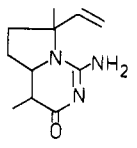
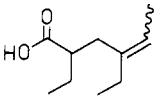
158.9 was highly suggestive of a guanidine moiety. Assembling these fragments led to the hypothesis that triophamine was the diacylguanidine 1 which is in rapid tautomeric equilibrium.[10]

Authentic diacetylguanidine (3) was prepared as a model compound.[11] It has UV characteristics [$\lambda_{max}$ 248 nm ($\epsilon$ 16 800, MeOH) $\lambda_{max}$ 212 nm ($\epsilon$ 19 900, MeOH/HCl)] and $^{13}C$ NMR resonances[12] ($\delta$ 159.0 and 180.1) in good agreement with triophamine (1). Diacetylguanidine (3) undergoes rapid base-catalyzed hydrolysis (MeOH/NaOH, room temperature) to give monoacetylguanidine (4) ($\lambda_{max}$ 230 nm ($\epsilon$ 14 300, MeOH)]. Triophamine (1) is converted to the monoacylguanidine 5 under the same reaction conditions [5: UV (MeOH) $\lambda_{max}$ 232 nm ($\epsilon$ 10 000); mass spectrum, $m/z$ 211 ($M^+$)]. Final proof of the structure was obtained by base-catalyzed hydrolysis of 1 ($CH_3OH$/NaOH, 48 h) which gave guanidine (identified as its 4,6-dimethylpyrimidine derivative[13]) and the carboxylic acid 6.[14]



7



6

(10) Monoacylguanidines exist almost exclusively as the acyl imine tautomer. Masumoto, K.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 552.
(11) Greenhalgh, R.; Bannard, R. A. B. *Can. J. Chem.* **1959**, *37*, 1810.
(12) The deshielding of the carbonyl carbons in triophamine (1) relative to diacetylguanidine (3) is almost equal in magnitude to the difference between propionamide ($\delta$ 177.2) and acetamide ($\delta$ 172.7). Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972; p 123.
(13) Beyermann, K.; Wisser, H. *Z. Anal. Chem.* **1969**, *245*, 376.

A number of marine natural products contain guanidine functionalities. These include the acarnidines,[15] the polyandrocarpidines,[16] ptilocaulin,[17] saxitoxin,[18] and tetrodotoxin,[19] Triophamine, however, is to the best of our knowledge the first example of a naturally occurring diacylguanidine. Arenaine (7),[20] a terrestrial monoterpenoid alkaloid, is one example of a naturally occurring monoacylguanidine. The acyl residues found in triophamine also contain ten carbon atoms, but it is difficult to rationalize their biogenesis from a terpenoid pathway.

**Acknowledgment.** We acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada. We thank Mike LeBlanc and the staff at the Bamfield Marine Station for assistance in collecting *Triopha catalinae*. We thank Dr. D. J. Faulkner for helpful discussions about guanidine chemistry and Sandra Millen for identifying the nudibranch.

**Registry No.** 1, 81256-25-9; 2, 81256-26-0; 3, 81256-27-1; 4, 5699-40-1; 5, 81256-28-2; 6, 81256-29-3; guanidine, 113-00-8.

(14) Acid 6 shows the following: high-resolution mass spectrum, $m/z$ 170.1298 ($M^+$; calcd for $C_{10}H_{18}O_2$, 170.1307); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7 Hz, 3 H), 0.95 (t, $J$ = 7 Hz, 3 H), 1.57 (d, $J$ = 7 Hz, 3 H), 1.52–1.62 (m, 2 H), 2.04 (q, $J$ = 7 Hz, 2 H), 2.14 (dd, $J$ = 7, 15 Hz, 1 H), 2.33 (dd, $J$ = 9, 15 Hz, 1 H), 2.47 (m, 1 H), 5.23 (q, $J$ = 7 Hz, 1 H).
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# Synthesis of Benzannelated Pyranosides†

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*Received December 7, 1981*

Ethyl and benzyl 2,3-dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranosid-4-uloses (e.g., 9–11) were prepared from D-glucal. The enones reacted with 1-methoxy-1,3-butadiene or 1-[(trimethylsilyl)oxy]-1,3-butadiene to afford the corresponding [4 + 2] cycloadducts. DDQ aromatization and subsequent elaboration of the cycloadducts gave benzannelated pyranosides. Amino sugar derivatives also were prepared. Aromatization of the (trimethylsilyl)oxy adducts directly afforded the corresponding phenols, but the reaction was found to be of limited scope. The stereochemistry of intermediates and products and subtleties of the DDQ reaction are discussed.

The importance of deoxy sugars as both synthetic and biological intermediates[1] promoted us to investigate the synthesis of functionalized derivatives. As part of a program concerned with the annelation of carbohydrate moieties, we have examined the cycloaddition reactions of some unsaturated sugars and the synthesis of benzannelated pyranosides. This paper reports the results of our study.

Ethyl and benzyl 2,3-dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranosid-4-uloses were chosen as initial substrates because of their ease of preparation and the position of the desired unsaturation. The synthesis of enones 9–11 is essentially that of Fraser-Reid[2] with some modifications (Scheme I). Diacetates 2 and 3 were prepared from tri-*O*-acetyl-D-glucal according to the method of Ferrier,[3] and although 2 was isolated directly as the $\alpha$ anomer, 3 was obtained as a 9/1 ($\alpha/\beta$) mixture. This mixture was separated at the diol

† Contribution No. 2983.

