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PREPARATION AND DIELS-ALDER REACTIONS OF A PYRANOID VINYL GLYCAL: MODEL STUDIES FOR ANTHRAQUINONE AGLYCONE AND CARBOHYDRATE SYNTHESES★

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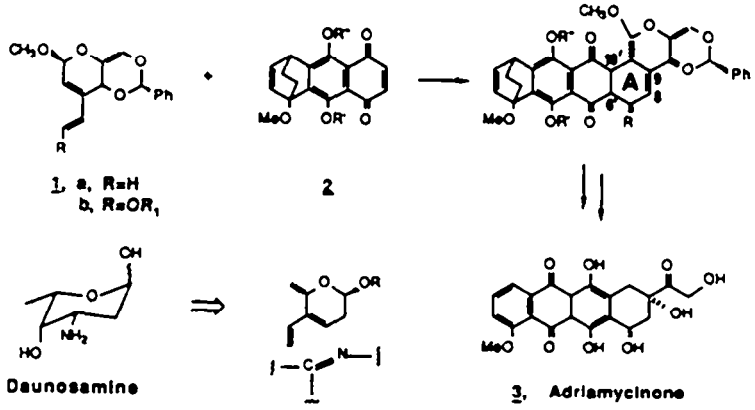
Abstract: The preparation of a conjugated pyranoid vinyl glycal is reported, along with several of its thermal [4+2] cycloaddition reactions with a variety of dienophiles. Applications to the anthraquinone antitumor agents are discussed.

Carbohydrates, both as chiral educts and as targets of synthetic endeavors, still occupy a highly valued position in organic chemistry.[2] One type of sugar moiety which is remarkably underdeveloped is the glycal unit containing a conjugated (substituted) vinyl residue which should be capable of effecting "chiral transcription"[3] *via* Diels-Alder processes with appropriate dienophiles. We are aware of only two literature examples of such a process,[4] one of which involves a furanoid glycal.[4a] We envisioned construction of a pyranoid analog, e.g., vinyl glycal **1**, which upon [4+2] cycloaddition with an achiral tricyclic quinone **2**,[5] would lead to the carbon skeleton characteristic of a number of anthraquinone antitumor agent (AAA) aglycones[6], e.g., adriamycinone, **3**. By the judicious choice of stereochemistry for the alkoxy group at the anomeric center in **1**, approach of the dienophile should be controlled based primarily on steric factors. Exo/endo selectivity, while expected in an intermolecular case to be primarily the latter, is irrelevent in terms of the overall synthetic objective (i.e., these two centers, C-6'and C-10', would be lost *en route* to **3**). For the D-glucose derived vinyl glycal **1b** (R_1 = hydroxyl protecting group), unidirectional approach of a quinone from the α-face would translate into generation of the required C-7 hydroxyl function (AAA numbering) in protected, homochiral form. Moreover, the resultant double bond at C-8, C-9 is suitably positioned for epoxidation[7]-hydride reduction[8] of the free allylic alcohol in the newly formed aglycone A ring, which would thereby establish C-9 of correct absolute stereochemistry. Such a strategy for AAA aglycone synthesis has the potential as well for applications to the preparation of the carbohydrate portion of these same natural products. Since these tend to be aminoglycosides (e.g., daunosamine)[6], there is incentive to investigate reactions of heteroatom dienophiles with vinyl glycals. Of course, the desired location of the amino group in the target sugar will dictate the positioning of the butadiene framework in the precursor. Hence, in principle, pyranoid vinyl glycals may enjoy the unique

★Dedicated to Professor E. C. Taylor on the occasion of his 65th birthday.

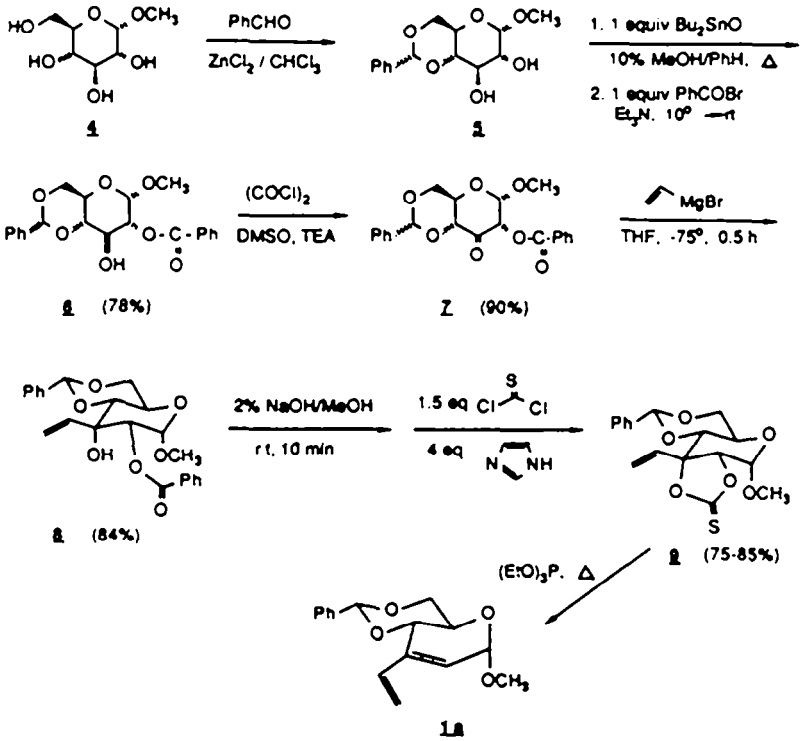
opportunity to serve as precursors to both components of the AAA's. In this report we describe the preparation of a conjugated pyranoid vinyl glycal, 1a, along with model studies of its Diels-Alder reactions aimed at addressing both goals of AAA aglycone and aminosugar syntheses.



Preparation of Vinyl Glycal 1a.

As illustrated in Scheme 1, the synthesis of vinyl glycal 1a begins with commercially available α-D-methylglucoside (4), the benzylidenation[9] of which gives 5. Treatment of 5 with Bu_2SnO[10] in hot 10% MeOH /benzene followed by cooling to 10°C and introduction of benzoyl chloride and Et_3N (1.5 equiv) gives monobenzoate 6, along with varying amounts of the corresponding dibenzoate.[11] Swern oxidation at -78°C[12] gives the 3-keto sugar 7, which adds vinyl Grignard (but not vinyllithium) cleanly and quickly predominantly from the equatorial face,[13] affording 8 (84%). Saponification of the benzoate gives a cis-vicinal diol which is best converted to the thionocarbonate 9 in refluxing $CHCl_3$ using thiophosgene (1.5 equiv)[14] in the presence of excess imidazole.[15] Upon thermolysis of 9 in neat

Scheme 1.

