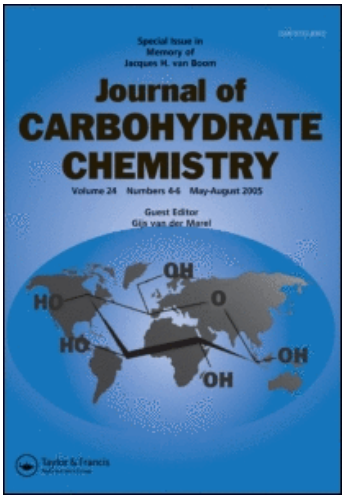

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STEREOCHEMICAL STUDY OF CYCLOADDITIONS USING ERYTHROSE AND THREOSE BASED DIENES AS SOURCE OF 2-NONULOSONIC ACID ANALOGS

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ABSTRACT

The stereochemical outcome of the hetero Diels Alder reaction of an erythrose based diene with sodium glyoxylate was rationalized by preparing the same compounds via decarboxylation of 2-carbethoxy-2-deoxy-2-ulosonic esters, obtained by cycloaddition with diethyl ketomalonate. Further chemical transformations of cycloadducts allowed us to prepare a series of new 2-nonulosonic acid derivatives.

INTRODUCTION

The aqueous hetero Diels Alder reaction has been shown to be a useful methodology.[2] Reaction of glyoxylic acid as dienophile has been reported to be an efficient way to produce bicyclic α-hydroxy lactones,[3] and reaction of conjugated dienes with a number of α-activated carbonyl compounds allowed for preparation of substituted dihydropyrans directly from their commercial aqueous solution.[4] The reaction has been used to access the 2-deoxy-2-ulosonic acid skeleton in which the C-2-C-3 and C6-O-6 bonds were created in the cycloaddition step, providing new syntheses of KDO and some of its

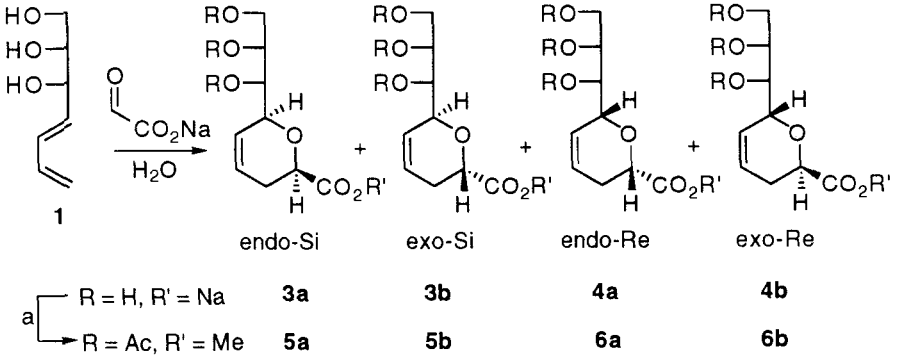
analogs,[5] as well as a short synthesis of racemic 2-heptulosonic acid derivatives.[6] The present report describes a study of the reaction based on the same strategy in the nine-carbon series starting from an erythrose based diene.[7] The structural study of 2-carbethoxy-2-deoxy-2-nonulosonates obtained by cycloaddition of various dienes with diethyl ketomalonate, made it possible to determine the streochemical outcome of the reaction. Further transformations of adducts obtained either from cycloaddition with glyoxylate (2-deoxy) and ketomalonate (2-carbethoxy-2-deoxy) provide new heavily substituted 2-nonulosonic acid analogs.[8]

RESULTS AND DISCUSSION

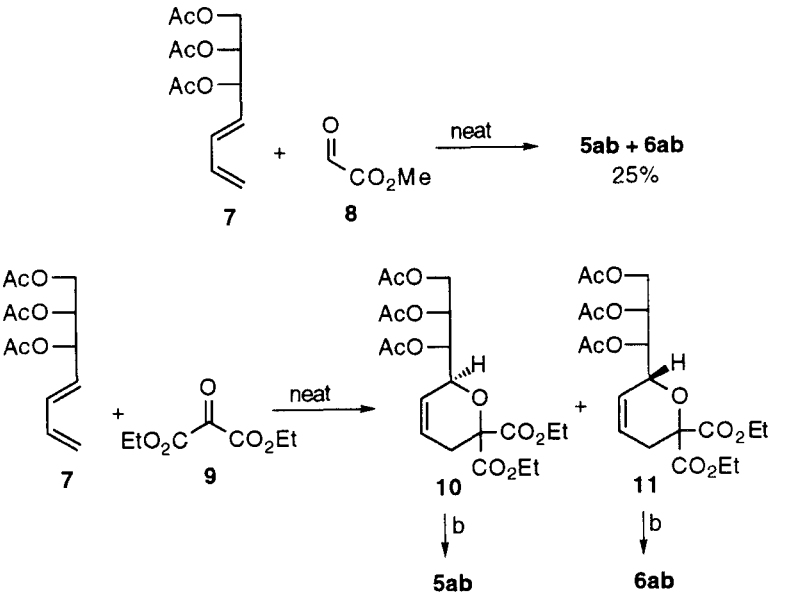
The cycloaddition in water (2.5 d at reflux) of (*E*)-hepta-4,6-diene-1,2,3-triol (**1**), having the D-*erythro* configuration, with sodium glyoxylate (**2**) provided a mixture of four adducts **3ab** and **4ab** that arise from *endo* and *exo* transition states and attack of the dienophile on both faces of the chiral diene (Scheme 1). These adducts were protected as their methyl tri-*O*-acetyl esters whose configurations were later determined as **5ab** and **6ab** (28:31:16:25, endo:exo = 44:56, Re:Si = 41:59),[9] and isolated in a global 67% yield from **1**. These results are compared to the low 25% yield obtained from the reaction of acetylated diene **7** with methyl glyoxylate (38:27:13:22, endo:exo = 65:35, Re:Si = 40:60). The high temperature required for the reaction with methyl glyoxylate (4 h, 140 °C) was not compatible with the stability of both the diene and the products, giving an additional example of the usefulness of using aqueous sodium glyoxylate as dienophile. It has to be noted that the reaction of diene **1** with sodium glyoxylate occurred faster in water than in other polar solvents such as ethanol or dimethylformamide.

In order to ascertain the structure of each of the four adducts produced in the reaction, the same compounds were prepared by cycloaddition of diene **7** with diethyl ketomalonate that provided adducts **10** and **11** (Re:Si = 35:65), which were decarboxylated and reprotected separately in 51% yield from **7**. This allowed us to divide the four adducts in two groups, endo and exo Si (**5ab**) and endo and exo Re (**6ab**). The absolute configuration at C-6 was determined after careful structural study of adducts obtained from various dienes (*vide infra*).

In order to study the influence of the hydroxyl group protection on the facial selectivity, we prepared variously substituted dienes (Scheme 2). Thus,

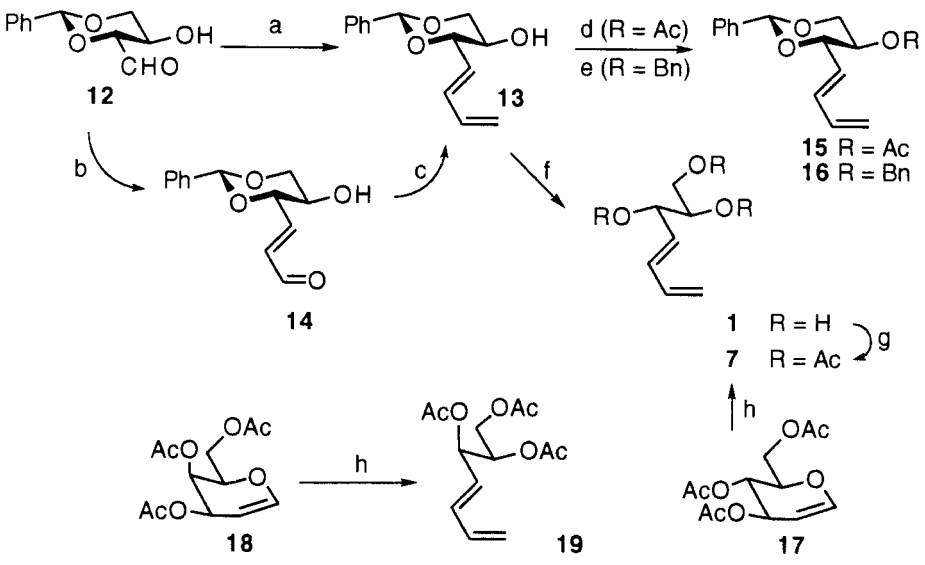


a. 1. CH_3I, DMF 2. Ac_2O, Py 67% from **1**



b. 1. LiOH, H_2O 2. Dowex 50X8, H^+, 100 °C 3. CH_2N_2, Et_2O
4. Ac_2O, Py 51% from **7**

SCHEME 1



a. $BrPh_3PAll$, BuLi, THF, 45%; b. $Ph_3P{=}CHCHO$, THF, 76%; c. $Ph_3P{=}CH_2$, THF, 76%; d. Ac_2O, py, 92%; e. NaH, BnBr, THF, 70%. f. 80% aq AcOH, 60 °C, 30 min, 90%; g. Ac_2O, py, quant.; h. reference 11.

