A New Approach to the Synthesis of Hexoses: An Entry to (±)-Fucose and (±)-Daunosamine

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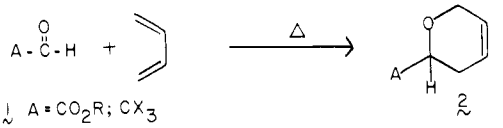
Abstract: The preparation and reactions of three of the four geometrical isomers of 1-(benzoyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,3-butadiene are described. The Lewis acid catalyzed cyclocondensations of these dienes with acetaldehyde afford selectively (±)-*cis*-2-methyl-3-(benzoyloxy)-2,3-dihydro-4-pyrone (**13**). The conversion of **13** to derivatives of (±)-fucose and (±)-daunosamine has been accomplished.

Background

Thermally induced cycloadditions of certain aldehydes of the type **1** bearing activating groups (cf. A) with conjugated dienes to afford dihydropyrans such as **2** are well-known.[1,2] The po-



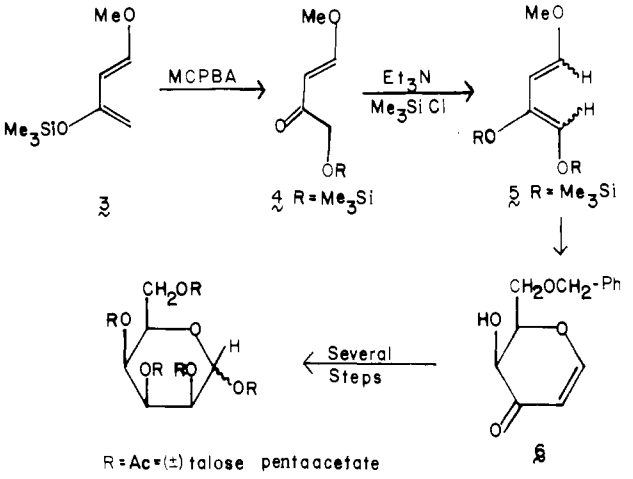
1 2

tentialities of even these limited thermal reactions to the synthesis of various hexoses were well recognized and exploited by Zamojski[3] and by David.[4] The use of 1-alkoxy dienes, where the alkoxy group corresponds to a hexose, is the key step in David's ingenious nonglycosylative route to disaccharides.[4]

Recently our laboratory has investigated the Lewis acid mediated cyclocondensation reaction of activated dienes with aldehydes. Through this chemistry, the range of participating aldehydes and dienes has been enormously increased and stereochemical control becomes more feasible.[5-8]

As part of our early examination of the scope of the catalyzed reaction, we prepared and evaluated the behavior of the diene **5**.[5a] This compound arose from the enol silylation of silyloxy ketone **4**, which was obtained from silyloxy diene **3**. As described in our previous report,[5a] diene **5** is a very unstable substance, which, in our hands, did not lend itself to purification. However, in crude form, with $BF_3 \cdot OEt_2$ as the Lewis acid catalyst, **5** did react with (benzoyloxy)acetaldehyde to afford dihydropyrone **6**. While the yield of the pyrone was quite modest, it was interesting to find that the chiral centers at C_4 and C_5 (hexose numbering) were produced in a cis relationship. The NMR spectrum of the crude reaction mixture indicated the presence of some trans (i.e., "gluco") epimers, but it was clear that a stereoselective route to the cis (i.e., "galacto") series had been realized. By a series of straightforward manipulations, **6** was transformed to the "all cis" (±)-talose series,[5a]

Below we relate (i) the preparation of more stable versions of such dienes, (ii) the application of these compounds to the synthesis



of the biologically important hexoses, fucose[9] and daunosamine,[10-12] and (iii) the evaluation of the relationship of the stereochemistry of the pyrone resulting from cyclocondensation with acetaldehyde as a function of the geometry of the diene and the nature of the Lewis acid catalyst.

Results

Reaction of diene **3**[13] with *m*-chloroperoxybenzoic acid according to Rubottom[14] affords silyloxy diene **4** (90% yield). Desilylation with excess methanol gives rise to the labile **7**, which, upon reaction with benzoyl chloride and pyridine, produces the benzoyloxy ketone **8**, mp 74–75 °C, in 48% yield from **3**.

Enol silylation was most conveniently accomplished by reaction of **8** with *tert*-butyldimethylsilyl triflate in the presence of triethylamine–carbon tetrachloride.[15] Not surprisingly these reactions give rise to an *E,Z* mixture about the "enediolate" 1,2-double bond. More surprisingly, a third component, in which the homogeneous (*E*)-methoxy ene system of **8** had undergone partial trans-to-cis isomerization, was also encountered. Thus, NMR

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(3) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.
(4) David, S.; Lubineau, A.; Vatele, J. M. *Nouv. J. Chim.* **1980**, *4* (8–9), 547.
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(8) For full accounts of the studies of the mechanism and stereochemistry of these reactions, see the preceding two papers in this issue.
(9) Flowers, H. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 279.
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(12) (a) Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Org. Chem.* **1983**, *48*, 909. (b) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686.
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(15) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, H.; Hergott, H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

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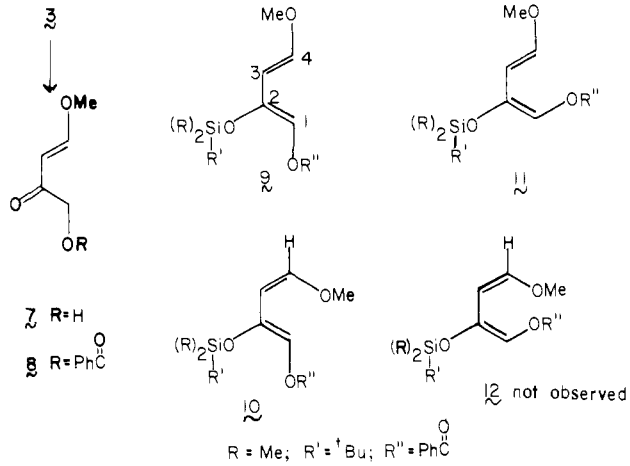
analysis indicates that, under all conditions, a three-component mixture of **9**, **10**, and **11** is produced. The other potential compound, **12**, bearing 1,2-*E* and 3,4-*Z* olefins was not observed.



The ratio of olefin isomers is somewhat sensitive to reaction conditions (vide infra). In all cases that we investigated, the 1,2-*E* isomer **11** was the minor product. However, the ratio of the 3,4-*E* (**9**)/3,4-*Z* (**10**) isomers could be varied from ca. 1:1 to ca. 2.5:1. When enol silylation was carried out at −78 °C (and the reaction mixture was allowed to warm to room temperature over 1.5 h), the ratio of **9**:**10** was ca. unity. However, when enol silylation was performed at 0 °C for a few minutes and quenched, a 2.5:1 ratio of these isomers was obtained. In all cases the ratio of (**9** + **10**)/**11** ranged between 6:1 and 8.5:1.