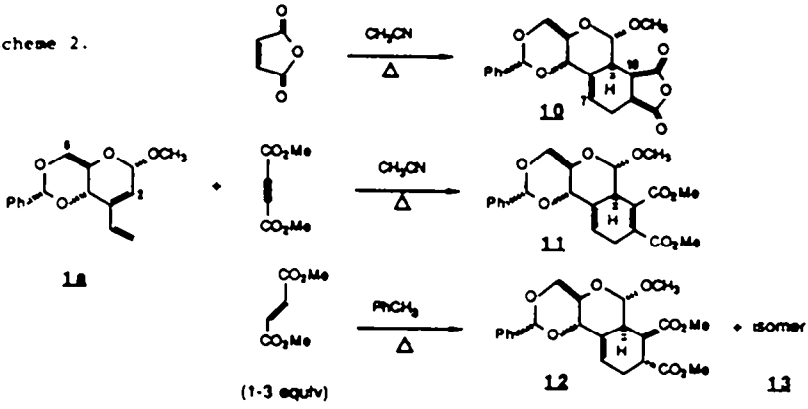


$(EtO)_3P$, vinyl glycal **1a** is produced (49% isolated, 72% based on recovered starting material)[15] as a stable, white crystalline solid. Thermal decomposition of **9** to **1a** is performed under relatively dilute conditions (ca.0.05M) and stopped prior to consumption of thionocarbonate, since prolonged heating generates products of cycloaddition of **1a** with itself.

Cycloaddition Reactions of Vinyl Glycal **1a**.

The Diels-Alder reactions of **1a** with several carbon dienophiles (1-3 equivalents) were investigated, as summarized in Scheme 2. Maleic anhydride and dimethyl acetylenedicarboxylate reacted smoothly in refluxing CH_3CN to each afford a single cycloadduct, **10** and **11**, respectively. Dimethyl fumarate gave a 1:1 mix of regioisomeric products **12** and **13** under similar conditions. A number of dienophiles did not undergo reaction with butadiene **1a**, including diethyl ketomalonate,[16] α-acetoxyacrylonitrile,[17] and α-chloroacrylonitrile.[18] Using excess dienophile and prolonged reaction times (>24h) and relatively elevated temperatures (refluxing toluene) did not afford any of the desired cycloadducts. Rather surprisingly, only products of self-cycloaddition were observed.[19,20] Attempts to use Lewis acid catalysis (e.g., $ZnCl_2$, (+)-Eu(hfc)$_3$[19]) either lead to no reaction or, on occasion (with e.g., $BF_3 \cdot Et_2O$), the decomposition of the starting diene, not unexpected given the presence of the benzylidene moiety.

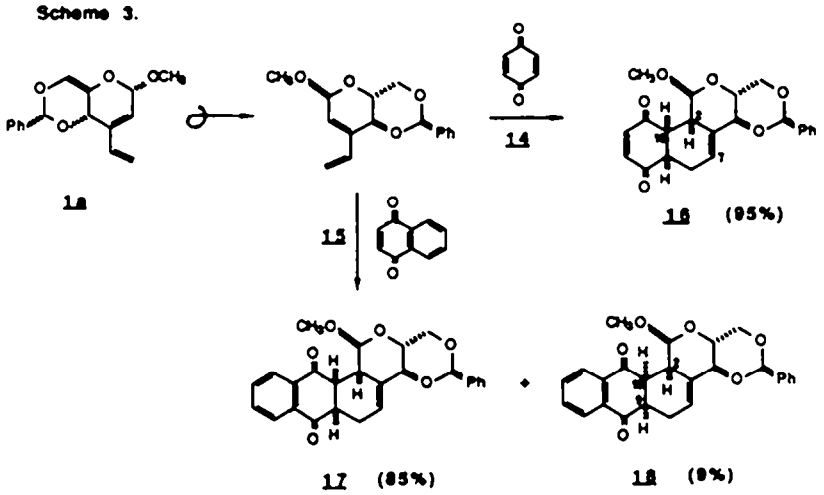
Scheme 2.



The stereochemistry of the adducts with regard to the newly formed chiral center at C-2 in the pyranose ring was anticipated from models which clearly indicate that for the α-glycoside, **1**, β-face attack by a dienophile should be highly preferred. ^{1}H NMR analyses of the C-1, C-2 coupling constant for the proton at the anomeric center ($J_{1,2}$ = 5-8 Hz) confirms the directionality of the cycloaddition to be as predicted, in all cases. The endo nature of adduct **10** follows from ^{1}H NMR analysis, which shows a $J_{2,10}$ value of 5.4 Hz indicative of a cis relationship between H-2 (δ 2.81 ppm) and H-10 (δ 3.59 ppm).[4]

Of particular interest, both p-quinone **14** and naphthoquinone **15** were likewise exposed to **1a** in CH_3CN or toluene. It was gratifying to find that each afford again one major product (**16** and **17**, respectively) in excellent yields (Scheme 3). ^{1}H NMR analyses ($J_{1,2}$ = 8Hz) dictate that each is derived via addition to vinyl glycal **1a** from the face away from the methoxy group. Assignment of each major product as resulting from endo or exo addition also follows from ^{1}H NMR data for H-10 which appears at δ 3.61 ppm as a triplet, indicative of a collapsed doublet of doublets resulting from the cis relationships between H-2,10 and H-9,10 in **16**. In the case of naphthoquinone, a second product assigned as the exo isomer was isolated in 9% yield, which showed a $J_{1,2}$ value of 7.5 Hz likewise implying topside attack to diene **1a**. Hence, of the four possible products which may form from the cycloaddition between **1a** and either **14** or **15** (i.e., β-face/exo and/or endo,

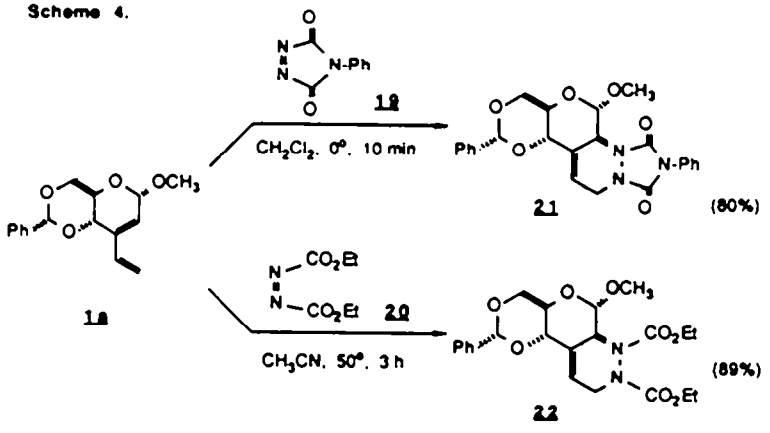
Scheme 3.