SCHEME 2

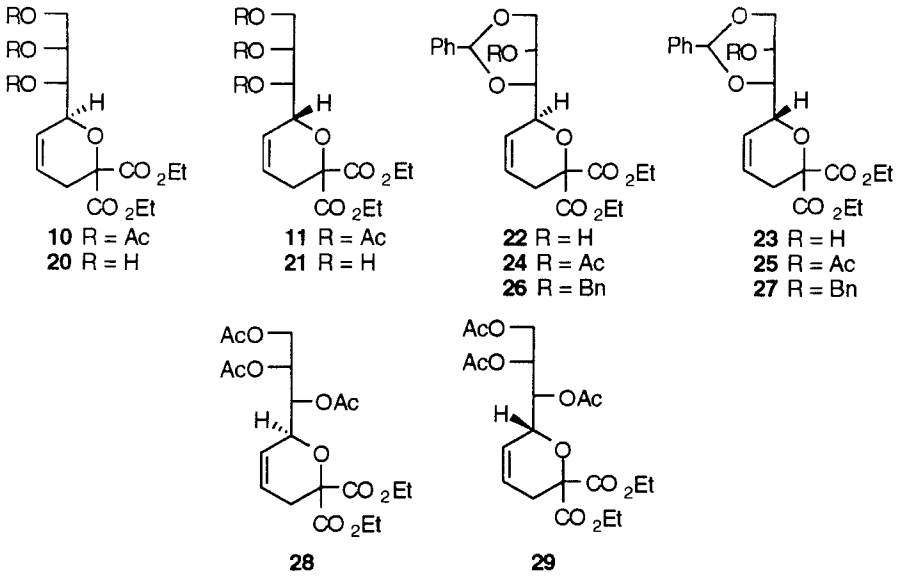
reaction of 2,4-di-*O*-benzylidene-D-erythrose (**12**)[10] with allyltriphenylphosphorane in THF gave a 4:1 mixture of *E* and *Z* dienes (56%) out of which the major *E* diene **13**[11] crystallized. This reaction required two equivalents of phosphorane because of the presence of a free hydroxyl group in aldehyde **12**. An alternative route to diene **13** consisted in two consecutive Wittig reactions, first with the stabilized triphenylphosphoranylideneacetaldehyde giving *E* enal **14** (76%) which provided diene **13** after methylenation (76%). Careful acidic hydrolysis of the acetal linkage of diene **13** (80% aq AcOH, 60 °C, 30 min) gave diene **1** in 90% yield;[12] increased reaction time led to degradation of the diene. Dienes **15** and **16** were obtained from **13** by standard procedures. Triacetylated diene **7** could either be obtained from acetylation of **1** or following a known procedure from tri-*O*-acetyl-D-glucal (**17**).[11,13]

The same sequence starting from tri-*O*-acetyl-D-galactal provided diene **19**, epimer of **7** at C-7, having the D-*threo* configuration.

The outcome of the cycloaddition for the six dienes was studied using diethyl ketomalonate. Adducts **20** to **29** were obtained in fair to good yields (Scheme 3).[14] As shown in Table 1, the substitution on hydroxyl groups of erythrose diene had little effect on the facial selectivity that varied between a 2:1 and a 1:1 ratio. Ratio for the mixture **20** + **21**, arising directly from unprotected diene **1**, was determined, after acetylation (Ac_2O, Py), upon comparison (^1H NMR study of crude mixture) with adducts **10** and **11**, arising from acetylated diene **7**. Mixtures **22** + **23** and **26** + **27**, obtained from benzylidene dienes **13** or **16**, were hydrogenated (5 atm. H_2, Pd/C) and acetylated (Ac_2O, Py) for comparison with fully reduced compounds **30** + **31** (cf. Scheme 4) arising from adducts **10** and **11** after double bond reduction (1 atm. H_2, Pd/C). Finally, mixture of adducts **24** + **25** arising from acetylated benzylidene diene **15** was compared with an acetylation mixture of **22** + **23**.

Comparison of the results obtained for dienes **7** and **19**, epimeric at the allylic stereogenic center and leading to a reversal of the diastereofacial selectivity, allowed the determination of the absolute configuration at C-6 in adducts **10** and **11**. Indeed, as depicted in Scheme 4, H-6-H-7 coupling constants in hydrogenated adducts **30** and **31** arising from "erythrose" adducts **10** and **11**, and **32** and **33** arising from "threose" adducts **28** and **29**, were consistent with the general trend in such structure, namely a small $J_{6,7}$ (0-2 Hz) in KDN or sialic acid type chairs, and a large $J_{6,7}$ (8-10 Hz) in KDO type chairs.[15]

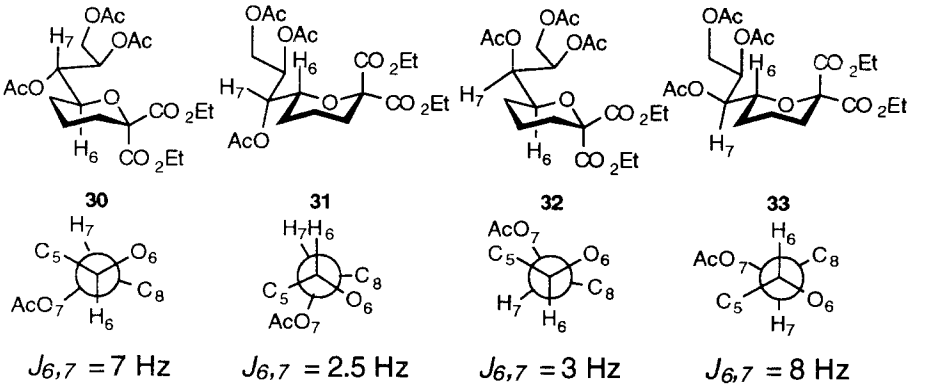
Taking into account the low facial selectivity observed in these cycloadditions, this reaction has to be considered as an access to both series of dihydropyrans epimers at C-6, each of them being intermediates to interesting targets. Having in hand a range of 2,6-disubstituted dihydropyrans, and relying on our previous work on the functionalization of 2-deoxy derivatives in the heptulosonic[6] and octulosonic[5] acid series, we studied the further chemical elaboration of some of the newly made nonulosonate esters. Notably, adduct **11**, having the same stereochemistry at position 6,7 and 8 as in KDN, was an interesting candidate for further functionalization, as depicted in Schemes 5 and 6. Thus, bishydroxylation of **11** via catalytic osmylation produced *cis* diol **34** in 81% yield, with total facial selectivity that assured correct stereochemistry at position 5. An oxidation-reduction sequence could permit inversion of the hydroxyl group at C-4. This step was achieved directly using diol **34** without further protection employing the stannylene methodology via the 4-hydroxy-3-ketone **35** which



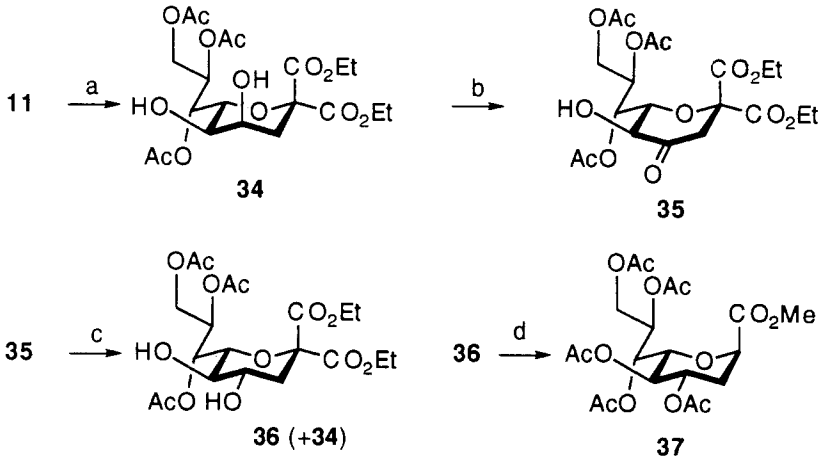
SCHEME 3

Table 1. Facial selectivity for cycloadditions with diethyl ketomalonate.