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(2) Fraser-Reid, B.,; McLean, A.; Usherwood, E. W.; Yunker, M. *Can. J. Chem.* **1970**, *48*, 2877.
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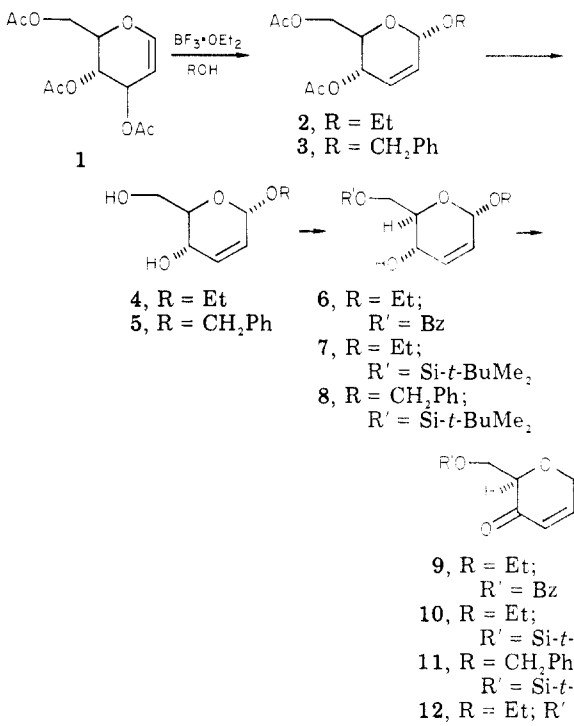
Scheme I



1

2, R = Et
3, R = $CH_2Ph$

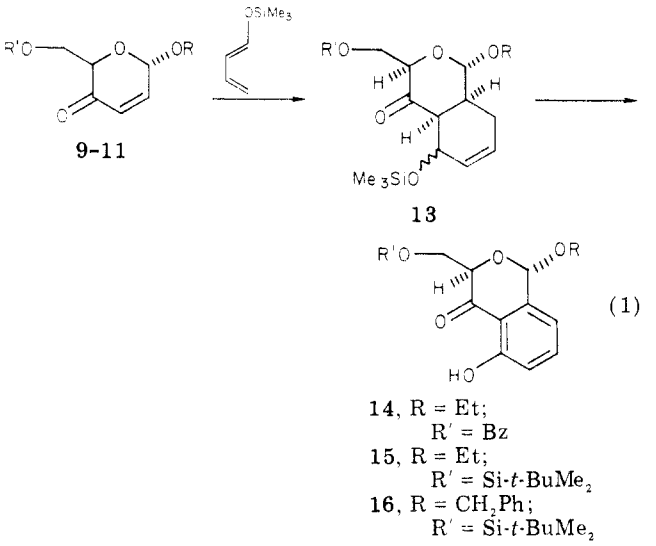
4, R = Et
5, R = $CH_2Ph$

6, R = Et; R′ = Bz
7, R = Et; R′ = Si-*t*-BuMe$_2$
8, R = $CH_2Ph$; R′ = Si-*t*-BuMe$_2$

9, R = Et; R′ = Bz
10, R = Et; R′ = Si-*t*-BuMe$_2$
11, R = $CH_2Ph$; R′ = Si-*t*-BuMe$_2$
12, R = Et; R′ = H

stage and afforded the pure $\alpha$ anomer of **5**. Enone **9** was prepared from **4** according to the literature[2] except that pyridinium chlorochromate (PCC) was found to give consistently higher yields of **9** than did manganese dioxide. For several reasons we desired to prepared 6-*O*-silylated derivatives of the enones, but the known sensitivity of hydroxy ketone **12**[2] precluded its use as a precursor to **10** and **11**. To overcome this, diols **4** and **5** were silylated[4] (>90%) at the primary position with *tert*-butyldimethylsilyl chloride and subsequently oxidized with PCC to give **10** (61%) and **11** (76%). Apparently because of steric effects, alcohols **7** and **8** were relatively inert to $MnO_2$ under conditions which readily oxidized **4** or **6**. The structures of enones **10** and **11** follow from their mode of synthesis and their IR, $^1H$ NMR, and $C^{13}$ NMR spectra (see Experimental Section). In addition, the first-order splitting pattern for H-1, H-2, and H-3 are diagnostic of this system.[2]

A logical method for the synthesis of benzannelated pyranosides appeared to involve a Diels–Alder reaction of the alkyl 2,3-dideoxyhex-2-enopyranosid-4-uloses with various dienes and subsequent aromatization of the newly formed ring. Indeed, treatment of enones **9–11** with oxygenated dienes (vide infra) followed by DDQ aromatization of the initial cycloadducts afforded benzannelated derivatives. Thus, when enones **9–11** were allowed to react with excess 1-[(trimethylsilyl)oxy]-1,3-butadiene[5] in refluxing toluene the corresponding [4 + 2] cycloadducts (**13**, eq 1) were formed. These adducts were not isolated but were treated directly with DDQ in refluxing benzene to afford **14–16** in 50–70% isolated yields.[6] Sturctural assignments are based on the expected regiochemistry[7] in the cycloaddition reaction as well as the IR and $^1H$ NMR spectra

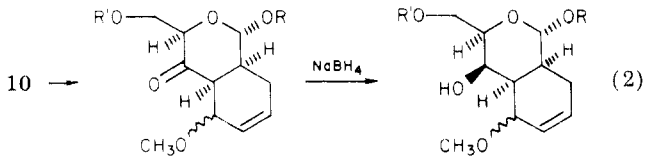


**9–11** → **13** → (1)

**14**, R = Et; R′ = Bz
**15**, R = Et; R′ = Si-*t*-BuMe$_2$
**16**, R = $CH_2Ph$; R′ = Si-*t*-BuMe$_2$

of the products. The $^1H$ NMR spectra of **14–16** display a one-proton singlet at $\delta$ 11.3–11.4 which is suggestive of a phenolic proton that is hydrogen bonded to the carbonyl group. Corroborating this are their carbonyl absorption bands (1650–1660 cm$^{-1}$) which resonate at ~30 cm$^{-1}$ lower than normal aryl ketones (1680–1690 cm$^{-1}$).[8] Methylation of **15** (vide infra) raises the carbonyl absorption frequency to 1690 cm$^{-1}$, thus confirming the regiochemistry of **14–16**.