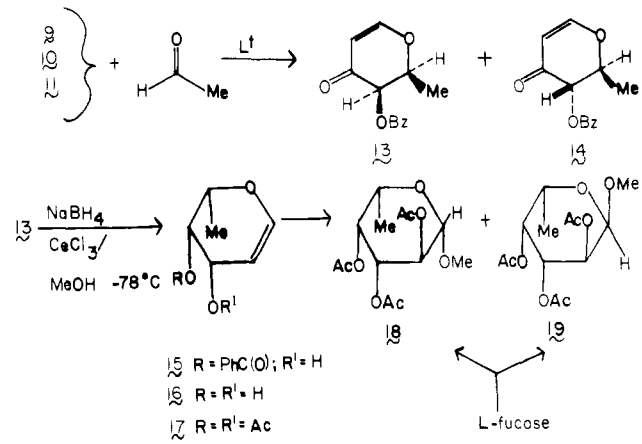
For synthetic purposes, the mixture of isomers could be utilized in the cyclocondensation reaction with acetaldehyde using appropriate Lewis acid catalysts. For purposes of gaining an insight into the relationship between the geometry of the dienes and the stereochemistry of the resultant dihydropyrone, the individual isomers could be separated by flash chromatography on silica gel. By conducting the chromatography in a jacketed column at 0 °C, the total recovery of dienes was 70%. Each of the three components was characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy (see Experimental Section).

It seemed likely that dihydropyrone **13** would be a valuable intermediate for the synthesis of both fucose and daunosamine. Accordingly, the cycloadditions of dienes **9**–**11** with acetaldehyde were investigated. For this purpose we studied the use of BF_3·OEt_2, zinc chloride,[1b] and Eu(hfc)$_3$[1b,16] as catalysts. As will be seen, only diene **9** undergoes cycloaddition with acetaldehyde under Eu(hfc)$_3$ mediation. Hence, from a synthetic standpoint, this is the least desirable catalyst since a large portion (vide supra) of the diene mixture is lost from exploitation. The margin between zinc chloride and BF_3·OEt_2 was relatively slight. Somewhat better total yields were realized with the former, though the stereoselectivity was slightly better with the latter.

Reaction of a 4:2:1 mixture of **9**, **10**, and **11** generated from **8** as described above, with acetaldehyde in the presence of anhydrous zinc chloride in tetrahydrofuran produced, after workup with trifluoroacetic acid, a 90% yield (based on **8**) of a 3.3:1 mixture of **13**/**14**. The ratio using the individual dienes will be described shortly. Similarly, by using a 3.1:3.4:1 mixture of **9**/**10**/**11** with BF_3·OEt_2 and acetaldehyde in ether (−78 °C) followed by similar workup a 73% yield (from **8**) of a 4:1 ratio of **13** and **14** was obtained. The epimers were readily separated by silica gel chromatography and subsequent chemistry was carried out only with the major, desired isomer **13**, mp 69.0–70.5 °C.

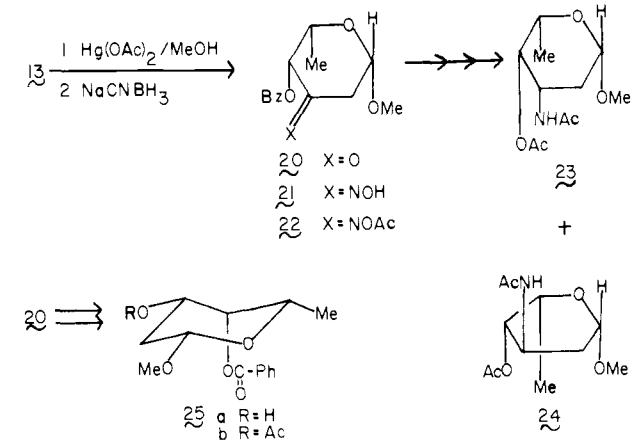
We first report the conversion of **13** to the fucose series. The differentiated fucal derivative **15** was obtained (92%) by reduction of **13** with sodium borohydride–cerous chloride in methanol at −78 °C.[17,18] Treatment of **15** with potassium carbonate in methanol afforded (±)-fucal (**16**) (90%). Upon acetylation of **16** with acetic anhydride, the diacetate **17**, mp 64.5–66 °C, was obtained in 95% yield.

Reaction of **17** with *m*-chloroperoxybenzoic acid in methanol[19] followed by acetylation afforded an 82% yield of an anomeric mixture of the methyl fucosides **18** and **19** in a 2:1 ratio. These



were separated by silica gel chromatography. The NMR and infrared spectra of these compounds were identical with those of the authentic β- and α-methyl fucoside triacetates obtained from L-fucose as described in the Experimental Section.

The dihydropyrone **13** also provided a convenient entry to the (±)-daunosamine series. Reaction of **13** with mercuric acetate in methanol afforded an α-mercurial ketone which, upon reduction with sodium cyanoborohydride, gave a 57% yield of the β-methoxy ketone **20**. Compound **20** reacted with hydroxylamine, giving oxime **21** in 95% yield. The major component of the oxime mixture could be obtained in crystalline form, mp 159–160.5 °C. However, for synthetic purposes the mixture was carried forward by reaction with triethylamine–acetic anhydride to give a 96% yield of the oxime acetates **22**. Treatment of this mixture with borane–THF[20] produced the desired 3-amino system, though with less than satisfactory selectivity. After cleavage of the benzoate and acetylation of both the hydroxy and amino functions, a 75–80% yield of a 2:1 ratio of two compounds was obtained. These could be separated by silica gel chromatography. The major compound, obtained in 50–55% yield is the (±)-methyl 3,4-diacetyldaunosamide (**23**), with the equatorial methoxy group. The



structure and stereochemical assignment originally rested on comparison of its NMR spectrum with published data for the same compound.[21] In addition, an authentic sample of the L-antipode

(16) Tris[3-(heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III).
(17) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(18) The stereoselectivity of the reduction was highly dependent on the reaction temperature. Only one isomer was detected with slow addition of the sodium borohydride at −78 °C.
(19) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, 1571.
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of **23** was prepared as the minor methyl glycoside starting from L-α-methyl daunosaminide hydrochloride, as described in the Experimental Section.