Diene	conditions (°C, d)	yield (%)	products	Re : Si
1	60 (5)	57	**20** + **21**	30 : 70
1	80 (0.7)	85	**20** + **21**	40 : 60
7	10 (1)	83	**10** + **11**	35 : 65
13	10 (1)	72	**22** + **23**	40 : 60
15	10 (1)	57	**24** + **25**	52 : 48
16	10 (1)	87	**26** + **27**	55 : 45
19	10 (1)	50	**28** + **29**	63 : 37



SCHEME 4

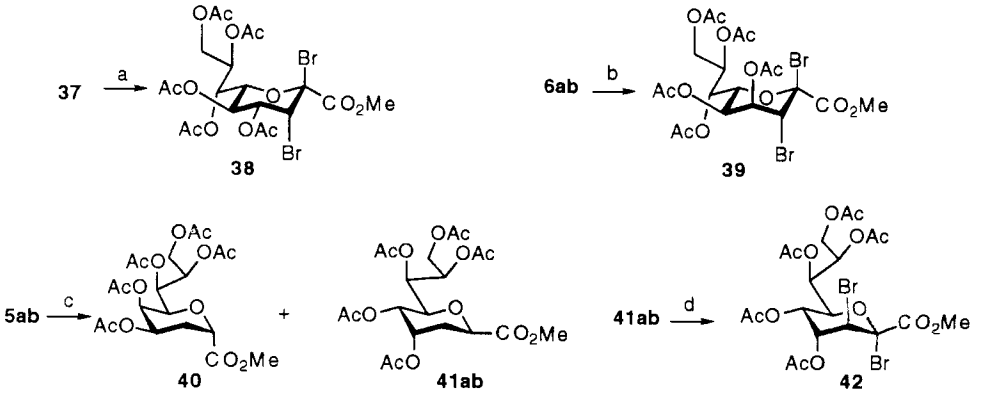


a. cat OsO_4-NMO, Me_2CO-H_2O, r.t., 6 h, 81%; b. 1) Bu_2SnO, tol, Dean-Stark, 4 h; 2) Br_2, CH_2Cl_2, r.t., 80%; c. $NaBH_4$, $CeCl_3$, MeOH, r.t., 91% (**36**:**34** = 4:1); d. 1)LiOH, H_2O, r.t., 1 d; 2) pH2, 100 °C, 8 h; 3) pH 7-8 then CH_3I, DMF, r.t., 2 d; 4) Ac_2O, Py, r.t., 15 h, 73%.

SCHEME 5

was selectively obtained in 80% yield by bromine oxidation of stannylene derivative of **34**.[16] Reduction of **35** under Luche conditions[17] gave the desired trans diol **36** in 73% yield along with 18% of cis diol **34**. Compound **34** is a protected 2-deoxy-2-carbethoxy KDN derivative which could be decarboxylated and reprotected to provide a 2-deoxy KDN derivative (**37**) in 73% yield.

Activation of anomeric center was achieved using the methodology developed in the heptulosonic series,[6] namely a *N*-bromosuccinimide mediated dibromination at C-2 and C-3 (Scheme 6). Methyl tetra-*O*-acetyl-2,3-dibromo-2,3-dideoxy-β-D-*erythro*-L-*manno*-2-nonulosonate (**38**) was thus obtained in 76% yield.[18] Dibromides **39** + **42** were obtained in 59% yield from the mixture **5ab** + **6ab**. The orientation of substituents was again shown to have a strong influence on the outcome of this reaction. For example, adducts **6ab** led to a low yield of dibromide **39** (C-4 epimer of **38**), while reaction of triacetates **41ab** (obtained from **5ab** together with **40**) gave dibromide **42** in a satisfactory 73% yield.



a. excess NBS, CCl_4, reflux, 5 d, 76%; b. 1) cat OsO_4-NMO, Me_2CO-H_2O, r.t., r.t., 3 h, 82%; 2) same as a., 1 d, 34%; c. 1) same as b., 3 h, 90%; d. same as a., 7 h, 76%.

SCHEME 6

In conclusion, we have shown, that the hetero Diels Alder reaction, creating C-2-C-3 and the C-6-O-6 bonds, and subsequent dihydroxylation at C-4 and C-5, starting from an erythrose based diene, is a valuable route for preparation of new 2-deoxy-2-nonulosonic acid analogs. Stereochemistry of adducts at C-6 was established by preparing 2-carbethoxy-2-deoxy-2-nonulosonates, that are formal *C*-glycosides of 2-nonulosonic acid, by reaction of various dienes with diethyl ketomalonate and subsequent decarboxylation. Further chemistry on either 2-carbethoxy-2-deoxy- or 2-deoxy-2-nonulosonate provided a range of new 2-nonulosonic acid derivatives, including new protected KDN analogs.

EXPERIMENTAL

General. NMR spectra were recorded with Brüker AM 250 and 400 and AC 200 and 250 spectrometers. Chemical shifts are given in ppm downfield from internal tetramethylsilane; signal multiplicity is indicated as follows: s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet and br for broad. IR spectra were recorded using a Brüker FT

instrument. Flash-chromatography was performed using 6-35 μ silica gel (60) purchased from S.D.S. company. TLC was run using Merck 60 F254 plates, and visualized first with UV light and second by heating after alcoholic sulfuric or phosphomolybdic acid treatment. Melting points were measured on a Reichert apparatus and are uncorrected. Elementary analyses were performed at the "Service Central de Microanalyse du C.N.R.S."

(2-*R*,3-*S*)-1,3-*O*-Benzylidene-hepta-4,6-diene-1,2,3-triol (13). To a solution of allyltriphenylphosphonium bromide (1.42 g, 5 mmol) in THF (20 mL) was added dropwise *n*-butyllithium (1.6 M in hexane, 3.13 mL, 5 mmol). The orange-red solution was then warmed up to 55 °C, and a solution of 2,4-benzylidene-D-erythrose[18] **12** (416 mg, 2 mmol) in THF (20 mL) was added. After 5 min, the mixture was cooled to room temperature, diluted with ether and washed with brine. The organic layer was concentrated under vacuum and flash-chromatography of the residue (3:7 AcOEt-hexane) gave a mixture of diene **13** and its *Z* isomer in a 83:17 ratio (270 mg, 58%). Crystallization (AcOEt-hexane) gave the pure *E* diene **13** as white needles: mp 89-90 °C; $[\alpha]_D^{20}$ -103° (*c* 1.6, CH_2Cl_2) [lit.[11] mp 88-89 °C, $[\alpha]_D^{20}$ -106° ($CHCl_3$)]. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.91 (brs, 1 H, OH), 3.56-3.72 (m, 2 H, $H_{6,7ax}$), 4.07 (brt, *J* = 7 Hz, 1 H, H_5), 4.33 (dd, *J* = 16, 10 Hz, 1 H, H_{7eq}), 5.18 (dd, *J* = 10, 1 Hz, 1 H, H_1), 5.30 (dd, *J* = 16, 1 Hz, 1 H, $H_{1'}$), 5.54 (s, 1 H, PhC**H**), 5.80 (dd, *J* = 14, 7 Hz, 1 H, H_4), 6.27-6.53 (m, 2 H, $H_{2,3}$), 7.30-7.56 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 70.69 (C_7), 65.31, 82.45 ($C_{5,6}$), 100.87 (Ph**C**H), 119.00 (C_1), 126.10, 128.20, 128.96, 139.30, 134.65, 135.87, 137.36 ($C_{2,3,4}$,Ph).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.66. Found: C, 72.53; H, 6.81; O, 20.85.

Preparation of diene **13** via aldehyde **14**. 1) Preparation of aldehyde **14**: to a solution of aldehyde **12**[19] (416 mg, 2 mmol) in THF (10 mL) was added portionwise (triphenylphosphoranylidene) acetaldehyde (670 mg, 2.2 mmol). After 6 h at room temperature, the solvent was evaporated, and flash-chromatography (9:1 toluene-acetone) of the residue gave aldehyde **14** (357 mg, 76%). 2) Preparation of diene **12** : to a solution of aldehyde **14** (117 mg, 0.5 mmol) in THF (2 mL), a salt-free 1 M solution of methylenetriphenylphosphorane in toluene (1.1 mL) was added dropwise. The mixture was immediately poured in a CH_2Cl_2 / pH7 phosphate buffer mixture. The organic layer was concentrated and flash-chromatography of

the residue (1:3 AcOEt-hexane) gave diene **13** (88 mg, 76%) identical with an authentic sample.

(2-*R*,3-*S*)-2-*O*-Acetyl-1,3-*O*-benzylidene-hepta-4,6-diene-1,2,3-triol (15). A solution of diene **13** (464 mg, 2 mmol) in acetic anhydride (2 mL) and pyridine (2 mL) was stirred overnight at room temperature. Evaporation of solvents and coevaporation with toluene followed by flash-chromatography of the residue (AcOEt-hexane, 1:4) gave diene **15** (507 mg, 92%) which crystallized from hexane: mp 85-86 °C, $[\alpha]_D^{20}$ -63° (*c* 1.9, CH_2Cl_2) [lit.[11] mp 78-80 °C, $[\alpha]_D^{20}$ -58° ($CHCl_3$)]. ^1H NMR ($CDCl_3$, 200 MHz) δ 2.00 (s, 3H, CH_3) 3.63 (t, *J* = 10 Hz, 1 H, H_{7ax}), 4.23 (dd, *J* = 9.5, 6 Hz, 1 H, H_5), 4.37 (dd, *J* = 10, 5 Hz, 1 H, H_{7eq}), 4.84 (dt, *J* = 9.5, 9.5, 5 Hz, 1 H, H_6), 5.12 (dd, *J* = 10, 1 Hz, 1 H, H_1), 5.23 (dd, *J* = 16, 1 Hz, 1 H, $H_{1'}$), 5.53 (s, 1 H, PhC**H**), 5.71 (dd, *J* = 14, 6 Hz, 1 H, H_4), 6.20-6.44 (m, 2 H, $H_{2,3}$), 7.30-7.55 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.62 (CH_3), 67.96 (C_7), 66.21, 79.57 ($C_{5,6}$), 101.05 (Ph**C**H), 118.71 (C_1), 126.08, 128.13, 128.59, 128.94, 134.29, 135.88, 137.14 ($C_{2,3,4}$, Ph), 169.46 (C=O).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; O, 23.33. Found: C, 70.08; H, 6.82; O, 23.30.

