Regioselective Synthesis of Substituted 1-Thiohex-2-enopyranosides

Lois V. Dunkerton,*[1] Nancy K. Adair,[1] Jack M. Euske,[1] Kevin T. Brady,[2] and Paul D. Robinson[3]

Department of Chemistry and Biochemistry and Department of Geology, Southern Illinois University at Carbondale, Carbondale, Illinois 62901

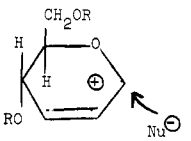
Received August 4, 1987

A variety of 1-thiohex-2-enopyranosides have been prepared from their corresponding 3-*O*-methyl- or 3-*O*-acetylglycals by using trimethylsilyl thiols catalyzed by BF_3 etherate. This method is regioselective for thiolation at C-1 in contrast to the same reaction with thiols which produces C-3 products under thermodynamic control. The stereoselectivity of the reaction depended on the choice of trimethylsilyl thiol and the leaving group at C-3 of the glycal. [(Trimethylsilyl)thio]benzene gave α-anomers as the only products, whereas (thionoacetoxy)trimethylsilane gave more β-anomer products from 3-*O*-methylglycals than from 3-*O*-acetylglycals. Examples reported include the synthesis of *S*-(2′-pyridyl) 2,3,6-trideoxy-4,6-di-*O*-acetyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (**6**), *S*-(2′-pyridyl) 2,3,6-trideoxy-4-*O*-acetyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (**9**), *S*-(2′-pyridyl) 2,3-dideoxy-4,6-di-*O*-methyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (**12**), *S*-phenyl 2,3-dideoxy-4,6-di-*O*-methyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (**13**), *S*-phenyl 2,3,6-trideoxy-4-*O*-methyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (**15**), *S*-acetyl 2,3,6-trideoxy-4-*O*-methyl-1-thio-β-L-*erythro*-hex-2-enopyranoside (**16**), *S*-acetyl 2,3-dideoxy-4,6-di-*O*-methyl-1-thio-α,β-D-*erythro*-hex-2-enopyranosides (**17**, **18**), *S*-acetyl 2,3-dideoxy-4,6-di-*O*-acetyl-1-thio-α,β-D-*erythro*-hex-2-enopyranosides (**19**, **20**), and *S*-acetyl 2,3,6-trideoxy-4-*O*-acetyl-1-thio-α,β-L-*erythro*-hex-2-enopyranosides (**21**, **22**).

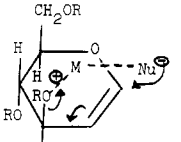
Introduction

In the course of extending our palladium-assisted carbohydrate methodology, multiple reasons arose for preparing 1-thiohex-2-enopyranosides,[4,5] including investigation of their allylic rearrangements[6,7] and stereoselective functionalization of C-3 via [2,3]sigmatropic processes.[8,9] Most urgent was the need to use the thioacetyl group in place of the *O*-acetyl group for palladium-assisted C-glycosylation.[10,11] Priebe and Zamojski had carefully defined a set of kinetically controlled conditions for S_N2' acid-catalyzed reactions of glycals with thiols which gave α-1-thiohex-2-enopyranosides as the major products, along with 3-thioglycals as minor products.[12] In our hands for synthetic purposes, this method suffered two disadvantages. In the course of preparative silica gel separation of the undesired 3-thioglycals from the desired 1-thiohex-2-enopyranosides, the silica gel caused complete equilibration, resulting only in isolation of 3-thioglycals. In addition, β-1-thiohex-2-enopyranosides were not available by this reaction.

The generalization by Priebe and Zamojski that the regioselectivity of nucleophilic attack on the intermediate carbenium ion **1** could be rationalized by the HSAB principle, with the C-1 being hard and C-3 being soft, led us to postulate that making the thiol sulfur harder, that is, increasing its nucleophilicity, would lead to greater regioselectivity for attack at C-1. Also, some β-selectivity, that is, S_N2' syn selectivity on readily available glucals was envisioned to be possible by nucleophilic attack on an earlier transition state **2** with participation of a gegencation.[13,14]



1



2

The use of silicon to enhance nucleophilicity and its hard acid character combine to render trimethylsilyl nucleophiles as extremely useful reagents in organic synthesis.[15] Although the literature example by Mukaiyama did not provide stereochemical precedent, it did show that [(trimethylsilyl)thio]benzene reacted with α,β-unsaturated thioacetals in good yield with excellent regioselectivity on the basis of steric factors.[16] Although we were not aware of literature precedents for stereoselectivity of S_N2' reactions of trimethylsilyl sulfides with allylic systems, after our stereoselectivity had been verified, it was very gratifying to read the elegant details of Danishefsky's carbon–Ferrier reactions including the role of the electron-withdrawing capacity of the leaving group at C-3 of the glycal.[17] The elegant stereoselectivity of palladium-catalyzed alkylations of allylic systems combined with the availability of either carbohydrate allylic reactant would provide an optimum combination for versatility in the synthesis of naturally occurring 2,6-dialkylated tetrahydropyrans.[17]

Results and Discussion

For comparison purposes the initial reaction involved the BF_3 etherate catalyzed addition of thiophenol to 3,4,6-tri-*O*-acetyl-D-glucal (**3**) in which a complex mixture

(1) Department of Chemistry and Biochemistry, Southern Illinois University.
(2) Department of Chemistry, University of Southern California. Preparation of compound **6** based upon work reported in Ph.D. Thesis, University of Southern California, 1982.
(3) Department of Geology, Southern Illinois University, responsible for X-ray of **6**.
(4) Palladium-Assisted Carbohydrate Reactions. 5. For 4, see ref 7.
(5) Preliminary results were reported: Dunkerton, L. V.; Euske, J. M. *Abstracts of Papers*, 187 National Meeting of the American Chemical Society, American Chemical Society: Washington, DC, 1984; Carb., 27. Dunkerton, L. V., Euske, J. M. *Abstract of Papers*, 190 National Meeting of the American Chemical Society, American Chemical Society: Washington, DC, 1985; Carb. 7. Dunkerton, L. V.; Euske, J. M.; Serino, A. J. 13th International IUPAC Carbohydrate Symposium, Cornell University, Ithaca, NY, August, 1986. Dunkerton, L. V.; Adair, N. K.; Euske, J. M. *Abstracts of Papers*, 8th International IUPAC Symposium on Organosilicon Chemistry, St. Louis, MO, June, 1987.
(6) Dunkerton, L. V.; Brady, K. T.; Mohamed, F. *Tetrahedron Lett.* **1982**, *23*, 599.
(7) Dunkerton, L. V.; Brady, K. T.; McKillican, B. P.; Mohammed, F. *J. Carbohydr. Chem.*, in press.
(8) Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides*; Academic Press: New York, 1975.
(9) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341.
(10) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812.
(11) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.*, in press.
(12) Priebe, W.; Zamojski, A. *Tetrahedron* **1980**, *36*, 274.
(13) Badi, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 1352.
(14) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(15) Ho, T. L. *Tetrahedron* **1985**, *41*, 1.
(16) Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* **1974**, 1013.
(17) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