α-face/exo and/or endo), only one is highly favored (i.e., the face opposite to the alkoxy group at the anomeric center). Based on these results, it follows that cycloaddition of 1b is expected to lead to the desired C-7 hydroxyl group bearing the natural 7S configuration.[6]

To test the prospects for aminoglycoside generation, 1a was reacted with dienophiles 19 and 20. Both cycloadditions proceeded readily, each affording a single product in good yield (Scheme 4). Thus, given the option of locating the vinyl group as desired on the glycal at, e.g., C-2,3,or 4, and the choice of absolute stereochemistry of the starting material (i.e., a D or L sugar), it seems that nitrogen can indeed be introduced onto a pyranose skeleton.

Scheme 4.



Summary

A conjugated pyranoid vinyl glycal (1a) has been prepared from D-glucose and it's Diels-Alder reactions studied with a variety of carbon and nitrogen dienophiles. Both new carbocyclic rings and amino sugars have been realized from this scheme. In the specific case of quinone cycloadditions, control of facial attack onto 1a to afford a predominant, if not exclusive cycloadduct argues in favor of pursuing the preparation of 1b, the cycloaddition of which may ultimately lead to the A ring characteristic of the anthraquinone antitumor agents in homochiral fashion. Further work along these lines, including variations in double bond locations and intramolecular processes, will be reported in due course.

Experimental Section

General. ^{1}H-NMR spectra were recorded at 300 MHz (Nicolet NT-300) or 500 MHz (General Electric GN-500). ^{13}C-NMR spectra were recorded at 125 MHz (GN-500). Chemical shifts for proton and carbon resonances are reported in ppm (δ) relative to tetramethylsilane (δ0.0). Infrared (IR) spectra were recorded on a Perkin Elmer Model 283. Optical rotations were measured with a Rudolph Instruments Autopol III at the sodium D-line (unless otherwise specified). Mass spectrometry data were obtained on a VG 70-250HF instrument. Melting points are reported uncorrected as taken on a Fisher-Johns apparatus.

TLC was performed on E. Merck & Co. TLC plates (0.25 mm) precoated with silica gel. Silica gel 60 for flash chromatography was purchased from Fluka (230-400 mesh). THF was distilled from sodium/benzophenone ketyl. Triethylphosphite was stirred over sodium overnight, decanted, and distilled under reduced pressure. Toluene was distilled from sodium. Imidazole was sublimed before use. Skelly Solve (SS, a mixture of petroleum ethers) was distilled at a boiling range of 40-50°C. Chloroform was distilled from P_2O_5. Dioxane was distilled from lithium aluminum hydride. Benzaldehyde, acetonitrile, methylene chloride, dimethylsulfoxide, triethylamine, benzene, methanol, and dimethyl acetylenedicarboxylate were distilled from CaH_2. Methyl-α-D-glucopyranoside was obtained from Pfanstiehl Laboratories. Dibutyltin oxide, vinylmagnesium bromide (as 1.0M solution in THF), and thiophosgene were purchased from Aldrich.

All experiments, unless otherwise indicated, were performed under an Argon atmosphere with magnetic stirring.

Methyl-4,6-O-benzylidene-α-D-glucopyranoside, 5.

Prepared by a literature procedure.[9] Compound 5 was obtained as a white crystalline solid (75%); mp 156-158° (lit.[9] 161-163°); $[\alpha]_D^{20}$ = +111.5° (c 2.0, $CHCl_3$, lit. $[\alpha]_D^{20}$ = +110°)[8]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.47 ppm (m,2H), 7.40-7.35(m,3H), 5.53 (s,1H), 4.79 (d,1H,J=3.9Hz) 4.29 (dd,1H,$J_{1,2}$=3.9,9.3Hz), 3.93 (t,1H,J=9.3Hz), 3.82-3.78 (m,1H), 3.75 (dd,1H,J=9.3,10.2Hz), 3.65-3.58 (br m,1H), 3.51 (d,1H,J=9.0Hz), 3.46 (s,3H), 3.02-2.90 (br s,1H), 2.52-2.37 (br s,1H); IR (KBr disc) cm^{-1}, 3400, 2930, 2860, 1630, 1450, 1370, 1210, 1190, 1140, 1125, 1070, 1030, 1000; EIMS m/z (relative intensity), 282 (M^+,10), 281 (7), 251 (M^+-OCH_3, 2), 179 (25), 162 (13), 149 (14), 133 (30), 107 (base), 106 (20), 105 (98), 91 (31), 77 (29), 75 (53).

Methyl-2-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside, 6.

Prepared according to the procedure described by Szmant;[11] mp 171-173° (lit.[11] 173-175°); $[\alpha]_D^{25}$ = +110.8° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ8.11-8.06 (m,2H), 7.59-7.37 (m, 8H), 5.84 (s, 1H), 5.09-5.02 (m,2H), 4.60-4.30 (m,2H), 3.90 (dd, 1H, J=4.8, 9.0 Hz), 3.80 (t, 1H, J=10.2 Hz), 3.64 (t, 1H, J=9.3 Hz), 3.40 (s,3H) 2.49 (d,1H, J=2.4 Hz); IR (KBr disc) cm^{-1}, 3460, 3060, 2940, 2880, 1730, 1600, 1450, 1380, 1270, 1100, 1045, 1025, 985; CIMS m/z (relative intensity), 387 (M^++1,7), 386 (M^+,3), 385 (M^+-1,7), 355 (19) 281 (7), 249 (11), 149 (13), 107 (11), 105 (100), 77 (19).

Methyl-2-O-benzoyl-3-oxo-4,6-O-benzylidene-α-D-glucopyranoside 7.

