prepared solution of diazomethane (30 mmol) in anhydrous ether (60 mL) was cooled to 0 °C and stirred at high speed. To this cooled solution was added hexadecanoyl chloride (2.75 g, 10 mmol) in anhydrous ether (20 mL) dropwise over 20 min. The resulting reaction mixture was stirred cold for an additional 30 min and then at room temperature for 60 min. After this period of time the reaction was complete, and excess diazomethane was removed by evacuating the flask with a water aspirator pump in the hood. After the diazomethane had been removed, the remaining ethereal solution was concentrated by rotary evaporation to give crude compound. Pure 1-diazo-2-heptadecanone was obtained as a yellow solid (2.61 g, 93% yield) by chromatography on silica gel using 10% ethyl acetate/hexane as an eluent. ^{1}H NMR: δ 5.24 (s, 1H), 2.27−2.38 (m, 2H), 1.58−1.64 (m, 2H), 1.23 (br s, 24H), 0.86 (t, J = 7.0, 3H). ^{13}C NMR: δ 195.4, 54.2, 41.1, 31.9, 29.7 (3C), 29.6 (2C), 29.5 (2C), 29.4 (2C), 29.2, 25.3, 22.7, 14.1. IR: ν 2120, 2100, 1620 cm^{-1}. ESIHRMS: calcd for $C_{17}H_{32}N_2O$ [M]$^+$ 280.2515, found 280.2520.

1-Diazoundecane. 1-Diazoundecane was prepared following the procedure reported by Shechter and Holton.[19] Undecanal (1.36 g, 8.0 mmol) was added to stirred anhydrous hydrazine (2.56 g, 80.0 mmol) at 55 °C. The reaction was continued for 45 min at 55−65 °C. After the mixture had been cooled to room temperature, methylene chloride (25 mL) was added. The solution was washed with saturated aqueous sodium chloride (3 × 10 mL), dried over potassium carbonate, and concentrated under reduced pressure to a volume of 5 mL. Dimethylformamide (10 mL) was added, and remaining methylene chloride was removed by vacuum evaporation. The solution of undecanal hydrazone in dimethylformamide was cooled to −78 °C (15 min) and diluted with cold tetramethylguanidine (4 mL). Lead tetraacetate (3.90 g, 8.8 mmol) was added in 5 min, and the mixture was stirred for 60 min at −78 °C. The reaction solution was diluted with cold hexane (3 × 20 mL) and extracted at −78 °C. The combined cold hexane extracts were washed with cold (−30 °C) 30% aqueous potassium hydroxide (2 × 10 mL), small pieces of dry ice were added, and the solution was then filtered to give a rose-red solution of 1-diazoundecane in hexane, which was used directly in further reaction.

9-Diazo-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorononane. 4,4,5,5,6,6,-7,7,8,8,9,9,9-Tridecafluorononanal (8.0 mmol) was added to stirred anhydrous hydrazine (2.56 g, 80.0 mmol) at 55 °C. The reaction was continued for 45 min at 55−65 °C. After the mixture had been cooled to room temperature, methylene chloride (25 mL) was added.

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(16) It can be similarly inferred that the reaction of rhodium carbenoids with protein-based tryptophan described by Francis is likely not compatible with the presence of nucleophilic sulfur as in cysteine and methionine.

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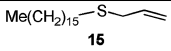
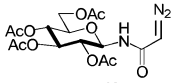
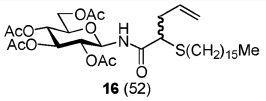
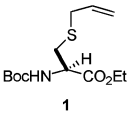
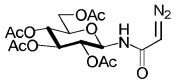
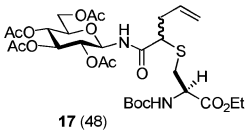
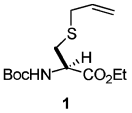
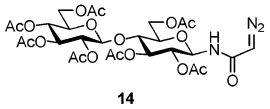
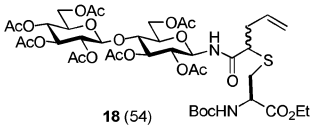
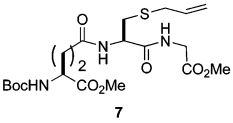
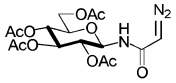
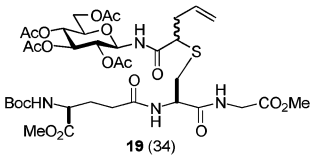
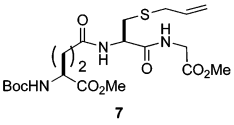
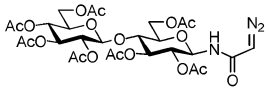
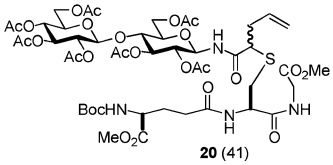
TABLE 3. $Rh_2(OAc)_4$-Catalyzed Glycosylation