0022-3263/88/1953-0845$01.50/0

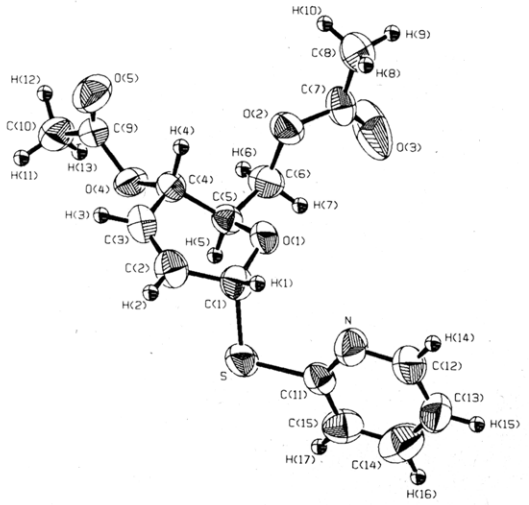
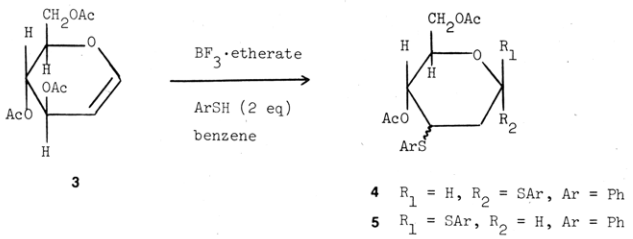


Figure 1. X-ray structure of **6**.

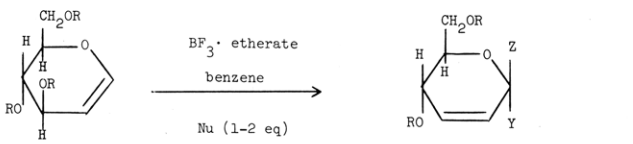
Scheme I



3

4 R_1 = H, R_2 = SAr, Ar = Ph
5 R_1 = SAr, R_2 = H, Ar = Ph

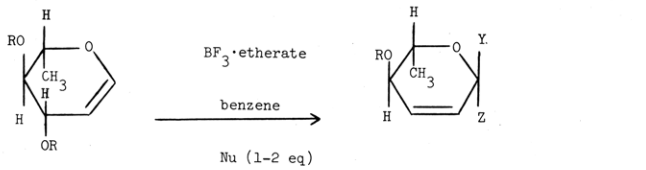
Scheme II



3 R = Ac Nu = HS–(N) **6** R = Ac, Y = S–(N), Z = H
10 R = CH_3 Nu = Me_3SiS–(N) **12** R = CH_3, Y = S–(N), Z = H
10 R = CH_3 Nu = Me_3SiSPh **13** R = CH_3, Y = SPh, Z = H
10 R = CH_3 Nu = $Me_3SiO\overset{S}{C}CH_3$ **17** R = CH_3, Y = $SC\overset{O}{C}H_3$, Z = H
18 R = CH_3, Y = H, Z = $SC\overset{O}{C}H_3$
3 R = Ac Nu = $Me_3SiOC\overset{S}{C}H_3$ **19** R = Ac, Y = $SC\overset{O}{C}H_3$, Z = H
20 R = Ac, Y = H, Z = $SC\overset{O}{C}H_3$

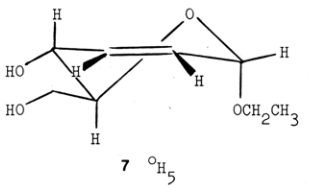
of products suggested by the ^1H NMR spectrum showing a lack of olefinic absorptions allowed the tentative assignment of the products to the mixture of possible diastereomeric bis-thiophenylated products **4** through **5** as shown in Scheme I. In contrast, using the same method, 2-thiopyridine reacted with **3** to give exclusively *S*-(2′-pyridyl) 2,3-dideoxy-4,6-di-*O*-acetyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (**6**) shown in Scheme II, which was confirmed to be the α-anomer by X-ray structure determination of the product recrystallized from methanol as shown in Figure 1. The preferred conformation of **6** can

Scheme III

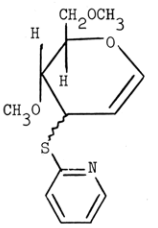


8 R = Ac Nu = HS–(N) **9** R = Ac, Y = S–(N), Z = H
14 R = CH_3 Nu = Me_3SiSPh **15** R = CH_3, Y = SPh, Z = H
14 R = CH_3 Nu = $Me_3SiO\overset{S}{C}CH_3$ **16** R = CH_3, Y = H, Z = $SC\overset{O}{C}H_3$
8 R = Ac Nu = $Me_3SiOC\overset{S}{C}H_3$ **21** R = Ac, Y = $SC\overset{O}{C}H_3$, Z = H
22 R = Ac, Y = H, Z = $SC\overset{O}{C}H_3$

be suggested from the $J_{1,2}$ value of 2.8 Hz and $J_{4,5}$ of 8 Hz to be an equilibrating mixture of the $^OH_5$ conformation with a small contribution of the alternate ^5H_O conformation, or the solution conformation could be the same as that observed in the crystal structure shown in Figure 1. This result is not totally unexpected due to the decrease in anomeric affect of thiols compared to alcohols. It is in contrast to the $^OH_5$ conformation preference observed in both the crystal structure and the solution conformation of ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**7**)



7 $^OH_5$



11

as reported by Jeffrey and co-workers.[18] The extension of this reaction to 3,4-di-*O*-acetyl-L-rhamnal (**8**) also gave only the α product *S*-(2′-pyridyl) 2,3,6-trideoxy-4-*O*-acetyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (**9**) shown in Scheme III. Pertinent spectral data for assignment of **9** as the α anomer were $J_{1,2}$ = 2.9 Hz and $J_{4,5}$ = 9.2 Hz, indicating probable preference for the $^OH_5$ conformation. When this reaction was carried out on 3,4,6-tri-*O*-methyl-D-glucal (**10**), the products after chromatography included the 3-(2′-thiopyridyl)glycals **11**, suggesting equilibration of a mixture during silica gel chromatography and the effect of a leaving group at C-3 on the net regioselectivity. This result led us to examine the companion reaction of [(trimethylsilyl)thio]pyridine with glycal **10** in which only one product was formed, *S*-(2′-pyridyl) 2,3-dideoxy-4,6-di-*O*-methyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (**12**) whose spectral data compared favorably to that of **6**, confirming its assignment as the α-anomer. In addition to regio- and stereoselective α C-1 addition of [(trimethylsilyl)thio]pyridine, [(trimethylsilyl)thio]benzene was also used to prepare the corresponding *S*-phenyl α-anomers **13** and **15** from their respective glycals as shown in Schemes II and III. Their configurations were assigned as α on the basis of comparison of $J_{1,2}$ and $J_{4,5}$ to that of **6**, **9**, and **12** along with supporting ^{13}C NMR, and $J_{C\text{-}1,H}$ data shown in Table I. Compared to the C-4 acetyl products, the C-4 *O*-methyl products apparently undergo faster equilibration between the $^OH_5$ and ^5H_O conformers, resulting in broading of H-1 in the ^1H NMR, a result also

(18) Wingert, L. M.; Ruble, J. R.; Jeffrey, G. A. *Carbohydr. Res.* **1984**, *28*, 1.
(19) Glass, R. S. *J. Organomet. Chem.* **1973**, *61*, 83.
(20) Gornowicz, G. A.; Ryan, J. W. *J. Org. Chem.* **1966**, *31*, 3439.