When treated with 1-methoxy-1,3-butadiene in refluxing toluene, **10** quantitatively afforded **17** (eq 2) as a mixture



**10** → (NaBH$_4$) → **18** (2)

**17**, R = Et; R′ = Si-*t*-BuMe$_2$

of two isomers with one predominating (~4:1, NMR). Presumably, these are the $\alpha$- and $\beta$-methoxyl group isomers, but after they were separated (preparative LC), we were unable to assign methoxy group stereochemistry because of the similarity between the $^1H$ NMR spectra. This similarity suggests that both isomers are of the same regiochemistry as is indicated in structure **17**. The fact that the major isomer eventually leads to **19** (vide infra) confirms its regiochemistry. The assignment of the indicated ring junction stereochemistry in **17** is based upon the steric hinderance present on the $\alpha$ face of enones such as **10**, the observed coupling constants, and the result of a reported cycloaddition reaction of this system.[9] In the $^1H$ NMR spectrum of **17**, H-1 (carbohydrate numbering) appears as a doublet with $J_{1,2}$ = 4 Hz, but this intermediate value did not allow an assignment of an axial or equatorial configuration to H-2. However, reduction of the minor isomer with $NaBH_4$ stereospecifically (attack from the convex face) afforded **18** (90%) in which H-1 is a singlet ($\delta$ 4.58) and suggests that H-2 is indeed equatorial.[9,10]

Surprisingly, when the individual isomers of **17** were subjected to DDQ in refluxing benzene, only the predom-

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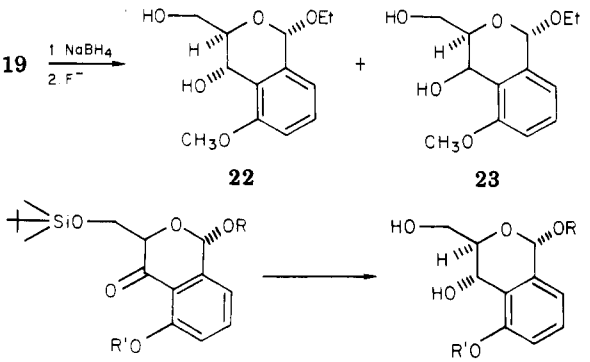
(5) Bazouin, A. R. M.; Dunogues, J. P.; Lefort, L.; M. J. C. U.S. Patent 3472888.
(6) The trimethylsilyl group is lost during the aromatization step, rendering this a simple phenol synthesis. However, attempts to utilize this methodology by employing a variety of other dienophiles afforded only low yields of the corresponding phenols.
(7) Sauer, J.; Sustmann, R. *Angew, Chem., Int. Ed. Engl.* **1980**, *19*, 779 and references cited therein.
(8) Bellamy, L. J. "The Infra-red Spectra of Complex Molecules"; Chapman and Hall: London, 1975.
(9) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1980**, 6.
(10) $^1H$ NMR spectrum of **18**: $\delta$ 0.88 (s, 6 H), 0.92 (s, 9 H), 1.18 (t, 3 H, $J$ = 7 Hz), 1.85–2.42 (m, 4 H), 2.65 (m, 1 H), 3.33 (s, 3 H), 3.38–3.88 (m, 7 H), 4.58 (s, 1 H), 5.91 (m, 2 H).

Scheme II

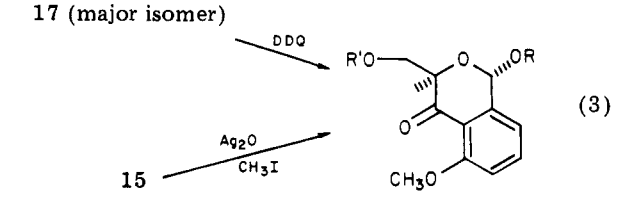


15, R = Et; R′ = H
16, R = $CH_2Ph$; R′ = H
20, R = $CH_2Ph$; R′ = $CH_3$

24, R = Et; R′ = H
25, R = $CH_2Ph$; R′ = H
26, R = $CH_2Ph$; R′ = $CH_3$

inate isomer aromatized to give **19** (eq 3). The minor isomer was inert to DDQ in refluxing xylene, even after an extended period of time. We suggest that this contrasting behavior is the result of stereoelectronic control becasue in the absence of the methoxyl or (trimethylsilyl)oxy functionalities no aromatization occurs.[11] The predominate isomer of **17** most likely contains a $\beta$ (pseudoequatioral) methoxy group, assuming an endo transition state in the cycloaddition reaction. It seems reasonable that only the equatorial methoxy is capable of stabilizing the adjacent incipient carbonium ion which would result from reaction with DDQ.[12] This result was also observed during aromatization of **13** but is of less consequence since the unreactive isomer comprised only ~10% of the mixture.

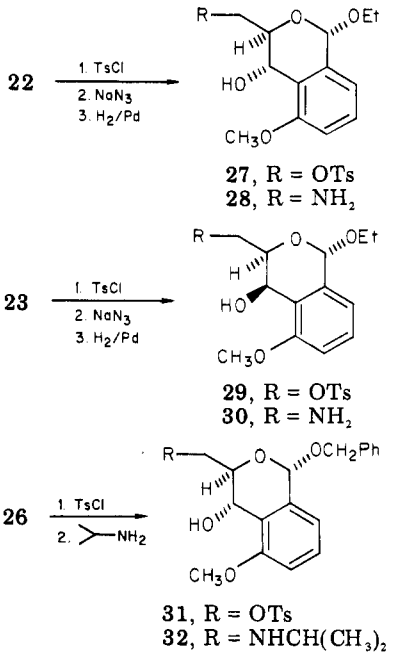
Large-scale preparations of **19** may be obtained by direct aromatization of crude **17**, but silver(I) oxide catalyzed methylation of **15** afforded **19** in quantitative yield (eq 3) and is the method of choice.[13] Attempts to methylate **15** via potassium carbonate and methyl iodide were unsuccessful.