Oxalyl chloride (0.39 mL, 4.5 mmol) was taken up in 9.0 mL dry CH_2Cl_2 and cooled to -75°C. DMSO (0.64 mL, 9.0 mmol) in 1.5 mL dry CH_2Cl_2 was added *via* a pressure equalizing addition funnel. The resulting clear bubbling solution was stirred at -75°C for 10 min and then the funnel was charged with 6 (1.580 g, 4.09 mmol) that had been dried azeotropically with toluene and dissolved in 3 mL of 1:1: CH_2Cl_2:DMSO. The solution was added over 10 min and the resulting milky solution was stirred for an additional 20 min, at which time dry triethylamine (2.8 mL, 20 mmol) was added dropwise to give an unstirable mixture. The reaction was then allowed to warm to ambient temperature, and after stirring for 30 min, it was worked up by pouring into 10 mL H_2O and 15 mL CH_2Cl_2 and extracted with CH_2Cl_2 (5x15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and the volatiles were then removed *in vacuo*. Isolation of the ketone 4 was effected *via* silica gel chromatography eluting with 5% acetone in CH_2Cl_2 (R_f = 0.58), to give 1.395 g (89%) product; mp 212-215° (lit. 211-213°)[13]; $[\alpha]_D^{25}$ = +97.8° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$), δ 8.13 (d,2H,J=7.2Hz), 7.65-7.36 (m,8H), 5.63 (d,1H,$J_{2,1}$ = 4.2Hz), 5.60 (s,1H), 5.35 (d,1H,$J_{1,2}$ = 4.2Hz), 4.80-4.41 (m,2H), 4.20 (dt,1H,$J_{5,6eq}$ = 4.5, $J_{5,4}$ =$J_{5,6ax}$ = 9.6Hz), 3.99 (t,1H,$J_{6ax,5}$ = $J_{6ax,6eq}$ = 9.9Hz), 3.50 (s,3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 191.86, 165.11, 136.27, 133.58, 130.07, 129.26, 128.73, 128.39, 128.21, 126.31, 101.85, 101.36, 82.04, 74.80, 69.27, 65.37, 55.65 ppm; IR (KBr disc) cm^{-1}, 3070, 3040, 3010, 2980, 2950, 2940, 2880, 1760, 1730, 1605, 1450, 1405, 1390, 1330, 1290, 1265, 1115, 1090, 1050, 990, 980; EIMS m/z (relative intensity), 384 (M^+, 0.2), 383 (M^+-1, 0.3), 353 (0.2), 178 (6.1), 106 (9.7), 105 (100) 77 (21.9).

Methyl-2-O-benzoyl-3-vinyl-4,6-O-benzylidene-α-D-allopyranoside, 8.

The ketone 7 (2.230 g, 5.81 mmol), following azeotropic drying with toluene (2x5 mL), was taken up in 39 mL dry THF and cooled to -78°C. Dropwise addition of 15 mL of a 1M solution of vinylmagnesium bromide in THF over 10 min gave an orange coloured solution that was allowed to stir at -75°C for 0.5 h. The reaction mixture was then quenched with 10 mL of saturated NH_4Cl, 10 mL H_2O, and diluted with 40 mL ethyl acetate. After warming to room temperature, the product was extracted with EtOAc (5x25 mL), washed with brine, and dried over anhydrous Na_2SO_4. The volatiles were then removed *in vacuo* and the resulting residue was flash chromatographed on silica, eluting with 30% acetone in SS. The allylic alcohol 8 (R_f = 0.44) was obtained in 77% (1.85 g) yield along with 165 mg of starting ketone (R_f = 0.36); hence, 84% based on recovered starting material; mp 60-63°; $[\alpha]_D^{24}$ = +98.4° (c 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$), δ 8.12-8.07 (m,2H), 7.62-7.57 (m,1H), 7.50-7.33 (m,7H), 5.79 (dd of ABX system,1H,$J_{X,B}$ = 10.5,$J_{X,A}$ = 17Hz) 5.595 (d of ABX,1H,$J_{A,X}$ = 18Hz), 5.59 (s,1H), 5.28 (d of ABX, 1H, $J_{B,X}$ = 11.5Hz), 5.11 (d,1H,$J_{1,2}$ = 4.0Hz) 5.04 (d,1H,$J_{2,1}$ = 4.0Hz), 4.42 (dd,1H,$J_{6eq,5}$ = 5.0Hz,$J_{6eq,6ax}$ = 10Hz), 4.27 (dt,1H,$J_{5,6eq}$ = 5.0Hz, $J_{5,6ax}$ = 10Hz), 3.81 (t, 1H,$J_{6ax,6eq}$ = 10Hz), 3.64 (t,1H,$J_{4,5}$ = 5.0Hz), 3.62 (s,1H), 3.48 (s,3H); IR ($CHCl_3$) cm^{-1}, 3510, 3070, 3020, 2940, 2875, 2860, 1720, 1600, 1585, 1450, 1380, 1320, 1270, 1215, 1105, 1000; EIMS m/z (relative intensity), 411 (M^+-1,0.2), 381 (0.2), 234 (5.6), 233 (17.9), 149 (2.6), 146 (2.2), 112 (11.8), 106 (10.1), 105 (100), 95 (3.3), 91 (4.4), 77(16.5).

Methyl-3-vinyl-4,6-O-benzylidene-α-D-allopyranoside.