Table I. Spectral Data Pertinent to Stereochemical Assignments of Products

product	δ(H-1)	$J_{1,2}$ (Hz)	$J_{4,5}$ (Hz)	δ(C-1)	δ(C-5)	$J_{C\text{-}1,H}$ (Hz)
6	6.53	2.8	8.0	79.86	65.05	175
9	6.61–6.60	2.9	9.2	79.5	77.6	170
12	6.52	2.9		80.73	76.2	170
13	5.76		8.5	84.1	69.3	166
15	5.72–5.68	3.0		83.6	66.15	166
16	6.23–6.16	2.9		78.43	69.16	169
17	6.12–6.10	2.3	8.4	77.14	77.25	165
18	6.24–6.23	1.7	8.7	78.66	72.73	170
19	6.14–6.13	1.9	6.7	77.20	74.81	166
20	6.39–6.38	<1	9.4	78.21	69.95	171
21	6.18–6.17	2.2	6.4	76.41	73.24	177
22	6.20	<1	9.0	78.17	70.16	172

observed with α-C-glycosides.[11,17] Consequently, the assignment relied primarily on chemical shift comparison and $J_{4,5}$ rather than $J_{1,2}$. The high regio- and stereoselectivity of this reaction is noteworthy, including the fact that the leaving group at C-3 appears not to have a strong effect on the stereoselectivity of the reaction, with the α-anomer being produced exclusively for both *O*-methyl and *O*-acetate leaving groups. This suggests that trimethylsilyl thiols are strong nucleophiles and prefer to add from the axial face in the normal Ferrier-type transition state.

In contrast to these results, (thionoacetoxy)trimethylsilane underwent reactions with glycals with exclusive regioselectivity for attack at C-1, but with the stereoselectivity being more amenable to the choice of leaving group at C-3. The results are summarized in Schemes II and III. The structure of the products **16–22** and their anomeric configurations were established by detailed and comparative analysis of their ^1H and ^{13}C NMR spectra with supporting evidence from their $J_{C\text{-}1,H}$ values as listed in Table I. The formation of the minor products with the acetate leaving group was extremely helpful for comparative purposes in assigning the configuration of the major products of these reactions and the exclusive products formed from the 3-*O*-methylglycals. As observed before, the minor α-anomers **17**, **19**, and **21** formed in this reaction showed characteristic patterns in the ^1H NMR spectrum similar to those of the respective *S*-phenyl analogues, including smaller $J_{1,2}$ values and $J_{4,5}$ values indicative of a higher proportion of their ^5H_O conformers than in the β-anomers. The ^{13}C NMR data was also useful especially the upfield shift of C-1 in the minor α-products compared to the downfield shift for the β-anomers due to the γ-gauche effect. Although the difference is small for anomeric pairs, it was considered useful because it was not dependent upon the conformational equilibrium. In contrast the $J_{C\text{-}1,H}$ values for all of these compounds appeared to both depend on configuration and conformation, a phenomena which has been observed before in unrelated carbohydrates.[21] We conclude that in the α series a significant population of ^5H_O conformation exists, and the resulting 1,3-diaxial interaction of H-1 and C-6 contribute to a decrease in $J_{C\text{-}1,H}$, causing it to be less than that of the β-anomers, which exist primarily in the $^OH_5$ conformation.

The circular dichroism spectra of products **16–22** were taken to establish the absolute configuration and the results are shown in Figures 2 and 3. In Figure 2 the λ_{min} around 220 nm for the α-anomeric products **19** and **21** is of greater magnitude than the corresponding peaks for **20** and **22**, suggesting that the stereochemical assignments are self-consistent, especially when the NMR data is used as supporting evidence.[22] In Figure 3, the Cotton effects at

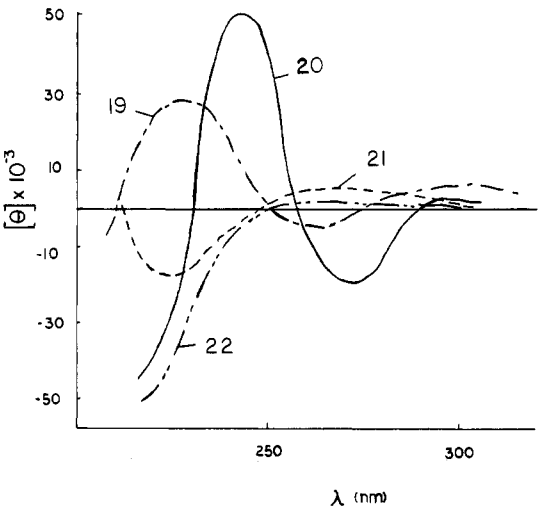


Figure 2. Circular dichroism spectra of *S*-acetyl 4-*O*-acetyl compounds **19–22** in methanol.

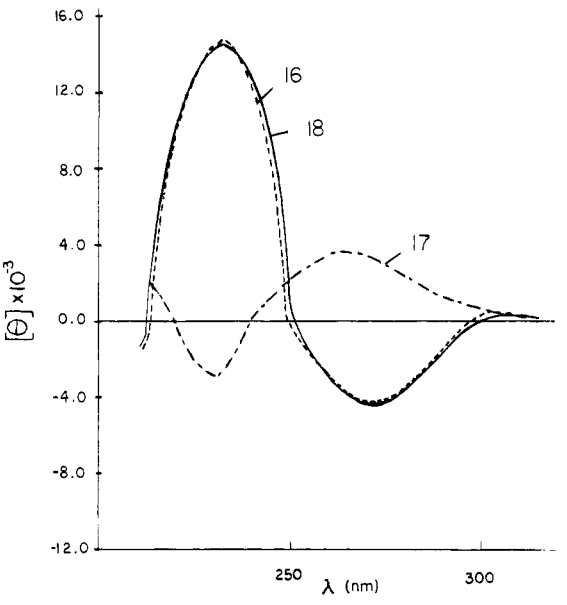


Figure 3. Circular dichroism spectra of *S*-acetyl 4-*O*-methyl compounds **16–18** in methanol.

lower λ appear to be obscured by conformational mobility, and caution must be exercised in weighting the relative significance of $J_{1,2}$, $(^{13}C)\delta$ of C-1, and the CD profiles. We have concluded that with small differences, the γ-gauche effect is most reliable which establishes **18** as the β-anomer, and with supporting spectral data, **16** is also identified as a β-anomer.