19, R = Et; R′ = Si-*t*-$BuMe_2$
20, R = $CH_2Ph$; R′ = Si-*t*-$BuMe_2$

Elaboration of the benzannelated pyranosid-4-uloses (**15**, **16**, **19**, and **20**) into pyranosides **22–26** was accomplished via sodium borohydride reduction and subsequent disily-

Scheme III



27, R = OTs
28, R = $NH_2$

29, R = OTs
30, R = $NH_2$

31, R = OTs
32, R = $NHCH(CH_3)_2$

lation[4] with fluoride ion. In this manner, **19** afforded both **22** (60%) and **23** (20%), while only the erythro isomers (**24–26**) were obtained as a major reaction product from **15**, **16**, and **20** (Scheme II). The stereochemistry at C-4 in **22** and **24–26** was deduced from their $^1H$ NMR spectra in which H-4 ($\delta$ 4.5–5.0) appears as a doublet with $J_{4,5}$ = 9 Hz which is indicative of axial–axial coupling. In contrast, the spectrum of **23** shows H-4 ($\delta$ 4.75) as a broad singlet.

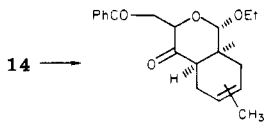
Attempts to prepared derivatives with a free C-1 hydroxyl group via acid-catalyzed hydrolysis of molecules such as **22** rapidly afforded dehydrated products. In contrast, treatment of the carbonyl derivatives (such as **14**) with methanolic hydrogen chloride over an extended period gave the transglycosylated products in 30% conversion; the remainder of the starting material was recovered unchanged. The desired products were obtained by catalytic hydrogenation of benzyl glycosides **25** and **26**. These products gave satisfactory mass spectral data, but 220-MHz $^1H$ NMR revealed that these molecules exist as a mixture of the various possible pyranose and furanose configurations.

The importance of amino sugars in biological systems prompted us to prepare amino analogues of the benzannelated pyranosides. The synthesis of the C-6 amino derivatives **28**, **30**, and **32** (Scheme III) was accomplished via nucleophilic substitution on the tosylates **27**, **29**, and **31** by the appropriate nitrogen nucleophile and subsequent elaboration.

## Experimental Section

**General Methods.** All reactions were performed under a nitrogen atmosphere. Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 or Nicolet 7199 FT-IR spectrometer. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter. $^1H$ NMR spectra were obtained in chloroform-*d* on a Varian EM-390, IBM NR-80, or Varian HR-220 spectrometer and are referenced to internal tetramethylsilane. $^{13}C$ NMR spectra were determined on a Bruker WH-90 spectrometer and are referenced to internal tetramethylsilane. Mass spectra were recorded at 70 eV on a VG Micromass 70–70H double-focusing high-resolution spectrometer. Preparative liquid chromatography was performed on a Waters

(11) Lewis acid catalyzed treatment of **14** with isoprene according to the method of Fraser-Reid[9] afforded **21**. All attempts to aromatize **21** either via DDQ or various other methods were unsuccessful.



21

(12) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972, and references cited therein.
(13) Garden, J. F.; Thomson, R. H. *J. Chem. Soc.* **1957**, 2483.

Prep LC/System 500 instrument. UV spectra were determined on a Cary 17 spectrophotometer.

**Benzyl 4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside (3).** To a solution of triacetyl-D-glucal[14] (100 g, 368 mmol) and benzyl alcohol (64 mL) in anhydrous benzene (400 mL) was added $BF_3$-$OEt_2$ (20 mL). After the mixture was stirred 1 h at room temperature, $Na_2CO_3$ (200 g) was added, and the resulting mixture was filtered and concentrated. Chromatography on silica gel (1:1 hexane/ether) and distillation afforded **3** (93 g, 79%) as a 9/1 $\alpha/\beta$ mixture as determined by NMR: bp 187–192 °C (0.05 mm); mp 37–39 °C; IR (neat) 1745, 740, 690 $cm^{-1}$; $^1H$ NMR $\delta$ 2.02 (s, 6 h) 4.08 (m, 3 H), 4.6 (q, 2 H, $J$ = 12 Hz), 5.13 (m, 2 H), 5.75 (m, 2 H), 7.22 (m, 5 H); $[\alpha]_D$ +71.4° (*c* 1.01, toluene).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.89; H, 6.26.

**Benzyl 2,3-Dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranoside (5).** A solution of **3** (35.9 g, 112.3 mmol) in 500 mL of MeOH/$H_2O$/$Et_3N$ (5:4:1) was stirred at room temperature for 4 h. Removal of the solvents under reduced pressure and preparative LC (EtOAc) afforded **5**: 18.6g (70%); colorless solid; mp 88–90 °C; IR (KBr) 3320, 1090, 1060, 995, 735, 695 $cm^{-1}$; $^1H$ NMR $\delta$ 2.84 (br, 1 H), 4.57 (q, 2 H, $J$ = 11 Hz), 4.96 (s, 1 H), 5.5–5.9 (m, 2 H), 7.23 (s, 5 H); $[\alpha]_D$ +49° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.24; H, 9.90.