The minor diacetate derived from **22** through the borane–THF reduction sequence was the (±)-3-epidaunosamine derivative **24**. This assignment rests securely on its high-field NMR spectrum (see Experimental Section), which clearly defines an axial disposition for the 3-acetamido function.

Several initiatives to improve upon this stereochemical ratio were not rewarding. These attempts, which involved the use of lithium aluminum hydride, Raney nickel, 9-BBN, or borane–DMS as reducing agents on **21** or **22**, resulted in sharply reduced chemical yields and little or no improvement in stereoselectivity.

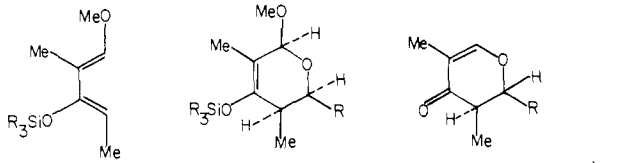
In another approach to achieving stereochemical control, the reduction of ketone **20** with K-Selectride (Aldrich) was attempted. The hope was to obtain the axial alcohol at C_3 (a 2,6-dideoxygulose derivative) which would have lent itself to derivatization and introduction of the required equatorial amino group required for daunosamine. Surprisingly, under a variety of conditions, even with K-Selectride, reduction of the ketone **20** affords the equatorial alcohol **25a**. The stereochemical assignment is based on ^{1}H NMR decoupling experiments carried out on the acetate **25b**. The prospects for converting **25** to daunosamine in a straightforward way seemed to be unpromising. Though in itself surprising, the reduction of equatorial methyl glycosides of 3-ketohexoses with axial delivery of hydride is apparently a general reaction and will be described in detail shortly.

For the moment then, a very concise entry to the important daunosamine series and potentially interesting derivatives thereof is flawed by poor selectivity in the reduction of the imino linkages in **21** and **22**. We note that high selectivities in favor of the daunosamine (3-equatorial amino) stereochemistry have previously been claimed in somewhat related reductions. In the light of our results, it would appear that this is not a general phenomenon but is a function of specific structural features in those particular substrates.

The ability of dienes **9–11** to provide, through the cyclocondensation reaction, a reasonably specific entry to the *cis*-dihydropyrone series, even with acetaldehyde, is synthetically valuable. Indeed, with crotonaldehyde, the trend is even more pronounced, and this was used as the first step in our recent synthesis of lincosamine.[22] As noted above, a similar reaction, using diene **2** and (benzoyloxy)acetaldehyde, was used in our stereoselective synthesis of talose.

Previously we have studied the Lewis acid catalyzed cyclocondensations of alkylated siloxy dienes such as **26**, with various aldehydes. We have found that with zinc chloride[8a] and Eu(fod)$_3$[8b] a predominance of cis products **28** arising from cycloaddition intermediates **27** was produced.

On the other hand, with BF_3·OEt_2, in a mechanistically more complex process, a preference for the production of *trans*-dihydropyrone **29** was encountered. That result runs counter to



Ratio of **13**:**14**

Diene	Eu(hfc)$_3$	$ZnCl_2$	BF_3 OEt_2
9	15:1	5:1	1:1
10	no rx	2.7:1	2:1
11	no rx	1:1	1:1

the observation in this study, wherein cis stereochemistry predominates with the trioxygenated dienes. To gain more insight into the stereochemistry of the reaction described above, the **9**, **10**, and **11** mixture was separated into its components. The cycloadditions of the individual dienes with acetaldehyde with the three catalyst systems, Eu(hfc)$_3$/chloroform; zinc chloride/tetrahydrofuran, and boron trifluoride etherate/ether, were examined. The data are expressed in terms of the ratio of **13**:**14** as a function of the starting diene and the catalyst system.

The results of the Eu(hfc)$_3$-mediated reactions are in excellent accord with our previous findings.[7b] This catalyst had been found to promote the pericyclic pathway. Thus, not surprisingly, from general Diels–Alder considerations, diene **9** is the only one which reacts with Eu(hfc)$_3$ and gives virtually clean *cis*-dihydropyrone.

The zinc chloride results are also in reasonable accord with those observed with alkylated dienes.[7a] Thus, diene **9** gives the highest cis ratio. This diene would be expected to manifest the highest tendency for the pericyclic mode. This tendency is understandably eroded in the case of diene **10**, but cis perference is still slightly maintained. In a strictly pericyclic model, diene **11** should have manifested *trans*-dihydropyrone selectivity. While no selectivity is observed, it is at least qualitatively encouraging that the highest ratio of trans compound is indeed produced from diene **11**.

The BF_3·OEt_2-mediated reaction is the most interesting. The trend, showing increasing percentages of *trans*-dihydropyrone as one goes from **9** to **10** to **11**, is consistent with previous findings. The interesting feature is the radically different behavior exhibited by dienes **9** and **26**. At the present writing we lack the data to relate this difference to the differing inductive effects of methyl vs. benzoyloxy, or to potential chelating effects by the additional hetero group. Moreover, differences in the behavior of **26** relative to its 2-demethyl derivative have been noted.[23] Thus, the degree of substitution as well as the nature of the substituents may be important in determining the stereochemical outcome.

Experimental Section

General Procedures. Reagents and solvents were purified and dried using standard methods. Spectra were recorded on the following instruments. IR: Perkin-Elmer Spectrophotometer 710 B. ^{1}H NMR: Varian EM-390 (90 MHz), Bruker HX-270 (270 MHz), and Bruker WM-500 (500 MHz). ^{13}C NMR: Jeol FX 90 Q (22.5 MHz). Mass spectra: Hewlett-Packard 5985. NMR spectra were obtained using $CDCl_3$ as the solvent. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were formed by Dr. R. Rittner, Olin Corp., New Haven, CT, and Galbraith Laboratories, Knoxville, TN.

(*E*)-1-(Trimethylsiloxy)-4-methoxy-3-buten-2-one (4). To a vigorously stirred suspension of *m*-chloroperoxybenzoic acid (85%) (21 g, 0.104 mol) in hexane (1.25 L) at −78 °C under nitrogen was added diene **3** (17.91 g, 0.104 mol) in hexane (100 mL). The cooling bath was removed 15 min after addition of the diene, and the reaction was stirred for an additional hour. The reaction mixture was filtered and the solids were washed with hexane (300 mL). The filtrate was transferred to a separatory funnel and washed with saturated $NaHCO_3$ solution (3 × 200 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product 4 as a light yellow oil (19.5 g) which was 90% pure by NMR. The product was used without further purification: ^{1}H NMR (90 MHz) δ 0.15 (s, 9 H), 3.72 (s, 3 H), 4.16 (s, 2 H), 5.87 (d, J = 12 Hz, 1 H), 7.73 (d, J = 12 Hz, ^{1} H); ^{13}C NMR ($CDCl_3$) δ 0.27, 57.59, 67.96, 100.0, 162.17, 196.49; IR (thin film) 2920, 1893, 1673, 1595, 1426 cm^{-1}.