In summary, several 1-thiohex-2-enopyranosides have been prepared regioselectively by using trimethylsilyl thiols catalyzed by BF_3 etherate. No products from attack at C-3

(21) Szilagyi, L.; Gyorgydeak, Z. *Carbohydr. Res.* **1985**, *148*, 21.
(22) Cheng, J. C.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3083.

Table II. Summary of C-1 Stereoselectivity

reactant glycal	C-3 group of reactant	C-1 group of product	product ratio	% yield
3	OAc		6 (only α)	90
8	OAc		9 (only α)	83
10	OCH_3		12 (only α)	82
10	OCH_3	SPh	13 (only α)	90
14	OCH_3	SPh	15 (only α)	64
14	OCH_3	$SC(=O)CH_3$	16 (only β)	52
10	OCH_3	$SC(=O)CH_3$	17(α):18(β) = 1:3	90
3	OAc	$SC(=O)CH_3$	19(α):20(β) = 1:1.5	86
8	OAc	$SC(=O)CH_3$	21(α):22(β) = 1:1.7	86

were observed, showing that this method is regiospecific for attack at C-1. The stereoselectivity observed depended on the trimethylsilyl thiol and the leaving group at C-3 of the glycal as summarized in Table II. With 2-thiopyridine and the *O*-acetyl group at C-3 only the C-1 α-anomers **6** and **9** were produced. However, with the OCH_3 leaving group the reaction was both regiospecific and α-stereospecific using [(trimethylsilyl)thio]pyridine to give **12** or [(trimethylsilyl)thio]benzene to give **13** and **15**. In contrast to the α-stereoselectivity, (thionoacetoxy)trimethylsilane was stereoselective for the β-anomers. With the poorer OCH_3 leaving group, the β-selectivity was higher as shown by stereospecific formation of **16**, and stereoselective formation of **18** (α:β = 1:3). With the better *O*-acetyl leaving group, the β-anomers **20** and **22** were still the major products, but the ratios were only α:β = 1:1.5 and 1:1.7, respectively. On the basis of comparative Ferrier reactions with other nucleophiles these results suggest that if the nucleophile is not coordinated to the leaving group at C-3, the α C-1 anomers are produced by an anomeric-controlled earlier transition state than the β-anomers. The β-products could arise from attack on an ion pair from a later transition state. Alternatively, the β-selectivity of (thionoacetoxy)trimethylsilane can also be rationalized from a **2**-like transition state in which silicon is coordinated to the leaving group during nucleophilic attack, a more likely possibility for the poorer leaving group. The mechanistic suggestions based on these results will be further investigated with better leaving groups at C-3, with anticipation of achieving better α-selectivity, and additional anomeric proof on a crystalline derivative will be obtained.

Experimental Section

NMR spectra were recorded for solutions in $CDCl_3$ on either Nicolet 200, Varian VXR 300, or Varian VXR 500 spectrometers. ^1H NMR spectra are reported referenced to internal Me_4Si at 200, 300, or 500 MHz with coupling constants reported in hertz. ^{13}C NMR spectra were reported at 50.3, 75.5, or 125.7 MHz referenced to $CDCl_3$ (77.00). Multiplicities from off-resonance decoupling experiments are in agreement with the assignments, and ^1J values were obtained in the gated mode. Mass spectra were obtained on either a Kratos MS-80 or an MS-52 mass spectrometer in either low resolution electron impact (EI) or chemical ionization (CI, CH_4) mode or in the high resolution mode with appropriate peak-matching references. IR spectra were recorded on a Nicolet FTIR spectrometer. Optical rotations were measured on a Rudolph Autopol III polarimeter and circular dichroism spectra were measured on a JASCO J 500A spectropolarimeter. TLC and column chromatography were performed on silica gel GF_{254} (230–400 mesh, Merck). Analytical HPLC was performed by using a 30-cm Waters 5μ Microporasil column, semipreparative HPLC was performed by using a 50-cm Whatman Magnum 9 silica gel column, and radial chromatography was performed on a Chromatotron (Harrison Research) using 2 mm and 4 mm silica gel 60 (Merck, PS 254). All solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran, benzene, and dimethoxyethane were distilled from sodium metal in the presence of benzophenone ketyl. All air-sensitive reactions were performed under an atmosphere of argon. 3,4,6-Tri-*O*-acetyl-D-glucal and 3,4-di-*O*-acetyl-L-rhamnal were purchased from Pfanstiehl Laboratories.

3,4,6-Tri-*O*-methyl-D-glucal (10). D-Glucal (5.36 g, 36.7 mmol) was prepared by the method of Blackburne,[23] dissolved in dry THF (35 mL) and added dropwise with stirring into a 0 °C suspension of oil-free sodium hydride (3.52 g, 147 mmol) in THF (100 mL). Additional solvent (10 mL, 0.25 M total) was used to complete the transfer. The mixture was stirred at 0 °C until hydrogen evolution had ceased and then stirred for 1 h at room temperature. Methyl iodide (26.1 g, 184 mmol) was then added dropwise with stirring and the mixture was allowed to stir overnight. The reaction mixture was then cooled to 0 °C and quenched by addition of MeOH (20 mL, 495 mmol) before being partitioned between water (75 mL) and ether (25 mL). The aqueous layer was washed with additional ether (3 × 75 mL) and the combined ether extracts were washed with water (1 × 50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed in vacuo, yielding **10** as a pale yellow oil (5.1 g, 74%) which was identified on the basis of its ^1H NMR spectrum and used without further purification. Data for **10**: R_f 0.65 (30% EtOAc/hexane); ^1H NMR δ 6.44–6.37 (dd, J = 6.1, 1.3, H-1), 4.88–4.81 (dd, J = 6.1, 2.8, H-2), 4.04–3.93 (ddd, J = 8.3, 4.8, 3.4, H-5), 3.93–3.86 (d, J = 6.0, H-3), 3.69–3.64 (d, J = 4.9, H-6), 3.52–3.41 (dd, J = 8.3, 6.0, H-4), 3.42 (s, OCH_3), 3.41 (s, OCH_3), 3.44 (s, OCH_3).