Ester 8 (1.70 g, 4.13 mmol) was dissolved in 5 mL methanol and treated with 10 mL of 2% NaOH in MeOH at room temp. The saponification was complete after 10 min and the mixture was then quenched with 10 mL saturated NH_4Cl and immediately diluted with 50 mL ethyl acetate and 10 mL water. The product was extracted with EtOAc (5x20 mL) and washed with brine. The combined aqueous layers were back extracted with EtOAc (2x15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the volatiles removed *in vacuo*. The resulting residue was flash chromatographed on silica gel eluting with 30% acetone in SS to give the *cis*-vicinal diol (R_f = 0.27) in 92% (1.172 g) yield. $[\alpha]_D^{24}$ = +123° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.50-7.43(m,2H), 7.39-7.32 (m,3H), 5.86 (dd of ABX, system,1H,$J_{X,B}$ = 11.7Hz,$J_{X,A}$ = 16.6Hz), 5.55 (s,1H), 5.54 (d of ABX,1H,$J_{A,X}$ =17Hz), 5.39 (d of ABX,1H,$J_{B,X}$ = 10.5Hz), 4.82 (d,1H,$J_{1,2}$ = 3.9Hz), 4.38 (dd of AA'XX' system where $J_{A,A'}$ = $J_{A,X}$,1H,$J_{6eq,5}$= 5.4Hz, $J_{6eq,6ax}$ = 10.2Hz), 4.11 (dt of AA'XX' 1H, $J_{5,6eq}$ =5.4Hz, $J_{5,4}$ =$J_{5,6ax}$ = 10.2Hz), 3.77 (t of AA'XX' system,1H,$J_{6ax,5}$ = $J_{6ax,6eq}$ = 10.2 Hz), 3.61 (dd,1H,$J_{2,1}$ = 3.9Hz,$J_{2,alc}$ = 10.8Hz), 3.51 (multiplet with predominant singlet, 4H), 2.90(s,1H) 2.58 (d,1H,$J_{alcohol,2}$ = 10.8Hz); IR (KBr disc) cm^{-1}, 3490, 3070, 2970, 2940, 2900, 2840, 1650, 1430, 1410, 1370, 1270, 1210, 1120, 1085, 1070, 1000, 985; CIMS m/z (relative intensity) 309 (M^++1,6.7), 277 (12.2), 259 (7.8), 199 (10.0), 179 (27.2), 177 (11.5), 171 (21.6), 157 (42.4), 153 (45.2), 129 (57.0), 125 (38.0), 107 (100), 105 (33.6), 91 (30.9), 79 (23.5).

Methyl-2,3-O-thionocarbonate-3-vinyl-4,6-O-benzylidine-α-D-allopyranoside, 9.

In a 25 mL 2-neck round bottom flask, the *cis*-vicinal diol (1.170 g, 3.80 mmol) was azeotroped with toluene (2x3 mL) and then taken up in 9.5 mL dry $CHCl_3$ to which sublimed imidazole (1.05 g, 15.2 mmol) was added. The flask was equipped with a reflux condenser and the solution heated to reflux. Then utilizing a syringe pump, thiophosgene (0.43 mL, 5.7 mmol) was added as a 1M solution in $CHCl_3$ over 0.5 h. The solution immediately turned yellow/orange (color of thiophosgene) and a white precipitate (imidazole-HCl) was formed about halfway through the addition. After 12 h, the mixture was cooled and treated with 5 mL saturated NH_4Cl, 5 mL of H_2O, and diluted with 50 mL ethyl acetate. The product was extracted with EtOAc (5x20 mL) and washed with brine. The combined aqueous layers were backed washed with EtOAc (2x10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtering through a silica gel plug with 30% acetone in SS, the thionocarbonate 9 (1.16 g) was obtained in 87% yield; mp 74-77° (glass); $[\alpha]_D^{24}$ = +219° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.47ppm (m,2H), 7.37-7.35 (m,3H), 5.88 (dd of ABX,1H,$J_{X,B}$ = 10.8Hz,$J_{X,A}$ = 16.8Hz), 5.63 (d of ABX,1H,$J_{A,X}$ = 17.1Hz), 5.54 (s,1H), 5.50 (d of ABX,1H,$J_{B,X}$ = 10.8Hz), 4.95 (d,1H,$J_{1,2}$ = 5.4Hz), 4.76 (d,1H,$J_{2,1}$ =

5.4Hz), 4.39 (dd,1H,$J_{6eq,5}$ = 5.4Hz,$J_{6eq,6ax}$ = 10.2Hz), 4.22 (m,1H), 3.77 (m,2H), 3.48 (s,3H); IR ($CHCl_3$) cm^{-1}, 3020, 2940, 2870, 1815, 1450, 1370, 1335, 1310, 1220, 1145, 1095, 1080, 1050, 990; CIMS m/z (relative intensity), 351 (M^++1, 22.4), 350 (M^+, 5.5), 319 (3.5), 273 (3.9), 245 (9.0), 185 (13.8), 141 (15.1), 139 (11.4), 135 (12.3), 127 (15.1), 125 (30.5), 124 (35.1), 121 (75.2), 107 (100), 105 (41.7), 97 (30.7), 95 (35.7), 91 (35.7), 79 (37.8), 77 (17.3).

Methyl-2,3-dideoxy-2,3-ene-3-vinyl-4,6-O-benzylidene-α-D-glucopyranoside, 1a.

To 20 mL of dry triethylphosphite was added 331 mg (0.945 mmol) of thionocarbonate 9. The 0.047 M solution was not homogeneous until heated. The solution was subjected to reflux for 7.5 h (at which time subsequent cycloaddition was observed by TLC). It was then cooled and the bulk of the solvent was removed by vacuum distillation with minimal heat applied. To the residue was added 7 mL H_2O and 15 mL ethyl ether. The product was extracted with Et_2O (6x15 mL). The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting residue was flash chromatographed on silica gel eluting with 30% acetone in SS. The desired butadiene (128 mg) was obtained (R_f = 0.64) in 49% isolated yield as fine white needles, mp 130-133°. The remaining unreacted thionocarbonate (0.30 mmol) was recovered, giving a 72% yield of 1a based on recovered starting material; $[\alpha]^{23}_{365nm}$ = -52° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.50-7.47ppm (m,2H), 7.38-7.35 (m,3H), 6.28 (dd of ABX, 1H,$J_{X,B}$ = 11.4Hz,$J_{X,A}$ = 17.7 Hz), 5.73-5.70 (m,2H), 5.64 (s,1H), 5.22 (d of ABX,1H,$J_{B,X}$ = 11.4Hz), 4.95 (d,1H,$J_{1,2}$ = 2.1Hz), 4.33 (m,2H), 3.98 (dt of AA'XX',1H,$J_{A,X}$ = 4.5Hz,$J_{A,A'}$ =8.7Hz, and $J_{A,X}$ = 10.2Hz), 3.85 (t of AA'XX',1H,$J_{X,A}$ = $J_{X,X}$ = 10.2Hz), 3.45 (s,3H); ^{13}C-NMR (125 MHz, $CDCl_3$), δ 138.77, 137.45, 132.70, 128.90, 128.19, 126.09, 123.94, 118.38, 101.83, 96.30, 76.17, 69.32, 63.40, 55.74; IR (KBr disc) cm^{-1}, 3110, 3095, 3070, 3040, 2995, 2970, 2940, 2920, 2880, 2840, 1825, 1735, 1605, 1500, 1470, 1450, 1390, 1365, 1350, 1320, 1310, 1300, 1275, 1215, 1200, 1190, 1150, 1125, 1090, 1070, 1050, 1020, 990, 970, 950; EIMS m/z (relative intensity), 274 (M^+,2.5), 243 (14.2), 168 (19.5), 150 (10.4), 149 (87.4), 125 (41.7), 108 (21.1), 107 (18.0), 105 (24.3), 97 (24.6), 95 (30.1), 91 (100), 81 (15.8), 79 (24.8), 77 (27.8); HREI, observed m/z: 274.1187, calculated : 274.1205.