	Substrate	Diazo Compound	Product (%yield)
1	 **15**	 **13**	 **16** (52)
2	 **1**	 **13**	 **17** (48)
3	 **1**	 **14**	 **18** (54)
4	 **7**	 **13**	 **19** (34)
5	 **7**	 **14**	 **20** (41)

The solution was washed with saturated aqueous sodium chloride (3 × 10 mL), dried over potassium carbonate, and concentrated under reduced pressure to a volume of 5 mL. Dimethylformamide (10 mL) was added, and remaining methylene chloride was removed by vacuum volatization. The solution of 1,1,1,2,2,3,3,4,4,5,5,6,6,-tridecafluorononanal hydrazone in dimethylformamide was cooled to −78 °C (15 min) and diluted with cold tetramethylguanidine (4 mL). Lead tetraacetate (3.90 g, 8.8 mmol) was added in 5 min, and the mixture was stirred for 60 min at −78 °C. The reaction solution was diluted with cold hexane (3 × 20 mL) and extracted at −78 °C. The combined cold hexane extracts were washed with cold (−30 °C) 30% aqueous potassium hydroxide (2 × 10 mL), small pieces of dry ice were added, and the solution was then filtered to give a rose-red solution of 9-diazo-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorononane in hexane, which was used directly.

***N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)diazoacetamide.** To a solution of tetra-*O*-acetyl-*β*-D-glucopyranosylamine (695 mg, 2.0 mmol, 1.0 equiv) and glyoxylic acid *p*-toluenesulfonylhydrazone[20] (533 mg, 2.2 mmol, 1.1 equiv) in ice-cold THF (20 mL) was added dropwise DCC (454 mg, 2.2 mmol, 1.1 equiv) in THF (10 mL). The mixture was allowed to warm to room temperature and stirring was continued overnight. Then the solid was filtered off. After removal of the solvent, the filtrate was purified by flash chromatography (hexanes/EtOAc, 2:3) to afford a yellow solid (582 mg, 51% yield).

To a solution of the yellow solid (100 mg, 0.175 mmol, 1.0 equiv) in methylene chloride (5.0 mL) was added triethylamine (0.35 mmol, 2.0 equiv) in a nitrogen atmosphere. The mixture was stirred at room temperature overnight. Then the solution was diluted with ethyl acetate (20 mL) and washed by water (2 × 10 mL) and brine (2 × 10 mL), dried over sodium sulfate, and concentrated. The remaining residue was then purified by flash chromatography (hexanes/EtOAc, 2:3) to afford the diazo compound (65 mg, 90% yield) as a viscous yellow oil. ^{1}H NMR: δ 6.10 (d, J = 9.5 Hz, 1H), 5.26−5.31 (m, 2H), 5.03 (t, J = 9.5 Hz, 1H), 4.88 (t, J = 9.5, 1H), 4.81 (s, 1H), 4.29 (dd, J = 12.5, 4.5 Hz, 1H), 4.06 (dd, J = 12.5, 2.0 Hz, 1H), 3.80−3.94 (m, 1H), 2.00−2.06 (m, 12H). ^{13}C NMR: δ 171.2, 170.7, 169.9, 169.7, 165.9, 78.5, 73.4, 72.7, 70.5, 68.2, 61.7, 48.1, 20.7 (4C). IR: ν 2111, 1750, 1653 cm^{-1}. ESIHRMS: calcd for $C_{16}H_{21}N_3O_{10}Na$ $[M + Na]^+$ 438.1125, found 438.1128.

***N*-(2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-*β*-cellobiosyl)diazoacetamide.** To a solution of hepta-*O*-acetyl-*β*-cellobiosylamine (857 mg, 1.35 mmol, 1.0 equiv) and glyoxylic acid *p*-toluenesulfonylhydrazone[20] (360 mg, 1.49 mmol, 1.1 equiv) in ice-cold THF (10 mL) was added dropwise DCC (306 mg, 1.49 mmol, 1.1 equiv) in THF (10 mL). The mixture was allowed to warm to room temperature and stirring was continued overnight. Then the solid was filtered off. After removal of the solvent, the filtrate was purified by flash chromatography (hexanes/EtOAc, 2:3) to afford a yellow solid (735 mg, 63% yield).