(2-*R*,3-*S*)-2-*O*-Benzyl-1,3-*O*-benzylidene-hepta-4,6-diene-1,2,3-triol (16). To a solution of diene **13** (232 mg, 1 mmol), benzyl bromide (0.14 mL, 1.2 mmol) in THF (2 mL) was added sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol). After the reaction mixture was strirred for 4 h at 50 °C, excess sodium hydride was destroyed by addition of water and the product was extracted with CH_2Cl_2. The organic layer was concentrated and flash-chromatography of the residue (1:9 AcOEt-hexane) gave diene **16** (225 mg, 70%) which crystallized neat when refrigerated: mp 69-71 °C; $[\alpha]_D^{20}$ -80° (*c* 1.4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 3.44 (ddd, *J* = 9.5, 8, 4 Hz, 1 H, H_6), 3.64 (t, *J* = 10 Hz, 1 H, H_{7ax}), 4.18 (dd, *J* = 8, 6 Hz, 1 H, H_5), 4.30 (dd, *J* = 10, 4 Hz, 1 H, H_{7eq}), 4.47-4.61 (AB system, 2 H, C**H**$_2$Ph), 5.13 (dd, *J* = 9, 1 Hz, 1 H, H_1), 5.24 (dd, *J* = 16, 1 Hz, 1 H, $H_{1'}$), 5.50 (s, 1 H, PhC**H**), 5.83 (dd, *J* = 14, 6 Hz, 1 H, H_4), 6.25-6.52 (m, 2 H, $H_{2,3}$), 7.30-7.55 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 69.50 (C_7), 72.79, 80.70 ($C_{5,6}$, **C**H_2Ph), 100.81 (Ph**C**H), 118.22 (C_1), 126.10, 127.93, 128.17, 128.41, 128.87, 130.04, 133.53, 136.27, 137.58, 137.68 ($C_{2,3,4}$, 2Ph).

Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88; O, 14.89. Found: C, 77.99; H, 6.82; O, 14.93.

(2-*R*,3-*S*)-Hepta-4,6-diene-1,2,3-triol (1). A solution of diene **13** (1.74 g, 7.5 mmol) in acetic acid and water (8:2, 20 mL) was stirred 35 min at 60 °C. Concentration to dryness followed by flash-chromatography of the residue (CH_2Cl_2-MeOH, 9:1) gave diene **1** (971 mg, 90%); mp 71-72 °C, $[\alpha]_D^{20}$ -41° (*c* 1.4, MeOH). ^1H NMR (CD_3OD, 200 MHz) δ 3.46-3.73 (m, 3 H, $H_{6,7,7'}$), 4.10 (dd, *J* = 6.5, 4 Hz, 1 H, H_5), 5.08 (dd, *J* = 9.5, 1 Hz, 1 H, H_1), 5.20 (dd, *J* = 16, 1 Hz, 1 H, $H_{1'}$), 5.82 (dd, *J* = 14, 6.5 Hz, 1 H, H_4), 6.20-6.50 (m, 2 H, $H_{2,3}$); ^{13}C NMR (CD_3OD, 50 MHz) ∂ 64.25 (C_7), 73.91, 75.98 ($C_{5,6}$), 117.48 (C_1), 133.48, 134.30, 137.86 ($C_{2,3,4}$).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39; O, 32.29. Found: C, 58.19; H, 8.28; O, 32.21.

(2-*R*,3-*S*)-1,2,3-Tri-*O*-acetyl-hepta-4,6-diene-1,2,3-triol (7). Acetylated diene **7** could be obtained either by quantitative acetylation of diene **1** (Ac_2O, pyridine, r.t.) or following the procedure described in ref. 11 from tri-*O*-acetyl-D-glucal; $[\alpha]_D^{20}$ +34° (*c* 2.4, CH_2Cl_2),+28° (*c* 3, $CHCl_3$) [lit.[11] +25° $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.04 (s, 3 H, CH_3), 2.07 (s, 6 H, 2 CH_3), 4.16 (dd, *J* = 12, 6.5 Hz, 1 H, H_7), 4.25 (dd, *J* = 12, 4 Hz, 1 H, $H_{7'}$), 5.13-5.36 (m, 3 H, $H_{1,1',6}$), 5.51 (dd, *J* = 7, 4.5 Hz, 1 H, H_5), 5.65 (dd, *J* = 14, 7 Hz, 1 H, H_4), 6.21-6.42 (m, 2 H, $H_{2,3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.57, 20.73, 20.82 (3 CH_3) 61.75 (C_7) 71.45, 72.12 ($C_{5,6}$) 119.65 (C_1), 125.96, 135.33, 135.64 ($C_{2,3,4}$), 169.48, 169.93, 170.42 (3 C=O).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71; O, 35.52. Found: C, 57.74; H, 6.60; O, 35.26.

(2-*R*,3-*R*)-1,2,3-Tri-*O*-acetyl-hepta-4,6-diene-1,2,3-triol (19). The same method as for diene **7** following ref. 10 from **18**[18] gave diene **19** in a 44% yield; $[\alpha]_D^{20}$ +16° (*c* 1.2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.07 (s, 3 H, CH_3), 2.10 (s, 6 H, 2 CH_3), 4.03 (dd, *J* = 12, 6 Hz, 1 H, H_7), 4.34 (dd, *J* = 12, 4 Hz, 1 H, $H_{7'}$), 5.18-5.35 (m, 3 H, $H_{1,1',6}$), 5.48-5.64 (m, 2 H, $H_{4,5}$), 6.20-6.40 (m, 2 H, $H_{2,3}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.21, 20.30, 20.45 ($3CH_3$), 61.77 (C_7), 70.91, 71.49 ($C_{5,6}$), 119.30 (C_1), 125.90, 135.16 ($C_{2,3,4}$), 169.16, 169.51, 169.95 (3C=O).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71; O, 35.52. Found: C, 58.06; H, 6.49; O, 35.40.

Cycloaddition of diene **1** with sodium glyoxylate. Preparation of adducts **5ab** and **6ab**. A solution of diene **1** (501 mg, 3.5 mmol) and sodium glyoxylate monohydrate (1.6 g, 14 mmol) in water (7 mL) was heated in a

closed tube at 120 °C in the presence of a small amount of hydroquinone. After 2.5 d, TLC (7:3 1-propanol-water) showed total disappearance of starting diene. The mixture was cooled to room temperature, diluted with water (10 mL total) and a 2:1 (vol.) mixture of DMF and CH_3I (15 mL) was added. After 4 d at room temperature, solvents were removed under vacuum and the mixture was dissolved in a 1:1 (vol) mixture of Ac_2O and pyridine (20 mL) and left overnight at room temperature. Removal of excess reagents by coevaporation several times with toluene gave a residue which was diluted with CH_2Cl_2 (50 mL). After washings (water, 50 mL, brine, 50 mL), the solvent was evaporated and the residue was purified by flash-chromatography (1:3 AcOEt-hexane) to give mixture of adducts **5ab** and **6ab** (850 mg, 68%) in a 44:56 endo:exo ratio and a 41:59 Re:Si ratio as determined by NMR analysis and comparison with same compounds prepared from **10** and **11**.

General procedure for the cycloadditions using diethyl ketomalonate. Cycloaddition of diene **7** with diethyl mesoxalate. Preparation of adducts **10** and **11**. Diene **7** (1.35 g, 5 mmol) and commercial diethyl mesoxalate (3.05 mL, 20 mmol) were heated at 100 °C in the presence of a catalytic amount of hydroquinone during 24 h. The mixture was then cooled, diluted with CH_2Cl_2 and washed with water (2x50 mL). After evaporation of the solvent, preparative HPLC of the residue (AcOEt-hexane, 1:3 then 1:2) gave in order of elution first the unreacted diene followed by the partially separated adducts **10** and **11** (1.592 g) in a 83% yield (based on starting diene recovery, 72% isolated yield). Pure fractions of each adduct were characterized.