3,4-Di-*O*-methyl-L-rhamnal (14). Using the O-alkylation procedure described by Brown,[24] L-rhamnal (9.41 g, 72.3 mmol), prepared by the method of Blackburne,[23] was dissolved in dimethoxyethane (50 mL) and added dropwise with stirring to a suspension of of oil-free potassium hydride (7.25 g, 181 mmol) in DME (150 mL). The mixture was stirred 1 h at 0 °C and then 1 h at room temperature, cooled to 0 °C, and methyl iodide (35.9 g, 253 mmol) added over a 30-min period. The reaction mixture was stirred at room temperature for 2 h and then quenched by addition of MeOH (10 mL) before being partitioned between water (25 mL) and ether (75 mL). The aqueous layer was extracted with additional ether (3 × 40 mL), and the combined ether extracts were washed with water (25 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed in vacuo to afford **14** as a yellow oil which was greater than 80% methylated by ^1H NMR. Filtration through silica gel (crude residue) gave **14** (59 g, 52%). Data for **14**: R_f 0.77 (30% EtOAc/hexane); ^1H NMR δ 6.39–6.33 (dd, J = 6.0, 1.1, H-1), 4.87–4.80 (dd, J = 6.1, 2.6, H-2), 3.98–3.82 (m, 2 H, H-3, 5), 3.57 (s, OCH_3), 3.41 (s, OCH_3), 3.20–3.10 (dd, J = 8.6, 6.3, H-4), 1.42–1.34 (d, J = 6.4, CH_3).

General Procedure for BF_3 Etherate Catalyzed Additions of Thiol Derivatives to Glycals. Following the general procedure for additions described by Zamojski,[12] a solution of the glycal and the thiol derivative (1.2 equiv) in benzene (0.28 M) at 5 °C was stirred for 5 min followed by addition of BF_3 etherate (1.2 equiv). The cooling bath was removed and the mixture stirred until the reaction was complete (monitored by TLC). The mixture was quenched by either addition of aqueous sodium bicarbonate and extraction with CH_2Cl_2 or by nonaqueous workup with addition of solid $NaHCO_3$, stirring for 30 min, and evaporation to dryness, and the residue was taken up in CH_2Cl_2 and filtered. The resulting CH_2Cl_2 solutions were evaporated and the residue filtered through a short silica gel column eluting with CH_2Cl_2. After evaporation the crude product was chromatographed on silica gel, eluting with EtOAc/hexane to afford each product as a yellow oil characterized as follows.

Reaction of 3,4,6-Tri-*O*-acetyl-D-glucal (3) with Thiophenol. Using the method above with the nonaqueous workup, a mixture of four components, inseparable by flash chromatography (5% EtOAc/pentane), was obtained. They were tentatively identified as a mixture of **4** and **5** on the basis of the ^1H NMR

(23) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 331.
(24) Diner, V. E.; Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1591.

spectrum of the mixture. Data for the mixture: R_f 0.74 (7:3 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.53–7.14 (m, SC_6H_5), 5.83–5.38 (m, 2 H), 4.92–4.79 (m, 1 H), 4.43–3.98 (m, 3 H), 3.79–3.04 (m, 3 H), 1.97, 1.96, 1.09 (s, OAc); $[\alpha]^{25}_D$ +13.90 (*c* 0.1240, $CHCl_3$).

***S*-(2′-Pyridyl) 2,3-Dideoxy-4,6-di-*O*-acetyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (6).** From 3,4,6-tri-*O*-acetyl-D-glucal (**3**) (0.178 g, 0.655 mmol) and 2-thiopyridine (0.146 g, 2.0 eq) using the above procedure was obtained after 45 min, nonaqueous workup, and filtration through silica gel crude **6** which was recrystallized from hot MeOH, to yield **6** as white needles (0.196 g, 90%, mp 123.0–123.5 °C). Data for **6**: R_f 0.62 (7:3 toluene/EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.41–8.36 m, (1 H), 7.56–6.93 (m, 3 H), 6.53 (dd, J = 2.8, 1.5, H-1), 6.10–5.97 (ddd, J = 11, 2.8, 1.5, H-2), 5.88–5.77 (ddd, J = 11, 1.5, 1.5, H-3), 5.40–5.31 (dddd, J = 8.0, 1.5, 1.5, 0.5, H-4), 4.32–4.02 (m, H-5, H-6, H-6′), and 2.08, 1.95 (s, OAc); ^{13}C NMR ($CDCl_3$) δ 169.32, 168.76 (OAc), 155.82 (C-2′), 148.60 (C-5′), 135.67 (C-4′), 127.68 (C-2), 127.13 (C-3), 122.59 (C-3′), 120.07 (C-6′), 79.86 (C-1), 68.44 (C-4), 65.05 (C-5), 62.91 (C-6), 21.68, 21.39 (OAc); $J_{C\text{-}1,H}$ = 175; IR ($CHCl_3$) 3020, 2920, 1740, 1575, 1560, 1450, 1430, 1425, 1370, 1240, 1120, 1080, 1050, 985, 950, 780, 750, and 705 cm^{-1}; MS (HRCI–CH_4), calcd for $C_{15}H_{18}NO_5S$ 324.0906, found 324.0899; $[\alpha]^{25}_D$ +113.51° (*c* 0.0232, $CHCl_3$).

***S*-(2′-Pyridyl) 2,3,6-Trideoxy-4-*O*-acetyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (9).** From 3,4-di-*O*-acetyl-L-rhamnal (**8**) (1 g, 4.67 mmol) was obtained after 45 min stirring, workup, and chromatography **9** as yellow needles (1.02 g, 83%, mp 98 °C). Data for **9**: ^{1}H NMR δ 8.52–8.51, 7.6–7.1 (m, SPy), 6.61–6.60 (dd, J = 3.0, 2.0, H-1), 6.1–6.0 (ddd, J = 10.4, 2.8, 1.9, H-2), 5.90–5.84 (ddd, J = 10.1, 3.2, .6, H-3), 5.18–5.13 (ddd, J = 9.3, 3.7, 2.0, H-4), 4.20–4.02 (dq, J = 9.1, H-5), 2.11 (s, OAc), 1.57–1.56 (d, J = 6.18, C-6); ^{13}C NMR 176.3 (OAc), 157.4, 149.5, 136.5, 122.9, 120.3 (SPy), 128.4, 128.1 (C-2, C-3) 79.5 (C-1), 70.4 (C-4), 77.6 (C-5), 20.9 (OAc), 17.9 (C-6); $J_{C\text{-}1,H}$ = 170; IR (cm^{-1}) 3020, 2925, 1740, 1577, 1559, 1454, 1418, 1374, 1264, 1241, 1216, 1123, 1093, 1065, and 1043; MS (CI-CH_4), m/z 206, 289, 95; HREI calcd for $C_{13}H_{15}NO_3S$ 265.0782, found 265.0774; $[\alpha]^{25}_D$ −246° (*c* 0.0107, $CHCl_3$).

Reaction of 2,4,6-Tri-*O*-methyl-D-glucal (10) with 2-Thiopyridine. From 2,4,6-tri-*O*-methyl-D-glucal (**10**) (0.3 g, 1.6 mmol) was obtained after 2 h, workup, and filtration through silica gel a mixture of two products (34 g, 89%). The ^{1}H NMR of the mixture showed them to be a 1:1 mixture of **11a** and **11b**. ^{1}H NMR data for **11** from the mixture: **11a** δ 8.44–8.42 (m, 1 H), 7.52–6.99 (m, 3 H), 6.40–6.37 (d, J = 5.5, 1 H), 5.18 (dd, J = 5.0, 5.3, 1 H), 4.68–4.64 (dd, J = 2.2, 6.3, 1 H), 3.87–3.81 (m, 1 H), 4.08–4.01 (m, 1 H), 3.73–3.71 (m, 2 H), 3.42 (s, 3 H), 3.28 (s, 3 H); **11b** δ 6.43–6.40 (J = 5.6, 1 H), 5.01–4.98 (dd, J = 5.7, 5.7, 1 H), 4.87–4.83 (ddd, J = 2.7, 2.8, 1.6, 1 H), 3.78–3.71 (m, 1 H), 4.08–4.01 (m, 1 H), 3.73–3.71 (m, 2 H), 3.56 (s, 3 H), 3.43 (s, 3 H).