To a solution of the yellow solid (735 mg, 0.86 mmol, 1.0 equiv) in methylene chloride (10 mL) was added triethylamine (1.72 mmol, 2.0 equiv) in a nitrogen atmosphere. The mixture was stirred at room temperature overnight. Then the solution was diluted with ethyl acetate (20 mL) and washed by water (2 × 10 mL) and brine (2 × 10 mL), dried over sodium sulfate, and concentrated. The remaining residue was then purified by flash chromatography (hexanes/EtOAc, 2:3) to afford the diazo compound (560 mg, 93% yield) as a yellow solid. ^{1}H NMR: δ 5.98 (d, J = 9.5 Hz, 1H), 5.22−5.26 (m, 2H), 5.12 (t, J = 9.5 Hz, 1H), 5.05 (t, J = 9.5 Hz,

(20) (a) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53. (b) Ouihia, A.; Rene, L.; Badet, B. *Tetrahedron Lett.* **1992**, *33*, 5509.

1H), 4.89 (t, J = 9.5 Hz, 1H), 4.79 (t, J = 9.5 Hz, 1H), 4.78 (s, 1H), 4.48 (dd, J = 12.5, 4.5 Hz, 1H), 4.42 (dd, J = 12.5, 4.5 Hz, 1H), 4.34 (dd, J = 12.5, 4.5 Hz, 1H), 4.07−4.12 (m, 2H), 4.01 (dd, J = 12.5, 2.0 Hz, 1H), 3.72−3.76 (m, 2H), 3.62−3.65 (m, 1H), 1.95−2.12 (m, 21H). ^{13}C NMR: δ 171.1, 170.5, 170.3, 170.2, 169.5, 169.3, 169.1, 166.1, 100.6, 78.3, 76.2, 74.5, 72.9, 72.5, 71.8, 71.5, 70.7, 67.8, 62.0, 61.5, 60.4, 47.9, 20.7. IR: ν 2111, 1751, 1654 cm^{-1}. ESIHRMS: calcd for $C_{28}H_{37}N_3O_{18}Na$ [M + Na]$^+$ 726.1970, found 726.1981.

General Procedure for Ylide Formation and Rearrangement. To a solution of allyl sulfide compound (0.1 mmol, 1.0 equiv) in 1,2-dimethoxyethane (5 mL) ws added $Rh_2(OAc)_4$ (0.005 mmol, 0.05 equiv), followed by addition of diazo compound in a nitrogen atmosphere. The reaction mixture was stirred vigorously at room temperature for 10 h. Then another portion of diazo compound was added, and vigorous stirring was continued at room temperature for an additional 12 h. The solvent was removed by evaporation, and the remaining residue was purified by flash chromatography to afford the corresponding product.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-ethoxycarbonyl-1-buten-4-yl)-L-cysteine ethyl ester (3)** was prepared according to the general procedure using 10 equiv of ethyl diazoacetate to give a colorless oil. ^{1}H NMR: δ 5.72−5.77 (m, 2H), 5.37 (br d, J = 9.0 Hz, 1H), 5.29 (br d, J = 8.0 Hz, 1H), 5.06−5.13 (m, 4H), 4.54−4.55 (br s, 2H), 4.16−4.23 (m, 8H), 3.40 (t, J = 7.0 Hz, 1H), 3.32 (dd, J = 8.5, 6.5 Hz, 1H), 3.03−3.14 (m, 3H), 2.91−2.95 (m, 1H), 2.56−2.59 (m, 2H), 2.38−2.43 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H), 1.27−1.29 (m, 12H). ^{13}C NMR: δ 171.8, 170.8, 155.1, 133.9, 133.8, 118.0, 80.1, 61.8, 61.7, 61.4, 61.3, 53.4, 53.0, 46.7, 46.2, 35.8, 35.5, 33.9, 28.3, 14.2. ESIHRMS: calcd for $C_{17}H_{29}NO_6S$ [M + Na]$^+$ 398.1614, found 398.1607.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-ethoxycarbonyl-2-methyl-1-buten-4-yl)-L-cysteine ethyl ester (4)** was prepared according to the general procedure using 10 equiv of ethyl diazoacetate to give a colorless oil. ^{1}H NMR: δ 5.35 (br d, J = 8.1 Hz, 1H), 5.28 (br d, J = 7.8 Hz, 1H), 4.81 (s, 2H), 4.74 (d, J = 7.5, 2H), 4.55 (br s, 2H), 4.15−4.23 (m, 8H), 3.47−3.59 (m, 2H), 3.06−3.15 (m, 4H), 2.92−2.95 (m, 2H), 2.56−2.61 (m, 2H), 2.31−2.35 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H), 1.29−1.30 (m, 12H). ^{13}C NMR: δ 172.0, 170.8, 155.2, 141.5, 141.4, 113.1, 80.1, 61.8, 61.4, 61.3, 53.4, 53.0, 45.3, 44.9, 39.6, 39.4, 33.8, 28.3, 22.3, 14.2. ESIHRMS: calcd for $C_{18}H_{31}NO_6S$ [M + H]$^+$ 390.1950, found 390.1944.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-trimethylsilanyl-1-buten-4-yl)-L-cysteine ethyl ester (5)** was prepared according to the general procedure using 5.0 equiv of trimethylsilyl diazomethane to give a colorless oil. ^{1}H NMR: δ 5.89−5.91 (m, 2H), 5.35 (br d, J = 8.0 Hz, 1H), 5.29 (br s, 1H), 5.02−5.11 (m, 4H), 4.48 (br s, 2H), 4.17−4.22 (m, 4H), 2.86−3.03 (m, 6H), 2.48−2.50 (m, 2H), 2.29−2.32 (m, 2H), 1.92−1.93 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.26−1.29 (m, 6H), 0.15 (s, 9H), 0.14 (s, 9H). ^{13}C NMR: δ 171.1, 155.2, 137.3, 116.4, 116.3, 80.0, 61.7, 61.6, 53.3, 53.2, 38.5, 36.2, 32.6, 32.0, 28.3, 14.2, −2.3. ESIHRMS: calcd for $C_{17}H_{33}NO_4SSi$ [M + Na]$^+$ 398.1798, found 398.1793.