Preparation of carbocyclic adduct 10 from maleic anhydride and vinyl glycal 1a.

In a 5 ml round bottom flask equipped with a reflux condenser was placed the glycal 1a (31 mg, 0.113 mmol) and sublimed maleic anhydride (25 mg, 0.255 mmol). The mixture was taken up in 0.5 mL dry acetonitrile and heated to reflux for 1.5 h. The mixture was then cooled and the volatiles removed under vacuum. The resultant residue was flash chromatographed on silica gel eluting with 5% Et_2O in CH_2Cl_2. The product 10 (R_f = 0.46) was obtaining in 70% yield (29.3 mg) as a clear oil: $[\alpha]_D^{24}$ = +79° (c 1.4,$CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.50-7.47 (m,2H), 7.38-7.36 (m,3H), 6.11 (m,1H), 5.61 (s,1H), 5.52 (d,1H,$J_{1,2}$ = 5.1Hz), 4.37 (dd,1H,J=3.1Hz,9.0Hz), 4.23-4.19 (br.m,1H), 3.86-3.73 (m,2H), 3.59 (dd,1H,J=5.4Hz,9.9Hz), 3.49 (s,3H), 3.46-3.42 (m,1H), 2.81 (dd,1H,J=7.2Hz,15.9Hz), 2.65-2.62 (m,1H), 2.29-2.18 (br.m,1H); IR (KBr disc) cm^{-1}, 3070, 3040, 2960, 2940, 2860, 1850, 1780, 1450, 1385, 1330, 1280, 1250, 1140, 1125, 1090, 1075, 1035, 1000, 970; CIMS m/z (relative intensity), 373 (M^++1, 3.6), 372 (M^+, 4.0), 371 (3.8), 341 (12.2), 313 (17.8), 274 (5.1), 273 (28.3), 267 (22.5), 235 (50.3), 223 (37.5), 221 (31.5), 207 (26.5), 177 (32.6), 149 (95.3), 105 (44.9), 91 (100); HRCI observed m/z: 372.1249; calculated: 372.1249.

Preparation of carbocyclic adduct 11 from dimethyl acetylenedicarboxylate and vinyl glycal 1a.

In a 5 mL round bottom flask equipped with a reflux condenser was placed the diene 1a (32.0 mg, 0.117 mmol), dimethyl acetylenedicarboxylate (50 μL, 0.35 mmol), 0.5 mL of dry acetonitrile, and the mixture was then heated to reflux. After 8.5 h, the diene had been consumed and the volatiles were removed *in vacuo*. The resulting residue was flash chromatographed on silica gel eluting with 5% Et_2O in CH_2Cl_2. The vinylic diester 11 (R_f = 0.35, 35.4 mg) was isolated in 73% yield as a white solid; mp 140-142°; $[\alpha]_D^{23}$ = -31° (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.51-7.48 (m,2H), 7.37-7.35 (m,3H), 6.16-6.14 (m,1H), 5.63 (s,1H), 4.66 (d,1H,$J_{1,2}$ = 7.5 Hz), 4.35 (dd,1H,J = 3.3Hz,9.9Hz), 4.12-4.03 (m,2H), 3.82 (s,3H), 3.79-3.72 (m,5H), 3.35 (s,3H), 3.28-3.12 (m,1H), 3.05-2.91 (m,1H); IR (KBr disc)cm^{-1}, 3040,

2990, 2970, 2950, 2910, 2845, 1730, 1635, 1455, 1435, 1390, 1380, 1360, 1280, 1260, 1250, 1200, 1160, 1085, 1060, 995, 955; CIMS m/z (relative intensity), 417 (M^++1, 1.7), 416 (M^+, 1.7), 415 (1.9), 385 (47.6), 383 (25.2), 353 (41.3), 325 (38.2), 324 (17.0), 279 (89.6), 265 (33.0), 251 (17.7), 250 (10.1), 249 (24.5), 247 (29.0), 218 (100), 189 (93.2), 149 (48.1), 121 (43.6), 105 (40.3), 91 (56.1); HRCI observed m/z (M^+-OCH_3, $C_{21}H_{21}O_7$): 385.1274, calculated: 385.1287.

Preparation of 12 and 13 from dimethyl fumarate and vinyl glycal 1a.

In a 5mL round bottom flask equipped with a reflux condenser, the diene 1a (28.3 mg, 0.103 mmol) and dimethyl fumarate (30 mg, 0.206 mmol) were dissolved in 0.5 mL of dry toluene. The mixture was heated to reflux for 9 h, at which time the diene had been consumed, and the volatiles were then removed *in vacuo*. The resulting residue was flash chromatographed on silica eluting with 5% Et_2O in CH_2Cl_2. The two regioisomers (12 and 13) were readily separable affording equal amounts of each product. The first isomer to elute was 12 (R_f = 0.42) and 14 mg were obtained (32.5% yield); $[\alpha]_D^{23}$ = -78.0° (c 0.75, $CHCl_3$); ^{1}H-NMR (300MHz, $CDCl_3$), δ 7.50-7.48 (m,2H), 7.37-7.34 (m,3H), 6.13-6.10 (m,1H), 5.61 (s,1H), 4.66 (d,1H,$J_{1,2}$ = 7.5Hz), 3.70 (dd,1H,J=4.2Hz,9.9Hz), 4.15-4.10 (m,2H), 3.74-3.67 (multiplet with prominant singlet,7H), 3.33 (s,3H), 3.29-3.20 (m,1H), 3.18-3.12 (m,1H), 2.96-2.89 (m,1H), 2.52-2.30 (br.m,2H); IR (KBr disc) cm^{-1}, 3040, 3010, 2990, 2960, 2940, 2890, 2840, 1740, 1455, 1445, 1435, 1385, 1360, 1355, 1325, 1285, 1275, 1255, 1210, 1200, 1180, 1165, 1080, 1060, 1015, 1005, 990, 955; CIMS m/z (relative intensity), 418 (M^+, 5), 401 (10.3), 387 (61.1), 385.5 (35.4), 355 (18.0), 354 (29.0), 327 (20.9), 282 (16.8), 281 (100), 267 (17.8), 251 (23.8), 249 (18.4), 221 (24.9) 220 (17.5), 209 (14.4), 192 (15.9), 177 (19.0), 149 (98.4), 121 (54.8), 105 (32.4), 177 (19.0), 149 (98.4), 121(54.8), 105 (32.4), 91 (46.8), 59 (22.0); HRCI observed m/z (M^+ -OCH_3,$C_{21}H_{23}O_7$) : 387.1444; calculated: 387.1443.