***S*-(2′-Pyridyl) 2,3-Dideoxy-4,6-di-*O*-methyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (12).** From 3,4,6-tri-*O*-methyl-D-glucal (**10**) (0.3 g, 1.6 mmol) and [(trimethylsilyl)thio]pyridine (0.33 g, 1.9 mmol) was obtained after 1 h, nonaqueous workup, and flash chromatography **12** as a yellow oil (350 mg, 82%). Data for **12**: R_f 0.42 (30% EtOAc/hexane); ^{1}H NMR δ 8.47–8.45 (m, 1 H), 7.65–7.62 (m, 3 H), 6.52 (dd, J = 2.9, 1.8, H-1), 6.12–6.06 (dd, J = 11.0, 1.2, H-3), 6.04–6.02 (ddd, J = 10.5, 3.0, 1.8, H-2), 4.10–4.00 (m, H-4, H-5), 3.71–3.56 (m, H-6,6′), 3.42 (s, OCH_3), 3.36 (s, OCH_3); ^{13}C NMR δ 154.0, 147.6, 136.6, 123.4, 121.5 (SPy), 128.7, 127.3 (C-2, C-3), 80.73 (C-1), 76.2 (C-5), 71.4 (C-4), 76.51 (C-6), 59.2 (OCH_3), 56.59 (OCH_3); $J_{C\text{-}1,H}$ = 170; MS (HREI), calcd for $C_{13}H_{17}O_3N_5$ 267.09301, found 267.0971.

***S*-Phenyl 2,3-Dideoxy-4,6-di-*O*-methyl-1-thio-α-D-*erythro*-hex-2-enopyranoside (13).** From 3,4,6-tri-*O*-methyl-D-glucal (**10**) (3 g, 16 mmol) and [(trimethylsilyl)thio]benzene[19] (6 g, 26 mmol) was obtained after 4 h of stirring, nonaqueous workup, and flash chromatography **13** as a yellow oil (3.81 g, 90%). Data for **13**: R_f 0.84 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.5–7.1 (m, Ph), 6.06–6.02 (d, J = 10.5, H-3), 5.99–5.94 (ddd, J = 10.5, 2.0, 2.0, H-2), 5.76 (br s, H-1), 4.23–4.13 (ddd, J = 8.5, 2.5, 4.0, H-4), 4.05–3.90 (ddd, J = 8.5, 2.0, 2.0, H-5), 3.80–3.61 (m, H-6), 3.41 (s, OCH_3), 3.34 (s, OCH_3); ^{13}C NMR ($CDCl_3$) δ 136, 131, 129, 128 (SPh), 127.4 (C-2), 127.2 (C-3), 84.1 (C-1), 71.6 (C-5), 71.5 (C-4), 69.3 (C-6), 59.3 (OCH_3), 56.3 (OCH_3); $J_{C\text{-}1,H}$ = 166; MS (HREI), calcd for $C_{14}H_{18}O_3S$ 266.0977, found 266.0966.

***S*-Phenyl 2,3,6-Trideoxy-4-*O*-methyl-1-thio-α-L-*erythro*-hex-2-enopyranoside (15).** From 3,4-di-*O*-methyl-L-rhamnal (**14**) (1.5 g, 10.8 mmol) was obtained after 1.58 h of stirring, nonaqueous workup, and chromatography **15** as a yellow oil (1.6 g, 64%). Data for **15**: R_f 0.78 (30% EtOAc/hexane); ^{1}H NMR δ 7.5–7.1 m, (SPh), 6.03–5.94 (ddd, J = 10.0, 3.0, 1.5, H-3), 5.93–5.86 (ddd, J = 16.0, 1.7, 1.2, H-2), 5.72–5.68 (ddd, J = 3, 1.0, 1.0, H-1), 4.07–3.88 (m, H-4, H-5), 1.36–1.30 (d, J = 5.7, C-6); ^{13}C NMR 131.4, 129.2, 129.0, 127.4 (SPh), 127.5, 127.2 (C-2, C-3), 83.6 (C-1), 77.01 (C-5), 66.15 (C-4), 56.4 (OCH_3), 18.0 (C-6); $J_{C\text{-}1,H}$ = 166; MS (CI-CH_4), m/z 236, 203, 137; (HREI) calcd for $C_{13}H_{16}O_2S$ 236.0872, found 236.0890.

***S*-Acetyl 2,3,6-Trideoxy-4-*O*-methyl-1-thio-β-L-*erythro*-hex-2-enopyranosides (16).** From 3,4-di-*O*-methyl-L-rhamnal (**14**) (1.99 g, 12.6 mmol) and (thionoacetoxy)trimethylsilane[20] (3.74 g, 25.2 mmol) after 1 h of stirring, nonaqueous workup, and silica gel chromatography was obtained **16** as a yellow oil (2.34 g, 92%). Data for **16**: R_f 0.70 (30% EtOAc/hexane), t_R 7 min (10% EtOAc/hexane, 1.0 mL/min); ^{1}H NMR δ 6.23–6.16 (ddd, J = 2.9, 1.5, H-1), 6.08–5.99 (ddd, J = 10.2, 1.5, 1.5, H-2), 5.87–5.77 (ddd, J = 10.2, 3.0, 1.6, H-3), 3.66–3.45 (m, 2 H, H-4, 5), 3.42 (s, OCH_3), 2.37 (s, $SCOCH_3$), 1.36–1.25 (d, J = 5.6, CH_3); ^{13}C NMR δ 194.38 (C=O), 128.46, 126.85 (C-2, 3), 78.43 (C-1), 77.51 (C-5), 69.16 (C-4), 56.66 (OCH_3), 30.98 ($SCOCH_3$), 18.29 (CH_3); $J_{C\text{-}1,H}$ = 169; IR (film) 3020, 2970, 2930, 2870, 2815, 1698, 1693, 1685, 1120, and 1095; MS (EI), m/z (relative intensity) 203 (21), 202 (0.7), 179 (22), 127 (100), 95 (38), 90 (37); (HREI) calcd for $C_9H_{14}O_3S$ 202.0664, found 202.0667; $[\alpha]^{25}_D$ −212° (*c* 0.0345, $CHCl_3$).