**Benzyl 6-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranoside (8).** Treatment of **5** as above afforded **8**: 91%; colorless liquid; bp (Kugelrohr) 180–190 °C (0.05 mm); IR (neat) 3410, 735, 695 $cm^{-1}$; $^1H$ NMR $\delta$ 0.11 (s, 6 H), 0.91 (s, 9 H), 2.84 (d, 1 H, $J$ = 4.5 Hz), 3.7 (m, 3 H), 4.06 (br, 1 H), 4.57 (q, 2 H, $J$ = 11 Hz), 4.92 (br s, 1 H), 5.72 (m, 2 H), 7.23 (s, 5 H); $[\alpha]_D$ +30.4° (*c* 1.03, EtOH).

Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.13; H, 8.41.

**Ethyl-6-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranosid-4-ulose (10).** A solution of **7** (14.59 g, 50.6 mmol) in $CH_2Cl_2$ (930 mL) was stirred with pyridinium chlorochromate (32.6 g) for 24 h at room temperature. Removal of the solvents under reduced pressure, chromatography on silica gel (2:1 hexane/ether), and distillation afforded **10**: 8.82g (61%); colorless liquid; bp 85–92 °C (0.05 mm); IR (neat) 1700 $cm^{-1}$; $^1H$ NMR $\delta$ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.28 (t, 3 H, $J$ = 7 Hz), 3.75 (q, 2 H, $J$ = 7 Hz), 4.06 (m, 2 H), 4.48 (dd, 1 H), 5.36 (d, 1 H, H-1, $J$ = 3.5 Hz), 6.1 (d, 1 H, H-3, $J$ = 10 Hz), 6.88 (dd, 1 H, H-2, $J$ = 3.5, 10 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.8, 143.6, 127.3, 92.4, 75.5, 64.0, 62.0, 25.3, 17.7, 14.5, 5.89; $[\alpha]_D$ +18.8° (*c* 1.06, EtOH).

Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.62; H, 9.22.

**Benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-$\alpha$-D-*glycero*-hex-2-enopyranosid-4-ulose (11).** Treatment of **8** by the above procedure gave **11**: 76%; colorless liquid; bp 178–180 °C (5 nm); IR (neat) 1715, 740, 700 $cm^{-1}$, $^1H$ NMR $\delta$ 0.09 (s, 6 H), 0.88 (s, 9 H), 3.95 (m, 2 H), 4.41 (dd, 1 H, H-5, $J$ = 3.5, 4.5 Hz), 4.68 (q, 2 H, $J$ = 11 Hz), 5.3 (d, 1 H, H-1, $J$ = 3.5 Hz), 6.01 (d, 1 H, H-3, $J$ = 10.5 Hz), 6.76 (dd, 1 H, H-2, $J$ = 3.5, 10.5 Hz), 7.26 (s, 5 H); $[\alpha]_D$ −22.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.02; H, 8.02.

**[1*S*-(1$\alpha$,3$\beta$)]-3-[(Benzoyloxy)methyl]-3,4-dihydro-1-ethoxy-5-hydroxy-1*H*-2-benzopyan-4-one (14).** A solution of **9** (528 mg, 2 mmol) and 1-[(trimethylsilyl)oxy]-1,3-butadiene[5] (710 mg, 5 mmol) in toluene (10 mL) was heated at 100 °C for 66 h. The solvent was removed under reduced pressure, and the residue was dissolved in benzene (10 mL). To this solution was added DDQ (3.39 g, 15 mmol), and the resulting mixture was refluxed for 2 h. The reaction mixture was filtered through Celite, concentrated under reduced pressure, and chromatographed on silica gel (3:2 hexane/ether) to give **14**: 460 mg (67%); colorless solid; mp 111–112 °C (2-PrOH); IR (KBr) 3410, 1729, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 1.26 (t, 3 H, $J$ = 7 Hz), 3.75 (m, 2 H), 4.74 (m, 2 H), 4.88 (m, 1 H), 5.62 (s, 1 H), 6.66 (d, 1 H, $J$ = 8 Hz), 6.83 (d, 1 H, $J$ = 8 Hz), 7.28 (m, 4 H), 7.84 (m, 2 H), 11.35 (s, 1 H); $[\alpha]_D$ +24.8° (*c* 0.91, $CHCl_3$).

(14) Aldrich Chemical Co.

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.57; H, 5.27.

**[1*S*-(1$\alpha$,3$\beta$)]-3-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dihydro-1-ethoxy-5-hydroxy-1*H*-2-benzopyran-4-one (15).** By use of the above procedure, **10** (8.58 g, 30 mmol) afforded **15**: 6.44 g (61%); light yellow oil; bp (Kugelrohr) 165–170 °C (0.09 mm); IR (neat) 3000, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 0.07 (s, 6 H), 0.84 (s, 9 H), 1.26 (t, 3 H, $J$ = 7 Hz), 3.76 (m, 2 H), 4.05 (d, 2 H, $J$ = 4.5 Hz), 4.55 (d, 1 H, $J$ = 4.5 Hz), 5.63 (s, 1 H), 6.65 (d, 1 H, $J$ = 7.5 Hz), 6.82 (d, 1 H, $J$ = 8.0 Hz), 7.36 (dd, 1 H, $J$ = 7.5, 8.0 Hz), 11.3 (s, 1 H); $[\alpha]_D$ +42.8° (*c* 0.98, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}O_5Si$: C, 61.33; H, 8.01. Found: C, 61.36; H, 8.15.