***N*-(*tert*-Butoxycarbonyl)-*S*-(2-methyl-5-oxo-4-icosyl)-L-cysteine ethyl ester (6)** was prepared according to the general procedure using 5.0 equiv of 1-diazo-2-heptadecanone to give a pale yellow oil. ^{1}H NMR: δ 5.27−5.30 (m, 2H) 4.81 (s, 2H), 4.69 (s, 2H), 4.49 (br s, 2H), 4.21 (q, J = 7.0 Hz, 4H), 3.45−3.48 (m, 2H), 2.81−2.97 (m, 4H), 2.52−2.58 (m, 6H), 2.32−2.36 (m, 2H), 1.71 (s, 6H), 1.44 (s, 18H), 1.25−1.37 (m, 58 H), 0.87 (t, J = 11.0 Hz, 6H). ^{13}C NMR: δ 206.3, 206.2, 170.8, 155.1, 141.6, 113.1, 80.2, 61.9, 53.2, 53.0, 51.0, 38.8, 38.1, 32.5, 29.7, 29.6, 29.4, 29.3, 29.2, 28.3, 23.9, 22.7, 22.5, 14.2. ESIHRMS: calcd for $C_{31}H_{57}NO_5S$ [M + H]$^+$ 556.4036, found 556.4027.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-ethoxycarbonyl-1-buten-4-yl)-glutathione dimethyl ester (8)** was prepared according to the general procedure using 10 equiv of ethyl diazoacetate to give a pale yellow oil. ^{1}H NMR: δ 7.16 (br d, J = 5.0 Hz, 2H), 6.99 (br d, J = 6.5 Hz, 1H), 6.89 (br d, J = 6.0 Hz, 1H), 5.72−5.75 (m, 2H), 5.35 (br d, J = 5.5 Hz, 2H), 5.09−5.14 (m, 4H), 4.62−4.67 (m, 2H), 4.32−4.38 (m, 2H), 4.18−4.24 (m, 4H), 4.01−4.09 (m, 4H), 3.74 (s, 6H), 3.73 (s, 6H), 3.52 (t, J = 7.3 Hz, 1H), 3.44 (t, J = 7.5 Hz, 1H), 3.19 (dd, J = 14.3, 6.3 Hz, 2H), 2.94−3.02 (m, 2H), 2.59−2.65 (m,2H), 2.44−2.48 (m, 2H), 2.32−2.38 (m, 4H), 2.16−2.21 (m, 2H), 1.93−2.01 (m, 2H), 1.43 (s, 18H), 1.24−1.29 (m, 6H).^{13}C NMR: δ 172.9, 172.6, 172.3, 170.4, 169.9, 155.7, 133.8, 118.1, 80.2, 61.7, 52.6, 47.2, 41.3, 35.7, 33.5, 33.0, 32.1, 28.6, 14.2. ESIHRMS: calcd for $C_{24}H_{39}N_3O_{10}S$ [M + Na]$^+$ 584.2254, found 584.2255.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-phenyl-1-buten-4-yl)glutathione dimethyl ester (9)** was prepared according to the general procedure using 5.0 equiv of phenyl diazomethane to give a pale yellow oil. ^{1}H NMR: δ 7.31−7.32 (m, 4H), 7.22−7.25 (m, 6H), 7.02 (br s, 1 H), 6.82 (br s, 1H), 6.67 (br d, J = 6.5 Hz, 1H) 6.60 (br d, J = 7.0 Hz, 1H), 5.63−5.70 (m, 2H), 5.37 (br s, 2H), 4.95−5.04 (m, 4H), 4.32−4.45 (m, 4H), 3.86−3.98 (m, 8H), 3.73 (s, 6H), 3.72 (s, 6H), 2.83 (dd, J = 12.0, 5.8 Hz, 1H), 2.69−2.71 (m, 2H), 2.58−2.64 (m, 5H), 2.27−2.31 (m, 2H), 2.21−2.24 (m, 2H), 2.11−2.18 (m, 2H), 1.89−1.96 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ172.9, 172.2, 172.1, 170.6, 170.0,-169.9, 155.7, 142.0, 141.9, 135.1, 135.0, 128.7, 127.9, 127.5, 117.3, 80.2, 52.8, 52.5, 52.4, 52.2, 50.2, 50.0, 49.9, 41.3, 40.7, 40.6, 32.8, 32.2, 28.7, 28.5, 28.3. ESIHRMS: calcd for $C_{27}H_{39}N_3O_8S$ [M + Na]$^+$ 588.2356, found 588.2364.