(*E*)-1-Hydroxy-4-methoxy-3-buten-2-one (7). The α-silyloxy enone 4 (9.50 g, 0.054 mol) was dissolved in absolute methanol (30 mL) and stirred at 0 °C for 1 h and then at room temperature for 1 h. An aliquot of the reaction was withdrawn and concentrated in vacuo. The ^{1}H NMR of the aliquot revealed that the reaction was complete. The entire reaction was then concentrated. The crude product was redissolved in dichloromethane (30 mL) and the solution was concentrated again. The product was used immediately without further purification: ^{1}H NMR (90 MHz) δ 3.75 (s, 3 H), 4.30 (s, 2 H), 5.59 (d, J = 13.5 Hz, 1 H), 7.73 (d, J = 13.5 Hz, 1 H).

(*E*)-1-(Benzoyloxy)-4-methoxy-3-buten-2-one (8). To a solution of the crude hydroxy ketone **7** in pyridine (30 mL) at 0 °C was added benzoyl chloride (6.4 mL, 0.054 mol). The reaction was stirred at 0 °C for 1 h then room temperature for 1 h. The reaction was diluted with

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(22) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6715.
(23) Larson, E. R., unpublished results from these laboratories.

ethyl acetate (400 mL) and washed with 1.0 N HCl (3 × 150 mL), saturated $NaHCO_3$ solution (3 × 150 mL), saturated brine, and dried ($MgSO_4$). The solution was concentrated in vacuo and chromatographed on a short silica gel column (85 g) eluted with 10% ethyl acetate/hexane (1 L) then 20% ethyl acetate/hexane (1 L) to give **8** (5.90 g, 53%), a tan crystalline product homogeneous by TLC (3:1 ether/hexane) and ^1H NMR. Recrystallization from ether provided an analytical sample of white crystals: mp 74–75 °C; ^1H NMR (90 MHz) δ 3.71 (s, 3 H), 4.90 s, 2 H), 5.69 (d, J = 13.5 Hz, 1 H), 7.27–7.58 (m, 3 H), 7.71 (d, J = 13.5 Hz, 1 H), 8.04–8.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 57.7, 67.5, 100.6, 128.2, 129.3, 129.6, 133.1, 163.7, 165.6, 191.1; IR ($CHCl_3$) 1720, 1690, 1615, 1600, 1440, 1425, 1405 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.39; H, 5.40.

Preparation of 1-(Benzoyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,3-butadienes 9–11. To a solution of benzoyloxy ketone **8** (1.0 g, 4.54 mmol) in CCl_4 (40 mL) and triethylamine (1.26 mL, 9.08 mmol) at room temperature under nitrogen was added *tert*-butyldimethylsilyl triflate (1.25 mL, 5.44 mmol) via syringe. The ^1H NMR of the crude reaction after 10 min showed the reaction to be complete. The reaction was diluted with CCl_4 (40 mL) and triethylamine (2 mL), transferred to a separatory funnel, washed with saturated $NaHCO_3$ solution (50 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product (1.67 g) as a dark red oil.

Purification of Dienes 9–11. The crude diene mixture (250 mg) was chromatographed on silica gel (10 g) in a 1.5 × 17 cm jacketed column cooled to 0 °C by circulating ice water. The elution solvent (2% ether/hexane was precooled to −78 °C under nitrogen and transferred by syringe. The column was eluted under a slight nitrogen pressure. The column fractions were analyzed by thin-layer chromatography in 1:9 ether/hexane.

9: R_f 0.48, 120 mg; ^1H NMR (90 MHz) δ 0.13 (s, 6 H), 0.82 (s, 9 H), 3.41 (s, 3 H), 5.10 (d, J = 12 Hz, 1 H), 6.63 (d, J = 12 Hz, 1 H), 6.71 (s, 1 H), 7.23–7.39 (m, 3 H), 7.84–7.96 (m, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −4.12, 18.26, 25.74, 56.40, 100.04, 119.25, 128.34, 129.36, 129.85, 133.17, 137.49, 149.60, 163.47; IR ($CHCl_3$) 1724, 1660, 1619, 1461, 1453, 1442, 1355, 1343 cm^{-1}; MS, m/e (relative intensity) 334 (24.1, M^+), 229 (74.8), 172 (8.9), 105 (100).

10: R_f 0.37, 34 mg; ^1H NMR (90 MHz) δ 0.14 (s, 6 H), 0.98 (s, 9 H), 3.73 (s, 3 H), 4.58 (d, J = 5 Hz, 1 H), 5.98 (d, J = 5 Hz, 1 H), 7.40–7.50 (m, 3 H), 7.57 (s, 1 H), 8.07–8.18 (m, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −4.42, 18.09, 25.64, 60.60, 101.37, 124.17, 128.30, 129.63, 129.85, 133.01, 135.44, 147.05, 163.26; IR ($CHCl_3$) 1720, 1655, 1465, 1455, 1445; MS, m/e 334 (9.2, M^+), 229 (43.1), 105 (100), 73 (62.1).

11: R_f 0.57, 25 mg; ^1H NMR (90 MHz) δ 0.23 (s, 6 H), 0.99 (s, 9 H), 3.65 (s, 3 H), 5.81 (d, J = 12 Hz, 1 H), 6.85 (d, J = 12 Hz, 1 H), 7.02 (s, 1 H), 7.4–7.57 (m, 3 H), 8.0–8.11 (m, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ −4.55, 18.25, 25.81, 56.90, 97.80, 121.42, 128.51, 129.56, 129.68, 133.20, 140.69, 150.50, 163.37; IR ($CHCl_3$) 1720, 1659, 1464, 1458, 1444 cm^{-1}; MS, m/e 334 (3.0, M^+), 229 (12.6), 105 (100), 73 (23.7).