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*ribo*-non-4-en-2-ulosonate (10). $[\alpha]_D^{20}$ +25° (*c* 2.5, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27, 1.28 (2 t, 3 H each, 2 CH_3), 2.04 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3) 2.61 (ddt, *J* = 17, 4, 3, 3 Hz, 1 H, H_3), 2.82 (dddd, *J* = 17, 6, 3, 1 Hz, 1 H, $H_{3'}$), 4.10-4.40 (m, 5 H, 2 CH_2, H_9), 4.62 (dd, *J* = 12, 2 Hz, 1 H, $H_{9'}$), 4.64-4.74 (m, 1 H, H_6), 5.19 (dd, *J* = 5, 4 Hz, 1 H, H_7), 5.39 (ddd, *J* = 6, 4, 2 Hz, 1 H, H_8), 5.69 (brd, *J* = 10 Hz, 1 H, H_5), 5.92-6.04 (m, 1 H, H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.48, 13.60 (2 CH_3 Et), 20.31, 20.42 (3 CH_3 Ac), 28.50 (C_3), 61.64, 61.84, 62.43 (2 CH_2 Et, C_9), 69.67, 71.08, 72.77 ($C_{6,7,8}$), 79.38 (C_2), 123.91, 124.06 ($C_{4,5}$), 167.04, 167.58, 169.42, 169.61, 170.16 (5 C=O).

Anal. Calcd for $C_{20}H_{28}O_{11}$: C, 54.05; H, 6.35; O, 39.60. Found: C, 53.78; H, 6.31; O, 39.67.

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*arabino*-non-4-en-2-ulosonate (11). $[\alpha]_D^{20}$ +58° (*c* 1.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25, 1.28 (2 t, *J* = 7 Hz, 3 H each, 2 CH_3), 2.05 (s, 6 H, 2 CH_3), 2.10 (s, 3 H, CH_3), 2.58 (ddt, *J* = 17, 4, 3, 3 Hz, 1 H, H_3), 2.73 (dddd, *J* = 17, 6, 3, 1 Hz, 1 H, $H_{3'}$), 4.10-4.40 (m, 5 H, 2 CH_2, H_9), 4.46 (dd, *J* = 12.5, 2.5 Hz, 1 H, $H_{9'}$), 4.83-4.91 (m, 1 H, H_6), 5.32 (dd, *J* = 6.5, 2 Hz, 1 H, H_7), 5.41 (ddd, *J* = 6.5, 6, 2 Hz, 1 H, H_8), 5.57 (brd, *J* = 10 Hz, H_5), 5.87-5.99 (m, 1 H, H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.63, 13.79 (2 CH_3 Et), 20.45, 20.59 (3 CH_3 Ac), 28.56 (C_3), 61.65, 61.91, 62.12 (2 CH_2 Et, C_9), 69.40, 70.72, 71.51 ($C_{6,7,8}$), 79.42 (C_2), 124.40, 124.65 ($C_{4,5}$), 167.04, 168.05, 169.53, 169.73, 170.38 (5 C=O).

Anal. Calcd for $C_{20}H_{28}O_{11}$, C : 54.05, H : 6.35, O : 39.60. Found, C : 53.77, H : 6.35, O : 39.62.

Cycloaddition of diene **1** with diethyl mesoxalate. Diene **1** (144 mg, 1 mmol) was heated with diethyl mesoxalate (0.31 mL, 2 mmol) in presence of a catalytic amount of hydroquinone at 80 °C for 17 h. Flash-chromatography of the mixture (95:5 CH_2Cl_2-MeOH) gave a 40:60 ratio of **20** and **21** (194 mg, 61%, 85% based on starting diene recovery), which were identified with **10** and **11** after quantitative peracetylation (Ac_2O-pyridine, 1:1).

Methyl 2,3,4,5-Tetradeoxy-D-*arabino*-non-4-en-2-ulosonate (6ab). This reaction could be achieved either from **11** or **21**. Adduct **21** (161 mg, 0.5 mmol) was treated overnight with aqueous LiOH (1M, 2 mL). When TLC (1-propanol-water, 7:3) indicated the disappearance of both ester fonctions, the mixture was acidified with Dowex-50X8 H^+ (1.3 g), until the pH decreased to 2, and then heated at 100 °C. After 24 h, TLC showed that decarboxylation had occurred. The mixture was then cooled and filtered over celite. After evaporation of the solvent, the residue was dissolved in methanol, and treated with a freshly prepared solution of diazomethane in ether. After concentration, flash-chromatography of the residue (95:5 CH_2Cl_2-MeOH) gave a mixture (70 mg, 60%), which was quantitatively acetylated with a mixture of acetic anhydride and pyridine (1:1 vol, 2 mL). Partial separation of the two epimers by flash-chromatography (AcOEt-hexane, 1:3) allowed assignment of the following values in their NMR spectra. **6a**: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.06, 2.08, 2.10 (3s, 3 H each, 3 CH_3), 2.25-2.45 (m, 2 H, $H_{3,3'}$), 3.77 (s, 3 H, CO_2Me), 4.18 (dd, *J* = 10, 7 Hz, 1 H, H_2), 4.24 (dd, *J* = 12.5, 6 Hz, 1 H, H_9), 4.47-4.54 (m, 1 H, H_6), 4.59 (dd, *J* = 12.5, 2.5 Hz, 1 H, $H_{9'}$), 5.32 (dd, J = 6, 2.5 Hz, 1 H, H_7), 5.42 (dt, J = 6, 6, 2.5

Hz, 1 H, H_8), 5.53-5.67 (m, 1 H, H_5), 5.90-6.04 (m, 1 H, H_4). **6b**: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.07, 2.09, 2.11 (3s, 3 H each, 3 CH_3), 2.25-2.53 (m, 2 H, $H_{3,3'}$), 3.75 (s, 3 H, CO_2Me), 4.24 (dd, J =12.5, 5.5 Hz, 1 H, H_9), 4.41 (dd, J = 12.5, 3 Hz, 1 H, $H_{9'}$), 4.54 (t, J = 5.5 Hz, 1 H, H_2), 4.66-4.74 (m, 1 H, H_6), 5.31 (dd, J = 7, 3.5 Hz, 1 H, H_7), 5.34-5.46 (m, 1 H, H_8), 5.57-5.73 (m, 1 H, H_5), 5.97 (ddt, J = 10, 4, 4, 2 Hz, 1 H, H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.62 ($3CH_3$ Ac), 26.40 (C_3), 51.97 (CO_2Me), 61.89 (C_9), 69.23, 69.45, 70.52, 71.46 ($C_{2,6,7,8}$), 124.81, 125.61 ($C_{4,5}$), 169.70, 170.56, 171.62 (4 C=O).

Anal. Calcd for $C_{16}H_{22}O_9$ (mixture **6ab**): C, 53.63; H, 6.19. Found: C, 54.24; H, 6.24.

Methyl 2,3,4,5-Tetradeoxy-D-*ribo*-non-4-en-2-ulosonate (5ab). Employing the same decarboxylation procedure as above from isomer **10** lead to the mixture of peracetylated compounds **5a** and **5b**. The following NMR assignments have been made. **5a** : ^1H NMR ($CDCl_3$, 200 MHz) δ 2.04, 2.06, 2.12 (3s, 3 H each, 3 CH_3) 2.27-2.58 (m, 2 H, $H_{3,3'}$), 3.77 (s, 3 H, CO_2Me), 4.21 (dd, J = 10, 5 Hz, 1 H, H_2), 4.35 (dd, J = 12.5, 8 Hz, 1 H, H_9), 4.41-4.52 (m, 1 H, H_6), 4.58 (dd, J = 12.5, 3 Hz, 1 H, $H_{9'}$), 5.13 (dd, J = 5, 4 Hz, 1 H, H_7), 5.35-5.46 (m, 1 H, H_8), 5.65-5.77 (m, 1 H, H_5), 5.92-6.05 (m, 1 H, H_4). **5b**: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.05 (s, 6 H, 2 CH_3), 2.11 (s, 3 H, CH_3), 2.27-2.61 (m, 2 H, $H_{3,3'}$), 3.75 (s, 3 H, CO_2Me), 4.28 (dd, J =12, 7.5 Hz, 1 H, H_9), 4.46 (dd, J = 12, 3 Hz, 1 H, $H_{9'}$), 4.56 (t, J = 5.5 Hz, 1 H, H_2), 4.63-4.73 (m, 1 H, H_6), 5.22 (dd, J = 6.5, 4 Hz, 1 H, H_7), 5.43 (ddd, J = 7.5, 4, 3 Hz, 1 H, H_8), 5.63-5.76 (m, 1 H, H_5), 5.87-6.02 (m, 1 H, H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.69 ($3CH_3$ Ac), 26.09 (C_3), 51.99 (CO_2Me), 62.13 (C_9), 69.56, 69.81, 72.49 ($C_{2,6,7,8}$), 124.44, 124.73 ($C_{4,5}$), 169.60, 169.95, 170.50, 171.59 (4 C=O).

Anal. Calcd for $C_{16}H_{22}O_9$ (mixture **5ab**): C, 53.63; H, 6.19. Found: C, 53.89; H, 6.32.