***N*-(*tert*-Butoxycarbonyl)-*S*-(5-oxo-4-icosyl)glutathione dimethyl ester (10)** was prepared according to the general procedure using 5.0 equiv of 1-diazo-2-heptadecanone to give a pale yellow oil. ^{1}H NMR: δ 7.11−7.13 (br s, 2H), 6.81 (br d, J = 6.0 Hz, 1H), 6.80 (br d, J = 6.5 Hz, 1H), 5.69−5.77 (m, 2H), 5.34−5.35 (br d, J = 7.0 Hz, 2H), 5.07−5.09 (m, 4H), 4.55−4.59 (m, 2H), 4.36 (br s, 2H), 3.95−4.09 (m, 4H), 3.74 (s, 12H), 3.44−3.49 (m, 2H), 2.80−2.90 (m, 4H), 2.55−2.62 (m, 6H), 2.32−2.46 (m, 6H), 2.14−2.17 (m, 2H), 1.91−1.97 (m, 2H), 1.51−1.57 (m, 4H), 1.42 (s, 18H), 1.16−1.28 (m, 48H), 0.85−0.88 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 207.7, 207.3, 172.9, 172.3, 172.2, 170.4, 170.3, 169.9, 155.7, 134.2, 134.1, 118.1, 118.0, 80.2, 52.8, 52.7, 52.6, 52.5, 52.4, 52.2, 41.3, 39.7, 39.6, 34.5, 32.4, 32.2, 32.1,31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.7, 28.5, 28.3, 23.9, 22.7, 14.1. ESIHRMS: calcd for $C_{37}H_{65}N_3O_9S$ [M + Na]$^+$ 750.4340, found 750.4322.

***N*-(*tert*-Butoxycarbonyl)-*S*-(1-tetradecen-4-yl)glutathione dimethyl ester (11)** was prepared according to the general procedure using 5.0 equiv of 1-diazoundecane to give a pale yellow oil. ^{1}H NMR: δ 7.16 (br d, J = 5.0 Hz, 2H), 6.84 (br d, J = 7.0 Hz, 2H), 5.81−5.84 (m, 2H), 5.33 (br d, J = 6.5 Hz, 2H), 5.05−5.10 (m, 4H), 4.52−4.53 (m, 2H), 4.39 (br d, J = 4.5 Hz, 2H), 3.98−4.05 (m, 4H), 3.74 (s, 12H), 2.97−2.98 (m, 2H), 2.76−2.79 (m, 4H), 2.34−2.38 (m, 8H), 2.11−2.19 (m, 2H), 1.85−1.96 (m, 2H), 1.51−1.54 (m, 2H), 1.43 (s, 18H), 1.24−1.39 (m, 34H), 0.85−0.88 (m, 6H).^{13}C NMR: δ 172.9, 172.1, 170.7, 169.9, 155.7, 135.6, 135.5, 117.3, 117.2, 80.2, 52.8, 52.7, 52.5, 52.4, 46.3, 45.9, 41.3, 39.1, 34.6, 34.2, 32.3, 32.1, 31.9, 29.6, 29.5, 29.4, 28.6, 28.3, 26.8, 26.7, 22.7, 14.1. ESIHRMS: calcd for $C_{31}H_{55}N_3O_8S$ [M + H]$^+$ 630.3788, found 630.3773.