***S*-Acetyl 2,3-Dideoxy-4,6-di-*O*-methyl-1-thio-α,β-D-*erythro*-hex-2-enopyranosides (17, 18).** From 3,4-6-tri-*O*-methyl-D-glucal (**10**) (4.72 g, 25.1 mmol) and (thioacetoxy)trimethylsilane (50.2 mmol) was obtained after 3 h of stirring, aqueous workup, silica gel chromatography, and HPLC eluting with 20% EtOAc/hexane **17** and **18** as a yellow oil (5.25 g, 90%, **17**:**18** = 25:75). Data for **17**: R_f 0.49 (30% EtOAc/hexane), t_R 34 min (20% EtOAc/hexane, 3.0 mL/min); ^{1}H NMR (500 MHz) δ 6.12–6.10 (ddd, J = 2.3, 2.2, 2.2, H-1), 6.09–6.06 (ddd, J = 10.1, 2.4, 2.4, H-2), 5.86–5.84 (ddd, J = 10.2, 1.9, 1.9, H-3), 3.86–3.83 (ddd, J = 8.4, 2.2, 2.1, H-4), 3.80–3.77 (ddd, J = 8.3, 3.6, 1.6, H-5), 3.62–3.61 (dd, J = 9.6, 2.2, H-6), 3.61–3.60 (dd, J = 10.6, 3.4, H-6), 3.41 (s, 3 H), 3.59 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR δ 193.36 (C=O), 128.12, 127.97 (C-2, C-3), 77.25 (C-5), 77.14 (C-1), 71.79 (C-6), 70.87 (C-4), 59.29, 56.50 (OCH_3), 30.62 (CH_3); $J_{C\text{-}1,H}$ = 165; $[\alpha]^{25}_D$ 138° (*c* 0.0415, $CHCl_3$).

Data for **18**: R_f 0.49 (30% EtOAc/hexane); t_R 31 min (20% EtOAc/hexane, 3.0 mL/min); ^{1}H NMR (500 MHz) δ 6.24–6.23 (dddd, J = 1.7, 1.6, 1.5, 1.5, H-1), 6.03–6.01 (ddd, J = 10.2, 1.7, 1.6, H-2), 5.83–5.78 (ddd, J = 10.1, 3.1, 1.9, H-3), 3.92–3.89 (ddd, J = 8.73, 2.19, H-4), 3.63–3.59 (m, H-5, H-6), 3.42 (s, CH_3), 3.40 (s, OCH_3), 2.37 (s, $SCOCH_3$); ^{13}C NMR: δ 193.78 (C=O), 128.34, 127.01 (C-2, C-3), 78.66 (C-1), 72.73 (C-5), 71.52 (C-4), 71.37 (C-6), 59.34 (OCH_3), 56.64 (OCH_3), 30.91 ($SCOCH_3$); $J_{C\text{-}1,H}$ = 170; IR (film) 3020, 2980, 2920, 2880, 2815, 1698, 1693, 1685, 1110, 1095, and 1080 cm^{-1}; MS (HRCI) calcd for MH^+ $C_{10}H_{17}O_4S$ 233.0843, found 233.0849; (HREI) calcd for M − CH_3OH $C_9H_{12}O_3S$ 200.0506, found 200.0508.

***S*-Acetyl 2,3-Dideoxy-4,6-di-*O*-acetyl-1-thio-α,β-D-*erythro*-hex-2-enopyranosides (19, 20).** From 3,4,6-tri-*O*-acetyl-D-glucal (**3**) (236 mg, 1.258 mmol) and (thionoacetoxy)-trimethylsilane (372 mg, 2.05 mmol) was obtained after 1 h of stirring, aqueous workup, silica gel chromatography, and semipreparative HPLC **19** and **20** (311 mg, 86%, **19**:**20** = 1:1.5). Data for **19**: R_f 0.36 (1:3 EtOAc/hexane); t_R 10 min (20% EtOAc/hexane, 3.0 mL/min); ^{1}H NMR (500 MHz) δ 6.14–6.13 (dd, J = 1.9, 1.6, H-1), 5.92–5.88 (m, H-2, H-3), 5.25–5.23 (ddd, J = 6.7, 2.1, 1.6, H-4), 3.98–3.95 (ddd, J = 6.4, 6.1, 3.9, H-5), 4.22–4.18 (dd J = 12.1, 5.8, H-6), 4.17–4.15 (dd, J = 11.9, 3.9, H-6), 2.37 (s, $SCOCH_3$), 2.08 (s, OAc), 2.08 (s, OAc); ^{13}C NMR (75 MHz) δ 193.06 (C=O), 170.75 (C=O), 170.21 (C=O), 129.38, 126.75 (C-2, C-3), 77.20 (C-1), 74.81 (C-5), 64.01 (C-4), 62.88 (C-6), 30.70 ($SCOCH_3$), 20.97 (OAc), 20.83 (OAc); $J_{C\text{-}1,H}$ = 166; IR (film) 3056, 2485, 2903, 2870, 1793, 1704, 1700, 1380, 1242, and 1097.

Data for 20: R_f 0.39 (30% EtOAc/hexane); t_R 9 min (20% EtOAc/hexane, 30 mL/min); ^{1}H NMR (500 MHz) δ 6.39–6.38 (s, H-1), 5.91–5.87 (ddd, J = 10.19, 2.6, 1.7, H-3), 5.86–5.83 (d, J = 10.15, H-2), 5.38–5.35 (ddd, J = 9.4, 3.5, 1.7, H-4), 4.24–4.20 (dd,

J = 12.2, 4.9, 1 H), 4.15-4.12 (dd, J = 12.2, 2.4, 1 H), 3.90-3.86 (ddd, J = 9.5, 5.0, 2.5, H-5), 2.35 (s, $SCOCH_3$), 2.06 (s, OAc), 2.05 (s, OAc); ^{13}C NMR (75 MHz) δ 193.13 (C=O), 170.15 (C=O), 170.02 (C=O), 127.99, 127.75 (C-2, C-3), 78.21 (C-1), 69.95 (C-5), 64.58 (C-4), 62.67 (C-6), 30.93 ($SCOCH_3$), 20.95, 20.75 (OAc); $J_{C\text{-}1,H}$ = 171; IR (film) 3056, 2985, 2903, 2870, 1793, 1704, 1700, 1242, and 1097; MS (CI-C_4H_{10}), m/z (relative intensity) 289 (5, MH^+); (HREI) calcd for $M^+ - SCOCH_3$ $C_{10}H_{13}O_6$, 213.0765 found 213.0958.