Preparation of hydrogenated adducts **30** and **31.** Adducts **10** or **11** (1.5 mmol) were dissolved in ethyl acetate (20 mL) and 10% Pd/C (200 mg) was added. After 5 h of hydrogenation (1 atm) conditions, the mixture was filtered over celite to give adducts **30** and **31** (94 and 97% resp.) after concentration to dryness.

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*ribo*-non-2-ulosonate (30). $[\alpha]_D^{20}$ +41° (*c* 2.4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.90, 2.31-2.43 (m, 12 H, 2 CH_3, $H_{3,3',4,4',5,5'}$), 2.05 (s, 3 H, CH_3), 2.07 (2 s, 6 H, 2 CH_3), 3.87 (ddd, J = 10.5, 7, 2 Hz, 1 H, H_6), 4.22, 4.28 (2 q, J = 7 Hz, 4 H, 2

CH_2), 4.45 (dd, J = 12.5, 8 Hz, 1 H, H_9), 4.55 (dd, J = 12.5, 3 Hz, 1 H, $H_{9'}$), 5.08 (dd, J = 7, 3 Hz, 1 H, H_7), 5.49 (dt, J = 8, 3, 3 Hz, 1 H, H_8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.33, 13.49 (2 CH_3 Et), 20.12, 20.26 (3 CH_3 Ac), 18.84, 26.02, 28.77 ($C_{3,4,5}$), 61.28, 61.43, 62.01 (2CH_2 Et, C_9), 69.95, 71.88, 73.14 ($C_{6,7,8}$), 81.24 (C_2), 167.19, 167.71, 169.12, 169.45, 169.94 (5 C=O).

Anal. Calcd for $C_{20}H_{30}O_{11}$: C, 53.80; H, 6.77; O, 39.42. Found: C, 54.08; H, 6.84; O, 39.39.

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*arabino*-non-2-ulosonate (31). $[\alpha]_D^{20}$ -1° (*c* 3, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.90, 2.25-2.38 (m, 12 H, 2 CH_3, $H_{3,3',4,4',5,5'}$), 2.04, 2.10, 2.14 (3 s, 3 H each, 3 CH_3), 4.05 (dt, J = 10.5, 2.5, 2.5 Hz, 1 H, H_6), 4.14-4.40 (m, 5 H, 2 CH_2, H_9), 4.54 (dd, J = 12.5, 2.5 Hz, 1 H, $H_{9'}$), 5.21 (dd, J = 6, 2.5 Hz, 1 H, H_7), 5.37 (dt, J = 6, 6, 2.5 Hz, 1 H, H_8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.35, 13.53 (2CH_3 Et), 20.16,20.39 (3 CH_3 Ac), 19.26, 25.27, 28.59 ($C_{3,4,5}$), 61.19, 61.41, 61.80 (2CH_2 Et, C_9), 69.93, 71.73, 72.25 ($C_{6,7,8}$), 81.32 (C_2), 167.17, 167.84, 169.64, 169.74, 170.09 (5 C=O).

Anal. Calcd for $C_{20}H_{30}O_{11}$: C, 53.80; H, 6.77; O, 39.42. Found: C, 53.67; H, 6.55; O, 39.17.

Preparation of compounds **28**, **29**, **32** and **33**. Adducts **28** and **29** were obtained from diene **19** following the general procedure for cycloadditions using diethyl ketomalonate and subsequent hydrogenation (cf. preparation of compounds **30** and **31**).

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*xylo* and *lyxo*-non-4-en-2-ulosonate (28 + 29). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.45 (m, 6 H, 2 CH_3), 1.98, 2.14, 2.18 (3 s, 3 $CH_{3(29)}$), 1.99, 2.02, 2.05 (3 s, 3 $CH_{3(28)}$), 2.54-2.85 (m, 2 H, $H_{3,3'}$), 4.05 (dd, J = 12, 6 Hz, $H_{9(29)}$), 4.12-4.45 (m, 5 H, 2 CH_2+ $H_{9'}$), 4.56 (dd, J = 12, 6 Hz, $H_{9(28)}$), 4.62-4.78 (m, 1 H, H_6), 5.18 (dd, J = 7, 4 Hz, 1 H, $H_{7(29)}$), 5.32 (dd, J = 7, 3 Hz, 1 H, $H_{7(28)}$), 5.40-5.56 (m, 1 H, H_8), 5.57-5.68, 5.88-6.00 (2 m, 2 H, $H_{4,5}$)

Anal. Calcd for $C_{20}H_{28}O_{11}$: C, 54.05; H, 6.31; O, 39.60. Found: C, 54.34; H, 6.42; O: 39.33.

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*xylo*-non-2-ulosonate (32). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.35 (m, 6 H, 2 CH_3), 1.40-1.90, 2.26-2.38 (m, 6 H, $H_{3,3',4,4',5,5'}$), 2.04, 2.07, 2.12 (3 s, 3 H each, 3 CH_3), 4.02 (dt, J = 11, 3, 3 Hz, 1 H, H_6), 4.16-4.35 (m, 4 H, 2 CH_2), 4.46 (dd, J = 12, 4 Hz, 1 H, H_9), 4.62 (dd, J = 12, 3 Hz, 1 H, $H_{9'}$), 5.20 (dd, J = 7.5, 3 Hz, 1 H, H_7), 5.40

(ddd, J = 7.5, 4, 3 Hz, 1 H, H_8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.80, 13.96 (2 CH_3 Et), 20.76 (3CH_3 Ac), 19.39, 25.59, 29.03 ($C_{3,4,5}$), 61.77, 61.93, 62.22 (2CH_2 Et, C_9), 70.51, 72.27, ($C_{6,7,8}$), 81.74 (C_2), 167.52, 168.59, 169.98, 170.35, 170.57 (5 C=O).

Ethyl 2-Carbethoxy-2,3,4,5-tetradeoxy-D-*lyxo*-non-2-ulosonate (33). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23-1.37 (m, 6 H, 2 CH_3), 1.37-1.90, 2.25-2.40 (m, 6 H, $H_{3,3',4,4',5,5'}$), 2.04, 2.10, 2.14 (3 s, 3 H each, 3 CH_3), 3.90 (ddd, J = 10, 8, 2 Hz, 1 H, H_6), 4.06-4.40 (m, 6 H, 2 CH_2 + $H_{9,9'}$), 5.14 (dd, J = 8, 4 Hz, 1 H, H_7), 5.48 (dt, J = 6, 6, 4 Hz, 1 H, H_8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.75, 13.92 (2 CH_3 Et), 20.56, 20.72 (3 Ac), 19.28, 26.33, 29.30 ($C_{3,4,5}$), 61.55, 61.88, 63.17 (2CH_2 Et, C_9), 68.84, 71.58, 72.42 ($C_{6,7,8}$), 81.58 (C_2), 167.66, 168.02, 168.22, 169.87, 170.49 (5 C=O).

Ethyl 7,8,9-Tri-*O*-acetyl-2-carbethoxy-2,3-dideoxy-D-*glycero*-D-*talo*-non-2-ulosonate (34). Compound **11** (1.6 g, 3.6 mmol) and *N*-methyl morpholine oxide (0.95 g, 7 mmol) were dissolved in a water-acetone mixture (1:8, 10 mL) and a 0.1 M solution of OsO_4 in *t*-BuOH (2 mL, 0.2 mmol, 0.055 eq) was added dropwise. After 6 h of stirring at room temperature, saturated aqueous sodium hydrogenosulfite was added, and the mixture was extracted with AcOEt (2 x 80 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give quantitatively the crude diol **34** which was further purified after chomatography (AcOEt : hexane, 2:1, 1.4 g, 81%); $[\alpha]_D^{20}$ +12° (*c* 1.2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18-1.35 (m, 6 H, 2 CH_3), 2.04, 2.13, 2.18, 2.10-2.26 (3 s + m, 10 H, 3 Ac + H_{3a}), 2.67 (dd, J = 14,3 Hz, 1 H, H_{3e}), 3.20 (br s, 1 H, 4-OH), 3.29 (ddd, J = 9,5,2 Hz, 1 H, H_5), 3.65 (brd, 1 H, 5-OH), 4.10-4.28 (m, 5 H, 2 CH_2 + H_4), 4.33 (dd, J = 12,5 Hz, 1 H, H_9), 4.46-4.58 (m, 2 H, H_6+$H_{9'}$), 5.38 (dd, J = 5,1 Hz, 1 H, H_7), 5.46 (dt, J = 5,5,1.5 Hz, 1 H, H_8). ^1H NMR (d_6-DMSO, 250 MHz) δ 1.08-1.25 (m, 6 H, 2 CH_3), 1.98, 2.01, 2.06, 2.03-2.15 (3 s + m, 10 H, 3 Ac + H_{3a}), 2.39 (dd, J = 11,3,1 Hz, 1 H, H_{3e}), 3.17-3.26 (m, 1 H, H_5), 3.84-3.89 (m, 1 H, H_4), 3.97-4.18 (m, 5 H, 2 CH_2 + H_9), 4.40 (dd, J = 8,1.5 Hz, 1 H, H_6), 4.48 (dd, J = 9,2 Hz, 1 H, H_9), 4.76 (d,J = 6 Hz, 1 H, 5-OH), 4.93 (d, J = 2 Hz, 1 H, 4-OH), 5.20 (ddd, J = 5.5,3.5,2 Hz, 1 H, H_8), 5.42 (dd, J = 3.5,1.5 Hz, 1 H, H_7). ^{13}C NMR ($CDCl_3$, 62 MHZ) δ 13.41, 13.55 (2 CH_3 Et), 20.38, 20.65 (3 CH_3 Ac), 35.02 (C_3), 61.18, 61.92, 62.00 (2 CH_2 Et, C_9), 65.93, 66.11, 69.49, 69.99 ($C_{4,5,6,7,8}$), 77.77 (C_2) 166.83, 167.93, 169.96, 170.41, 171.63 (5 C=O).