***N*-(*tert*-Butoxycarbonyl)-*S*-(1-tridecafluorododecen-4-yl)glutathione dimethyl ester (12)** was prepared according to the general procedure using 5.0 equiv of 9-diazo-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorononane to give a pale yellow oil. ^{1}H NMR: δ 7.11 (br s, 2H), 6.88 (br s, 2H), 5.74−5.77 (m, 2H), 5.45 (br s, 2H), 5.33−5.36 (m, 2H), 5.12−5.18 (m, 4H), 4.57−4.58 (m, 1H), 4.31−4.42 (m, 2H), 3.98−4.13 (m, 4H), 3.75 (s, 12H), 3.29−3.32 (m, 2H), 3.04−3.23 (m, 4H), 2.74−2.95 (m, 4H), 2.33−2.51 (m, 4H), 2.17−2.20 (m, 2H), 1.89−2.16 (m, 4H), 1.44 (s, 9H), 1.45 (s, 9H).^{13}C NMR: δ 172.8, 171.9, 171.4, 169.9, 155.6, 133.4, 133.2, 118.4, 118.2, 80.7, 52.9, 52.7, 52.5, 45.8, 41.4, 39.5, 34.9, 34.3, 32.4, 32.2, 31.7, 29.7, 29.3, 28.8, 28.3,28.2, 27.8, 24.6. F^{19} NMR: δ −8.3, −41.7, −49.5, −50.5, −50.9, −53.7. ESIHRMS: calcd for $C_{29}H_{38}F_{13}N_3O_8S$ [M + H]$^+$ 836.2245, found 836.2247.

***N*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-2-(hexadecylsulfanyl)-4-pentenamide (16)** was prepared according to the general procedure using 5.0 equiv of *N*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)diazoacetamide to give a colorless oil. ^{1}H NMR: δ 7.21−7.30 (m, 2H), 5.66−5.79 (m, 2H), 5.30 (t, J = 9.5 Hz, 2H), 5.19−5.23 (m, 2H), 5.01−5.33 (m, 6H), 4.96−5.00 (m, 2H), 4.28−4.32 (m, 2H), 4.05−4.08 (m, 2H), 3.79−3.82 (m, 2H), 3.25−3.28 (m, 2H), 2.38−2.49 (m, 6H), 2.17 (s, 6H), 2.07 (s, 6H), 2.03 (s, 6H), 2.02 (s, 6H), 1.52−1.55 (m, 4H), 1.24−1.33 (m, 54H), 0.87 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 172.5, 172.4, 170.6, 170.4, 170.0, 169.6, 133.9, 133.8, 118.2, 117.9, 78.4, 73.6, 72.9, 72.8, 70.3, 68.2, 61.7, 49.5, 49.4, 36.5, 36.2, 31.9, 31.5, 31.4, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 28.9, 22.7, 20.7, 20.6, 14.2. ESIHRMS: calcd for $C_{35}H_{59}N_3O_{10}S$ [M + Na]$^+$ 708.3758, found 708.3732.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-*N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)aminocarbonyl-1-buten-4-yl)-L-cysteine ethyl ester (17)** was prepared according to the general procedure using 5.0 equiv of *N*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)diazoacetamide to give a pale yellow oil. ^{1}H NMR: δ 7.41 (br d, J = 8.5 Hz, 1H), 7.27 (br s, 1H), 5.55−5.74 (m, 2H), 5.64−5.74 (m, 1H), 5.50 (br d, J = 7.5 Hz, 1H), 5.19−5.30 (m, 4H), 4.98−5.12 (m, 6H), 4.43 (br, 2H), 4.25−4.30 (m, 2H), 4.15−4.21 (m, 4H), 4.02−4.11 (m, 4H), 3.77−3.81 (m, 2H), 3.30−3.33 (m, 2H), 3.09 (br d, J = 13.0 Hz, 1H), 2.94−2.97 (m, 1H), 2.68−2.74 (m, 2H), 2.60−2.65 (m, 1H), 2.48−2.54 (m, 1H), 2.33−2.40 (m, 2H), 1.98−2.05 (m, 24H), 1.47 (s, 9H), 1.46 (s, 9H), 1.21−1.27 (m, 6H). ^{13}C NMR: δ 171.8, 171.6, 171.2, 170.7, 170.6, 170.4, 169.9, 169.5, 169.4, 155.5, 155.4, 133.9, 133.4, 118.2, 118.1, 80.5, 80.4, 73.6, 72.9, 72.7, 70.3, 68.1, 68.0, 62.0, 61.9, 61.7, 61.5, 60.4, 53.0, 49.8, 48.0, 36.2, 35.8, 34.2, 33.7, 28.4, 21.1, 20.7, 20.6, 14.2. ESIHRMS: calcd for $C_{29}H_{44}N_2O_{14}S$ [M + Na]$^+$ 699.2406, found 699.2410.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-*N*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetylcellobiosyl)aminocarbonyl-1-buten-4-yl)-L-cysteine ethyl ester (18)** was prepared according to the general procedure using 5.0 equiv of *N*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-*β*-cellobiosyl)diazoacetamide to give a pale yellow oil. ^{1}H NMR: δ 7.26 (br d, J = 9.0 Hz, 1H), 7.13 (br d, J = 9.0 Hz, 1H), 5.59−5.61 (m, 2H), 5.46 (br d, J = 6.6 Hz, 1H), 5.21−5.28 (m, 3H), 5.03−5.19 (m, 10H), 4.88−4.92 (m, 4H), 4.40−4.49 (m, 6H), 4.33−4.35 (m, 2H), 4.08−4.19 (m, 8H), 3.98−4.01 (m, 2H), 3.62−3.71 (m, 6H), 3.26−3.31 (m, 2H), 3.03−3.08 (m, 1H), 2.91−2.96 (m, 1H), 2.68−2.73 (m, 1H), 2.59−2.66 (m, 1H), 2.45−2.51 (m, 1H), 2.31−2.39 (m, 2H), 1.95−2.09 (m, 42H), 1.45 (s, 9H), 1.42 (s, 9H), 1.21−1.27 (m, 6H). ^{13}C NMR: δ 171.6, 171.4, 170.8, 170.7, 170.6, 170.5, 170.2, 169.4, 169.3, 169.0, 155.3, 133.7, 133.4, 118.2, 118.1, 100.7, 80.378.3, 78.2, 76.2, 74.5, 72.9, 72.2, 72.1, 72.0, 71.5, 70.5, 67.8, 62.0, 61.9, 61.6, 60.4, 53.5, 53.1, 49.8, 48.4, 36.2, 35.8, 34.1, 33.5, 28.4, 21.1, 20.8, 20.7, 20.5, 14.2. ESIHRMS: calcd for $C_{41}H_{60}N_2O_{22}S$ [M + H]$^+$ 965.3431, found 965.3424.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-*N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)aminocarbonyl-1-buten-4-yl)glutathione dimethyl ester (19)** was prepared according to the general procedure using 5.0 equiv of *N*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)diazoacetamide to give a pale yellow oil. ^{1}H NMR: δ 7.69 (br d, J = 8.5 Hz, 2H), 7.35 (br s, 2H), 7.01 (br d, J = 7.5 Hz, 2H), 5.73−5.76 (m, 2H), 5.35 (br s, 2H), 5.26−5.31 (m, 4H), 4.99−5.14 (m, 6H), 4.82 (br s, 2H), 4.32−4.40 (m, 4H), 4.03−4.14 (m, 4H), 3.82−3.87 (m, 2H), 3.73−3.79 (m, 12H), 3.63 (br s, 2H), 2.96−3.31 (m, 4H), 2.62−2.64 (m, 2H), 2.52−2.54 (m, 2H), 2.35−2.37 (m, 4H), 2.00−2.19 (m, 28H), 1.43 (s, 9H), 1.42 (s, 9H). ^{13}C NMR: δ 172.9, 172.3, 172.1, 170.8, 170.6, 170.3, 170.0, 169.6, 155.6, 133.9, 133.8, 118.2, 80.2, 78.3, 73.9, 73.1, 70.6, 70.5, 68.2, 68.1, 61.7, 60.4, 52.8, 52.6, 52.1, 52.0, 49.2, 45.4, 41.3, 41.2, 36.0, 35.2, 33.8, 32.6, 31.9, 28.3, 24.0, 21.0, 20.8. ESIHRMS: calcd for $C_{36}H_{54}N_4O_{18}S$ [M + H]$^+$ 885.3046, found 885.3059.