(±)-*cis*-2-Methyl-3-(benzoyloxy)-2,3-dihydropyrone (13). Zinc Chloride Procedure. Zinc chloride (1.23 g, 9.02 mmol) was fused under vacuum in the reaction flask, cooled under nitrogen, and then dissolved in dry THF (25 mL). The crude diene mixture (1.67 g, 4:2:1 ratio of **9**/**10**/**11**) prepared from benzoyloxy ketone **8** (1 g, 4.54 mmol) as previously described was added in THF (25 mL). Immediately thereafter was added freshly distilled acetaldehyde (5 mL, 88.5 mmol). The reaction was stirred for 24 h at room temperature, then diluted with ether (250 mL), washed with saturated $NaHCO_3$ solution (2 × 125 mL) and saturated brine, and dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product as a mixture of the pyrones **13** and **14** and enol ether adducts. Complete conversion to the pyrones was effected by treatment of the crude with trifluoroacetic acid (1 mL) in $CHCl_3$ (10 mL). The reaction was monitored by TLC in ether/hexane (3:1). Concentration of the reaction in vacuo and chromatography on silica gel (50 g) in 20% ethyl acetate/hexane gave **13**, 0.735 g (70%) as an oil. Crystallization from ether provided an analytical sample, mp 69.0–70.5 °C. The *trans*-pyrone **14** (0.220 g, 20%) was isolated as an oil.

13: ^1H NMR (270 MHz) δ 1.48 (d, J= 6.7 Hz, 3 H), 4.81 (dq, J= 6.7, 4.0 Hz, 1 H), 5.53 (dd, J = 6.0, 0.6 Hz, 1 H), 5.65 (dd, J = 4.0, 0.6 Hz, 1 H), 7.42 (d, J = 6.0 Hz, 1 H), 7.43–7.63 (m, 3 H), 8.05–8.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.14, 71.30, 77.04, 105.27, 128.46, 128.95, 129..93, 133.50, 162.54, 165.03, 186.82; IR ($CHCl_3$) 1728, 1685, 1600, 1445, 1405, 1374 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.95; H, 5.02.

14: ^1H NMR (270 MHz) δ 1.53 (d, J = 6.8 Hz, 3 H), 4.68 (m, 1 H), 5.52 (d, J = 11.4 Hz, 1 H), 5.51 (d, J = 6.9 Hz, 1 H), 7.39 (d, J = 6.9 Hz, 1 H), 7.45–7.63 (m, 3 H), 8.07–8.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.50, 73.52, 77.31, 105.16, 128.56, 129.01, 129.87, 133.45, 162.92, 165.03, 188.06; IR ($CHCl_3$) 1711, 1671, 1581, 1429, 1375 cm^{-1}; MS, m/e 232 (0.2, M^+), 175 (20.3), 105 (100).

BF_3·OEt_2 Procedure. To a solution of dienes **9**, **10**, and **11** (3.1:3.4:1) prepared from benzoyloxy ketone **8** (100 mg, 0.454 mmol) and freshly distilled acetaldehyde (0.4 mL, 7.08 mmol) in ether (4 mL) under nitrogen was added BF_3·OEt_2 (0.056 mL, 0.454 mmol). The reaction was stirred for 4.5 h and then quenched at −78 °C with saturated $NaHCO_3$ solution (1 mL) and warmed to room temperature. The mixture was diluted with ether (30 mL), extracted with saturated $NaHCO_3$ solution (3 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo and the crude product was redissolved in $CHCl_3$ (2 mL) and trifluoroacetic acid (0.3 mL) for 1 h. Concentration of the reaction in vacuo and chromatography on silica gel (10 g), ether/hexane (1:3), gave *cis*-pyrone **13** (64.0 mg, 61%) and *trans*-pyrone **14** (12.8 mg, 12%).

Eu(hfc)$_3$ Procedure. A solution of the dienes **9**, **10**, and **11** (6.0:2.5:1) prepared from benzoyloxy ketone **8** (100 mg, 0.454 mmol), acetaldehyde (0.25 mL, 4.1 mmol), and tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) (54 mg, 0.045 mmol) in $CDCl_3$ (0.6 mL) was reacted at room temperature for 48 h. The reaction was monitored by ^1H NMR. The reaction was quenched with $CHCl_3$ (6 mL) and trifluoroacetic acid (0.3 mL) and stirred for 2 h. Concentration of the solution and chromatography on silica gel (10 g) ether/hexane (1:3) gave **13** (46.9 mg, 44%).

(±)-4-*O*-Benzoylfucal (15). To a solution of the *cis*-dihydropyrone **13** (400 mg, 1.72 mmol) and cerium(III) chloride heptahydrate (639 mg, 1.72 mmol) in methanol (16 mL) at −78 °C under nitrogen was added sodium borohydride (71.7 mg, 1.89 mmol) dissolved in absolute ethanol (4 mL) slowly over a period of 2 h. The reaction was diluted with ethyl acetate (100 mL), transferred to a separatory funnel, extracted with saturated $NaHCO_3$ solution (3 × 25 mL) and brine (25 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo and chromatographed on silica gel (25 g) in 30% ether/hexane to give 370 mg (92%) of **15** isolated as an oil: ^1H NMR (90 MHz) δ 1.30 (d, J = 7 Hz, 3 H), 2.01 (d, J = 7 Hz, 1 H, OH), 4.21 (br q, J = 7 Hz, 1 H), 4.55–4.76 (m, 2 H), 5.37 (dd, J = 5, 2 Hz, 1 H), 6.43 (dd, J = 5, 2 Hz, 1 H), 7.28–7.56 (m, 3 H), 8.01–8.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.91, 63.72, 69.79, 71.74, 102.18, 128.36, 129.61, 129.82, 133.18, 144.72, 166.71; IR ($CHCl_3$) 1721, 1642, 1596, 1443, 1376, 1310 cm^{-1}; MS, m/e 234 (1.6, M^+), 177 (3.6), 162 (5.6), 112 (3.7), 105 (100).

(±)Fucal (16). The glycal **15** (310 mg, 1.32 mmol) was stirred with potassium carbonate (20 mg) in methanol (12 mL) for 3 h at room temperature. The reaction was concentrated in vacuo and chromatographed on silica gel (10 g) with methanol/$CHCl_3$ gradient elution (0.5–5% methanol) to give 154 mg of **16** as a foam. An analytical sample was obtained by vacuum sublimation at room temperature (0.1 mmHg): ^1H NMR (90 MHz) δ 1.37 (d, J = 7 Hz, 3 H), 2.43 (s, 2 H, OH), 3.67 (m, 1 H), 4.00 (br q, J = 7 Hz, 1 H), 4.34 (m, 1 H), 4.64 (dt, J = 6, 2 Hz, 1 H), 6.33 (dd, J = 6, 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.90, 64.96, 68.21, 73.25, 102.43, 144.71; IR ($CHCl_3$) 3550, 3000, 1641, 1513, 1395 cm^{-1}.

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.02; H, 7.48.