Anal. Calcd for $C_{20}H_{30}O_{13}$: C, 50.21; H, 6.32; O, 43.47. Found: C, 50.05; H, 6.25; O, 43.48.

Ethyl 7,8,9-Tri-*O* acetyl-2-carbethoxy-2,3-dideoxy-4-oxo-D-*glycero*-D-*talo*-non-2-ulosonate (35). Diol **34** (872 mg, 1.82 mmol) and dibutylstannyl oxide (498 mg, 2 mmol) were refluxed in toluene (50 mL) during 4 h with azeotropic removal of water. The solvent was then partially removed by distillation (until a ~ 2 mL volume was reached) and the mixture was cooled to room temperature. Anhydrous dichloromethane (2 mL) was added, and tributylstannyl methoxide (610 mg, 1.9 mmol) was added in one portion. A solution of bromine in dichloromethane (0.25 M, 8 mL, 2 mmol) was then added dropwise as long as decoloration occured. Concentration to dryness and flash-chromatography of the residue (1:1 AcOEt-hexane) allowed isolation of the pure hydroxyketone **35** (369 mg, 80%) as a pale yellow oil; $[\alpha]_D^{20}$ -17° (*c* 2.8, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22-1.35 (m, 6 H, 2 CH_3), 2.08, 2.11, 2.20 (3s, 9 H, 3 Ac), 3.07 (dd, *J* = 14,1 Hz, 1 H, H_{3a}), 3.23 (d, *J* = 14 Hz, 1 H, H_{3e}), 3.58 (brd, *J* = 3.5 Hz, 1 H, 5-OH), 3.98 (ddd, *J* = 10, 3.5, 1 Hz, 1 H, H_5), 4.09 (dd, *J* = 10,1.5 Hz, 1 H, H_6), 4.18-4.36 (m, 5 H, 2 CH_2 + H_9), 4.50 (dd, *J* = 12, 2 Hz, 1 H, H_9), 5.40 (ddd, *J* = 6, 5, 2 Hz, 1 H, H_8), 5.57 (dd, *J* = 6,1.5 Hz, 1 H, H_7). ^{13}C NMR ($CDCl_3$, 62 MHZ) δ 13.83 ($2CH_3$ CO_2Et), 20.65, 20.71 (3 CH_3 Ac), 43.46 (C_3), 61.87, 62.77, 62.99 ($2CH_2$ Et, C_9), 68.68, 69.61, 72.09, 77.19 ($C_{5,6,7,8}$), 82.32 (C_2), 165.49, 166.36, 169.90, 170.64, 171.63 (5 C=O), 203.29 (C_4).

Anal. Calcd for $C_{20}H_{28}O_{13}$: C, 50.42; H, 5.92; O, 43.66; Found: C, 50.89; H, 6.11; O : 43.60.

Ethyl 7,8,9-Tri-*O*-acetyl-2-carbethoxy-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonate (36). The hydroxy ketone **35** (565 mg, 1.18 mmol) and cerium chloride (1.33 g, 3.56 mmol) were dissolved in methanol (5 mL) at room temperature. After a few minutes, sodium borohydride (76 mg, 2 mmol) was added and reduction occurred immediately. Acetic acid was then added dropwise until pH rose to neutrality. After dilution with water and extraction with ether (3 x 50 mL), the organic layer was dried over sodium sulfate and the solvent was evaporated, giving rise to a pale yellow oil which was shown to be a 4:1 mixture of *cis* and *trans* diols **34** and **36** (513 mg, 91%). Chromatography (AcOEt : hexane, 2:1) of the mixture gave, as the second fraction in order of elution, the pure diol **36**; $[\alpha]_D^{20}$ -8° (*c* 1.8, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23-1.34 (m, 6 H, 2 CH_3), 1.96 (dd, *J*

= 13.5, 11.5 Hz, 1 H, H_{3a}), 2.05, 2.13, 2.21 (3s, 3 H each, 3 Ac), 2.73 (dd + brs, J = 13.5, 4 Hz, 2 H, H_{3e} + OH), 3.02 (brt, J = 9 Hz, 1 H, H_5), 3.57 (brs, 1 H, OH), 3.61 (ddd, J = 11.5, 8, 4 Hz, 1H, H_4), 3.83 (dd, J = 9.5, 1.5 Hz, 1 H, H_6), 4.14-4.30 (m, 4 H, 2 CH_2), 4.37 (dd, J = 12, 4 Hz, 1 H, H_9), 4.49 (dd, J = 12, 2 Hz, 1 H, $H_{9'}$), 5.28 (dd, J = 7,1.5 Hz, 1 H, H_7), 5.43 (ddd, J = 7.5,4,2 Hz, 1 H, H_8). ^{13}C NMR ($CDCl_3$, 50 MHZ) δ 13.49, 13.63 (2 CH_3 Et), 20.38, 20.47, 20.62 (3 CH_3 Ac), 35.85 (C_3), 61.77, 61.87, 62.06 (2 CH_2 Et, C_9), 68.72, 69.42, 70.40, 74.25 ($C_{4,5,6,7,8}$), 80.92 (C_2), 166.28, 167.19, 169.82, 170.41, 171.77 (5 C=O).

Anal. Calcd for $C_{20}H_{30}O_{13}$: C, 50.21; H, 6.32; O, 43.4. Found: C, 50.36; H, 6.58; O, 43.58.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonate (37). Compound **36** (125 mg, 0.26 mmol) was treated with aq LiOH (1 M, 2 mL) for 1 d. After addition of 4 N aq HCl (until pH 1-2 was reached) the mixture was heated under reflux during 8 h, and then cooled to room temperature before readjusting the pH to 7-8 by adding 10% aq $NaHCO_3$. The solvent was removed under reduced pressure and DMF (2 mL) and CH_3I (2 mL) were added. The mixture was stirred at room temperature for 2 d, concentrated to dryness, and then treated overnight at room temperature with a 1:1 (vol) mixture of Ac_2O-pyridine (8 mL). Coevaporation with toluene followed by flash-chromatography of the residue (1:2 AcOEt-hexane) gave **37** (90 mg, 73%). $[\alpha]_D^{30}$ = -51° (*c* 2.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.02, 2.03, 2.05, 2.12, 2.17 (5 s, 15 H, 5 Ac), 1.95-2.10 (1 m, 1 H, H_{3ax}), 2.52 (ddd, J = 14, 4, 1.5 Hz, 1 H, H_{3eq}), 3.77 (s, 3 H, Me), 3.83 (dd, J = 9.5, 1.5 Hz, 1 H, H_6), 4.17 (dd, J = 12, 4 Hz, 1 H, H_9), 4.29 (dd, J = 10, 2 Hz, 1 H, H_6), 4.30 (dd, J = 12, 2 Hz, 1 H, $H_{9'}$), 4.57 (br d, J = 6 Hz, 1 H, H_2), 4.82 (t, J = 10 Hz, 1 H, H_5), 4.96 (ddd, J = 10, 8, 4 Hz, 1 H, H_4), 5.32-5.43 (m, 2 H, $H_{7,8}$). ^{13}C NMR ($CDCl_3$, 50 MHZ) δ 20.54, 20.65, 20.84, 21.01, 31.49, 52.32, 61.93, 66.64, 68.11, 68.24, 69.79, 71.29, 71.62, 169.71, 169.86, 170.01, 170.14, 170.25, 170.65. IR (neat, cm^{-1}) 2955.9, 1749.7, 1436.7, 1371.0, 1225.5, 1151.9, 1118.1, 1057.7.

Anal. Calcd for $C_{20}H_{28}O_{13}$: C, 50.42; H, 5.92; O, 43.66. Found: C, 50.95; H, 5.96; O, 43.28.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dibromo-2,3-dideoxy-β-D-*erythro*-L-*manno*-non-2-ulosonate (38). To a refluxing solution of **37** (120 mg, 0.25 mmol) in CCl_4 (10 mL) was added *N*-bromosuccinimide (2 g, excess).