**[1*S*-(1$\alpha$,3$\beta$)]-3-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dihydro-1-(benzyloxy)-5-hydroxy-1*H*-2-benzopyran-4-one (16).** The procedure was as above, and **11** (7.0 g, 20 mmol) and 1-[(trimethylsilyl)oxy]-1,3-butadiene (5.68 g, 40 mmol) afforded **16**: 4.25 g, (51%); colorless syrup; bp (Kugelrohr) 187–193 °C (0.1 mm); IR (neat) 3100, 1660 $cm^{-1}$; $^1H$ NMR $\delta$ 0.09 (s, 6 H), 0.85 (s, 9 H), 4.05 (m, 2 H), 4.57 (t, 1 H, $J$ = 4.5 Hz), 4.73 (q, 2 H, $J$ = 12 Hz), 5.68 (s, 1 H), 6.61 (d, 1 H, $J$ = 7 Hz), 6.81 (d, 1 H, $J$ = 8 Hz), 7.27 (m, 6 H), 11.32 (s, 1 H).

Anal. Calcd for $C_{25}H_{29}O_5Si$: C, 66.64; H, 7.29. Found: C, 66.35; H, 7.53.

**Cycloadduct 17.** A solution of **10** (2.86 g, 10 mmol) and 1-methoxy-1,3-butadiene (8.4 g, 100 mmol) in toluene (30 mL) was heated at 100 °C for 25 h. Removal of the volatiles under reduced pressure afforded a viscous residue that was separated into two main fractions by HPLC (3:1 hexane/ether).

**Fraction I** was 940 mg (23%) of a yellow oil that is tentatively identified as **17$\alpha$**: IR (neat) 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.25 (t, 3 H, $J$ = 7 Hz), 2.0–2.44 (m, 4 H), 3.2 (m, 1 H), 3.31 (s, 3 H), 3.42–4.3 (m, 5 H), 4.73 (d, 1 H, $J$ = 2.5 Hz), 5.77 (m, 2 H); mass spectrum, $m/e$ calcd for $C_{15}H_{25}O_5Si$ ($M^+ - C_4H_9$) 313.1470, found 313.1474.

**Fraction II** was 1.33 g (33%) of **17$\beta$** isolated as an oil: IR (neat) 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.24 (t, 3 H, $J$ = 7 Hz), 2.13 (m, 3 H), 2.44 (m, 1 H), 3.28 (m, 3 H), 3.43–4.21 (m, 6 H), 4.67 (d, 1 H, $J$ = 4 Hz), 5.46–6.13 (m, 2 H); mass spectrum, $m/e$ calcd for $C_{15}H_{25}O_5Si$ ($M^+ - C_4H_9$) 313.1470, found 313.1474.

**[1*S*-(1$\alpha$,3$\beta$)]-3-[(*tert*-Butyldimethylsiloxy)methyl]-3,4-dihydro-1-ethoxy-5-methoxy-1*H*-2-benzopyran-4-one (19).** To a solution of **15** (5.44 g, 15.4 mmol) and methyl iodide (4.6 mL) in chloroform (75 mL) was added freshly prepared $Ag_2O$ (6.18 g, 26.6 mmol). After the mixture was stirred 1 h at room temperature, methyl iodide (2.3 mL) and $Ag_2O$[15] (2.68 g, 11.6 mmol) were added and stirring was continued for 1 h. Then an additional portion of methyl iodide (2.3 mL) and $Ag_2O$ (2.68 g) was added, and the resulting mixture was allowed to stir overnight. Filtration through Celite and concentration under reduced pressure afforded **19**: 5.60g (99%); colorless semisolid; bp (Kugelrohr) 173–180 °C (0.08 mm); mp 53–56 °C; IR (Nujol) 1690, 1610 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 6 H), 0.81 (s, 9 H), 1.25 (t, 3 H, $J$ = 7 Hz), 3.76 (m, 2 H), 3.85 (s, 3 H), 4.05 (m, 2 H), 4.42 (m, 1 H), 5.66 (s, 1 H), 6.85 (m, 2 H), 7.45 (dd, 1 H, $J$ = 7.0, 7.5 Hz); UV ($CHCl_3$) $\lambda_{max}$ 253 nm ($\epsilon$ 7980), 316 (5100).

**[1*S*-(1$\alpha$,3$\beta$,4$\alpha$)]- and [1*S*-(1$\alpha$,3$\beta$,4$\beta$)]-3,4-Dihydro-1-ethoxy-4-hydroxy-3-(hydroxymethyl)-5-methoxy-1*H*-2-benzopyran (22 and 23).** To a solution of **19** (5.12 g, 14 mmol) in EtOH (85 mL) at 0 °C was added $NaBH_4$ (700 mg, 18.9 mmol). After 50 min at 0 °C, the reaction mixture was poured into water and extracted with $CH_2Cl_2$. Drying ($MgSO_4$) and concentration afforded a syrupy residue. This residue was dissolved in THF (25 mL), cooled to 0 °C, and treated with 1 M tetra-*n*-butylammonium fluoride (38 mL). After 10 min at 0 °C and 1 h at room temperature, the reaction mixture was poured into water and extracted with $CH_2Cl_2$. The usual isolation procedure afforded a brownish residue that was chromatographed (preparative LC; EtOAc) and gave two fractions.

**Fractrion I (22)**: 2.14 g (60%); colorless syrup; IR (neat) 3450, 1590, 790, 735 $cm^{-1}$; $^1H$ NMR $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 2.42 (br

(15) Campaigne, D.; LeSuer, W. M. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 919.

s, 1 H), 3.43–4.18 (m, 9 H), 4.86 (d, 1 H, $J$ = 9 Hz), 5.45 (s, 1 H), 6.75 (d, 2 H, $J$ = 7.5 Hz), 7.16 (dd, 1 H, $J$ = 7.5, 8.0 Hz); $[\alpha]_D$ +22.1° ($c$ 1.02, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.40; H, 7.14.