***N*-(*tert*-Butoxycarbonyl)-*S*-(4-*N*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetylcellobiosyl)aminocarbonyl-1-buten-4-yl)glutathione dimethyl ester (20)** was prepared according to the general procedure using 5.0 equiv of *N*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-*β*-cellobiosyl)diazoacetamide to give a pale yellow oil. ^{1}H NMR: δ 7.55 (br d, J = 9.1 Hz, 1H), 7.28 (br d, J = 7.0 Hz, 1H), 6.98 (br d, J = 8.1 Hz, 1H), 5.62−5.71 (m, 1H), 5.33 (br d, J = 8.1 Hz, 1H), 5.20−5.27 (m, 4H), 5.10−5.14 (m, 3H), 5.03−5.07 (m, 4H), 4.89−4.92 (m, 4H), 4.61−4.68 (br s, 1H), 4.48−4.52 (m, 5H), 4.34−4.37 (m, 2H), 4.25 (br s, 1H), 4.03−4.12 (m, 8H), 3.71−3.76 (m, 10H), 3.64−3.66 (m, 3H), 3.12 (br s, 1H), 3.01 (br s, 1H), 2.52−2.61 (m, 1H), 2.50−2.51 (m, 1H), 2.35−2.37 (m, 2H), 1.98−2.13 (m, 21H), 1.42 (s, 9H). ^{13}C NMR: δ 173.0, 172.3, 171.5, 170.6, 170.5, 170.3, 170.2, 169.9, 169.8, 169.3, 169.0, 155.6, 133.9, 133.8, 118.0, 100.6, 80.3, 78.1, 76.4, 74.9, 73.2, 73.1, 71.9, 71.8, 71.6, 70.5, 67.8, 61.8, 61.7, 61.5, 52.9, 52.6, 52.5, 52.4, 46.4, 41.4, 35.1, 32.8, 32.0, 28.3, 20.8. ESIHRMS: calcd for $C_{48}H_{70}N_4O_{26}S$ [M + H]$^+$ 1151.4072, found 1151.4071.