(±)-3,4-Di-*O*-acetylfucal (17). The diol **16** (126 mg, 0.968 mmol) was acetylated with acetic anhydride (0.32 mL, 3.38 mmol), triethylamine (0.8 mL, 5.74 mmol), and 4-(dimethylamino)pyridine (catalytic) in dichloromethane (1.5 mL) for 12 h at room temperature. The reaction was concentrated in vacuo and chromatographed on silica gel (20 g) in 1:1 ether/hexane to give 196.8 mg (95%) of **17** as a crystalline solid. Recrystallization from hexane provided an analytical sample: mp 64.5–66 °C; ^1H NMR (90 MHz) δ 1.27 (d, J = 7 Hz, 3 H), 2.00 (s, 3 H), 2.14 (s, 3 H), 4.20 (br q, J = 7 Hz, 1 H), 4.62 (dt, J = 6 Hz, 2 Hz, 1 H), 5.26 (m, 1 H), 5.56 (m, 1 H), 6.45 (dd, J = 6, 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.58, 20.75, 20.92, 65.12, 66.32, 71.57, 98.34, 146.12, 170.39, 170.72; IR ($CHCl_3$) 1740, 1648, 1370 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.80; H, 6.31.

Methyl β-L- and α-L-Tri-*O*-acetylfucopyranosides 18 and 19. L-Fucose (250 mg) was stirred at reflux with Amberlite IR 120[24] ion exchange resin (400 mg) in methanol (5 mL) for 24 h. The reaction was filtered and concentrated in vacuo to give an oil. Crystallization from ethanol gave a mixture of the methyl α- and β-fucopyranosides. Acetylation of the crystalline product mixture was acetic anhydride and triethylamine in dichloromethane gave methyl α- and β-L-tri-*O*-acetylfucopyranosides, which could be separated by chromatography on silica gel ether/hexane (1:3).

(24) Zehavi, U.; Sharon, N. *J. Org. Chem.* **1972**, *37*, 2141.

β-L anomer **18**: mp 96.5–98.0 °C (lit. 96–97 °C);[25] ^{1}H NMR (270 MHz) δ 1.21 (d, J = 6.8 Hz, 3 H), 1.95 (s, 3 H), 2.02 (s, 3 H), 2.14 (s, 3 H), 3.48 (s, 3 H), 3.79 (br q, J = 6.8 Hz, 1 H), 4.34 (d, J = 7.8 Hz, 1 H), 4.98 (dd, J = 10.4, 3.5 Hz, 1 H), 5.13 (dd, J = 10.4, 7.8 Hz, 1 H), 5.20 (d, J = 3.2 Hz, 1 H); IR ($CHCl_3$) 1750 cm^{-1}.

α-L anomer **19**: mp 64.5–65.5 °C (lit. 67 °C);[25] ^{1}H NMR (270 MHz) δ 1.14 (d, J = 6.6 Hz, 3 H), 1.96 (s, 3 H), 2.07 (s, 3 H), 2.15 (s, 3 H), 3.37 (s, 3 H), 4.10 (br q, J = 6.6 Hz, 1 H), 4.91 (d, J = 3.6 Hz, 1 H), 5.13 (dd, J = 10.8, 3.6 Hz, 1 H), 5.27 (dd, J = 3.4, 1.1 Hz, 1 H), 5.33 (dd, J = 10.8, 3.4 Hz, 1 H); IR ($CHCl_3$) 1745 cm^{-1}.

(±)-Methyl β- and α-Tri-*O*-acetylfucopyranosides 18 and 19. The diacetyl fucal **17** (77 mg, 0.359 mmol) was stirred with *m*-chloroperoxybenzoic acid (80%) (80 mg, 0.37 mmol) in methanol (6.5 mL) for 24 h. The reaction was concentrated in vacuo and the crude product was redissolved in dichloromethane (4 mL) and acetylated with acetic anhydride (0.4 mL), triethylamine (0.8 mL), and a catalytic amount of 4-(dimethylamino)pyridine. Concentration of the reaction and chromatography on silica gel (25 g) in ether/hexane (1:3) gave **18** (60.2 mg, 55%) and **19** (30 mg, 27%). The 270-MHz ^{1}H NMR and IR spectra of these compounds were identical with those of the respective authentic methyl β- and α-L-tri-*O*-acetylpyranosides obtained from L-fucose.

(±)-Methyl-4-*O*-benzoyl-2,6-dideoxy-β-*threo*-hexopyranosid-3-ulose (20). The *cis*-dihydropyrone **13** (0.865 g, 3.72 mmol) was reacted with mercuric acetate (1.23 g, 3.85 mmol) in methanol (17 mL) for 24 h at room temperature. The reaction was diluted with methanol (5 mL) and cooled to −78 °C under nitrogen. To the above cooled solution was added sodium cyanoborohydride (86 mg, 1.37 mmol) in methanol (6 mL). Almost immediate deposition of elemental mercury was observed. The reaction was stirred for 2.5 h at −78 °C. The reaction was then diluted with ethyl acetate (~40 mL), decanted, and filtered through a Celite pad. Concentration of the solution in vacuo and chromatography on silica gel (50 g) ether/hexane (1:3–1:1) gave **20** (560 mg, 57%); ^{1}H NMR (270 MHz) δ 1.47 (d, J = 6.6 Hz, 3 H), 2.84 (d, J = 4.8 Hz, 2 H), 3.52 (s, 3 H), 4.26 (dq, J = 6.6, 4.1 Hz, 1 H), 4.88 (t, J = 4.8 Hz, 1 H), 5.36 (d, J = 4.1 Hz, 1 H), 7.41–7.62 (m, 3 H), 8.07–8.11 (m, 2 H); ^{13}C ($CDCl_3$) δ 16.47, 46.16, 56.13, 71.90, 76.23, 101.75, 128.36, 128.84, 129.76, 133.39, 165.03, 199.49; IR ($CHCl_3$) 1720, 1591, 1469, 1441 cm^{-1}; MS (chemical ionization, methane), m/e 265 (M + 1, 1.2), 233 (37.1), 205 (8.3), 105 (100).

Oximes 21. The β-methoxy ketone **20** (356 mg, 1.34 mmol) was reacted for 2 h with a 0.2 M ethanolic solution of hydroxylamine (6.7 mL, 1.34 mmol) prepared from hydroxylamine hydrochloride and sodium hydroxide. The reaction was concentrated in vacuo, redissolved in $CHCl_3$, and filtered through a plug of silica gel. Concentration of the filtrate gave a mixture of oximes **21** (355 mg, 95%). Crystallization from ether gave a pure sample of the major anti oxime isomer; mp 159–160.5 °C; ^{1}H NMR (270 MHz) δ 1.37 (d, J = 6.4 Hz, 3 H), 2.25 (dd, J = 14.5, 9.7 Hz, 1 H), 3.53 (ddd, J = 14.5, 2.6, 0.5 Hz, 1 H), 3.59 (s, 3 H), 3.86 (dq, J = 6.4, 1.6 Hz, 1 H), 4.46 (dd, J = 9.7, 2.6 Hz, 1 H), 5.50 (br s, 1 H), 7.42–7.62 (m, 3 H), 7.98 (s, 1 H, OH), 8.10–8.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.36, 28.88, 56.67, 70.92, 72.17, 101.10, 128.35, 129.44, 129.92, 133.28, 152.57, 165.57; IR ($CHCl_3$) 1718, 1595, 1445 cm^{-1}.