S-Acetyl 2,3,6-Trideoxy-4-O-acetyl-1-thio-α,β-L-erythro-hex-2-enopyranosides (21, 22). From 3,4-di-O-acetyl-L-rhamnal (**8**) (100 mg, 0.46 mmol) and (thionoacetoxy)trimethylsilane (136 mg, 0.92 mmol) after 1 h of stirring, nonaqueous workup, chromatography, and semipreparative HPLC were obtained **21** and **22** (81 mg, 86% **21**:**22** = 1:1.7). Data for **21**: R_f 0.72 (30% EtOAc/hexane); t_R 11.2 min (20% EtOAc/hexane, 2.0 mL/min); ^1H NMR (500 MHz) δ 6.18-6.17 (d, J = 2.2, H-1), 5.89-4.97 (m, H-2, H-3), 5.07-5.04 (ddd, J = 6.3, 1.7, 1.3, H-4), 3.95-3.90 (dq, J = 6.4, 6.4, H-5), 2.39 (s, $SCOCH_3$), 2.11 (s, OAc), 1.31-1.30 (d, J = 6.4, C-6); ^{13}C NMR (75 MHz) δ 1.93.37 (C=O), 170.36 (C=O), 129.66, 126.73 (C-2, C-3), 76.41 (C-1), 73.24 (C-5), 68.97 (C-4), 30.65 ($SCOCH_3$), 20.98 ($OCOCH_3$), 18.18 (CH_3); $J_{C\text{-}1,H}$ = 177; IR (film) 3149, 3051, 2985, 1733, 1701, 1375, 1264, 1244, 1045.

Data for **22**: R_f 0.72 (30% EtOAc/hexane); t_R 11.6 min (20% EtOAc/hexane, 2.0 mL/min); ^1H NMR (500 MHz) δ 6.20 (br s, H-1), 5.82-5.80 (d, J = 9.9, H-2), 5.90-5.85 (ddd, J = 10.0, 3.0, 1.7, H-3), 5.30-5.26 (ddd, J = 9.0, 3.6, 1.7, H-4), 3.96-3.90 (dq, J = 9.0, 6.13, H-5), 2.36 (s, $SCOCH_3$), 2.07 (s, OAc), 1.22-1.21 (d, J = 6.18, C-6); ^{13}C NMR (75 MHz) δ 193.90 (C=O), 179.32 (C=O), 128.16, 128.04 (C-2, C-3), 78.17 (C-1), 70.16 (C-5), 68.26 (C-4), 30.95 ($SCOCH_3$), 21.04 ($OCOCH_3$), 18.01 (CH_3); $J_{C\text{-}1,H}$ = 172; IR (film) 3149, 3051, 2985, 1733, 1701, 1375, 1264, 1244, and 1045; MS (CI-C_4H_{10}), m/z (relative intensity) 289 (5, MH^+); (HREI) calcd for $C_{13}H_{11}O_3$ ($M^+ - SCOCH_3$) 155.0708, found 155.0709.

Acknowledgment. Support for this research from the National Institutes of Health (CA 21162), the American Cancer Society, Department of Energy, and the Materials Technology Center at Southern Illinois University is gratefully acknowledged. Several spectroscopic facilities, their funding agencies, and staff personnel are acknowledged as follows: Southern Illinois University Crystallographic Laboratory, Dr. P. D. Robinson; Purdue University Biomagnetic Resonance Laboratory (NIH), Dr. W. M. Westler; Southern Illinois University at Carbondale NMR Facility, Dr. J. Lee and Mitch Sasa; Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska (NSF CHE-8211164), Drs. Ken Tomar and Ronald L. Cerny; Mass Spectrometry Laboratory Research Center, Southern Illinois University at Carbondale (DOE), Ken Walsh; Washington University Department of Chemistry Circular Dichroism Facility (NIH), Dr. Marilyn Holtzer.

Registry No. **3**, 2873-29-2; **4** (diastereomer 1), 112247-47-9; **4** (diastereomer 2), 112247-48-0; **5** (diastereomer 1), 112247-49-1; **5** (diastereomer 2), 112247-50-4; **6**, 112247-51-5; **8**, 34819-86-8; **9**, 112247-52-6; **10**, 16740-98-0; **11** (diastereomer 1), 112247-53-7; **11** (diastereomer 2), 112344-70-4; **12**, 112247-54-8; **13**, 112247-56-0; **14**, 53657-41-3; **15**, 112247-57-1; **16**, 112247-58-2; **17**, 112247-59-3; **18**, 112247-60-6; **19**, 4631-35-0; **20**, 23025-38-9; **21**, 112247-61-7; **22**, 112247-62-8; PhSH, 108-98-5; Me_3SiSPh, 4551-15-9; $Me_3SiOC(S)CH_3$, 13247-83-1; D-glucal, 13265-84-4; 2-thiopyridine, 2637-34-5; 2-[(trimethylsilyl)thio]pyridine, 112247-55-9.

Supplementary Material Available: X-ray data of **6** including X-ray diffractometer set up, methods, tables of fractional coordinates, thermoparameters, interatomic distances and angles, intramolecular distances, torsional angles and least-squares planes for **6** and list of CD data of compounds in Figures 2 and 3 (9 pages). Ordering information is given on any current masthead page.

Intramolecular Cycloaddition Reactions of *N*-Acyl Imines. A Stereoselective Approach to the N-Terminal Amino Acid Component of Nikkomycin B

Michael J. Melnick and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received August 31, 1987

Diels-Alder cyclizations of *N*-acyl imines derived from glyoxylates **5** and **8** stereoselectively produced cis-fused bicyclo-1,3-dihydrooxazine γ-lactones **7** and **10**, respectively. The cycloaddition failed to yield the corresponding δ-lactone **12** derived from precursor **11**. Selective ring cleavages of cycloadduct **2** afforded hydroxy amide **13** and α-amino lactone **14**. Efficient application of this methodology to the stereoselective synthesis of the N-terminal amino acid portion **15** of nikkomycin B (**16**) is described. Diels-Alder precursor **21**, readily available in three steps from known allylic chloride **17**, was cyclized to the bicyclodihydrooxazine **22**. This compound was readily converted to lactone **26**.

In 1984 we described the first example of an intramolecular [4 + 2]-cycloaddition involving an *N*-acyl imine and an alkene[1a,2] (eq 1). The reaction proved to be totally stereoselective and afforded the cis-fused bicyclic dihydro-1,3-oxazine γ-lactone shown in structure **2**. This result prompted us to investigate the type of cycloaddition shown in eq 2.[1b] In these cases trans-fused bicyclic dihydrooxazines such as **4** were formed exclusively. Interestingly, the systems in eq 2 cyclized under Lewis acid catalysis, but *not* thermally. We have postulated that in the thermal cyclization (eq 1) an acyl imine **1** is involved, whereas in the BF_3·Et_2O-promoted reactions (eq 2) an acyl iminium complex **3** is an intermediate. Moreover, we have previously attempted to rationalize these stereochemical results,[1] although we are still not certain if **2** is in fact a kinetic reaction product. Since we initially investigated only a single example of a cyclization of a glyoxylate-derived acyl imine **1**,[1a] we decided to look at a few additional cases of this type and to explore the application of this

(1) (a) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (b) Scola, P. M.; Weinreb, S. M. *Ibid.* **1986**, *51*, 3248.

(2) For reviews of intermolecular cycloadditions of this type see: Schmidt, R. R. *Synthesis* **1972**, 333. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212. See also: Boger, D. R.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: Orlando, 1987.

0022-3263/88/1953-0850$01.50/0