***N*-(*tert*-Butoxycarbonyl)-*S*-(2-methyl-5-oxo-4-icosyl)-L-cysteinyl-L-alanyl-L-tryptophan methyl ester (21)** was prepared according to the general procedure using 5.0 equiv of 1-diazo-2-heptadecanone, which was contaminated by approximately 10% of **22**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.59 (s, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.34 (m, 2H) 7.16 (m, 2H), 7.09 (m, 2H), 7.00 (s, 1H), 6.98 (s, 1H), 6.80−6.67 (m, 4H), 5.28 (m, 1H), 5.15 (m, 1H), 4.89−4.80 (m, 4H), 4.73 (s, 1H), 4.70 (s, 1H), 4.47−4.37 (m, 2H), 4.20−4.10 (m, 2H), 3.694 (s, 3H), 3.692 (s, 3H), 3.53 (m, 2H), 3.37−3.23 (m, 4H), 2.74−2.73 (m, 4H), 2.62−2.50 (m, 6H), 2.38−2.31 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H,), 1.63−1.56 (m, 4H), 1.47 (s, 18H), 1.31 (d, J = 7.1 Hz, 6H), 1.30−1.20 (m, 52H), 0.88 (t, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 207.4, 172.04, 171.99, 171.1, 170.13, 170.07, 155.6, 141.6, 141.5, 136.3, 127.5, 127.4, 123.23, 123.19, 122.06, 122.04, 113.3, 111.38, 111.33, 109.5, 79.8, 54.0, 53.4, 53.1, 52.7, 52.4, 50.9, 50.8, 48.9, 39.1, 39.0, 38.0, 37.9, 32.4, 32.2, 31.9, 29.68, 29.65, 29.5, 29.4, 29.3, 29.2, 28.3, 27.4, 27.3, 23.9, 22.7, 22.4, 17.5, 17.4, 14.1. ESIHRMS: calcd for $C_{44}H_{71}N_4O_7S$ [M + H]$^+$ 799.5038, found 799.5038; calcd for $C_{44}H_{70}N_4O_7SNa$ [M + Na]$^+$ 821.4858, found 821.4560.

***N*-(*tert*-Butoxycarbonyl)-*S*-(2-methylallyl)-L-cysteinyl-L-alanyl-L-N_ω-(2-oxo-heptadecyl)tryptophan methyl ester (22)** was prepared according to the general procedure using 5.0 equiv of 1-diazo-2-heptadecanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.7 Hz, 1H), 7.20 (m, 1H), 7.14−7.10 (m, 2H), 6.90 (s, 1H), 6.84 (br d, J = 7.7 Hz, 1H), 6.59 (br d, J = 7.6 Hz, 1H), 5.29 (m, 1H), 4.93−4.79 (m, 4H), 4.45 (quint, J = 7.4 Hz, 1H), 4.14 (m, 1H), 3.68 (s, 3H), 3.33 (d, J = 5.6 Hz, 2H), 3.03 (d, J = 13.4 Hz, 1H), 2.96 (d, J = 13.4 Hz, 1H), 2.72 (dd, J = 13.7, 5.9 Hz, 1H), 2.65 (dd, J = 13.7, 6.7 Hz, 1H), 2.35 (t, J = 7.4 Hz, 2H), 1.77 (s, 3H), 1.56 (m, 2H), 1.44 (s, 9H), 1.32 (d, J = 7.1 Hz, 3H), 1.30−1.20 (m, 26H), 0.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 171.8, 171.3, 170.4, 140.7, 136.6, 128.1, 127.6, 122.4, 119.8, 119.0, 114.5, 109.6, 108.9, 80.4, 55.2, 53.8, 52.6, 52.5, 48.9, 39.4, 33.1, 31.9, 29.7, 29.5, 29.4, 29.1, 28.3, 27.3, 23.4, 22.7, 20.6, 18.0, 14.1. FABHRMS: calcd for $C_{44}H_{70}N_4O_7SNa$ [M + Na]$^+$ 821.4863, found 821.4859.

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Supporting Information Available: Copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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