More NBS was added (1 g each day) in order to compensate bromine loss. After 5 d, the mixture was cooled to room temperature, filtered, and the filtrate concentrated. Flash-chromatography of the residue (1:2 AcOEt-hexane) gave **38** (120 mg, 76%); $[\alpha]_D^{30}$ -49° (*c* 4.5, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02,-2.18 (5 s, 15 H, 5 Ac), 3.92 (s, 3 H, Me), 4.14 (dd, *J* = 12.5, 5 Hz, 1 H, H_9), 4.41 (dd, *J* = 12.5, 2 Hz, 1 H, $H_{9'}$), 4.45 (dd, *J* = 9.5, 2 Hz, 1 H, H_6), 5.09 (d, *J* = 3 Hz, 1 H, H_3), 5.31 (ddd, *J* = 8, 5, 2 Hz, 1 H, H_8), 5.45 (dd, *J* = 8, 2 Hz, 1 H, H_7), 5.50 (t, *J* = 9.5 Hz, 1 H, H_5), 5.56 (dd, *J* = 9.5, 3 Hz, 1 H, H_4). ^{13}C NMR ($CDCl_3$, 62 MHZ) δ 20.44, 20.52, 20.61, 20.68, 20.91, 52.46, 53.89, 61.65, 63.67, 65.82, 68.73, 69.65, 74.98, 91.08, 163.74, 169.14, 169.77, 170.56. IR (neat, cm^{-1}) 3058.8, 2955.9, 1753.9, 1436.8, 1371.1, 1266.0, 1230.1, 1068.4.

Anal. Calcd for $C_{20}H_{26}Br_2O_{13}$: C, 37.88; H, 4.13; Br, 25.20; O, 32.79. Found: C, 37.92; H, 4.21; Br, 24.57; O, 32.51.

Preparation of **39** and **42** directly from the mixture **5ab+6ab**. The same procedure as for preparation of **39** was applied to a mixture of adducts **5ab** and **6ab** (850 mg, 2.37 mmol), providing a mixture of 2,3-dideoxy derivatives (800 mg, 71%) that was treated by NBS, giving finally **39** + **42** (552 mg, 52%).

Anal. Calcd for $C_{20}H_{26}Br_2O_{13}$: C, 37.88; H, 4.13; Br, 25.20; O, 32.79. Found: C, 37.95; H, 4.35; Br, 25.31; O, 32.51.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dibromo-2,3-dideoxy-β-D-*erythro*-L-*altro*-non-2-ulosonate (39). Starting from mixture of adducts **6ab** (145 mg, 0.405 mmol), bishydroxylation following the same procedure as for preparation of compound **34** followed by Ac_2O-pyridine acetylation gave a mixture (157 mg, 82%). A portion of the mixture (145 mg, 0.3 mmol) of intermediate 2,3-dideoxy compounds, was submitted to the foregoing NBS oxidation procedure using 217 mg of NBS (1.2 mmol). Reflux during 1 d and usual work-up gave **39** (64 mg, 34%). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.04, 2.06, 2.10, 2.11, 2.21 (5 s, 15 H, 5 Ac), 3.90 (s, 3 H, Me), 4.18 (dd, *J* = 12.5, 4 Hz, 1 H, H_9), 4.45 (dd, *J* = 12.5, 2 Hz, 1 H, $H_{9'}$), 4.57 (dd, *J* = 10, 2 Hz, 1 H, H_6), 4.92 (d, *J* = 2 Hz, 1 H, H_3), 5.33 (ddd, *J* = 7, 4, 2 Hz, 1 H, H_8), 5.50 (t, *J* = 3 Hz, 1 H, H_4), 5.56 (dd, *J* = 7, 2 Hz, 1 H, H_7), 5.58 (dd, *J* = 10, 3 Hz, 1 H, H_5). ^{13}C NMR ($CDCl_3$, 62 MHZ) δ 20.44, 20.66, 21.01, 46.92, 53.66, 61.12, 61.52, 66.22, 68.75, 69.53, 71.14, 88.66, 164.20, 169.25, 169.50, 169.69,

170.51. IR (neat, cm^{-1}) 3057.4, 2958.2, 1755.8, 1440.2, 1371.9, 1266.4, 1220.8, 1075.1.

Preparation of **42**. Starting from mixture of adducts **5ab** (97 mg, 0.27 mmol), bishydroxylation following the same procedure as for preparation of compound **34** followed by Ac_2O-pyridine acetylation gave **40** (45 mg) and **41ab** (70 mg) in a global 90% yield. Equatorial isomer **41a** could be isolated from the mixture by further chromatography.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-D-*glycero*-D-*manno*-non-2-ulosonate (40). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.97, 1.98, 2.03, 2.05, 2.07 (5 s, 15 H, 5 Ac), 2.10-2.40 (m, 2 H, $H_{3,3'}$), 3.82 (s, 3 H, Me), 4.29 (dd, J = 9.5, 1 Hz, 1 H, H_6), 4.40 (dd, J = 12, 7 Hz, 1 H, H_9), 4.49 (dd, J = 12, 3 Hz, 1 H, $H_{9'}$), 4.51 (dd, J = 5, 1 Hz, 1 H, H_2), 4.93 (ddd, J = 11, 5, 3 Hz, 1 H, H_4), 5.21 (dd, J = 9.5, 2 Hz, 1 H, H_7), 5.23-5.27 (m, 1 H, H_5), 5.47 (ddd, J = 7, 3, 2 Hz, 1 H, H_8). ^{13}C NMR ($CDCl_3$, 50 MHZ) δ 20.44, 20.55, 20.68, 20.73, 20.81, 29.58, 52.47, 61.62, 64.74, 66.49, 68.21, 70.34, 70.59, 72.25, 169.46, 169.92, 170.10, 170.41, 170.62, 170.91.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-D-*allo*-non-2-ulosonate (41a). $[\alpha]_D^{30}$ 46° (*c* 0.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.04, 2.05, 2.13, 2.15 (4 s, 15 H, 5 Ac), 1.96-2.23 (1 m, 2 H, $H_{3,3'}$), 3.87 (s, 3 H, Me), 4.03 (dd, J = 10, 2 Hz, 1 H, H_6), 4.22 (dd, J = 12, 7 Hz, 1 H, H_9), 4.37 (dd, J = 12, 2.5 Hz, 1 H, H_2), 4.64 (dd, J = 12, 2 Hz, 1 H, H_9), 4.92 (dd, J = 10, 3 Hz, 1 H, H_5), 5.23 (ddd, J = 7, 4, 2 Hz, 1 H, H_8), 5.38 (dd, J = 4, 2 Hz, 1 H, H_7), 5.56 (q, J = 3 Hzn 1 H, H_4). ^{13}C NMR ($CDCl_3$, 50 MHZ) δ 20.38, 20.56, 20.66, 32.50, 53.35, 62.29, 65.95, 67.35, 70.07, 70.23, 71.25, 73.35, 169.45, 169.52, 169.78, 169.87, 170.44. IR (neat, cm^{-1}) 2957.8, 1745.9, 1439.3, 1373.0, 1223.1, 1146.4, 1061.1.

Anal. Calcd for $C_{20}H_{28}O_{13}$: C, 50.42; H, 5.92. Found: C, 50.22; H, 6.19.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dibromo-2,3-dideoxy-α-D-*erythro*-D-*altro*-non-2-ulosonate (42). Mixture **41ab** (320 mg, 067 mmol) was submitted to NBS oxidation (480 mg, 2.7 mmol) in refluxing CCl_4 (25 mL) during 6.5 h. Usual work-up gave **42** (310 mg, 73%). **42**: $[\alpha]_D^{28}$ 55° (*c* 1.3, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03, 2.08, 2.11, 2.14, 2.20 (5 s, 15 H, 5 Ac), 3.91 (s, 3 H, Me), 4.27 (dd, J = 12, 5.75 Hz, 1 H, H_9), 4.55 (dd, J = 12, 2 Hz, 1 H, $H_{9'}$), 4.63 (dd, J = 10.5, 2 Hz, 1 H, H_6), 4.92 (d, J = 2.5 Hz, 1 H, H_3), 5.31 (dt, J = 2, 5.75 Hz, 1 H, H_8), 5.51 (dd, J = 5.75, 2 Hz, 1 H, H_7), 5.57 (t, J = 2.5 Hz, 1 H, H_4), 5.77 (dd, J = 10.5, 2.5 Hz, 1 H, H_5). ^{13}C NMR ($CDCl_3$,

62 MHZ) δ 20.40, 20.61, 20.79, 20.94, 47.06, 53.61, 61.86, 63.05, 68.59, 69.07, 69.62, 72.60, 87.70, 164.30, 169.06, 169.43, 169.74, 170.43. IR (neat, cm^{-1}) 2958.6, 1756.5, 1440.6, 1372.0, 1224.1, 1045.4.

Anal. Calcd for $C_{20}H_{26}Br_2O_{13}$: C, 37.88; H, 4.13; Br, 25.20; O, 32.79. Found: C, 38.82; H, 4.37; Br, 24.55; O, 32.17.

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