**Fraction II (23)**: 710 mg (20%) isolation as a colorless solid; mp 154–156 °C; IR (KBr) 3500, 1590 $cm^{-1}$; $^1H$ NMR $\delta$ 1.25 (t, 3 H, $J$ = 7.5 Hz), 2.46 (br, 2 H), 3.56–4.24 (m, 8 H), 4.75 (br s, 1 H), 5.57 (s, 1 H), 6.76 (d, 2 H, $J$ = 9 Hz), 7.13–7.3 (m, 1 H); $[\alpha]_D$ +47.1° ($c$ 1.01, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.40; H, 7.19.

**[1*S*-(1α,3β,4α)]-3,4-Dihydro-1-ethoxy-4,5-dihydroxy-3-(hydroxymethyl)-1*H*-2-benzopyran (24).** A 0 °C solution of **15** (7.19 g, 20.4 mmol) in EtOH (160 mL) was reduced with $NaBH_4$ (2.01 g, 52.9 mmol) over a 1-h period. The reaction was quenched by addition of dilute oxalic acid, and the products were partitioned between $H_2O/CHCl_3$. The resulting organic residue was desilylated as previously described. Preparative LC (2:1 EtOAc/hexane) gave **24**: 1.03 g, (21%); colorless solid; mp 101–105 °C; IR (KBr) 3360, 1468, 1100, 1040, 1019 $cm^{-1}$; 220-MHz $^1H$ NMR $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 3.47–4.09 (m, 8 H), 4.93 (d, 1 H, $J$ = 9 Hz), 5.48 (s, 1 H), 6.69 (d, 1 H, $J$ = 7.5 Hz), 6.76 (dd, 1 H, $J$ = 8, 1.5 Hz), 7.13 (dd, 1 H, $J$ = 7.5, 8.0 Hz); mass spectrum, calcd for $C_{12}H_{16}O_5$ ($M^+$) $m/e$ 240.0997, found ($M^+$) 240.0987; $[\alpha]_D$ +16.6° ($c$ 1.04, EtOH).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.20; H, 6.61.

**[1*S*-(1α,3β,4α)]-3,4-Dihydro-1-(benzyloxy)-4,5-dihydroxy-3-(hydroxymethyl)-1*H*-2-benzopyran (25).** Phenol **16** was reduced and desilylated according to the above procedure. Preparative LC (2:1 EtOAc/hexane) afforded **25** as a colorless solid: mp 101–104 °C; IR (KBr) 3370 $cm^{-1}$; 220 MHz $^1H$ NMR $\delta$ 3.75 (br, 2 H), 4.0 (m, 1 H), 4.71 (q, 2 H, $J$ = 12 Hz), 4.89 (d, 1 H, J = 9 Hz), 5.5 (s, 1 H), 6.61 (dd, 1 H, J = 7.5, 1 Hz), 6.74 (dd, 1 H, $J$ = 8, 1 Hz), 7.09 (dd, 1 H, $J$ = 7.5, 8 Hz), 7.3 (m, 5 H); $[\alpha]_D$ +18° ($c$ 0.99, $CHCl_3$).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.35; H, 6.02.

**[1*S*-(1α,3β,4α)]-3,4-Dihydro-1-ethoxy-4-hydroxy-3-[(toluenesulfonyloxy)methyl]-5-methoxy-1*H*-2-benzopyran (27).** To a solution of **22** (1.90 g, 7.48 mmol) in pyridine (35 mL) at −5 °C was added $p$-toluenesulfonyl chloride (1.70 g, 9 mmol), and the resulting solution was kept at −15 °C for 22 h. The mixture was poured into water and extracted with $CH_2Cl_2$, and the organic layer was washed with water, dried ($MgSO_4$), and concentrated. Column chromatography (1:1 hexane–EtOAc) gave **27**: 2.10g (69%); mp 96.5–99 °C; $^1H$ NMR $\delta$ 1.24 (t, 3 H, $J$ = 7 Hz), 2.42 (s, 3 H), 3.51–4.0 (m, 6 H), 4.11–4.47 (m, 3 H), 4.8 (dd, 1 H, $J$ = 9, 2 Hz), 5.44 (s, 1 H), 6.8 (d, 2 H, half of AB, $J$ = 8 Hz), 7.27 (m, 3 H), 7.82 (d, 2 H, half of AB, $J$ = 8 Hz).

Anal. Calcd for $C_{20}H_{24}O_7S$: C, 58.81; H, 5.92. Found: C, 59.06; H, 5.99.

**[1*S*-[1α,3β,4β)]-3,4-Dihydro-1-ethoxy-4-hydroxy-3-[(toluenesulfonyloxy)methyl]-5-methoxy-1*H*-2-benzopyran (29).** By use of the above procedure, **23** (830 mg, 3.26 mmol) afforded **29**: 1.19 g (89%); colorless soild; mp 106–108.5 °C; $^1H$ NMR $\delta$ 1.23 (t, 3 H, $J$ = 7 Hz), 2.22 (br, 1 H), 2.42 (s, 3 H), 3.5–3.98 (m, 5 H), 4.36 (m, 3 H), 4.66 (br d, 1 H, $J$ = 4 Hz) 5.52 (s, 1 H), 6.8 (d, 2 H, half of AB, $J$ = 8 Hz), 7.38 (m, 3 H), 7. 81 (d, 2H, half of AB, $J$ = 7 Hz).

Anal. Calcd for $C_{20}H_{24}O_7S$: C, 58.81; H, 5.92. Found: C, 58.84; H, 5.76.

**[1*S*-(1α,3β,4α)]-3-(Aminomethyl)-3,4-dihydro-1-ethoxy-4-hydroxy-5-methoxy-1*H*-2-benzopyran (28).** A solution of **27** (4.22 g, 10.34 mmol) and $NaN_3$ (2.7 g, 41 mmol) in DMF (50 mL) was heated at 90 °C for 3 h. The mixture was poured into $H_2O$ and extracted with ether. The organic phase was washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated to give **28**: 2.86 g (99%); light yellow syrup; IR (neat) 3490, 2100 $cm^{-1}$; $^1H$ NMR $\delta$ 1.3 (t, 3 H), 3.5–4.1 (m, 8 H), 4.25 (m, 1 H), 4.85 (d, 1 H, $J$ = 9 Hz), 5.5 (s, 1 H), 6.85 (m, 2 H), 7.25 (m, 1 H).