Chromatography of the mixture on silica gel in ether/hexane (1:2) gave a pure sample of the syn oxime **21**: ^{1}H NMR (500 MHz) δ 1.36 (d, J = 6.4 Hz, 3 H), 2.61 (d, J = 6.0 Hz, 2 H), 3.58 (s, 3 H), 3.76 (dq, J = 6.4, 1.2 Hz, 1 H), 4.52 (t, J = 6.0, 1 H), 6.33 (d, J = 1.2, 1 H), 7.44–7.47 (m, 2 H), 7.57–7.60 (m, 1 H), 7.71 (br s, 1 H, OH), 8.11–8.12 (m, 2 H); ^{13}C NMR δ 16.47, 35.06, 56.67, 63.28, 71.46, 102.46, 128.46, 129.33, 130.03, 133.39, 152.45, 165.42; IR ($CHCl_3$) 1721, 1592, 1443 cm^{-1}.

Oxime Acetates (22). A mixture of the oximes **21** (150 mg, 0.537 mmol) was acetylated with acetic anhydride (0.1 mL), triethylamine (0.3 mL, and 4-(dimethylamino)pyridine (catalytic) in dichloromethane (6 mL) for 6 h at room temperature. The reaction was concentrated in vacuo and chromatographed on silica gel (10 g) in ether/hexane (1:2 to 1:1) to give the syn and anti oxime acetates **22** (165 mg, 96%), which were not separable by chromatography. However, acetylation of the pure oxime isomers of **21** provided a pure sample of the syn and anti oxime acetate isomers **22**. Anti oxime acetate: mp 154–156 °C; NMR (500 MHz) δ 1.35 (d, J = 6.4 Hz, 3 H), 2.26 (dd, J = 14.4, 9.6 Hz, 1 H), 3.53 (dd, J = 14.4, 2.4 Hz, 1 H), 3.59 (s, 3 H), 3.86 (dq, J = 6.2, 1.4 Hz, 1 H), 4.47 (dd, J = 9.6, 2.4 Hz, 1 H), 5.50 (br s, 1 H), 7.43–7.59 (m, 3 H), 8.10–8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.93, 19.02, 30.78, 56.19, 70.00, 71.68 100.12, 128.03, 128.68, 129.39, 133.07, 159.62, 164.44, 167.58; IR ($CHCl_3$) 1721, 1595, 1575 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; N, 4.36. Found: C, 60.01; H, 6.05; N, 4.60.

Syn oxime acetate: mp 98–100 °C; ^{1}H NMR (90 MHz) δ 1.37 (d, J = 6 Hz, 3 H), 2.20 (s, 3 H), 2.5–2.9 (m, 2 H), 3.56 (s, 3 H), 3.74 (dq, J = 6, 1 Hz, 1 H), 4.52 (dd, J = 8, 3 Hz, 1 H), 7.28–7.57 (m, 3 H), 7.97–8.09 (m, 2 H); IR ($CHCl_3$) 1761, 1721 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.58; H, 6.08; N, 4.24.

(±)-Methyl 3-Acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-*lyxo*-hexopyranoside (23). To a solution of the oxime acetates **22** (250 mg, 0.778 mmol) in THF (7.5 mL) at −78 °C under nitrogen was added (2.44 mL, 2.44 mmol) borane–tetrahydrofuran complex (1 M in THF) via syringe. The reaction was stirred at −78 °C for 3 h, then allowed to warm to room temperature, and stirred for an additional 21 h. The reaction was quenched with 0.1 N NaOH (3 mL) and stirred for 2 h. The reaction mixture was concentrated in vacuo to dryness, redissolved in methanol (25 mL), and stirred with potassium carbonate (130 mg) for 6 h. The reaction was concentrated in vacuo to dryness and acetylated with acetic anhydride (2 mL), triethylamine (4 mL), and 4-(dimethylamino)pyridine (catalytic) in dichloromethane (3 mL). The reaction was diluted with $CHCl_3$ (25 mL) and filtered through a Celite pad. The filtrate was concentrated, and the crude product was chromatographed on silica gel (40 g) in methanol/$CHCl_3$ (gradient elution 0–1% methanol). Rechromatography of the mixed fractions gave as a total recovery of **23** (102 mg, 53%), mp 167–168 °C (ethyl acetate/hexane). The 270-MHz ^{1}H NMR and IR spectra of **23** were identical with that of the reference sample obtained from methyl α-L-daunosaminide hydrochloride.

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 54.00; H, 7.90; N, 5.68.

In addition, the C_3 epimer (±)-methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-*xylo*-hexopyranoside (**24**), mp 135–136 °C (ethyl acetate/hexane), was obtained (48 mg, 25%): ^{1}H NMR (500 MHz) δ 1.27 (d, J = 6.7 Hz, 3 H), 1.77 (m, 1 H), 2.00 (s, 3 H), ~2.0 (m, 1 H), 2.12 (s, 3 H), 3.49 (s, 3 H), 3.94 (dq, J = 6.7, 2.5 Hz, 1 H), 4.31 (m, 1 H; irradiation at 4.81 gives dt, J = 7.5, 3.7 Hz), 4.57 (dd, J = 7.9, 2.4 Hz, 1 H), 4.81 (dd, J = 4.9, 2.5 Hz, 1 H), 5.64 (br, 1 H); IR ($CHCl_3$) 1733, 1675 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.66; H, 7.67; N, 5.59.