The second regioisomer to elute was 13 (R_f = 0.39) and 14 mg were obtained (32.5%); $[\alpha]_D^{23}$ = -2.5° (c 0.75, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.51-7.48 (m,2H), 7.37-7.34 (m,3H), 6.06-6.03 (m,1H), 5.61 (s,1H), 4.58 (d,1H,$J_{1,2}$ = 7.5Hz), 4.36 (dd,1H,J = 4.5Hz,10.2Hz), 4.15-3.98 (m,2H), 3.73-3.70 (multiplet with prominant singlet,4H), 3.67 (s,3H), 3.34 (s,3H), 3.26-3.21 (m,1H), 3.05-2.97 (m,1H), 2.64 (t,1H,J = 11.1Hz), 2.57-2.54 (m,1H), 2.34-2.21 (br.m,1H); CIMS m/z (relative intensity), 447 (M^+ + C_2H_5, 6.8), 401 (11.8), 388 (16.8), 387 (71.6), 386 (37.3), 358 (10.6), 357 (21.7), 355 (34.7), 354 (54.1), 327 (40.1), 326 (47.4), 281 (100), 267 (25.6), 252 (42.2), 251 (27), 249 (29.6), 221 (46.7), 220 (39.7), 192 (53), 149 (90.3), 133 (31.0), 121 (55.2), 105 (62), 91 (83.6); HRCI observed m/z (M^+ -OCH_3,$C_{21}H_{23}O_7$): 387.1429, calculated 387.1443.

Preparation of 16 from 1,4-benzoquinone (14) and vinyl glycal 1a.

In a 5 mL round bottom flask equipped with a reflux condenser, the diene (31.5 mg, 0.115 mmol) and quinone (25 mg, 0.23 mmol) were dissolved in 0.6 mL dry acetonitrile and heated to reflux. After 4 h, the diene had been consumed and the mixture was cooled and the volatiles removed *in vacuo*. The resulting residue was flash chromatographed on silica gel, eluting with 5% Et_2O in CH_2Cl_2. The anticipated semiquinone 16 (R_f = 0.36) was isolated, in 95% (42.0 mg) yield as a colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$), δ 7.50-7.48 (m,2H), 7.35-7.34 (m,3H), 6.68 (d,1H,J=10.0Hz), 6.58 (d,1H,J=10.0Hz), 5.84-5.82 (m,1H), 5.62 (s,1H), 5.42 (d,1H,$J_{1,2}$=8.0Hz), 4.40 (dd of AA'MX, $J_{A,A'}$ = $J_{A,X}$,1H,$J_{6eq,5}$ = 5.0Hz,$J_{6eq,6ax}$ = 10.0Hz), 4.33-4.31 (m of AA'MX,1H), 4.02 (dt of AA'MX,1H,$J_{5,6ea}$ = 5.0Hz,$J_{5,6ax}$ = $J_{5,4}$ = 10.0 Hz), 3.75 (t of AA'MX,1H,$J_{6ax,6eq}$ = $J_{6ax,5}$ = 10.0Hz), 3.61 (t,1H,J=4.0Hz), 3.40 (s,3H), 3.24-3.19 (m,1H), 2.90-2.84 (m,1H), 2.54-2.47 (m,1H), 2.24-2.18 (m,1H); IR (KBr disc) cm^{-1}, 2950, 2840, 1690, 1450, 1385, 1265, 1140, 1115, 1085, 1060, 990 cm^{-1}; CIMS m/z (relative intensity), 382 (M^+, 4.1), 351 (21.5), 350 (18.7), 274 (18.7), 273 (100), 245 (47.8), 149 (71.8), 121 (20.6), 107 (28.7), 105 (41.8), 91 (81.9), 77 (28.9); HRCI observed m/z ($C_{22}H_{22}O_6$) : 382.1427, calculated : 382.1416.

Preparation of 17 and 18 from reaction of 1,4-naphthoquinone (15) and vinyl glycal 1a.

In a 5 mL pear shaped flask equipped with a reflux condenser, the diene 1a (41.2 mg, 0.15 mmol) and naphthoquinone (35.7 mg, 0.225 mmol) were dissoved in 0.6 mL of dry toluene and heated to reflux. After 4.5 h, the diene had been consumed and the volatiles were removed *in vacuo*. The resulting green residue was flash chromatographed on silica, eluting with CH_2Cl_2. The first cycloadduct to elute

(R_f=0.29) was the product of β-facial/exo-addition, **18**, was isolated (6.2 mg) in 9% yield; mp 215-218° (dec); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07-8.04 (m,1H), 7.96-7.93 (m,1H), 7.76-7.73 (m,2H), 7.50-7.46 (m,2H), 7.36-7.34 (m,3H), 6.08 (br.s,1H), 5.57 (s,1H), 4.57 (d,1H,$J_{1,2}$ = 7.5Hz), 4.26 (dd of AA'MX, $J_{A,A}$ = $J_{A,X}$,1H, $J_{6eq,5}$ = 4.8Hz,$J_{6eq,6ax}$ = 10.2Hz), 4.10-4.06 (m of AA'MX,1H), 3.83 (dt of AA'MX, 1H,$J_{5,6eq}$ = 4.8Hz, $J_{5,4}$ = $J_{5,6ax}$ = 9.9Hz), 3.63 (t of AA'MX system, 1H,$J_{6ax,6eq}$ = $J_{6ax,5}$ = 10.2Hz), 3.44-3.40 (m,1H), 3.23 (s,3H), 3.16 (dd,1H,J=4.2Hz,J=10.2Hz), 3.11-3.06 (m,1H), 2.99-2.88 (br.m,1H), 2.35-2.25 (br.m,1H); CIMS m/z (relative intensity), 433 (M^++1, 1.2), 432 (M^+, 1.8), 401 (21.6), 355 (11.1), 431 (5.7), 323 (6.5), 309 (13.8), 295 (39.9), 277 (21.1), 265 (22.5), 249 (16.6), 149 (23.8), 133 (22.5), 121 (37.7) 107 (100); HRCI, observed m/z ($C_{26}H_{24}O_6$): 432.1596; calculated: 432.1573.