This syrup (azide) was dissolved in EtOH (120 mL) and hydrogenated at ~1 atm of $H_2$ over a catalytic amount of 10% Pd/C. The resulting residue was chromatographed on silica gel (1:1 EtOAc/MeOH) to afford **28**: 2.22 g (81%); viscous syrup; IR (neat) 3450–3100, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.28 (t, 3 H), 2.57 (br s, 3 H), 2.78–4.14 (m, 8 H), 4.78 (d, 1 H, $J$ = 9 Hz), 5.57 (s, 1 H), 6.82 (m, 2 H), 7.25 (m, 1 H); mass spectrum, $m/e$ 253; $[\alpha]_D$ +23.1° ($c$ 1.27, EtOH).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 60.17; H, 7.48; N, 5.21.

Treatment of **28** with 2 equiv of benzoyl chloride afforded a dibenzoyl derivative, mp 68–70 °C.

Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.32; H, 6.03; N, 2.98.

**[1*S*-(1α,3β,4β)]-3-(Aminoethyl)-3,4-dihydro-1-ethoxy-4-hydroxy-5-methoxy-1*H*-2-benzopyran (30).** Amine **30** (83%) was synthesized by the same procedure as above: IR (KBr) 3420, 1590, 1470, 1120, 1065, 1040 $cm^{-1}$; $^1H$ NMR $\delta$ 1.27 (t, 3 H, $J$ = 7 Hz), 2.32 (s, 3 H), 3.15 (m, 2 H), 3.54–4.15 (m, 6 H), 4.77 (d, 1 H, $J$ = 2.5 Hz), 5.62 (s, 1 H), 6.82 (m, 2 H), 7.24 (m, 1 H); $[\alpha]_D$ +51.4° ($c$ 1.11, EtOH).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.36; H, 7.28; N, 5.28.

**[1*S*-(1α,3β,4α)]-1-(Benzyloxy)-3,4-dihydro-4-hydroxy-3-[(toluenesulfonyloxy)methyl]-5-methoxy-1*H*-2-benzopyran (31).** Diol **26** (1.59 g, 5.03 mmol) in pyridine (35 mL) was cooled to 0 °C and treated with $p$-toluenesulfonyl chloride (1.14 g, 6.03 mmol). After all solids had dissolved, the flask was stoppered and kept at 0 °C for 48 h. The usual workup and chromatography (1:1 hexane–EtOAc) afforded **31**: 2.20 g (93%); viscous syrup; $^1H$ NMR $\delta$ 2.41 (s, 3 H), 3.84 (s, 4 H), 4.18 (m, 1 H), 4.35 (m, 2 H), 4.7 (q, 2 H, $J$ = 12 Hz), 4.81 (d, 1 H, $J$ = 8 Hz), 5.5 (s, 1 H), 6.74 (d, 1 H, $J$ = 7.5 Hz), 6.78 (d, 1 H, $J$ = 8.0 Hz), 7.25 (m, 8 H), 7.82 (d, 2 H, $J$ = 8 Hz).

**[1*S*-(1α,3β,4α)]-1-(Benzyloxy)-3,4-dihydro-4-hydroxy-3-[(isopropylamino)methyl]-5-methoxy-1*H*-2-benzopyran (32).** To a solution of **31** (2.20 g, 4.68 mmol) in DMF (10 mL) was added 2-propylamine (3.4 mL, 40 mmol). The resulting solution was heated at 85 °C, employing a dry ice condenser. After 6 h, the mixture was poured into water and extracted with $CHCl_3$. A workup as usual and column chromatography (EtOAc) afforded **32**: 980 mg (58.6%); yellow syrup; IR (neat) 3600, 1630 $cm^{-1}$; $^1H$ NMR $\delta$ 1.1 (d, 6 H, $J$ = 7 Hz), 2.54–3.23 (m, 5 H), 3.83 (s, 3 H), 4.24 (m, 1 H), 4.79 (m, 3 H) 5.55 (s, 1 H), 6.77 (m, 2 H), 7.1–7.53 (m, 6 H); exact mass calcd for $C_{21}H_{27}NO_4$ ($M^+$) $m/e$ 357.1933, found 357.1977.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.35; H, 7.60; N, 4.27.

**Registry No.** α-**3**, 81389-84-6; β-**3**, 81389-85-7; α-**5**, 81389-86-8; **7**, 58888-62-3; **8**, 81389-87-9; **9**, 25474-13-9; **10**, 81389-88-0; **11**, 81389-89-1; **14**, 81389-90-4; **15**, 81408-05-1; **16**, 81389-91-5; α-**17**, 81389-92-6; β-**17**, 81389-93-7; **18**, 81389-94-8; **19**, 81389-95-9; **20**, 81389-96-0; **21**, 81408-30-2; **22**, 81389-97-1; **23**, 81389-98-2; **24**, 81389-99-3; **25**, 81390-00-3; **26**, 81390-01-4; **27**, 81390-02-5; **28**, 81390-03-6; **28** dibenzoyl derivative, 81390-04-7; **28** azide, 81408-06-2; **29**, 81390-05-8; **30**, 81444-81-7; **31**, 81390-06-9; **32**, 81390-07-0; triacetyl-D-glucal, 2873-29-2; 1-[(trimethylsilyl)oxy]-1,3-butadiene, 6651-43-0; 1-methoxy-1,3-butadiene, 3036-66-6.