Methyl 3-Acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside (23). Preparation of Reference Sample. Methyl α-L-daunosamide hydrochloride (46.8 mg) (Pfanstiehl) was acetylated with acetic anhydride (0.042 mL) and triethylamine (0.1 mL) in dichloromethane (1 mL) for 20 min at room temperature. The reaction was concentrated and chromatographed in silica gel (10 g) in methanol/$CHCl_3$ (gradient elution 0–5% methanol) to give methyl *N*-acetyl-α-L-daunosamide (44.4 mg, 92%): IR ($CHCl_3$) 3400, 1661 cm^{-1}. Hydrolysis was carried out in acetic acid (0.3 mL) and H_2O (1.5 mL) at reflux for 0.5 h. The reaction was concentrated in vacuo to dryness, redissolved in 0.1 N methanolic HCl for 0.5 h, and then concentrated again. TLC analysis (1:9 methanol/$CHCl_3$) of the crude product showed the equatorial methyl pyranoside was a minor component of at least a four-component mixture, which was chromatographed on silica gel (10 g) methanol/$CHCl_3$. The product-containing fractions were pooled, and the other fractions were recycled using the above procedure. After two recycles, a total of 5 mg of the methyl *N*-acetyl-β-L-daunosamide was obtained. Acetylation with acetic anhydride–trimethylamine followed by final purification by HPLC (SiO_2), 4% isopropyl alcohol in ethyl acetate, gave 2 mg of the methyl β-L-daunosamide **23**: ^{1}H NMR (270 MHz) δ 1.18 (d, J = 6.4 Hz, 3 H), 1.62 (m, 1 H), 1.92 (m, 1 H), 1.94 (s, 3 H), 2.16 (s, 3 H), 3.51 (s, 3 H), 3.69 (dq, J = 6.4, 0.8 Hz, 1 H), 4.25 (m, 1 H), 4.44 (dd, J= 9.3, 2.2 Hz, 1 H), 5.02 (br d, J = 2.9 Hz, 1 H), 5.61 (br d, J = 8.0, 1 H); IR ($CHCl_3$) 1740, 1672 cm^{-1}.

(±)-Methyl 4-*O*-Benzoyl-2,6-dideoxy-β-*lyxo*-hexopyranoside (25a). To a solution of the ketone **20** (127 mg, 0.48 mmol) in THF (5 mL) at −78 °C was added 0.57 mL of K-selectride (1 M in THF) via syringe. The reaction was stirred for 2 h at −78 °C and quenched with saturated $NaHCO_3$ solution (1 mL). The reaction mixture was diluted with ethyl acetate (25 mL), extracted with $NaHCO_3$ (10 mL) and brine (10 mL), and dried ($MgSO_4$). Concentration of the solution in vacuo and chromatography on silica gel (25 g), 40% ethyl acetate/hexane, gave **25** (80 mg, 62%). Recrystallization from ether provided an analytical sample: mp 102–104 °C; ^{1}H NMR (90 MHz) δ 1.28 (d, J = 6.5 Hz, 3 H), 1.56–2.25 (m, 2 H), 3.53 (s, 3 H), 3.69 (dq, J = 6.5, 1 Hz, 1 H), 3.83–4.15 (m, 1 H), 4.39 (dd, J = 9, 2 Hz, 1 H), 5.18 (dd, J = 3, 1 Hz, 1 H), 7.28–7.57 (m, 3 H), 8.0–8.13 (m, 2 H); IR ($CHCl_3$) 3450, 1708 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.01; H, 6.88.

(25) Hockett, R. C.; Phelps, F. P.; Hudson, C. S. *J. Am. Chem. Soc.* **1939**, *61*, 1658.

(±)-Methyl 3-*O*-Acetyl-4-*O*-benzoyl-2,6-dideoxy-β-*lyxo*-hexopyranoside (**25b**). The alcohol **25a** (22 mg, 0.083 mmol) was acetylated with acetic anhydride (0.1 mL), triethylamine (0.2 mL), and 4-(dimethylamino)pyridine (catalytic) in dichloromethane (0.25 mL) for 12 h. Concentration of the reaction and chromatography on silica gel (ether/hexane) gave **25b** (23 mg, 90%): ^{1}H NMR (270 MHz) δ 1.29 (d, J = 6.7 Hz, 3 H), 1.97 (s, 3 H), 2.0–2.05 (m, 2 H), 3.58 (s, 3 H), 3.80 (dq, J = 6.7, 1 Hz, 1 H), 4.51 (m, 1 H), 5.09 (m, 1 H, irradiation at 5.37 gives dd, J = 11.2, 6 Hz), 5.37 (br d, J = 3.0 Hz, 1 H), 7.30–7.63 (m, 3 H), 8.13–8.16 (m, 2 H); IR ($CHCl_3$) 1714 cm^{-1}. MS, m/e 308 (0.2, M^+), 204 (13.2), 105 (100).

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A Totally Synthetic Route to Lincosamine: Some Observations on the Diastereofacial Selectivity of Electrophilic Reactions on the Double Bonds of Various 5-(1-Alkenyl)arabinopyranosides

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Abstract: Under the influence of boron trifluoride etherate, crotonaldehyde reacts with 1-methoxy-3-((trimethylsilyl)-oxy)-4-(benzoyloxy)-1,3-butadiene to afford (*E*)-*cis*-2-(1-propenyl)-3-(benzoyloxy)-2,3-dihydro-4-pyrone. The latter is converted to (±)-β-methylinocosaminide with high stereochemical selectivity.

Background

There has been relatively little effort addressed to the total synthesis of saccharides.[1,2] With few exceptions, such targets have been attacked by partial synthesis, using the common sugars as matrices. The pioneering Sharpless discovery of asymmetric epoxidation[3] has awakened interest in saccharide total synthesis, since major new opportunities for the introduction and manipulation of oxygen functionality are now available. The asymmetric synthesis of the eight aldohexoses by the MIT school, via catalytically mediated enantiospecific and diastereospecific oxidation of acyclic intermediates, must be seen as a landmark accomplishment.[4]

The recently demonstrated Lewis acid catalyzed cyclocondensation of activated dienes with aldehydes provides a direct route to functionalized pyran rings.[5] Extensive functionality may be incorporated via inclusion in the diene and in the "R" group of the aldehyde.[6] Moreover, the unsaturated linkages in the pyranoids produced from the cyclocondensation reaction offer convenient access points for the introduction of hetero (or branched) functionality.[7] A potential relationship with saccharide synthesis presented itself.

The total synthesis of unusual hexoses including talose,[8a] 4-deoxymannose,[8a] chalcose,[8b] fucose,[8c] and daunosamine[8c] by cycloaddition technology was first demonstrated. Several of these targets had previously been prepared by partial synthesis, though often only after rather laborious exercises in functional group modification.

With the feasibility of this approach for the total synthesis of some of the rarer hexoses well demonstrated, its applicability to the construction of the higher monosaccharide was next investigated. The varied substitution and chirality patterns of the higher monosaccharides and their presence as substructures in a variety of physiologically active compounds[9] should serve to heighten interest in their total synthesis. In spite of such apparent inducements, all efforts at the preparation of the higher monosaccharides had hitherto involved partial synthesis via chain elongation and functional group modifications of the common

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