The major product **17** (R_f=0.20), was next to elute and obtained in 85% (55.1 mg) yield as an oil; $[\alpha]_D^{23}$ = +99.5° (c 1.1, $CHCl_3$), ^{1}H-NMR (500 MHz, $CDCl_3$), δ 8.08-8.06 (m,1H), 7.96-7.94 (m,1H), 7.77-7.74 (m,2H), 7.53-7.49 (m,2H), 7.37-7.34 (m,3H), 5.85-5.83 (m,1H), 5.65 (s,1H), 5.51 (d,1H,$J_{1,2}$ = 8.0Hz), 4.43 (dd of AA'MX, $J_{A,A'}$ = $J_{A,X}$,1H,$J_{6eq,5}$ = 5.0Hz,$J_{6eq,6ax}$ = 10.0Hz), 4.40-4.36 (m of AA'MX,1H), 4.07 (dt of AA'MX, 1H,$J_{5,6eq}$ = 5.0Hz, $J_{5,4}$ = $J_{5,6ax}$ = 10.0Hz), 3.78 (t of AA'MX,1H,$J_{6ax,5}$ = $J_{6ax,6eq}$ = 10.0Hz), 3.75 (t,1H,J=4.0Hz), 3.40 (multiplet with prominant singlet, 4H), 2.97-2.94 (m,1H), 2.57-2.51 (br.m,1H), 2.21-2.14 (br.m,1H); ^{13}C-NMR (125 MHz, $CDCl_3$), δ 197.70, 196.97, 137.51, 135.28, 134.45, 134,32, 132.56, 131.75, 128.94, 128.21, 127.29, 126.42, 126.16, 119.27, 101.38, 99.73, 76.90, 70.09, 64.00, 55.52, 48.99, 47.26, 40.93, 26.39 ppm; IR (KBr disc), 3060, 2930, 2840, 1695, 1590, 1450, 1380, 1295, 1280, 1250, 1210, 1120, 1085, 1070, 1060, 995, 970 cm^{-1}; EIMS m/z (relative intensity), 432 (M^+, 1.7), 401 (5.6), 400 (14.0), 274 (18.5), 273 (100), 149 (73.1), 133 (36), 105 (42.8), 77 (35.4); HRCI, observed m/z (M^+ -OCH_3,$C_{25}H_{21}O_5$): 401.1375, calculated: 401.1389.

Preparation of hetereocyclic adduct **21**. Cycloaddition of vinyl glycal **1a** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).

In a 5 mL round bottom flask, diene **1a** (11 mg,0.04 mmol) was dissolved in 0.2 mL of dry CH_2Cl_2 and cooled to 0°C. PTAD (14 mg,0.08 mmol) was added, as a 1M solution in CH_2Cl_2, dropwise until the solution persisted with the color of PTAD (pink/violet) (ca. 10 min). Without work-up, the mixture was flash chromatographed on silica gel eluting with 5% Et_2O in CH_2Cl_2. The cycloadduct **21** (R_f = 0.41), was obtained as a white solid (14.4 mg) in 80% yield; mp 220-222° (decf; ^{1}H-NMR (500 MHz, $CDCl_3$), δ 7.53-7.48 (m,7H), 7.39-7.36 (m,3H), 6.29 (br.s,1H), 5.69 (s,1H), 5.27 (d,1H,$J_{1,2}$ = 5.0Hz), 4.72 (dd,1H,J=4.5Hz,5.0Hz), 4.42 (dd,1H,J=4.5Hz,10.0Hz), 4.34-4.30 (m,2H), 4.16-4.08 (m,2H), 3.79 (t,1H,J=10.0Hz), 3.51 (s,3H); EIMS m/z (relative intensity), 449 (M^+, 58.0), 418 (8.6), 360 (100), 300 (50.6), 283 (29.7), 254 (54.5), 135 (80.6), 119 (71.3), 108 (57.5), 107 (47.8), 105 (76.7), 91 (89.4), 79 (58.0), 77 (50.0); HREI observed m/z ($C_{24}H_{23}N_3O_6$) : 449.1559, calculated : 449.1586.

Reaction of vinyl glycal **1a** with diethyl azodicarboxylate (DEAD); Preparation of cycloadduct **22**.

In a 5 mL pear shaped flask equipped with a reflux condenser, the diene **1a** (10 mg, 0.036 mmol) was dissolved in 0.15 mL of dry acetonitrile at room temperature. DEAD (7 µL, 0.044 mmol) was added giving an orange (color of DEAD) solution. The solution was then heated to 50°C, for 3.5 h. The volatiles were then removed and the resulting residue was flash chromatographed on silica gel eluting with 5% Et_2O in CH_2Cl_2. The dicarbamate, **22** (R_f = 0.25), was isolated as an oil (14.4 mg) in a 89% yield; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.52-7.49 (m,2H), 7.37-7.36 (m,3H), 6.33 (br.s,1H), 5.62 (s,1H), 5.23-4.98 (br.s,1H), 4.64-4.57 (m,2H), 4.39 (dd,1H,J=4.0Hz,10.0Hz), 4.28-4.11 (br.m,6H), 3.75 (t,1H,J=10.0Hz), 3.69-3.59 (m,1H), 3.48 (s,3H), 1.28 (t,6H,J=6.5Hz); IR (film) cm^{-1}, 3020, 2990, 2940, 1710, 1700, 1650, 1470, 1415, 1380, 1340, 1300, 1220, 1085; EIMS m/z (relative intensity), 448 (M^+, 14.6), 376 (42.1), 315 (38.2), 287 (73.0), 227 (24.9), 195 (27.0), 181 (45.5), 149 (41.2), 137 (59.2), 135 (45), 107 (69), 105 (100), 91 (72.5), 77 (75.1); HREI observed m/z ($C_{22}H_{28}N_2O_8$) : 448.1855; calculated: 448.1845.

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